



Role of immunotherapy in allergic fungal rhinosinusitis

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Purpose of review

Our understanding of the pathogenesis and treatment of allergic fungal rhinosinusitis (AFRS) continues to evolve. This article serves to update the reader on the diagnosis and management of AFRS and pays particular attention to the recent literature regarding efficacy and safety of immunotherapy in this patient population.

Recent findings

The mainstay of treatment of AFRS remains a thorough surgery; however, adjunctive medical management is also critical to achieve optimal outcomes. Oral steroid use in AFRS remains recommended. Immunotherapy, both fungal and nonfungal, may be considered for patients exhibiting a type I hypersensitivity to specific allergens. To date, limited studies do show improvement with reduction of postoperative exacerbations and revision surgeries. There remains no evidence of unusual side-effects or formation of immune complexes from immunotherapy in AFRS patients. Double-blind placebo controlled trials on immunotherapy and AFRS are lacking, and ultimately, conclusive evidence of efficacy is not present to date.

Summary

Treatment of AFRS requires multimodality therapy with immunotherapy playing a significant, yet inconclusive, role. Further studies remain warranted.

Keywords

allergic fungal rhinosinusitis, chronic rhinosinusitis, immunotherapy, outcomes

INTRODUCTION

The clinical entity of allergic fungal rhinosinusitis (AFRS) continues to evolve in both its pathogenesis and optimum management protocol. It is estimated that 4–7% of all patients with chronic sinusitis requiring surgery involve AFRS [1]. This article serves as an update to diagnosis and management of AFRS, with a focus on the recent literature regarding efficacy and safety of immunotherapy in AFRS patients.

A PubMed search was performed using the key terms ‘Allergic Fungal Sinusitis’, ‘Allergic Fungal Rhinosinusitis’ and ‘Immunotherapy’ from 1990 to 15 September 2014. Articles were reviewed and only relevant articles discussing AFRS patients treated with immunotherapy and specific outcomes were included and reviewed. General update articles were also reviewed for opinions and updated thoughts that are interspersed throughout this article.

DEFINING CHARACTERISTICS AND DEMOGRAPHICS

There is yet to be recognized a universal set of diagnostic criteria for AFRS. AFRS remains a subtype

of CRS. This noninvasive form of fungal rhinosinusitis is thought to be the result of both an allergic and immunologic response from an atopic individual to extramucosal fungi in the sinuses [2[¶]].

Bent and Kuhn [3] published the most commonly referenced criteria for AFRS. These criteria include: type 1 hypersensitivity to fungi that is confirmed by skin test or serum-specific blood testing, nasal polyposis, characteristic computed tomography findings, presence of fungus on culture or direct microscopy and eosinophilic mucus without fungal invasion.

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KEY POINTS

- Primary management of AFRS remains surgical with removal of allergic mucin and disease load.
- Adjunctive therapy with immunotherapy may be considered for patients exhibiting a type I hypersensitivity to allergens; however, surgery should be performed first and it is recommended to wait at least 6–8 weeks from the surgery date before starting immunotherapy.
- Fungal or antifungal immunotherapy may show improvement in posttreatment outcomes with decreased exacerbations and decreased risk of recurrence in AFRS.
- Data to date show lack of risks beyond the usual risks of inhalant subcutaneous immunotherapy.
- Double-blind placebo controlled trials on immunotherapy and AFRS are lacking and ultimately conclusive evidence of efficacy is not present

A clinical diagnostic challenge may present with patients who meet most criteria for AFRS with the exception of a few elements. For example, an identical form of CRS meeting all criteria with the exception of type I hypersensitivity is noted. Controversy exists over either dropping the type I hypersensitivity from the description of AFRS or creating a broader term, eosinophilic fungal rhinosinusitis (EFRS), to incorporate both disease entities. Eosinophilic mucin rhinosinusitis (EMRS) has also been described for patients with the same disease characteristics, but without type I hypersensitivity and without fungi [4–6].

