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REVIEW

The spectrum of allergic fungal diseases of the upper and lower airways

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SUMMARY

Fungi cause a wide spectrum of fungal diseases of the upper and lower airways. There are three main phyla involved in allergic fungal disease: (1) *Ascomycota* (2) *Basidiomycota* (3) *Zygomycota*. Allergic fungal rhinosinusitis (AFRS) causes chronic rhinosinusitis symptoms and is caused predominantly by *Aspergillus fumigatus* in India and *Bipolaris* in the United States. The recommended treatment approach for AFRS is surgical intervention and systemic steroids. Allergic bronchopulmonary aspergillosis (ABPA) is most commonly diagnosed in patients with asthma or cystic fibrosis. Long term systemic steroids are the mainstay treatment option for ABPA with the addition of an antifungal medication. Fungal sensitization or exposure increases a patient's risk of developing severe asthma and has been termed severe asthma associated with fungal sensitivity (SAFS). Investigating for triggers and causes of a patient's asthma should be sought to decrease worsening progression of the disease.

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Introduction

Fungi are ubiquitous, and fungal spores are present in every breath we take. In biologic taxonomy, fungi are classified as a kingdom, just as plants, animals, and bacteria are. They can exist as unicellular organisms called yeasts, or in the form of multicellular filaments called hyphae. A mass of branching hyphae is called a mycelium, and fungi that grow in this form are referred to as molds. In most cases, these fungi dwell within us symbiotically or saprophytically without causing serious disease. Depending on a variety of pathogen and host factors, the pathogenicity of fungi can range from innocuous colonization to rapidly lethal disease. As seen in Table 1, this kingdom contains three main phyla responsible for allergic fungal disease: *Ascomycota* (containing the genera *Alternaria*, *Curvularia*, *Cladosporium*, *Aspergillus*, *Penicillium*, *Fusarium*, *Trichophyton*, *Stacybotrys*, and *Epicoccum*), *Basidiomycota* (containing the genera *Malassezia*, *Rhodotorula*, *Psilocybe*, *Schizophyllum*, and *Coprinus*), and *Zygomycota* (containing the genera *Rhizopus* and *Mucor*).^[1,2] Many major allergens have been identified among the different genera, and allergic sensitization to these fungal allergens can be detected by skin testing or in vitro immunoglobulin E (IgE) testing. Sensitization to airborne fungi has been known to exacerbate many atopic conditions such as asthma, rhinitis, and atopic dermatitis.

Allergic fungal diseases of the upper airway

Fungi are an important entity in the sinonasal microbiome. Depending on a variety of factors, these fungi can exist symbiotically, invade respiratory passages, or provide an arsenal of

antigens against which the host immune system may mount a hypersensitivity or inflammatory response. In 1791, Plaigaud described a case of a 22-year-old soldier with maxillary pain, who was said to have developed a 'fungal tumor' that was cured by cautery, which is possibly the first description of presumed fungal sinusitis in literature.^[3,4] In 1885, Schubert described a case of noninvasive nasal and paranasal aspergillosis.^[3,5] Then in 1897, Oppe described a case of invasive aspergillosis with intracranial extension.^[3,6] Hora was the first to classify fungal sinusitis into invasive and noninvasive subtypes.^[7] Since then, we have come a long way in our understanding of invasive and noninvasive forms of fungal sinusitis. However, for the purpose of this review, we will focus on allergic fungal rhinosinusitis (AFRS), a clinical entity of hypersensitivity to fungal antigens.

Allergic fungal rhinosinusitis

Background

Similar to the pathophysiology of allergic bronchopulmonary aspergillosis (ABPA) in the lungs, AFRS is due to an allergic hypersensitivity reaction to *Aspergillus* colonization of the upper respiratory tract and sinuses. The first reference to such a condition was made in 1976 by Safirstein, a British allergist with a special interest in the area of ABPA.^[8] He described a woman with intractable nasal obstruction due to nasal polyps, nasal mucosal ulcerations, and thick purulent nasal discharge. Her polyps were infiltrated with eosinophils and plasma cells, and the sinus culture was positive for *Aspergillus fumigatus*. She was later found to have ABPA and was treated with corticosteroids, which also helped her nasal

Table 1. Taxonomic distribution of allergic fungi.

Phylum ascomycota	Phylum basidiomycota	Phylum zygomycota
<i>Acremonium</i>	<i>Agaricus</i>	<i>Mucor</i>
<i>Alternaria</i>	<i>Calvatia</i>	<i>Rhizopus</i>
<i>Aspergillus</i>	<i>Cantharellus</i>	
<i>Aureobasidium</i>	<i>Cyathus</i>	
<i>Botryotrichum</i>	<i>Ganoderma</i>	
<i>Botrytis</i>	<i>Geastrum</i>	
<i>Candida</i>	<i>Lentinus</i>	
<i>Cephalosporium</i>	<i>Pleurotus</i>	
<i>Chaetomium</i>	<i>Polyporus</i>	
<i>Chrysosporium</i>	<i>Psilocybe</i>	
<i>Cladosporium</i>	<i>Puccinia</i>	
<i>Claviceps</i>	<i>Rhodotorula</i>	
<i>Coniosporium</i>	<i>Serpula</i>	
<i>Curvularia</i>	<i>Sporotrichum</i>	
<i>Cylindrocarpon</i>	<i>Tilletia</i>	
<i>Daldinia</i>	<i>Urocystis</i>	
<i>Didymella</i>	<i>Ustilago</i>	
<i>Drechslera</i>	<i>Wallemia</i>	
<i>Epicoccum</i>	<i>Xylobolus</i>	
<i>Erysiphe</i>		
<i>Eurotium</i>		
<i>Fusarium</i>		
<i>Gliocladium</i>		
<i>Helminthosporium</i>		
<i>Monilia</i>		
<i>Nigrospora</i>		
<i>Neurospora</i>		
<i>Paecilomyces</i>		
<i>Penicillium</i>		
<i>Phoma</i>		
<i>Pyrenochaeta</i>		
<i>Saccharomyces</i>		
<i>Scopulariopsis</i>		
<i>Stachybotrys</i>		
<i>Stemphylium</i>		
<i>Torula</i>		
<i>Trichoderma</i>		
<i>Trichophyton</i>		
<i>Ulocladium</i>		

symptoms. Thus, the understanding of ABPA as a disease entity paved the way for recognizing AFRS. In 1981, Millar et al. described the presentation of five patients with chronic sinusitis, of whom only one had previously diagnosed ABPA.[9] However, he noticed that the material from the sinuses of these patients had a histological resemblance to the plugs expectorated by patients with ABPA. Also, all of these patients showed a marked immediate hypersensitivity to *A. fumigatus*. This led him to coin the term ‘allergic aspergillosis of the paranasal sinuses’. In 1983, Katzenstein et al. examined the microscopic slides of 119 specimens surgically excised from the paranasal sinuses.[10] In nine of these cases, they found that the material obtained from the paranasal sinuses was indistinguishable from mucoid impaction of the bronchi in patients with ABPA. Histologically, this material was rich in clumps of necrotic eosinophils in a background of amorphous mucin, so they called this material ‘allergic mucin’. In seven of these patients, they also identified hyphae of *Aspergillus* occurring exclusively within the mucin, without evidence of surrounding tissue invasion. They coined the term ‘allergic aspergillus sinusitis’ (AAS) to describe these patients, due to their marked histopathological resemblance to patients with ABPA. In subsequent years, it became apparent that various other fungal species such as *Bipolaris*, *Curvularia*, *Drechslera*, *Alternaria*, and *Fusarium* could cause AFRS, in addition to

Aspergillus, and this led to the coining of the term ‘allergic fungal sinusitis’(AFS).[3,11–13]

Classification

The nomenclature and classification of AFRS has been a matter of debate. In order to reach a consensus, the International Society for Human and Animal Mycology convened a working group in 2009. [14] Accordingly, fungal rhinosinusitis is broadly classified into invasive and noninvasive subtypes. Details of this classification along with salient features of each subtype are summarized in Tables 2 and 3.[3,15–18] Noninvasive fungal rhinosinusitis (Table 2) occurs in immunocompetent individuals and includes local fungal colonization, fungal ball, and AFRS. Fungal colonization is due to poor mucociliary clearance and is typically asymptomatic or causes a foul-smelling nasal discharge. It responds well to nasal rinses and/or endoscopic removal. Fungal ball is due to poor mucociliary clearance and causes purulent nasal discharge, facial pain, or may be asymptomatic. *Aspergillus* is the most common mold responsible for this condition, and treatment involves endoscopic removal. AFRS is reviewed in greater detail below. Invasive fungal rhinosinusitis (Table 3) occurs in immunocompromised individuals and includes acute invasive fungal rhinosinusitis (AIFRS), chronic invasive fungal rhinosinusitis (CIFRS), and granulomatous invasive rhinosinusitis (GIFRS). AIFRS occurs in patients with poorly controlled diabetes, malignancy, and cytotoxic therapy and causes fever, nasal eschar, epistaxis, and periorbital and intracranial spread. Causative fungi include *Zygomycetes* (*Rhizopus*, *Mucor*, *Rhizomucor*, *Absidia*) and *Aspergillus*. Morbidity and mortality are high, and treatment involves administration of antifungal medication and performance of surgical debridement. CIFRS also occurs in patients with poorly controlled diabetes and chronic corticosteroid use. In GIFRS, the symptoms are more indolent with fever, facial pain, epistaxis, and nasal polyps. *Mucor*, *Rhizopus*, *Penicillium*, *Aspergillus*, *Bipolaris*, and *Candida* are the usual fungi isolated. Treatment involves surgical debridement and antifungal therapy. GIFRS occurs in immunocompetent individuals and is manifested by a slow-growing mass in the sinuses with possible extension into the orbit and/or brain. *Aspergillus flavus* is the most common fungus isolated. Treatment involves surgical debridement and antifungal therapy.

In 1999, Ponikau et al. cultured commonly encountered airborne fungi from nasal washings in 96% of 210 patients with <25% incidence of Type I hypersensitivity and proposed the term ‘eosinophilic fungal rhinosinusitis’ (EFRS) to highlight the role of eosinophils rather than a true IgE-mediated allergic process.[19] However, they also cultured airborne fungi from 100% of their health volunteers, confirming the ubiquitous nature of fungi. Cody et al. used the term ‘AFS-like syndrome’ to describe cases of sinusitis that had histopathological evidence of characteristic allergic mucin without the presence of fungal hyphae or cultures positive for fungi.[20] In 2000, Ferguson et al. proposed the term ‘eosinophilic mucin rhinosinusitis’ (EMRS) to describe the condition where eosinophilic mucin is present in the absence of fungi.[21] Differences between AFRS and EMRS have been summarized in Table 4. [21–23] Whether EMRS is truly a distinct clinical entity is still a matter of debate, and it is speculated that EMRS and AFRS may be differing manifestations of the same pathophysiological process.[14]

Table 2. Classification of noninvasive fungal rhinosinusitis.

