Clinical reviews in allergy and immunology

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Fungi and allergic lower respiratory tract diseases

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Date of Original Release: February 2012. Credit may be obtained for these courses until January 31, 2014.

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Activity Objectives

1. To describe the most common environmental factors affecting fungal spore dispersal .
2. To list the diagnostic criteria for allergic bronchopulmonary aspergillosis (ABPA).
3. To identify the genetic characteristics that might increase susceptibility to fungal diseases of the lower airway.
4. To formulate a treatment plan for ABPA and other fungal diseases of the lower airway.

Recognition of Commercial Support: This CME activity has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: J. G. Demain is a fellow with the ACAAI and the AAP; is a member of the AMA; and is an associate clinical professor for the University of Washington and an adjunct clinical professor for the University of Alaska. D. W. Denning is founder and shareholder of F2G Ltd. P. A. Greenberger has provided expert witness testimony on the topic of allergic bronchopulmonary aspergillosis. R. M. Niven has attended an advisory board and given paid advice to Vecture Limited and has received research support from The Moulten Foundation. A. J. Wardlaw has received research support from Pfizer. The rest of the authors declare that they have no relevant conflicts of interest.

Asthma is a common disorder that in 2009 afflicted 8.2% of adults and children, 24.6 million persons, in the United States. In patients with moderate and severe persistent asthma, there is significantly increased morbidity, use of health care support, and health care costs. Epidemiologic studies in the United States and Europe have associated mold sensitivity, particularly to *Alternaria alternata* and *Cladosporium herbarum*, with the development, persistence, and severity of asthma. In addition, sensitivity to *Aspergillus fumigatus* has been associated with severe persistent asthma in adults. Allergic bronchopulmonary aspergillosis (ABPA) is caused by *A fumigatus* and is characterized by exacerbations of asthma, recurrent transient chest radiographic infiltrates, coughing up thick mucus plugs, peripheral and pulmonary eosinophilia, and increased total serum IgE and fungus-specific IgE levels, especially during exacerbation. The airways appear to be chronically or

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Received for publication December 8, 2011; accepted for publication December 12, 2011.

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0091-6749/$36.00

doi:10.1016/j.jaci.2011.12.970

intermittently colonized by *A fumigatus* in patients with ABPA. ABPA is the most common form of allergic bronchopulmonary mycosis (ABPM); other fungi, including *Candida*, *Penicillium*, and *Curvularia* species, are implicated. The characteristics of ABPM include severe asthma, eosinophilia, markedly increased total IgE and specific IgE levels, bronchiectasis, and mold colonization of the airways. The term severe asthma associated with fungal sensitization (SAFS) has been coined to illustrate the high rate of fungal sensitivity in patients with persistent severe asthma and improvement with antifungal treatment. The immunopathology of ABPA, ABPM, and SAFS is incompletely understood. Genetic risks identified in patients with ABPA include HLA association and certain T_H2-prominent and cystic fibrosis variants, but these have not been studied in patients with ABPM and SAFS. Oral corticosteroid and antifungal therapies appear to be partially successful in patients with ABPA. However, the role of antifungal and immunomodulating therapies in patients with ABPA, ABPM, and SAFS requires additional larger studies. (J Allergy Clin Immunol 2012;129:280-91.)

Key words: *Allergic bronchopulmonary aspergillosis, allergic bronchopulmonary mycosis,* Aspergillus fumigatus*,* Alternaria alternata*,* Cladosporium herbarum*, severe asthma with fungal sensitivity*

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Asthma is a common disorder that in 2009 afflicted 8.2% of adults and children, 24.6 million persons, in the United States.[1] Sensitization to fungi is an important factor in patients with allergic respiratory tract diseases, playing a major role in the development, persistence, and severity of lower airway disease, particularly asthma. Direct associations between increased fungal exposure and loss of asthma control are numerous,[2] but only recently have direct causal associations with the development of asthma become apparent. Arbes et al[3] demonstrated that *Alternaria alternata* is independently associated with asthma. Jaakkola et al[4] showed that fungal sensitivity, particularly to *Aspergillus* and *Cladosporium* species, increases the risk of adult-onset asthma. Harley et al[5] found that children exposed to basidiospores and ascospores in the first 3 years of life had an increased risk of asthma.

Fungal sensitization might also contribute to the persistence of active symptoms of asthma. In a large survey of US housing, Salo et al[6] reported that exposure to *A alternata* antigens correlated with active asthma symptoms. Stern et al[7] showed that sensitization to *Alternaria* species at age 6 years correlated with persistent asthma at age 22 years (odds ratio, 7.4). Sensitization to *Alternaria* and other species has been associated with severe and potentially fatal episodes of asthma.[2,8,9] Epidemics of asthma caused by increased airborne *Alternaria* spores that occur during thunderstorms further illustrate this association.[10]

PREVALENCE OF FUNGAL SENSITIVITY

The precise prevalence of fungal sensitivity is unclear. The National Health and Nutrition Examination Survey III study[11] reported that among US citizens aged 6 to 59 years, 12.9% have positive skin prick test (SPT) responses to *Alternaria* species, whereas in another US study 21% of 102 atopic subjects had positive skin test results to 1 or more fungal allergens.[12] In European studies 78% of 824 Spanish patients with allergic respiratory symptoms had positive SPT responses to *Alternaria* species.[13] Although various studies report that 12% to 42% of atopic patients are mold sensitive,[13-16] others are as high as 80%.[17] Newer diagnostic approaches, such as fungal enzyme microarrays,[18] fluorescent halogen immunoassays,[19] and other approaches, might allow for a more accurate assessment of fungal sensitization.

