



Current understanding of allergic fungal rhinosinusitis and treatment implications

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Purpose of review

The pathophysiology of allergic fungal rhinosinusitis (AFRS) is not fully understood and is in constant evolution. Although initial theories favored an immunoglobulin E-mediated immune response to fungal antigens as having a primary role in the immunopathologic process of AFRS, the purpose of this review is to highlight recent studies that suggest a more complex, epithelial cell-driven immune response being central to the pathophysiology of the disease. Treatment implications are considered.

Recent findings

Recent studies demonstrate a central role of cytokines derived from respiratory epithelial cells, including interleukin (IL)-25, IL-33, and thymic stromal lymphopoietin, in the orchestration of both innate and adaptive T helper 2 immune responses that are important components of the immunopathology of chronic rhinosinusitis with nasal polyposis and AFRS. In addition, the robust Th2 adaptive response may be mediated by both fungal antigens and *Staphylococcus aureus* superantigens.

Summary

Given the evolving understanding of AFRS pathophysiology, management continues to maintain a broad focus on minimizing the burden of the inflammatory trigger(s) and suppressing the inflammatory cascade. This is primarily accomplished through surgery and corticosteroid therapy. Immunotherapy, antimicrobial therapy, and other immunomodulatory medications may help mediate the disease process as well.

Keywords

allergic fungal rhinosinusitis, chronic rhinosinusitis with nasal polyposis, cytokines, management, pathophysiology

INTRODUCTION

Allergic fungal rhinosinusitis (AFRS), originally described in 1983 by Katzenstein *et al.* [1], represents a subclass of chronic rhinosinusitis (CRS) that accounts for up to 10% of CRS cases in the United States [1,2]. It most commonly affects young, atopic, immunocompetent individuals, may present either unilaterally or bilaterally, and has a geographic predilection to both humid and arid environments such as those seen in the Southern United States, Middle East and Africa [2–5]. Consensus clinical guidelines, based on widely accepted criteria proposed by Bent and Kuhn [6], define AFRS by the following characteristics: presence of nasal drainage, nasal obstruction, decreased sense of smell or facial pressure for 12 weeks, mucin within the sinus cavity containing fungal hyphae and degranulating eosinophils, endoscopic evidence of nasal polyps within the sinus cavity, computed tomography (CT) or MRI findings consistent with chronic impaction of eosinophilic mucin within diseased sinuses,

evidence of fungal-specific IgE by skin prick or serum IgE testing, and no evidence of invasive fungal disease. Fungal culture is variably sensitive; therefore, the histologic appearance of fungal elements within eosinophilic mucin remains the more reliable indicator of AFRS [5,7]. Typical histologic findings include branching, noninvasive fungal hyphae, lamellated sheets of eosinophils, and elongated eosinophilic breakdown products known as Charcot–Leyden crystals. Endoscopic evidence of

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KEY POINTS

- The pathophysiology of AFRS is complex involving activation of both an innate and adaptive Th2 immune response.
- Epithelial cell-derived cytokines appear to have a central role in the orchestration of both innate and adaptive Th2 immune responses, important in the pathophysiology of CRSwNP and AFRS.
- Surgery and corticosteroid therapy are currently at the cornerstone of AFRS management.
- A role may exist for immunotherapy, antimicrobial therapy, and biologics in treating AFRS, but further study is necessary.

inflammation typically shows polypoid mucosa in proximity to thick, highly viscous discolored secretions. Characteristic CT findings include expansion of involved sinuses with demineralization of cortical bone and dual density secretions. MRI often shows isodense or hypodense secretions on T1-weighted imaging, and hypodense secretions on T2-weighted imaging; adjacent mucosa enhances on both modalities. Total serum immunoglobulin E (IgE) level is typically elevated between 500 and 4000 kUA/l [8].

PATHOPHYSIOLOGY

The pathophysiology of AFRS remains unclear. Characterization of the local immune cells and cytokines within nasal polyps shows elevated eosinophils and T helper 2 (Th2) cytokines such as interleukin (IL)-4, IL-5, and IL-13 [9,10]. Initial theories centered on IgE-mediated immune response to fungal antigens were based on proposed mechanisms for allergic bronchopulmonary aspergillosis. However, recent studies that will be highlighted in this review suggest a more complex immune response with a more centralized role of epithelial cells orchestrating this immunopathologic response.