Types	Local fungal colonization	Fungal ball	AFRS
Demographic	Any individual	Middle aged or elderly, nonatopic females	Young patients, Southern United States, India
Predisposing factors	Prior sinus surgery, impaired mucociliary clearance	Impaired mucociliary clearance	Genetics, geography, low socioeconomic status, atopy, structural abnormalities, breach in innate immunity
Clinical symptoms	Asymptomatic or malodorous nasal discharge	Purulent nasal discharge, facial pain, nasal obstruction, postnasal discharge, cacosmia. May present in an asymptomatic patient.	Thick, tenacious, peanut butter-like nasal discharge
Exam/diagnosis	Macroscopically visualized colonization of nasal mucosa	Mucopurulent cheesy material within sinus cavity	'Eosinophilic mucin' and in severe cases: facial deformity, hypertelorism, proptosis
Microscopy	Not routinely performed	GMS stains may show fungal hyphae, inflammatory infiltrate with lymphocytes, plasma cells, and mast cells with no evidence of tissue invasion.	Allergic mucin, prominent eosinophils, necrotic cellular debris, Charcot-Leyden crystals, fungal hyphae without evidence of tissue invasion
Imaging	Usually normal	CT: heterogeneous opacities within sinus cavity, punctate calcifications within hyphal masses MRI: Central hypointensity on T1- and T2-weighted images, signal void on T2	CT: Hyperattenuating allergic mucin Bone expansion with thinning of bony walls MRI: Central hypointensity on T1- and T2-weighted images, signal void on T2 scans
Immune status	Immunocompetent	Immunocompetent	Immunocompetent
Fungi	Ubiquitous fungi	<i>Aspergillus</i> (most common), <i>Pseudallescheria boydii</i> , <i>Alternaria</i>	<i>Aspergillus</i> , <i>Demitaceous molds</i> (<i>Alternaria</i> , <i>Bipolaris</i> , <i>Curvularia</i>), <i>Hyaline Molds</i> (<i>Paecilomyces</i> , <i>Fusarium</i> , <i>Scedosporium</i>)
Treatment	Endoscopic removal, sinus rinses	Endoscopic removal	Surgical debridement + systemic corticosteroids + nasal rinses ± allergen immunotherapy
Prognosis	Good, curable	Curable, low recurrence rate	Controllable with therapy, may recur

Abbreviations: AFRS, allergic fungal rhinosinusitis; CT, computerized tomography.

Table 3. Classification of invasive fungal rhinosinusitis.

Types	AIFRS	CIFRS	GIFRS
Demographic	Immunosuppressed, critically ill individuals	Mildly immunosuppressed, otherwise well appearing patients	Common in the Indian subcontinent, Middle East, and parts of Africa. Few cases in the United States.
Predisposing factors	Patients with poorly controlled diabetes or severe neutropenia	Poorly controlled diabetes, chronic oral corticosteroid use	Unknown
Clinical symptoms	Painless, necrotic nasal septal ulcer, fulminant sinusitis, fever, facial pain, epistaxis, rapid orbital and intracranial spread leading to death.	Slow indolent course with fevers, facial pain, epistaxis, nasal polyps. Erosion of cribriform plate, chronic headaches, altered mental status, focal neurological deficits. Erosion of skull base, cranial neuropathies	Slow-growing mass with possible orbital or intracranial extension. Fever, cough, nasal crusting. Altered mental status with intracranial extension.
Exam/diagnosis	Endoscopic exam: edema, necrotic tissue, black eschar	Endoscopic evaluation: polypoid mucosa, soft-tissue masses	Soft-tissue mass, aka primary paranasal granuloma
Microscopy	Hyphal angioinvasion, hemorrhage, tissue infarction, neutrophilic infiltrates	Dense accumulation of fungal hyphae, occasional angioinvasion	Noncaseating granulomas, dense fibrosis, Langerhans giant cells, plasma cells, vasculitis, sparse hyphae.
Imaging	CT: hypoattenuating mucosal thickening, soft-tissue attenuation within sinus lumen. Aggressive bone destruction. MRI: Obliteration of periantral fat, Leptomeningeal enhancement, hypotense granulomas on T1- and T2-weighted images.	CT: mass-like soft-tissue collection MRI: decreased signal intensities on T1- and T2-weighted images. Sclerotic changes in bony walls.	Similar to CIFRS
Immune status	Immunosuppressed	Immunocompetent or low-level immune suppression	Immunocompetent
Fungi	In diabetes: <i>Zygomycetes</i> (<i>Rhizopus</i> , <i>Mucor</i> , <i>Rhizomucor</i> , <i>Absidia</i>) In neutropenic patients: <i>Aspergillus</i>	<i>Mucor</i> , <i>Rhizopus</i> , <i>Penicillium</i> , <i>Aspergillus</i> , <i>Bipolaris</i> , <i>Candida</i>	<i>Aspergillus flavus</i>
Treatment	Aggressive surgical debridement + systemic antifungals + immune reconstitution	Surgical debridement + systemic antifungals + immune reconstitution if immunosuppressed	Surgical debridement + systemic antifungals
Prognosis	High morbidity and mortality	Better prognosis than AFRS, but still potentially lethal	Fair if limited to sinus, but high relapse rate. Poor prognosis with intracranial involvement.

Abbreviations: AIFRS, acute invasive fungal rhinosinusitis; CIFRS, chronic invasive fungal rhinosinusitis; GIFRS, granulomatous invasive fungal rhinosinusitis.

It is also important to differentiate AFRS from the more commonly encountered chronic rhinosinusitis with nasal polyps (CRSwNP), formerly termed 'chronic hypertrophic rhinosinusitis'. In contrast to patients with AFRS, patients with

CRSwNP are predominantly older at the time of diagnosis, nonatopic, Caucasian, have higher per capita income, lower quantitative serum IgE levels, and lower Lund-Mackay scores (LMSs) (please see section on diagnostic criteria and disease

Table 4. Differentiation of allergic fungal rhinosinusitis from eosinophilic mucin rhinosinusitis.

Factor	AFRS	EMRS
Age at diagnosis	Younger patients	Older patients
Nasal obstruction	Very common (almost 100%)	Less common (1/3rd of cases)
Laterality	May be unilateral or bilateral disease	Bilateral disease more common (90–100% of cases)
Orbital involvement at diagnosis	More common. Lamina papyracea more commonly involved	Less common. Lamina papyracea less commonly involved.
Total serum IgE	Elevated	Low or normal
Histology of fungi	Allergic mucin with fungal hyphae or positive fungal cultures	Allergic mucin without fungal hyphae. Negative fungal cultures
Gene expression	Genes for Cathepsin B, sialyltransferase 1, GM2 ganglioside activator protein, and S100 calcium-binding protein not expressed	Genes for Cathepsin B, sialyltransferase 1, GM2 ganglioside activator protein, and S100 calcium binding protein expressed

Abbreviations: AFRS, allergic fungal rhinosinusitis; EMRS, eosinophilic mucin rhinosinusitis.

staging).[24] While patients with CRSwNP have thick nasal discharge, the nasal discharge in patients with CRSwNP is much thicker with a ‘peanut butter-like consistency’.[13] *Alternaria* and *Cladosporium* are the most common molds in CRSwNP, while *Bipolaris* and *Aspergillus* are the most common molds in AFS. There are also prominent differences in imaging, as patients with AFRS show a greater degree of sinus opacification with central hyperattenuation due allergic mucin. In a study by Hutcherson et al., patients with AFRS were found to have higher mean total serum IgE levels, anti-*Alternaria* IgG antibodies, incidence of atopy, and number and intensity of IgE antifungal bands on immunoblotting.^{*A} Human leukocyte antigen (HLA) studies indicate that *DQB1*0301* and **0302* are much more prominent in AFRS as compared to CRSwNP.[25] Salient differentiating factors between AFRS and CRSwNP are summarized in Table 5.[13]

Epidemiology

A variety of factors predispose individuals to develop AFRS. Warm and humid areas are a hub for AFRS, indicating a

geographic predisposition for the disease. In the United States, the southern and central regions seem to have an increased incidence, particularly along the Mississippi basin.[26] This region is sometimes referred to as the ‘I-35 corridor’ of AFRS, I-35 being the interstate that starts in Laredo, Texas, and stretches through Oklahoma, Kansas, Missouri, Iowa, and Minnesota.[26] Studies from India indicate that AFRS may account for 56–63% of all cases of fungal sinusitis.[27,28] While dematiaceous fungi (melanin-producing fungi, especially those of the genera *Bipolaris* and *Curvularia*) are the common etiological agents for AFRS in the United States,[29–32] *Aspergillus* is the most common causative species in India, accounting for up to 96% of all AFRS cases.[27,28] Patients with AFRS are typically atopic with elevated total IgE levels and specific IgE to fungi. AFRS is more common in young African American males,[24] with complications such as bony erosion also being more common in this cohort.[33–36] AFRS is also more common in uninsured, poorer populations with lesser access to health care.[24,37] Compared with CRSwNP, patients with AFRS have higher markers of disease, including higher LMSs (please see section on diagnostic criteria and disease staging).[24] Host genetics also seem to be an important predisposing factor in the development of AFRS. Patients with AFRS and CRSwNP both carry *HLA-DQB1*03* alleles as a significant risk factor for disease. However, AFRS has a higher association, with *HLA-DQB1*0301* and *HLA-DQB1*0302* being the most frequent allelic variants.[25] However, a routine genetic analysis is not recommended currently, as the precise role of genetics in the pathophysiology of the disease has not been defined.[15] A summary of the pathophysiology of AFRS is depicted in Figure 1.

Diagnosis

The diagnosis of AFRS should be suspected in any patient with symptoms of chronic rhinosinusitis that is recalcitrant to conventional medical therapy, especially in the absence of any evidence of immune suppression. A precise diagnosis is made with an overall consideration of clinical features, microscopic examination, or culture of nasal discharge, imaging, and immune studies.