Abbreviations used

ABPA:	Allergic bronchopulmonary aspergillosis
ABPM:	Allergic bronchopulmonary mycosis
CF:	Cystic fibrosis
IL-4RA:	IL-4 receptor α chain
ITGB3:	Integrin β3
IUIS:	International Union of Immunological Societies
MBL:	Mannose-binding lectin
PAR:	Protease-activated receptor
SAFS:	Severe asthma with fungal sensitivity
sIgE:	Specific IgE
SNP:	Single nucleotide polymorphism
SPT:	Skin prick test
TLR:	Toll-like receptor

DEVELOPMENT OF SENSITIZATION

Sensitization arises from a combination of genetic factors and exposure. Sensitization to *Alternaria* species has been associated with increased risk of maternal sensitization in patients' offspring to this allergen, although the risk of asthma is unknown.[20] Environmental exposure to fungi occurs both indoors and outdoors. A recent study showed that in fungus-sensitized asthmatic children, outdoor mold exposure rather than indoor mold exposure was linked with asthma exacerbations.[21] Nevertheless, other studies report an association between indoor mold exposures and lower airway symptoms. A Finnish cohort study reported a correlation between visible mold growth in homes and wheezing episodes in children.[22] Bundy et al[23] demonstrated that indoor *Penicillium* species levels correlated with peak expiratory flow rate variability in asthmatic children.

Allergic rhinitis and asthma both have been associated with exposure to fungal contamination in homes.[24] A quantitative meta-analysis of 33 epidemiologic studies showed an increase of 30% to 50% in adverse respiratory health outcomes in occupants because of dampness and mold exposure.[25] Recent reviews from the United States,[26] Europe,[27] and the World Health Organization[28] affirm that a damp indoor environment is a factor in asthma development. Fungi in water-damaged homes of asthmatic children have been found to differ from fungi in control homes without visible water damage. The dominant fungi in the dust of water-damaged homes fluctuated with the geographic location.[29-31]

ROLE OF CLIMATE CHANGE IN FUNGUS-RELATED RESPIRATORY TRACT DISEASES

Further factors that might influence the frequency of fungal sensitization and lower respiratory tract disease in the future are the effects of global climate change.[30,31] There is growing evidence of the effect of climate change on other aeroallergens, including mold sporulation.[32-36] The plant response to increasing

CO_2 concentrations includes greater biomass and a greater carbon/nitrogen ratio of plant tissues; thus fungi growing on plant materials encounter changes in substrate. When grown on plant material in higher CO_2 environments, *A alternata* exhibits increased spore production, as well as increased antigen levels per plant.[37] Lake and Wade[38] demonstrated an acceleration of pathogenic plant fungal growth in increased CO_2 environments; increasing CO_2 concentrations from 400 to 800 ppm increased established mycelia colonies by 40%. Increases in regional temperature at 2 sites in the United Kingdom over a 27-year period correlated with an increased number of days in which *Cladosporium* species spore counts exceeded 4000/m^3.[39] In a prospective study of patients with mild-to-moderate asthma (60% atopic), a positive relationship was established between high basidiospore levels and asthma symptom scores, with a modest but significant risk ratio of 1.19. Days with high basidiospore levels also correlated with nocturnal awakening and increased medication use.[40] Studies directly linking increases in CO_2 concentrations with increases in fungi formation and sporulation are limited. Klironomos et al[41,42] demonstrated a 4-fold increase in airborne fungal spores in response to increasing CO_2 concentration. Thus climate change joins the ranks of potential contributing factors to the increase in the prevalence and severity of respiratory disease.

TABLE I. Taxonomic distribution of allergenic fungi

Kingdom Chromista	**Ascomycota (continued)**	**Phylum Basidiomycota**
Phylum Oomycota	*Drechslera*	*Agaricus*
Phytophthora	*Epicoccum*	*Calvatia*
Plasmopara	*Erysiphe*	*Cantharellus*
	Eurotium	*Cyathus*
Kingdom Fungi	*Fusarium*	*Ganoderma*
Phylum Ascomycota	*Gliocladium*	*Geastrum*
Acremonium	*Helminthosporium*	*Lentinus*
Alternaria	*Monilia*	*Pleurotus*
Aspergillus	*Nigrospora*	*Polyporus*
Aureobasidium	*Neurospora*	*Psilocybe*
Botryotrichum	*Paecilomyces*	*Puccinia*
Botrytis	*Penicillium*	*Rhodotorula*
Candida	*Phoma*	*Serpula*
Cephalosporium	*Pyrenochaeta*	*Sporotrichum*
Chaetomium	*Saccharomyces*	*Tilletia*
Chrysosporium	*Scopulariopsis*	*Urocystis*
Cladosporium	*Stachybotrys*	*Ustilago*
Claviceps	*Stemphylium*	*Wallemia*
Coniosporium	*Torula*	*Xylobolus*
Curvularia	*Trichoderma*	
Cylindrocarpon	*Trichophyton*	**Phylum Zygomycota**
Daldinia	*Ulocladium*	*Mucor*
Didymella		*Rhizopus*

FUNGI ASSOCIATED WITH LOWER AIRWAY ALLERGY

Aerobiological studies have shown the majority of fungal spores in outdoor air to be from the phyla Ascomycota and Basidiomycota (Table I).[43] The most commonly studied allergenic fungi are conidia-producing anamorphs of ascomycetes, such as *Alternaria*, *Aspergillus*, *Botrytis*, *Cladosporium*, *Epicoccum*, *Fusarium*, and *Penicillium* species. Asexually produced conidia represent 30% to 60% of the spores present in outdoor air, the remainder being comprised mostly of teleomorphic (sexual) spores of the Ascomycota and Basidiomycota, which are referred to as ascospores and basidiospores, respectively. Studies have suggested that the prevalence of hypersensitivity to basidiospores and conidial allergens might be comparable, although little is known about the allergenicity of ascospores.[43] Exposure to airborne fungi can occur in both outdoor and indoor environments. Spores are usually present in outdoor air throughout the year, frequently exceeding the pollen population by 100- to 1000-fold or more, depending on environmental factors, such as water, nutrients, temperature, and wind.[44,45] Spores and fungal fragments found indoors originate from fungi present outdoors and from fungi that might have grown inside the buildings on moist surfaces.[46,47]

