

Medical management of allergic fungal rhinosinusitis following endoscopic sinus surgery: an evidence-based review and recommendations

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Background: Allergic fungal rhinosinusitis (AFRS) is a subset of polypoid chronic rhinosinusitis that is characterized by the presence of eosinophilic mucin with fungal hyphae within the sinuses and a Type I hypersensitivity to fungi. The treatment of AFRS usually involves surgery in combination with medical therapies to keep the disease in a dormant state. However, what constitutes an optimal medical regimen is still controversial. Hence, the purpose of this article is to provide an evidence-based approach for the medical management of AFRS.

Methods: A systemic review of the literature on the medical management of AFRS was performed using Medline, EMBASE, and Cochrane Review Databases up to March 15, 2013. The inclusion criteria were as follows: patients >18 years old; AFRS as defined by Bent and Kuhn; post-sinus surgery; studies with a clearly defined end point to evaluate the effectiveness of medical therapy in postoperative AFRS patients.

Results: This review identified and assessed 6 medical modalities for AFRS in the literature: oral steroids; topical

steroids; oral antifungals; topical antifungals; immunotherapy; and leukotriene modulators.

Conclusion: Based on available evidence in the literature, postoperative systemic and standard topical nasal steroids are recommended in the medical management of AFRS. Nonstandard topical nasal steroids, oral antifungals, and immunotherapy are options in cases of refractory AFRS. No recommendations can be provided for topical antifungals and leukotriene modulators due to insufficient clinical research reported in the literature. © 2014 ARS-AAOA, LLC.

Key Words:

allergic fungal rhinosinusitis; AFRS; evidence-based medicine; medical management; endoscopic sinus surgery

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Recently, a number of evidence-based reviews with recommendations have been developed to assist otolaryngologists

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in their management of chronic rhinosinusitis (CRS).¹⁻⁷ However, there has been a lack of consensus in the medical management of allergic fungal rhinosinusitis (AFRS), a subtype of CRS that is increasingly recognized as a separate disease entity. AFRS was first recognized as an upper airway manifestation of allergic bronchopulmonary aspergillosis (ABPA) in the 1970s.^{8,9} It is a noninvasive fungal rhinosinusitis resulting from an allergic and immunologic response of an atopic host to the presence of extramucosal fungi in the sinuses.

The diagnosis of AFRS is based on a set of criteria proposed by Bent and Kuhn in 1994.¹⁰ It is based on classic clinical, radiographic, pathologic, and immunologic features. The original 5 main characteristics were as follows: (1) gross production of eosinophilic mucin without fungal invasion into sinonasal tissue; (2) positive fungal stain of sinus contents; (3) nasal polyposis; (4) characteristic radiographic findings; and (5) allergy to fungi.¹⁰

TABLE 1. Medical options to treat AFRS patients

Oral steroids
Topical steroids
Oral antifungals
Topical antifungals
Immunotherapy
Leukotriene modulators
Alternative medicine

AFRS = allergic fungal rhinosinusitis.

Although the management of AFRS has advanced tremendously with better understanding of the underlying pathogenesis, the optimal treatment strategy is still far from clear. Once a diagnosis of AFRS has been established, patients are enrolled into a committed long-term management program with regular and long-term follow-up considered critical to the success of the treatment. A combination of surgery with a comprehensive postoperative medical regimen to keep the disease under control is almost always required. Unlike the management of classical CRS, the cornerstone of the treatment of AFRS is surgery.¹¹ Surgery not only reestablishes ventilation and removes the antigenic stimulation for AFRS patients, but also provides wider access for surveillance, clinical debridement, and application of topical medication. The purpose of this review is to identify the medical options for management of AFRS after surgery. Recommendations for each intervention are then provided based on the level of evidence and evaluating the balance of benefit to harm. As recommendations may not apply to all AFRS patients, clinical judgment is required on a per case basis.

Patients and methods

This article was written by following a methodology established by Rudmik and Smith¹² for evidence-based review with recommendations. A systematic review of the literature was performed using Medline, EMBASE, and Cochrane Review Databases up to March 15, 2013. All medical therapies available for AFRS in the literature were identified using the search term “allergic fungal sinusitis,” “allergic fungal rhinosinusitis,” “eosinophilic fungal rhinosinusitis,” and “eosinophilic mucin rhinosinusitis.” A total 611 abstracts were reviewed and 6 medical options were identified for the treatment of AFRS after surgery (Table 1).

Another literature search for each individual medical option from Table 1 was then performed using keywords: “allergic fungal sinusitis” and each medical option from Table 1 (eg, “oral steroids”). This process was repeated for “allergic fungal rhinosinusitis,” “eosinophilic fungal rhinosinusitis,” and “eosinophilic mucin rhinosinusitis.” The reference list from all identified articles were reviewed for further articles and obtained. All abstracts were reviewed

for the following inclusion criteria: >18 years old; AFRS as defined by Bent and Kuhn¹⁰; post-sinus surgery; and studies with a clearly defined end point to evaluate the effectiveness of medical therapy in postoperative AFRS patient. Given the paucity of research in medical treatment of AFRS, we reported on all levels of evidence.

All included studies were reviewed and the level of evidence for each paper was given. This was followed by an aggregate grade of evidence and recommendations (Table 2) based on American Academy of Pediatrics Steering Committee on Quality Improvement and Management.¹³ Two authors (E.C.G. and A.T.) reviewed the literature and wrote the initial manuscript. One at a time, subsequent authors (A.R.J., L.R., P.H.H., and B.J.F.) reviewed the manuscript and critically appraised the paper following the online iterative process set by Rudmik and Smith.¹² Final recommendations were based on quality of research and balance of benefit vs harm.

