



CME Review

Mold allergy revisited

Jay M. Portnoy, MD; and David Jara, MD

Division of Allergy, Asthma & Immunology, Children's Mercy Hospitals & Clinics, Kansas City, Missouri



ARTICLE INFO

Article history:

Received for publication September 4, 2014.

Received in revised form October 4, 2014.

Accepted for publication October 7, 2014.

INSTRUCTIONS

Credit can now be obtained, free for a limited time, by reading the review article in this issue and completing all activity components. Please note the instructions listed below:

- Review the target audience, learning objectives and all disclosures.
- Complete the pre-test online at <http://www.annallergy.org> (click on the CME heading).
- Follow the online instructions to read the full version of the article; reflect on all content as to how it may be applicable to your practice.
- Complete the post-test/evaluation and claim credit earned; at this time, you will have earned up to 1.0 AMA PRA Category 1 Credit™. Please note that the minimum passing score on the post-test is 70%.

Release Date: February 1, 2015**Expiration Date:** January 31, 2017**Target Audience:** Physicians involved in providing patient care in the field of allergy/asthma/immunology**Learning Objectives:**

At the conclusion of this activity, participants should be able to:

- Advise patients on how to reduce exposure to fungi
- Diagnose patients with fungal allergy

Accreditation: The American College of Allergy, Asthma & Immunology (ACAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.**Designation:** The American College of Allergy, Asthma & Immunology (ACAAI) designates this journal-based CME activity for a maximum of 1 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.**Planning Committee Members:**

Jay M. Portnoy, MD (Author)

Mitchell H. Grayson, MD (CME Series Editor, Deputy Editor)

Gailen D. Marshall, Jr, MD, PhD (Editor-in-Chief)

Disclosure of Relevant Financial Relationships:

J.M. Portnoy has served as a speaker for Thermo Fisher Scientific. M.H. Grayson has received research grants from Children's Research Institute/Medical College of Wisconsin, Merck, National Institutes of Health (NIH), and Polyphor. G.D. Marshall has received research grants from Amgen, AstraZeneca, and National Institutes of Health (NIH). D. Jara has nothing to disclose. Reviewers and Education/Editorial staff have no relevant financial relationships to disclose. No unapproved/investigative use of a product/device is discussed.

Recognition of Commercial Support: This activity has not received external commercial support.**Copyright Statement:** © 2014–2017 ACAAI. All rights reserved.**CME Inquiries:** Contact the American College of Allergy, Asthma & Immunology at education@acai.org or 847-427-1200.

Introduction

Fungi are ubiquitous eukaryotic organisms that are members of their own kingdom. They are distinct from prokaryotes, plants, and animals. Fungi may exist as unicellular organisms, such as yeasts (eg, *Candida*) but more typically they have tubelike bodies, called

Reprints: Jay M. Portnoy, MD, Division of Allergy, Asthma & Immunology, Children's Mercy Hospitals & Clinics, 2401 Gillham Rd, Kansas City, MO 64108; E-mail: jportnoy@cmh.edu.

<http://dx.doi.org/10.1016/j.anai.2014.10.004>

1081-1206/© 2015 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

hyphae, which range from 2 to 10 μm in diameter. Hyphae grow at their tips and frequently branch, resulting in an interconnected network called a mycelium.

Fungi reproduce by making spores by asexual or sexual processes. Many of the structures that produce asexual spores are called *conidia*, the morphologic structure of which is often used to identify a fungus by genus and species. Fungi that lack an observable sexual stage historically were referred to as *Fungi imperfecti* or Deuteromycota; however, that term is no longer recognized and should no longer be used. When fungi reproduce sexually via meiosis, they produce 8 spores contained in an ascus or sack that are released when the ascus is disrupted.

Fungi do not rely on photosynthesis to convert carbon dioxide into carbohydrates as plants do. Instead, they secrete digestive enzymes onto the outside world and then absorb nutrients, using oxygen from the atmosphere to obtain energy. Their byproducts consist of a complex mixture of organic compounds, some of which consist of proteins that can induce and bind to IgE in humans¹ and others that can serve as proinflammatory compounds and irritants via non-IgE mechanisms.²

Allergenic Fungi

The taxonomy of fungi has been confusing, primarily because identification of species traditionally has relied on visual recognition of distinct morphologic features. This confusion was confounded by the fact that fungi can have differing morphologic features, depending on the substrate and environmental conditions in which they grow, whether they are in their sexual or asexual reproductive state, and the skill and biases of the mycologist performing the identification. Recently, a taxonomy based on molecular DNA techniques has been agreed on by experts in the field.³

Many allergenic fungal genera are represented by 3 phyla: Zygomycota, Ascomycota, and Basidiomycota (Table 1). The largest group is the Ascomycota. On the basis of cluster analysis, a close relationship has been observed between genetic fungal taxonomy and IgE sensitization.⁴ The IgE-based clustering divides the Ascomycota cluster into 2 separate clusters. The first cluster includes genera in the classes Sordariomycetes, Leotiomyces, and Eurotiomycetes and some genera from the Dothideomycetidae, whereas the second cluster contains genera from the Pleosporomycetidae, which is another subclass of the Dothideomycetidae. Genera from Saccharomycetes form a third cluster in the Ascomycota phylum. Fungi from the Zygomycota and Basidiomycota phyla form their own IgE sensitization clusters. Given these extensive cross-reactivity patterns, it might be possible to identify representative genera from each class to serve as a proxy for IgE directed to the group.

Major allergens have been identified for many fungal genera (Table 2). In addition to their ability to induce and bind to IgE, the

biologic function for most of these allergens has been determined. A comprehensive database of fungal allergens can be found at Allergome (<http://www.allergome.org/>).

Exposure to Fungi

Fungi can be found in virtually all environments in which there is a source of carbohydrate, moisture, and warmth. They serve a role as saprophytes by causing decay of plant materials. Airborne spores are typically counted using light microscopy after they are collected on adhesive-coated surfaces. The number and diversity of airborne fungi detected by this method may be underestimated. One study found that as many as 86% of genera detected by DNA sequencing were not routinely identifiable by microscopy, including some currently unrecognized aeroallergens.⁵

Typical 24-hour mean outdoor spore concentrations can range from as few as 50 spores/ M^3 during winter to as many as 50,000 spores/ M^3 during summer.⁶ In temperate regions, spores in outdoor air tend to peak in the middle to late summer and decrease with the first hard frost in regions that experience cold winter seasons, although they may briefly rebound during warmer periods. Xenophilic or dry air spores, such as *Cladosporium* and *Alternaria*, peak in the afternoon hours during periods of low humidity. Hydrophilic or wet air spores, such as ascospores and basidiospores (mushrooms and puffballs), tend to peak during predawn hours, when there is high humidity. Temperature and dew point appear to be the most important meteorologic factors that affect the presence of spores.⁷ A survey of outdoor fungal genera in Tulsa, Oklahoma, identified *Cladosporium*, *Alternaria*, *Epicoccum*, *Curvularia*, *Pithomyces*, *Drechslera*, smut, ascospores, basidiospores, and others.⁸

Epidemics of asthma have been reported to be associated with thunderstorms and increases in airborne *Alternaria*. In one study, there was an increased risk of thunderstorm-related asthma (odds ratio [OR], 9.31) if one was sensitive to *Alternaria*, which was even greater if sensitive both to *Alternaria* and *Cladosporium* (OR, 64).⁹

Indoors, fungal spores usually are present in low concentrations unless sources of indoor growth are present. Lacking such growth, the indoor microbiome depends largely on dispersal from the outdoors.¹⁰ The most common taxa found in surveys of contaminated indoor environments include *Penicillium*, *Aspergillus*, *Ascospores*, *Alternaria*, *Periconia*, *Basidiospores*, *Stachybotrys*, and *Wallemia*.