Precipitation is required for the discharge of basidiospores, with concentrations increasing during and after rainstorms.[48] The resultant airborne concentrations of actively wet spores discharging Basidiomycota is correlated with relative humidity rather than precipitation with minimal effect of wind speed on airborne spore counts.[49] During extended periods of rainfall, productivity might become a limiting factor, with re-establishment of spore concentrations dependent on replenishment of spores. Rainfall can also dislodge spores from surfaces, an effect heightened with larger raindrops.[49,50]

Many airborne conidia (asexual spores) are from fungal plant pathogens, and the mechanism responsible for spore release is not known for all; however, light might be an important factor in spore discharge.[50] The duration of sporulation is largely determined by temperature, humidity, and moisture, partly explaining why fungal spore counts are subject to seasonal periodicity.[51]

Alternatively, dry discharged spores from fungi, such as *Alternaria*, *Aspergillus*, *Cladosporium*, and *Penicillium* species, are mostly emitted when dry, warm, and windy conditions prevail.[49] Wind velocity required for detachment varies between fungi.[50,52] A minimum of 1.0 m/s is required for detachment of *Cladosporium* species, and 0.5 m/s is required for *Aspergillus* and *Penicillium* species.[51,52] Dry discharged spores are easily dispersed and can be carried long distances by the wind. Nonspherical spores fall slower and therefore have the potential to be carried farther by the wind than spherical spores, and similarly, spores released in clusters will fall faster than single spores.[50,52] In general, higher wind speed and drier air result in enhanced spore liberation.

Aspergillus fumigatus and related species are distributed widely in the environment.[53] *Aspergillus* and *Penicillium* species are closely related genera, the spores of which cannot be readily distinguished in studies relying solely on microscopy. They are present in outdoor air and are also considered major indoor fungi.[54] They are often present in the outdoor air throughout the year, although they might show seasonal fluctuations dependent on geographic region. In the United Kingdom they are the dominant spore type in the air in autumn and winter, but levels reach their peak in the autumn,[55] with levels higher outdoors during the day.[56]

Penicillium species are prevalent indoor fungi.[43] Inhalation of *Penicillium* species spores in quantities comparable with those encountered by natural exposure can induce both immediate and late asthma in sensitive persons. Among more than 100 known *Penicillium* species, *Penicillium citrinum*, *Penicillium chrysogenum (Penicillium notatum)*, *Penicillium oxalicum, Penicillium brevicompactum*, and *Penicillium spinulosum*, are considered the most common.

Cladosporium species spores are released during both wet and dry conditions and dispersed by rain splash. Spore release is dependent on fluctuations in humidity triggered particularly by rapid decreases in humidity.[57] Outdoor counts tend to be higher in warmer weather and during thunderstorms.[58] *Cladosporium* species spores occur abundantly worldwide and are the dominant airborne spores in many areas, especially in temperate climates.[59] *Cladosporium herbarum* frequently dominates indoor and outdoor air and is a major source of inhalant allergens.[60]

Alternaria species exhibits diurnal periodicity, with counts peaking during daylight hours.[49] Sporulation is induced by light rain or heavy dew, with sudden humidity changes stimulating release.[61,62] Although rainfall is required for sporulation, airborne levels are shown to decrease with precipitation.[63] Intermittent rainfall is more beneficial in the formation and dispersal of *Alternaria* species spores.[63] Temperature also affects concentrations, with counts higher in warmer weather.[58] Harvesting increases the concentration of airborne *Alternaria* species spores because of dislodgement from leaves.[63] Both intact and fragmented spores are observed in air samples during periods of harvest, which is likely problematic for allergic patients because the particles will be of more inhalable size and internal allergens will be exposed.[10,63] *Alternaria* species is a predominant outdoor fungus but has been reported in house dust samples.[64]

Another fungal spore of interest with regard to asthma and allergy is *Didymella* species, which is often observed in routine counts during the summer months, particularly during rainfall. *Didymella* species concentrations have been associated with asthma morbidity after thunderstorms[65] and positively correlate with humidity, with temperature being less important. Under favorable meteorological conditions, concentrations can reach explosive peaks of up to 30,000 spores/m^3 air.[66]

FUNGAL ALLERGENS

Most fungi possess multiple and diverse allergens. Some are metabolic products secreted outside the organism; others are cytoplasmic and structural components released on lysis or autolysis of the fungal cell. On the basis of the catalog of fungal allergens approved by the Allergen Nomenclature Sub-committee of the International Union of Immunological Societies (IUIS),[67] allergens that are fully characterized are listed in Table II. This listing includes isoallergens and variants from 25 fungal species belonging to the Ascomycota and Basidiomycota phyla. Intergenus and interspecies allergenic cross-reactivity must be distinguished from individual sensitization to multiple fungi. IgE-binding allergens of *A fumigatus*, *Penicillium* species, *A alternata*, and *C herbarum* have been obtained by using molecular cloning techniques.[68-74] Genomic analysis of *Aspergillus* species and homology comparisons with allergen sequences from other fungi have identified a core set of allergen-like proteins occurring across fungi. The IUIS listing includes 30 allergens from 5 species of *Aspergillus* (Table II), including proteins, polysaccharides and glycoproteins, and enzymes, including chymotrypsins, proteases, elastase, ribonucleases, catalases, and superoxide dismutases.[53,75] The most commonly encountered species associated with allergy are *A fumigatus, Aspergillus niger*, *Aspergillus oryzae*, *Aspergillus flavus*, and *Aspergillus terreus*. Several of these enzymes have been attributed to the pathogenesis of *Aspergillus* species–induced diseases. A number of these antigens demonstrate reactivity with specific IgE and IgG antibodies in patients with allergic bronchopulmonary aspergillosis (ABPA).[53,74-76] Polysaccharide fractions from the cell wall and cytoplasm also showed reactivity with sera of patients with ABPA. However, these allergens frequently show cross-reactivity with other fungal antigens.[74] Twelve antigens from *P citrinum* and 11 antigens from *P chrysogenum* have been shown to react with IgE from patients' sera by means of immunoblotting.[77] Sixteen *Penicillium* species allergens have also been characterized from 4 species (Table II). Ten allergens (Table II) have been characterized in *Cladosporium* species, 8 from *C herbarum*.[47] Only one of the 10 allergens is a fungal conidial allergen (Cla h HCh-1); the remainder are hyphal. Allergenic cross-reactivity between *Cladosporium cladosporioides, C herbarum*, and *Cladosporium sphaerospermum* has been reported.[78] *Alternaria* species possess both mycelial and metabolic antigens capable of causing allergy. The IUIS database recognizes 9 *Alternaria* species allergens, of which Alt a 1 is the most significant (Table II). Major fungal allergens, such as Asp f 1 and Alt a 1, are unique and have not been found to share sequence homology with any other known allergen.[79]

