

Allergic fungal rhinosinusitis



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

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Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: The authors declare that they have no relevant conflicts of interest. Z. K. Ballas (editor) disclosed no relevant financial relationships.

Activity Objectives:

1. To distinguish allergic fungal rhinosinusitis (AFRS) from other fungal sinus diseases and from chronic rhinosinusitis with nasal polypsis (CRSwNP).
2. To understand the pathogenesis of AFRS.
3. To recognize the evidence supporting different treatment modalities in patients with AFRS.

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

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Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: The exam authors disclosed no relevant financial relationships.

Allergic fungal rhinosinusitis (AFRS) is a subset of chronic rhinosinusitis with nasal polyps (CRSwNP) characterized by antifungal IgE sensitivity, eosinophil-rich mucus (ie, allergic mucin), and characteristic computed tomographic and magnetic resonance imaging findings in paranasal sinuses. AFRS develops in immunocompetent patients, with occurrence influenced by climate, geography, and several identified host factors. Molecular pathways and immune responses driving AFRS are still being delineated, but prominent adaptive and more recently recognized innate type 2 immune responses are important, many similar to those established in patients with other forms of CRSwNP. It is unclear whether AFRS represents merely a more extreme expression of pathways important in patients with CRSwNP or whether there are other disordered immune responses that would define a distinct endotype or endotypes. Although AFRS and allergic bronchopulmonary aspergillosis share some analogous immune mechanisms, the 2 conditions do not occur commonly in the same patient. Treatment of AFRS almost always requires surgical debridement of the involved

sinuses. Oral corticosteroids decrease recurrence after surgery, but other adjunctive pharmacologic agents, including topical and oral antifungal agents, do not have a firm evidence basis for use. There is good rationale for use of biologic agents that target eosinophilic inflammation or other type 2 responses, but studies in patients with AFRS are required. (*J Allergy Clin Immunol* 2018;142:341-51.)

Key words: Rhinosinusitis, fungal allergy, chronic rhinosinusitis with nasal polyps

Chronic rhinosinusitis (CRS) is comprised of a heterogeneous group of sinonasal disorders defined as being of at least 12 weeks' duration and resulting in a significant health care burden to affected subjects and society. Based on phenotyping by clinical characteristics and presentation, CRS can be broadly categorized as being either chronic rhinosinusitis without nasal polyps (CRSsNP) or chronic rhinosinusitis with nasal polyps

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Received for publication June 13, 2018; revised June 26, 2018; accepted for publication June 26, 2018.

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0091-6749/\$36.00

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<https://doi.org/10.1016/j.jaci.2018.06.023>

Abbreviations used

ABPA:	Allergic bronchopulmonary aspergillosis
AFRS:	Allergic fungal rhinosinusitis
AIT:	Allergen immunotherapy
CRS:	Chronic rhinosinusitis
CRSsNP:	Chronic rhinosinusitis without nasal polyps
CRSwNP:	Chronic rhinosinusitis with nasal polyps
CT:	Computed tomography
ILC2:	Group 2 innate lymphoid cell
MRI:	Magnetic resonance imaging
NK:	Natural killer
SCIT:	Subcutaneous immunotherapy

(CRSwNP).^{1,2} CRSsNP has been classically associated with type 1 cytokine expression (particularly IFN- γ), whereas CRSwNP has cytokine expression skewed to the type 2 profile (eg, IL-5 and IL-13). However, recent evidence suggests that both broad categories can be driven by a variety of molecular and inflammatory mechanisms that can functionally and pathologically define disease as different endotypes.¹⁻⁶ The majority of patients with CRSwNP can be further subcategorized into 2 generally recognized phenotypes: CRSwNP with aspirin-exacerbated respiratory disease and CRSwNP without aspirin-exacerbated respiratory disease. In addition, allergic fungal rhinosinusitis (AFRS) is often considered another phenotype of CRSwNP, although there is some controversy about the definition of AFRS and even whether it is a distinct clinical phenotype of CRSwNP, as articulated by the EPOS European Position Paper 2012.¹

This review will present AFRS as a distinct phenotype of CRSwNP associated with eosinophil-rich mucus and type I hypersensitivity to fungi resident within the sinuses, as recognized by the 2014 US Joint Task Force document, “Diagnosis and management of rhinosinusitis: a practice parameter,”² and earlier by the 2006 Rhinosinusitis Initiative.⁷ This review also will discuss known pathogenetic pathways of AFRS, approach to diagnosis, and management of AFRS.

AFRS IN THE BROADER CONTEXT OF FUNGAL SINUS DISEASE

Fungi are important and ubiquitous components of the sinonasal microbiome. Depending on still incompletely understood factors, fungi can exist symbiotically, invade sinonasal tissues, serve as antigens against which the host immune system can mount a hypersensitivity or inflammatory response, or induce sinus mucosal disease through other mechanisms (eg, proteolytic effects that disrupt mucosal epithelial integrity).⁸

Historical perspective

The first report consistent with AFRS was made in 1976 by Safirstein,⁹ who described a woman, later given a diagnosis of allergic bronchopulmonary aspergillosis (ABPA), who had improvement of both sinonasal symptoms and ABPA with oral corticosteroids. In 1981, Millar et al¹⁰ introduced the term “allergic aspergillosis of the paranasal sinuses” to describe 5 patients with chronic sinusitis (1 previously given a diagnosis of ABPA), marked immediate hypersensitivity to *Aspergillus fumigatus*, and sinus material that histologically resembled the mucus plugs expectorated by patients with ABPA. In 1983, Katzenstein

et al¹¹ described “allergic aspergillus sinusitis” in reporting that in 9 of 119 specimens of material surgically excised from the paranasal sinuses, “allergic mucin” material was indistinguishable histologically from eosinophil-rich mucoid impaction of the bronchi in patients with ABPA. Although the term allergic mucin has persisted in the AFRS literature, it is actually a misnomer in that a more precise definition of mucin would refer only to glycoproteins present in mucus, and eosinophil-rich mucus can occur in the absence of allergy.