Fungi are adapted to varying moisture conditions. The types of fungal species present often change over time, reflecting changes in moisture as the building dries and becomes damp again. Room types most likely to have elevated spore counts include (in descending order) laundry rooms, bathrooms, basements, and bedrooms, with the lowest counts being found in living rooms, kitchens, and family/television rooms.¹¹ The total biomass of indoor

Table 1
Taxonomy of selected allergenic fungi^{4,a}

Phylum	Class	Order	Selected genera
Zygomycota	Zygomycetes	Mucorales	<i>Mucor</i> , <i>Rhizopus</i>
Ascomycota	Saccharomycetes	Saccharomycetales	<i>Candida</i> , <i>Saccharomyces</i>
		Capnodiales	<i>Cladosporium</i>
		Pleosporales	<i>Alternaria</i> , <i>Curvularia</i> , <i>Bipolaris</i> , <i>Stemphylium</i> , <i>Phoma</i> , <i>Epicoccum</i>
		Dothideales	<i>Aureobasidium</i>
		Eurotiomycetes	<i>Aspergillus</i> , <i>Penicillium</i>
	Sordariomycetes	Onygenales	<i>Trichophyton</i>
		Hypocreales	<i>Fusarium</i> , <i>Trichoderma</i> , <i>Stachybotrys</i>
		Sordariales	<i>Monilia</i> , <i>Neurospora</i> , <i>Chaetomium</i> , <i>Acremonium</i>
	Leotiomyces	Helotiales	<i>Botrytis</i>
		Sporidiobolales	<i>Rhodotorula</i>
Basidiomycota	Ustilaginomycetes	Ustilaginales	<i>Ustilago</i>

^aGenera in the same class tend to have substantial IgE cross-reactivity. Members of the *Sordariomycetes*, *Leotiomyces*, *Eurotiomycetes*, and *Dothideomycetidae* classes also exhibit substantial cross-reactivity.

Table 2Major allergens and their biologic activity for 4 major genera of allergenic fungi^a

Genus and allergen	Biologic activity
<i>Alternaria</i>	
Alt a 1	Unknown
Alt a 2	Protein initiation factor
Alt a 3	Heat shock protein 70
Alt a 4	Thioredoxin
Alt a 6	Enolase
Alt a 7	Flavodoxin
Alt a 8	Mannitol dehydrogenase
Alt a 10	Aldehyde dehydrogenase
Alt a 13	Glutathione S-transferase
<i>Cladosporium</i>	
Cla h 3	Alcohol dehydrogenase
Cla h 6	Enolase
Cla h 7	Flavodoxin
Cla h 8	Mannitol dehydrogenase
Cla h 9	Serine protease
Cla h 10	Aldehyde dehydrogenase
Cla h 12	Heat shock protein 90
<i>Aspergillus</i>	
Asp f 1	Mitogillin
Asp f 3	Peroxisomal membrane protein
Asp f 5	Serine protease
Asp f 6	Mn superoxide dismutase
Asp f 11	Cyclophilin peptidyl prolyl isomerase
Asp f 12	Heat shock protein 90
Asp f 18	Serine protease
Asp f 22	Enolase
Asp f 28	Thioredoxin
<i>Penicillium</i>	
Pen c 2	Serine protease
Pen c 3	Peroxisomal membrane protein
Pen c 13	Serine protease
Pen c 18	Serine protease
Pen c 19	Heat shock protein 70
Pen c 22	Enolase
Pen c 24	Glutathione S-transferase
Pen c 30	Catalase

^aCompiled from Allergome (<http://www.allergome.org/>).

fungi in such buildings is likely to be underestimated because most airborne fungal material is present in the form of mycelial fragments that cannot be easily be recognized as being fungal in origin.¹²

The National Survey of Lead and Allergens in Housing was a population-based study that measured indoor allergens in US homes. Of the surveyed homes, 51.5% had at least 6 detectable allergens, and 45.8% had at least 3 allergens that exceeded increased levels. An increased allergen level was defined as 7 $\mu\text{g/g}$ of Alt a 1 for *Alternaria alternata*. The most commonly found allergens detected at increased levels were cat, dog, and *Alternaria*. Children with high allergen exposure had increased odds of having asthma symptoms.¹³

Fungal Constituents

According to allergen databases (<http://www.meduniwien.ac.at/allergens/allfam/>), 189 fungal species are thought to produce allergens, and these consist of 61 protein families that contain approximately 132 allergens.¹⁴ Some allergens from the genera *Alternaria*, *Aspergillus*, and *Cladosporium* are well characterized, and some have even been purified.¹⁵ On the basis of genomewide studies of several species, fungi appear to share a highly conserved set of allergen orthologues. These allergens include enolases, heat shock proteins, cyclophilins, proteases, redoxins, and disulphide isomerases. Other allergens include peroxisomal membrane proteins, acid ribosomal proteins, and alcohol dehydrogenases.¹⁶

Fungi also produce a number of other nonvolatile metabolites, including ergosterol, β -glucans, and mycotoxins. Because ergosterol is nearly unique to fungi, its measurement has been used to estimate fungal load in house dust.¹⁷ Airborne ergosterol correlates

with airborne glucan; however, it is more highly correlated with the presence of visible mold.

β -Glucans are polysaccharides found in the outer cell membrane of fungi, higher plants, and some bacteria.¹⁸ The cell walls of grasses and fungi contain β -1,3-D-glucan, sometimes in mixtures with other glucans. Studies in humans suggest that there is a dose-response relationship between exposure to airborne fungal glucan and respiratory symptoms, itching skin, hoarseness, and fatigue.¹⁹ Exposure to glucans has also been associated with an increased prevalence of atopy and a decrease in forced expiratory volume.²⁰

Mycotoxins are low-molecular-weight organic chemicals produced by fungi to better compete for nutrient resources by eliminating growth of other microorganisms in the immediate environment. A person must be exposed to a sufficient concentration for a sufficient amount of time to experience a toxic effect. Because of agricultural exposure, human health effects of mycotoxins have been extensively studied.²¹ These effects include T-2 toxin from *Fusarium*, trichothecene mycotoxins from *Stachybotrys*, mitogillin from *Aspergillus*, and others. Most mycotoxins are rapidly metabolized and eliminated within hours after ingestion in farm animals and humans. Although commercial fungal extracts are not routinely assayed for mycotoxins, they are dialyzed, which should remove mycotoxins if they are present in the source material.

Volatile metabolites are often revered to as microbial volatile organic compounds. Such volatile compounds have a distinctive musty or moldy odor that can serve as reliable indications of mold growth. This odor often is transferred to clothes, leading individuals who live in moldy houses to smell musty. Occupants of moldy houses frequently become adapted to the smell and may be unaware of its presence. The direct health risk of microbial volatile organic compounds is unclear; however, they could act as irritants in susceptible individuals.²²

Fungal Sensitivity

Patients with a clinical history of fungal allergy develop symptoms when exposed to environments likely to have high fungal exposure. Examples of questions to ask patients suspected of having fungal allergy include whether symptoms are worse in old homes or buildings, basements, or other damp environments, after rain storms, and during raking or mowing the lawn.²³

Tests for Fungus Sensitization

Sensitization to fungi can be detected using prick^{24,25} and intradermal²⁴ skin tests with fungal extracts or in vitro tests for specific IgE antibodies.^{24–26} Fungal extracts currently are unstandardized in part due to variability among manufacturers and even between batches from the same manufacturer. The performance characteristics of diagnostic tests are not known with the exception of *Alternaria*, which has been studied in several clinical trials that used either nasal²⁴ or bronchial²⁵ provocation as the criterion standard for rhinitis and asthma, respectively (Table 3). In these studies, skin prick tests for *Alternaria* had high positive likelihood ratios and low negative likelihood ratios, indicating that the test effectively discriminated between patients with and without sensitivity for rhinitis and asthma. Intradermal tests had positive likelihood ratios near 1, indicating that for patients with negative skin prick test results, such tests did not provide useful information. In vitro tests had high positive likelihood ratios, but the negative likelihood ratio was not very low, indicating that the test is good at detecting sensitive patients but not so good at ruling out nonallergic ones.