Results

Oral steroids

The efficacy of oral steroids has been well-studied in the management of chronic rhinosinusitis with nasal polyposis (CRSwNP).¹⁴ However, their role in the management of AFRS is less clear. Our search strategy identified 4 studies (Level 2b: 2 studies; Level 4: 2 studies) that fulfilled our inclusion criteria (Table 3). Early reports by Kupferberg et al.¹⁵ and Kuhn and Javer¹⁶ demonstrated the potential benefits of postoperative oral steroids in AFRS patients. These were, however, retrospective case series that involved small number of patients and lacked controls.

In a recent evidence-based review and recommendation by Poetker et al.⁵ on the use of systemic corticosteroid in patients with CRSwNP and chronic rhinosinusitis without nasal polyposis (CRSsNP), oral corticosteroids were strongly recommended in CRSwNP patients, recommended in AFRS patients, and could be considered as a treatment option in CRSsNP patients. Four AFRS studies were included in their review. These studies were by Woodworth et al.,¹⁷ Landsberg et al.,¹⁸ Ikram et al.,¹⁹ and Rupa et al.²⁰ Although the studies by Ikram et al.¹⁹ and Rupa et al.²⁰ showed a beneficial effect of postoperative oral prednisolone on AFRS patients, these studies were excluded in our review due to a lack of adherence to the Bent and Kuhn criteria for the diagnosis of AFRS on their study patients. Ikram et al.¹⁹ was unclear on the Bent and Kuhn criteria used for the diagnosis of AFRS whereas Rupa et al.²⁰ used a modified criteria, replacing “Type I hypersensitivity” with an “immunocompetent host.”

In a prospective comparative study by Landsberg et al.,¹⁸ AFRS patients who received oral steroids preoperatively showed greater radiologic and endoscopic improvement compared to CRSwNP patients. However, in their study, there were only 7 patients with true AFRS (the 8th patient did not demonstrate allergic mucin on histology). Woodworth et al.¹⁷ analyzed the effects of oral

TABLE 2. Defined grades of evidence and recommendations

Grade	Research quality	Preponderance of benefit over harm	Balance of benefit and harm
A	Well designed RCTs	Strong recommendation	Option
B	RCT with minor limitations; overwhelming consistent evidence from observational studies	Strong recommendation/recommendation	Option
C	Observation studies (case control and cohort design)	Recommendation	Option
D	Expert opinion; case reports; reasoning from first principles	Option	No recommendation

RCT = randomized controlled trial.

prednisolone on the chemokine and cytokine levels as well as the 20-item Sino-Nasal Outcome Test (SNOT-20) and nasal endoscopic scores of AFRS and eosinophilic mucin rhinosinusitis (EMRS) patients. They found that although there was a nonstatistically significant improvement in the SNOT-20 score, there were significant improvements in nasal endoscopic scores and a decrease in the levels of interleukin-3 (IL-3), interleukin-5 (IL-5), eotaxin, and monocyte chemoattractant protein-4 (MCP-4) in patients with nasal polyps who have received oral prednisolone. The number of patients who subsequently underwent functional endoscopic sinus surgery (FESS) posttreatment was not mentioned.

Although steroids have been shown to improve mucosal disease and symptoms in AFRS patients immediately following surgery, long-term usage can cause significant side effects. Among some of the early side effects of oral steroids include psychosis, insomnia, weight gain, poorer control of blood glucose level (in diabetic patients) and blood pressure (in hypertensive patients), and gastric upset from peptic ulcer disease. The long-term adverse effects include Cushing's syndrome, adrenal insufficiency, accelerated osteoporosis, glaucoma, cataract formation, and avascular necrosis of the hip.²¹ Fortunately, adverse events from oral corticosteroid use in AFRS patients are relatively infrequent.⁵ Nonetheless, their use should be judicious and limited to short courses in the perioperative period and in acute exacerbations of AFRS to suppress growth of recurrent polyps. Larger randomized controlled trials (RCTs) will be required to determine the optimal dosage and duration of oral steroids in AFRS patients.

Summary of oral steroids

1. Aggregate quality of evidence: B (Level 2b: 2 studies; Level 4: 2 studies).
2. Benefit: Reduction in postoperative mucosal disease. Improved symptoms by endoscopic grading. Reduction in inflammatory markers.
3. Harm: Short-term side effects of oral steroids include weight gain, psychosis, insomnia, poorer control of blood glucose level (in diabetic patients) and blood pressure (in hypertensive patients), and gastric upset from

peptic ulcer disease. Long-term use can lead to Cushingoid features, adrenal insufficiency, accelerated osteoporosis, glaucoma, cataract formation, and avascular necrosis of the hip.

4. Cost: Low, range between \$1.77 and \$2.95 per day depending on dose.
5. Benefits-harm assessment: Preponderance of benefit over harm for short-term use.
6. Value judgments: Oral steroids are best used in the perioperative period and for acute exacerbation of mucosal disease.
7. Recommendation level: Recommendation.
8. Intervention: The dose and duration of oral steroids should be based on the patient's degree of symptoms, nasal endoscopy and risk assessment. The literature uses a variety of starting doses ranging from 0.4 mg/kg/day to 1 mg/kg/day. The course of treatment and the tapering regimen also varies. Therefore, the physician must take many factors into account and decide the dose and duration based on each individual patient.