The aforementioned clinical observations led to the concept that, similar to the pathophysiology of ABPA in the lungs, allergic aspergillus rhinosinusitis is due to an allergic hypersensitivity reaction to *Aspergillus* species colonization of the upper respiratory tract and sinuses. However, this analogy between *Aspergillus* species-induced pulmonary and sinus disease oversimplifies what is now known to be a much more complex array of mechanisms that underlie both disease processes. This probably explains current data showing that ABPA and allergic *Aspergillus* species-related rhinosinusitis are observed only occasionally in the same patients, although their coexistence has been highlighted.^{12,13} Subsequently, other patients were reported to have analogous presentations with rhinosinusitis and allergic mucin in association with fungal species other than *Aspergillus* species, such as *Alternaria*, *Bipolaris*, *Curvularia*, *Drechslera*, and *Fusarium*; this has led to introduction of the broader term allergic fungal sinusitis and, more recently, AFRS.¹⁴⁻¹⁸

In 2009 deShazo¹⁹ proposed criteria to differentiate AFRS as a unique entity among types of CRS. Cody et al²⁰ proposed the term allergic fungal sinusitis–like syndrome to describe cases of rhinosinusitis that had histopathologic evidence of characteristic allergic mucin without the presence of fungal hyphae or cultures positive for fungi. Ferguson²¹ proposed the term eosinophilic mucin rhinosinusitis when eosinophilic “mucin” is present without the presence of fungi.^{22,23} However, with the subsequent introduction of more sensitive techniques to identify the presence of fungi, there is debate about whether eosinophilic mucin-related rhinosinusitis is truly a distinct clinical phenotype and instead should be considered part of the spectrum of CRSwNP.¹⁷ With improved fungal detection techniques, some studies report fungal presence in nearly 100% of patients with CRS and control subjects.^{24,25}

Current definitions of fungal sinus disease

A 2009 consensus document of the International Society for Human and Animal Mycology¹⁷ broadly classified fungal rhinosinusitis into noninvasive and invasive subtypes.

Phenotypes of noninvasive fungal rhinosinusitis (Table I)⁸ occur in immunocompetent subjects and include (1) local fungal colonization, (2) fungal ball, and (3) AFRS. Subtypes of invasive fungal rhinosinusitis (Table II) include acute invasive fungal rhinosinusitis, chronic invasive fungal rhinosinusitis, and granulomatous invasive rhinosinusitis.

AFRS versus CRSwNP

Among patients with CRSwNP, a subgroup with AFRS can be defined by using the classic Bent-Kuhn criteria for AFRS with phenotypic differences. The original Bent-Kuhn diagnostic criteria are as follows: (1) nasal polyposis, (2) fungi on staining, (3) eosinophilic mucin without fungal invasion into sinus tissue, (4) type I hypersensitivity to fungi, and (5) characteristic

TABLE I. Noninvasive fungal rhinosinusitis subtypes

	Local fungal colonization	Fungal ball	AFRS
Patient profile	Immunocompetent	Immunocompetent, nonatopic, middle-aged or elderly; female subjects > male subjects	Immunocompetent, atopic, younger adults, low socioeconomic status, African American in United States
Predisposing factors	Previous sinus surgery, impaired mucociliary clearance	Impaired mucociliary clearance	Genetics? Structural abnormalities Geographic residence (eg, southern United States and India)
Symptoms	Asymptomatic to malodorous nasal discharge	Asymptomatic to symptomatic with facial pain, nasal purulence and obstruction, postnasal discharge, anosmia	Symptomatic with thick mucus; nasal and sinus symptoms, including anosmia
Examination	Macroscopically visualized colonization of nasal mucosa by means of endoscopy	Mucopurulent “cheesy”-appearing material from sinuses by means of endoscopy	Thick, tenacious, peanut butter–like nasal/sinus discharge In severe cases: facial deformity, hypertelorism, proptosis
Histology	Not routinely performed	GMS stains: Fungal hyphae, inflammatory infiltrate with lymphocytes, plasma cells, mast cells No evidence of tissue invasion	Eosinophil-rich mucus (allergic mucin), necrotic cellular debris, Charcot-Leyden crystals, fungal hyphae without evidence of tissue invasion
Fungi	Ambient	<i>Aspergillus</i> (most common), <i>Pseudallescheria</i> , <i>Alternaria</i> species	<i>Aspergillus</i> species, dematiaceous molds (<i>Bipolaris</i> , <i>Curvularia</i> more common than <i>Alternaria</i>), hyaline molds (<i>Paecilomyces</i> , <i>Fusarium</i> , <i>Scedosporium</i>)
CT imaging	Usually normal	Heterogenous opacities within sinus cavity, punctate calcifications within hyphae masses	Hyperattenuating “allergic mucin” Possible bone expansion with thinning of bony walls
MRI	Usually normal	Central hypointensity on T1- and T2-weighted images, signal void on T2-weighted image	Central hypointensity on T1- and T2-weighted images, signal void on T2-weighted scans
Treatment	Endoscopic removal of crusts	Endoscopic removal of fungal ball	Surgical debridement + systemic corticosteroids
Prognosis	Favorable, curable	Curable, low recurrence	Controllable but recurrence not uncommon

GMS, Gomori methenamine silver.

radiologic findings with soft-tissue differential densities on computed tomographic (CT) scanning.²⁶ Although the Bent-Kuhn criteria are widely used, several of these criteria are not unique to patients with AFRS.

