

TITLE: Rhinosinusitis: Current Concepts

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Rhinosinusitis affects 14% of the United States population (30 million people), at an estimated cost of \$2.4 billion per year (3). In fact, rhinosinusitis (RS) is the medical condition most commonly reported to the U.S. Census Department (36).

Successful management of rhinosinusitis via medical and/or surgical avenues is achieved in the majority of patients, or symptoms resolve spontaneously. Surgery is typically reserved for those patients with CRS or recurrent acute RS who have not responded adequately to medical therapy, or in those cases where experience dictates the condition will most likely not respond adequately to non-surgical therapy, alone (e.g., invasive fungal RS, allergic fungal RS (AFRS), a subset of cystic fibrosis patients, anatomic abnormalities such as septal deviation or paradoxical middle turbinates, etc.).

Reported success rates based upon symptomatic improvement from Functional Endoscopic Sinus Surgery (FESS) range from 85%-92% (7). The group receiving most of the attention in the medical literature over the last 10 years is the 8-15% of surgical patients who have responded to neither medical therapy nor sinus surgery.

The present discussion will focus on 4 topics that have gained particular attention in the literature over the past 7 years: topical intranasal medications, immunodeficiencies in patients with refractory CRS, cystic fibrosis, and AFRS. These topics relate directly to that subset of patients that does not respond adequately to current medical and surgical treatments for RS.

Topical Intranasal Medications

Topical treatment for sinusitis has been increasing in popularity in part due to marketing by commercial interests. These treatments may be especially efficacious in those patients who continue to suffer from sinusitis despite adequate sinus surgery to open sinonasal communication. Topical saline solutions have been commonly applied in patients with rhinitis and sinusitis for years, but investigators have begun evaluating their effects on nasal physiology at a quickening pace.

Bactroban nasal is currently the only topical antimicrobial FDA approved specifically for use in the nose. A recent review of the literature spanning 53 years by Goh and Goode found that authors have reported the use of streptomycin, nitrofurazone, gentamicin, rifampicin, tobramycin, alpha-2 interferon, and amphotericin B in the nose for various reasons (17). However, little is known about how intranasal medications interact with and affect the nasal mucosa. Published reports have established that Lactated Ringers has no effect on ciliary beat frequency *in vitro* (6). However, the safety and efficacy of various saline solutions for nasal irrigation has been brought into question, and only recently have studies been performed to examine the effects that saline has on mucociliary clearance. Symptomatic relief from the use of various saline preparations has been reported by a number of authors over a period of decades (38). Talbot, et al., prospectively compared the effects of 3% saline and 0.9% saline on mucociliary clearance in 21 healthy patients serving as their own controls. They found a statistically significant improvement of 17% in the saccharin clearance time using the 3% solution, while no significant improvement in clearance was noted in the 0.9% group (38). Hypertonic solutions are thought to pull interstitial fluid from the nasal mucosa and therefore exert a mucolytic effect, which may explain this finding.

In contrast, Boek, et al., studied the effects of 0.9%, 7%, and 14.4% NaCl solution on human ciliary beat frequency in healthy mucosa *in vitro*. That group found complete and irreversible ciliostasis when 14.4% solution was used, complete and partially reversible ciliostasis when 7% solution was used, and a 54% reversible decrease in ciliary beat frequency when 0.9% solution was used. While hypertonic solutions may have a place in cystic fibrosis (due to mucolytic effects), lactated ringers would be a better choice for routine mechanical irrigation of the paranasal sinuses since it does not affect ciliary function. Even normal saline appeared to deleteriously affect the delicate intranasal mucosa (6).

An acidic milieu is thought to cause the “gel” state (more viscous) of mucus to predominate, whereas an alkaline milieu is thought to cause the “sol” state to predominate. This is the rationale for adding baking soda to saline irrigation solutions. However, no data is available to support this (38).

With respect to intranasal antimicrobials, even petrolatum-based intranasal medications such as bactroban have been reported to result in myospherulosis, lipoid pneumonia, and bronchiectasis. However, bactroban applied to the nasal vestibule is generally thought to be safe and effective in sterilizing the nares in *Staphylococcus aureus* carriers (17).