Topical nasal steroids

The localized anti-inflammatory effects and excellent safety profile of topical nasal steroid sprays have made them a popular treatment modality in the management of CRS.¹ The advantage of topical nasal steroid sprays over oral steroids lies in the ability of topical nasal steroids to achieve an effective drug concentration at the sinonasal mucosa without associated systemic side effects. There are some differences in topical steroids systemic bioavailability; in those topical steroids with the lowest systemic bioavailability, long-term studies have shown no impairment of growth in children, a reassuring measure of the systemic safety. The efficacy of standard topical corticosteroids has been well established in CRSwNP, with recent meta-analyses showing reduced polyp size and improved symptoms compared to control.²²⁻²⁶ Side effects from standard topical nasal steroids are not common and include headache, epistaxis, and cough.²⁷ Based on a grade A evidence, a recent evidence-based review with recommendations by Rudmik et al.¹ provided a strong recommendation for the use of standard topical nasal steroids for the management of CRS.

TABLE 3. Oral steroids in postoperative AFRS summary

Study authors	Year	Study design	Bent and Kuhn criteria	Level of evidence	Subjects (n)	Study groups	Treatment protocol	Primary clinical end points	Complications/ side effects	Conclusion
Kupferberg et al. ¹⁵	1997	Case series	Fulfilled	4	26	Postoperative AFRS patients: (1) No treatment (n = 11); (2) Oral steroids alone (n = 10); (3) Oral steroids and oral antifungals (n = 2); (4) Oral antifungals alone (n = 3)	Oral steroids: 40 mg × 4 days, then 30 mg × 4 days, followed by 20 mg a day until first month visit. Oral antifungals: regimen not described. All patients also received topical nasal steroids and saline irrigations.	1. Endoscopic staging system (by Kupferberg et al. ¹⁵). 2. Symptom improvement	None	Patients who received postoperative steroids had less endoscopically confirmed disease. However, steroids were not curative as disease recurrence were seen upon cessation of steroids. Steroids alone: Symptoms improved in 9/10 patients. Steroids + antifungals: Symptoms in 2/2 patients.
Kuhn and Javer ¹⁶	2000	Case series	Fulfilled	4	11	AFRS patients	Postoperative regimen: 0.4 mg/kg/day for 4 days, 0.3 mg/kg/day for 4 days, 0.2 mg/kg/day maintenance dose (discontinued if endoscopic stage 0 for 4 months)	Endoscopic staging system (by Kupferberg et al. ¹⁵)	None	Endoscopic stage 0 maintained if postoperative maintenance steroid was kept for an average of 4.5 months
Woodworth et al. ¹⁷	2004	Prospective control	Fulfilled	2b	21	(1) AFRS patients (n = 8); (2) EMRS patients (n = 6); (3) Controls (n = 7)	60 mg daily for 3 days, 40 mg daily for 3 days, 30 mg daily for 3 days, 20 mg daily for 12 days	(1) SNOT-20; (2) Endoscopic appearance; (3) IL-5, IL-13, eotaxin, and MCP-4 assays	None	Significant reduction in nasal endoscopic scores, nonsignificant reduction in SNOT-20 scores, reduction in inflammatory markers
Landsberg et al. ¹⁸	2007	Prospective comparative study	Partially fulfilled (8th patient did not demonstrate allergic mucin on histology)	2b	18	(1) AFRS patients (n = 8); (2) CRSwNP (n = 10)	Prednisolone 1 mg/kg for 10 days preoperatively	1. Pretreatment and posttreatment Lund-Mackay CT scan scores. 2. Pretreatment and posttreatment endoscopic appearance.	None	Radiologic and endoscopic mucosal responses of AFRS to systemic steroids were significantly greater compared to CRSwNP

AFRS = allergic fungal rhinosinusitis; CRSwNP = chronic rhinosinusitis with nasal polyposis; CT = computed tomography; EMRS = eosinophilic mucin rhinosinusitis; immunoglobulin E; IL = interleukin; MCP = monocyte chemoattractant protein; SNOT-20 = 20-item Sino-Nasal Outcomes Test.

“Nonstandard” topical nasal steroids are not U.S. Food and Drug Administration (FDA)-approved for application in the nasal cavity and are used in an “off-label” indication. These include high-volume solutions such as budesonide sinonasal irrigations (0.25 mg/2 mL or 0.5 mg/2 mL in 240 mL saline) and low-volume solutions such as intranasal dexamethasone ophthalmic drops (0.1%), prednisolone ophthalmic drops (1%), ciprofloxacin/dexamethasone otic drops (0.3/0.15), and budesonide delivered via the mucosal atomization device (MAD).¹ Nonstandard topical nasals steroids have the advantage of delivering higher volume and/or high concentration of steroids into the sinonasal cavity. The main concern of nonstandard topical nasal steroids sprays is systemic absorption resulting in unwanted systemic side effects. Several studies have, however, demonstrated the lack of systemic absorption in nonstandard topical nasal steroids.^{28–31} In the review by Rudmik et al.,¹ one Level 1b study³² showed no benefit of nonstandard topical steroid spray in CRSwNP with Samter’s triad whereas five Level 4 studies^{28,29,33–35} demonstrated clinical benefits. In view of the paucity of high quality evidence, the use of nonstandard topical nasal steroids in CRS patients was reported as an “option.”