A recent study compared percentages of positive fungal skin prick test results with ImmunoCAP. Skin prick testing detected 100% of patients who were sensitized to only one of *Alternaria*, *Candida*, or *Trichophyton*, whereas ImmunoCAP detected 89%, 75%,

Table 3

Performance characteristics of skin prick test, intradermal skin test when skin prick test result is negative, and in vitro tests for specific IgE to *Alternaria*

Test	LR+	LR–	Sensitivity	Specificity	Standard	Reference
Skin prick test	11.75	0.05	95.2	91.9	Nasal	24
	9.45	0.02	97.8	89.7	Bronchial	25
Intradermal test (negative skin prick test result)	1.04	0.04	100	3.8	Bronchial	25
In vitro test	14	0.46	55.8	96	Nasal	24
	15	0.2	81.1	94.6	Nasal	26
	2.31	0.76	35.8	76	Bronchial	24

Abbreviations: LR+, positive likelihood ratio; LR–, negative likelihood ratio.

and 61%, respectively. When multiply fungus-sensitized patients were evaluated, the in vitro tests generally detected a higher percentage of patients than did the skin prick tests.²⁷

Fungi Tests

In one study, the most common skin prick test–positive genera among 3,248 patients with any allergy were *Alternaria* (12.6%) and *Candida* (8.5%). When only patients with a positive skin test result to a fungus were considered (19% of allergic patients), the most common positive test results were for *Alternaria* (66.1%), *Candida* (13.1%), *Cladosporium* (13.1%), *Aspergillus* (12.6%), and *Trichophyton* (10.2%). In patients who were sensitized to only 1 or 2 fungi, the most common genera consistently reactive were *Alternaria* and *Candida*. Multiply fungus-sensitized patients reacted in descending order to *Alternaria*, *Candida*, *Cladosporium*, *Aspergillus*, *Saccharomyces*, *Penicillium*, and *Trichophyton*.²⁷

This finding suggests that a limited number of skin tests with *Alternaria*, *Candida*, *Cladosporium*, *Aspergillus*, and *Trichophyton* could be used to identify patients with fungal sensitization because most will react to one of these. Because *Candida* and *Trichophyton* are not aeroallergens, their use in this context would be as markers for fungal sensitization and not to diagnose *Candida* or *Trichophyton* hypersensitivity disorders. A more extensive panel of fungi could be tested for if it is important to identify the specific sensitization pattern. This might be the case if immunotherapy is being considered or if evidence of an association between exposure and fungus-induced symptoms in a patient's environment is being sought.

Health Effects of Fungi

Exposure to airborne fungi is associated with morbidity in patients who have respiratory disorders, including rhinitis and asthma. Other conditions, such as atopic dermatitis, can be exacerbated by cutaneous fungi, such as *Malassezia* species. Several other diseases are known to be caused or triggered by exposure to fungi, including allergic bronchopulmonary mycosis, allergic fungal sinusitis, and hypersensitivity pneumonitis. *Candida* hypersensitivity is controversial because the syndrome is poorly defined and the association between *Candida* exposure and the condition has not been demonstrated.

Because fungi can cause adverse health effects via IgE- or non-IgE-mediated mechanisms,² it is not necessary for a person to be allergic to fungi to experience symptoms after exposure. Prevention of health effects due to fungal exposure can be separated into primary (exposures that cause development of asthma in young children), secondary (exposure that leads to morbidity in individuals who already have asthma), and tertiary (medications used to treat symptoms that already are present) prevention. This review will not address tertiary prevention.

Primary Prevention

Primary prevention is based on the assumption that exposure to fungi increases the risk of developing an adverse health effect (eg,

sensitization and asthma) and that reducing exposure can reduce that risk. Studies on the association between increased fungal exposure and increased risk of developing asthma generally are observational, which cannot be used to infer causality. Studies to prove causality would need to randomly assign children to live in an environment with various amounts of fungal exposure and then observe for subsequent health effects. Although this has been done for dust mites,²⁸ such studies have not been performed for fungi.

A comprehensive review found sufficient evidence to conclude that there is an association between indoor dampness (defined as sufficient water activity on indoor substrates to support fungal growth), fungal exposure, and increased risk of developing asthma in allergic and nonallergic individuals.²⁹ One study of 121 children 12 to 84 months of age who were age and sex matched with 2 control populations found that the risk of developing asthma correlated with the amount of moisture and the presence of visible fungi in the main living areas of the house regardless of the atopic status. The ORs for 2 amounts of moisture damage and the development of asthma were 2.8 (95% confidence interval, 1.4–5.4) and 4.0 (95% CI, 1.6–10.2), suggesting a dose-response between exposure and increased risk.³⁰

Additional evidence from the Cincinnati Childhood Asthma and Air Pollution Study provided additional evidence for an association between fungal exposure and development of childhood asthma. In this study, investigators found a significant relationship between fungal levels collected in household dust during infancy and subsequent development of recurrent wheeze and asthma at 1, 3, and 7 years of age.³¹

Finally, a systematic review of 11 cohort and 5 incident case-control studies found a significant relationship among fungal exposure, dampness, visible mold and moldy odor, and the development of asthma.³² Given this evidence, it appears that the amount of exposure to fungi in young children from atopic families is associated with an increased risk of developing asthma. What is not known is whether reducing fungal exposure would decrease that risk.

Secondary Prevention

Once a person has developed asthma or rhinitis, exposure to fungi can trigger symptoms regardless of sensitization. Secondary prevention involves reducing fungal exposure to decrease the likelihood of developing asthma and/or rhinitis symptoms. This approach is plausible because there is a dose-response relationship between fungal exposure and symptoms. In one study, increasing outdoor spore concentrations was associated with increased asthma symptoms and inhaler use and reduced evening peak flow, particularly when certain fungi, such as *Alternaria*, basidiospores, and hyphal fragments, were present.³³

Indoors, an association was found among the respiratory health of children, indoor dampness, and exposure to fungi in 15,000 homes in 30 Canadian communities. The prevalence of respiratory symptoms was higher in homes with fungal contamination or dampness even when controlling for other factors, including age, sex, smoking, and type of heat³⁴ and after adjusting for dust mite antigens and endotoxins.³⁵

A quantitative meta-analysis of the 33 studies that were reviewed by the Institute of Medicine looked at health outcomes categories, including upper respiratory tract symptoms, wheeze, cough, and a history of asthma diagnosis, as they related to visible mold, dampness, and airborne spores. A statistically significant increased risk was found between the presence of mold and dampness and development of upper respiratory tract symptoms (OR, 1.7), cough (OR, 1.67), wheeze (OR, 1.5), current asthma (OR, 1.56), and ever diagnosed as having asthma (OR, 1.37). In addition,

building dampness and mold were associated with increases of 30% to 50% in cough, wheeze, and asthma.³⁶

Because exposure to fungi increases the risk of having asthma and rhinitis symptoms, the next question is whether reducing exposure can decrease those symptoms. The best strategy for control of exposure to indoor fungi includes a combination of interventions that remove facilitative factors such as moisture, reduce sources of growth, remove reservoirs of fungal spores and allergens, and block pathways of dissemination from sources to occupants.³⁷

Interventional studies have found that remediation³⁸ or removal³⁹ from damp buildings can reduce asthma symptoms in adults. In addition, reduced exposure leads to decrease controller and reliever medication use in asthmatic patients and reduces rhinitis symptoms,⁴⁰ decreases overall respiratory symptoms,^{41,42} and reduces conjunctivitis and symptoms of allergic rhinitis.⁴³

In one prospective trial, 62 children with asthma living in moldy homes were randomly assigned to receive household repairs that focused water infiltration, removal of water-damaged building materials, and repairs to the heating, ventilation, and air conditioning system. A mold score revealed a significant decrease at 6 and 12 months only in the intervention group. That group experienced a decrease in symptom-days and fewer exacerbations, including emergency department visits and hospitalizations.⁴⁴ Although it is possible that reductions in nonfungal exposures could account for this result, the interventions in this study did not result in a decrease in exposure to dust mite, cockroach, mouse, rat, or endotoxin.

