Medical Management of Allergic Fungal Sinusitis

Dr. Fahad AlObaid

Presented by Dr. Ahmad Al Roqi
• Current strategies in the treatment of AFS have been developed to contend with the central problem of high AFS recurrence rates after sinus surgery

• Surgery for AFS without postoperative medical management leads to recurrence

• The reported recurrence rates for AFRS range from 10% to 100%
one longitudinal study showed that over a 7-year follow-up period, patients required an average of two surgical procedures and three courses of systemic steroids per year

AFRS is now considered an inflammatory disease and treatment approaches have been altered accordingly
• Coordinated medical–surgical postoperative follow-up leads to the best patient outcomes

• Adequate sinus surgery is believed to be a required first step in the treatment of any patient with AFS

• Incomplete surgery, with retention of cells filled with eosinophilic mucin appears to be a risk factor for early recurrence and may limit the effectiveness of topical medical treatments
Although there have been no studies comparing different surgical techniques, it has been suggested that limited FESS has been associated with higher rates of AFS recurrence than more aggressive surgical procedures that remove all dysfunctional obstructive hypertrophic/hyperplastic sinus mucosa as well as all inspissated allergic mucin.
• The analogy of AFS to ABPA has helped create the foundation for the current approach to the medical management of AFS.

• Both disorders are non–tissue-invasive fungal allergic/hypersensitivity disorders involving fungal-containing allergic mucin impaction and mucosal inflammation of airways, and both are highly recurrent
Unfortunately no fully controlled or double-blinded studies have been published for any treatment for AFS
The closest to any such study was a retrospective analysis of 67 consecutive AFS cases treated and followed over 8 years where roughly half the participants were treated with postoperative OCS and the other half were not; all were otherwise treated similarly with respect to sinus surgery, common aeroallergen immunotherapy, anti-inflammatory nasal sprays, and antihistamines.
Oral Corticosteroid (OCS)

- The OCS protocol for AFS was modified from that used in ABPA.
  - Patients were given prednisone, 0.5 mg/kg immediately postoperatively.
  - then daily as a single morning dose for 2 weeks,
  - then the same dose every other morning for several weeks,
  - with a gradual taper to 7.5 to 5.0 mg every other morning by 3 months postoperatively,
  - then maintained on 5.0 mg every other morning.

- The duration of prednisone treatment was up to 1 year, or longer in individual cases.
Any significant intercurrent acute viral, bacterial, or allergic rhinosinusitis episodes were treated with a short burst of prednisone, 20 or 30 mg daily for several days, with rapid taper to the baseline 5-mg dose, along with antibiotics if judged to be required or prudent.
• Parameters followed included clinical rhinosinusitis activity and need for recurrent sinus surgery

• It was found that at least 2 months of postoperative OCS treatment using this modified ABPA protocol gave clinical improvement for up to 1 year compared with no OCS therapy, although 1 year of OCS treatment was clearly better.
Both clinical rhinosinusitis activity and the need for recurrent sinus surgery were significantly reduced with OCS therapy. It was also found that follow-up measurements of total serum IgE and fungal-specific IgG had significant predictive power, rising during clinical exacerbation and falling during clinical improvement, similar to the fluctuation seen in ABPA. No tissue-invasive fungal disease occurred from treatment with OCS using this protocol.
Fig. 6. A 17-year-old man with *Bipolaris spicifera* AFS. (A) Sinus CT scan after three sinus surgeries over several years and 6 months of oral itraconazole. (B) Sinus CT scan 5 years after 6A. The patient underwent a fourth sinus surgery shortly after the CT scan in 6A had been obtained, immediately followed by 1 year of treatment with oral corticosteroids dosed according to the protocol published by Schubert and Goetz [61]. Other medical treatment included relevant inhalant allergen immunotherapy (*Bipolaris spicifera* was not available for treatment), nasal corticosteroids, and antihistamines; antifungal agents were not used.
A brief course of preoperative systemic corticosteroids will shrink polyps and decrease bleeding during surgery
Antifungal agents

- Toxic systemic antifungal drugs should be avoided. Systemic antifungal drugs have not been shown to be significantly effective in the primary treatment of either AFS or ABPA, presumably because these are not tissue-invasive fungal infections.

