Clinical Commentary Review

Allergic Fungal Rhinosinusitis

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This article reviews the history of allergic fungal rhinosinusitis and the clinical, pathologic, and radiographic criteria necessary to establish its diagnosis and differentiate this disease from other types of chronic rhinosinusitis. Allergic fungal rhinosinusitis is a noninvasive fungal form of sinus inflammation characterized by an often times unilateral, expansile process in which the typical allergic "peanut-butter-like" mucin contributes to the formation of nasal polyps, hyposmia/anosmia, and structural changes of the face. IgE sensitization to fungi is a necessary, but not sufficient, pathophysiologic component of the disease process that is also defined by microscopic visualization of mucin-containing fungus and characteristic radiological imaging. This article expounds on these details and others including the key clinical and scientific distinctions of this diagnosis, the pathophysiologic mechanisms beyond IgE-mediated hypersensitivity that must be at play, and areas of current and future research. © **2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:599-604)**

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Allergic fungal rhinosinusitis (AFRS) is a noninvasive fungal disease of the sinuses described within the past 40 years and is now recognized as a distinct form of chronic rhinosinusitis (CRS). This article reviews the current understanding of AFRS, including its clinical presentation, pathophysiology, and current treatment.

DEMOGRAPHICS

AFRS accounts for about 5% to 10% of CRS cases.[1] It presents as a variant of chronic rhinosinusitis with nasal polyposis (CRSwNP), is more common in warm climates such as that of the southern United States, and affects both adults and children. Although it occurs in all ages, it tends to present in younger versus older patients. For example, the average age of a cohort of patients with AFRS in North Carolina was 29 years.[2] Patients with AFRS are more commonly black and women, and they more commonly have a lower socioeconomic standing than do patients with other forms of CRS.[2-4]

CLINICAL CHARACTERISTICS

Safirstein published the first description of AFRS in 1976[5] in which he described a 24-year-old woman who presented with recurrent nasal obstruction and rhinorrhea along with blood-tinged nasal casts. Investigations revealed eosinophils in both the blood and nasal mucus as well as immediate and delayed hypersensitivity following intradermal skin testing to *Aspergillus fumigatus*, which was also found in her nasal cultures. Her symptoms were noted to improve with prednisone. Katzenstein et al[6] subsequently further described 7 similar cases, which she termed "allergic *Aspergillus* sinusitis." These cases highlight what are still considered the key clinical presentations of AFRS, as will be delineated below.

Clinical history

The presentation of AFRS may range from subtle to dramatic and thus the signs and symptoms enumerated in Table I are important when the diagnosis of this disease is suspected. Indolent symptoms, such as painless and gradual nasal obstruction, anosmia, and the production of mucin, may progress for years[7] before alarming complaints arise, such as visual changes.[8] The expansile changes of the paranasal sinuses can result in either diplopia, due to proptosis, or loss of visual acuity and/or visual field defects, due to encroachment on the optic canal. Patients with AFRS are often atopic with IgE sensitization to various aeroallergens, and they have concomitant allergic rhinitis (AR) and/or asthma. Nasal congestion, rhinorrhea, and posterior pharyngeal drainage are some of the most common symptoms and can present gradually. The mucin produced in AFRS is a brown, thick material, occasionally bloody with crusty casts (see Figure 1, *D*). Classically described as having a thick, "peanut-butter-like" appearance, this mucin is a trademark of AFRS.[9,10] These symptoms fail to respond to antihistamines and nasal corticosteroid sprays, which should lead the physician to entertain the diagnosis of AFRS.

Physical examination

Allergic mucin drives many of the physical examination findings. Allergic mucin, sometimes referred to as eosinophilic mucin, commonly found in eosinophilic CRS, is a thick, highly viscous mucus containing a dense accumulation of eosinophils often having signs of degranulation (such as Charcot-Leyden

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Abbreviations used
AFRS- allergic fungal rhinosinusitis
AR- allergic rhinitis
CRS- chronic rhinosinusitis
CRSwNP- chronic rhinosinusitis with nasal polyposis
CT- computed tomography

crystals).[11] AFRS, by definition, also contains fungal hyphae within the allergic mucin.[12] This mucin expands within the sinuses, causing the bones and tissues to expand, and, in some cases, results in a change in facial appearance including facial asymmetry and proptosis.[13] This can be indolent but, upon recognition, becomes quite concerning to the patient, and, if the patient is a child, is alarming to parents.[14] For many patients who have ignored their sinonasal symptomatology, this may be the presenting complaint. Upon inspection of the anterior nares, the nasal mucosa may be pale because of allergic inflammation, and polyps, potentially only unilateral as the disease process is often found to be, may be visible. On anterior rhinoscopy, the nasal cavity may reveal the thickened, purulent drainage, mucosal crusting, or dark mucus. Depending on the degree of disease, polypoid degeneration may be noted. On nasal endoscopy, the thickened, tenacious mucus may be more evident along with significant polyposis and possible proteinaceous debris. Finally, it should be appreciated that for many patients who present early in the disease process, the diagnosis of AFRS may not be suspected until sampling of mucus or pathological specimen reveals fungal elements.