Although topical nasal steroids sprays are commonly used in the medical management of AFRS following ESS, the evidence for its efficacy in this subgroup of CRS is scarce. In this review, we only identified 1 RCT that evaluated postoperative topical nasal steroid therapy in patients with AFRS (Table 4). In this study by Gupta et al.,³⁶ 34 postoperative AFRS patients were randomized into 3 arms: (1) itraconazole + nasal douche (n = 11); (2) topical nasal steroid + nasal douche (n = 12); and (3) nasal douche alone (n = 11). The type of topical steroid used was not provided. At 6 months, endoscopic assessment showed favorable but not statistically significant outcome for the itraconazole group compared to the other 2 groups and no benefit for topical nasal steroids. However, there were a few limitations in this study. Not all patients had documented Type I hypersensitivity, the number of patients in the study was small, the randomization method was not described, and the treatment durations were not equal. Although the evidence for the use of standard and nonstandard topical nasal steroids is lacking for AFRS, expert opinion would support that this form of medical treatment is a safe and viable option, given its proven efficacy and safety in CRSwNP patients. More research is warranted to establish the efficacy and safety profile of topical nasal steroids in AFRS patients.

Summary of topical nasal steroids

1. Aggregate quality of evidence: N/A (only one Level 1b study).
2. Benefit: Potential benefit in reduction of polyp size and nasal symptoms if extrapolated from studies involving CRSwNP subjects.
3. Harm: Headache, epistaxis, and cough. No evidence of clinically significant systemic absorption for nonstandard steroids in the short term.^{28,30,31}
4. Cost: Low to moderate depending on preparation (\$0.61/day to \$4.80/day).
5. Benefits-harm assessment: Preponderance of benefit over harm—assuming similar benefit to CRSwNP.
6. Value judgments: Difficult to provide a recommendation due to scarcity of evidence in AFRS patients. There is overwhelming high-level evidence to support the use of standard topical nasal steroids for CRSwNP, leading us to assume there is benefit in patients with AFRS.
7. Recommendation level: Recommendation for FDA-approved topical nasal steroids and an option for nonstandard topical nasal steroids that are not FDA-approved for application in the nasal cavity. The recommendation for FDA-approved topical nasal steroids is based on the literature on CRSwNP and the fact that AFRS is a subset of CRSwNP. The risk of harmful side effects from topical nasal steroid spray in CRSwNP is low.
8. Intervention: Standard low-volume metered-dose steroid spray. There is an option for common nonstandard topical steroid therapy protocols, which include budesonide sinonasal irrigations (0.25 mg/2 mL or 0.5 mg/2 mL in 240 mL saline or higher concentration). Well-designed RCTs to establish the role of topical nasal steroids in AFRS patients will be required.

Oral antifungals

The use of antifungal therapy (topical and systemic) in patients with CRS has provided limited therapeutic benefit.^{37–43} However, it has to be recognized that AFRS, although a subtype of CRS, is a separate disease entity with different pathogenesis. In true AFRS patients, many studies have provided evidence for a Type I and Type III hypersensitivity to fungi.^{44–50} Hence, in the correctly selected patients, antifungals should hypothetically decrease the antigenic load and inflammatory reactions in AFRS. As systemic antifungals are associated with risks of significant side effects such as elevated liver enzymes, congestive heart failure, nausea, rash, headache, malaise, fatigue, and edema,⁵¹ their usage should be judicious.

Oral antifungals are usually considered as a treatment option in patients with recalcitrant AFRS who have failed postsurgical oral and topical steroids. It is also used as a steroid-sparing medication, allowing some patients to be weaned off prolonged oral corticosteroid therapy.⁵² In this review, 5 studies evaluating oral antifungals in AFRS were identified. The studies by Khalil et al.⁵³ and Chan et al.⁵⁴ were subsequently excluded, as all their study subjects failed to fulfill the classic Bent and Kuhn criteria. Type I hypersensitivity was not demonstrated in the study subjects in both these studies. Hence, only 3 studies (all Level 4 studies) were included in this review (Table 5).

TABLE 4. Topical nasal steroids in postoperative AFRS summary

Study authors	Year	Study design	Bent and Kuhn criteria	Level of evidence	Subjects (n)	Study groups	Treatment protocol	Primary clinical end points	Complications/ side effects	Conclusion
Gupta et al. ³⁶	2007	RCT	Partially fulfilled (not all patients underwent IgE testing. Total IgE was elevated in 19/20 patients and fungal-specific IgE was elevated in 15/17 patients).	1b	34	Postoperative AFRS patients: 1. Oral itraconazole (n = 11). 2. Topical steroids (n = 12). 3. Nasal douches only (n = 11).	1. Itraconazole group: 200 mg twice daily (dosage varied with age) + nasal douches for 2 months. 2. Topical steroid group: topical budesonide 100 microgram twice daily in each nostril + nasal douche for 4 months. 3. Nasal douches group: alkaline saline douches for 6 months.	Endoscopic staging system (by Kupferberg et al. ¹⁵)	None reported	Postoperative oral itraconazole resulted in a more favorable but not statistically significant mucosal stage compared to the other 2 groups.

AFRS = allergic fungal rhinosinusitis; IgE = immunoglobulin E; RCT = randomized controlled trial.