ROLE OF FUNGI AND STAPHYLOCOCCUS

The heavy presence of fungi within entrapped eosinophilic mucin suggests a role of fungi in the pathophysiology of AFRS [5]. However, it is unclear whether fungal accumulation is a result of or an initiating trigger of the disease. Manning and Holman [7] investigated the relationship between fungal allergy and AFRS. Comparing eight *Bipolaris* culture-positive AFRS patients to 10 non-AFRS CRS patients, they found that 100% of the *Bipolaris*

culture-positive AFRS patients were positive to *Bipolaris* on skin prick testing and had elevated *Bipolaris*-specific IgE serum levels, whereas 80% of the non-AFRS CRS patients were negative on both tests [7]. Luong *et al.* [11] demonstrated further evidence supporting a fungal-induced Th2 immune response in AFRS patients. Challenging isolated peripheral blood mononuclear cells to common etiologic fungal antigens, mononuclear cells from only AFRS patients and not healthy control patients responded with elevated secretions of IL-4 and IL-5. These studies demonstrate that fungi trapped within diseased sinus cavities of AFRS patients can overcome the immune tolerance to these ubiquitous agents. And extrapolating from understanding of asthma, an analogous chronic Th2 inflammation involving the lower airway, a mouse model of asthma can be developed from airway challenge with fungal spores supporting a causal relationship [12].

Staphylococcus aureus, Gram-positive bacteria frequently cultured from CRS patients (20–30%), is another proposed etiologic and/or disease-modifying factor. Histologic analyses of nasal polyps show an increased colonization of Gram-positive bacteria and in those samples with fungal colonization, 77% were also co-colonized with bacteria [13]. Evaluating CRS subsets, Clark *et al.* [14[■]] found a higher colonization of *S. aureus* in AFRS as compared with other non-AFRS CRS patients with nasal polyps. The increased presence of *S. aureus* is also associated with a Th2 immunologic response. Elevated serum levels of IgE to *S. aureus* enterotoxin A and B in addition to fungal-specific IgE levels are found in AFRS patients [15[■]]. Enterotoxin A and B are known superantigens that can incite profound immune reactions through a nonspecific, polyclonal activation of T cells.

From the aforementioned studies, we can conclude that AFRS patients have elevated loads of fungi and *S. aureus* within diseased sinus cavities and have mounted an immunologic response to these antigens, but a causal relationship cannot be established [5,16]. Without an animal model for AFRS or a better understanding of the molecular signaling by fungi and *S. aureus* leading to the activation of a Th2 immune response, a causal relationship is difficult to establish given the ubiquitous nature of both organisms.

EPITHELIAL CELL-DERIVED CYTOKINES DRIVE LOCAL Th2 IMMUNE RESPONSE

The sinus cavity mucosa is lined by a single layer of pseudostratified ciliated respiratory epithelial cells. In addition to its barrier function, respiratory epithelial cells can orchestrate a local Th2 immune

reaction in response to various environmental triggers. Upon challenge, epithelial cell-derived cytokines IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) are released and initiate an innate and adaptive Th2 immune response.

IL-33 is an alarmin cytokine whose release was first linked to necrotic cells. Since its original description, other studies have described signaling means for IL-33 release without necessitating necrosis [17]. Its receptor, ST2, has been identified on a number of cells including mast cells, eosinophils, T cells, and newly described innate lymphoid cells (ILCs). Analogous to T helper cells, ILCs are divided by cytokine expression with three described subtypes: ILC1, ILC2 and ILC3 [18[■]]. Elevated expression of ST2 within inflamed sinus mucosa from CRS with nasal polyps (CRSwNP) patients is consistent with the known increase in cellular infiltrates of ST2 positive cells [19[■]]. Using flow cytometry analysis, Shaw *et al.* found a significant increase in ILC2s (ILC subtype associated with Th2 cytokines) within nasal polyp homogenates and that these cells are the primary source of IL-13 in response to IL-33 stimulation. Unlike T cells, these ILCs are early responders and reside within the sinonasal mucosa. Interestingly, one of the triggers responsible for IL-33 release from respiratory epithelial cells is fungi [19[■]]. In AFRS, fungal-induced IL-33 activation may play an important pathway in the observed local innate and adaptive Th2 immune response.