Skin testing and laboratory studies

Although the combination of CRS symptoms and the presence of allergic mucin may alert the clinician to a possible diagnosis of AFRS, sensitization to the causative fungus is a primary and requisite feature of AFRS. Evidence of sensitization may be identified through positive skin testing or serum specific IgE testing. Because these patients are usually atopic, fungal-specific IgE titers are elevated; however, the species to which such sensitization is present is not always the organism identified in surgical specimens.[15] Although fungal sensitization may be present in other forms of CRS, total IgE titers are typically much higher in AFRS.[16,17]

The most common fungi associated with AFRS include *Aspergillus* species and the dematiaceous (or "darkly pigmented") fungi[18,19] (such as species of *Alternaria*, *Bipolaris*, *Cladosporium*, and *Curvularia*), with geographic location often determining the more likely culprits of a region.[20] Identification of the causative fungi is often attempted with both histologic evaluation and culture. In a review of histologic findings, Granville et al[21] identified the causative fungus in 34 of 34 AFRS cases with Gomori methenamine silver stain. In contrast, fungi were not seen in any of 329 Gomori methenamine silver stains done on typical CRS samples. The efficacy of fungal cultures can be laboratory-dependent resulting in false-negative results, thus forcing the clinician to rely on histologic features for diagnostic purposes. As previously noted, the mucin in AFRS (referred to as "allergic mucin") is laden with intact eosinophils, eosinophil-secreted products (eg, eosinophil cationic protein), and Charcot-Leyden crystals (crystalized eosinophil-degradation products), and this mucin is colonized with noninvasive fungal hyphae (see Figure 1, *C*).[12]

Radiographic findings

Radiographic appearance of AFRS is unique and one of the most diagnostic findings in the disease process (Figure 1, *A* and *B*). Plain radiographs, as with most forms of sinusitis, are generally not helpful, but computed tomography (CT) and magnetic resonance imaging provide the classic findings. In contrast to CRS, AFRS may be limited to only a few sinuses and oftentimes is unilateral. Involved sinuses demonstrate the presence of an expansile lesion commonly with bone thinning and/or erosion; however, bony invasion is not seen.[13] AFRS CT findings also include heterogeneous opacities with areas of hyperattenuation (ie, increased density on a CT scan).[22] In areas in which erosion/expansion has not occurred, the surrounding bone may appear thickened or osteitic from the chronic inflammation as compared to the uninvolved areas. Although often described as being "calcific," the density of these opacities is actually a combination of the various metals (eg, iron, magnesium, and manganese) concentrated by the fungal organisms as well as the low water and high protein content of the mucin.[13] As a result, on magnetic resonance imaging the T2-weighted images demonstrate low signal intensity or signal void whereas on T1-weighted sequences a high or mixed intensity signal can be seen. One study reported that when used in combination with the presence of nasal polyps and Aspergillus specific IgE, the sensitivity and specificity of CT imaging is up to 70% and 100%, respectively.[23] This and other studies are limited by their being small series. Further as geographic location appears to have a significant impact on the underlying prevalence of this disease, the sensitivities and specificities of these findings may vary widely.

COMORBIDITIES

As noted, patients with AFRS are generally otherwise healthy. Commensurate with their previously noted atopy, AR and, less commonly, asthma[24] may be present although one study indicated that up to 37% of patients had concomitant asthma.[25] When present, AR can be especially challenging to treat because rhinitis symptoms are intertwined with those of AFRS.

PATHOPHYSIOLOGY

AFRS is an allergic disease in which noninvasive fungi cause significant morbidity by inducing hypersensitivity reactions. The inflammation observed in AFRS cannot, however, be simply explained by an uncomplicated, traditional IgE-mediated hypersensitivity reaction. Instead, AFRS reflects multiple cellular immune responses and centrally includes eosinophilic inflammation in response to IL-5 and other eosinophil-activating cytokines and chemokines.[26] Fungi colonize and proliferate within the sinuses, triggering a significant immunologic reaction, which drives the production of allergic mucin. Fungi are potent immunogens that directly interact with the nasal epithelium and innate immune cells, such as dendritic cells, through the expression of pathogen-associated molecular patterns and protease secretions. Pathogen-associated molecular patterns (eg, fungus-derived complex carbohydrates) are recognized by lectin and other receptors, whereas proteases activate protease-activating receptors are expressed on epithelial and innate immune cells.[27] Together, these processes create an aggressive inflammatory response, combining a type 2 cytokine-mediated adaptive immune response with a severe innate immune cytokine "storm."[28]