Clinical features

AFRS is typically a disease of atopic, immunocompetent young adults (Table 2). While it does affect adolescents, it is less common in young children.[38] Patients present with symptoms of chronic rhinosinusitis refractory to conventional medical therapy, almost always with concomitant nasal polyps. The nasal discharge from these patients generally has a thick, greenish-brown mucoid appearance with a ‘peanut butter’-like consistency along with green to black rubbery nasal plugs.[13] Severely neglected cases may also develop visual disturbances,[39,40] proptosis,[32] hypertelorism, facial deformity, and sometimes even intracranial sequelae such as pressure-induced intracranial neuropathies [41] or intracranial abscess.[42] The incidence of bony erosion in AFRS has been estimated to be between 20% and 90%.[29,31,33,43] This seems to be more common in patients who are younger, African American, and have higher LMSs, with no gender predisposition.[33] The orbit, specifically the lamina papyracea,

Table 5. Differentiation of AFRS from chronic rhinosinusitis with nasal polyps.

Factor	AFRS	CRSwNP
Secretions	Ultra-thick, peanut butter-like	Thick
Lund-MacKay scores	Higher	Lower
Imaging	Opacification with hyperdense areas	Opacification
Organisms involved	<i>Bipolaris</i> and <i>Aspergillus</i>	<i>Alternaria</i> , <i>Cladosporium</i>
Immune status	Atopic	Nonatopic
Serum IgE	Elevated	Normal
Allergy skin tests	Positive	Negative
Immunoblotting	Numerous IgE antifungal bands	Rare IgE antifungal bands
Predominant immune response	IgE	IgG
HLA	<i>DQB1*0301</i> and <i>*0302</i>	<i>DQB1*0301</i> and <i>*0302</i> less prominent

Abbreviations: AFRS, allergic fungal rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps.

Adapted with permission from Dr. Raymond Slavin [13]

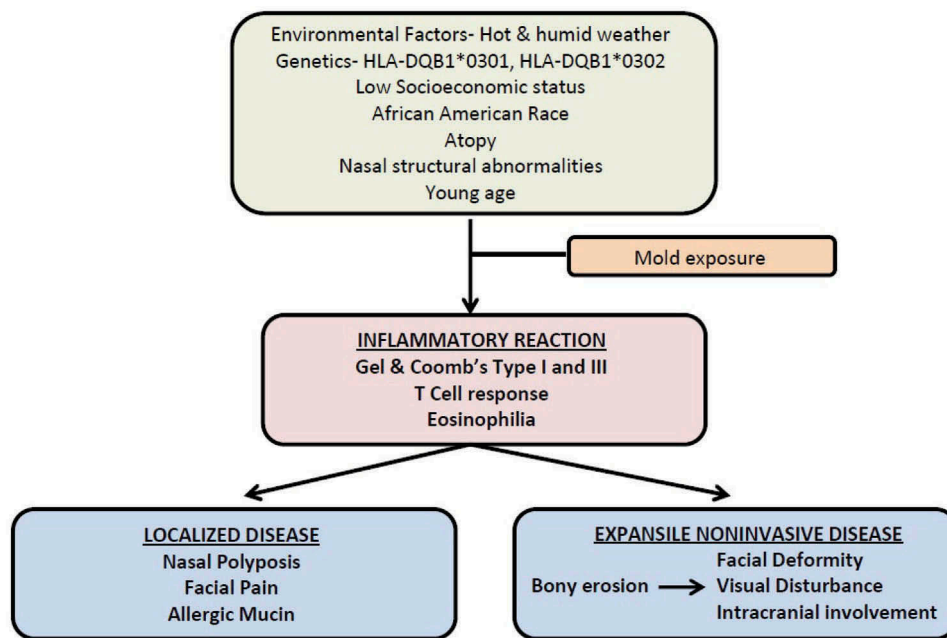


Figure 1. Pathophysiology of allergic fungal rhinosinusitis (AFRS) including predisposing factors, inflammatory reaction and development of disease.

is the most common site of extension, [29,33] and the anterior cranial fossa is the most commonly involved intracranial space. [29] However, it is important to note that in patients with bony erosion, no histological evidence of mucosal invasion by fungi has been demonstrated.[29] Therefore, tissue invasion by fungi is not the causative mechanism of bone erosion in AFRS. Sinus expansion by polyposis with resultant pressure atrophy and the action of inflammatory mediators have been hypothesized as possible mechanisms,[29] but direct evidence is lacking.

Microscopic examination and fungi

Microscopic examination of this discharge shows the characteristic appearance of 'allergic mucin' with prominent eosinophils, necrotic cellular debris, Charcot-Leyden crystals, fungal hyphae without evidence of tissue invasion, and a background of amorphous, eosinophilic mucin.[10,13] Hematoxylin and eosin (H&E) stains show a mixed inflammatory infiltrate composed of eosinophils, plasma cells, and lymphocytes, and sometimes show fungal elements and calcifications. Gomori methamine silver (GMS) or Fontana Mason stains may detect fungal hyphae when they are sparse and hard to identify on H&E staining.[15,22,32,44]

Depending on the technique used for fungal culture from allergic mucin, the yield of fungal cultures in AFRS can vary greatly from 10% to 93%.[15,44,45] It must be remembered that fungi are abundant in ambient air, and the growth of fungi in cultures alone is not diagnostic of AFRS in the absence of clinical, imaging, and immune criteria, as it may represent saprophytic contamination.

Immunologic studies

Immune studies are useful in the diagnosis of AFRS. With a history of atopy, patients with AFRS often present with high levels of IgE, although not as high as those with ABPA.

Patients with AFRS demonstrate type I IgE hypersensitivity to fungi as well as other aeroallergens.[15] In the evaluation of mold allergy, skin testing has a higher positive rate of detection than ImmunoCAP and is considered the gold standard.[46] ImmunoCAP testing has been found to have a higher specificity and negative predictive value (NPV) as compared to sensitivity and positive predictive value (PPV), when compared to skin prick test (SPT).[47] Also, patients with elevated total IgE have more positive ImmunoCAP results that usually outnumber the positive SPT results, a finding that needs to be interpreted with caution.[47] Stewart et al. showed that among patients with polypoid rhinosinusitis, patients with AFS had specific IgE elevations to an average of five molds versus only 0.1 in those without AFS.[44] They proposed that the presence of specific IgE (sIgE) to multiple fungi in the setting of an elevated total IgE is a good way of differentiating patients with AFRS from those with non-AFRS CRS. Fungal-specific IgG (sIgG) levels were elevated in all groups of polypoid rhinosinusitis, and the usefulness of this test is uncertain. Hutcherson et al. showed that patients with AFRS have a higher number and intensity of IgE antifungal bands on immunoblotting in comparison to patients with CRSwNP.[48] Fungal-specific precipitins may be present, albeit inconsistently, in patients with AFRS. Waxman et al. reported the presence of serum precipitins in 85% of patients with AFRS.[49]

Imaging studies

Zinreich et al. proposed that the demonstration of increased attenuation in paranasal sinus soft-tissue masses on computed tomography (CT) scan is highly suggestive of fungal sinusitis, while pointing out that MRI is more specific than CT to confirm this finding.[35] This increased attenuation has been described as central, 'serpiginous', or having a 'starry sky' appearance. [50] CT scans of the sinuses in AFRS typically show near-

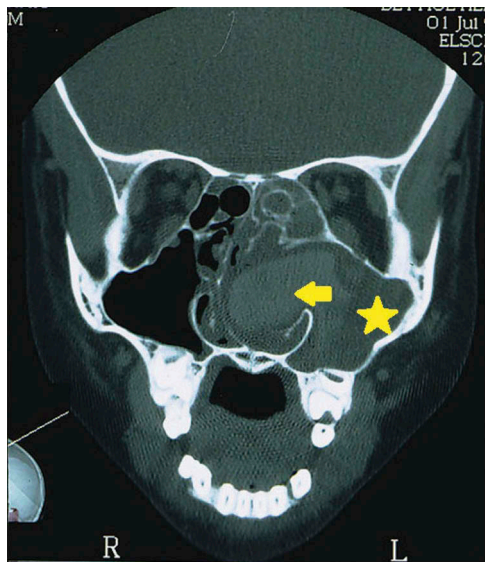


Figure 2. CT scan in allergic fungal rhinosinusitis (AFRS) showing complete opacification of the left maxillary sinus (star) with central hyperattenuation (arrow).

complete opacification with heterogenous radiodensity of the soft tissue of the sinuses, as seen in [Figure 2](#).^[15] The increased radiodensity seen in fungal sinusitis is not restricted to *Aspergillus* species.^[30]

MRI findings are more specific than CT and typically show central hypointensity on T1- and T2-weighted images, although this is a more consistent finding with T2-weighted images than T1-weighted images.^[16,50] Zinreich et al. postulated that decreased signal intensity seen on T1- and T2-weighted MRI images of fungal sinusitis could be secondary to ferromagnetic elements.^[35] Subsequent studies have also suggested that the signal void on T2 scans is seen due to high protein and low free water content in allergic mucin along with the presence of calcium, air, and paramagnetic metals such as iron, magnesium, and manganese.^[16,50] The mucosal lining of the sinuses is hypointense on T1-weighted images and hyperintense on T2-weighted images, with enhancement after administration of intravenous gadolinium contrast.^[16] In severely neglected cases, signs of orbital and/or intracranial extension may be seen.

Diagnostic criteria and disease staging

In 1977, Rosenberg et al. had proposed the clinical and immunological criteria for the diagnosis of ABPA, which included immediate skin reactivity and presence of precipitin antibodies to the *Aspergillus* antigen.^[51] In 1993, Loury et al. proposed analogous diagnostic criteria for AFRS, bearing in mind that the clinical picture of AFRS was not limited to *Aspergillus* as a causative pathogen.^[52] They listed the presence of eosinophilia, immediate skin reactivity to fungal antigens, precipitin antibodies (IgG) to fungal antigens, elevated total IgE, nasal obstruction, characteristic CT or MRI imaging findings, and confirmatory pathology of allergic mucin as the diagnostic criteria. In 1994, Cody et al. minimized the diagnostic criteria by suggesting that the presence of characteristic allergic mucin with fungal hyphae or cultures positive for fungi was sufficient to make a diagnosis of AFS.^[20] Although they did evaluate

parameters such as serum eosinophils, serum-specific IgE levels, and radiological findings, they did not consider these vital for diagnosis. In 1995, deShazo and Swain proposed diagnostic criteria that encompassed the presence of sinusitis on X-ray, visual or histopathological identification of allergic mucin, demonstration of fungal elements in nasal/sinus discharge by stain or culture, absence of immune suppression, and absence of invasive fungal disease.^[30] Saravanan et al. have proposed that only four features be used to distinguish AFRS from other entities such as EMRS ([Table 4](#)): type I hypersensitivity to fungi, CT findings of bone erosion, heterogenous opacification and sinus expansion, presence of allergic mucin with Charcot-Leyden crystals, and the demonstration of fungi on direct microscopy.^[53] However, the criteria proposed by Bent and Kuhn in 1994 remain the most popular set of criteria for the diagnosis of AFS and are summarized in [Table 6](#).^[43] These include nasal polyposis, presence of fungi on direct microscopy or sinus culture taken during surgery, eosinophilic mucin without fungal invasion into sinus tissue, IgE hypersensitivity to fungi demonstrated by skin testing or in vitro testing, and characteristic CT findings of sinus expansion or heterogenous opacification.