Interventions

Because fungal growth depends on the presence of moisture and a carbon source, the most effective strategy for reducing and preventing growth is to control the amount of moisture present. This would eliminate moist microclimates, which can encourage fungal growth that may spread within what would otherwise be a relatively mold-free environment. Reductions in pediatric asthma morbidity have occurred with remediation focused on reduction of home moisture sources.⁴⁴

The 2009 World Health Organization report on damp buildings and fungi reviewed this topic extensively and concluded that the presence of dampness when combined with fungal contamination can contribute to health problems.⁴⁵ The 3 primary sources of moisture in an indoor environment include intrusion, condensation, and leakage. Moisture from one of these 3 mechanisms in combination with an appropriate substrate can provide sufficient resources for indoor fungi to grow.

Intrusion refers to ingress of water from the outside, usually through holes or cracks in foundations, roofs, improperly installed windows, and other orifices and even through porous materials, such as concrete by a wicking action. Condensation occurs when surfaces are colder than the dew point as can occur with cold water pipes, concrete basement walls during the summer, and even toilet tanks full of cold water. Indoor sources of humidity include respiration, cooking, showers, and other activities in which water is involved. Leakage refers to uncontrolled water escape from pipes (both supply and drain), faucets, or reservoirs, such as water heaters.

Given sufficient moisture, many building materials, including wood, drywall ceiling tiles, and jute backed carpet, can serve as a nutrient source for fungal growth.⁴⁵ Some building materials, such as plaster, brick, cement, and fiber glass, do not support fungal growth unless they become coated with nutrient materials.

To remove fungi from nonporous surfaces, such as shower walls, hypochlorite (bleach)-containing products can denature and destroy protein allergens.⁴⁶ In one study, soap and water alone effectively reduced surface fungal contamination in showers;

however, regrowth occurred after several weeks. Use of a dilute bleach solution with a detergent prevented this regrowth.⁴⁷ For porous surfaces, fungal growth often penetrates deep into the substrate so cleaning generally is not effective. Extensively contaminated building materials therefore need to be replaced to reduce adverse health effects.

The National Asthma Survey found an association between asthma in children and humidifier use,⁴⁸ the health effects of which have been termed “humidifier fever.”⁴⁹ Proper maintenance or avoidance of cool mist or ultrasonic humidifiers is essential to prevent such effects. Another common concern is whether house plants can contribute to fungal growth. In one study, a modest numbers of undisturbed house plants did not promote fungal growth.⁵⁰

The main indoor reservoir for fungal contaminants is carpeting.⁵¹ Frequent vacuuming can reduce fungal spore levels in dust⁵²; however, replacement of carpeting with other types of flooring appears to be more effective.⁵³ Air filtration was recently reviewed by Sublett et al,⁵⁴ who reported positive results in 8 of 18 trials with 2 trials for fungi demonstrating reduced symptom and medication scores.

Toxic Mold Syndrome

The diagnosis of toxic mold syndrome is surrounded by a great deal of controversy. A study of 65 patients who claimed to have the syndrome reported symptoms that included rhinitis (62%), cough (52%), headache (34%), respiratory symptoms (34%), central nervous system symptoms (25%), and fatigue (23%). Only 53% of these patients were skin reactive to a panel of fungi.⁵⁵ Another study of a series of 32 indoor mold exposed patients using questionnaires and medical record reviews found that a few had fungal allergy, although a significant number had asthma symptoms. Exposures included *Stachybotrys chartarum*, *Aspergillus*, and *Penicillium*.⁵⁶

Controversy regarding this syndrome has revolved around exposure to *Stachybotrys chartarum*, the so-called toxic mold or black mold. This hydrophilic fungus tends to grow on water-damaged, cellulose-based materials and is a marker for damp environments. *Stachybotrys* toxicity has been linked to ingestions in sheep,⁵⁷ and in animal models it produces changes in respiratory epithelium, especially in developing lungs.⁵⁸ A review of mycotoxins in buildings concluded that the amount of exposure to humans was insufficient to cause significant health effects.⁵⁹

Mycotoxin exposure has been the subject of much fungus-related litigation and speculation, often involving ill-defined illness in the absence of a generally accepted, defined condition. The Institute of Medicine report on damp spaces and health reported “insufficient evidence to determine an association between mycotoxin exposure and a number of other reported health effects, including gastrointestinal problems, fatigue, neuro-psychiatric symptoms and skin problems.”⁶⁰ This was also the conclusion of the World Health Organization panel on mold and dampness.⁴⁵

Conclusion

Fungi serve a role as saprophytes by growing on decaying plant materials. In doing so, they exhibit complex physiologic features. Some of the byproducts of fungal metabolism are allergens that can trigger symptoms in sensitized individuals. On the basis of cluster analysis, patterns of IgE sensitization appear to closely match fungal taxonomy.

Fungi clearly can cause sensitization (production of specific IgE) and clinical allergy. Skin prick and in vitro tests can effectively identify patients with *Alternaria* sensitivity, whereas skin prick tests can rule out such sensitivity. Other fungi have not been subjected to the same type of analysis, so it is not clear whether these diagnostic tests would provide the same information.

The known health effects of fungal exposure include an increased risk of developing asthma in young children from atopic families and increased symptoms of asthma and rhinitis in individuals who already have these conditions. Interventional studies have found that a multifaceted series of interventions aimed at reducing indoor moisture, removing contaminated building materials, and reducing reservoirs can reduce fungal exposure sufficiently to reduce symptoms in affected individuals. This implies a causal relationship between exposure to fungi and morbidity and provides a rationale for environmental interventions to reduce it.

The most important interventions to reduce fungal exposure involve efforts to reduce moisture and dampness in indoor environments, including intrusion, condensation, and leakage. Removal of contaminated building materials is also important along with removal of reservoirs, including carpeting and dust.

Although there are still controversies that surround the role of fungal exposure toxic mold syndrome, the Institute of Medicine report on damp spaces and health found insufficient evidence for an association between mycotoxin exposure and adverse health effects.

Acknowledgment

We thank the Mold Allergy Assessment and Interventions Workgroup of the Joint Taskforce on Practice Parameters for insightful advice and discussions that helped us to formulate this review.