By definition, all patients with CRSwNP have nasal polyposis, and a large proportion have eosinophilic mucin without fungal invasion. EPOS 2012 concluded that type I hypersensitivity and characteristic CT findings are the only unique factors in Bent-Kuhn criteria for AFRS that allow it to be distinguished from other forms of sinus disease.¹ Although patients with CRSwNP have thick nasal discharge, nasal discharge in patients with AFRS, as defined by Bent-Kuhn criteria, is much thicker, with a “peanut butter–like consistency” (Table III). Compared with patients with CRSwNP, patients with AFRS have higher Lund-Mackay scores (calculated by using CT sinus radiographic criteria that stage the degree of inflammatory involvement of each sinus region and the ostiomeatal complexes), reflecting that patients with AFRS compared with those with CRSwNP show a greater degree of sinus opacification. In addition, patients with AFRS have central hyperattenuation caused by allergic mucin.²⁷

Alternaria and *Cladosporium* species are the most common fungi in patients with CRSwNP, whereas in those with AFRS, depending on geographic region, more commonly involved fungal

genera are *Aspergillus* and dematiaceous (melanin-producing) fungi other than *Alternaria* species, such as *Bipolaris* and *Curvularia* species. Hutcheson et al²⁸ reported that patients with AFRS have greater mean total serum IgE levels, antifungal IgG antibodies, and incidence of atopy and greater numbers and intensity of IgE antifungal bands on immunoblotting. However, others have reported that mean serum total IgE and IgG antifungal antibody levels are not significantly different between patients with AFRS and those with CRSwNP.¹ Differentiating features between patients with AFRS and those with CRSwNP are summarized in Table III.

HOST AND ENVIRONMENTAL FACTORS FOR AFRS

AFRS is typically a disease of atopic and immunocompetent young adults (Table II). Although it can occur in adolescents, it is less common in young children. Compared with patients with other forms of CRSwNP, those with AFRS are not only more likely to be atopic but also younger at diagnosis. In the United States patients with AFRS are more likely to be male and African American and also prone to have more significant bone erosion/expansion than other patients with CRSwNP, lower per capita income, and less access to health care.^{29–33} Host genetics appear to be an important predisposing factor in the development of AFRS,

TABLE II. Classification of invasive fungal rhinosinusitis

	AIFRS	CIFRS	GIFRS
Demographic	Immunosuppressed, critically ill	Mildly immunosuppressed, otherwise well	Can occur in immunocompetent patients Common in Indian subcontinent and parts of Middle East and Africa (especially Sudan)
Specific risk factors	Poorly controlled diabetes, severe neutropenia, AIDS	Poorly controlled diabetes, chronic oral corticosteroid use	Unknown
Time course	<4 wk	>12 wk	>12 wk
Symptoms	Painless, necrotic nasal septal ulcer Fulminant sinusitis, fever, facial pain, epistaxis, rapid orbital and intracranial spread leading to death	Slow indolent course Fever, epistaxis, facial pain and headaches, nasal polyps Can progress to erosion of cribriform plate, altered mental status, focal neurological deficits, erosion of skull base, cranial neuropathies	Fever, cough, nasal crusting Altered mental status with intracranial extension Slow-growing mass with symptoms from possible orbital or intracranial extension
Examination/diagnosis	Endoscopic examination: Edema, necrotic tissue, black eschar	Endoscopic evaluation: Polypoid mucosa, soft-tissue masses	Soft-tissue mass representing primary paranasal granuloma
Histology	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
CT imaging	More typically hypoattenuating mucosal thickening Aggressive bone destruction	Hyperdense material within sinuses more common Mass-like soft-tissue collection	Similar to CIFRS
MRI	T1: Intermediate low signal T2: Fungal mass intermediate to low signal	Decreased signal intensities on T1-weighted and T2-weighted images Sclerotic changes in bony walls	Similar to CIFRS
Fungi	In diabetes: <i>Zygomycetes</i> (<i>Rhizopus</i> , <i>Mucor</i> , <i>Rhizomucor</i> , and <i>Absidia</i> species) In neutropenic patients: <i>Aspergillus</i> species	<i>Mucor</i> , <i>Rhizopus</i> , <i>Penicillium</i> , <i>Aspergillus</i> , <i>Bipolaris</i> , <i>Candida</i> species	<i>Aspergillus</i> species
Treatment	Aggressive surgical debridement + systemic antifungals	Surgical debridement + systemic antifungals Address factors that might be immunosuppressive (poorly controlled diabetes, higher doses of corticosteroids)	Surgical debridement + systemic antifungals
Prognosis	High morbidity and mortality	Better prognosis than AIFRS but still potentially lethal	Fair if limited to sinuses on diagnosis but high relapse rate If intracranial involvement, poor prognosis

AIFRS, Acute invasive fungal rhinosinusitis; CIFRS, chronic invasive fungal rhinosinusitis; GIFRS, granulomatous invasive fungal rhinosinusitis.

although this is still incompletely defined. It remains speculative as to whether genetic factors can influence immune pathways that could help define AFRS as a distinct endotype of CRSwNP. As an example, using candidate gene studies driven by genetic findings in patients with ABPA, *HLA-DQB1*0301* and *HLA-DQB1*0302* have been found to be much more prevalent in patients with AFRS compared with those with CRSwNP.³⁴ To date, genome-wide association studies and genetic linkage analysis of patients with AFRS have not been reported, although these approaches are now being applied to identifying single nucleotide polymorphisms in patients with CRS and, more specifically, CRSwNP.³⁵

Climatic and geographic factors are known to influence risk for AFRS, with warm and humid regions having greater prevalence. In the United States AFRS is more common in southern and central regions, particularly along the Mississippi basin.³⁶ As noted earlier, although dematiaceous fungi and *Aspergillus*

species are common etiological agents for AFRS in the United States (prevalence of causal fungi varying by geographic region), geographically it is noteworthy that *Aspergillus* species account for up to 96% of all AFRS cases in India.^{37,38}

