

Allergic Fungal Rhinosinusitis and the Unified Airway: the Role of Antifungal Therapy in AFRS

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Abstract Allergic fungal sinusitis (AFS) or rhinosinusitis (AFRS) is a form of polypoid chronic rhinosinusitis that is believed to be due to hypersensitivity to fungal antigens. The disease is characterized by type 1 hypersensitivity to fungal allergens, dramatically elevated total serum IgE, accumulation of thick eosinophil-laden mucin with non-invasive fungal hyphae within the paranasal sinuses, nasal polyposis, and sinus bony remodeling. Because of many clinicopathologic similarities to allergic bronchopulmonary aspergillosis (ABPA), these conditions can be considered analogous examples of disease in the unified airway. However, these conditions rarely occur together and their treatment differs. The treatment of AFRS relies upon surgical removal of fungal hyphae in eosinophilic mucin, while antifungal therapy is used to clear fungi from the airways in ABPA. Several uncontrolled studies suggest there may be some benefit to antifungal agents in AFRS, but randomized trials of topical and systemic antifungal therapies have not shown beneficial results in chronic rhinosinusitis (CRS). Antifungal treatment within the sinonasal cavities does not appear to be an effective approach for most chronic sinusitis, and antifungal therapy for AFRS is unproven.

Keywords Allergic fungal rhinosinusitis · Fungal sinusitis · Chronic rhinosinusitis · Unified airway · Antifungal · Allergic bronchopulmonary aspergillosis

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Introduction

The nasal cavities are commonly exposed to inhaled fungal spores, and culture studies show high rates of recovery of viable fungus within nasal mucus, even in normal subjects [1•, 2]. Thus, the recovery of viable fungi from sinonasal secretions is not a marker for disease. Fungi may be an important extrinsic trigger for upper and lower airway inflammatory disease in susceptible individuals, however. It is well recognized that exposure to fungal antigens may cause airway inflammation. But, our understanding of allergic disease due to fungal antigens is complicated by the tremendous biodiversity of the fungi, incompletely defined major allergens, unclear exposure patterns, and lack of standardized allergen extracts. Similarly, our understanding of the pathogenesis of fungal sinus disease and the role of fungi in chronic rhinosinusitis is limited. Fungal airway disease may be dependent upon multiple factors including exposure levels, anatomic factors, mucociliary clearance, general mucosal health, and host immune factors.

Coherent descriptions of fungal sinus disease first emerged in the twentieth century. The terms “aspergillosis,” “mucormycosis,” “phaeohyphomycosis,” and “zygomycosis” alluded to the causative organism but failed to capture the clinical features of the disease. We have since learned that the causative fungus is less important than the host response to the fungus and any tissue invasion. The best described form of fungal sinusitis associated with hypersensitivity to non-invasive opportunistic fungi is allergic fungal rhinosinusitis.

Allergic Fungal Rhinosinusitis

Allergic fungal rhinosinusitis is a disease that affects the young and atopic; there is a clear association with allergic

rhinitis as well as asthma. The disease causes insidious onset nasal obstruction typical of other forms of chronic polypoid sinusitis, along with thick dark mucus rhinorrhea or postnasal drainage, hyposmia, facial pain and pressure, and orbital or facial distortion in advanced disease. The disease was first reported in a patient with allergic bronchopulmonary aspergillosis, with recognition of allergic bronchopulmonary aspergillosis (ABPA)-like mucus plugs within the paranasal sinuses [3]. Katzenstein et al. described additional cases and an association with asthma, coining the term “Allergic *Aspergillus* rhinosinusitis” [4•]. *Aspergillus* species are the most common cause of fungal sinus disease worldwide and allergic fungal rhinosinusitis was initially attributed to *Aspergillus*. It is now apparent that the dematiaceous fungi (*Alternaria*, *Bipolaris*, *Drechslera*, *Curvularia*, *Exserohilum*) are the most common organisms recovered in allergic fungal rhinosinusitis (AFRS) [5].