References

- [1] Cramer R, Zeller S, Glaser AG, Vilhelmsson M, Rhyner C. Cross-reactivity among fungal allergens: a clinically relevant phenomenon? *Mycoses*. 2009;52:99–106.
- [2] Chen J, Seviour R. Medicinal importance of fungal beta-(1→3), (1→6)-glucans. *Mycol Res*. 2007;111(pt 6):635–652.
- [3] Hawksworth DL, Crous PW, Redhead SA, et al. The Amsterdam declaration on fungal nomenclature. *IMA Fungus*. 2011;2:105–112.
- [4] Soeria-Atmadja D, Onell A, Borga A. IgE sensitization to fungi mirrors fungal phylogenetic systematics. *J Allergy Clin Immunol*. 2010;125:1379–1386.e1.
- [5] Pashley CH, Fairs A, Free RC, Wardlaw AJ. DNA analysis of outdoor air reveals a high degree of fungal diversity, temporal variability, and genera not seen by spore morphology. *Fungal Biol*. 2012;116:214–224.
- [6] Portnoy J, Barnes C. The National Allergy Bureau: pollen and spore reporting today. *J Allergy Clin Immunol*. 2004;114:1235–1238.
- [7] Troutt C, Levetin E. Correlation of spring spore concentrations and meteorological conditions in Tulsa, Oklahoma. *Int J Biometeorol*. 2001;45:64–74.
- [8] Burch M, Levetin E. Effects of meteorological conditions on spore plumes. *Int J Biometeorol*. 2002;46:107–117.
- [9] Pulimood TB, Corden JM, Bryden C, Sharples L, Nasser SM. Epidemic asthma and the role of the fungal mold *Alternaria alternata*. *J Allergy Clin Immunol*. 2007;120:610–617.
- [10] Adams RI, Amend AS, Taylor JW, Bruns TD. A unique signal distorts the perception of species richness and composition in high-throughput sequencing surveys of microbial communities: a case study of fungi in indoor dust. *Microbial Ecol*. 2013;66:735–741.
- [11] Portnoy J, Flappan S, Barnes C. A procedure for evaluation of the indoor environment. *Aerobiologia*. 2001;17:43–48.
- [12] Reponen T, Seo SC, Grimsley F, Lee T, Crawford C, Grinshpun SA. Fungal fragments in moldy houses: a field study in homes in New Orleans and Southern Ohio. *Atmos Environ*. 2007;41:8140–8149.
- [13] Salo PM, Arbes SJ Jr, Crockett PW, Thorne PS, Cohn RD, Zeldin DC. Exposure to multiple indoor allergens in US homes and its relationship to asthma. *J Allergy Clin Immunol*. 2008;121:678–684.e2.
- [14] Radauer C, Bublin M, Wagner S, Mari A, Breiteneder H. Allergens are distributed into few protein families and possess a restricted number of biochemical functions. *J Allergy Clin Immunol*. 2008;121:847–852.e7.
- [15] Kurup VP. Fungal allergens. *Curr Allergy Asthma Rep*. 2003;3:416–423.
- [16] Bowyer P, Fraczek M, Denning DW. Comparative genomics of fungal allergens and epitopes shows widespread distribution of closely related allergen and epitope orthologues. *BMC Genomics*. 2006;7:251.
- [17] Choi H, Byrne S, Larsen LS, et al. Residential culturable fungi, (1-3, 1-6)-beta-D-glucan, and ergosterol concentrations in dust are not associated with asthma, rhinitis, or eczema diagnoses in children. *Indoor Air*. 2014;24:158–170.
- [18] Cherid H, Foto M, Miller JD. Performance of two different *Limulus ameobocyte* lysate assays for the quantitation of fungal glucan. *J Occup Environ Hyg*. 2011;8:540–543.
- [19] Douwes J. (1→3)-Beta-D-glucans and respiratory health: a review of the scientific evidence. *Indoor Air*. 2005;15:160–169.
- [20] Thorn J, Rylander R. Airways inflammation and glucan in a rowhouse area. *Am J Respir Crit Care Med*. 1998;157(6, pt 1):1798–1803.
- [21] Miller J. Mycotoxins. In: Jorgenson S, ed. *Encyclopedia of Environmental Management*. New York, NY: Taylor & Francis; 2013:1696–1699.
- [22] Gunschera J, Fuhrmann F, Salthammer T, Schulze A, Uhde E. Formation and emission of chloroanisoles as indoor pollutants. *Environ Sci Pollut Res Int*. 2004;11:147–151.
- [23] Horner WE, Barnes C, Codina R, Levetin E. Guide for interpreting reports from inspections/investigations of indoor mold. *J Allergy Clin Immunol*. 2008;121:592–597.e7.
- [24] Escudero AI, Sanchez-Guerrero IM, Mora AM, et al. Cost-effectiveness of various methods of diagnosing hypersensitivity to *Alternaria*. *Allergol Immunopathol (Madr)*. 1993;21:153–157.
- [25] Fernandez C, Bevilacqua E, Fernandez N, et al. Asthma related to *Alternaria* sensitization: an analysis of skin-test and serum-specific IgE efficiency based on the bronchial provocation test. *Clin Exp Allergy*. 2011;41:649–656.
- [26] Williams PB, Dolen WK, Koepke JW, Selner JC. Comparison of skin testing and three in vitro assays for specific IgE in the clinical evaluation of immediate hypersensitivity. *Ann Allergy*. 1992;68:35–45.
- [27] Mari A, Schneider P, Wally V, Breitenbach M, Simon-Nobbe B. Sensitization to fungi: epidemiology, comparative skin tests, and IgE reactivity of fungal extracts. *Clin Exp Allergy*. 2003;33:1429–1438.
- [28] Arshad SH, Bojarskas J, Tsitoura S, et al. Prevention of sensitization to house dust mite by allergen avoidance in school age children: a randomized controlled study. *Clin Exp Allergy*. 2002;32:843–849.
- [29] Mendell MJ, Mirer AG, Cheung K, Tong M, Douwes J. Respiratory and allergic health effects of dampness, mold, and dampness-related agents: a review of the epidemiologic evidence. *Environ Health Perspect*. 2011;119:748–756.
- [30] Pekkanen J, Hyvarinen A, Haverinen-Shaughnessy U, Korppi M, Putus T, Nevalainen A. Moisture damage and childhood asthma: a population-based incident case-control study. *Eur Respir J*. 2007;29:509–515.
- [31] Reponen T, Vesper S, Levin L, et al. High environmental relative moldiness index during infancy as a predictor of asthma at 7 years of age. *Ann Allergy Asthma Immunol*. 2011;107:120–126.
- [32] Quansah R, Jaakkola MS, Hugg TT, Heikkinen SA, Jaakkola JJ. Residential dampness and molds and the risk of developing asthma: a systematic review and meta-analysis. *PLoS One*. 2012;7:e47526.
- [33] Delfino RJ, Zeiger RS, Seltzer JM, et al. The effect of outdoor fungal spore concentrations on daily asthma severity. *Environ Health Perspect*. 1997;105:622–635.
- [34] Dales RE, Zwanenburg H, Burnett R, Franklin CA. Respiratory health effects of home dampness and molds among Canadian children. *Am J Epidemiol*. 1991;134:196–203.
- [35] Dales RE, Miller D. Residential fungal contamination and health: microbial cohabitants as covariates. *Environ Health Perspect*. 1999;107(suppl 3):481–483.
- [36] Fisk WJ, Lei-Gomez Q, Mendell MJ. Meta-analyses of the associations of respiratory health effects with dampness and mold in homes. *Indoor Air*. 2007;17:284–296.
- [37] Krieger J, Jacobs DE, Ashley PJ, et al. Housing interventions and control of asthma-related indoor biologic agents: a review of the evidence. *J Public Health Manag Pract*. 2010;16(5 suppl):S11–S20.
- [38] Barnes CS, Amado M, Portnoy JM. Reduced clinic, emergency room, and hospital utilization after home environmental assessment and case management. *Allergy Asthma Proc*. 2010;31:317–323.
- [39] Sudakin DL. Toxicogenic fungi in a water-damaged building: an intervention study. *Am J Ind Med*. 1998;34:183–190.
- [40] Burr ML, Matthews IP, Arthur RA, et al. Effects on patients with asthma of eradicating visible indoor mould: a randomised controlled trial. *Thorax*. 2007;62:767–772.
- [41] Jarvis JQ, Morey PR. Allergic respiratory disease and fungal remediation in a building in a subtropical climate. *Appl Occup Environ Hyg*. 2001;16:380–388.
- [42] Ebbehøj NE, Hansen MO, Sigsgaard T, Larsen L. Building-related symptoms and molds: a two-step intervention study. *Indoor Air*. 2002;12:273–277.
- [43] Patovirta RL, Husman T, Haverinen U, et al. The remediation of mold damaged school—a three-year follow-up study on teachers' health. *Cent Eur J Public Health*. 2004;12:36–42.
- [44] Kercsmar CM, Dearborn DG, Schluchter M, et al. Reduction in asthma morbidity in children as a result of home remediation aimed at moisture sources. *Environ Health Perspect*. 2006;114:1574–1580.
- [45] World Health Organization. *WHO Guidelines for Indoor Air Quality: Dampness and Mould*. Copenhagen, Denmark: World Health Organization; 2009.
- [46] Barnes C, Pacheco F, Dhar M, Portnoy J. *Alternaria* and *Cladosporium* fungal allergen epitopes are denatured by sodium hypochlorite. *World Allergy Organ J*. 2009;2:296–302.
- [47] Reynolds KA, Boone S, Bright KR, Gerba CP. Occurrence of household mold and efficacy of sodium hypochlorite disinfectant. *J Occup Environ Hyg*. 2012;9:663–669.
- [48] Nguyen T, Lurie M, Gomez M, Reddy A, Pandya K, Medvesky M. The National Asthma Survey—New York State: association of the home environment with current asthma status. *Public Health Rep*. 2010;125:877–887.
- [49] Baur X, Behr J, Dewair M, et al. Humidifier lung and humidifier fever. *Lung*. 1988;166:113–124.