AFRS, EFRS and EMRS all have the underlying presence of so-called ‘allergic mucin’ (Fig. 1). Under microscopic examination, this allergic mucin is found to have ‘onionskin laminations’, or essentially clusters of degranulating and necrotic eosinophils as well as Charcot–Leyden crystals [7].

The radiographic findings (Fig. 2) of AFRS are typical and often include: opacification of multiple sinuses, bone remodeling and expansion of sinuses with ultimate erosion of the cribriform, lamina papyracea and orbital apex [8].

Computer tomography often shows heterogeneous densities, theoretically present because of elevated levels of iron, magnesium and manganese in the allergic mucin [9].

As AFRS is mostly considered a type 1 hypersensitivity, allergy testing is important to establish atopy. Results may show an immunoglobulin (Ig) E-mediated response to both fungal and other seasonal or perennial antigens [7]. Laboratory

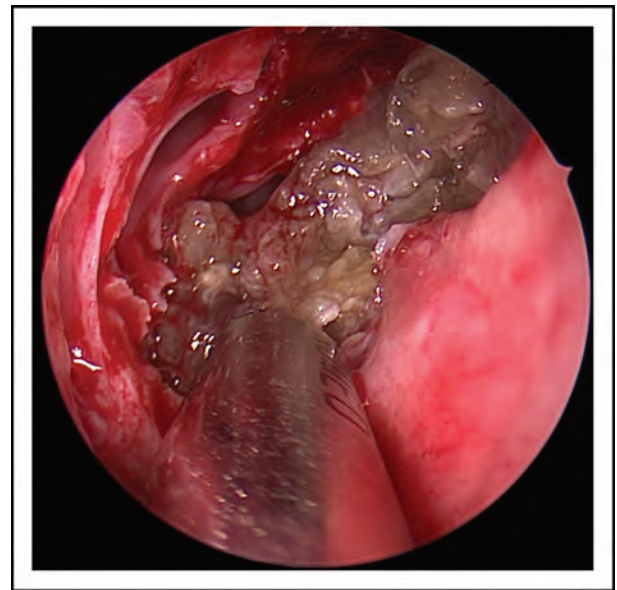


FIGURE 1. This is an endoscopic view of the sphenoid sinus in a patient with AFRS. There is an abundant amount of thick, inspissated secretions consistent with allergic or fungal or eosinophilic mucin within the sinus. Often this debris is very tenacious and frequently requires irrigation to completely remove.

abnormalities may include elevated total IgE levels to numbers exceeding 1000 IU/ml, whereas <180 is considered normal.

There is an increased incidence of AFRS in the south and along the Mississippi basin, likely because of climactic factors resulting in increased exposure to fungi. A study by Ferguson [6] noted the incidence of AFRS to be 10–23% in southern areas and 0–4% in northern areas. The most common fungi in AFRS is the dematiaceous fungi (*Alternaria*, *Bipolaris*, *Drechslera*, *Curvularia*, *Exserohilum*). In the other three forms of fungal rhinosinusitis (see differential



FIGURE 2. Typical findings on CT include unilateral disease, differential density within the sinuses as well as bony thickening of the sinuses. As opposed to a CT with a fungal ball, which demonstrates disease within one sinus (typically), patients with AFRS typically have multiple sinuses involved.

diagnosis section below), *Aspergillus* species is most common.

The classic patient with AFRS includes young adults and adolescents. The most common presenting symptoms of AFRS include nasal obstruction, nasal discharge, postnasal drip, cough, problems with smell, sore throat, fatigue and facial pain [10].

HISTORY OF ALLERGIC FUNGAL RHINOSINUSITIS

A significant portion of what is known about AFRS stems from the study and analysis of allergic bronchopulmonary aspergillosis (ABPA). In ABPA, high titers of serum fungal-specific IgG and IgE exist. In addition, peripheral eosinophilia and *Aspergillus fumigatus* within bronchial allergic mucin contents are noted. Katzenstein *et al.* [11] first described the sinonasal equivalent entity of AFRS in 1983.