ALLERGIC FUNGAL LUNG DISEASES

ABPA and related conditions

First described in 1952, ABPA is commonly caused by *A fumigatus*, an ubiquitous mold common indoors and frequently found around farm buildings and compost heaps.[80-85] ABPA is characterized by exacerbations of asthma, recurrent transient chest radiographic infiltrates, and peripheral and pulmonary eosinophilia, especially during an exacerbation. ABPA is a T_H2 hypersensitivity lung disease caused by bronchial colonization with *A fumigatus* that affects approximately 0.7% to 3.5% of asthmatic patients and 7% to 9% of patients with cystic fibrosis (CF).[80-85] The diagnosis of ABPA is based on clinical and immunologic reactivity to *A fumigatus*. The minimal criteria required for the diagnosis of ABPA are as follows: (1) asthma or CF with deterioration of lung function, (2) immediate *Aspergillus* species skin test reactivity, (3) total serum IgE level of 1000 ng/mL (416 IU/mL) or greater, (4) increased *Aspergillus* species–specific IgE and IgG antibodies, and (5) chest radiographic infiltrates. Additional criteria might include peripheral blood eosinophilia, *Aspergillus* species serum precipitating antibodies, central bronchiectasis, and *Aspergillus* species–containing mucus plugs.[80-85] Designation of ABPA-seropositive (ABPA-S) can be used to classify asthmatic patients who meet required criteria but lack proximal or central bronchiectasis (ABPA-CB). High-resolution computed tomography can demonstrate central bronchiectasis in the inner two thirds of the field, even in the absence of chest radiographic lesions.[86] PCR for detecting *Aspergillus* species in sputum is more sensitive than culture in ABPA but needs to be interpreted with other clinical and laboratory features.[87] At the time of radiographic exacerbation, the presence of sputum or blood eosinophilia is suggestive of ABPA, especially if the total IgE concentration has increased compared with baseline concentrations. Plasma levels of thymus and activation-regulated chemokines (CCL17) might be a better marker for ABPA than IgE levels, especially for exacerbations.[88]

ABPA is the most common form of allergic bronchopulmonary mycosis (ABPM). Other fungi, including *Candida*, *Penicillium*, and *Curvularia* species, are occasionally responsible for a similar syndrome.[83] Recently, Lötvall et al[89] proposed endotype classification of asthma syndromes, which included ABPM. The characteristics of ABPM included severe asthma, blood and pulmonary eosinophilia, markedly increased IgE and specific IgE levels,

TABLE II. Fungal allergens approved by the Nomenclature Subcommittee of the IUIS*