- [50] Burge HA, Solomon WR, Muilenberg ML. Evaluation of indoor plantings as allergen exposure sources. *J Allergy Clin Immunol*. 1982;70:101–108.
- [51] Causer S, Shorter C, Lewis R. Efficiency of vacuuming for the removal of cat allergen (Fel d 1) from worn and unworn wool carpets of different construction. *Textile Res J*. 2008;78:105–110.
- [52] Roberts JW, Clifford WS, Glass G, Hummer PG. Reducing dust, lead, dust mites, bacteria, and fungi in carpets by vacuuming. *Arch Environ Contam Toxicol*. 1999;36:477–484.
- [53] Dharmage S, Bailey M, Raven J, et al. Prevalence and residential determinants of fungi within homes in Melbourne, Australia. *Clin Exp Allergy*. 1999;29(11): 1481–1489.
- [54] Sublett JL, Seltzer J, Burkhead R, Williams PB, Wedner HJ, Phipatanakul W. Air filters and air cleaners: rostrum by the American Academy of Allergy, Asthma & Immunology Indoor Allergen Committee. *J Allergy Clin Immunol*. 2010;125: 32–38.
- [55] Edmondson DA, Nordness ME, Zacharisen MC, Kurup VP, Fink JN. Allergy and “toxic mold syndrome”. *Ann Allergy Asthma Immunol*. 2005;94:234–239.
- [56] Al-Ahmad M, Manno M, Ng V, Ribeiro M, Liss GM, Tarlo SM. Symptoms after mould exposure including *Stachybotrys chartarum*, and comparison with darkroom disease. *Allergy*. 2010;65:245–255.
- [57] Schneider DJ, Marasas WF, Dale Kuys JC, Kriek NP, Van Schalkwyk GC. A field outbreak of suspected stachybotryotoxicosis in sheep. *J S Afr Vet Assoc*. 1979; 50:73–81.
- [58] McCrae KC, Rand TG, Shaw RA, et al. DNA fragmentation in developing lung fibroblasts exposed to *Stachybotrys chartarum* (atra) toxins. *Pediatr Pulmonol*. 2007;42:592–599.
- [59] Burge HA. Fungi: toxic killers or unavoidable nuisances? *Ann Allergy Asthma Immunol*. 2001;87(6 suppl 3):52–56.
- [60] Terr AI. Are indoor molds causing a new disease? *J Allergy Clin Immunol*. 2004; 113:221–226.

Authors' response



We thank the authors for submitting their commentary on our article. The authors found, similar to our study and others, that most people were unable to use the inhalation device correctly on initial attempt. The number of patients who could demonstrate correct use has varied from 5.7% to 38% in previous reports.^{1,2} When studies have focused specifically on health care professionals, as the current one does, the numbers have increased to 5% to 69%, depending on the group examined.³ The current report is particularly interesting because of the use of a device that objectively measures performance of each user: the Aerosol Inhalation Monitor (Vitalograph AIM). We believe that measuring rate of flow is especially helpful because this is a challenging evaluation to make with the naked eye. Furthermore, examining synchronization between actuation of the inhaler and inhalation by the user and the length of breath hold is also important because it has been previously reported that metered-dose inhaler users frequently make errors in these steps. Unfortunately, the Aerosol Inhalation Monitor does not assess whether the user exhales to functional residual capacity or residual volume before actuating the canister, but that step can be evaluated reasonably well by simple observation. We believe this is a critical step to assess because 66% of incorrect users (61% of all participants) in our original study failed to perform this step.⁴

Of additional interest is the finding that correct use was increased from 18.3% to 46.9% with a single educational session. This finding is encouraging, especially because previous studies have reported mixed results of education in improving inhalation device technique.^{5–7} Two unanswered questions remain in our

minds: whether users retain the ability to use the device properly over time and whether additional educational sessions would result in even more users achieving the ability to use the device correctly. These are important areas for future research.

Rana S. Bonds, MD*

Ashish Asawa, MD*

Aasia I. Ghazi, MD†

*University of Texas Medical Branch
Galveston, Texas

†Allergy and Asthma Specialists
Dallas, Texas

rsbonds@utmb.edu

References

- [1] Arora P, Kumar L, Vohra V, et al. Evaluating the technique of using inhalation device in COPD and bronchial asthma patients. *Respir Med*. 2014;108:992–998.
- [2] O'Connor R, Wolf MS, Smith SG, et al. Health literacy, cognitive function, proper use and adherence to inhaled asthma controller medications among older adults with asthma [published online October 2, 2014]. *Chest*. <http://dx.doi.org/10.1378/chest.14-0914>.
- [3] Self TH, Arnold LB, Czosnowski LM, Swanson JM, Swanson H. Inadequate skill of healthcare professionals in using asthma inhalation devices. *J Asthma*. 2007;44:593–598.
- [4] Bonds RS, Asawa A, Ghazi AI. Misuse of medical devices: a persistent problem in self-management of asthma and allergic disease. *Ann Allergy Asthma Immunol*. 2015;114:74–76.e2.
- [5] Hardwell A, Barber V, Hargadon T, McKnight E, Holmes J, Levy M. Technique training does not improve the ability of most patients to use pressurized metered-dose inhalers (pMDIs). *Prim Care Respir J*. 2011;20:92–96.
- [6] Horner SD, Fouladi RT. Improvement of rural children's asthma self-management by lay health educators. *J Sch Health*. 2008;78:506–513.
- [7] Takemura M, Kobayashi M, Kimura K, et al. Repeated instruction on inhalation technique improves adherence to the therapeutic regimen in asthma. *J Asthma*. 2010;47:202–208.

Disclosures: Authors have nothing to disclose.

Funding: This study was supported by a grant from the Oliver Center for Patient Safety and Quality Healthcare at the University of Texas Medical Branch.

Response to “Mold Allergy Revisited”



I am writing in response to the article entitled “Mold Allergy Revisited” in the February 2014 issue of the *Annals of Allergy, Asthma & Immunology*.¹ I wish to question a number of assertions that are either unsupported or based on very tenuous scientific reports.