Parallel to ABPA, high serum levels of allergen-specific IgE to fungal antigens have been shown. Many studies also support AFRS to have an IgG-mediated hypersensitivity as well as an eosinophilic inflammatory late-phase reaction. The study by Manning and Holman [12] did show 100% of patients with AFRS to be positive via skin prick testing to *Bipolaris*, 82% were positive on allergen-specific IgE testing and 93% had allergen-specific serum IgG ($n = 16$).

A concomitant AFRS and ABPA infection in the same patient is named sinobronchial allergic mycosis. This disease process suggests hypersensitivity to fungus in both the upper and lower airways; however, coexistence in both airways is generally rare [13].

DIFFERENTIAL DIAGNOSIS

Currently, fungal rhinosinusitis includes four distinct groups, classified based on tissue invasion and immunologic response to fungi [13].

It is especially important to differentiate AFRS from invasive fungal sinusitis. Invasive fungal sinusitis can be further subdivided into acute invasive fungal rhinosinusitis (AIFS) and chronic invasive fungal sinusitis (CIFS). AIFS is characterized by necrosis and tissue invasion and must be considered high on the differential in immunocompromised patients. This usually develops over days to weeks. Ocular or intracranial involvement and vascular invasion resulting in mycotic thrombi may result in quick deterioration, extensive morbidity and often times mortality of the patient [14]. AIFS remains rare; however, its incidence in patients with cancer, leukemia or bone marrow transplant are anywhere from 1% to 2% [15].

CIFS can be seen in immunocompetent patients with subtle immune compromise, such as diabetes or a hematologic malignancy that is in remission. It can also be seen in endemic areas, such as the Sudan or India. The disease process can progress over months or years. Histologically, these patients have organisms surrounded by a foreign body response as well as hyphae invading tissue. This disease process distinctly lacks vascular invasion by fungi as is seen in the acute invasive form [15]. There is a granulomatous form of CIFS described that is thought to have improved prognosis [4]. This disease process is exceedingly rare in the United States with only a few small series and isolated case reports [16,17].

The two noninvasive groups of fungal rhinosinusitis include fungus balls and AFRS. These are considered more common than the invasive form. Fungal balls, formerly known as mycetomas, are large dense fungal collections (Fig. 3) found in immune competent individuals. They are in isolated sinuses approximately 90% of the time, specifically the maxillary and sphenoid sinus. Mucosal swelling is minimal or moderate and located only in the affected sinuses. There are excellent cure rates with surgery.

AFRS is noninvasive as well; however, it is known to develop in patients with atopy with the involvement of multiple sinuses. Typically, involvement of a single sinus with the absence of nasal polyps (Fig. 4) differentiates fungus balls from AFRS [18]. AFRS is the most common form of fungal rhinosinusitis.

Saprophytic fungal infestation can also occur, as fungus can grow off all crusts and purulent debris

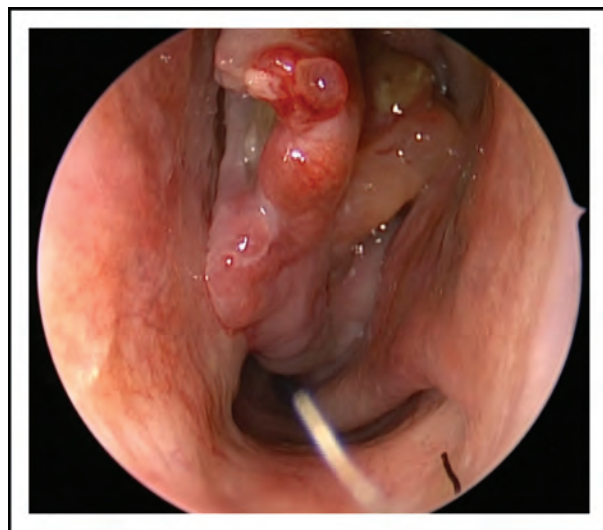


FIGURE 3. Endoscopy of patients with AFRS typically shows very hyperplastic mucosa as well as diffuse polyps. When suctioning is performed, often the secretions are thick and tenacious.