In addition to the IL-33 pathway, IL-25 and TSLP have both been linked to the Th2 immune response characteristic of CRSwNP. The ILC2s within nasal polyp homogenates also express the IL-25 receptor and can release IL-13 upon IL-25 and IL-2 stimulation [20]. And elevated TSLP expression and protein production in nasal polyps is associated with activation of mast cells [21[■]]. These two pathways along with IL-33 demonstrate the central role of respiratory epithelial cells in the orchestration of both innate and adaptive Th2 immune response that may serve as an important component of the immunopathology of CRSwNP and AFRS.

ACTIVATION OF BOTH INNATE AND ADAPTIVE IMMUNE RESPONSE

Recent studies have focused on the nature of the innate and adaptive immune response in CRSwNP. The innate immune response is the first, although nonspecific, response to environmental threats which include cells such as mast cells, eosinophils, macrophages, dendritic cells, ILCs and neutrophils. In AFRS patients, histologic and flow cytometry

analyses for these innate cells within inflamed sinus mucosa show significant infiltration of eosinophils, mast cells, ILCs and dendritic cells [9,19[■],22,23]. Eosinophilic infiltration has been associated with more severe disease and poorer treatment outcomes [24]. Elevated mast cell numbers are present in nasal polyp homogenates, independent of atopic status [22]. As discussed above, ILC2s represent the primary source of IL-13 in response to IL-33 stimulation [19[■]]. And nasal polyps are characterized by an increased infiltration of dendritic cells [25]. Activation of an innate response in AFRS is characterized by a Th2 immune profile that also supports skewing of a Th2 adaptive immune response.

In addition to the innate immune response, AFRS is characterized by a robust Th2 adaptive immune response. Elevated IgE production in AFRS patients, with total and fungal-specific serum levels significantly higher than other non-AFRS CRSwNP and allergic rhinitis patients, is evident of a robust Th2 adaptive immune response [15[■],26]. In addition, it was recently shown that serum *S. aureus* enterotoxin-IgE (SE-IgE) was present in 16 of 17 patients with AFRS, and there was a significant and strong correlation of SE-IgE to total IgE in these patients [15[■]]. Increased total and fungal-specific IgE levels are found not only in the serum but also locally within the diseased sinus mucosa of AFRS patients [27]. Elevated antigen-specific IgE levels were not limited to fungal-specific IgE, but included IgE to other antigens [27]. Consistent with this local increase in IgE production, inflamed sinus mucosa from AFRS patients have increased infiltration of lymphocytes, primarily consisting of CD8⁺ T cells. Taken together, these studies confirm an activated adaptive immune in diseased sinus mucosa of AFRS.

In summary, the diseased sinus mucosa in AFRS is characterized by the activation of an innate and adaptive Th2 immune response that seems to be driven in part by release of epithelial cell-derived cytokines. Although the mechanism remains unclear, fungi and *S. aureus* are capable of influencing these responses. A number of key immune cells and activated pathways associated with AFRS have been identified, but future studies are needed to delineate the molecular mechanisms leading to the infiltration, activation, and maintenance of this response. This understanding will allow utilization and development of more targeted therapies.

MANAGEMENT

Given the evolving understanding of the pathophysiology of AFRS, the cornerstone of its management remains surgery and corticosteroids aimed

broadly at minimizing the burden of the inflammatory trigger and suppressing the inflammatory cascade. Other currently available treatment options including immunotherapy, antimicrobial therapy, and other immunomodulatory medications will be discussed.

SURGICAL MANAGEMENT

Regardless of the mechanism, the pathophysiology suggests that exposure to an environmental trigger or triggers likely contribute to the chronic inflammation. One primary goal of the therapy is thus to reduce this exposure [4,5]. This is initially achieved through surgery. In addition to decreasing exposure burden, endoscopic surgical debridement of eosinophilic mucin from the sinus cavities also improves sinus aeration and enhances outflow. Additionally, marsupialization of sinus cavities allows improved access for postoperative debridement and mechanical irrigation with saline solution and/or topical medication [4].