Fungal species	Allergen	Molecular weight (kd)	Biological activity
Phylum Ascomycota			
Alternaria alternata	Alt a 1	28	
	Alt a 3		Heat Shock Protein 70
	Alt a 4	57	Disulfide isomerase
	Alt a 5	11	Ribosomal protein P2
	Alt a 6	45	Enolase
	Alt a 7	22	YCP4 protein
	Alt a 8	29	Mannitol dehydrogenase
	Alt a 10	53	Aldehyde dehydrogenase
	Alt a 12	11	Acid ribosomal protein P1
	Alt a 3	26	Gulathione-S-transferase
Aspergillus flavus	Asp fl 13	34	Alkaline serine protease
Aspergillus fumigatus	Asp f 1	18	Mitogillin family
	Asp f 2	37	
	Asp f 3	19	Peroxysomal protein
	Asp f 4	30	
	Asp f 5	40	Metalloprotease
	Asp f 6	26.5	Mn Superoxide dismutase
	Asp f 7	12	
	Asp f 8	11	Ribosomal protein P2
	Asp f 9	34	
	Asp f 10	34	Aspartate protease
	Asp f 11	24	Peptidyl-prolyl isomerase
	Asp f 12	90	Heat Shock protein P90
	Asp f 13	34	Alkaline serine protease
	Asp f 15	16	
	Asp f 16	43	
	Asp f 17		
	Asp f 18	34	Vacuolar serine protease
	Asp f 22	46	Enolase
	Asp f 23	44	Ribosomal protein L3
	Asp f 27	18	Cyclophilin
	Asp f 28	13	Thioredoxin
	Asp f 29	13	Thioredoxin
	Asp f 34	20	PhiA cell wall protein
Aspergillus niger	Asp n 14	105	Beta-xylosidase
	Asp n 18	34	Vacuolar serine protease
	Asp n 25	66-100	3-phytase B
Aspergillus oryzae	Asp o 13	34	Alkaline serine protease
	Asp o 21	53	TAKA-amylase A
Aspergillus versicolor	Asp v 13	43	Extracellular alkaline serine protease
Candida albicans	Cand a 1	40	Alcohol dehydrogenase
	Cand a 3	20	Peroxysomal protein
Candida boidinii	Cand b 2	20	Peroxysomal membrane protein A
Cladosporium cladosporioides	Cla c 9	36	Vacuolar serine protease
	Cla c 14	36.5	Transaldolase
Cladosporium herbarum	Cla h 2	45	
	Cla h 5	11	Acid ribosomal protein P2
	Cla h 6	46	Enolase
	Cla h 7	22	YCP4 Protein
	Cla h 8	28	Mannitol dehydrogenase
	Cla h 9		Vacuolar serine protease
	Cla h 10	53	Aldehyde dehydrogenase
	Cla h 12	11	Acid ribosomal protein P1
Curvlaria lunata	Cur l 1	31	Serine protease
	Cur l 2	48	Enolase
	Cur l 3	12	Cytochrome c
	Cur l 4	54	Vacuolar serine protease
Epicoccum purpurascens	Epi p 1	30	Serine protease
Fusarium culmorum	Fus c 1	11	Ribosomal protein P2
	Fus c 2	13	Thioredoxin-like protein
Penicillium brevicompactum	Pen b 13	33	Alkaline serine protease
	Pen b 26	11	Acidic ribosomal protein P1
Penicillium chrysogenum	Pen ch 13	34	Alkaline serine protease
	Pen ch 18	32	Vacuolar serine protease
	Pen ch 20	68	N-acetyl glucosaminidase
	Pen ch 31		Calreticulin
	Pen ch 33	16	
	Pen ch 35	36.5	Transaldolase
Penicillium citrinum	Pen c 3	18	Peroxysomal membrane protein
	Pen c 13	33	Alkaline serine protease
	Pen c 19	70	Heat shock protein P70
	Pen c 22	46	Enolase
	Pen c 24		Elongation factor 1 beta
	Pen c 30	97	Catalse
	Pen c 32	40	Pectate lyase
Penicillium oxalicum	Pen o 18	34	Vacuolar serine protease
Stachybotrys chartarum	Sta c 3	21	Extracellular alkaline Mg-dependent exodesoxyribo-nuclease
Trichophyton rubrum	Tri r 2		Putative secreted alkaline protease Alp 1
	Tri r 4		Serine protease
Trichophyton tonsurans	Tri t 1	30	
	Tri t 2	83	Serine protease

(Continued)

TABLE II. *(Continued)*

(Continued)

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Fungal species	Allergen	Molecular weight (kd)	Biological activity
Phylum Basidiomycota			
Coprinus comatus	Cop c 1	11	Leucine zipper protein
	Cop c 2		Thioredoxin
	Cop c 3		
	Cop c 5		
	Cop c 7		
Malassezia furfur	Mala f 2	21	Peroxysomal membrane protein
	Mala f 3	20	Peroxysomal membrane protein
	Mala f 4	35	Mitochondrial malate dehydrogenase
Malassezia sympodialis	Mala s 1		
	Mala s 5		
	Mala s 6		Cyclophilin
	Mala s 7		
	Mala s 8		
	Mala s 9		
	Mala s 10	86	Heat shock protein 70
	Mala s 11	23	Manganese superoxide dismutase
	Mala s 12	67	Glucose-methanol-choline oxidoreductase
	Mala s 3	13	Thioredoxin
Psilocybe cubensis	Psi c 1		
	Psi c 2	16	Cyclophilin
Rhodotorula mucilaginosa	Rho m 1		Enolase
	Rho m 2	47	Vacuolar serine protease

*Current as of April 29, 2010 (http://www.allergen.org).

bronchiectasis, and mold colonization of the airways. Genetic risks of ABPM can include CF variants and HLA association. Sensitization to *A fumigatus* is common, particularly in patients with more severe airway disease,[90] although few fulfill all the criteria for ABPA. The term severe asthma associated with fungal sensitivity (SAFS) has been coined to illustrate the high rate of fungal sensitivity in patients with severe asthma and response to oral antifungal therapy with itraconazole.[91] It is speculative whether ABPA represents one florid manifestation of a spectrum of fungus-associated airway disease.

Fungal sensitivity in patients with severe asthma

The human lung is not sterile from a fungal perspective in most persons. The conidia of *A fumigatus*, *Penicillium* and *Cladosporium* species, and presumably other fungi are nonreactive, only inducing an immune response when germination is initiated.[92] Excess mucus and airway architecture distortion can allow fungal germination and protection from immune attack, with a consequent inflammatory reaction. Although *A fumigatus* is the most common fungus found in the airways, much of which is not culturable,[87] other fungi can be cultured from sputum in asthmatic patients. In a study of 126 patients with severe asthma, 24 different fungal species were cultured from sputum, usually in association with *A fumigatus*. In approximately 50% of these patients, cultures were positive without evidence of IgE fungal sensitization, suggesting that fungal colonization of the airways is common, even in the absence of an allergic component. In patients with severe asthma, Fairs et al[93] reported that there was a significant association between *A fumigatus* IgE sensitization, colonization, and impaired postbronchodilator FEV_1. This observation is analogous with data emerging from patients with CF and *A fumigatus* colonization.[94] Given this, it is not surprising that patients with SAFS respond to antifungal therapy.