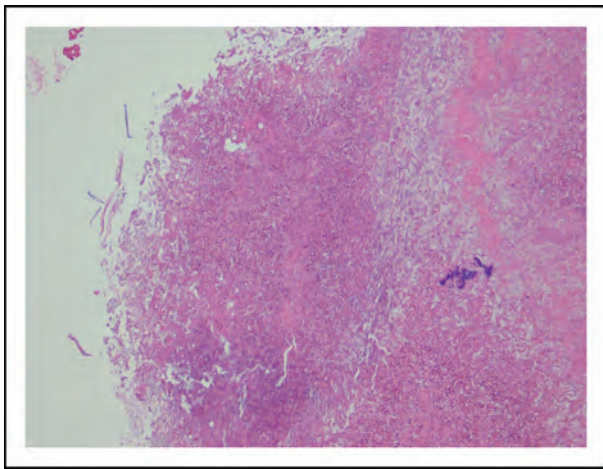


FIGURE 4. Histology of a fungal ball typically shows a dense collection of non-invasive fungal hyphae. Fungal elements can be present in AFRS, but they are not invasive.

within chronically diseased sinuses. The exact incidence of this is unknown. In 1999, the Mayo clinic postulated that all CRS may be caused by fungi, as fungus was cultured from the majority of sinuses using highly sensitive techniques [5]. However, fungus colonization has been noted in CRS and normal nasal sinuses [19]. It is therefore important to not confuse all positive fungal cultures with a pathologic state [15] and findings of fungus should only have relevance in the appropriate clinical setting.

TREATMENT

The mainstay of treatment of AFRS remains thorough surgical extirpation with adjunctive medical management. The ultimate goal is to break the so-called 'vicious cycle' of entrapped secretions and allergic stimuli [20]. In other words, the focus of all treatment is to interrupt the end-stage inflammatory process and allow normal mucosal function to return. Treatment options for consideration in AFRS are:

- (1) Surgery followed by debridements,
- (2) Sinus irrigations,
- (3) Steroids (oral and/or nasal),
- (4) Antileukotriene modulators,
- (5) Oral or topical antifungals,
- (6) Environmental controls,
- (7) Immunotherapy for fungal and nonfungal antigens.

SURGICAL TREATMENT

Endoscopic sinus surgery is a critical component to management of this disease process. The goal of

surgery involves complete removal of retained allergic mucin and nasal polyps, as well as establishing wide access to all sinuses for the delivery of topical therapies, assist with future debridements and to allow easy endoscopic surveillance. The goal should be removal of all allergic mucin and polyps while preserving normal sinus mucosa. This sort of meticulous dissection helps avoid crusting and scarring. Failure to thoroughly remove all fungal elements, allergic mucin, hypertrophied and polypoid mucosa decreases the patient's response to medical management [21].

MEDICAL THERAPY

Nasal irrigations with sodium chloride help mechanically debride thickened mucoid secretions and promote mucociliary clearance in both pre-operative and postoperative patients [22]. The delivery of this irrigant is substantially facilitated by complete endoscopic sinus surgery [23].