TABLE 5. Oral antifungals in postoperative AFRS summary

Study authors	Year	Study design	Bent and Kuhn criteria	Level of evidence	Subjects (n)	Study groups	Treatment protocol	Primary clinical end points	Complications/side effects	Conclusion
Kupferberg et al. ¹⁵	1997	Case series	Fulfilled	4	26	Postoperative AFRS patients: (1) No treatment (n = 11); (2) Oral steroids alone (n = 10); (3) Oral steroids and oral antifungals (n = 2); (4) Oral antifungals alone (n = 3).	Oral antifungals alone (n = 3). Oral steroids: 40 mg × 4 days, then 30 mg × 4 days, followed by 20 mg per day until first month visit. Oral antifungals: regimen not described. All patients also received topical nasal steroids and saline irrigations.	(1) Endoscopic staging system (by Kupferberg et al. ¹⁵); (2) Symptom	None	All patients who received postoperative steroids had less endoscopically confirmed disease. However, steroids were not curative as disease recurrence were seen upon cessation of steroids. Antifungal alone: Symptoms improved in 1 out of 3 patients. Steroids + antifungal: Symptoms improved in all of 2 patients.
Rains and Mineck ⁵⁵	2003	Case series	Partially fulfilled (Accepted a history of atopy for patients without Type I hypersensitivity, accepted gross or histologic appearance of allergic mucin, only 55% of patients demonstrated fungal specific allergy)	4	139	Postoperative AFRS patients	Oral prednisolone 30 mg/day for 3 days, 20 mg/day for 3 days, and 10 mg/day for 7 days postoperatively. Topical nasal steroids on postoperative day 14 onward. Itraconazole 400 mg/day for 1 month, 300 mg/day for 1 month, 200 mg/day for 1 month or until clear by endoscopy	Recurrence	Elevated liver enzymes >2× normal (4 patients); nausea (3 patients); rash (3 patients); headache (1 patient); malaise/depressed mood (1 patient); fatigue (2 patients); edema (4 patients)	Recurrence in 50.3% of patients, reoperation required in 20.5%.
Seiberling and Wormald ⁵²	2009	Case series	Fulfilled	4	23	Postoperative recurrent AFRS (9 patients), AFRS-like (1 patient), and NAFES patients (13 patients)	Itraconazole 100 mg twice daily for 6 months	(1) Symptom improvement; (2) Endoscopic assessment	Elevated liver enzymes (3 patients)	19/23 (83%) improved symptomatically and endoscopically. Oral itraconazole may be beneficial to patients with recalcitrant AFRS.

AFRS = allergic fungal rhinosinusitis; NAFES = nonallergic fungal eosinophilic sinusitis.

In a large retrospective case series of 137 AFRS patients treated with high-dose oral itraconazole by Rains and Mineck,⁵⁵ recurrence occurred in 69 patients (50.3%) at about 10.8 months postsurgery, and revision surgery was required in 17 patients (20.5%). In their regimen, itraconazole was given at 400 mg/day for 1 month, followed by 300 mg/day for 1 month, followed by 200 mg/day for 1 month or until clear by endoscopy. As the revision surgery rates have been reported to be between 48% and 56%,^{56,57} Rains and Mineck⁵⁵ concluded that high-dose antifungals reduced the requirement for repeated surgical debridement. However, they used a modified Bent and Kuhn criteria, by accepting “a history of atopy” and “characteristic appearance of eosinophilic mucin on endoscopic examination” if “[immunoglobulin E] IgE hypersensitivity to fungi” or “eosinophilic mucus on histology” were not present respectively. Using their modified criteria, 118 patients (82%) were diagnosed with AFRS. There was also no mention on the number of patients who did not demonstrate allergic or eosinophilic mucin on histology. Hence, a proportion of their study population may not consist of classic AFRS patients as described by Bent and Kuhn.

In a case series of 26 postoperative AFRS patients by Kupferberg et al.,¹⁵ patients were subjected to 4 different postoperative regimens: (1) no treatment (n = 9); (2) oral steroids (n = 10); (3) oral steroids and oral antifungals (n = 2); and (4) oral antifungals alone (n = 3). They found that patients who received postoperative systemic steroids had less endoscopically confirmed disease. However, they noted that the steroids were not curative and the disease recurred as the steroids were weaned off. Their oral antifungals alone arm involved only 3 patients and their regimen was not described. Apart from that, all patients also received topical nasal steroids and saline irrigation. Only 1 of 3 patients reported improvement in nasal symptoms after oral antifungals alone.

In a retrospective review of 23 patients with refractory AFRS and nonallergic fungal eosinophilic rhinosinusitis (NAFES), Seiberling and Wormald⁵² showed that 83% of patients (19/23 patients) responded to oral itraconazole with decreased nasal symptoms and improved endoscopic findings. Their study patients received oral itraconazole 100 mg twice a day for 6 months when disease recurred after surgery and oral steroids. Their AFRS population consisted of only 9 patients. Seven of 9 AFRS patients improved clinically after commencement of oral itraconazole. Of the 7 patients who responded, 2 patients had disease recurrence, requiring a second course of oral itraconazole to clear the disease.

The prevalence of transaminitis in AFRS patients on oral itraconazole has been reported to be between 4% and 19%.^{52,54} Asymptomatic transaminitis is not uncommon and cessation of treatment is usually sufficient for the elevated liver enzymes to revert back to normal. Hepatotoxicity, including liver failure and death, is rare but a serious complication of itraconazole.