PATHOGENESIS

The literature about the pathogenesis of AFRS is incomplete and confounded by several issues beyond the controversies about inclusion criteria for AFRS discussed earlier. With the hypothesis that AFRS is both a distinct phenotype and potentially endotype or endotypes under a broader group of CRSwNP, studies ideally should compare data from patients with AFRS, non-AFRS CRSwNP, and allergic rhinitis with fungal sensitivity but without sinusitis and healthy control subjects, but this has been done inconsistently. For some putative pathogenetic mechanisms, data

TABLE III. Differentiation of AFRS from CRSwNP

	AFRS	CRSwNP
Secretions	Ultrathick, peanut butter-like	Thick
Lund-MacKay CT scores	Higher	Lower
CT imaging	Opacification with hyperdense areas	Opacification
Fungi commonly isolated	<i>Bipolaris</i> , <i>Curvularia</i> , and <i>Aspergillus</i> species most common	<i>Alternaria</i> and <i>Cladosporium</i> species
Immune status	Atopic	Nonatopic in higher proportion than AFRS
Allergy skin testing to fungi	Usually positive to multiple fungi, including causal fungus	Less commonly positive to fungi and, if positive, against fewer fungi than AFRS
Immunoblotting	Numerous IgE antifungal bands	Rare IgE antifungal bands
Total serum IgE	Typically higher than in patients with CRSwNP	Typically lower than in patients with AFRS
HLA	<i>HLA-DQB1*0301</i> and <i>HLA-DQB1*0302</i>	<i>HLA-DQB1*0301</i> and <i>HLA-DQB1*0302</i> less prominent

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best established in patients with CRSwNP without AFRS have been extrapolated to AFRS and require further confirmation in patients with AFRS. Thinking critically, studies of AFRS that include a skewed population of patients with AFRS associated with a particular fungal genus (eg, *Aspergillus* species) might not necessarily apply to AFRS from other fungi if fungal genera or species differ in their intrinsic properties (eg, proteolytic activity) or potential to provoke host immune responses. Analogous to the finding that patients with CRSwNP in different geographic regions might differ (predominantly eosinophilic in Western countries and more neutrophilic in China),³⁹ it cannot be assumed that studies of the immunopathogenesis of AFRS are universally applicable when conducted in different geographic regions with different environmental fungal and other aeroallergen exposures, potentially different sinonasal fungal and bacterial microbiomes, different host genetic diversity in different populations, and associations with different fungi.

With those caveats, Fig 1^{3,5} presents a comprehensive overview of AFRS, including host and environmental factors known to influence its development and both established and putative pathogenetic mechanisms. Not surprisingly, most, but not all, of the cited mechanisms are similar to those established in patients with CRSwNP other than AFRS, and it remains to be fully determined whether some mechanisms are expressed more robustly in patients with AFRS than in those with other forms of CRSwNP. Current concepts of importance to AFRS pathogenesis are reviewed below, but several recent reviews⁴⁰⁻⁴² provide additional details about mechanisms relevant to CRSwNP and AFRS, including reduced mucociliary clearance, epithelial activation with consequent apoptosis of epithelial cells, loss of epithelial barrier integrity, release of proinflammatory chemokines and cytokines, and the role of biofilms.

Role of type 2 T cells and group 2 innate lymphoid cells in patients with CRSwNP: Role in AFRS?

As noted earlier, CRSwNP has been considered a type 2-mediated disease based on increased expression in diseased sinonasal tissue of IL-5 and IL-13 and greater numbers of T_H2 cells in patients with CRSwNP in comparison with those with CRSsNP and healthy control subjects.⁴³⁻⁴⁸ Patients with AFRS have notably higher levels of serum IgE antifungal antibodies, as well as eosinophil-rich mucus, both type 2 responses that have been attributed traditionally to exaggerated T_H2 adaptive immune responses. In addition, localized production of fungus-

specific IgE antibodies in the sinus mucosa of patients with AFRS has long been recognized.⁴⁹

More recently, it has been recognized that group 2 innate lymphoid cells (ILC2s) are the innate immunity analog to T_H2 cells in adaptive immunity in that both cell types produce IL-5, IL-13, and IL-4, the latter in T_H2 and some ILC2 subsets.⁵⁰

An important pathogenetic role for ILC2s in patients with CRSwNP is supported by their increased numbers in the inflamed mucosa of patients with CRSwNP compared with numbers seen in those with CRSsNP and healthy control subjects.⁵¹⁻⁵⁴ These ILC2s express the receptor for IL-33, IL-25, and thymic stromal lymphopoietin, all upstream sinonasal epithelial cell-derived cytokines. Increased numbers of ILC2s in mucosa correlate with clinical markers associated with more severe disease, including eosinophilia, the presence of allergy and asthma, nasal endoscopy score, and memory T-cell counts. Moreover, Shaw et al⁵¹ have demonstrated that the primary and initial source for IL-13 on IL-2/IL-33 stimulation of sinonasal mucosa from patients with CRSwNP is ILC2s and not mast cells or T cells. In response to environmental triggers, including fungi, bacteria, and viruses or damage to epithelial cells, IL-33 is released and therefore might be one of several upstream epithelial cell-derived cytokines that can initiate type 2 adaptive and innate immune responses. Another epithelium-derived cytokine, thymic stromal lymphopoietin, can induce IL-5 and IL-13 production from type 2 cells and ILC2s and is a potent activator of mast cells.^{55,56} More recently, gene expression profiling and immunohistochemistry have demonstrated that in both patients with CRSwNP and those with AFRS, there is robust expression of the IL-1RL1 receptor for IL-33 on eosinophils and mast cells.⁵⁷ Moreover, IL-1RL1 expression correlates with mast cell activity in polyp subtypes, including AFRS, and with other evidence supports a mast cell axis as being a key part of type 2 inflammation in nasal polyps.⁵⁷