TABLE I. Research and patient-care definitions of AFRS

Criteria	Research definitions of AFRS	Patient-care definitions of AFRS
Pattern of symptoms	≥12 wk	≥12 wk
Symptoms for diagnosis	Requires ≥1 of the following symptoms: • Anterior and/or posterior nasal drainage • Nasal obstruction • Decreased sense of smell • Facial pain, pressure, and/or fullness	Requires ≥1 of the following symptoms: • Anterior and/or posterior nasal drainage • Nasal obstruction • Decreased sense of smell • Facial pain, pressure, and/or fullness
Objective documentation	Requires all of the following: • Endoscopic evidence of allergic mucin (pathology showing fungal hyphae with degranulating eosinophils) and sinus inflammation • CT or magnetic resonance imaging findings consistent with rhinosinusitis • Evidence of fungal sensitization by skin testing or serum IgE • No histologic evidence of invasive disease	Requires all of the following: • Endoscopic evidence of allergic mucin (pathology showing fungal hyphae with degranulating eosinophils) and sinus inflammation • Evidence of fungal sensitization by skin testing or serum IgE • No histologic evidence of invasive disease
	Possible but NOT required: • Fungal culture • Increased total IgE • More than 1 imaging modality consistent with AFRS	The following is HIGHLY recommended: • Sinus CT imaging is not essential but is highly recommended because of tendency for bony erosions and extension of disease into adjacent anatomic areas. Possible but NOT required: • Fungal culture • Increased total IgE • More than 1 imaging modality consistent with AFRS

Table adapted from Meltzer et al, with permission.[12]

In addition to the specific immune response to fungal antigens, the underlying T_H2 process may be exacerbated by a nonspecific activation of T effector cells in response to superantigens, including those derived from the *Staphylococcus aureus* that routinely colonizes the sinuses of patients with AFRS.[29] Capable of activating T cells without the requirement for antigen processing and presentation, these superantigens can dramatically augment the type 2 cytokine response.[30] In some studies, *Staph aureus* colonization is more prominent in AFRS than in CRSwNP.[31] *Staph aureus* may also have a symbiotic relationship with the fungi in AFRS, because the fungi disturb the sinus epithelial barrier, creating a vulnerability on which the *Staph aureus* capitalizes.[32]

GENETICS

Limited genetic associations have been identified in CRS including AFRS, reflecting the many phenotypes of CRS and the historical absence of unambiguous clinical definitions.[33] In one study, Schubert et al[34] identified HLA-DQB1*03 in AFRS as a potential marker, finding that 66% of the patients with AFRS carried at least 1 HLA-DQB1*03 allele whereas only 50% of the patients with eosinophilic CRSwNP carried this major histocompatibility complex. Using microarray analysis, Orlandi et al[35] identified subtle differences in gene expression between AFRS and eosinophilic CRS but found that both groups were significantly distinct from normal controls; for example, the expression of genes that mediate lysosomal activity including cathepsin B, sialyltransferase 1, GM2 ganglioside activator protein, and S100 calcium-binding protein was elevated only in the eosinophilic CRS group and not in the AFRS group.[35]

BIOMARKERS

To make the diagnosis of AFRS, physical examination findings, laboratory evidence, and radiographic findings are paramount; however, minimally invasive, objective measurements can assist in the diagnosis. At present, serum total IgE levels serve as the most useful and readily measurable biomarker because these are elevated in AFRS,[36,37] with concentrations in AFRS generally being more than 500 IU/mL,[38] markedly higher than in those with idiopathic CRSwNP. Also, although this elevation in serum IgE cannot be completely explained by fungal-specific titers, these elevations need to be interpreted in the context of the patient's clinical picture because they are not pathognomonic for AFRS. Other biomarkers, such as the IL-13–dependent matrix protein periostin, have been explored. Consistent with its being a T_H2-mediated disease process, AFRS is associated with an increase in periostin[39]; however, this elevation did not distinguish AFRS from other presentations of eosinophilic CRS. A few proteomic studies have been performed attempting to identify an AFRS-specific "signature." In one pilot study, researchers used a novel protein pattern recognition technique (surface enhanced laser desorption/ionization time-of-flight mass spectrometry) to create a "proteomic fingerprint" of the disease. Using this proteomic profiling of patient's serum, they were able to identify patients with AFRS with 84% sensitivity and 90% specificity.[40] Given these very promising, yet preliminary results, this technique merits further investigation.