Elsewhere, various intranasal medications have been used with “success”: gentamicin (3.5 mg/side QD) in atrophic rhinitis, rifampicin in rhinoscleroma, alpha-2 interferon in colds caused by rhinovirus, and tobramycin in chronic rhinosinusitis (40 mg/side TID). However, the effects of these medications on the sinonasal mucosa and their therapeutic benefits are unproven. Their use at this time should be considered as a last resort until more information is available (17).

Immunodeficiency in Patients with Refractory Rhinosinusitis

There are more than 50 known immunodeficiency disorders. Immunodeficiency should be suspected in patients with recurrent acute RS that cannot be attributed to another underlying cause (anatomic obstruction, underlying mucociliary defect), a persistent infection that does not respond to adequate antibiotic therapy, infections at other sites (especially pneumonia, sepsis, and meningitis), unusual sinus pathogens or severe infections, or a family history of immunodeficiency (15).

The type of infection should guide the immunologic workup. Antibody deficiencies are associated with recurrent or persistent bacterial infections. T-cell deficiencies are associated with fungal, viral, and protozoal infections. Complement deficiencies are associated with gram-negative infections. Chronic granulomatous disease and leukocyte adhesion deficiency (both resulting from dysfunctional phagocytosis) are associated with infections from catalase-positive bacteria (e.g., *Staph aureus*), gram-negatives, and some fungi (15).

The most common immunodeficiency associated with chronic recurrent sinusitis is an IgG subclass deficiency. There are 4 IgG subclasses. IgG1 responds to bacterial protein antigens, and constitutes 67% of total serum IgG (IgG normal range 800-1800 mg/dL). IgG1 is tested functionally by a reaction to Tetanus and Diphtheria vaccinations.

IgG2 responds to bacterial polysaccharide capsules. It makes up 20-25% of total serum IgG. IgG2 can be tested functionally with the *Haemophilus influenzae* and *Streptococcus pneumoniae* vaccines.

IgG3 accounts for the most common subclass deficiency in adults. IgG3 responds to viral illness, *Moraxella catarrhalis*, and the M-component of *Streptococcus pyogenes*. The clinical importance of an IgG4 deficiency has not been elucidated (15).

Several authors have proposed guidelines for an “immunologic workup” (7,12,36). The workup should *always* start with a CBC with differential and an HIV test. Ig and IgG subclass concentrations should also be measured. In addition, IgG function should be assessed by the response to Diphtheria and/or Tetanus toxoid (protein antigens) and Pneumococcal vaccine (polysaccharide antigen), because the level of immunoglobulin could be normal but hypofunctional. A CH-50 test can be used to screen for complement deficiency when suspected. T-cell function can be tested *in vitro* (more sensitive) or *in vivo* based on delayed-type hypersensitivity to intradermal PPD or Candida.

The University of Iowa recently published a report examining the findings in 79 patients referred to the allergy and immunology clinic for persistent RS despite sinus surgery, or 3 episodes of acute sinusitis in the past year and no evidence of HIV, AFRS, CF, or primary ciliary dyskinesia. Workup included SET-testing, CBC with differential, quantitative IgG, IgA, IgM, and IgE (no IgG subclass), and T-cell function in selected patients. 53.3% had abnormal T-cell function (the most common abnormality encountered). 51% of patients had at least 1 positive result on SET. 29.2% had low IgE, 17.9% had low total IgG, 16.7% had low IgA, and 5% had low IgM. 19% of the original 79 patients were started on IVIG following their workup. This study suggested a high incidence of immune dysfunction in this population, and that T-cell dysfunction may play a significant role in hard-to-treat RS (7).

In an oft-cited paper by Sethi, et al., the authors examined 20 patients with CRS refractory to medical and surgical treatment found to have immunologic abnormalities. Results of the immunologic evaluation, which included IgG subclasses, stratified the subjects into 4 groups:

1. IgA deficiency in 8 patients
2. Ig deficiency with vaccine hyporesponsiveness in 5 patients (Common Variable Immunodeficiency, or CVID)
3. IgG1 deficiency, low IgG, and normal vaccine response in 4 patients (hypogammaglobulinemia)
4. IgG1 deficiency, normal IgG, and normal vaccine response in 3 patients.