It has been proposed that AFRS might be a more extreme version of CRSwNP because of the increased IgE responses, particularly to fungi, and the presence of nasal polyps compared with patients with CRSwNP and that most patients with CRSwNP have fungus present in their sinuses similar to patients with AFRS.^{50,58} Alternatively, Dietz and Luong⁵⁰ have proposed that AFRS might be a distinct disease in part because of a defect of the innate immune system that results in inability to clear fungus from the sinuses, with consequent colonization and growth and/or possible differences between patients with AFRS and those with CRSwNP in cytokine secretion profiles and receptor expression of ILC2s.⁵⁰

ALLERGIC FUNGAL RHINOSINUSTIS

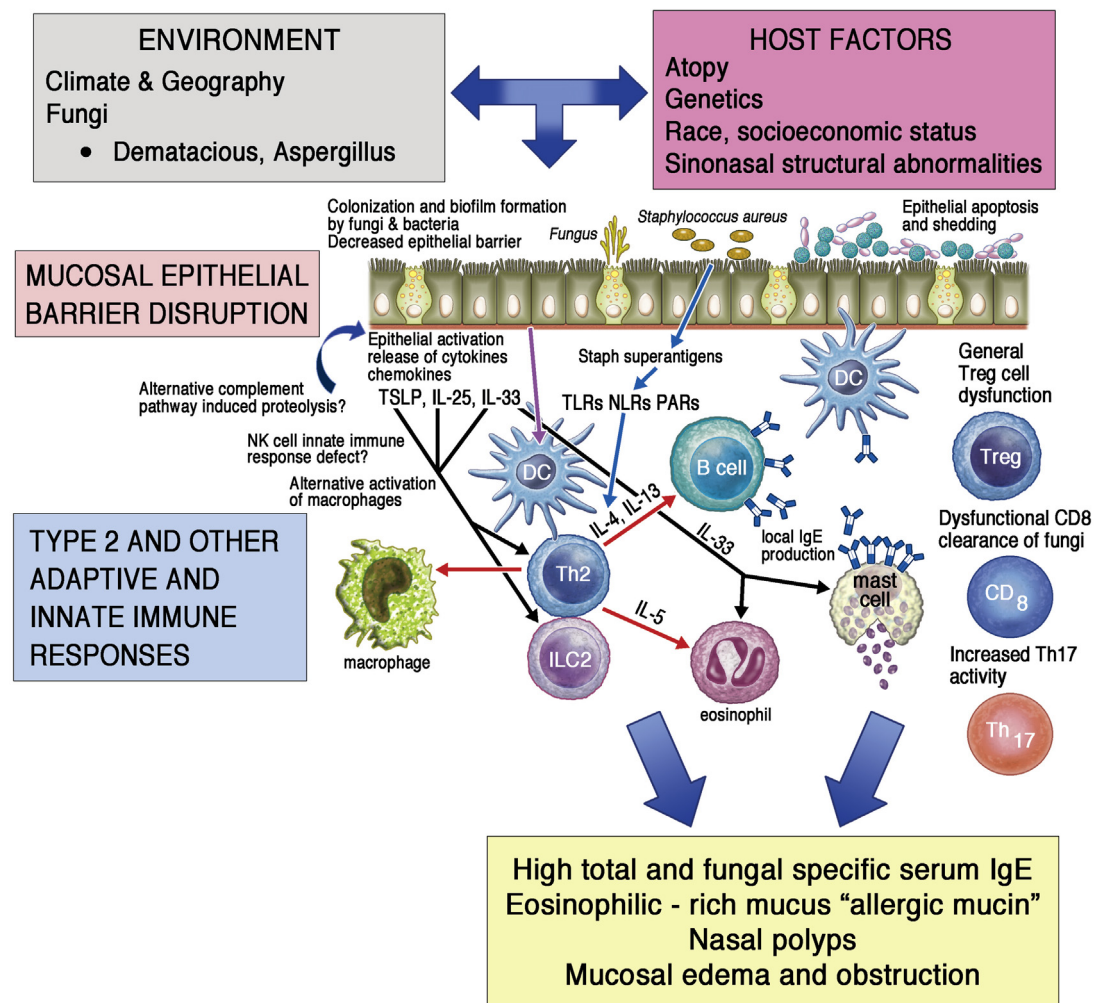


FIG 1. Pathogenesis and principal phenotypic presentation of AFRS. Host and environmental factors, including fungal exposures, influence development of a predominantly type 2 immune responses, which are now known to include both adaptive responses involving T_H2 cells and innate responses involving ILC2s. IL-5 (from T_H2 s, ILC2s) induces eosinophilia, and IL-4 and IL-13 (ILC2s, T_H2 s) induce local IgE production, including antifungal IgE. Sinonasal colonization with fungi and bacteria lead to activation of epithelium with consequent apoptosis of epithelial cells, loss of epithelial barrier integrity, and release of upstream proinflammatory chemokines and cytokines with increased thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 levels. Fungal clearance is impaired. Recently, IL-33 has been found to be of importance in mast cell activation in patients with AFRS. Ultimately, there is development of high total and fungus-specific serum IgE levels, eosinophil-rich mucus (allergic mucin), nasal polyps, and mucosal edema and obstruction. Altered inflammatory responses may also involve pattern recognition receptors: TLRs, Toll-like receptors; NLRs, nucleotide-binding and oligomerization domain (NOD)-like receptors; PARs, protease-activated receptors.⁴² Central graphics were adapted and modified from figures in Akdis et al³ and Bachert and Akdis.⁵