The first case series of AFRS patients described by Katzenstein et al. [4•] included patients who did not have all of the clinicopathological hallmarks of ABPA. Some subjects did not have positive immediate hypersensitivity against fungal antigens. Additionally, some subjects did not have detectable fungi in their “allergic mucin.” This inconsistency in the presence of fungi and the presence of detectable type 1 hypersensitivity to fungi has been noted by multiple investigators. The “allergic mucin” evacuated from the sinuses of some patients does not have identifiable fungal elements; these cases have been called “AFS-like disease” [6, 7], or “eosinophilic mucin rhinosinusitis” (EMRS) to describe cases in which fungus cannot be identified histologically [8•]. Thus, some investigators showed that abundant fungi were not necessarily required for disease. However, it was also noted that fungi can be universally recovered from the nose of chronic rhinosinusitis (CRS) patients if sensitive methods are used. Ponikau et al. coined the term “eosinophilic fungal sinusitis” and proposed that allergy was not a necessary factor in the disease [1•]. Other additional terminology has been used to denote cases of polypoid CRS associated with accumulation of thick, tenacious eosinophil-laden mucus in the sinuses (also known as eosinophilic mucin chronic rhinosinusitis); proposed subdivisions include non-allergic non-fungal eosinophilic sinusitis (NANFES) and non-allergic fungal eosinophilic sinusitis (NAFES) [9]. Whether these subdivisions based on detection of fungi or type 1 hypersensitivity have any clinical meaning is unclear, and this manuscript will focus on AFRS as classically described.

The correct diagnosis of AFRS relies on multiple factors (Table 1) and no single feature is pathognomonic for the condition. Testing is important to establish evidence of atopy. Skin or in vitro testing in AFRS patients will usually show immediate hypersensitivity (preformed IgE) to multiple fungal and non-fungal allergens. Peripheral eosinophilia and dramatically elevated total IgE levels are also common. Asthma

Table 1 Diagnostic criteria for AFRS (adapted from [28])

Bent and Kuhn diagnostic criteria for AFRS	
Type 1 hypersensitivity confirmed by history, skin test, or serology	
Nasal polyposis	
Eosinophilic mucin demonstrating fungal hyphae without tissue invasion	
Characteristic CT findings (high attenuation sinus contents with bony remodeling)	
CT computed tomography	

is a comorbidity in approximately 50 % of cases but is not required for the diagnosis [10].

Computed tomography (CT) imaging findings are an important component of the diagnosis of AFRS. Imaging in AFRS shows multiple opacified sinuses with central hyperattenuation, individual sinus mucocoele formation, and erosion of the bony confines of the sinuses, orbit, and skull base. The disease is usually asymmetric, which is an important clue to distinguish AFRS from other forms of chronic hyperplastic eosinophilic rhinosinusitis such as aspirin-exacerbated respiratory disease [8•].

One important diagnostic criterion for AFRS is the presence of “eosinophilic mucin” (or “allergic mucin”): thick tenacious dark yellow to brown to green colored debris that fills the involved sinuses. This material is grossly and microscopically similar to the mucus plugs retrieved in ABPA. However, allergy is not always associated with this material, and “allergic mucin” is no longer the preferred terminology. “Eosinophilic mucin” contains *Charcot-Leyden* crystals, “onionskin laminations,” and clusters of eosinophils. Fungal hyphae are present in variable abundance and may not be evident unless a fungal stain is used. By definition, the fungal hyphae do not invade the mucosa. Rather, hyphae are resident within the sinonasal secretions. Adjacent mucosa and polyps demonstrate a prominent eosinophilic inflammatory infiltrate.

The presumed pathogenesis of AFRS was very early ascribed to the mechanisms underlying ABPA pathogenesis [4•]. This presumption was based on histopathologic similarities of AFRS and ABPA, not because they are comorbid illnesses. Regardless of this lack of clinical association, since its early description, AFRS has been considered to be the upper airway correlate of ABPA and the two conditions share many similar features (Table 2).

The development of AFRS is believed to require a convergence of local, environmental, anatomic, and host immunological factors (Fig. 1). Fungi enter the nose and sinuses during normal respiration and induce an inflammatory reaction. The total amount of fungal exposure may be an important factor that explains the uneven geographic distribution of the disease. The many possible inflammatory mechanisms at play in AFRS are unclear, but the classic explanation is that fungal antigens trigger a Gell and Coombs types I and III response,