Few modalities of disease staging have been proposed in the medical literature. In 1996, Kupferberg and Bent proposed a postoperative endoscopic staging system to classify patients into stage 0 (disease free), stage I (allergic mucin and mucosal edema), stage II (allergic mucin and polypoid edema), and stage III (nasal polyps and/or fungal debris).^[38] The LMS was proposed in the early 1990s, and in 1997, the American Academy of Otorhinolaryngology and Head & Neck Surgery recommended the LMS as a means of disease staging of rhinosinusitis.^[54–56] Although the original LMS contained symptom, surgery, and endoscopy scores, it is the radiological scoring system that has remained popular.^[57] The LMS scores each sinus cavity (maxillary, frontal, sphenoid, anterior ethmoid, and posterior ethmoid), based on opacification as visualized on CT scan, as 0 (no abnormality), 1 (partial opacification), or 2 (complete opacification). Since it is difficult to apply this grading system to the osteomeatal complex, disease affecting this complex is graded as 0 (no obstruction) or 2 (obstructed). Using this scoring system, the total combined score for all sinus cavities ranges from 0 to 24. This scoring system has gained popularity as it does not require radiological training and is very well defined, leading to high inter-observer reliability.^[57] To avoid complexity, the absence of a sinus cavity is scored as a 0 in the LMS system. Acknowledging that partial opacification needs to be further stratified and that the absence of sphenoid and frontal sinuses in young children may lead to reduced score amplitudes in children, Araujo Neto et al. proposed a system based on opacification percentages, which they called the opacification/development ratio (ODR).^[56] However, the LMS remains the most

Table 6. Bent and Kuhn diagnostic criteria of allergic fungal rhinosinusitis.

Nasal polyposis
Presence of fungi on direct microscopy or sinus culture taken during surgery
Eosinophilic mucin without fungal invasion into sinus tissue
Type I hypersensitivity to fungi demonstrated by skin testing or in vitro testing
Characteristic CT findings – Sinus expansion or heterogenous opacification

widely used score for staging rhinosinusitis. In 2009, Wise et al. proposed a radiological staging system for the disease severity of AFRS.[34] Since the preexistent Lund-MacKay scoring system did not address bone erosion or sinus expansion, they scored expansion or erosion seen on non-contrast thin-cut axial and coronal CT scans for each of the sinuses and devised a scoring system with a maximum score of 24 points. They proposed this scoring system as a rapid tool to stratify disease severity in patients with AFRS with bone remodeling.

Treatment

Current recommendations support surgical intervention followed by adjuvant medical therapy. Functional endoscopic sinus surgery (FESS) is the intervention of choice in the early surgical management of AFRS.[58] While tissue preservation to ensure normal mucociliary clearance would be ideal, debridement of all allergic mucin and fungal debris is extremely important, as incomplete clearance has been linked to early recurrence of the disease.[58]

Adjuvant medical therapy is an integral part of the treatment of AFRS. Systemic steroids help decrease sinomucosal edema and cause regression of polyps by reducing the inflammatory response. They could be beneficial preoperatively by decreasing symptoms of mechanical obstruction and augmenting visualization of sinonasal anatomy during FESS.[58] Many studies have shown that postoperative oral corticosteroids are beneficial, especially in preventing recurrence.[59,60] Using a modified corticosteroid treatment regimen adapted from ABPA literature, Schubert and Goetz reported that patients undergoing as little as 2 months of corticosteroid therapy post-surgery had significant clinical improvement for up to 12 months, with patients undergoing 12 months of therapy faring the best clinically. Kupferberg et al. showed that patients who received postoperative systemic corticosteroid therapy could be maintained in lower stages of the disease (stages 0 and I).[61] Some authors are proponents of the use of topical corticosteroids such as budesonide sinonasal rinses after completion of oral corticosteroid taper in order to prevent recurrence.[58,62]

The use of antifungals in AFRS has had mixed results, with few studies showing benefit. While a Cochrane review showed no benefit of using oral or topical antifungals in treating CRS,[63] there have been reports supporting the use of oral antifungals in remittent or refractory AFRS.[64] In a recent study, Patro et al. reported that the preoperative use of itraconazole for 1 month prior to surgery was associated with decreased SNOT 20 scores, LMSs, Kupferberg nasal endoscopic grades, polyp size, hyperdensities on CT imaging, and postoperative fungal cultures in patients with AFRS as compared to controls.[65] This corroborated the findings from other studies pertaining to the use of itraconazole in the treatment of ABPA.[66] There remains insufficient evidence to support the use of topical antifungals in the treatment of AFRS.[62]

There has been evidence supporting the use of allergen immunotherapy (AIT) in AFRS. Mabry et al. have published outcomes after 3 years of immunotherapy for AFS, which show a benefit with use of AIT as an adjunct to standard therapy.[67–69] In their study, patients on AIT for relevant molds had a decrease in polyp recurrence, nasal crusting,

decreased allergic mucin, and decreased need for systemic steroids, without the development of any severe adverse reactions. AIT did not decrease the levels of fungal IgE. After discontinuation of AIT, none of the patients had recurrence of polyps or allergic mucin, even 7–17 months after cessation of AIT. Folker et al. reported that patients with AFS receiving subcutaneous immunotherapy (SCIT) had improvement in endoscopic disease staging and required decreased systemic corticosteroids.[70] Bassichis et al. showed that the addition of AIT to standard postoperative management led to decreased office visits for medical intervention and decreased re-operation rates.[71] Greenhaw et al. studied the safety of high-dose fungal SCIT in 14 patients with AFS and did not find an increased risk of immediate local or large local reactions, delayed local reactions, or the need for dose adjustments.[72] In a recent study by Melzer et al., sublingual immunotherapy (SLIT) therapy in patients with AFRS was shown to decrease subjective complaints, physical findings, Lund-McKay scores, and serum IgE levels. Patients in this study did not experience any major side effects secondary to SLIT therapy, suggesting that SLIT may be a useful adjunct in the treatment of AFRS.[73]

Some other modalities have been studied as possible adjuvant therapies in AFRS. There is one case report of successful postoperative treatment of AFRS with a leukotriene receptor antagonist (LTRA), montelukast 10 mg daily, as an adjuvant to intranasal corticosteroids.[74] There is also one case report of successful treatment of AFRS refractory to FESS and systemic corticosteroids with omalizumab.[75] Controlled studies are lacking to support the use of LTRA or omalizumab in the treatment of AFRS.

Prognosis

AFRS is often a chronic, recurrent disease. Waxman et al. divided patients after surgery, based on prognosis, into three groups: those that were cured, those who had recurrence within months, and those who had delayed recurrence in years.[49] The tendency for recurrent disease could be reduced with postsurgical oral steroid therapy. Schubert and Goetz reported that an increase in total serum IgE of 10% or more in patients with AFRS after sinus surgery was 79% sensitive and 77% specific for detecting the recurrence of sinus disease and in predicting the need for recurrent sinus surgery.[59] Kupferberg et al. showed that endoscopic evidence of disease could precede clinical symptoms during periods of recurrence and recommended nasal endoscopy every 4–6 weeks for surveillance of recurrence.[38] However, in a later study by White et al. [33] SNOT 20 and endoscopy scores were inadequate markers to suggest bony erosion. The authors suggested the early use of imaging, especially in higher-risk patients, i.e. those who are younger, African American, and have higher Lund-McKay scores.

Allergic fungal diseases of the lower airway

Allergic bronchopulmonary aspergillosis

Background

ABPA was first reported in 1952 by Hinson et al. [76] while describing three patients with recurrent exacerbations due to

hypersensitization of *A. fumigatus* causing radiologic changes in the lung, blood eosinophilia, and sputum production. Since that time, other fungal species such as *Candida*, *Penicillium*, and *Curvularia* have been identified as causing symptoms similar to ABPA.[77,78] Patients who have symptoms resembling ABPA but with identification of a fungus other than *A. fumigatus* in their lungs are classified as having allergic bronchopulmonary mycoses (ABPM).[77–79] Chowdhary et al. reviewed 143 cases worldwide of ABPM and found that *Candida albicans* is the most common fungus causing ABPM seen in 60% of the cases. Of note, 70% of the cases from the review with ABPM did not have asthma, which is a clear distinction from ABPA.[80]

Aspergillus is a fungus prevalent in the environment commonly found in decaying matter. It is located throughout the world and is ubiquitous in the Midwest and on the East coast of the United States.[81] Its small fungal spores (conidia), 2.5–3.5 µm in size, allow it to be inhaled and get deposited into the lungs (Figure 3A–C).[79] In normal healthy lungs, the fungal spores are able to be cleared and do not cause symptoms. However, if the conidia are deposited into lung parenchyma in patients with asthma or cystic fibrosis (CF), then they can survive and proliferate (Figure 3C). Airway remodeling, poor ciliary clearance, and an increase in mucus production, which are seen in patients with CF and asthma, allow *Aspergillus* to more readily germinate and produce hyphae. The hyphae cause disruption to the epithelial cells and initiate a predominant helper T cell type 2 (Th2) inflammatory response.[79,81–85] This response produces an increase in interleukin-4 (IL-4), IL-5, IL-13, IgE, and the recruitment of inflammatory cells, especially eosinophils.[83,86,87] It is estimated that ABPA affects approximately 2% of asthmatic patients and 7–15% of patients with CF, though the exact prevalence is unknown and likely underreported as ABPA is often overlooked as a diagnosis in these patients.[81,88–90] Maturu and Agarwal performed a meta-analysis of *Aspergillus* sensitization and ABPA in CF patients.[91] Children and adults had similar prevalence of sensitization at approximately 39.1%, while adults had higher prevalence of ABPA at 8.9%. This supports that sensitization occurs early in life for CF patients and may progress to ABPA later in their life. However, not all patients with asthma or CF develop ABPA, and the exact mechanism is still unclear. It usually occurs in patients during their third or fourth decade of life, though many cases have been identified in the pediatric population.[92–96] There is some emerging evidence showing that males may be more susceptible to developing ABPA compared to females, as noted in recent study by Singh et al. [93]