- Several recent controlled ABPA studies comparing the addition of oral itraconazole or placebo during OCS treatment found additional clinical benefit with itraconazole,
however. Results have been questionable with the few cases reported in which oral antifungal agents were added to OCS in the treatment of AFS. Particularly for AFS, more studies are required to determine whether such dual therapy is superior to OCS alone.
Two recent studies suggested clinical benefit using amphotericin B sinonasal lavage in non-\texttt{AFS} patients with hypertrophic sinus disease but treatment controls were not used.
• There is little evidence that antifungals decrease reliance on systemic steroids.

• The fungi in AFRS are not invasive and are often present in scant numbers.

• Antifungal drugs have many serious toxicities and prolonged treatment may be expensive.
The efficacy of agents such as itraconazole may not be due to a reduced fungal burden in the nose, but rather due to the antiinflammatory properties of the molecule or its inhibition of prednisone metabolism.

Despite the purported fungal cause of AFRS, antifungal therapies need further investigation to establish their efficacy before their use is widely adopted.
Immunotherapy

• Allergen immunotherapy has been reported to help reduce AFS recidivism. Unfortunately, like all studies in the treatment of AFS, no double-blind, placebo-controlled studies have been published.

• One case report described subjective improvement with Bipolaris spicifera–specific immunotherapy in a patient with Bipolaris spicifera AFS.
The largest study of allergen immunotherapy over 3 years showed clinical improvement in the postoperative management of AFS when all skin test– and RAST positive aeroallergens were included in the immunotherapy mix.
The same group published a 6-year follow-up of 17 AFS patients and found that 9 of the 10 patients initially treated with immunotherapy had discontinued treatment, but patients were doing well overall with roughly equivalent symptom scores and endoscopic staging. The specific AFS-etiologic mold was not identified or used for most patients,
The antiinflammatory effect of specific allergen immunotherapy has the potential to decrease reliance on systemic steroids in the treatment of AFRS or may reduce the need for revision surgery.
• Given that AFRS is often a severe and refractory condition that requires multiple sinus surgeries and repeated or prolonged courses of systemic steroids, it is rational to attempt to control concomitant allergic inflammation via immunotherapy.
Although subcutaneous immunotherapy has clearly demonstrated efficacy in allergic rhinitis and asthma, randomized, controlled trials that examine the efficacy of immunotherapy specifically for AFRS are lacking.
In the most rigorous study to date Folker and colleagues compared AFRS patients treated with and without immunotherapy. Patients underwent comprehensive allergy testing and immunotherapy was begun approximately 1 month after endoscopic sinus surgery.
Dosing consisted of weekly injections escalated to a maximally tolerated dose and continued for 3 to 5 years. After an average 33 months of follow-up, they showed that the immunotherapy-treated patients had better endoscopic mucosal appearance, lower CRS survey scores, required fewer courses of oral steroids (0 vs 2), and showed less reliance on nasal steroids (27% vs 73%).
Topical Agents

- Nasal corticosteroids are commonly used as adjunctive medical treatment for AFS.

- Although not systematically studied in AFRS, topical steroids have been shown to be effective in the treatment of nasal polyp disease.

- In the treatment of nasal polyp disease there does appear to be a dose response effect, with higher doses conferring greater benefit. For AFRS, some investigators have recommended that nasal steroid sprays be used at up to three times the usual dosage to boost their efficacy.
One emerging topical therapy is the use of budesonide respules, delivered as a drop, atomized spray, or low-volume irrigant.

Topical budesonide treatment delivers a larger total dose of steroid compared with conventional steroid nasal sprays.

The mode of delivery can improve distribution to the sinus mucosa in postsurgical patients.

Topical budesonide therapy has not been systematically studied in AFRS.
Antihistamines are also commonly added, and a recent case report described successful treatment of AFS with the oral cysteinyl leukotriene receptor antagonist montelukast.