DIAGNOSIS OF THIS PHENOTYPE

Fungal involvement of the sinuses can be roughly divided into 2 groups: invasive and noninvasive, the latter being the category for AFRS. Other noninvasive forms of fungal sinusitis include fungus ball (commonly but mistakenly often referred to as "mycetoma") and certain presentations of eosinophilic CRS. Nearly 20 years after its initial description as an Allergic Bronchopulmonary Aspergillosis-like disease of the upper airway in 1976, Bent and Kuhn[41] sought to establish diagnostic criteria on

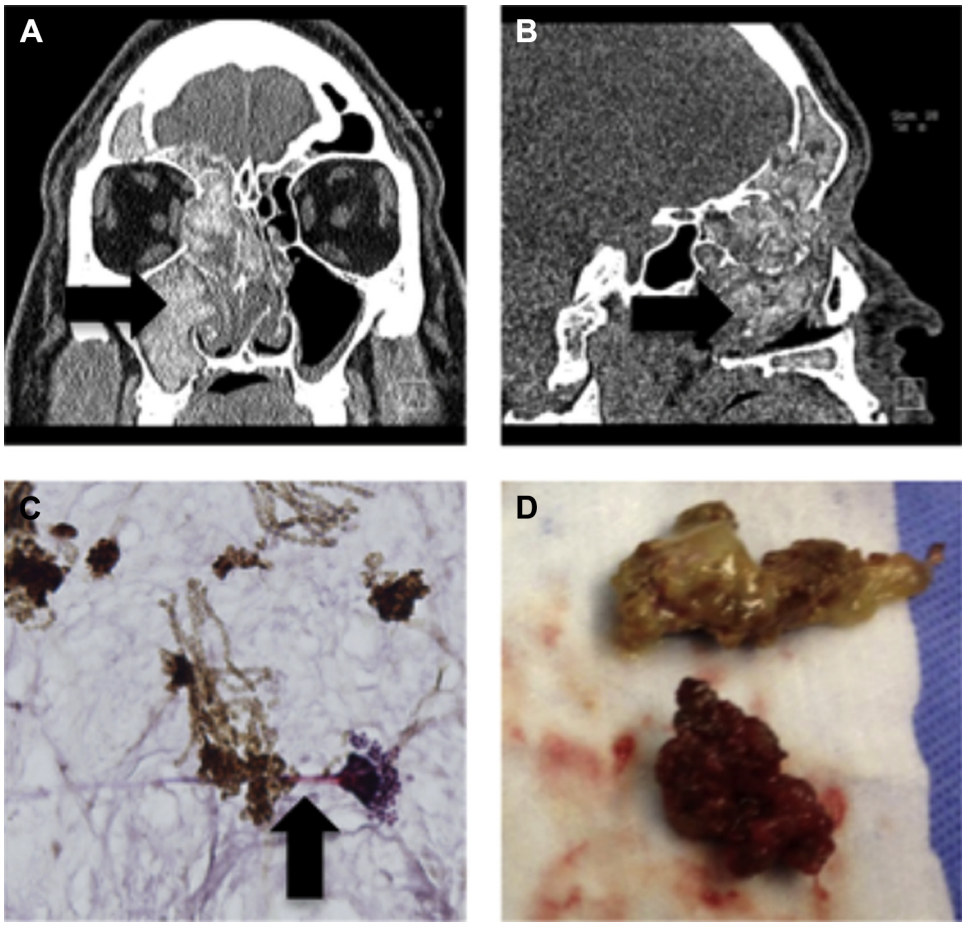

FIGURE 1. CT imaging, microscope imaging, and gross imaging of AFRS. **A** and **B**, CT imagining of AFRS and its unilateral, noninvasive, expansile appearance with heterogeneous opacities (arrows). **C**, Microscopic imaging of *Aspergillus fumigatus* contained within allergic mucin; note the short stalk-like conidiophore (arrow) with conical terminal vesicle and single-row phialides. **D**, Appearance of allergic mucin.

the basis of commonalities observed in their patients with AFRS. Five major criteria and other minor criteria are listed in Table II.[41] Because patients with eosinophilic CRS can have eosinophilic mucin and atopy,[42] the diagnosis of AFRS ideally requires all 5 major criteria including the CT findings, which are fairly unique to AFRS.[43] Also, patients with AFRS can present with unilateral disease, and polyps may not be present. The major differences between AFRS and other forms of fungal sinusitis are as follows: (1) in AFRS, the fungi never invade the sinus tissue, and (2) the mucin of AFRS is the product of an allergic hypersensitivity reaction to the fungi as opposed to a simple overgrowth of mycelial elements as is seen in fungus balls.