Table 2 Clinical features of ABPA and AFRS

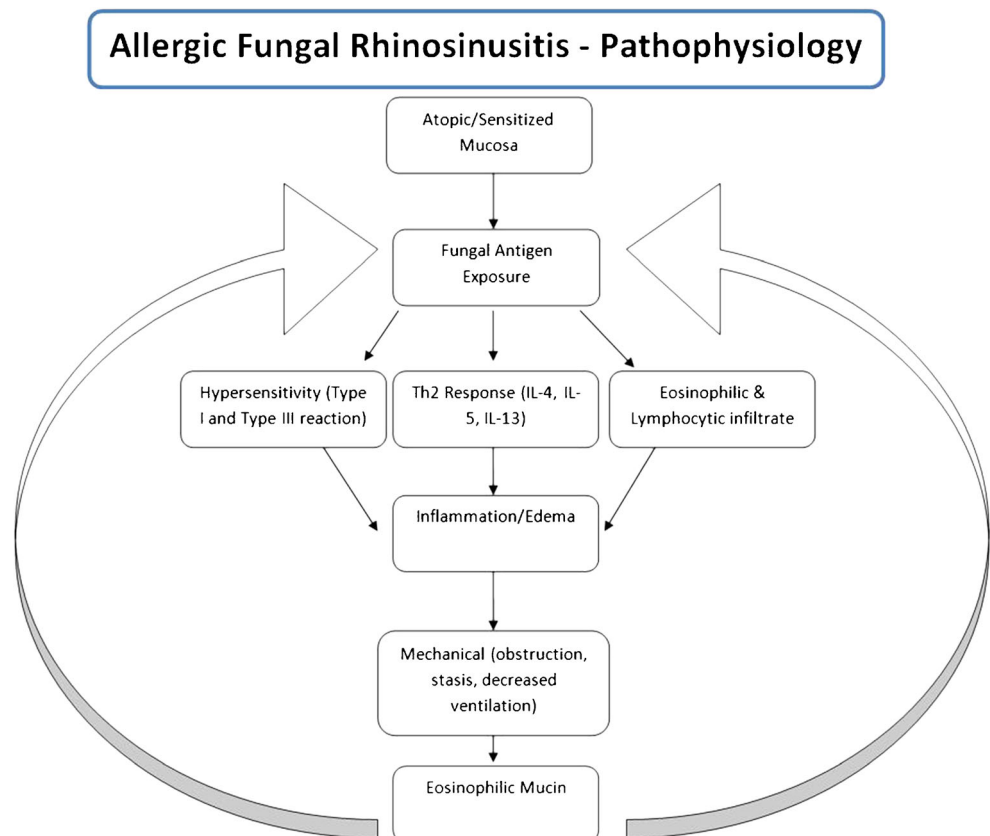
Clinical features of ABPA and AFRS		
	Allergic bronchopulmonary aspergillosis	Allergic fungal rhinosinusitis
Asthma	+	50 %
Immediate hypersensitivity to <i>Aspergillus</i>	+	+ for many fungi
Elevated serum IgE	+	+
Brown mucus plugs	+	+
Precipitating antibodies to <i>Aspergillus</i> antigen	+	
Pulmonary infiltrates	+	
Paranasal sinus mucocoeles		+
Nasal polyps		+

IgE immunoglobulin, *ABPA* allergic bronchopulmonary aspergillosis, *AFRS* allergic fungal rhinosinusitis

leading to elaboration of TH2 type cytokines and a consequent eosinophilic inflammation. This inflammation in turn leads to impaired intrinsic host defenses such as mucociliary clearance. Mucus stasis and sinus outflow tract obstruction due to polyp formation then lead to fungal proliferation and accumulation of eosinophils in the trapped mucin. This entrapped mucin with fungal elements serves as an ongoing stimulus

for inflammation (Fig. 1). Multiple reports have described elevations of specific IgE and IgG to lend support to the hypothesis that Gell and Coombs types I and III hypersensitivity to fungi are involved in the pathophysiology of the disease [5, 11]. Just as the initiation of the disease is somewhat mysterious, explanations for its persistence are based primarily on clinical observations. In AFRS, massive polyps form that obstruct the sinonasal passages, and fungal mucocoeles distort the sinus anatomy. Anatomic factors related to sinus drainage and nasal airflow are a potential explanation for asymmetric sinus involvement in the disease. Fungi are trapped in the sinuses and serve as an ongoing pro-inflammatory stimulus. The large numbers of activated eosinophils trapped within the eosinophilic mucin may be an additional driver of ongoing inflammation. Given the great degree of similarity between AFRS and ABPA, it is surprising that these conditions have rarely been reported to occur together [12, 13].