Children with a high fungal allergen exposure in the home are said to have an increased risk of developing asthma symptoms.² This study implies that fungal exposure in the home may promote asthma symptoms. Only 7 allergens were studied. *Alternaria* was the most common allergen found to exceed accepted levels and the only fungal allergen studied. Other allergens included cockroach, cat and dog dander, house dust mite (Der f 1 and Der p 1), and mouse. Among atopic individuals, high allergen burden was significantly associated with current asthma as assessed by questionnaire only. Outdoor levels of *Alternaria* were not measured. It is well known that if mold sensitivity contributes to the development of asthma, it is far more likely to be the result of exposure to outdoor mold.³

The authors state that there is a dose-response relationship between exposure to airborne fungal glucans and respiratory symptoms, itching skin, hoarseness, and fatigue. They cite a review article by Douwes.⁴ This review relies heavily on an earlier study by

the same author that measured the levels of extracellular polysaccharides of *Aspergillus* and *Penicillium* species in house dust by an enzyme immunoassay as a marker for fungal exposure. The association between these levels and home dampness and respiratory symptoms in children was then assessed. Although the extracellular polysaccharides in house dust were actually measured, the respiratory symptoms and resident-reported home dampness were extrapolated from a questionnaire, which is a major limitation of this study and many other studies that are relied on in this review.⁵ In fact, the authors of this review state that the currently available epidemiologic data do not permit conclusions to be drawn regarding the presence (or absence) of an association between environmental (1-3)- β -D-glucan exposure and specific adverse health effects. It is also not clear from the available evidence which specific immunologic mechanisms underlie the presumed health effects.⁴

Another referenced study is said to support the assertion that volatile organic compounds could act as irritants in susceptible individuals.⁶ However, the study cited does not address fungal volatiles exacerbating respiratory symptoms. Instead, it is a study to identify chemicals responsible for the odor that was traced to a pentachlorophenol used as a wood preservative in frame homes.

With respect to investigating fungal sensitization, the authors appear to marginalize the use of skin testing with fungal extracts by

Disclosures: Dr Bardana performs worker's compensation evaluations for the States of Oregon, Alabama, Idaho, and Washington.

emphasizing that with the exception of *Alternaria*, the performance characteristics of other fungal allergens are not known. It would have been preferable to make a statement supporting the practical utility of puncture skin testing and/or in vitro testing to identify clinically relevant sensitization to fungal allergens as long as their limitations are considered.³ I agree with the observation that intradermal testing with fungal allergens is not likely to provide useful information.⁷ A previous study has recommended a combination of epicutaneous skin tests and specific serum IgE levels to more accurately diagnose fungal allergy.⁸

The authors state that fungi can cause adverse health effects via IgE- or non-IgE-mediated mechanisms and individuals need not be allergic to experience symptoms. This concept is said to be supported by the work of Chen et al.⁹ However, the article by Chen et al extols the glucans as potent immunologic activators and does not address or assess any health effects. The article by Mendell et al¹⁰ is cited to support the contention that dampness and mold induces respiratory and other health effects. This review concludes that its findings should be considered provisional “until the production of quantitative summary estimates of risk ratios based on a more thorough consideration of all available findings.” This is not a compelling scientific effort because most of the studies considered are cross-sectional or retrospective in nature. Many of the epidemiologic studies on dampness, mold, and health used self-declared reports (questionnaires) to assess exposure or health effects with significant potential for reporting bias. The study by Pekkanen et al¹¹ is cited to support a dose-response relationship between moisture and fungal exposure and increased risk for developing asthma.¹¹ This is a poorly designed study with an inappropriate definition of atopy and use of a questionnaire on health and risk factors for asthma with significant potential for reporting bias.

Finally, toxic mold syndrome is discussed by the authors by describing its symptoms as reported by Edmondson et al.¹² The study by Edmondson et al reports on 65 individuals presenting to a clinic with this alleged condition. The source of these patients (ie, random, physician referred, attorney referred, and so on) is not revealed. Mycotoxins were not measured in any instance. Home environmental surveys were performed by different industrial hygienists. The authors admit that the cause of patient symptoms was unclear but some may have been allergic. The other article cited describes mold-attributed symptoms that appeared to mimic a symptom complex of self-described symptoms referred to as sick building syndrome (another clinical nonentity). The methods in this study depended on medical record reviews and follow-up questionnaires. Mycotoxins were not measured.¹³

The subject of mold-induced health effects continues to engender public fear fueled by distorted media coverage and myriad mold websites that promote the epidemic of health effects. This has contributed to litigation that often is based on unproven, pseudoscientific premises. The specialty of allergy and immunology should be at the forefront of efforts to curb and correct this situation. The article by Portnoy and Jara, although well intended, uses a number of studies that are provisional or poorly designed to generate statements that can be interpreted as scientific fact by the uninitiated.

Emil J. Bardana, Jr, MD, MACP
Lake Oswego, Oregon
bardanaem@comcast.net

References

- [1] Portnoy JM, Jara D. Mold allergy revisited. *Ann Allergy Asthma Immunol*. 2015; 114:83–89.
- [2] Salo PM, Arbis SJ Jr, Crockett PW, Thome PS, Cohn R, Zeldin DC. Exposure to multiple indoor allergens in U.S. homes and its relationship to asthma. *J Allergy Clin Immunol*. 2008;121:678–684.
- [3] Bash RK, Portnoy JM, Saxon A, Terr AI, Wood RA. The medical effects of mold exposure (Position Paper). *J Allergy Clin Immunol*. 2006;117:326–333.
- [4] Douwes J. (1-3)- β -D-glucans and respiratory health: a review of the scientific evidence. *Indoor Air*. 2005;15:160–169.
- [5] Douwes J, van der Sluis B, Doekes G, et al. Fungal extracellular polysaccharides in housedust as a marker for exposure to fungi: relations with culturable fungi, reported home dampness, and respiratory symptoms. *J Allergy Clin Immunol*. 1999;103:494–500.
- [6] Gunschera J, Fuhrmann F, Salthammer T, et al. Formation and emission of chloroanisoles as indoor pollutants. *Environ Sci Pollut Res Int*. 2004;11:147–151.
- [7] Schwindt CD, Hutcheson PS, Leu SY, Dykewicz MS. Role of intradermal skin tests in the evolution of clinically relevant respiratory allergy assessed using patient history and nasal challenges. *Ann Allergy Asthma Immunol*. 2005;94:627–633.
- [8] O'Driscoll BR, Powell G, Chew F, et al. Comparison of skin prick tests with specific serum IgE in the diagnosis of fungal sensitization in patients with severe asthma. *Clin Exp Allergy*. 2009;39:1677–1682.
- [9] Chen J, Seviour R. Medicinal importance of fungal β -(1-3), (1-6)-glucans. *Mycol Res*. 2007;111:635–652.
- [10] Mendell MJ, Mirer AG, Cheung K, Tong M, Douwes J. Respiratory and allergic health effects of dampness, mold and dampness-related agents: a review of the epidemiologic evidence. *Environ Health Perspect*. 2011;119: 748–756.
- [11] Pekkanen J, Hyvärinen A, Haverinen-Shaughnessy U, et al. Moisture damage and childhood asthma: a population-based incident case-control study. *Eur Respir J*. 2007;29:509–515.
- [12] Edmondson DA, Nondness ME, Zacharisen MC, Kurup VP, Fink JN. Allergy and “toxic mold syndrome”. *Ann Allergy Asthma Immunol*. 2005;94:234–239.
- [13] Al-Ahmad M, Manno M, Ng V, et al. Symptoms after mold exposure including *Stachybotrys chartarum*, and comparison with darkroom disease. *Allergy*. 2010;65:245–255.

Author's response

I appreciate the effort that was put into the letter regarding our recent review article “Mold Allergy Revisited.”¹ The author clearly is very passionate about the topic; however, I disagree with many of his assertions.