Low-dose oral steroid and intranasal steroid sprays are often mainstays of therapy to combat inflammation. There is level 1a evidence for topical steroids in the use of patients with chronic rhinosinusitis without nasal polyps as well as chronic rhinosinusitis with nasal polyps and grade A evidence from the 2012 European position paper [24]. The initial use and rationale of oral steroids in AFRS was based in large part on known medical effectiveness of corticosteroids in management of ABPA. Based on this, additional studies specific to AFRS and long-term prednisone administration have been performed. The effectiveness of oral steroids in the management of AFRS has been studied; however, there is only a mix of level 2b and level 4 studies concerning its use. A recent evidence-based review with recommendations found an overall benefit over harm and recommended oral steroids in the management of AFRS (aggregate quality of evidence grade B) [2^{••}]. Benefits included a reduction in mucosal disease in the postoperative period, improved symptoms scores using endoscopic grading and the reduction of inflammatory markers. The usual short and long-term risks of steroids are noted, however, and caution is advised against long-term use.

The review by Gan *et al.* [2^{••}] excluded studies that lacked complete adherence to Bent and Kuhn criteria. Specifically, a placebo-controlled trial of 24 patients in 2010 did conclude that at least 3 months of systemic steroid therapy after endoscopic sinus surgery can be effective in controlling AFRS disease and preventing early recurrence; however, this study had been excluded from recent analysis because of lack of complete adherence to all Bent

and Kuhn criteria [25]. Exact dosing regimens and optimal duration of steroid therapy remains poorly understood.

Topical and oral antifungal therapy has proven ineffective in management of this disease entity [26,27]. Some specific studies have shown safety and efficacy with use of oral antifungals; however, in the majority of these studies, patients were also on oral steroids making the data diluted. Gan *et al.* reviewed three level 4 studies that met strict Bent and Kuhn criteria for AFRS with an ultimate category C recommendation for an option to consider itraconazole in selected cases of postsurgical refractory AFRS [28]. Seiberling and Wormald's [28] study was the most convincing noting 83% of patients responding to oral itraconazole with ultimately decreased nasal symptoms and an improvement in endoscopic findings. Ultimately, the lack of convincing evidence toward response to antifungals combined with the generalized risk of systemic antifungal therapy such as hepatotoxicity and cardiotoxicity has resulted in this treatment modality falling out of favor, except under specific situations in which patients may be recalcitrant to more standard therapy or may need to be weaned from steroids. The mixed results from various studies continue to emphasize the need for further work in this area.

Leukotriene modulators have not been thoroughly investigated for AFRS, and therefore the effects are not known. There is one clinical case report of a patient with AFRS with three prior sinus surgeries and on budesonide irrigations, with resultant dramatic symptomatic improvement and reduction in mucosal swelling with use of montelukast 10 mg. Given the lack of adequate studies, no recommendation can be provided on use of this [29,29].

THE ROLE OF ALLERGY MANAGEMENT

Despite optimal surgical and medical therapy, recurrence of disease is common. For this reason, adjunctive therapy continues to be sought. Although the exact characteristics of AFRS continue to be discussed and debated, nearly all patients with AFRS are atopic. On testing, these patients may have IgE-mediated sensitivity not only to fungus, but often to other aeroallergens. Two-thirds of these patients have a history of allergic rhinitis, 90% have elevated specific IgE to at least one if not more fungal antigens and up to 50% have asthma. Many of these patients have obtained immunotherapy at some point in their past [20].

It is commonly believed that antigen stimulation is driving a Th2 response that ultimately

drives eosinophilic inflammation in both AFRS and some forms of CRS. Specifically, one study noted fungal antigens from AFRS patients as the source of stimulation of peripheral blood mononuclear cells, ultimately secreting Th2-type cytokines [30]. Additional studies are supporting this role of humoral immune factors in AFRS [30,31].

In the past, concerns existed regarding the safety of immunotherapy for AFRS. It was thought that allergen-specific immunoglobulin G (IgG) created by immunotherapy could create a Gell and Coombs type III (immune complex mediated) reaction. This concern has not been founded. There are no known reports of type III complex-mediated reactions, or an increased risk of local or generalized reactions compared with standard patients on immunotherapy.