Of note in this group was the incidence of CVID (25%); the incidence of CVID in the University of Iowa study was 9.9%. 9/20 (45%) patients in Sethi's study were eligible for IVIG (7,36).

Success has been reported with the following treatment modalities (36):

1. IVIG – indicated for CVID, total IgG deficiency, and IgG subclass deficiency with a decreased response to vaccine (use of IVIG is controversial in patients with a subclass deficiency and a normal vaccine response); IVIG is NOT of benefit in IgA or complement deficiencies
2. Long-term antibiotic prophylaxis – Sethi reported good results with a regimen of Augmentin 500 mg QD
3. Genetic counseling/testing of other family members

Cystic Fibrosis

Abnormalities in the CFTR gene have recently been implicated in chronic or recurrent sinusitis in otherwise healthy individuals. Cystic fibrosis (CF) is the most common lethal autosomal recessive disease in Caucasians, with a prevalence of 1:2,000 live births in whites. The heterozygous carrier rate among Caucasians is 1:20-25. However, outside of the white population, cystic fibrosis is rare; incidence rates are 1:90,000 for Asians and 1:30,000 for African-Americans (31).

The hallmark of CF is thick, inspissated exocrine gland mucus 30-60 times more viscous than non-CF mucus that results in mucostasis and, in the sinonasal passages, obstruction. The mucociliary transport system is NOT directly affected, though cilia can be injured secondarily due to mechanical obstruction, inflammation, and infection (31).

The disease is caused by a mutation in the CF transmembrane conductance regulator (CFTR) gene on chromosome 7q31 coding for a chloride transport protein. In the most common mutation -- Delta-F508, which accounts for 70% of CF mutations – the CFTR protein fails to migrate to the cell membrane, remaining stuck in the cytoplasm. As a result, decreased chloride permeability leads to dessication of the extracellular fluid within the exocrine gland duct (15,31).

On a macroscopic level, this results in a multisystem disease characterized by chronic endobronchial infections, progressive obstructive pulmonary disease, pancreatic insufficiency (resulting in maldigestion), male infertility, and chronic rhinosinusitis with or without nasal

polyposis. Cultures from respiratory tract discharge taken during infections in CF most often grow out *Pseudomonas aeruginosa* followed by *Staphylococcus aureus*. Death usually occurs secondary to renal failure or cor pulmonale (31).

The incidence of polyps in CF is 6-48%. Unlike allergic polyps, CF polyps display a relatively normal basement membrane, few eosinophils, and acidic rather than neutral mucin (31).

On presentation, CF patients often report minimal or no nasal symptoms, even in the face of massive disease by exam or CT scan; <10% of patients with CF report troubling nasal symptoms. This is thought to be due to the congenital nature of the disease (their noses have *always* been congested). The most common signs and symptoms, in descending order, are cough, nasal airway obstruction, rhinorrhea, and recurrent acute RS. 12% of patients report anosmia, though objective testing has revealed anosmia in 71% of the CF population (31).

The sweat test is the gold standard for diagnosis of CF (sweat chloride >60 mmol/L). This involves iontophoresis of pilocarpine into the skin at 5 mV for 5-10 minutes. All sweat must be collected from the same site. A negative sweat test in a patient highly suspicious for CF should be followed by a repeat sweat test and/or genetic testing. Of note, adrenal insufficiency, anorexia nervosa, hypothyroidism, and hypogammaglobulinemia are all capable of causing false positive sweat tests. The diagnosis of CF requires 2 positive sweat tests, or 1 positive sweat test and the identification of 2 CF mutations (15, 40).

Common findings on physical exam, aside from polyps, include broadening of the nasal bridge (36%), mouth breathing (34%), and medial bulging of the lateral nasal wall (12%). This medial bulging is associated with a mucocele-like phenomenon within the maxillary sinuses that also tends to displace the uncinate process from its usual position (31).