Given the lack of high-level evidence for the use of oral antifungals in AFRS patients and the potential harm from their side effects, oral antifungals should be reserved for those who have failed topical and oral steroids or to reduce dependence of patients on long-term oral steroids. Even then, the evidence for their use is limited and the benefits must be balanced against the potential side effects. Oral antifungals are an option that can be considered in the management of AFRS patients, but their efficacy, safety, and dosage should be more clearly defined by well-designed RCTs. The antifungal activity against typical AFRS pathogens such as *Aspergillus*, *Curvularia*, and *Dermatiaceous* hyphae is greatest with the oral “azole” antifungals such as voriconazole and itraconazole and less with fluconazole, which is used primarily for *Candida* infections.⁵⁸

Summary of oral antifungals

1. Aggregate quality of evidence: C (Level 4: 3 studies).
2. Benefit: Reduction in symptoms, reduction in dependence on oral steroids and prevention of disease recurrence.
3. Harm: Elevated liver enzymes (most common side effect), congestive heart failure, nausea, rash, headache, malaise, fatigue, and edema.
4. Cost: High (\$13.38/day for 200 mg by mouth [PO] daily; 26.76/day for 400 mg PO daily).
5. Benefits-harm assessment: Equal balance of benefit to harm.
6. Value judgments: Difficult to provide recommendation due to a lack of high level evidence. Classic AFRS criteria as described by Bent and Kuhn was also only partially fulfilled in the largest retrospective study by Rain and Mineck. Clinicians should disclose the limited data on effectiveness and discuss the potential risks and cost of oral antifungal therapy with patients before beginning therapy. Further research in this area is warranted.
7. Recommendation: Option—in select cases of postsurgical refractory AFRS.
8. Intervention: Itraconazole at 200 mg to 400 mg PO daily in divided doses have shown benefits in Level 4 studies.

Topical antifungals

As oral antifungals have risks of significant systemic side effects, the use of topical antifungals has been explored in the management of AFRS patients. Like their oral counterparts, topical antifungals have not been proven to be effective in the management of CRS.^{1,37,38,40,59} Proponents of topical antifungals for AFRS will argue that it should eradicate extramucosal fungus and decrease fungal antigen load.

In this review, there were 2 studies on the use of topical antifungals in patients with AFRS. Although both studies, by Khalil et al.⁵³ and Jen et al.,⁶⁰ showed potential benefits of topical antifungals in AFRS patients, these studies were excluded from this review due to flaws in their inclusion criteria. The study by Khalil et al.⁵³ did not fulfill the Bent

and Kuhn criteria whereas the study by Jen et al.⁶⁰ was unclear on the criteria used for the diagnosis of AFRS. Well-designed RCTs will be required to establish the role of topical antifungals in the management of AFRS.

Summary of topical antifungals

1. Aggregate quality of evidence: None.
2. Benefit: None.
3. Harm: None.
4. Cost: Moderate (\$3.04/day).
5. Benefits-harm assessment: None.
6. Value judgments: None.
7. Recommendation: No recommendation.
8. Intervention: None.

Immunotherapy

Allergen immunotherapy (IT) is used to treat IgE-mediated hypersensitivity and there are a number of studies that have investigated its use in the treatment of allergic rhinitis^{61–63} and asthma.^{64–66} When evaluating the effect of IT for AFRS, the highest level of evidence is 3b, consisting of 2 case-control studies (Table 6).^{67–69}

Folker et al.⁶⁷ performed a case control study assessing 11 patients who received IT for at least 12 months (mean 30 months) to 11 control patients without IT. Patients on IT were tested for fungal and nonfungal antigens and then placed on IT based on their sensitivities. Doses ranged (average 0.05 mL of a 1:100 wt/vol concentration) for each patient depending on their local and systemic reaction. This study showed significant improvement in all 3 clinical outcomes: (1) endoscopic mucosal staging ($p < 0.001$); (2) quality of life scale ($p = 0.002$); and (3) reliance on systemic ($p < 0.001$) and oral ($p = 0.043$) corticosteroids. These findings are appreciated in the context that patients were treated in a similar fashion, but the length of adjuvant therapies was likely different among patients. In general, patients were treated the same in both groups, starting with systemic corticosteroids postoperatively, which ended by the fourth week, followed by nasal saline irrigation and topical nasal corticosteroids. Nasal corticosteroids were withdrawn if mucosa appeared healthy and there was no presence of allergic mucin or nasal polyps after 2 consecutive evaluations. IT was generally started within 6 to 8 weeks of surgery after the mucosa had healed from surgery.

Bassichis et al.⁶⁸ did a case-control study reviewing a database of 82 patients. They reviewed 36 patients who received IT and 24 patients who did not receive IT. The paper concluded significant reduction in office visits requiring intervention ($p < 0.005$) and revision surgery ($p < 0.01$). The paper did not indicate the length of IT. Moreover, the postoperative management varied among individuals, which may have included nasal irrigation, intranasal steroids, crust removal, systemic steroids, and antibiotics.

There are a number of prospective case series published by Mabry et al.^{70–72} Mabry et al.⁷⁰ initially showed the effects of IT in 9 patients treated for 1 year postoperatively for

evidence of recurrent disease, medication requirements, and secondary infections. Descriptive analysis showed no evidence of recurrent disease and minimal additional steroid use was required. After 1 year, patients were changed from weekly to biweekly treatment. In a 2-year follow-up study, Mabry and Mabry⁷¹ reported a continued decrease in nasal crusting, with minimum amount of recurrent polypoid mucosa and reduced requirement of corticosteroids. No adverse effects were noted. Mabry et al.⁷² continued with another publication providing their 3 years of experience and continued to support their clinical suspicion that IT improves outcomes in AFRS patients. However, it was unclear if all of the AFRS patients in Mabry et al.'s studies^{70–72} had Type I hypersensitivity. The lack of a prospective design and a control group were recognized by the authors as weaknesses of their studies.