Genetic risks of ABPA

Various genetic risk factors have been shown to increase the predisposition for development of ABPA. In 2011, these were reviewed by Knutsen and Slavin and are outlined in Table 7. [81] human leukocyte antigen - antigen D related (*HLA-DR*) restriction has been shown to be a risk factor for the development of ABPA. Asthmatic patients with *HLA-DR2* and/or *DR5* who lacked *HLA-DQ2* were at increased risk for ABPA after exposure to *A. fumigatus*. [97–99] There are restricted genotypes within *HLA-DR2* and *HLA-DR5*. In particular, *HLA-DR2*

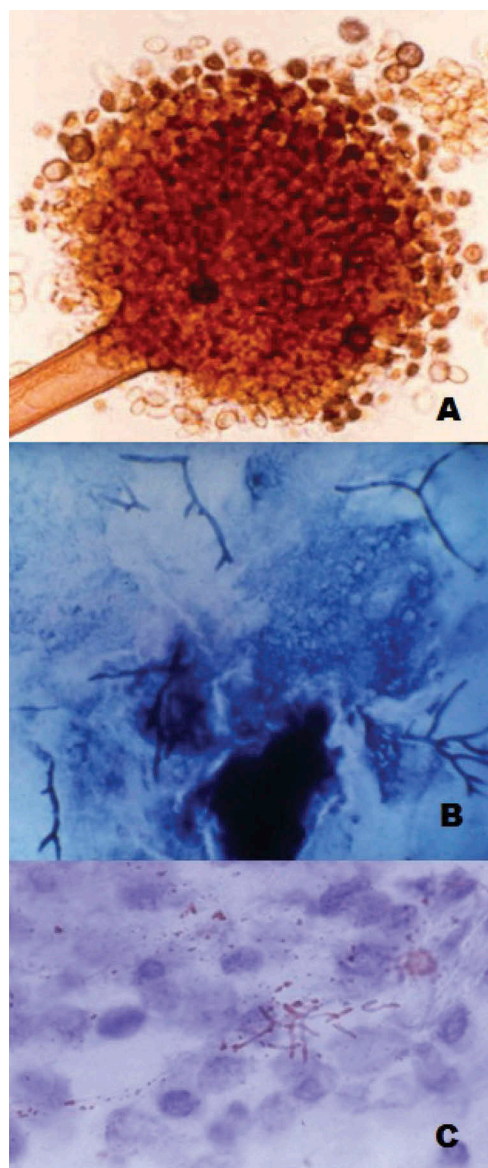


Figure 3. *Aspergillus fumigatus* conidia (A). *Aspergillus fumigatus* hyphae in sputum (B) and fragment of hyphae in the pulmonary interstitium (C) from a patient with allergic bronchopulmonary aspergillosis.

*HLA-DRB1*1501* and *HLA-DRB1*1503* genotypes were reported to provide high relative risk. However, 40–44% of non-ABPA atopic *Aspergillus*-sensitive individuals have the *HLA-DR2* and/or *DR5* type. Further studies indicated that the presence of *HLA-DQ2*, especially *DQB1*0201*, provided protection from the development of ABPA. Another potential risk factor may be gain-of-function in the IL-4RA subunit, which may be responsible for B-cell hyperreactivity in ABPA. In studies by Knutsen et al., the presence of the *VAL75* allele, located within the IL-4 binding region, was found in 80% of the ABPA subjects examined.[100] Although the *VAL75* allele appears to be common in the general population, its high prevalence in ABPA suggests that it may be a risk factor in the development of the disease. The *–1082GG* genotype of the IL-10 promoter is associated with colonization of *A. fumigatus* and the development of ABPA in patients with CF.[101] The *–1082GG* polymorphism has been associated with increased IL-10 synthesis; whereas

Table 7. Genetic risk factors in the development of allergic bronchopulmonary aspergillosis.

HLA-DR restriction and HLA-DQ protection
HLA-DR2: HLA-DRB1*1501 and *HLA-DRB1*1503
HLA-DR5
HLA-DQ2 protective, decreased in ABPA
DQB1*0201
IL-4RA polymorphisms
IL-4RA ile75val
IL-10 polymorphisms
Promoter -1082 GG genotype
Surfactant protein A2 (SP-A2) polymorphisms
SP-A2 ala91pro
Cystic fibrosis transmembrane conductance regulator (CFTR) mutations
Heterozygous CFTR mutations in asthmatic patients with ABPA
Toll-like receptor (TLR) polymorphisms
TLR9 T-1237C

Abbreviations: HLA, human leukocyte antigen; IL, interleukin

the -1082A allele has lower IL-10 synthesis. Polymorphisms (ALA91PRO, ARG94ARG) in the collagen region of pulmonary surfactant protein A2 (SP-A2) have been reported in ABPA patients, and these subjects had more elevated total IgE levels and higher percentages of eosinophilia than observed in those patients who lacked the polymorphisms.[102] CF transmembrane conductance regulator (CFTR) gene mutations were found to be at a higher frequency in asthmatic patients who developed ABPA, 6 of 21 (28.5%), versus control asthmatics, 2 of 43 (4.6%).[103] These ABPA patients were heterozygous for the mutations (one patient was compound heterozygote and reclassified as atypical CF), did not have a clinical diagnosis of CF, and had sweat chlorides <60 mEq/L. In a meta-analysis performed by Agarwal et al., they also noted a higher incidence of CFTR mutations in ABPA patients compared to a control group or those with asthma.[104] It is postulated that there may be an association between ABPA severity and the presence of CFTR mutations. ABPA patients have increased frequency of allele C for the toll-like receptor 9 (TLR9) T-1237C polymorphism compared to control patients.[105] TLR-9 is a receptor that recognizes CpG motifs prevalent in bacterial and viral DNA. *Aspergillus* hyphae and conidia do signal through TLR-9 on murine neutrophils.[106] The TLR9C allele of T-1237C results in decreased expression.[107] Thus, decreased TLR-9 protective function may be an underlying susceptibility in the development of ABPA. However, in patients with severe asthma associated with fungal sensitivity (SAFS) who are predominantly *Aspergillus*-sensitive, there was no association of polymorphisms of TLR2, TLR4, or TLR9.[105]

Clinical presentation

ABPA usually presents exclusively in patients with asthma or CF; however, it can occur in patients with other structural lung diseases as well. There are suggestions that ABPA may occur in patients with chronic obstructive pulmonary disease (COPD). [108,109] A prospective case-control study by Agarwal et al. evaluated *Aspergillus* hypersensitivity in patients with COPD, which was demonstrated in 8.5% of the patients, and 1% of the patients met the criteria for ABPA.[108] Patients with ABPA have worsening lung function usually associated with wheeze and productive cough with thick brown sputum.[51,77,79]

Patients may also have other constitutional symptoms such as fever and generalized fatigue.[51,79,110]

Dhooria et al. demonstrated, through a prospective case-control study of patients with pulmonary tuberculosis (PTB), that the prevalence of *Aspergillus* sensitization was 32%.[111] This is similar to the prevalence noted in patients with asthma. They found a statistically significant relationship between those with airflow obstruction on spirometry and *Aspergillus* sensitization ($p = 0.01$). It is unclear if *Aspergillus* sensitization actually affects their airway disease. Patients with PTB and recurrence of respiratory symptoms are often treated empirically for relapse of the disease process despite negative acid-fast bacilli sputum studies. This subset of patients may warrant an evaluation for *Aspergillus* as the cause of their symptoms.

Case reports of ABPA have also been described in patients with Kartagener syndrome.[112] This is a rare primary ciliary dyskinesia disorder associated with dextrocardia, bronchiectasis, and chronic sinusitis. It is recommended that these patients be evaluated for *Aspergillus* sensitization routinely and especially if they have worsening of their disease to possibly decrease further bronchiectasis, which is inevitable in these patients.

Diagnosis

Rosenberg et al. [51] defined criteria in 1977 for diagnosing ABPA in patients. Since that time, the criteria have been modified; however, there are no defined international criteria for this disease. The minimum criteria (Table 8) for the diagnosis of ABPA, which were documented in *The Journal of Allergy and Clinical Immunology* 2012 review, article consisted of (1) worsening lung function in patients with asthma or CF; (2) positive SPT with *A. fumigatus*; (3) total serum IgE greater than 1000 ng/mL (416 IU/mL); (4) increased antibodies to *Aspergillus* species-specific IgE and IgG; and (5) infiltrates noted on chest radiography.[77] Additional criteria for the diagnosis of ABPA include increase in serum eosinophilia when patient is not on corticosteroids, *Aspergillus* species-specific precipitating antibodies, central bronchiectasis, and *Aspergillus* species-specific containing mucus plugs (Table 8). [77,83,84,86,87] In 2013, the International Society for Human and Animal Mycology (ISHAM) proposed new criteria for diagnosis to simplify the clinical evaluation of patients.[113] The ISHAM diagnostic criteria consist of (1) bronchial asthma or CF; (2) positive SPT with *A. fumigatus* or elevated *Aspergillus* species-specific IgE levels; (3) total IgE levels >1000 IU/mL (or

Table 8. Diagnostic criteria of allergic bronchopulmonary aspergillosis in asthmatics and cystic fibrosis.

Minimum criteria
Patients with asthma or cystic fibrosis
Worsening lung function
Positive skin prick test with <i>Aspergillus</i> species
Total serum IgE greater than 1000 ng/mL (416 IU/mL)
Increased <i>Aspergillus</i> species-specific IgE and IgG antibodies
Infiltrates noted on chest radiography
Additional criteria
Increase in serum eosinophilia when patient is not on corticosteroids (>400 eosinophils/ μ L)
<i>Aspergillus</i> species-specific precipitating antibodies
Central bronchiectasis
<i>Aspergillus</i> species-specific containing mucus plugs

<1000 IU/mL if all other criteria are met) and at least two of the following three criteria (a) precipitating or IgG antibodies against *A. fumigatus* in serum, (b) radiographic pulmonary opacities consistent with ABPA (transient or permanent), and (c) total eosinophil count >500 cells/ μ L in steroid-naïve patients.[113]

There are discrepancies regarding the criteria to diagnose ABPA. This can pose dilemmas in patient care and treatment as well as research outcomes. A concise diagnostic criteria algorithm would be beneficial for patients, clinicians, and researchers. Both of the currently proposed criteria include asthma and CF as required for diagnosis. This has been well established in the medical community; however, as noted previously, ABPA is also being diagnosed in patients with other underlying structural lung diseases such as COPD, PTB, and Kartagener syndrome. In the future, expanding the first criteria to include any patient with underlying structural lung disease may be warranted.