CORTICOSTEROID THERAPY

Like surgery, uses of oral and topical steroid therapy are mainstays in the treatment of AFRS. Although the nasal polyps may respond dramatically to preoperative oral corticosteroids (OCS), surgery is still a necessary treatment step for reasons described above [28]. In cases of recurrent disease after previous sinus surgery, steroids may obviate the need for revision surgery, if access to the affected sinus cavity is improved such that complete mechanical debridement can be achieved. Topical steroids are only effective in postsurgical patients with ample access to diseased sinus mucosa [4]. In the immediate postoperative AFRS patient, a lack of oral steroid use is associated with eventual recurrence of disease, and use of OCS demonstrate improved outcomes in AFRS patients as compared with steroid-free patients [29–31]. A recent prospective, placebo-controlled trial randomized 24 postoperative AFRS patients to either oral steroids or placebo. All 12 patients receiving a tapering dose of prednisone for 12 weeks versus only one patient treated with placebo were completely symptom-free and disease-free by nasal endoscopy at the 3 month follow-up [32]. Similar benefits of OCS were seen in a retrospective study in which 63 postoperative AFRS patients either underwent sinus surgery alone ($n=30$) or received oral and topical steroid therapy in the postoperative period ($n=33$). A 50% recurrence rate of nasal polyps within 2 years was found in the surgery only group as compared with only 15% recurrence rate in the steroid-treated group [33].

Despite its nonspecific nature, extended tapering doses of oral steroids following sinus surgery has proven to be an efficacious algorithm for the management of AFRS. However, chronic oral steroid use is limited by known side-effects. On the contrary, topical steroids have a positive safety profile, and when added to saline irrigations provide an additional mechanical benefit [34,35[¶]]. In a Cochrane review of topical corticosteroids for the treatment of nasal polyps, topical corticosteroids were associated with improved symptoms, decreased polyp size, and reduction of recurrence of nasal polyps [36]. Therefore, topical steroid irrigations are typically added to the treatment of the postoperative AFRS patient as the oral steroids are tapered.

IMMUNOTHERAPY

Characterized by high serum total and fungal-specific IgE levels, fungal immunotherapy represents a means of targeting the activated adaptive immune response in AFRS. However, its efficacy for AFRS remains controversial. Studies performed by Mabry *et al.* [37–40] using relatively dilute antigen concentrations in postoperative AFRS patients showed improved outcomes over a 3–5-year period. Similarly, a retrospective study comparing 36 postoperative AFRS patients who received immunotherapy to 24 who did not, found a significantly lower rate of disease recurrence and subsequent revision surgery over 1 year in the group treated with immunotherapy. Additional benefit was seen when immunotherapy was initiated promptly after surgery [41]. A recent study evaluating the safety profile of high-dose subcutaneous immunotherapy in AFRS patients reported no differences in the local reactions and no evidence of immune complex reactions over a 5-year follow-up [42]. These findings allow for future studies using high-dose fungal immunotherapy in AFRS patients [43]. The published experience with fungal immunotherapy supports its use as adjuvant therapy for AFRS.

ANTIMICROBIAL THERAPY

The data supporting fungi and *S. aureus* as environmental triggers in AFRS implicate the use of antifungals and antibacterials. Oral and topical antifungals have been extensively evaluated for the treatment of CRS after a series of studies proposed a broader role of fungi in the pathophysiology of all types of CRS [44]. A comprehensive meta-analysis in 2011 revealed six randomized controlled trials assessing efficacy of antifungals in the treatment of CRS; evidence was overwhelmingly against the use of antifungal therapy [45]. Importantly

though, studies specifically assessing the efficacy of antifungals in the treatment of AFRS alone have a more positive response, warranting further study within this specific CRS subtype [46]. However, given the ubiquitous nature of fungi and the non-invasive nature of the disease, antifungals alone may prove to have limited effectiveness even in AFRS patients.

The association of *S. aureus* in AFRS supports the use of antibacterial therapy. Mupirocin nasal irrigation is an ideal antimicrobial treatment option in that it reduces both planktonic and biofilm forms of *S. aureus* [47]. Therefore, mupirocin can be incorporated with the topical corticosteroid saline irrigations in the postoperative treatment of AFRS. Nevertheless, a recent review on topical therapy in CRS highlighted a need for further study, noting that a recommendation on high volume antimicrobial irrigations could not be made because of a lack of available evidence [48¹¹].