When CT is used to evaluate sinus disease in CF, it is extremely rare not to encounter sinus disease. Characteristic findings include a higher incidence of frontal sinus agenesis, medial bulging of the lateral nasal wall (63-100%), and impressive maxilloethmoid sinus opacification. Several authors recommend a sinus CT in every patient, at the very least as a baseline examination. If the patient is symptomatic, or bulging is noted on physical exam, this should be done immediately. Asymptomatic patients, particularly children, can wait until they are able to tolerate a CT scan without sedation (or until symptoms develop) (31).

Analogous to the relationship between sinonasal disease and asthma, patients with severe pulmonary involvement frequently improve significantly following sinus surgery (31).

The initial treatment for CF is medical, and includes antibiotics, intranasal steroids, buffered hypertonic nasal saline irrigation, short courses of systemic and topical decongestants, and steroid bursts. During evaluation, these patients should also be assessed for allergy, since the incidence is comparable to the incidence in the general population. Surgery results in significant improvement for CF patients. Indications for surgery include persistent nasal obstruction despite medical treatment, a medialized lateral nasal wall on physical exam or CT, pulmonary exacerbations that seem to correlate with sinonasal symptoms *or* worsening

pulmonary status, facial pain or headaches affecting quality of life, and patient dissatisfaction with the results of medical management. Long-term, all CF patients should have regular “wellness” visits with an otolaryngologist (31).

The latest development with respect to CF is the role that CFTR mutations may play in the development of chronic rhinosinusitis in patients without a clinical diagnosis of CF. This could be a major development in the evaluation of RS given the high carrier rate of CFTR mutations in the Caucasian population. Wang, et al, performed a study comparing 147 white patients with CRS to 123 disease-free white patients with respect to the presence of CFTR mutations. They found 11 people in the CRS group (7.5%) with CFTR mutations, one of whom was ultimately diagnosed with CF by sweat test. Of note, 10 of these 11 patients were found to have double CFTR mutations. In the control group, 2 patients (1.63%) were found to have CFTR mutations (both single mutations). The odds ratio of CRS in CF carriers was 4.9 (though this did not achieve statistical significance). This study raises the possibility that certain *double* mutations in CFTR may result in significant epithelial dysfunction without producing outright CF (40).

A group from the University of Washington was the first to address the role that CFTR mutations play in rhinosinusitis in non-CF patients. They took sinonasal mucosa preserved from prior FESS cases and compared the distribution of CFTR proteins among non-CF children, CF children, and non-CF adults. With immunostaining, they determined whether CFTR was found primarily in the apical membrane, primarily in the cytoplasm, or mixed evenly. This was based on the fact that the delta-F508 mutation, and select other CFTR mutations, cause mistrafficking of the CFTR protein away from the apical membrane. They found that 73.7% of CFTR proteins were properly located in the apical membrane in non-CF adults requiring sinus surgery. In contrast 88.2% of CF children and 75% of non-CF children requiring sinus surgery had CFTR proteins located in either the cytoplasm or mixed between cytoplasm and membrane. This suggests that mutations causing mistrafficking of the CFTR protein may account, at least in part, for sinus disease severe enough to require surgery in children *without* a clinical diagnosis of CF (9).

Allergic Fungal Rhinosinusitis

Likely the hottest topic in rhinology, allergic fungal rhinosinusitis (AFRS) was first described by Safirstein in 1976; at that time, he referred to the entity as “allergic aspergillus sinusitis” and noted its similarity to allergic bronchopulmonary aspergillosis (ABPA). The pathophysiology of AFRS still is not clearly understood, and debate continues over just what AFRS is (26).

To begin, a brief overview of fungus is appropriate. Molds refer to fungi when present as hyphae (Confusingly, “mold” is also a term used generally by allergists to refer to fungal allergens). Yeasts refer to fungus when present as spores (spherical or ellipsoidal single cells measuring 3-15 micrometers in diameter). “Pseudohyphae” refer to budding spores that fail to detach, resulting in a chain of elongated yeast cells that mimics hyphae. Dimorphic fungi refer to fungi capable of growing as a yeast or a mold depending on environmental conditions. Cell wall polysaccharides and glycoproteins account for most fungal allergens. The dematiaceous

fungi are a group of yeasts and molds with melanin in the cell wall, resulting in brown or black pigmentation. The dematiaceous fungi – the fungi most often associated with AFRS – include *Bipolaris* (the most common AFRS-associated species), *Alternaria*, *Cladosporium*, *Curvularia*, *Drechslera*, and *Exserohilum*. *Aspergillus* and *Fusarium*, in contrast, are hyaline molds (capable of producing toxins). *Mucor* and *Rhizopus* are Zygomycetes. *Helminthosporium* refers to a group of fungi that has since been broken down into 3 species: *Bipolaris*, *Drechslera*, and *Exserohilum*. Though there is no commercially available antigen for *Bipolaris*, *Helminthosporium* is commercially available (20,24,28).