Patients may also benefit from the addition of sinonasal saline lavage.
A practical approach to treatment

- Starts with sinus surgery to remove all diseased and obstructing sinus mucosa and inspissated fungal containing allergic mucin

- Intraoperative findings, including the description of any characteristic allergic mucin, should be noted
• All surgical specimens should be sent for pathologic evaluation, and the pathologist should be alerted to the need for histologic fungal stains

• Surgical bacterial and fungal cultures should be obtained
• Medical evaluation if treatment with OCS is being considered.

• Conditions that could contraindicate the use of OCS include diabetes mellitus, chronic hepatitis, blood dyscrasias, immunodeficiency, an untreated positive purified protein derivative (PPD) skin test, osteoporosis, glaucoma, and cataracts,
Suggested laboratory tests include:

- skin testing for type I immediate hypersensitivity to common aeroallergens (including the etiologic mold, if already known),
- total serum IgE,
- complete blood count with differential,
- serum chemistries for electrolytes,
• glucose, liver, and renal function, calcium, albumin, total protein, uric acid, and cholesterol, erythrocyte sedimentation rate,

• quantitative serum IgG, IgA, and IgM, delayed hypersensitivity skin tests to T-cell recall antigens including PPD with Candida as a positive control,

• urinalysis, spirometry chest radiograph, and eye examination for glaucoma and cataracts.

• Bone densitometry should also be obtained if clinically indicated.
OCS treatment should be started postoperatively as soon as the diagnosis of AFS is properly made.

Use of the referenced OCS protocol or a similar protocol should be considered.

Excessive delay in starting OCS treatment after sinus surgery has been shown to be associated with early AFS recurrence.
Allergen immunotherapy to all relevant aeroallergens as identified by proper testing for type I immediate hypersensitivity should be strongly considered (the AFS-etiologic mold may be included, if available), along with topical nasal corticosteroids, antihistamines, and oral antileukotrienes if not contraindicated.
• Total serum IgE should be obtained at baseline and serially during postoperative follow-up.
  • A falling total serum IgE is a favorable sign, encouraging OCS tapering per protocol.
  • A rising total serum IgE often indicates renewed AFS activity, and temporarily increasing the OCS dose with rapid taper to baseline dosing should be followed by clinical re-evaluation.
If the total serum IgE rises again, particularly in concert with worsening clinical findings, surgical evaluation should be urgently undertaken for presumed AFS relapse.
• Early aggressive sinus surgery for recurrence should be coordinated with restarting the OCS protocol from the beginning.

• Inability to remove all AFS and obstructing dysfunctional sinus mucosa at surgery can lead to OCS dependency with unwanted side effects
• This modified ABPA OCS protocol can be continued for up to 1 year if needed, or even longer in individual cases, if indicated.

• Excessive OCS dosing that clearly leads to side effects should be avoided
• Follow-up serum chemistries, bone densitometry, and eye evaluation may be required.

• The goals of treatment are
  • to reduce rhinosinusitis symptoms,
  • to prevent surgical AFS relapse,
  • to be able to taper off OCS without AFS recurrence, and
  • to avoid OCS-related side effects.

• Coordination of treatment and follow-up with both medical and surgical specialists leads to the best patient outcomes.
Thank You
Allergic fungal sinusitis

Mark S. Schubert, MD, PhD\textsuperscript{a,b,*}

\textsuperscript{a}Allergy Asthma Clinic, Ltd., 300 West Clarendon, Suite 120 Phoenix, AZ 85013, USA
\textsuperscript{b}Department of Medicine, University of Arizona College of Medicine, Tucson and Phoenix, AZ, USA

Allergic Fungal Rhinosinusitis

Matthew W. Ryan, MD

Disclosures: The author is on the speaker’s bureau for Merck, Inc.
Department of Otolaryngology, The University of Texas Southwestern Medical Center, 5323
Harry Hines Boulevard, Dallas, TX 75390-9035, USA
E-mail address: Matthew.Ryan@utsouthwestern.edu

Otolaryngol Clin N Am 44 (2011) 697–710
doi:10.1016/j.otc.2011.03.015
0030-6665/11/$ – see front matter © 2011 Elsevier Inc. All rights reserved.