The papers reviewed indicated no adverse events with IT in the treatment of AFRS. One paper's main objective investigated the safety of IT in AFRS vs CRS patients.⁶⁹ This case-control study showed no differences in local or systemic reactions (either immediately or delayed) between the 2 groups. Each group had 1 patient who had a mild systemic urticarial reaction. Beyond potential mild reactions seen with other IT for pollen, there does not seem to be any additional risks with IT for AFRS. They also used a modified Bent and Kuhn criteria, replacing "Type I hypersensitivity" with an "immunocompetent host"; therefore, this paper was not included in the final aggregate of quality of evidence and recommendation.

Based on the current evidence, there is support that indicates IT maybe beneficial in AFRS patients. However, all studies used IT in conjunction with other medical therapies. Despite case-control studies, none of the comparison groups were placed on the same medical regimen to decipher the true effect of IT. A prospective study with similar comparison groups is required to determine the true impact of IT in AFRS. Given the minimal adverse effects of IT and the biological plausibility of IT in treatment of AFRS, it can be considered an option for AFRS recalcitrant to steroids.

Summary of immunotherapy

1. Aggregate quality of evidence: C (Level 3b: 2 studies; Level 4: 3 studies).
2. Benefit: Potentially reduces mucosal inflammation and the amount of topical/systemic corticosteroids required. Potential adjuvant therapy with corticosteroids.
3. Harm: Patients have the same risks as other forms of allergen IT. Local irritation, flu-like symptoms (fever, chills, nausea and loss of appetite, fatigue). Anaphylaxis rare.
4. Cost: High (yearly costs range between \$3100 to \$3800).
5. Benefits-harm assessment: Equal balance of benefit to harm.
6. Value judgments: Challenging to recommend IT use in the management of AFRS based on level C evidence.

TABLE 6. Immunotherapy in postoperative AFRS summary

Study authors	Year	Study design	Bent and Kuhn criteria	Level of evidence	Subjects (n)	Study groups	Treatment protocol	Primary clinical end points	Complications/ side effects	Conclusion
Folker et al. ^{6,7}	1998	Case control	Fulfilled	3b	22	1. Immediate postoperative AFRS group; immunotherapy with fungal and nonfungal antigens, corticosteroids, antibiotics. 2. Immediate postoperative AFRS group; corticosteroids, antibiotics	Highest tolerated concentration given to fungal and antifungal antigens sensitivities; minimum 12 months treatment	1. Endoscopic mucosal staging. 2. Chronic Sinusitis Survey. 3. Corticosteroid requirements.	None	1. Improvement endoscopic mucosal staging ($p < 0.001$). 2. Improvement quality of life ($p = 0.002$). 3. Reduce reliance on systemic ($p < 0.001$) and topical ($p = 0.043$) corticosteroids.
Mabry et al. ⁷⁰	1997	Prospective case series	Fulfilled (however, does not clearly state if Type I hypersensitivity tested)	4	9	(1) Single postoperative AFRS group	IT given weekly basis based on sensitivities to fungal and antifungal antigens up to 12 months; highest tolerated concentration given	1. Evidence of recurrent disease. 2. Medication requirements. 3. Complicating secondary infections.	None	Clinical suspicion IT reduces reaccumulation of crusts and allergic mucin, topical and systemic steroids, and improved quality of life.
Mabry and Mabry ⁷¹	1997	Prospective case series	Partially fulfilled (7 tested for Type I hypersensitivity, unclear with other patients)	4	10	(1) Single postoperative AFRS group	IT given initially weekly for a year then extended to biweekly basis; total average therapy 20 months; IT based on sensitivities to fungal and antifungal antigens	1. Evidence of recurrent disease. 2. Medication requirements. 3. Complicating secondary infections. 4. Adverse outcomes	None	Continue to support findings from original study.

(Continued)

TABLE 6. Continued

Study authors	Year	Study design	Bent and Kuhn criteria	Level of evidence	Subjects (n)	Study groups	Treatment protocol	Primary clinical end points	Complications/ side effects	Conclusion
Mabry et al. ⁷²	1998	Prospective case series	Partially fulfilled (results illustrate 7 tested for IgE levels, unclear with other patients)	4	11	(1) Single postoperative AFRS group	IT given initially weekly for a year then extended to bi-weekly basis; total average therapy 28 months; IT based on sensitivities to fungal and antifungal antigens	<ol style="list-style-type: none"> Evidence of recurrent disease. Medication requirements. Complicating secondary infections. Adverse outcomes. 	None	Continue to support findings from original study.
Bassichis et al. ⁶⁸	2001	Case-control	Fulfilled	3b	60	<ol style="list-style-type: none"> 36 postoperative AFRS patients given IT and variety of topical/systemic medications. 24 postoperative AFRS patients not given IT and variety of topical/systemic medications. 	IT given for relevant antifungal and fungal antigens; duration of treatment unknown	<ol style="list-style-type: none"> Office visits requiring intervention. Requiring revision surgery. 	None	<ol style="list-style-type: none"> IT group required less visits needing intervention ($p < 0.05$). IT group required less revision surgery ($p < 0.05$).

AFRS = allergic fungal rhinosinusitis; IgE = immunoglobulin E; IT = immunotherapy.