While an effective treatment approach to AFRS is multidimensional, the primary treatment of allergic fungal sinusitis is surgery. The goals of surgery are to remove the polyps, widely open the involved sinuses, evacuate all eosinophilic mucin, and create access for topical intranasal medication [10]. Failure to completely open the sinuses or to completely remove trapped eosinophilic mucin usually results in persistence of inflammation and resistance to anti-inflammatory medical treatment. AFRS is notorious for its propensity to

Fig. 1 Pathophysiologic model of AFRS

recur, and surgical treatment alone is not adequate. One longitudinal study showed that over 7 years of follow-up, patients required an average of two surgical procedures, three courses of systemic steroids per year, and had persistent polypoid mucosal edema and elevated total IgE [14].

Medical therapy for AFRS is directed toward suppressing inflammation, preventing reaccumulation of allergic mucin, and maintaining sinus drainage. Saline irrigations and topical intranasal steroids are mainstays of treatment. Local treatments may not be sufficient to dampen the brisk inflammatory reaction of AFRS and prevent recurrence, however.

Systemic anti-inflammatory agents are usually required in the treatment of AFRS. Usually, this means short 1- to 3-week tapered courses of oral steroids such as prednisone, prescribed to achieve “medical polypectomy” in the case of an exacerbation or recurrence of polyps. Prolonged treatment with systemic steroids may completely abrogate the vicious cycle of mucosal inflammation in AFRS but are less frequently employed. Protocols for prednisone treatment in ABPA have been adopted in AFRS: for example, prednisone 0.5 mg/kg/day for 2 weeks, then reduced to every other day for 3–6 months with a slow reduction in dosage while monitoring clinical symptoms, endoscopic exam, radiographs, and serum IgE levels. The ideal dosing and treatment course are not defined, and in general, prolonged courses of systemic steroids are to be avoided in sinus disease. As in ABPA, many patients with AFRS are dependent upon systemic steroids to keep their inflammation controlled. Leukotriene modifiers and anti-inflammatory macrolide antibiotics are often employed to try to reduce steroid requirements, but it is unknown if these improve outcomes or reduce the need for revision surgery. Clinical decisions about prolonged corticosteroid treatment must be made based on a patient’s age, concomitant medical conditions, and response to treatment.

Antifungal Treatment for Allergic Fungal Rhinosinusitis

Antifungal treatment with itraconazole is now an accepted primary approach for the management of ABPA. The goals of antifungal treatment are to reduce the fungal antigenic stimulus for inflammation and thus reduce corticosteroid requirements [15]. Given the apparent similarity of AFRS, it is rational to consider antifungal therapy to accomplish the same goals. The benefits of itraconazole in ABPA are substantiated by randomized controlled trials. Unfortunately, the studies in AFRS to date are retrospective in nature or have serious methodologic flaws that limit the conclusions that can be reached. Rains and Mineck retrospectively reviewed the outcomes of 139 patients with AFRS. Patients were treated with short-course systemic steroids or systemic steroids and oral itraconazole (200–400 mg/day for 3 months or greater, based upon response) in addition to long-term topical corticosteroids. The “recurrence rate” in the itraconazole treated group

was 20 % compared to 50 % in those receiving steroids alone. The rationale for allocation of some patients to itraconazole treatment is not clear in this 12-year retrospective cohort, and recurrence was defined as a need for additional medical therapy [16].

Chan et al. reported results on 32 patients with allergic fungal rhinosinusitis who did not respond adequately to sinus surgery, short course oral corticosteroids, and nasal amphotericin B therapy (6 mL three times a day of 0.1 mg/mL amphotericin B deoxycholate). All patients were treated with oral itraconazole (200–300 mg/day) for 3 months. Twelve patients demonstrated endoscopic scoring improvement, while 15 demonstrated no difference, and five demonstrated worsening [17].

Seiberling et al. in 2009 performed a retrospective chart review of 23 patients with AFRS as well as non-allergic eosinophilic fungal rhinosinusitis who previously “failed” medical therapy as well as sinus surgery. Patients received 100 mg itraconazole BID for a minimum of 6 months. Three patients were required to stop treatment secondary to hepatic side effects, four patients showed no response, and 16 patients showed subjective symptom improvement as well as decrease in use of oral steroids with an improved endoscopic appearance (decreased eosinophilic mucin and polyps) [18].

Khalil et al. evaluated 50 adult patients who were diagnosed with AFRS who underwent sinus surgery. Postoperatively, patients were treated with systemic and topical steroids and assigned into five treatment arms receiving either (1) oral itraconazole, (b) fluconazole nasal spray, (c) combination of oral itraconazole and fluconazole nasal spray, (d) fluconazole nasal irrigation, and (e) placebo. The authors reported a decreased incidence of “recurrence” in the groups treated with topical fluconazole, but the addition of itraconazole did not seem to confer a benefit [19].