Given the safety profile and the proven type I hypersensitivity to fungal antigens shown in many studies, there certainly is a possibility that immunotherapy may decrease or prevent the host's inflammatory response. Over the years, however, it is established that the actual causative organism, that is the specific fungal elements found, is not the most critical feature of AFRS [16]. Therefore, many studies on immunotherapy and AFRS include treatment not only for fungal sensitivities, but also for nonfungal sensitivities.

ENVIRONMENTAL CONTROL

Skin prick versus serum-specific IgE testing is reasonable to explore in patients found to have AFRS. If the patient indeed is allergic to molds, environmental avoidance, including avoidance of food such as wine, beer and cheese, could be considered [20].

IMMUNOTHERAPY

To date, there are no double-blind, placebo-controlled studies comparing fungal or nonfungal desensitization in AFRS patients with a control group. Limited case reports and retrospective studies using immunotherapy as a treatment option have shown improvement in nasal crust formation, polyp formation, decreased systemic corticosteroid use and improved quality of life. Two case-control studies, consisting of level 3b evidence, remain the highest level of evidence for immunotherapy at this time [29].

The initial study of AFRS and immunotherapy was published in 1993 with a retrospective review by Ferguson [32]. This included a retrospective review of seven patients with AFRS who received immunotherapy. Five of the patients received immunotherapy prior to surgical management of the disease entity and showed either progression of symptoms

or lack of improvement. The two patients receiving immunotherapy after surgery did show improvement [32]. This small study implied the importance of administering immunotherapy only after surgical removal of mucin, hence avoiding an ongoing antigenic load with possible increased propensity toward complications from therapy such as immune complex deposition or increased delayed or local reactions.

From 1995 to 1998, additional studies in support of immunotherapy and AFRS were published. These studies included a single case report treating a patient with failure to surgery, antibiotics and nasal steroids, with *Bipolaris* immunotherapy with subsequent resolution of the patient's symptoms and polyps after 18 months of therapy [33]. Mabry *et al.* at this time performed multiple investigations on AFRS and immunotherapy. Skin end-point titration methods were used to determine dosing of immunotherapy, however, and this technique is often critiqued because of the possibility of resultant decreased immunotherapy concentrations [34[■]].

The first study by Mabry's group included nine patients on weekly posttreatment immunotherapy with resultant reduction of nasal crusting and reaccumulation of allergic mucin within 12 weeks of starting immunotherapy. These patients also had a reduction in the need for topical steroids and lack of need for systemic steroids after 2 months [35]. A follow-up study with an average of 20 months of immunotherapy showed seven out of the 10 patients to remain symptom-free [36]. Another follow-up study, now with a mean of 28 months of follow-up, showed 0 of the 11 patients to require revision surgery with continued support of the original studies [37].

Folker *et al.*'s [38] was the earliest case-control study, wherein 11 patients who received immunotherapy for both fungal and nonfungal antigens (mean duration of 33 months) were compared with 11 without immunotherapy. This study noted significant improvement in all three measured clinical outcomes. These included improvement in endoscopic mucosal staging ($P < 0.001$), quality of life scale ($P = 0.002$) and reliance on both topical ($P < 0.043$) and systemic steroids ($P < 0.001$). Immunotherapy was generally started 6–8 weeks after surgery, when the mucosa was healed. Again, there were no adverse reactions. The exact duration of immunotherapy may have varied on patients; however, postoperative care was standardized [38].

Bassichis *et al.* [39] performed the second case-control study of patients with AFRS who underwent endoscopic sinus surgery and evaluated the effect of immunotherapy on outcomes. In one group, 36 patients were treated with various systemic and

topical medications as well as immunotherapy (for fungal and nonfungal antigens). This group was compared with 24 patients who were also treated with various systemic and topical medications, but did not receive immunotherapy. There were no reported adverse side-effects in the immunotherapy group. After a mean follow-up time of 48.5 months, the study concluded that patients receiving immunotherapy incurred significantly fewer visits that required intervention ($P < 0.005$) and fewer revision surgeries when compared with those who did not receive immunotherapy (11.1% vs. 33.3%; $P < 0.001$) [39]. The limitations to this study include the varied and inconsistent postoperative adjunctive medical management of all patients as well as the unclear timeline of immunotherapy administration.