Other innate immune responses

Functional studies of peripheral natural killer (NK) cells from patients with CRSwNP suggest an impaired ability to degranulate and to produce $IFN-\gamma$,⁵⁹ with more severe defects in NK cell effector functions associated with more treatment-recalcitrant disease. However, to date, no conclusive studies have been published examining NK cell function or the role of group 1 innate lymphoid cells or group 3 innate lymphoid cells in patients with AFRS. Sinus mucosal biopsy specimens from both patients with AFRS and those with CRSwNP display upregulation of the complement pathway, particularly the alternative pathway (factor B) and common pathways (C3 and C5), suggesting that

complement-driven mechanisms might participate in enhanced innate responses that drive inflammatory response.⁶⁰

Dysfunctional $CD8^+$ T-cell responses to fungi

Pant and Macardle⁶¹ compared peripheral blood $CD4^+$ and $CD8^+$ T-cell responses to fungus in patients with AFRS, CRSwNP, eosinophilic mucus-associated CRS (essentially equivalent to EMCS, as defined by Ferguson), or allergic rhinitis with fungal allergy (ARFA) and healthy control subjects.⁶¹ In contrast to $CD4^+$ T-cell proliferation to fungus, which occurred in all samples, $CD8^+$ T cells did not proliferate or activate in

patients with AFRS and those with eosinophilic mucus-associated CRS but did respond in patients with ARFA, healthy control subjects, and most patients with CRSwNP. Although the numbers of subjects studied were relatively small (5-10 in each group), the results raise the question of whether dysfunctional CD8⁺ T-cell responses to fungus predispose to ineffective clearance and accumulation of fungi in the sinuses of patients with AFRS.

Regulatory T and T_H17 cells

There have been conflicting reports on the role of T_H17 and regulatory T cells in patients with AFRS of different ethnicities; a recent study in Asian Indian patients with AFRS (predominantly from *Aspergillus* species) found that compared with healthy control subjects, there were lower percentages of peripheral regulatory T cells (which could result in increased type 2 responses) but also increased numbers of T_H17 cells, suggesting that a T_H17-driven response could promote aggravation of nasal polyposis.⁶²

Role of bacterial cocolonization and superantigens

Dutre et al⁶³ studied 17 patients with AFRS caused by *Aspergillus* species and found that *Staphylococcus aureus* coexisted with *Aspergillus* species within the sinuses, nearly all subjects had serum IgE to *S aureus* enterotoxin superantigens, and levels correlated with total serum IgE levels. They hypothesized that *S aureus* might play a crucial role in AFRS by synergizing with or making use of *Aspergillus* species in creating a T_H2 tissue signature. This would promote nonspecific T-cell activation through *S aureus* superantigenic activities, resulting in the high total IgE concentrations typically found in patients with AFRS. They proposed that *Aspergillus* species and *S aureus* benefit from each other's potential to overcome the mucosal barrier, bias the immune system, and cause AFRS.

CLINICAL RECOGNITION AND DIAGNOSIS

The diagnosis of AFRS should be a differential consideration in any patient with symptoms of CRS resistant to conventional medical therapy, especially in the absence of any evidence of immune suppression. Diagnosis is made based on clinical features, microscopic examination or culture of nasal discharge, imaging, and immune studies.

Clinical features

Patients with AFRS present with symptoms of CRS refractory to conventional medical therapy, nearly always with concomitant nasal polyps. Nasal discharge typically has a thick, greenish-brown mucoid appearance with a peanut butter–like consistency usually associated with green to black rubbery nasal plugs.¹⁶ Without timely intervention, possible complications in patients with AFRS can include visual disturbances,^{64,65} proptosis,⁶⁶ facial deformity, and intracranial sequelae, such as pressure-induced intracranial neuropathies or intracranial abscesses.^{67,68} The incidence of bony erosion in patients with AFRS has been reported to be between 20% and 90%^{29,69} and is more common in patients who are younger, are African American, and have higher Lund-Mackay CT scores. The most common site of extension is the orbit, specifically the lamina papyracea, and the anterior cranial fossa is the most commonly

involved intracranial space. In patients with bony erosion, no histologic evidence of mucosal invasion by fungi has been demonstrated.⁶⁹ Because tissue invasion by fungi is not the causative mechanism of bone erosion in patients with AFRS, sinus expansion by polyposis with resultant pressure atrophy and the action of inflammatory mediators have been hypothesized as causal mechanisms, but this has not been demonstrated conclusively.

Microscopic examination and fungi

Microscopic examination of sinonasal discharge finds 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.^{11,16} Hematoxylin and eosin stains demonstrate a mixed inflammatory infiltrate composed of eosinophils, plasma cells, and lymphocytes, sometimes with fungal elements and calcifications. Gomori methenamine silver or Fontana Mason stains can detect fungal hyphae when they are sparse and not well identified on hematoxylin and eosin staining.²² Depending on the technique used for fungal culture from allergic mucin, the yield of fungal cultures in patients with AFRS can vary greatly. As noted earlier in this review, fungi are abundant in ambient air, and therefore the growth of fungi in cultures alone might represent saprophytic contamination and is not diagnostic of AFRS in the absence of clinical, imaging, and immune criteria.

Immunologic studies

Immune studies are essential in the diagnosis of AFRS. With a history of atopy, patients with AFRS often present with high total serum IgE levels, although not as high as those in patients with ABPA. Patients with AFRS demonstrate type I IgE hypersensitivity to fungi, as well as other aeroallergens.¹⁸ Stewart and Hunsacker⁷⁰ reported that among patients with polypoid rhinosinusitis, patients with AFRS had increases specific IgE levels to an average of 5 molds versus only 0.1 in those without AFRS. They proposed that finding specific IgE to multiple fungi in the setting of an increased total IgE level is a useful measure to differentiate patients with AFRS from those with non-AFRS CRS. Because fungus-specific IgG levels were increased in all groups of patients with polypoid rhinosinusitis, the clinical utility of such testing is uncertain. Hutcheson 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,²⁸ although such testing is not widely available.