However, based on the consistency of lower level evidence to demonstrate clinical effectiveness, we feel it should be discussed as a possible therapeutic option with the patient. Given the potential detrimental side effects if not correctly administered, only a physician with training in IT should provide IT.

7. Recommendation: Option.
8. Intervention: Initiation of IT can be started as early as 6 weeks postoperatively once the sinus mucosa has healed.

Leukotriene modulators

Despite a number of review articles addressing leukotriene modulators as a potential treatment option in AFRS,^{73,74} there is only 1 clinical case report⁷⁵ on the effects of leukotriene modulators on AFRS (Table 7). The case involved a healthy 41-year-old female with 3 previous sinus surgeries who continued to have persistent symptoms of AFRS. Her nasal therapy only included budesonide nasal aerosol. A computed tomography (CT) scan was organized and done with intentions of having another surgery. While waiting, the patient was placed on 10 mg of oral montelukast daily and continued with topical budesonide. One month later, her symptoms had dramatically improved, with decrease in endoscopic mucosal inflammation and improved CT scan staging.

Summary of leukotriene modulators

1. Aggregate quality of evidence: N/A (only 1 study at Level 4).
2. Benefit: Based on 1 case report, reduction in mucosal inflammation and improved symptoms.
3. Harm: Potential side effects include skin rash, bruising, muscle weakness, and potential worsening of sinus or asthma symptoms.
4. Cost: Moderate (\$6.30 per day).
5. Benefits-harm assessment: Equal balance between benefit and harm.
6. Value judgments: Require more research.
7. Recommendation: No recommendation.
8. Intervention: Case report used montelukast 10 mg oral once a day.

Overall summary

Based on the best available evidence, an evidence-based therapy protocol in the management of postoperative AFRS would include a short course of postoperative oral corticosteroids. A short tapering dose of oral corticosteroid (prednisolone rescue) can be considered for acute exacerbations. Although there is no set standard regimen for prednisolone rescue, the protocol used by the senior author (A.R.J.) is as follows: oral prednisolone 40 mg daily for 4 days, followed by 30 mg daily for 4 days, followed by 20 mg daily for 4 days, and 10 mg daily for 4 days. Multiple repeated prednisolone rescue or long-term use of oral prednisolone is associated with significant side effects and therefore should be avoided. Although standard topical nasal corticosteroid sprays have been proven to be beneficial in patients with CRSwNP, the literature on its efficacy in AFRS patients is scarce. In most studies on the medical treatment of AFRS patients, topical nasal steroids were included as part of the standard treatment regimen in addition to other therapies. As AFRS is a subset of CRSwNP, topical nasal corticosteroids in postoperative AFRS patients should be recommended. However, this recommendation is based on data extrapolated from patients with CRSwNP and not evidence-based for AFRS patients. Future studies to prove its effectiveness in AFRS should be performed. Oral antifungal and immunotherapy are therapeutic options for refractory postsurgical AFRS that are weakly supported in the literature. Based on limited evidence, it is challenging to provide recommendations on when to use 1 treatment modality over another. Therefore, the clinician must make therapeutic decisions on a per case basis. There is currently no evidence in the literature for the use of topical antifungals for AFRS patients. The use of leukotriene modulators has shown some positive impact in AFRS but requires more research before it can be recommended. This work does not include nasal saline irrigation as an option in the medical management of AFRS following endoscopic sinus surgery because the search strategy did not find any papers investigating the use of nasal saline irrigation specifically for AFRS. However, nasal saline irrigation is a mainstay treatment in CRS^{1,2}; therefore, it should be considered as an option in the treatment of AFRS.


TABLE 7. Leukotriene modulators in postoperative AFRS Summary

Study authors	Year	Study design	Bent and Kuhn criteria	Level of evidence	Subjects (n)	Study groups	Treatment protocol	Primary clinical end points	Complications/ side effects	Conclusion
Schubert ⁷⁵	2001	Case report	Fulfilled	4	1	4 previous sinus surgery, multiple therapies including IT, topical/systemic steroids	10 mg oral montelukast once a day	CT mucosal disease	None	Dramatic improvement in hypertrophic mucosal disease

AFRS = allergic fungal rhinosinusitis; CT = computed tomography; IT = immunotherapy.

Conclusion

This article has evaluated the literature on 6 different medical therapies in the management of postoperative AFRS and provided an evidence-based review with recommendations. The evidence supports the use of postoperative oral corticosteroids and, indirectly, topical corticosteroids in postoperative management of AFRS patients. In recalcitrant AFRS, medical options include oral prednisolone rescue, oral antifungals, and immunotherapy. There is currently no literature to provide recommendations for the use

of topical antifungals in the medical management of AFRS. The use of leukotriene modulators has been described but no recommendations can be provided based on the lack of evidence. Physicians should engage the patients in discussion regarding the medical options available and review all risks, benefits, and costs. Given the paucity in research within this subgroup of CRS, clinical judgment is required when determining the most appropriate postoperative care for patients with AFRS. Further research is required for all medical therapies used to manage AFRS. 

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UPCOMING MEETING ANNOUNCEMENT 2014

The 33rd ISIAN meeting (International Society of Inflammation and Allergy of the Nose), in combination with the IRS (International Rhinologic Society) will be held in **Dubai, November 20th to 24th 2014**, under the leadership of Reda Kamel, M.D. This major international meeting promises to bring together rhinologic leaders from around the globe. For more information, please go to <http://isian-irs-pars2014.org/about-dubai.php>