Aspergillus fumigatus sensitization can be determined either by specific serum IgE or SPT. It is recommended to assess with both tests due to the possible discordance between the two testing modalities and the importance of identifying all patients with fungal sensitization.[114,115] *Aspergillus fumigatus* SPT can be an immediate reaction (10–20 minutes) or a late reaction (4–8 hours), which occurs in about one-third of patients with ABPA.[81,116] Standardization of fungal allergens for SPT or in vitro testing needs to occur to improve disease diagnosis since it is the first step in assessing for ABPA.

Total serum IgE is an important laboratory finding for initial evaluation as well as monitoring response to treatment for ABPA. Defining the specific cut-off value of total IgE is debatable. As per the 2012 review article in *The Journal of Allergy and Clinical Immunology*, if the total serum IgE level is greater than 1000 ng/mL (417 IU/mL), then it is very suggestive of ABPA.[77,86] According to the 2013 ISHAM diagnostic criteria, the total IgE cut-off value has been increased from 417 to >1000 IU/mL to distinguish SAFS from ABPA patients.[113] However, an exception is noted in the ISHAM criteria that a diagnosis of ABPA can be made if the IgE level is <1000 IU/mL when all other criteria are met. This signifies that there are patients with ABPA who do not have significantly elevated IgE levels; nonetheless, most patients with ABPA usually have significantly elevated total serum IgE levels, often exceeding 10,000 ng/mL.[79,81] If total serum IgE levels are between 500 and 1000 ng/mL, then it is recommended to closely monitor every 6 weeks, which may warrant initiating or adjusting treatment.[79,81,116] If ABPA is suspected in patients with CF and IgE levels are 200 to 500 IU/mL, it is recommended to repeat total serum IgE levels in 1 to 3 months.[81] If the patient is taking oral steroids, then testing should be repeated once steroid treatment is complete.

Agarwal et al. evaluated the cut-off values for laboratory studies used to diagnose ABPA in patients.[117] In the study, 372 patients with asthma were identified and ABPA was diagnosed in 76 patients. They determined the cut-off values for *Aspergillus* serum IgE, total IgE, and serum eosinophils to differentiate asthma from ABPA. The best cut-off value for *Aspergillus* serum IgE was found to be 1.91 kUA/L, which had a sensitivity of 99% and a specificity of 87%. A total IgE cut-off

level of 2347 IU/mL provided a sensitivity of 87% and a specificity of 81%; whereas an eosinophil count of 507 cells/ μ L was 79% sensitive and 76% specific. However, when all three of these diagnostic tests were combined, Agarwal et al. found a specificity of 100%, which is beneficial in confirming a patient's diagnosis. Additional studies would provide validation on what tests and cut-off values are most applicable in identifying patients with ABPA so appropriate treatment and management can be initiated.

Radiologic findings may provide additional information for the diagnosis and staging of ABPA. The current diagnostic criteria regarding radiologic findings are infiltrates on chest radiography with or without central bronchiectasis. In the new proposed criteria by Agarwal et al., opacities noted on radiographic studies is a criterion that may or may not be met to classify a patient with ABPA.[113] Previous literature has described radiographic changes as large, homogenous, triangular, lobar or patchy opacifications, predominantly in the upper lobes, which are the preferred sites of colonization for *A. fumigatus*. [81] These lesions have been described as 'fleeting' since they are not always persistent on imaging and are often mistaken for pneumonia.[79] 'Tram lines' are often noted, which are indicative of inflammation of bronchial airway walls.[81] Agarwal et al. performed a prospective observational study of 60 consecutive glucocorticoid-naïve patients with ABPA who underwent both chest radiography and high-resolution CT (HRCT).[118] Their study revealed no abnormalities in 50% of the patients, and 28% had consolidations on chest radiography. Upon completion of a HRCT, the consolidations were found to be mucus-filled bronchi, which is counter to what has been previously understood. The mucus was often hypodense. This needs to be differentiated from hyperdense mucus, also known as high-attenuation mucus (HAM), which is denser than the paraspinal skeletal muscle.[118–121] These findings may not always be apparent on chest radiographic studies, so further evaluation with CT can be more revealing, including identifying any bronchiectasis or mucus plugs. [79,81,86] However, the diagnosis of ABPA should not be based on radiographic changes since patients may be diagnosed prior to developing any lung abnormalities that could be found on chest radiography or CT. Therefore, patients who do not fulfill radiologic diagnostic criteria may still have ABPA.[118]

HAM has been proposed by Agarwal et al. to be evaluated with HRCT.[119–122] Based on multiple studies, Agarwal et al. have found that the presence of HAM is pathognomonic of ABPA.[122] They have also investigated the immunologic severity of these patients with HAM. They, along with ISHAM, have proposed a change in the severity and classification based on radiographic studies as follows: mild ABPA-serologic (ABPA-S), moderate ABPA-central bronchiectasis (ABPA-CB), and severe ABPA-CB-HAM.[122] In a study of 234 patients, Agarwal et al. found 25% with normal HRCT, 76.5% with CB, 20.9% with HAM, and 11.5% with other radiologic findings.[120] It was noted that patients with CB or HAM had frequent relapses; however, those with HAM had significantly elevated immunologic markers compared to the other groups, which was correlated with more severe cases of ABPA. Of note, failure to achieve remission was associated

Table 9. Classification of allergic bronchopulmonary aspergillosis and severe asthma associated with fungal sensitivity.

Classification	Findings
ABPA-S	Meet minimum requirements of ABPA but do not have central or peripheral bronchiectasis
ABPA-CB	Meet minimum requirements of ABPA and have central or peripheral bronchiectasis
SAFS	Do not meet the minimum criteria for ABPA but have severe asthma and sensitivity to fungi

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; ABPA-S, ABPA-seropositive; ABPA-CB, ABPA- central bronchiectasis; SAFS, severe asthma associated with fungal sensitivity.

with CB, not with HAM.[119] HAM has been shown to be 100% specific in the diagnosis of ABPA.[121] Radiologic studies provide an additional tool for identifying patients with ABPA and those who are at risk for developing frequent relapses or failure to achieve remission. We must be cognizant that these radiologic tools are limited since not all patients with ABPA will have changes upon initial diagnosis.

Classification of ABPA

There are various classifications of ABPA depending on the criteria that a patient meets (Table 9). Patients with asthma who meet the minimum requirements but do not have central or peripheral bronchiectasis are classified as serologic ABPA or ABPA-seropositive (ABPA-S).[77,79,123] Patients who meet the minimum criteria for ABPA and have central bronchiectasis are classified as ABPA-CB.[77,79,123] Patients who have severe asthma and have sensitivity to fungi but do not meet the criteria for ABPA are classified as SAFS. SAFS patients have responded to antifungal medications, like itraconazole, with improvement in their symptoms.[77,79,123] It is important to identify and properly diagnose patients with ABPA so appropriate treatment and monitoring can be initiated. This is crucial to hopefully prevent worsening lung function, the development of bronchiectasis (if not present at diagnosis), and the risk of pulmonary fibrosis resulting in respiratory failure.[78,79,110]

As mentioned previously, it has been proposed to modify the current classification scheme based on studies by Agarwal et al., which defined four categories based on recent studies evaluating the utility of radiological studies in ABPA (Table 10). [113] ABPA-S are patients who have all the diagnostic features of ABPA without any abnormalities noted on HRCT.[113] ABPA-bronchiectasis (ABPA-B) are patients with ABPA and bronchiectasis. ABPA-HAM are patients with features of ABPA and the presence of HAM on HRCT. ABPA-chronic pleuropulmonary fibrosis (ABPA-CPF) are patients with ABPA and at least two of the following radiologic findings – pulmonary fibrosis, parenchymal scarring, fibro-cavitary lesions, aspergilloma, and pleural thickening without the presence of mucoid impaction or HAM.[113] This newly defined classification strategy does provide more specific details to classify patients with ABPA if changes are noted on imaging studies.

Stages of ABPA

There are various stages (stages I–V) of ABPA once the diagnosis has been made to classify these patients (Table 11).[77,81,83] The stages are acute, remission, exacerbation, corticosteroid-

Table 10. Radiological classification of allergic bronchopulmonary aspergillosis based on HRCT chest findings.

Classification	Diagnostic features of	
	ABPA	HRCT findings
Serologic ABPA	+	None
ABPA with bronchiectasis	+	Bronchiectasis
ABPA with high-attenuation mucus	+	High-attenuation mucus
ABPA with chronic pleuropulmonary fibrosis	+	At least two of the following in absence of mucoid impaction or high-attenuation mucus: • Pulmonary fibrosis • Parenchymal scarring • Fibro-cavitary lesions • Aspergilloma • Pleural thickening

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; HRCT, high-resolution computed tomography.

Table 11. Staging of allergic bronchopulmonary aspergillosis in asthmatics.

Stage	IgE level	Precipitins	Eosinophilia	IgE-Af	IgG-Af	Pulmonary infiltrates
(I) Acute	+++	+	+	+	+	+
(II) Remission	+	±	–	±	±	–
(III) Exacerbation	+++	+	+	+	+	+
(IV) Corticosteroid-dependent	++	±	±	±	±	–
(V) Fibrotic	+	±	–	±	±	–

Abbreviations: IgE, Immunoglobulin E; IgE-Af, IgE antibody to *A. fumigatus*; IgG-Af, IgG antibody to *A. fumigatus*.