Diagnosis of fungal sensitization

SPTs and specific serum IgE tests are used to determine sensitization to various fungi.[95] Common fungi tested included *A fumigatus*, *C albicans*, *A alternata (Alternaria tenuis)*, *P chrysogenum (P notatum)*, *C herbarum*, and *Saccharomyces cerevisiae*. Fungi less commonly tested, although some reagents are available, included other species of *Aspergillus*, *Botrytis cinerea*, *Trichophyton* species, *Malassezia* species, *Aureobasidium pullulans*, *Helminthosporium halodes*, *Epicoccum* species, *Fusarium* species, *Mucor* species, *Rhizopus* species, and *Coprinus* species. The accuracy of SPTs for positive results is approximately 50% to 60%, with variations dependent on the reagent and manufacturer, potency of extracts, and interpretation of results. The negative predictive result has a 95% accuracy.[96-99] Major geographic and age variations in the frequency of sensitization to fungi are seen.[97,98]

In vitro measurement of specific IgE antibodies can be useful in patients who cannot undergo SPTs.[96-99] Smits et al[96] found that only 43% of patients reacted to both SPTs and serum specific IgE (sIgE) tests when tested for common aeroallergens and foods. O'Driscoll et al[99] described a general lack of concordance between positive SPT responses and serum sIgE testing in patients with severe asthma, with the best concordance noted in *Alternaria* species (56%) and the worst in *Botrytis* species (14%). Both authors recommended the use of both tests for a definitive diagnosis because not all sensitivities will be identified with the use of one alone. It has been reported that SPTs are more sensitive but less specific than serum sIgE tests to diagnose allergic sensitization in subjects with asthma or rhinitis.[98] O'Driscoll et al[99] prospectively examined SPT and serum sIgE test results to individual fungi together and separately in patients with severe asthma in the United Kingdom. Among 121 patients, 66% demonstrated sensitization to 1 or more fungi on either test. Nine of these patients had a total serum IgE level of greater than 1000 IU/mL: 6 likely had ABPA, and 3 had ABPM to other fungi (1 to *Candida* species and 2 to *Trichophyton* species). Sensitization to multiple fungi or sensitization to cross-reacting allergens can occur.[100] Others have demonstrated relatively high rates of sensitization to other fungi in asthmatic patients, including *Rhizopus* and *Mucor* species.[101]

PATHOPHYSIOLOGY OF FUNGAL DISEASES OF THE LOWER AIRWAYS

β-Glucan and dectin receptors

(1→3)-β-*D*-glucans are part of the carbohydrate structures in the cell walls of molds, some bacteria, and plants; up to 60% of the dry weight of the cell wall of fungi might be glucans.[102] An association between high β-glucan levels and increased peak expiratory flow variability has been observed in children with asthma.[103] The presence of visible mold and exposure to β-glucan

in infancy appear to be risk factors for asthma by age 3 years.[104] On the other hand, high levels of β-glucan exposure might have an opposite effect on asthma risk compared with visible mold. Indoor fungal species vary widely in their content of β-glucan, and although *Aspergillus* and *Alternaria* species are highly allergenic, they have relatively low levels of β-glucan. Of the 36 indoor fungal species tested, *Cladosporium* and *Aspergillus* genera were the most important contributors to the indoor β-glucan levels[105]; *A alternata* did not seem to be an important contributor to indoor β-glucan levels.

Dectin-1 is a receptor for β-glucan on macrophages, neutrophils, and dendritic cells that transduces signals for vigorous cell response with phagocytosis, oxidative burst, and production of inflammatory mediators, including IL-8, IL-6, IL-12, IL-18, and TNF-α.[106,107] In mice dectin-1 and Toll-like receptor (TLR) 2–mediated neutrophil recruitment and TNF-α and macrophage inflammatory protein 2 secretion when germinating conidia of *A fumigatus* were administered into murine trachea.[108,109] The dectin-1–mediated response to fungi can also be involved in adaptive immune responses, including the regulation of the T_H17 response and generation of regulatory T cells.[107,109]

Fungal proteases and protease-activated receptors

Fungi contain many proteases that are required for growth and are also fungal allergens.[2,110] It is possible that the proteolytic activity of fungal proteases contributes to their own immunogenicity or that of other fungus-derived proteins. *In vitro* fungal proteases damage an epithelial layer system with shrinkage, desquamation, and disruption of intercellular adhesion.[2,110] Once the epithelial layer is damaged, proteases/allergens have better access to the mucosal and subepithelial layer. Damaged, activated, or both epithelial cells produce IL-6 and IL-8; these proinflammatory cytokines could lead to an exacerbation of asthma. Damage in the airway mediated by protease activities shows pathologic changes analogous to that of asthma.[110] Protease activities can be recognized by unique receptors, protease-activated receptors (PARs), which are expressed by tissue cells and cells involved in the immune response in the airways. PAR-1, PAR-2, PAR-3, and PAR-4 are present on the epithelium in bronchial biopsy specimens from asthmatic patients and healthy subjects.[111] PAR-2 is overexpressed on epithelial cells from asthmatic patients compared with that seen in healthy control subjects, suggesting increased vulnerability of asthmatic patients to proteases from fungi or other sources.

Chitinases

Chitin is a major structural component of the outer coatings of many organisms, such as fungi, parasitic nematodes, and arthropods.[112,113] Reese et al[114] found that mice treated with chitin have an allergic response, characterized by a build-up of IL-4–expressing innate immune cells. Shuhui et al[115] proposed that chitin-degrading enzyme acidic mammalian chitinases in epithelial cells stimulates the release of monocyte chemoattractant proteins 1 and 2, macrophage inflammatory protein 1, and eotaxin. Chitinase can also stimulate airway smooth muscle. Increased chitinase levels have been associated with asthma and increased IgE levels, perhaps through an IL-13 pathway.[116,117] Furthermore, polymorphisms in the promoter of acidic mammalian chitinase have been associated with atopic asthma and increased IgE levels.[117]

Mycotoxins and volatile organic compounds

Patients with asthma tend to be more readily symptomatic by respiratory exposure to airborne irritants, such as perfume and smoke, than healthy subjects. Fungi produce mycotoxins as nonvolatile secondary metabolites and volatile organic compounds as byproducts of metabolism.[118] The volatile organic compounds are potential asthma triggers[119]; however, the amount and duration of exposure to mycotoxins are difficult to quantify.