AFRS is believed to account for 5-10% of chronic rhinosinusitis cases. It typically presents in adolescents and young adults (mean age 21.9 years). Most cases occur in warm, humid climates – particularly the Mississippi basin and the Southern United States – resulting in a marked variation in prevalence by region. Ferguson questioned 45 different otolaryngologists across the country in 2000, and found Memphis (23%) and Dallas (15%) to be the top two spots with respect to AFRS among chronic rhinosinusitis patients undergoing FESS.

Findings associated with AFRS include allergic rhinitis (67%), elevated specific IgE to at least 1 fungal antigen (90%), and asthma (50%). The typical presentation involves gradual nasal airway obstruction with semi-solid nasal crusts. As the disease progresses, extensive nasal polyposis develops, along with the development of sinusitis (unilateral in approximately ½ of cases, and almost always one-side dominant). Pain is uncommon, and suggests concomitant bacterial sinusitis. The disease is typically recalcitrant despite medical and surgical therapy. Patients are generally unresponsive to antihistamines, intranasal steroids, and immunotherapy (before surgery). Systemic steroids often provide some relief, but relapse usually follows once the steroids are withdrawn.

As allergic mucin accumulates, the involved sinus begins to behave like a mucocele with bony remodeling and decalcification that can mimic invasion on CT scan. Proptosis, telecanthus, and intracranial extension without invasion can occur. Proptosis is particularly common in children with AFRS. The allergic mucin has a very characteristic appearance. It is thick, tenacious, and highly viscous. The color varies from light tan, to brown to dark green, and has been likened to peanut butter and/or axle grease. 75% of patients describe expelling darkly colored, rubbery nasal casts (20,26).

The characteristic mucin is the key to establishing the diagnosis of AFRS, and it is usually discovered at the time of surgery. Histologically, one sees branching, noninvasive fungal hyphae within sheets of eosinophils and Charcot-Leyden crystals. The Charcot-Leyden crystals consist of lysophospholipase. The hyphae are often sparsely scattered throughout the mucin; silver stains are helpful in visualizing the fungal elements, and the Fontana-Masson stain is particularly good at distinguishing Dematiaceous fungi. Meanwhile, fungal cultures are unreliable; a negative culture does not rule out AFRS, nor does a positive culture rule in AFRS. In fact, fungi are most likely present in most non-diseased noses. Of note, histologic examination of the sinonasal mucosa is not important for the diagnosis, but should be done to rule out invasion (20,26,33).

CT findings are very characteristic, with areas of high attenuation within expanded sinuses thought to represent proteinaceous allergic mucin, and hyperdense areas representing the accumulation of heavy metals and calcium salts within the allergic mucin. Bony erosion is very common (up to 98% of scans), but the dura and periorbita are NOT invaded. On MRI one sees central hypointensity on T1 and central signal void on T2 with increased peripheral T1 and T2 enhancement (20,25,26).

Beyond imaging, further workup includes total serum IgE and SET testing for both fungal and nonfungal antigens. Total IgE is typically >1,000 U/ml prior to treatment, and may be followed as an indicator of clinical activity during treatment (26).

Most authors cite some variation of the 5 Bent and Kuhn criteria (1994) for the diagnosis of AFRS:

- 1) Type-I Hypersensitivity confirmed by history, skin tests, or serology
- 2) Nasal polyposis
- 3) Characteristic computed tomography signs
- 4) Eosinophilic mucus without fungal invasion into sinus tissue
- 5) Positive fungal stain of sinus contents removed during surgery (and/or positive fungal culture) (5)

Treatment for AFRS has progressed significantly since the 1970's. Initially, it was treated much like invasive fungal sinusitis, with wide debridement of the involved sinuses. Much of this had to do with the frightening appearances AFRS can have on imaging. This approach resulted in high morbidity and was still plagued by frequent disease recurrence (26).