Reprinted with permission from Knutsen AP and Slavin RG. [77]

dependent asthma, and fibrotic. Stage I (acute) is the stage where patients present with many of the characteristic features of ABPA (Table 8).[81,124] The goal of treatment is for the total serum IgE levels to decline by 35% after 6 weeks of corticosteroid treatment.[124] Stage II (remission) is the stage where patients have responded to oral corticosteroid treatment, as shown by resolution of infiltrates noted on radiological studies and/or decrease of eosinophilia for 6 months after steroids have been discontinued.[78,81,124] Stage III (exacerbation) occurs where there is a significant increase in total serum IgE; levels are often doubled and new pulmonary infiltrates may be seen on radiographic studies.[81,124] Symptoms may or may not be present during the exacerbation stage.[124] Stage IV (corticosteroid-dependent asthma) defines patients who are unable to tolerate being off of any corticosteroids to control their asthma symptoms or prevent recurrence of ABPA.[81,124] There can be associated increase in total serum IgE levels during this stage.[124] Stage V (fibrotic) demonstrates irreversible lung obstruction due to severe fibrotic upper lobes.[81,124] These patients often do not improve on corticosteroids, yet steroids are part of the management to maintain optimal lung function.[78] These patients may progress to develop pulmonary hypertension and cor pulmonale.[81,124]

ISHAM has proposed a new staging classification for patients with ABPA based on specific definitions outlining each of the stages. They have proposed six main stages with some stages further divided into subsets.[113] Stage 0 patients (Asymptomatic) are those with controlled asthma and ABPA. ISHAM does advocate for routinely screening asthmatic patients for ABPA even if they are not symptomatic. This recommendation is to capture patients early in their disease process to hopefully prevent progression of the disease. Stage 1 patients (Acute) are those with uncontrolled or symptomatic asthma with initial diagnosis of ABPA. Stage 1 is further divided into Stage 1a (Acute with mucoid impaction), where patients meet criteria for Stage 1 with mucoid impaction found on imaging or bronchoscopy. Stage 1b (Acute without mucoid impaction) are patients who meet criteria for Stage 1 without any mucoid impaction on imaging or bronchoscopy. Stage 2 patients (Response) are those who have clinical improvement in their symptoms, demonstrate improvement in their radiological imaging, and their IgE levels decrease by $\geq 25\%$ from their baseline at 8 weeks with treatment. Stage 3 (Exacerbation) captures patients who have clinical and/or radiological worsening and an increase of their total IgE by $\geq 50\%$. Stage 5a (Treatment-dependent ABPA) identifies patients who relapse two or more times within 6 months of completing treatment or those patients who have recurrence of symptoms while on a treatment taper. Stage 5b patients (Glucocorticoid-dependent asthma) are those who require steroids to control their asthma while their ABPA is controlled based on IgE levels and imaging. Stage 6 patients (Advanced ABPA) are those who have fibrotic disease and/or bronchiectasis that cause respiratory failure and/or cor pulmonale. This newly proposed staging scheme focuses on the clinical status, IgE levels, and imaging to categorize these patients. It is proposed that these stages with more detailed definitions may provide more consistency across the world in properly identifying patients as well as for research purposes.[113]

Management of ABPA

The main treatment goals of ABPA are to resolve clinical symptoms, decrease recurrence of exacerbations, preserve lung function, and prevent development of bronchiectasis or fibrosis.[78,79,81] The primary treatment of ABPA involves the administration of corticosteroids.[77–79,81] Steroids decrease the inflammatory response elicited by *A. fumigatus* in the lung parenchyma.[81,110] There is general consensus on the use of corticosteroids for long periods of time in these patients; however, there are no trial data assessing the dose and duration of treatment with steroids.[81] A typical plan to treat ABPA is prednisone 0.5 mg/kg daily for 2–4 weeks, then continuing the dose every other day for 6–8 weeks, with a taper by 5–10 mg every 2 weeks.[77,78,81,87] An alternative strategy has been proposed for a more aggressive approach using prednisolone 0.75 mg/kg daily for 6 weeks, then 0.5 mg/kg daily for an additional 6 weeks with a tapering schedule of 5 mg every 6 weeks for a total treatment course of 6–12 months.[78,125] Patients on steroid therapy should be monitored every 6 weeks for a change in total serum IgE levels (goal is at least a 35% reduction), resolution of chest radiologic findings, and improved symptoms.[77,78,125]

Inhaled corticosteroids are important for the treatment of patient's underlying asthma; however, studies have not demonstrated a role in treating ABPA even at high doses.[126] This class of medication should be used as a supplemental medication to control their asthma symptoms.

The use of antifungal medications has been studied and demonstrated to reduce the need for prolonged courses of corticosteroids.[78,81] Studies have demonstrated that the antifungal medication, itraconazole, can provide improvement in lung function, decrease in steroid dose, and reduced exacerbations.[127,128] For patients who have relapse after a course of steroids, it is recommended to start itraconazole at a dose of 200 mg twice a day for 4–6 months, then taper over the following 4–6 months.[77,78] Levels should be monitored to ensure adequate absorption of the medication. It is important to review a patient's complete medication list to assess if any other medication may interfere with the absorption or metabolism of itraconazole. Proton-pump inhibitors and H₂ blockers can decrease the absorption of itraconazole.[77] Other antifungal medications such as voriconazole or posaconazole can be used if itraconazole is not tolerated or there is contraindication for its use.[77,78]

Omalizumab, a humanized monoclonal antibody that binds free IgE, has been used in patients with refractory ABPA.[129] Current dosing of omalizumab is based on total serum IgE levels. However, patients with ABPA can have IgE levels that far exceed the upper limit of omalizumab dosing, as part of their disease process. Therefore, they should be treated with the maximum recommended weight-based dose of omalizumab. Collins et al. [130] performed a retrospective chart review of 21 patients who had received omalizumab for refractory ABPA. This group of patients overall had a decrease in steroid use, decrease in levels of total serum IgE, and improved symptoms, which were noted with an increase in Asthma Control Test (ACT) scores.[130] In France, Tillie-Leblond et al. [131] evaluated 16 patients with ABPA who received omalizumab for 1 year. This group of patients had decreased exacerbations and need for oral steroids during this time.[131] More recently, Voskamp et al. [132] performed a randomized, double-blind, placebo-controlled, cross-over trial with two treatment phases of 4-month duration. Thirteen patients with asthma and ABPA were identified and underwent the active treatment phase with omalizumab 375 mg every 2 weeks for 4 months with a wash-out period of 3 months, as well as 4 months of placebo every 2 weeks. Patients during the omalizumab treatment phase of the study had decreased exhaled nitric oxide (FeNO), number of exacerbations, basophil sensitivity to *A. fumigatus*, surface-bound IgE and FcεR1 compared to data while on the placebo treatment phase.[132] These recent studies and many case reports show the benefit this additional treatment option offers patients with ABPA.

Recent studies have shown utility of inhaled amphotericin B to provide localized treatment of ABPA and thereby decrease side effects.[133–135] Additionally, hypertonic saline has been used to help clear mucus from the airways in patients with bronchiectasis, though patients must be monitored carefully with their first dose as it can induce bronchoconstriction.[136,137] Macrolide antibiotics have been used for anti-inflammatory effect in patients with bronchiectasis, though no studies

have been done in patients with ABPA or to compare macrolide versus itraconazole therapy.[114]

Despite the increased awareness of this disease, it is still often overlooked and missed due to the many overlapping features of an exacerbation of the underlying disease process of asthma or CF. ABPA should be investigated in patients who have worsening asthma despite optimal medications.[86] This is vital for stopping the progression of developing bronchiectasis, lung fibrosis, and worsening lung function.

Concomitant ABPA and AFRS

ABPA and AFRS are presumed to share the same immunopathogenic mechanism since the eosinophilic or allergic mucin described in AFRS is histopathologically similar to the mucous plugs coughed up by patients with ABPA. However, despite the histopathological similarities, the coexistence of AFRS and ABPA has not been reported often. Venarske and deShazo coined the term 'sinobronchial allergic mycosis' or SAM syndrome to highlight this coexistence.[138] They noted that the presence of SAM syndrome was higher in atopic individuals with asthma, rhinosinusitis, and high levels of total and fungal-specific IgE. The existence of SAM syndrome as a clinical entity was supported in subsequent reports.[139] In one series, 7 of 95 patients with ABPA were diagnosed with concomitant AAS.[140] Although uncommon, the number of reports citing coexistence of ABPA and AFRS is steadily increasing.[138–145]

Fungal-associated asthma

Background

Asthmatic patients comprise a significant proportion of the allergist's practice, as the disease affects 5–30% of children and 2–30% of adults.[146,147] One factor of interest in the development and exacerbation of asthma is fungal exposure. Estimates of skin prick sensitivity to fungi in the United States, Europe, and the Middle East range from 12% to 80% in both the general and atopic population.[77] Fungal sensitization or exposure has been associated with risk of developing or having asthma as well as several measures of asthma morbidity and severity.[77,148–150] Studies have correlated fungal spore counts with albuterol use and ED visits for asthma.[149,151] O'Hollaren et al. reported that exposure to *Alternaria alternata* is a risk factor for respiratory arrest in children and young adults with asthma.[152] Some studies have shown that mold exposure may tie in to the 'agricultural asthma paradox', where exposure in a rural setting early in life is associated with decreased risk of atopic asthma, though it has been associated with higher rates of nonatopic asthma in later life.[153]

Of all the agents, such as dust mites and pollen, capable of causing an exaggerated immune response in patients with airway hyperresponsiveness, fungi are the only agents that can live and thrive in the airway. However, it is important to differentiate sensitization to fungi from fungal allergy, as many people with elevated specific serum IgE to fungi may not develop any symptoms.[114] While fungal allergy is an immune-mediated inflammatory response to a fungus, fungal sensitization often lacks evidence of inflammation or tissue

damage.[114] The precise reasons that determine whether a patient remains asymptomatic, colonized, or afflicted by allergic disease remain unclear. Some authors suggest that this may be related to 'fungal burden' or chronicity of respiratory colonization of atopic individuals by fungi,[150] although this has not been satisfactorily validated in studies. Knutsen et al. have proposed genetic risk factors.[154,155] They reported that children with moderate to severe asthma had significantly increased sensitivities to *A. fumigatus* while sensitivities to *Alternaria* were similar in both moderate to severe and mild asthmatics. The frequency of *HLA-DRB1*13* and *HLA-DRB1*03* alleles tended to be increased in mold-sensitive moderate to severe asthmatics. However, the frequency of *HLA-DQB1*03* alleles was significantly decreased in mold and *Alternaria*-sensitive moderate to severe asthma and was associated with increased *in vitro* Th2 IL-5 and IL-13 synthesis in *Alternaria*- and Asp f3-stimulated cultures. This suggests that *HLA-DQB1*03* may be protective of the development of *Alternaria*-sensitive severe asthma.[154] In a separate study comparing 60 children with *Alternaria*-sensitive moderate to severe asthma to 49 children with *Alternaria*-sensitive mild asthma, Knutsen et al. reported an increased Th2 response to *Alternaria* stimulation and increased sensitivity to IL-4 stimulation in children with *Alternaria*-sensitive moderate to severe asthma.[156] They noted that this skewing toward a Th2 response was associated with an increased frequency of the IL-4RA ile75val polymorphism. Consistent with their prior study, there was a decreased frequency of *HLA-DQB1*03* in *Alternaria*-sensitive moderate to severe asthmatic children once again, suggesting that *HLA-DQB1*03* may be protective against the development of mold-sensitive severe asthma.[156]