TABLE II. Bent and Kuhn criteria

Major criteria	Minor criteria
Type I hypersensitivity to fungi (confirmed by skin test or IgE ImmunoCAP)	Bone erosion
Nasal polyposis	Charcot-Leyden crystals
Characteristic CT findings	Unilateral disease
Eosinophilic mucus without invasion into the sinus tissue	Peripheral eosinophilia
Positive fungal stain of sinus content removed during surgery	Positive fungal culture

Table adapted from criteria proposed by Bent and Kuhn,[41] with permission.

UNIQUE THERAPEUTIC IMPLICATIONS OF THIS PHENOTYPE

The treatments of AFRS can be divided into medical and surgical approaches. Often times, patients are already on—and failing—medical therapy for AR and/or CRS when the diagnosis of AFRS is finally made. Unlike other forms of CRS, early surgical intervention is essential to eradicate as much fungi and "allergic" mucin as possible such that subsequent and necessary medical interventions are more effective. Complete extirpation of the mucin is necessary to halt or prevent future deformations of the facial skeleton bony confines of the paranasal sinuses. It is universally agreed that although surgical intervention represents the first major step in addressing the disease, continued and long-term medical therapy is essential for preventing relapse.

Myriad therapies have been attempted including oral and topical corticosteroids, oral and topical antifungals, subcutaneous and sublingual allergen immunotherapy, leukotriene antagonists, and even alternative therapies such as manuka honey, a specific

honey that has been widely studied for its antimicrobial and anti-inflammatory properties. Corticosteroids are universally agreed upon in the treatment of AFRS given their significant effect on the production, activation, and migration of eosinophils,[25] and current recommendations include systemic corticosteroids postoperatively until nasal lavage corticosteroids can be started.[44,45] Argument remains, however, on the optimal duration of systemic therapy, with some authors, for example, advocating for protracted courses of oral corticosteroids until there is resolution of all visible signs of inflammation.[46]

Given the role of fungus in the etiology of the disease, it would seem logical to use an antifungal approach in addition to addressing the inflammation. Although systemic and topical antifungals have been frequently used,[47] most studies find little or no evidence for their efficacy.[45] A Cochrane review of antifungal therapies in all forms of CRS did not specifically address their use in AFRS because studies involving these patients did not fulfill their inclusion criteria.[48] Despite this controversy, the use of certain azole antifungals such as itraconazole, which have been noted to have an anti-inflammatory effect,[49] may have the potential to reduce recurrence.[47,50]

Allergen immunotherapy is an even more controversial area of AFRS management. The previously debated concern that allergen immunotherapy may exacerbate a type III hypersensitivity reaction has been dismissed because type III hypersensitivity is neither a mechanism contributing to the pathogenesis of AFRS nor a known complication of immunotherapy.[51] Several studies have reported that immunotherapy is helpful in AFRS as an adjunct therapy.[52-55] These studies report better quality of life and mucosal staging as well as diminished corticosteroid requirements and repeat surgery compared with the controls.[54,56,57] However, all these studies have suffered from the absence of well-characterized controls and doubt has been raised from their interpretations given the poor outcomes of fungal immunotherapy when used for other conditions such as AR and asthma.[58] Sublingual immunotherapy has been evaluated in the setting of AFRS and also found to be a safe adjunct therapy[59]; however, its efficacy has never been validated. As a result, immunotherapy remains an option for treatment rather than a recommendation.

Other treatments have also been attempted and, at best, poorly studied. Leukotriene antagonists are not routinely used although a favorable response has been reported.[60] In addition, topical manuka honey has been studied and although some patients felt better, no endoscopic objective improvement in sinus disease was reported.[61]

PROPOSED CLINICAL AND RESEARCH DEFINITION OF THIS PHENOTYPE

The commonly accepted criteria for AFRS remain those that were proposed by Bent and Kuhn in 1994 (Table II). To maintain the sensitivity and increase the specificity of diagnosis criteria, delegates of the American Academy of Allergy, Asthma, & Immunology, the American Academy of Otolaryngic Allergy, the American Academy of Otolaryngology − Head & Neck Surgery, the American College of Allergy, Asthma, and Immunology, and the American Rhinologic Society met in 2003 and agreed upon newer criteria for the diagnosis of AFRS that should be used in clinical research studies (Table I).[12] These newer criteria emphasize the duration of symptoms (≥12 weeks) to bring the diagnostic criteria in line with other forms of CRS and incorporate newer procedures, such as rhinoscopy, by which diagnosis is possible without surgery. The European Position Paper on Rhinosinusitis and Nasal Polyps 2012 also addressed the diagnosis of AFRS.[43] They specifically highlight the fact that because many patients with other forms of CRSwNP may commonly have 3 of the Bent-Kuhn criteria (ie, nasal polyposis, fungi on staining, and eosinophilic mucin without fungal invasion into the tissue), the additional documentation of both IgE-mediated hypersensitivity (though also potentially seen in nonfungal CRSwNP) and the presence of characteristic CT findings is essential.[62]

RESEARCH QUESTIONS AND FUTURE DIRECTIONS

Much remains to be known about AFRS. Some of the more pressing research explorations:

- What are the immunologic differences between AFRS and other forms of CRS?
- What are the roles of fungal-specific IgE and other innate and adaptive immune responses in AFRS?
- What biomarkers differentiate AFRS from other forms of CRS?
- What are the best preoperative and postoperative medical regimens that will most effectively provide improved, long-term quality of life and disease treatment?
- What is the role of allergen immunotherapy?
- Do certain antifungal therapies, such as itraconazole, play a role in treating AFRS?