HLA class II antigens

In patients with ABPA, HLA-DR2 (HLA-DRB1*15 and B1*16)/HLA-DR5 (HLA-DRB1*11 and HLA-DRB1*12) restriction was reported as a risk factor for the development of ABPA.[120] Furthermore, HLA-DQB1*02 was protective in the development of ABPA. Similarly, DQB1*03 appeared to be protective in the development of *Alternaria* species– and mold-sensitive moderate-to-severe asthma in children.[121] The HLA-DQB1*03 genotype was associated with decreased *Alternaria* species–stimulated IL-5 and IL-13 synthesis.

IL4RA and *IL13* polymorphisms

Single nucleotide polymorphisms (SNPs) of IL-4 receptor α chain *(IL4RA)*, *IL4*, *IL10*, *IL13*, and *CD14* have been described in patients with asthma.[122] A number of SNPs of these genes are associated with atopy prevalence and asthma severity.[123] Increased frequency of the ser503pro *IL4RA* polymorphism was observed in adults with severe asthma.[124] *IL13* 110gln was associated with increased IgE levels and increased asthma severity[125]; the 110gln polymorphism is significantly more active than wild-type *IL13* in stimulating signal transducer and activator of transcription 6 phosphorylation, CD23 upregulation, and IgE synthesis. In patients with ABPA, Knutsen et al[126] reported that *IL4RA* SNPs and in particular the ile75val SNP in the IL-4 binding region was another risk factor. In studies of *Alternaria* species–sensitive patients with moderate-to-severe asthma, the presence and allele frequency of the *IL4RA* ile75val SNP was also significantly increased.

Polymorphisms in innate immune receptors

Carvalho et al[127] examined *TLR* polymorphisms of *TLR2*, *TLR4*, and *TLR9* in patients with cavitary pulmonary aspergillosis, ABPA, and SAFS. No association of *TLR2*, *TLR4*, or *TLR9* polymorphisms was found in SAFS. Patients with ABPA had increased frequency of allele C for the *TLR9* T-1237C polymorphism compared with control subjects. Novak et al[128] reported that the mechanism might be that the *TLR9* C allele of T-1237C decreases expression of TLR9. Decreased TLR9 protective function might be an underlying susceptibility in the development of ABPA and asthma.

Integrin β3 *(ITGB3)* encodes a β-integrin that comprises part of the platelet- and monocyte-specific heterodimeric receptor for fibrinogen and the receptor for vitronectin. Polymorphisms of *ITGB3* have been associated with asthma and mold sensitization.[129] Smit et al[130] reported that the *TLR2*/+596 C polymorphism was associated with asthma. Furthermore, they identified that *ITGB3* SNPs are associated with mold sensitization in patients with asthma and hypothesized that an association of the *TLR2*/1596 genotype and *ITGB3* SNPs might influence the association of mold sensitization in adults with asthma.

TABLE III. Possible treatments of ABPA

Therapy	Typical dose	Typical duration	Objectives of therapy	Monitoring	Comments
Prednisone (prednisolone)	Adults: 40-50 mg qd Pediatric patients: 0.5-1 mg/kg/d	10 d-6 wk, depending on response; convert to alternate-day prednisone after 1-2 wk for longer-term treatment	Improvement of wheeze and allows resolution of mucoid impactions	Chest radiograph and clinical. IgE level slow to decrease, expected to decrease by 33% in 6 wk; blood glucose	Attempt to stop in all patients; sometimes not possible
Inhaled corticosteroids	Variable	Long-term	Asthma control; of no proved value for exacerbation of ABPA	PF, FEV_1, symptoms	Interactions with itraconazole, increasing exposure
Hypertonic saline, nebulized	4 mL, 7% unit dose bid	Exacerbations or long-term	Reduce viscosity of sputum to ease expectoration	Sputum thickness, ease of expectoration and dyspnea	Always challenge first dose under supervision because bronchospasm an issue; beware those with FEV_1 <1.0 L/s.
Itraconazole	Adults: 300-400 mg qd or 500 mg bid in patients with CF Pediatric patients: 5-10 mg/kg/d, divided bid if ≥200 mg	Long-term	Steroid sparing; eradication of *Aspergillus* species in airways; improved asthma control	Itraconazole levels to optimize initially and check compliance; cortisol and total steroid dose Fungal cultures and MICs; *Aspergillus* species PCR in sputum if available; sensory disturbance	Toxicity minimized if blood levels in therapeutic range; resistance can occur, PCR positive an indication of resistance; new pulmonary infiltrates can occur with elevation of total serum IgE
Voriconazole	Adults: 200-600 mg qd Pediatric patients: <40 kg 100 mg bid ≥40 kg 200 mg bid	Months or years	Same as itraconazole	Voriconazole levels to optimize initially and check compliance; photosensitivity; fungal cultures and MICs; *Aspergillus* species PCR in sputum; sensory disturbance	For those intolerant or who fail itraconazole; photosensitivity limiting in some white subjects; increases prednisone exposure by approximately 30%; limited experience in ABPA
Posaconazole	Adults: 800 mg qd Pediatric patients: ≥13 y 400 mg bid	Long-term	Same as itraconazole	Fungal cultures and MICs; *Aspergillus* species PCR in sputum; posaconazole levels if adverse events to determine whether dose can be decreased	For those intolerant or in whom itraconazole and voriconazole fail; limited experience in ABPA
Azithromycin	Adults: 250 mg qd or 3× weekly Pediatric patients: 5 mg/kg/d qd or in CF <40 kg 250 3× weekly ≥40 kg 500 3× weekly	Long-term	Airway anti-inflammatory action	Cough frequency and nocturnal wakening; sputum production	If no effect after approximately 2-3 mo, should be stopped
Omalizumab	75-600 mg SC 2-4 weekly	Long-term, if effective at 16 wk	Reduction in IgE-mediated asthma	Asthma control	Limited experience in ABPA

bid, Twice daily; *MIC*, minimum inhibitory concentration; *PF*, peak flow; *qd*, once daily; *SC*, subcutaneously.