Fungal sensitization arises from a combination of host genetic factors and both indoor and outdoor environmental exposure. Fungi most often cause allergic symptoms when conditions allow them to germinate, which removes the spores' immunologically inert coating of hydrophobin,[157–159] though some hyphae and fragmented spores can also cause sensitivity.[160] The increased mucus in the asthmatic lung provides an ideal environment for fungal germination.[77] Weiss et al. demonstrated that *ITGB3* polymorphisms are associated with asthma and mold sensitization.[161] Although Carvalho et al. [105] found no association between *TLR2*, *TLR4*, and *TLR9* polymorphisms and SAFS, Smit et al. reported that *TLR2*/+596C polymorphisms and *ITGB3* single nucleotide polymorphisms are associated with mold sensitization in asthmatics.[162]

Fungal proteins, such as proteases, can damage the respiratory epithelium, initiate and enhance bystander reactions, and act as allergens.[150] Allergenicity of fungi is thought to be due to chitinases [77] and proteases on fungal hyphae, [77,149,150] possibly by activating protease-activated receptors,[163–165] though the mechanism is not firmly established. Of all fungal allergens, proteases appear to be an important initiator of the allergic respiratory response. Porter PC et al. determined that fungi are the major source of active proteases in house dust.[166] They further challenged mice with low doses of *Aspergillus niger* conidia and found that this induced experimental asthma with airway hyperreactivity,

goblet cell metaplasia, highly polarized TH2 responses, and serum fungus-specific antibodies in these mice.[166] *A. niger* readily infected the mouse airway, produced hyphae, and induced an allergic asthma disease phenotype. However, when they challenged the mice with mutant *A. niger* strains that were devoid of active proteases, induction of allergic lung disease did not take place. This showed the importance of active fungal proteases secreted during active infection in inducing allergic lung disease. Various cellular proteins have been suggested as potential targets of fungal proteinases, mostly by extrapolation of evidence from other respiratory allergens, including airway epithelial tight junctions, CD23 and CD25, protease-activated receptor 2 (PAR2), C3a anaphylatoxin receptor, complement protein 3 (C3), and IL 25.[166–171] In a separate study, Porter et al. observed a higher likelihood of positive fungal culture from the sinuses of patients with TH2-mediated diseases such as allergic asthma, CRS with nasal polyps, and AFRS compared to patients without these conditions.[172]

There is also evidence that fungi may cause nonallergic inflammation through beta-glucans[148] and volatile organic compounds.[148,173–181] *Penicillium* and *Aspergillus* species, in particular, have easily inhalable spores due to their property of being readily suspended in the air and small size (2–3 µm).[182]

Clinical presentation

There are several classic presentations of fungal asthma: allergic asthma, thunderstorm asthma, SAFS, and *Trichophyton* asthma.

Thunderstorm asthma

Fungus-sensitive asthmatic patients often have a flare in symptoms after a thunderstorm. This is due to fungal spores, with specific evidence that *Didymella*,[183] *Alternaria*,[184,185] and *Cladosporium* [186] species spores are elevated during or after storms.

Severe asthma associated with fungal sensitivity

In 2006, Denning et al. [150] coined the term ‘SAFS’ to describe severely asthmatic patients who are sensitive to fungi and respond to itraconazole. This entity is estimated to affect 6.5 million patients based on frequencies of severe asthma and fungal sensitization.[114] When compared to other asthmatic patients of similar disease severity, those with IgE sensitivity to *A. fumigatus* have more fixed airflow obstruction and more bronchiectasis.[149] It may be complicated by pulmonary cavitation and fibrosis,[114] as well as infrequent chronic pulmonary aspergillosis,[187] though not much is yet known about the natural history of SAFS.

Trichophyton asthma

Trichophyton species cannot colonize or infect the lung and instead cause skin infections; however, sensitization to this fungus is independently associated with asthma severity.[188–192]

Diagnosis of fungal allergic asthma

As with other IgE-mediated sensitivities, the mainstay of diagnosis is skin prick testing and specific serum IgE.[193] Patients can show sensitization to a particular fungus on one or both

testing modalities.[115,194] Therefore, some authors recommend using both testing modalities to uncover all sensitizations.[115,195] Commonly tested fungi are *A. fumigatus*, *C. albicans*, *A. alternata*, *P. chrysogenum*, *C. herbarum*, *S. cerevisiae*, *Trichophyton* species, and *Malassezia* species.[77,196] *A. fumigatus* component testing may become helpful in the future (Asp f 1 and Asp f 3 have been associated with fungal allergy, whereas Asp f 2, Asp f 4, and Asp f 6 have been associated with ABPA). [197–199] Depending on the specific extracts and reagents used, SPTs can have a 95% NPV and 50–60% PPV.[77] Identification of the fungi colonizing a patient’s airway is a difficult goal to achieve as fungal culture of sputum or other respiratory samples can be contaminated with upper airway colonizers,[196,200] or be biased toward faster-growing species. Methods of increasing the yield of fungal culture are being explored.[113,182,201–203] Other more specific biomarkers are in development, such as measurement of volatile organic compounds exhaled by the patient.[204,205] Porter et al. recently conducted a study demonstrating that using an enzyme-linked immunospot assay for IL-4-secreting cells, patients could be classified as having TH2-mediated disease (including AFRS, CRS with nasal polyps, and asthma) with 100% specificity and 73% sensitivity. Of note, the fungi cultured from these patients’ airways were not always the same ones that provoked IL-4 response in the assay.[172] Diagnostic criteria for SAFS are not yet uniformly defined, but Denning et al. [114] proposed the following criteria: severe asthma; total IgE < 1000 IU/mL; and sensitization to a fungus by SPT or sIgE.

Management of SAFS

As in other allergic diseases, avoidance of allergic triggers is paramount in treating fungal asthma. Investigated environmental controls against fungal exposure in fungus-sensitive patients include decreasing humidity and repair of water damage, but these studies have had mixed and inconsistent results in both the home and workplace.[114]

In addition to standard asthma management based on consensus guidelines, patients with SAFS can benefit from antifungal therapy in the form of oral itraconazole 200 mg twice daily. The FAST study [206] found improvement in Asthma Quality of Life Questionnaire after treatment for 32 weeks, with a number needed to treat of 3.22. Pasqualotto et al. [207] found that patients had decreased need for oral steroids after 24 weeks of treatment. However, patients in the FAST trial returned to their pretreatment status after 4 months without antifungal therapy.[206] Additionally, caution should be exercised when treating asthmatic patients with itraconazole as it decreases metabolism of inhaled corticosteroids, thereby boosting the effective levels in the lungs. Patients should be monitored for adrenal insufficiency if on long-term dual therapy. This effect is mainly seen with budesonide and fluticasone, but less so with ciclesonide or beclomethasone.[114]

Voriconazole and posaconazole have also shown promise in small trials as second- and third- line treatments for SAFS, [208] but a more recent study did not find benefit of 12 weeks of voriconazole therapy.[209] It is notable that azole antifungals have anti-inflammatory effects, which may also contribute to their effectiveness in treating asthmatics.[210,211]

Trichophyton asthma can be treated with fluconazole [192,212] or itraconazole. There is a case report of terbinafine being used to treat *Trichophyton* infection in an asthmatic patient with improvement in asthma symptoms.[213] Of note, fluconazole has a much narrower spectrum of antifungal activity than itraconazole and may not be as effective in patients with sensitivities to multiple fungi. As in other patients with severe asthma with a prominent allergic trigger, omalizumab therapy can also be beneficial.[214–216] Future therapies may include fungal AIT. Currently, there are no large randomized double-blind placebo-controlled trials to support the use of AIT, although there are many case reports and small studies reporting benefit.[217,218] Additionally, IL-33 may be a target for future therapies.[219]

Expert commentary and five-year view

We have come a long way in defining allergic fungal diseases as an entity, but there is still more to be done. Standardizing fungal allergens for SPTs and in vitro testing would be a major step in defining a gold standard for initial evaluation of these patients. There is a need for large studies of anti-fungal agents in allergic fungal diseases of the upper airway in order to better validate or negate their role in treatment regimens. Many advances have been made in the diagnosis and treatment arena for patients with ABPA since its initial description by Hinson et al. in 1952.[76] However, there is still much to be learned and applied to this complex disease. Diagnostic criteria that help better differentiate ABPA from overlapping syndromes such as hyper IgE syndrome, *Aspergillus* bronchitis, chronic pulmonary aspergillosis, and Churg–Strauss syndrome need to be defined.[114] It is now well known that patients with HAM have higher immunological markers, frequent relapses, and poorer outcomes, but the reason for these findings remains

unclear. Additional research to better understand the mechanisms and appropriate treatment options for patients with ABPM needs to continue. In addition, there needs to be a consensus on appropriate cut-offs for various tests employed by physicians in the diagnosis of ABPA and ABPM. This is crucial since these tests guide diagnosis and treatment. Steps have been made by Agarwal et al., [117] which has started the conversation, yet the work needs to be continued to validate what has been done. Further research into the different genetic risk factors needs to be continued, since it may shed light on the disease course of ABPA patients and dictate how aggressive treatment should be to prevent complications. There is a need for further studies to determine host genes that recognize fungal antigens and trigger allergic responses. Additional exploration of various treatment modalities for ABPA is also needed, especially for those patients who require long-term treatment.

Conclusion

Diagnosis of the wide spectrum of fungal diseases of the upper and lower airways may often be overlooked due to variations in presentation. Early recognition of this entity is key to initiating appropriate management to prevent progression of the disease. Ongoing research endeavors continue to expand our knowledge of this intriguing spectrum of diseases.

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Key issues

- Fungi are prevalent in our environment and cause a wide spectrum of fungal diseases of the upper and lower airways.
- The pathogenicity of the fungi in conjunction with host factors determines if a patient may have asymptomatic colonization with fungi or suffers from allergic or potentially lethal invasive disease.
- There are three main phyla involved in allergic fungal disease: (1) Ascomycota (2) Basidiomycota (3) Zygomycota.
- AFRS causes chronic rhinosinusitis symptoms and is caused predominantly by *A. fumigatus* in India and Bipolaris in the United States.
- AFRS usually presents with thick, tenacious nasal discharge and is more common in patients living in the southern and central portions of the United States.
- The recommended treatment approach for AFRS is surgical intervention and systemic steroids.
- ABPA is most commonly diagnosed in patients with asthma or CF.
- Long-term systemic steroids are the mainstay treatment option for ABPA with the addition of an antifungal medication such as itraconazole.
- Omalizumab has been shown as a beneficial adjunctive therapy for ABPA.
- Fungal sensitization or exposure increases a patient's risk of developing severe asthma and has been termed SAFS.
- Investigating for triggers and causes of a patient's asthma should be sought to decrease the worsening progression of SAFS.

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