More recently, treatment attacks the disease on three fronts: immunotherapy for atopy, FESS (and antifungal medications) to remove the fungal antigenic burden, and corticosteroids (topical and systemic) to halt the inflammatory cascade. However, even with maximal medical and surgical therapy, disease recidivism is the norm, making long-term followup essential (26).

Surgery is the cornerstone of treatment. Polyposis tends to result in bleeding and distortion of sinonasal anatomy. However, the polyps and mucin also tend to expand the sinonasal passages, facilitating access to normally hard-to-reach areas. In addition, one can "follow polyps to the disease", since the mucin is typically trapped behind polyps. The goals of surgery are threefold: complete extirpation of all allergic mucin and fungal debris, permanent drainage and ventilation for the affected sinuses while maintaining intact mucosa, and post-operative access to the previously diseased areas. Postoperatively, encephaloceles are a concern because removal of large polyps in the setting of bony skull base erosion can result in prolapse of intracranial contents into the nose (25,26).

Most authors recommend systemic steroids before surgery, typically 40-60 mg prednisone per day for the week leading up to surgery (postoperative recommendations are more variable) (21,26). Post-operatively, patients should perform nasal irrigation with frequent (e.g., weekly) clinic visits for debridement.

Children with AFRS are treated differently from adults in that revision surgery is clearly preferred to prolonged systemic steroid usage (20).

Both systemic and topical steroids are important in preventing the recurrence of disease. INS should be part of the standard post-operative treatment. However, they tend not to be as effective preoperatively because of restricted nasal access. Systemic steroids have proven effective in decreasing recurrence rates of disease, but morbidity associated with long-term steroid use is high. Part of the aim of medical and surgical treatment in AFRS should be to minimize the dependence on systemic steroids (13).

Immunotherapy has been controversial in the treatment of AFRS; Ferguson reported in her experience that patients either worsened or did not improve when receiving immunotherapy preoperatively (13). However, Mabry published some promising results with immunotherapy when administered postoperatively, showing no recurrence after 4.5 years (24). The thought is that immunotherapy is not effective in AFRS until after the fungal (antigenic load) has been removed; preoperatively, immunotherapy can increase the level of IgG, which, in turn, could intensify a Type III hypersensitivity reaction. SET or RAST may be performed before or after surgery; the optimal timing for initiation of immunotherapy is thought to be 4-6 weeks postoperatively. Of interest, it is unclear how immunotherapy works in the case of AFRS, because the concentration of fungal-specific IgE has not been found to decrease in these patients, nor has the concentration of IgG or fungal-specific IgG (blocking antibodies) been found to increase. SET testing should involve a wide variety of fungal and non-fungal antigens. Of note, most AFRS patients tend to respond to multiple fungal antigens; an 18 kD protein has been found to exist common to multiple fungi, and there is some speculation that this may represent a fungal pan-antigen (20).

There is even less agreement regarding antifungal medications. Oral itraconazole has proven safe and may be somewhat effective (causing decreases in prednisone requirements and total serum IgE of approximately 80% when used for greater than 2 months). However, the cost of a 3 month course is approximately \$1500. There is currently no data regarding the use of topical antifungals and, again, the safety of intranasal topical antifungals is unknown (13).

In a 1996 review of 263 patients, Manning found that Dematiaceous fungi accounted for 87% of positive fungal cultures (*Bipolaris* being the most common); *Aspergillus* accounted for the remaining 13%. In 1997, Feger found Eosinophilic Cationic Protein present in much higher concentrations in AFRS mucin as compared to controls (suggesting an important role for eosinophils in the disease). In 1998, Manning and Holman examined a cohort of 8 patients with AFRS and found they all had *Bipolaris*-specific IgE and IgG, as well as a positive skin reaction to *Bipolaris* (26).