Molecules in the collectin family, such as mannose-binding lectin (MBL), pentraxin 3, and surfactant proteins, have all been demonstrated to bind *Aspergillus* species. Polymorphism of *MBL2* at G+1011 in intron 1 results in increased MBL levels and has been associated with development of ABPA. Saxena et al[131] reported that patients with ABPA with polymorphisms (ala91pro and arg94arg) in the collagen region of pulmonary surfactant protein A2 had more increased total IgE levels and higher percentages of eosinophilia than patients who lacked the SNPs. They found that 80% of patients carrying both SNPs had ABPA, suggesting an additive effect.

TREATMENT OF ALLERGIC FUNGAL LUNG DISEASES

ABPA

Exacerbations of ABPA are best treated with a course of oral steroids over 3 to 6 weeks (Table III).[132] No prospective studies with corticosteroids have been conducted to evaluate efficacy rates, optimum dose, and duration or relapse rates. There are conflicting data concerning the clinical utility of inhaled corticosteroids in reducing exacerbation frequency, but they are important in controlling underlying asthma (Table III).[133,134] The potential utility of systemic antifungal therapy for ABPA was first shown in the early 1990s.[135] Two placebo-controlled randomized studies demonstrated benefit from itraconazole treatment (200 mg twice daily initially).[136,137] The outcomes that were assessed in the first study were as follows: reduction in corticosteroid oral dose, reduction in total IgE levels, and increases in exercise tolerance or pulmonary function on testing.[136] In the second study eosinophils in sputum, total serum IgE levels and *Aspergillus* IgG levels, and exacerbations requiring corticosteroid courses were significantly reduced in itraconazole-treated subjects ($P = .03$).[137] Overall, about 60% of patients benefit from itraconazole (number needed to treat = 3.58). Itraconazole levels should be monitored to optimize exposure. Sufficient exposure to itraconazole is probably important to ensure efficacy, and low plasma levels (ie, <5 mg/L [bioassay] or <1.0 mg/L [HPLC]) might require switching between capsules and oral solution and sometimes increasing the dose. Proton-pump inhibitors and H_2 blockers reduce absorption of itraconazole capsules, and different capsule formulations differ in bioavailability. Excessive itraconazole concentrations often result in adverse events, and dose reduction is advised. The duration of itraconazole therapy is not clear but should not be less than 6 months in those who tolerate it and might be extended safely with benefit for years. In patients who cannot tolerate itraconazole, voriconazole or posaconazole might be helpful (Table III). Two retrospective series of voriconazole in patients with ABPA and CF suggest benefit, and our experience in patients without CF is similar or better. There are a number of case series of patients reporting the benefit of omalizumab in the therapy of ABPA[138-140] but no randomized studies, and therefore efficacy is uncertain. Exacerbations of ABPA or difficult-to-treat asthma (with fungal sensitization) necessitate considering the home and workplace environment or the patient's activities, such as gardening with fungus-laden mulches, that might be subject to change.

Bronchiectasis is a common sequela of ABPA. Sometimes patients with bronchiectasis do better with long-term macrolide treatment (ie, azithromycin) if they are highly symptomatic; no large randomized controlled studies have been done, but clinical experience is positive for many patients.[141-143] Initiation of azithromycin therapy should immediately follow a different class of antibiotic in those with purulent sputum to "clean out the airways" to minimize the immediate acquisition of macrolide resistance.

SAFS and ABPM

Patients with SAFS usually have severe asthma requiring multiple medications. Inhaled corticosteroids and frequent courses of oral corticosteroids usually control patients' worst symptoms but at the long-term cost of well-known adverse events. Antifungal therapy with itraconazole (200 mg twice daily) is beneficial in having a major effect on pulmonary and nasal symptoms in 60% of treated patients (number needed to treat = 3.22).[144] Early evidence suggests that omalizumab might also be beneficial.[138-140]

Exposure reduction

Reductions in asthma morbidity subsequent to interventions for improving overall indoor air quality, decreasing humidity, and remediation of moisture incursion have been demonstrated.[145-147]

Fungal allergen immunotherapy

Large-scale, double-blind, placebo-controlled studies of fungal allergen immunotherapy are wanting, in part because of the lack of standardized therapeutic reagents. A limited number of controlled trials with *A alternata* and *C herbarum* have shown some clinical benefit.[148] Immunotherapy for ABPA is not generally recommended; however, patients might receive or continue allergen immunotherapy for treatment of allergic rhinitis or asthma. Historically, fungal (mold) extracts are not included in the treatment mixes.

What do we know?

- **Sensitivity to molds, especially *Alternaria* and *Cladosporium* species, is associated with the development, persistence, and severity of allergic asthma.**
- **ABPA is the most common form of ABPM. ABPA might represent an extreme manifestation of a spectrum of immunologically mediated fungus-associated airway disease.**
- **Sensitization to *A fumigatus* is common in asthmatic patients with more severe airway disease (ie, so-called SAFS).**
- **Both ABPA and SAFS might respond to antifungal therapy, as well as corticosteroids. What is still unknown?**
- **The pathophysiology and genetic risks of mold sensitivity in patients with severe asthma remain to be fully elucidated.**
- **The diagnostic criteria of ABPA, ABPM, and SAFS need to be better defined.**
- **The role of antifungal and immunomodulating therapies in the treatment of ABPA, ABPM, and SAFS requires further controlled clinical trials for validation and determination of the role in overall management.**

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