Imaging studies

CT scans of the sinuses in patients with AFRS typically show near-complete opacification with heterogeneous radiodensity of the soft tissue of the sinuses, as seen in Fig 2. Zinreich et al²⁷ proposed that increased attenuation in paranasal sinus soft-tissue masses on CT scan is highly suggestive of fungal sinusitis and that magnetic resonance imaging (MRI) is more specific than CT scanning to confirm this finding. This increased attenuation has been described to be central and have a “serpiginous” or “starry sky” appearance.⁷¹ MRI findings typically show central hypointensity on T1- and T2-weighted images, but these are

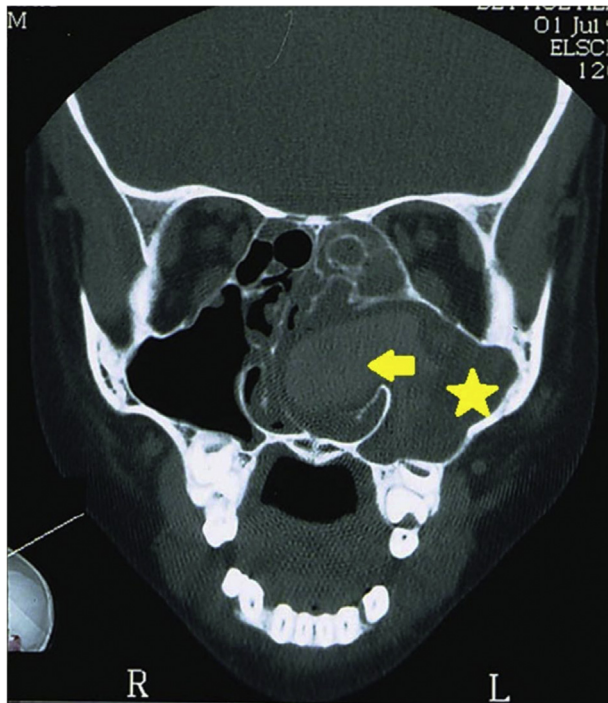


FIG 2. CT scan in patients with AFRS demonstrating complete opacification of the left maxillary sinus (star) with central hyperattenuation (arrow).

more consistently found with T2-weighted images. Although Zinreich et al²⁷ hypothesized that decreased signal intensity seen on T1- and T2-weighted MRI images of fungal sinusitis could be secondary to ferromagnetic elements, subsequent studies have also ascribed this 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.^{71,72} The mucosal lining of the sinuses are hypointense on T1-weighted images and hyperintense on T2-weighted images, with enhancement after administration of intravenous gadolinium contrast.

Diagnostic criteria

As noted earlier under the heading of AFRS versus CRSwNP, Bent-Kuhn criteria for diagnosis of AFRS are commonly used. Although the Lund-MacKay CT scoring system is widely used to quantitate the severity and extent of sinus disease, it does not address bone erosion or sinus expansion. In 2009, Wise et al³⁰ proposed a radiologic staging system for disease severity of AFRS that includes scoring of expansion or erosion for each of the sinuses seen on noncontrast thin-cut axial and coronal CT scans, 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

Except for the mildest cases, AFRS requires surgical intervention, followed by adjuvant medical therapy. Overall recurrence rates after surgery are reported to range from 10% to 100%.¹ The vast majority of clinical studies in the AFRS literature indicate that medical therapy alone is usually ineffective in alleviating symptoms and that surgical intervention, alone or in combination with medical therapy, leads to

improved clinical outcomes.¹ Functional endoscopic sinus surgery is usually the preferred modality of surgical intervention. Complete debridement of all fungal debris and eosinophilic mucin is vital because incomplete debridement has been linked to early recurrence of the disease and the need for revision surgery.^{1,73}

Adjuvant medical therapy is integral for successful treatment of AFRS, and a variety of agents have been studied, such as oral and topical steroids, oral and topical antifungals, leukotriene antagonists, omalizumab, and immunotherapy.^{1,8} Systemic steroids reduce the inflammatory response, which in turn causes polyp regression and decreased sinonasal edema. When given preoperatively, steroids decrease symptoms arising from mechanical obstruction and improve intraoperative visualization of sinonasal anatomy during functional endoscopic sinus surgery. Postoperative oral steroids help decrease disease recurrence.^{74,75} In a study by Schubert and Goetz,⁷⁴ patients taking postoperative oral corticosteroids for as little as 2 months had significant clinical improvement for 12 months, with 12 months of therapy having the best clinical outcome. Patients receiving postoperative oral corticosteroids can also be maintained in lower stages of the disease (stage 0 and 1).⁷⁶ In a study by Rupa et al,⁷⁵ all patients receiving postoperative systemic steroids (50 mg/d $\times$ 6 weeks and then an additional 6-week taper) had an improvement in symptoms and endoscopy at 12-week follow-up. All patients in this study received intranasal fluticasone nasal spray and oral itraconazole. However, patients in the steroid arm also had side effects from systemic steroids, including weight gain, Cushingoid features, acne, and steroid-induced diabetes mellitus.