BIOLOGICS

The goal of obtaining a molecular understanding of the pathophysiology of AFRS is to identify more therapeutic targets. Current available options include anti-IgE and anti-IL-5. Only one randomized controlled trial, considered underpowered, has been performed using anti-IgE in CRSwNP patients, which found no objective or symptomatic improvement [49]. Anti-IL-5 therapy in CRSwNP patients shows more promise. IL-5, a key cytokine involved in eosinophil inflammatory activity via a Th2 response, can be targeted directly with human anti-IL-5 monoclonal antibodies [50¹²]. In a randomized, double-blind placebo controlled trial of 30 CRSwNP patients with symptoms refractory to oral steroid therapy, the anti-IL-5 group had significantly decreased polyp size and less sinus opacification for at least 1 month after therapy [51]. As is the case with most of the current evidence in chronic sinusitis, the AFRS subclass has not distinctly been studied. Future targets may focus on the epithelial cell-derived cytokines and their associated pathways.

CONCLUSION

Though the understanding of AFRS pathophysiology continues to evolve, management currently relies on broadly attacking the immunopathologic response, primarily through surgery and corticosteroid therapy. Future studies are necessary in order to further elucidate molecular mechanisms that allow for the activation and maintenance of the disease process. This understanding will allow

for the development and utilization of targeted therapies.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

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

- of special interest
- of outstanding interest

1. Katzenstein A, Greenberger P, Sale S. Allergic aspergillus sinusitis: a newly recognized form of sinusitis. *J Allergy Clin Immunol* 1983; 72:89–93.
 2. Schubert MS. Allergic fungal sinusitis: pathophysiology, diagnosis, and management. *Med Mycol* 2009; 47 (Suppl 1):S324–S330.
 3. Ferguson BJ, Barnes L, Bernstein JM, et al. Geographic variation in allergic fungal rhinosinusitis. *Otolaryngol Clin North Am* 2000; 33:441–449.
 4. Marple BF. Allergic fungal rhinosinusitis: current theories and management strategies. *Laryngoscope* 2001; 111:1006–1019.
 5. Agarwal G, Citardi MJ, Fakhri S, Luong A. Allergic fungal rhinosinusitis. In: Kountakis SE, editor. *Encyclopedia of otolaryngology, head and neck surgery*, 1st ed. New York: Springer; 2013.
 6. Bent JP 3rd, Kuhn FA. Diagnosis of allergic fungal sinusitis. *Otolaryngol Head Neck Surg* 1994; 111:580–588.
 7. Manning SC, Holman M. Further evidence for allergic pathophysiology in allergic fungal sinusitis. *Laryngoscope* 1998; 108:1485–1496.
 8. Callejas CA, Douglas RG. Fungal rhinosinusitis: what every allergist should know. *Clin Exp Allergy* 2013; 43:835–849.
 9. Bachert C, Gevaert P, Holtappels G, et al. Nasal polyposis: from cytokines to growth. *Am J Rhinol* 2000; 14:279–290.
 10. Bachert C, Gevaert P, Holtappels G, et al. Mediators in nasal polyposis. *Curr Allergy Asthma Rep* 2002; 2:481–487.
 11. Luong A, Davis LS, Marple BF. Peripheral blood mononuclear cells from allergic fungal rhinosinusitis adults express Th2 cytokine response to fungal antigens. *Am J Rhinol* 2009; 23:281–287.
 12. Porter P, Susarla SC, Polikepahad S, et al. Link between allergic asthma and airway mucosal infection suggested by proteinase-secreting household fungi. *Mucosal Immunol* 2009; 2:504–517.
 13. Ferguson BJ, Seethala R, Wood WA. Eosinophilic bacterial chronic rhinosinusitis. *Laryngoscope* 2007; 117:2036–2040.
 14. Clark DW, Wenaas A, Luong A, et al. *Staphylococcus aureus* prevalence in ■ allergic fungal rhinosinusitis vs other subsets of chronic rhinosinusitis with nasal polyps. *Int Forum Allergy Rhinol* 2013; 3:89–93.
- This article implicates a potential role for *Staphylococcus aureus* in the pathophysiology of AFRS. This observation may support the use of antimicrobial therapy directed at this microbe in management.
15. 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.
- This study describes the presence of SE-IgE in the sera of nearly all patients with AFRS, an effect not appreciated in CRSwNP patients. Additionally, SE-IgE correlated with total IgE levels. Furthermore, microscopy showed the presence of biofilms containing both fungi and *S. aureus* in the AFRS patients that were tested. All this suggests a possible significant, synergistic role between fungi and *S. aureus* in the pathogenesis of AFRS.
16. Bachert C, van Steen K, Zhang N, et al. Specific IgE *Staphylococcus aureus* enterotoxins: an independent risk factor for asthma. *J Allergy Clin Immunol* 2012; 130:376–381.
 17. Kouzaki H, Iijima K, Kobayashi T, et al. The danger signal, extracellular ATP, is a sensor for an airborne allergen and triggers IL-33 release and innate Th2-type responses. *J Immunol* 2011; 186:4375–4387.
 18. Bernink J, Mjösberg J, Spits H. Th1 and Th2-like subsets of innate lymphoid ■ cells. *Immunol Rev* 2013; 252:133–138.
- This article describes the newly identified ILCs, which other literature suggests may play a role in the pathophysiology of AFRS.