The first comment relates to a study by Salo et al.² This study used data obtained by the National Survey of Lead and Allergens in Housing. Samples were obtained from homes and were assayed for allergens, including *Alternaria* (the only allergen usually measured in most studies as a proxy for mold). Patients also were surveyed about whether they had asthma or allergies. Multivariable logistic regression identified a number of factors that correlated with disease when other factors were accounted for. Mold and moisture-related problems were found to independently

predict such health outcomes. It is true that only 7 allergens were studied, but so what? The investigators had to measure a finite number of things, and this is what they measured. *Alternaria* was the most common allergen found, which tends to boost the assertion that is associated with health problems. This indoor exposure was independently associated with disease. Outdoor exposure could be associated too, but that was not the point of the study. I should point out that a systematic review and meta-analysis of early exposure studies³ concluded that dampness and fungi in homes are determinants of developing asthma. The evidence clearly suggests that early exposure to fungi is associated with later sensitization and development of disease. As I mentioned in the review article, causality cannot be inferred from such observational data, so I do not know if the exposure is causing the disease.

The review by Douwes⁴ looked at 21 articles that studied β -(1 $\rightarrow$ 3)-D-glucan exposure and associated health effects. Exposure was measured using the limulus lysate or enzyme-linked immunosorbent assay in schools, homes, offices daycare centers, and a variety of occupational settings. Study designs included epidemiologic studies, a case study, and human challenge studies. Health effects found to be associated with exposure included cough, pulmonary function, and throat and nose irritation, and some studies did not find any changes. The 4 human challenge studies found that exposure led to nose and throat irritation, reduced forced expiratory volume in 1 second, tumor necrosis factor α secretion, and decreased blood lymphocytes. A few of these studies relied on questionnaires, but others involved direct observation of responses. What the author actually concluded was that there is an association between exposure and airway inflammation and symptoms. What he acknowledged was that results are mixed so an association with specific symptoms cannot be identified. This lack of specificity illustrates caution on the part of the author but does not negate the fact that these studies generally reveal an association.

The article by Gunschera et al⁵ describes identification of chloroanisoles as being responsible for musty odors in houses. These are produced in response to microbial activity, particularly in areas with increased dampness, and are one of many types of volatile organic compounds that produce such odors. Given sufficient exposure, such compounds can serve as irritants; however, this particular study did not find sufficient concentrations in the homes to cause health effects, so perhaps this was not the best study to illustrate the point.

I am puzzled by the statement that skin testing with fungal extracts are marginalized in this review. It is true that the performance characteristics of skin testing with fungal extracts other than *Alternaria* are not known. How would making a vague statement about using other fungal extracts as long as their limitations are considered improve this review? Instead, we included a table with the known data related to *Alternaria* skin testing, which could be useful. These results could be generalized to other extracts, but I do not have an evidence basis for doing that. In addition, I seriously question the validity of using combined skin and specific IgE tests to accurately diagnose fungal allergy. The study by O'Driscoll et al⁶ cited by the correspondent looked at sensitization using skin and IgE tests but did not perform challenges to determine which patients were actually allergic to these fungi. This approach makes it impossible to draw conclusions regarding the true performance characteristics of these tests.

We cited the article by Mendell et al⁷ to support the assertion that fungal exposure is associated with health effects. This was a systematic review of studies related to health effects of dampness and fungal exposure and was intended to extend the review that the Institute of Medicine performed in 2003.⁸ The authors found 103 studies that met the inclusion criteria that evaluated 16 health outcomes. Statistically significant associations with dampness and mold exposure were found for asthma exacerbations, cough, wheeze, upper respiratory tract infections, development of asthma, current asthma, ever-diagnosed asthma, bronchitis, allergic rhinitis, and eczema. In addition, exposure to the fungal metabolites ergosterol, endotoxin, and β -D-glucans were associated with asthma and wheeze. The author's conclusion was that there is sufficient evidence of an association between indoor dampness—related factors and measures related to fungi with a wide range of respiratory or allergic health effects.

The point is that if individual studies are looked at in isolation, the evidence is not strong for any health-related assertions. That is why meta-analyses of systematic reviews are performed. The combined strength of evidence provides the statistical rigor to draw conclusions that individual studies are unable to achieve. The review by Sauni et al⁹ is an excellent example of this. This Cochrane systematic review included 8 randomized clinical trial studies and concluded that remediation of homes with fungal contamination reduced asthma-related symptoms, which basically implies causality between fungi and health effects. The study by Kercsmar et al¹⁰ cited in the review article was included in that review.

We cited the study by Edmondson et al¹¹ for historical purposes because it described the phenomenon of toxic mold syndrome. The details of that study were of no interest to us because our conclusion was that there is no evidence that exposure to fungi causes this phenomenon. This conclusion is also supported by the World Health Organization¹² and the Institute of Medicine.⁸

I agree that the subject of mold-induced health effects continues to engender public fear and that media coverage is distorted. I also agree that litigation often is based on unproven, pseudoscientific premises. Even so, denying what we do know about the association between exposure to fungi and risk of developing or triggering health effects will not ameliorate those concerns. Instead, it would be better to recognize what we do know, identify what we do not know, and work together to answer some of these important questions.

Jay M. Portnoy, MD
Children's Mercy Hospital
Kansas City, MO 64108
jportnoy@cmh.edu

References

- Portnoy J, Jara D. Mold allergy revisited. *Ann Allergy Asthma Immunol*. 2015; 114:83–89.
- Salo PM, Arbes SJ Jr, Crockett PW, Thorne PS, Cohn RD, Zeldin DC. Exposure to multiple indoor allergens in US homes and its relationship to asthma. *J Allergy Clin Immunol*. 2008;121:678–684.e2.
- Quansah R, Jaakkola MS, Hugg TT, Heikkinen SA, Jaakkola JJ. Residential dampness and molds and the risk of developing asthma: a systematic review and meta-analysis. *PLoS One*. 2012;7:e47526.
- Douwes J. (1-3)-beta-D-glucans and respiratory health: A review of the scientific evidence. *Indoor Air*. 2005;15:160–169.
- Gunschera J, Fuhrmann F, Salthammer T, Schulze A, Uhde E. Formation and emission of chloroanisoles as indoor pollutants. *Environ Sci Pollut Res Int*. 2004;11:147–151.
- O'Driscoll BR, Powell G, Chew F, et al. Comparison of skin prick tests with specific serum immunoglobulin E in the diagnosis of fungal sensitization in patients with severe asthma. *Clin Exp Allergy*. 2009;39:1677–1683.
- Mendell MJ, Mirer AG, Cheung K, Tong M, Douwes J. Respiratory and allergic health effects of dampness, mold, and dampness-related agents: a review of the epidemiologic evidence. *Environ Health Perspect*. 2011;119:748–756.
- Institute of Medicine. *Damp Indoor Spaces and Health*. Washington, DC: National Academy of Sciences, Board on Health Promotion and Disease Prevention, National Academies Press; 2004.
- Sauni R, Uitti J, Jauhiainen M, Kreiss K, Sigsgaard T, Verbeek JH. Remediating buildings damaged by dampness and mould for preventing or reducing respiratory tract symptoms, infections and asthma. *Cochrane Database Syst Rev*. 2011;9:CD007897.
- Kercsmar CM, Dearborn DG, Schluchter M, et al. Reduction in asthma morbidity in children as a result of home remediation aimed at moisture sources. *Environ Health Perspect*. 2006;114:1574–1580.
- Edmondson DA, Nordness ME, Zacharisen MC, Kurup VP, Fink JN. Allergy and “toxic mold syndrome”. *Ann Allergy Asthma Immunol*. 2005;94:234–239.
- World Health Organization. *WHO Guidelines for Indoor Air Quality: Dampness and Mold*. Copenhagen, Denmark: World Health Organization; 2009.