Topical corticosteroid monotherapy has not been studied in patients with AFRS. Most studies in patients with AFRS used topical steroids only in conjunction with other modalities, such as oral corticosteroids or surgery. Based on a systematic review, topical corticosteroid therapy, such as budesonide sinonasal rinses, after completion of oral corticosteroid therapy has been proposed as a means to prevent disease recurrence, but the recommended duration is uncertain.⁷⁷ With at least 2 years of follow-up, patients who received a variable duration of combined oral and topical corticosteroids postoperatively had a better clinical outcome and decreased disease recurrence compared with those undergoing surgery alone.⁷⁸

Antifungals

There are only a few reports that have described the benefit of oral antifungals in patients with refractory AFRS.^{79,80} In a study by Patro et al,⁸¹ patients with AFRS receiving preoperative itraconazole for 1 month before surgery had decreased Sino-Nasal Outcome Test 20 scores, Lund-MacKay scores, Kupferberg nasal endoscopic grades, polyp size, hyperdensities on CT imaging, and postoperative fungal cultures compared with control subjects. However, a Cochrane review of topical and systemic antifungal therapies in patients with all phenotypes of CRS did not demonstrate any clinical benefit.⁸²

Other pharmacologic modalities

There is insufficient evidence to support the use of other modalities, such as montelukast or omalizumab, in the treatment

of AFRS. There is 1 case report citing successful postoperative treatment of AFRS with 10 mg/d montelukast, a leukotriene receptor antagonist, as an adjuvant to intranasal corticosteroids.⁸³ One case published reported successful use of omalizumab to treat AFRS refractory to surgery and oral corticosteroids,⁸⁴ and 1 retrospective review of 7 patients reported that omalizumab therapy could help reduce the dependence on corticosteroid and antifungal treatments in patients with AFRS.⁸⁵

Allergen immunotherapy

No firm conclusions about efficacy of allergen immunotherapy (AIT) in AFRS can be made because of a general lack of placebo-controlled arms in studies. Both subcutaneous immunotherapy (SCIT) and sublingual AIT have been reported to confer clinical benefit in patients with AFRS. Even high-dose fungal AIT has been shown to be safe in 8 patients with AFRS, one treated for up to 43 months, with no increased risk of local reactions or need for dose adjustments.⁸⁶

In generally uncontrolled studies by Mabry et al,⁸⁷⁻⁸⁹ patients with AFRS had improved clinical outcomes after 1-3 years of SCIT, with a decrease in polyp recurrence, nasal crusting, allergic mucin, need for systemic steroids, and absence of any severe adverse reactions. Patients in these studies did not have decreases in fungal serum IgE levels after completion of AIT; however, there was no disease recurrence during a relatively limited follow-up period of 7 to 17 months after discontinuation of AIT. Mabry's group has also reported that patients with AFRS receiving SCIT compared to those who did not have greater improvement in endoscopic disease staging, decreased need for systemic steroids, decreased office visits for medical intervention, and decreased reoperation rates.^{90,91}

The use of sublingual immunotherapy in 10 patients with AFRS has been associated in an uncontrolled study with favorable outcomes with decrease in subjective symptoms, physical findings, serum IgE levels, and Lund-McKay scores, with the absence of any significant side effects.⁹²

Biologics

In asthmatic patients endotyping (through identification of increased blood and tissue eosinophilia, IgE levels, and expression of type 2 inflammatory biomarkers, such as IL-4, IL-5, IL-13, and periostin) has been successfully applied to selection of biologic agents that benefit asthma. Beyond limited reports of omalizumab use in AFRS cited earlier,^{84,85} there is a good rationale for use of biologic agents in patients with AFRS, given that it is a type 2–driven disease and previous evidence of benefit of some agents in patients with CRSwNP.⁹³ Formal studies of biologics in patients with AFRS are required.

PROGNOSIS

AFRS is often a chronic recurrent disease. Waxman et al⁹⁴ divided patients after surgery based on prognosis into 3 groups: those who were cured, those who had recurrence within months, and those who had delayed recurrence in years. The tendency for recurrent disease could be reduced with postsurgical oral steroid therapy. Schubert and Goetz⁷⁴ reported that an increase in total serum IgE level of 10% or more in patients with AFRS after

sinus surgery was 79% sensitive and 77% specific for detecting recurrence of sinus disease and in predicting the need for recurrent sinus surgery.

Kupferberg et al⁷⁶ showed that endoscopic evidence of disease could precede clinical symptoms during periods of recurrence and recommended nasal endoscopy every 4 to 6 weeks for surveillance of recurrence. However, in a later study by White et al,²⁹ Sino-Nasal Outcome Test 20 and endoscopy scores were inadequate markers to suggest bony erosion. The authors suggested the early use of imaging, especially in higher-risk patients (ie, those who are younger, African American, and have higher Lund-MacKay scores).

What do we know?

- Host and environmental factors can increase the risk for AFRS.
- Fungi most commonly associated with AFRS can differ from those that cause infectious fungal sinusitis.
- AFRS is predominantly driven by type 2 inflammatory responses, both adaptive and innate.
- Sinus surgery is essential for management of most patients.
- Oral corticosteroids have demonstrated benefit in patients with AFRS.
- AFRS is often a recurrent and chronic disease.

What is still unknown?

- What is the precise contribution of environmental factors, fungi, and bacteria to the inflammatory cascade in patients with AFRS?
- What are the mechanisms that contribute to poor clearance of fungi from patients with AFRS?
- Why are some fungi more likely than others to cause AFRS?
- What is the role of bacterial cocolonization with fungi and, more generally, differences in the sinonasal microbiome in patients with AFRS?
- What are the cellular sources of inflammatory cytokines in patients with AFRS?
- Does AFRS represent a distinct endotype of CRSwNP, and what is the best approach to diagnosis?
- How can AFRS be better managed, and will emerging biologics (eg, type 2 inflammation modifiers and anti-thymic stromal lymphopoietin) prove useful in treatment of AFRS?
- In well-controlled trials, will AIT be demonstrated to be effective?
- Why do some patients have recurrence of AFRS, whereas others do not?

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