CONCLUSIONS

AFRS should be considered a distinct presentation of CRS that is unique in its interaction with fungi and the role of fungal-specific IgE/T_H2 immune responses. It is a noninvasive form of fungal sinusitis and diagnosis requires the presence of nasal polyps, IgE hypersensitivity to the relevant fungus, unique CT findings, "allergic" mucin, and a positive fungal stain of sinus content. Treatment requires surgical removal of the allergic mucin before starting effective medical therapy, which includes systemic followed by topical corticosteroids. The role of other adjunct treatments such as allergen immunotherapy and antifungal medications has not been fully established and the lack of high-level evidence prevents them from being generally recommended.

REFERENCES

1. de Souza C, Rodrigues JP. Fungal Rhinosinusitis. In: Stucker FJ, de Souza C, Kenyon GS, Lian TS, Draf W, Schick B, eds. Rhinology and Facial Plastic Surgery. Philadelphia, PA: Springer Science & Business Media; 2009.
2. Lu-Myers Y, Deal AM, Miller JD, Thorp BD, Sreenath SB, McClurg SM, et al. Comparison of socioeconomic and demographic factors in patients with chronic rhinosinusitis and allergic fungal rhinosinusitis. Otolaryngol Head Neck Surg 2015;153:137-43.
3. Miller JD, Deal AM, McKinney KA, McClurg SW, Rodriguez KD, Thorp BD, et al. Markers of disease severity and socioeconomic factors in allergic fungal rhinosinusitis. Int Forum Allergy Rhinol 2014;4:272-9.
4. Wise SK, Ghegan MD, Gorham E, Schlosser RJ. Socioeconomic factors in the diagnosis of allergic fungal rhinosinusitis. Otolaryngol Head Neck Surg 2008; 138:38-42.
5. Safirstein BH. Allergic bronchopulmonary aspergillosis with obstruction of the upper respiratory tract. Chest 1976;70:788-90.
6. Katzenstein AL, Sale SR, Greenberger PA. Allergic Aspergillus sinusitis: a newly recognized form of sinusitis. J Allergy Clin Immunol 1983;72:89-93.