A study in 2002 by Mabry's group, however, failed to show benefit from immunotherapy. This began to question the true efficacy of immunotherapy. This study of 17 patients, with 10 receiving immunotherapy posttreatment failed to show significant improvement outcomes for patients receiving immunotherapy compared with other adjunct treatment measures. Seventy-six percent of the patients in this study were doing well based on the appearance of normal sinus mucosa, mild edema only or improved SNOT-20 scores, but a statistical significance for immunotherapy was not found [40]. This study highlights the controversy and the lack of a large enough study to truly understand immunotherapy's benefits or lack thereof.

Greenshaw *et al.* [41] published a key case-control study reiterating safety of immunotherapy with AFRS. This study compared 14 patients with AFRS on high-dose immunotherapy with 14 controls (non-AFRS CRS) on IT. With a mean follow-up duration of 21.8 months, there was no difference in adverse reactions. Both groups had one isolated episode of mild systemic urticarial reactions [41].

In summary, adjunctive therapy with immunotherapy, both fungal and nonfungal, may be considered for patients exhibiting a type I hypersensitivity to allergens. To date, the majority of the limited studies do show improvement with reduction of postoperative exacerbations and revision surgeries. There remains no evidence of unusual side-effects or formation of immune complexes from immunotherapy in AFRS patients. Gan *et al.*'s most recent review of the literature concludes that it is challenging to definitely recommend immunotherapy in AFRS given the level C evidence [2[■]]. However, given the potential benefit in some refractory patients, it may be considered with proper informed consent in the right patient population.

MONOCLONAL ANTIBODIES

Monoclonal antibodies against IgE (omalizumab) have been studied in isolated cases of ABPA in cystic fibrosis patients [41–44]. There are no reports of use of omalizumab in the specific treatment of AFRS however [45].

DISCUSSION AND CONCLUSION

It is believed that fungal involvement is central to the diagnosis of AFRS. Although some researchers have attributed the majority of CRS to fungal involvement [5], one cannot be certain just how critical specific fungal hypersensitivity is to the AFRS disease process and treatment approach. In 50–100% of patients with AFRS, cultures will reveal fungal growth. Lackner *et al.* [19] demonstrated that fungus could be cultured from the nasal mucosa in 94% of neonates. Given the lack of improvement with antifungals, the current theory remains that fungus being cultured is simply commensurate to the nose and unlikely to be pathologic organisms [8]. Certain fungal antigens, however, do appear to have the ability to trigger an immune reaction in either an allergic or nonallergic method. One hypothesis is that AFRS is caused by fungal subtypes that are not yet identifiable by known techniques. There is a deficiency in the availability of mold extracts available from manufacturers. Commercially available mold extracts are thought to be low in allergen and variable in nature [46,47].

Ultimately, the clinical entity of AFRS continues to evolve. Surgical management with complete removal of all allergic mucin is a mainstay of treatment. Nasal and oral steroid sprays in the operative and/or perioperative period are recommended.

Double-blind placebo controlled trials studying AFRS and immunotherapy are lacking. Therefore, there is no conclusive evidence of efficacy relating to immunotherapy and AFRS. However, there is a trend toward improved outcome and safety with use of immunotherapy in AFRS. Immunotherapy may be geared toward both fungal and nonfungal antigens for which the patient has a proven IgE sensitivity [2nd, 34th]. Caution would be advised to pursue immunotherapy prior to surgical removal of all allergic mucin however. Immunotherapy should only be administered by appropriately trained physicians, as there are known risks of immunotherapy including local and rarely systemic reactions. In summary, adjuvant immunotherapy should be discussed and considered in the management of AFRS patients. Further studies remain warranted.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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