Antifungal Treatment for Chronic Rhinosinusitis

In 1999, Ponikau et al. proposed that CRS is caused by a non-allergic immunologic response to fungi within nasal secretions, an “eosinophilic fungal sinusitis.” This theory, known as the “fungal hypothesis,” generated significant interest because it offered an explanation for the extrinsic trigger of persistent inflammation in CRS patients [1••]. The important corollary of the fungal hypothesis is that antifungal treatment administered either topically or systemically might be an effective treatment approach for CRS. Indeed, initial uncontrolled cohort studies suggested that amphotericin B nasal irrigation improved symptoms and endoscopic findings in CRS patients [20]. The excitement over this development led to several well-designed randomized placebo controlled trials to evaluate the efficacy of antifungal agents for the treatment of CRS.

There has been one randomized controlled trial evaluating a systemic antifungal therapy (terbinafine) for patients with CRS. Fifty-three adult patients with CRS were randomized to receive 625 mg of terbinafine daily for 6 weeks or placebo. There was no statistically significant difference recorded on any of the measured outcomes including Lund-Mackay CT score, patient and physician evaluation of therapeutic response, as well as Rhinosinusitis Disability Index scores [21].

Several studies have evaluated the effect of amphotericin B sprays and irrigations with different dosing schedules and treatment durations. These studies have uniformly failed to show a clinically significant benefit of topical intranasal amphotericin B for CRS either with or without nasal polyps. Weschta et al. randomized 78 patients with CRS with nasal polyposis (CRSwNP) to receive topical amphotericin B topical nasal spray (200 µL of 3 mg/mL for 8 weeks) or isotonic saline placebo spray. There was no significant difference between treatment and placebo arms using the Lund-Mackay CT score, and in fact, the placebo group had better rhinoconjunctivitis quality of life scores [22]. A subsequent analysis failed to show any effect of antifungal treatment on fungal recovery rates or markers of inflammation (ECP, tryptase) in sinus lavage samples in these patients [23].

Ponikau et al. randomized 30 patients with CRS to receive 20 mL of amphotericin B (250 µg/mL) or placebo via bulb syringe for 6 months. Antifungal treatment did not impact markers of inflammation or fungal burden in the sinuses, nor was there any improvement in sinus symptoms as assessed by the sinonasal outcomes test-20 score [24].

Ebbens et al. randomized 116 adult patients with CRS to receive 25 mL amphotericin B solution (100 µg/mL) intranasal irrigation twice daily for 3 months with a control arm performing saline irrigations. Amphotericin B treatment failed to reduce clinical signs and symptoms in patients with CRS [25].

Liang et al. randomized 70 CRS patients without nasal polyps to receive nasal irrigation with amphotericin (5 mg/mL) or placebo for a total study time of 4 weeks. Neither symptoms nor nasal endoscopy scores improved with antifungal treatment [26].

Finally, Gerlinger et al. recruited 33 adult patients with CRSNP, all of whom had undergone prior polypectomy. Patients were randomized to receive amphotericin B nasal spray (100 µL, 2 puffs BID 5 mg/mL) or saline placebo spray. The study was continued over 1 year. Again there were no significant benefits of amphotericin treatment [27].

Conclusion

Because of a large body of evidence, antifungal therapy has not been widely adopted in the treatment of CRS with or without nasal polyps. It remains to be determined whether antifungal treatment might be effective in certain subpopulations with chronic sinusitis, such as allergic fungal rhinosinusitis. However, the clinical evidence to date is

insufficient to suggest a beneficial effect in AFRS of either topical intranasal antifungal agents or systemic therapies such as itraconazole. It is rational to employ long-term antifungal agents in ABPA as a way to reduce fungal antigenic exposure in the lungs due to trapped hyphae in airway mucin. While AFRS and ABPA share many clinicopathologic similarities, anatomic differences between the paranasal sinuses and lungs may predicate different treatment strategies. The fungal antigenic burden in allergic fungal sinusitis can be alleviated by sinus surgery, office debridement, and saline irrigations. These mechanical methods to remove the fungal stimulus for inflammation may make an antifungal treatment approach irrelevant.

Compliance with Ethical Standards

Conflict of Interest Drs. Ryan and Clark have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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