7. Marple BF. Allergic fungal rhinosinusitis: a review of clinical manifestations and current treatment strategies. Med Mycol 2006;44:S277-84.
8. Marple BF, Gibbs SR, Newcomer MT, Mabry RL. Allergic fungal sinusitis-induced visual loss. Am J Rhinol 1999;13:191-5.
9. Marple BF. Allergic fungal rhinosinusitis: current theories and management strategies. Laryngoscope 2001;111:1006-19.
10. Glass D, Amedee RG. Allergic fungal rhinosinusitis: a review. Ochsner J 2011; 11:271-5.
11. Meltzer EO, Hamilos DL. Rhinosinusitis diagnosis and management for the clinician: a synopsis of recent consensus guidelines. Mayo Clin Proc 2011;86: 427-43.
12. Meltzer EO, Hamilos DL, Hadley JA, Lanza DC, Marple BF, Nicklas RA, et al. Rhinosinusitis: establishing definitions for clinical research and patient care. J Allergy Clin Immunol 2004;114:155-212.
13. Aribandi M, McCoy VA, Bazan C. Imaging features of invasive and noninvasive fungal sinusitis: a review. Radiographics 2007;27:1283-96.
14. McClay JE, Marple B, Kapadia L, Biavati MJ, Nussenbaum B, Newcomer M, et al. Clinical presentation of allergic fungal sinusitis in children. Laryngoscope 2002;112:565-9.
15. Thompson GR, Patterson TF. Fungal disease of the nose and paranasal sinuses. J Allergy Clin Immunol 2012;129:321-6.
16. Telmesani LM. Prevalence of allergic fungal sinusitis among patients with nasal polyps. Ann Saudi Med 2009;29:212-4.
17. Bakhshaee M, Fereidouni M, Mohajer MN, Majidi MR, Azad FJ, Moghiman T. The prevalence of allergic fungal rhinosinusitis in sinonasal polyposis. Eur Arch Otorhinolaryngol 2013;270:3095-8.
18. Revankar GS. Phaeohyphomycosis: infection due to dark (dematiaceous) molds. In: Hospenthal RD, Rinaldi GM, eds. Diagnosis and treatment of fungal infections. Cham, Switzerland: Springer International Publishing; 2015:151-7.
19. Ferguson BJ, Barnes L, Bernstein JM, Brown D, Clark CE, Cook PR, et al. Geographic variation in allergic fungal rhinosinusitis. Otolaryngol Clin North Am 2000;33:441-9.
20. Montone KT, Livolsi VA, Feldman MD, Palmer J, Chiu AG, Lanza DC, et al. Fungal rhinosinusitis: a retrospective microbiologic and pathologic review of 400 patients at a single university medical center. Int J Otolaryngol 2012;2012: 684835.
21. Granville L, Chirala M, Cernoch P, Ostrowski M, Truong LD. Fungal sinusitis: histologic spectrum and correlation with culture. Hum Pathol 2004; 35:474-81.
22. Reddy CE, Gupta AK, Singh P, Mann SB. Imaging of granulomatous and chronic invasive fungal sinusitis: comparison with allergic fungal sinusitis. Otolaryngol Head Neck Surg 2010;143:294-300.
23. Dhiwakar M, Thakar A, Bahadur S, Sarkar C, Banerji U, Handa KK, et al. Preoperative diagnosis of allergic fungal sinusitis. Laryngoscope 2003;113:688-94.
24. Manning SC, Holman M. Further evidence for allergic pathophysiology in allergic fungal sinusitis. Laryngoscope 1998;108:1485-96.
25. Uri N, Ronen O, Marshak T, Parpara O, Nashashibi M, Gruber M. Allergic fungal sinusitis and eosinophilic mucin rhinosinusitis: diagnostic criteria. J Laryngol Otol 2013;127:867-71.
26. Schubert MS. Allergic fungal sinusitis: pathogenesis and management strategies. Drugs 2004;64:363-74.
27. Shin SH, Lee YH, Jeon CH. Protease-dependent activation of nasal polyp epithelial cells by airborne fungi leads to migration of eosinophils and neutrophils. Acta Otolaryngol 2006;126:1286-94.
28. Ebert CS, McKinney KA, Urrutia G, Wu M, Rose AS, Fleischman GM, et al. Expression of protease-activated receptors in allergic fungal rhinosinusitis. Int Forum Allergy Rhinol 2014;4:266-71.
29. Plonk DP, Luong A. Current understanding of allergic fungal rhinosinusitis and treatment implications. Curr Opin Otolaryngol Head Neck Surg 2014;22:221-6.
30. Schubert MS. A superantigen hypothesis for the pathogenesis of chronic hypertrophic rhinosinusitis, allergic fungal sinusitis, and related disorders. Ann Allergy Asthma Immunol 2001;87:181-8.
31. Clark DW, Wenaas A, Luong A, Citardi MJ, Fakhri S. *Staphylococcus aureus* prevalence in allergic fungal rhinosinusitis vs other subsets of chronic rhinosinusitis with nasal polyps. Int Forum Allergy Rhinol 2013;3:89-93.
32. Dutre T, Al Dousary S, Zhang N, Bachert C. Allergic fungal rhinosinusitis—more than a fungal disease? J Allergy Clin Immunol 2013;132:487-489.e481.
33. Hsu J, Avila PC, Kern RC, Hayes MG, Schleimer RP, Pinto JM. Genetics of chronic rhinosinusitis: state of the field and directions forward. J Allergy Clin Immunol 2013;131:977-93. 993.e971-5.
34. Schubert MS, Hutcheson PS, Graff RJ, Santiago L, Slavin RG. HLA-DQB1 *03 in allergic fungal sinusitis and other chronic hypertrophic rhinosinusitis disorders. J Allergy Clin Immunol 2004;114:1376-83.