19. Shaw JL, Fakhri S, Citardi MJ, *et al*. IL-33-responsive innate lymphoid cells are an important source of IL-13 in chronic rhinosinusitis with nasal polyps. *Am J Respir Crit Care Med* 2013; 188:432–439.
- This article described an increased presence of ILCs type 2 in CRSwNP patients compared with CRS without nasal polyps patients and healthy controls. These ILC2s are the main source of IL-13 in response to IL-33, whose release from respiratory epithelial cells can be stimulated by challenge to fungal antigen. These findings highlight the role of ILC2s and IL-33 in the pathophysiology of CRSwNP.
20. Mjösberg JM, Trifari S, Crellin NK, *et al*. Human IL-25- and IL-33-responsive type 2 innate lymphoid cells are defined by expression of CCR2 and CD161. *Nat Immunol* 2011; 12:1055–1062.
21. Nagarkar DR, Poposki JA, Tan BK, *et al*. Thymic stromal lymphopoietin activity is increased in nasal polyps of patients with chronic rhinosinusitis. *J Allergy Clin Immunol* 2013; 132:593–600.
- This study identifies TSLP as another epithelial cell derived cytokine in the pathogenesis of CRSwNP.
22. Shaw JL, Ashoori F, Fakhri S, *et al*. Increased percentage of mast cells within sinonasal mucosa of chronic rhinosinusitis with nasal polyp patients independent of atopy. *Int Forum Allergy Rhinol* 2012; 2:233–240.
23. Ayers CM, Schlosser RJ, O'Connell BP, *et al*. Increased presence of dendritic cells and dendritic cell chemokines in the sinus mucosa of chronic rhinosinusitis with nasal polyps and allergic fungal rhinosinusitis. *Int Forum Allergy Rhinol* 2011; 1:296–302.
24. Nakayama T, Yoshikawa M, Asaka D, *et al*. Mucosal eosinophilia and recurrence of nasal polyps: new classification of chronic rhinosinusitis. *Rhinology* 2011; 49:392–396.
25. Mulligan JK, White DR, Wang EW, *et al*. Vitamin D3 deficiency increases sinus mucosa dendritic cells in pediatric chronic rhinosinusitis with nasal polyps. *Otolaryngol Head Neck Surg* 2012; 147:773–781.
26. Stewart AE, Hunsaker DH. Fungus-specific IgG and IgE in allergic fungal rhinosinusitis. *Otolaryngol Head Neck Surg* 2002; 127:324–332.
27. Wise SK, Ahn CN, Lathers DM, *et al*. Antigen-specific IgE in sinus mucosa of allergic fungal rhinosinusitis patients. *Am J Rhinol* 2008; 22:451–456.
28. Wright ED, Agrawal S. Impact of perioperative systemic steroids on surgical outcomes in patients with chronic rhinosinusitis with polyposis: evaluation with the novel Perioperative Sinus Endoscopy (POSE) scoring system. *Laryngoscope* 2007; 117 (Suppl 15):1–28.
29. Bent JP 3rd, Kuhn FA. Allergic fungal sinusitis /polyposis. *Allergy Asthma Proc* 1996; 17:259–268.
30. Schubert MS, Goetz DW. Evaluation and treatment of allergic fungal sinusitis. II. Treatment and follow-up. *J Allergy Clin Immunol* 1998; 102:395–402.
31. Kuhn FA, Javer AR. Allergic fungal rhinosinusitis: perioperative management, prevention of recurrence, and role of steroids and antifungal agents. *Otolaryngol Clin North Am* 2000; 33:419–433.
32. Rupa V, Jacob M, Mathews MS, Seshadri MS. A prospective, randomized, placebo-controlled trial of postoperative oral steroid in allergic fungal sinusitis. *Eur Arch Otorhinolaryngol* 2010; 267:233–238.
33. Ikram M, Abbas A, Suhail A, *et al*. Management of allergic fungal sinusitis with postoperative oral and nasal steroids: a controlled study. *Ear Nose Throat J* 2009; 88:E8–11.