All of these findings supported what has become the working explanation of AFRS first proposed by Manning in 1989. AFRS, treated as a nasal correlate of ABPA (first described by Hinson in 1952), requires that an atopic host be exposed to fungi (the antigenic stimulus). Type I (IgE) and Type III (IgG immune complex) reactions occur, resulting in an intense eosinophilic inflammatory response. Inflammation, in turn, results in obstruction of the sinus ostia, which, in turn, results in stasis, which, in turn, results in further proliferation of fungus, which results in

increased antigen burden, which results in a vicious cycle with the accumulation of copious allergic mucin (13,20,26).

However, Ponikau, et al., forced everyone to take a second look at the proposed mechanism of disease in AFRS. This group used a highly efficient method of collecting mucin and culturing for fungus. They cultured 210 people with chronic rhinosinusitis(CRS), and compared them to 14 asymptomatic patients with no inflammatory changes of the nasal mucosa. 96% of the CRS patients grew out fungus (an average of 2.7 species per subject). 100% of the healthy control group grew out fungus (an average of 2.3 species per subject). Of the 101 patients from the CRS group who underwent surgery, 93% met their criteria for the diagnosis of AFRS: CRS, the presence of allergic mucin, and the presence of fungal organisms within the mucin. "Allergic mucin" was based upon a histology of eosinophil-dominated mucus (gross appearance was not considered). Thus, their conclusion was that 93% of patients with CRS really have AFRS (33). It is important to note that this group disregarded atopy as a diagnostic criteria for AFRS. In addition, the study suggests an important role for eosinophils in CRS in general, which has been confirmed elsewhere. Furthermore, the presence of fungus in the nose (without a host predisposed to a dysregulated immune response) likely has very little clinical significance; this is not surprising, since the average male inhales 57,000,000 spores per day.(20).

However, Ponikau is not alone in questioning the role of atopy in AFRS. At this point, most agree that the disease is not caused directly by fungus in an immunocompromised host, but by otherwise harmless fungus in an immunologically "hypercompetent" host. Problems exist with the theory pointing to Type I and Type III hypersensitivity reactions. First, why would AFRS so often present unilaterally if it is a question of fungal-specific IgE in the serum? Second, immunotherapy does improve symptoms in AFRS, but it does so without affecting the levels of fungal-specific IgE. Third, IgG immune complexes, which have been found in ABPA patients, have not been found in AFRS patients (20).

The T-helper cell (TH-2 CD-4 cells) is another piece of the puzzle in AFRS that only recently has been discussed in the literature. These T-helper cells are prominent in IgE-mediated disease, are believed to play a role in the inflammatory cascade in ABPA, and release a variety of cytokines (IL-4, IL-5, IL-10, IL-13) which act directly to increase the number and activity of eosinophils and IgE. TH-2 activity is kept in check by TH-1 function, and vice-versa (20). Possibly the most promising theory to explain AFRS has come from Schubert, who refers not to allergic fungal sinusitis, but to "hypertrophic sinus disease" (HSD), minimizing the role that fungus plays in AFRS (merely a variant of HSD). All HSD is characterized by a nasal mucosa packed with eosinophils and plasma cells. He postulates that HSD is a disorder involving TH-2 activation, similar to asthma. Allergic/atopic patients have a TH-2 predominance, while non-allergic patients have a TH-1 predominance. He also notes that *Staphylococcus aureus* is also commonly cultured from AFRS patients. Certain *S. aureus* strains produce enterotoxins that can act as one of several known superantigens (other common ones being EBV and Rabies virus). Superantigens activate an inflammatory cascade by simultaneously binding HLA-II molecules on Antigen Presenting Cells and T-cell receptors on T-cells, thus bypassing classical antigen specificity. Superantigens are 3,000 times more potent at T-cell activation than classic, specific antigens. He postulates that enterotoxin-producing strains of *S. aureus*, dematiaceous fungi, and

retroviruses may all act as superantigens which, in a host with TH-1/TH-2 dysregulation, can result in dramatic local or regional inflammatory responses resulting in HSD (35). The relationship between T-cell function and CRS is further bolstered by the recent report from the University of Iowa mentioned previously (7). As more work is done our understanding of the pathophysiology of CRS may change dramatically and radically alter our treatment of this troublesome problem.

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