35. Orlandi RR, Thibeault SL, Ferguson BJ. Microarray analysis of allergic fungal sinusitis and eosinophilic mucin rhinosinusitis. Otolaryngol Head Neck Surg 2007;136:707-13.
36. Hutcheson PS, Schubert MS, Slavin RG. Distinctions between allergic fungal rhinosinusitis and chronic rhinosinusitis. Am J Rhinol Allergy 2010; 24:405-8.
37. Akdis CA, Bachert C, Cingi C, Dykewicz MS, Hellings PW, Naclerio RM, et al. Endotypes and phenotypes of chronic rhinosinusitis: a PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol 2013;131:1479-90.
38. Schubert MS, Goetz DW. Evaluation and treatment of allergic fungal sinusitis, I: demographics and diagnosis. J Allergy Clin Immunol 1998;102:387-94.
39. Laury AM, Hilgarth R, Nusrat A, Wise SK. Periostin and receptor activator of nuclear factor κ-B ligand expression in allergic fungal rhinosinusitis. Int Forum Allergy Rhinol 2014;4:716-24.
40. Das S, Maeso PA, Becker AM, Prosser JD, Adam BL, Kountakis SE. Proteomics blood testing to distinguish chronic rhinosinusitis subtypes. Laryngoscope 2008;118:2231-4.
41. Bent JP, Kuhn FA. Diagnosis of allergic fungal sinusitis. Otolaryngol Head Neck Surg 1994;111:580-8.
42. Rachelefsky GS. National guidelines needed to manage rhinitis and prevent complications. Ann Allergy Asthma Immunol 1999;82:296-305.
43. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinol Suppl 2012;50:130.
44. Hall AG, deShazo RD. Immunotherapy for allergic fungal sinusitis. Curr Opin Allergy Clin Immunol 2012;12:629-34.
45. Bachert C, Pawankar R, Zhang L, Bunnag C, Fokkens WJ, Hamilos DL, et al. ICON: chronic rhinosinusitis. World Allergy Organ J 2014;7:25.
46. Kuhn FA, Javer AR. Allergic fungal rhinosinusitis: our experience. Arch Otolaryngol Head Neck Surg 1998;124:1179-80.
47. Khalil Y, Tharwat A, Abdou AG, Essa E, Elsawy AH, Elnakib O, et al. The role of antifungal therapy in the prevention of recurrent allergic fungal rhinosinusitis after functional endoscopic sinus surgery: a randomized, controlled study. Ear Nose Throat J 2011;90:E1-7.
48. Sacks PL, Harvey RJ, Rimmer J, Gallagher RM, Sacks R. Topical and systemic antifungal therapy for the symptomatic treatment of chronic rhinosinusitis. Cochrane Database Syst Rev 2011;(8):CD008263.
49. Kanda N, Enomoto U, Watanabe S. Anti-mycotics suppress interleukin-4 and interleukin-5 production in anti-CD3 plus anti-CD28-stimulated T cells from patients with atopic dermatitis. J Invest Dermatol 2001;117:1635-46.
50. Seiberling K, Wormald PJ. The role of itraconazole in recalcitrant fungal sinusitis. Am J Rhinol Allergy 2009;23:303-6.
51. Doellman MS, Dion GR, Weitzel EK, Reyes EG. Immunotherapy in allergic fungal sinusitis: the controversy continues. A recent review of literature. Allergy Rhinol (Providence) 2013;4:e32-5.
52. Mabry RL, Mabry CS. Immunotherapy for allergic fungal sinusitis: the second year. Otolaryngol Head Neck Surg 1997;117:367-71.
53. Mabry RL, Manning SC, Mabry CS. Immunotherapy in the treatment of allergic fungal sinusitis. Otolaryngol Head Neck Surg 1997;116:31-5.
54. Mabry RL, Marple BF, Folker RJ, Mabry CS. Immunotherapy for allergic fungal sinusitis: three years' experience. Otolaryngol Head Neck Surg 1998;119:648-51.
55. Mabry RL, Mabry CS. Allergic fungal sinusitis: the role of immunotherapy. Otolaryngol Clin North Am 2000;33:433-40.
56. Folker RJ, Marple BF, Mabry RL, Mabry CS. Treatment of allergic fungal sinusitis: a comparison trial of postoperative immunotherapy with specific fungal antigens. Laryngoscope 1998;108:1623-7.
57. Bassichis BA, Marple BF, Mabry RL, Newcomer MT, Schwade ND. Use of immunotherapy in previously treated patients with allergic fungal sinusitis. Otolaryngol Head Neck Surg 2001;125:487-90.
58. Greenhaw B, deShazo RD, Arnold J, Wright L. Fungal immunotherapy in patients with allergic fungal sinusitis. Ann Allergy Asthma Immunol 2011;107:432-6.
59. Melzer JM, Driskill BR, Clenney TL, Gessler EM. Sublingual immunotherapy for allergic fungal sinusitis. Ann Otol Rhinol Laryngol 2015;124:782-7.
60. Schubert MS. Antileukotriene therapy for allergic fungal sinusitis. J Allergy Clin Immunol 2001;108:466-7.
61. Thamboo A, Philpott C, Javer A, Clark A. Single-blind study of manuka honey in allergic fungal rhinosinusitis. J Otolaryngol Head Neck Surg 2011; 40:238-43.
62. Chakrabarti A, Denning DW, Ferguson BJ, Ponikau J, Buzina W, Kita H, et al. Fungal rhinosinusitis: a categorization and definitional schema addressing current controversies. Laryngoscope 2009;119:1809-18.