34. Sachanandi NS, Piccirillo JF, Kramer MA, *et al*. The effect of nasally administered budesonide respules on adrenal cortex function in patients with chronic rhinosinusitis. *Arch Otolaryngol Head Neck Surg* 2009; 135:303–307.
35. Man LX, Farhood Z, Luong A, *et al*. The effect of intranasal fluticasone propionate irrigations on salivary cortisol, intraocular pressure, and posterior subcapsular cataracts in postsurgical chronic rhinosinusitis patients. *Int Forum Allergy Rhinol* 2013; 3:953–957.
- This article supports the well tolerated use of topical steroid irrigations in CRS therapy.
36. Kalish L, Snidvongs K, Sivasubramanian R, *et al*. Topical steroids for nasal polyps. *Cochrane Database Syst Rev* 2012; 12:CD006549.
37. Mabry RL, Mabry CS. Immunotherapy for allergic fungal sinusitis: the second year. *Otolaryngol Head Neck Surg* 1997; 117:367–371.
38. Mabry RL, Marple BF, Folker RJ, Mabry CS. Immunotherapy for allergic fungal sinusitis: three years' experience. *Otolaryngol Head Neck Surg* 1998; 119:648–651.
39. Mabry RL, Mabry CS. Allergic fungal sinusitis: the role of immunotherapy. *Otolaryngol Clin North Am* 2000; 33:433–440.
40. Mabry RL, Marple BF, Mabry CS. Outcomes after discontinuing immunotherapy for allergic fungal sinusitis. *Otolaryngol Head Neck Surg* 2000; 122:104–106.
41. Bassichis BA, Marple BF, Mabry RL, *et al*. Use of immunotherapy in previously treated patients with allergic fungal sinusitis. *Otolaryngol Head Neck Surg* 2001; 125:487–490.
42. Greenhaw B, deShazo RD, Arnold J, Wright L. Fungal immunotherapy in patients with allergic fungal sinusitis. *Ann Allergy Asthma Immunol* 2011; 107:432–436.
43. Hall AG, deShazo RD. Immunotherapy for allergic fungal sinusitis. *Curr Opin Allergy Clin Immunol* 2012; 12:629–634.
44. Shin SH, Ponikau JU, Sherris DA, *et al*. Chronic rhinosinusitis: an enhanced immune response to ubiquitous airborne fungi. *J Allergy Clin Immunol* 2004; 114:1369–1375.
45. Sacks PL, Harvey RJ, Rimmer J, *et al*. Topical and systemic antifungal therapy for the symptomatic treatment of chronic rhinosinusitis. *Cochrane Database Syst Rev* 2011; 8:CD008263.
46. Thanasumpun T, Batra PS. Oral antifungal therapy for chronic rhinosinusitis and its subtypes: a systematic review. *Int Forum Allergy Rhinol* 2011; 1:382–389.
47. Le T, Psaltis A, Tan LW, Wormald PJ. The efficacy of topical antibiofilm agents in a sheep model of rhinosinusitis. *Am J Rhinol* 2008; 22:560–567.
48. Rudmik L, Hoy M, Schlosser RJ, *et al*. Topical therapies in the management of chronic rhinosinusitis: an evidence-based review with recommendations. *Int Forum Allergy Rhinol* 2013; 3:281–288.
- This article evaluates topical therapy for CRS in a systematic manner using evidence-based medicine. It highlights a need for further study regarding the use of topical steroid irrigation and topical antibiotic irrigation in the treatment of CRS. It also describes the lack of efficacy in oral and topical antifungal therapy in CRS; however, AFRS patients have not been distinctly studied using antifungal therapy to date.
49. Pinto JM, Mehta N, DiTineo M, *et al*. A randomized, double-blind, placebo-controlled trial of anti-IgE for chronic rhinosinusitis. *Rhinology* 2010; 48:318–324.
50. Cain RB, Lal D. Update on the management of chronic rhinosinusitis. *Infect Drug Resist* 2013; 6:1–14.
- This update provides a comprehensive review on the current management of the multiple subclasses of CRS.
51. Gevaert P, Van Bruaene N, Cattaert T, *et al*. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy Clin Immunol* 2011; 128:989–995.