Since the initial description of allergic fungal sinusitis (AFS) in 1981, approximately 7% of all chronic sinusitis cases requiring surgery have been attributed to AFS. Before its description in the 1980s, AFS presumably was diagnosed incorrectly as bacterial rhinosinusitis or another form of fungal sinusitis. Even when it is recognized, no uniformly accepted or effective treatment exists. Cases of AFS have been reported across the United States, Canada, and Europe, although AFS is more prevalent in the warm humid climates of the Southern United States. AFS patients have no unique symptoms, which set them apart from other chronic rhinosinusitis patients. Consequently, the disease process described only 18 years ago must be suspected to be diagnosed and, once diagnosed, the subsequent challenge is treatment.

The disease first was described by Millar et al in 1981 as allergic *Aspergillus* sinusitis. Their five patients demonstrated significant Type 1 hypersensitivity (IgE mediated) to *Aspergillus fumigatus*. Sinus pathologic findings were observed in these patients similar to the pulmonary findings in allergic bronchopulmonary aspergillosis (ABPA) patients. ABPA is a disease characterized by asthma, increased total serum IgE, pulmonary eosinophilia, specific allergic immune response, and thick tenacious mucus-producing bronchial obstruction and bronchiectasis.
Katzenstein reported nine allergic sinusitis cases caused by *Aspergillus* in a retrospective pathologic study of 119 surgical sinus cases. These patients also shared several pathologic features with ABPA. Several reports then appeared describing this disease associated with other fungi, notably the dematiaceous family of black moulds. Consequently, the disease has become known as allergic fungal sinusitis.

Little uniformity exists in defining inclusion criteria for patients in AFS studies. The Mayo Clinic reported that 51 out of 789 (6.5%) histologic sinus specimens were consistent with a diagnosis of AFS. Their inclusion criteria were an absence of microscopic tissue invasion and characteristic allergic mucin with fungal hyphae detectable by special stain or with a positive fungal culture. They also reported an AFS-like syndrome without microscopic or culture positive evidence of fungus.

Bent and Kuhn outlined the clinical and pathologic features in 15 consecutive AFS patients. They evaluated 11 findings, 5 of which were common to all 15 patients. These are now referred to as major criteria. They decided all 5 were necessary to define a patient study population. These criteria are: (1) evidence of type I (IgE mediated) hypersensitivity; (2) nasal polyposis; (3) characteristic CT findings; (4) eosinophilic mucus; and (5) positive fungal smear. Three of these criteria, evidence of IgE mediated hypersensitivity, eosinophilic mucus and positive fungal smear, are common to ABPA on which the original understanding of this disease was based. They have since included or “positive fungal culture” in positive fungal smear. The other 6 findings (minor criteria) were: (6) asthma; (7) unilateral predominance; (8) radiographic bone erosion; (9) fungal culture; (10) Charcot-Leyden crystals; and (11) serum eosinophilia. These additional findings support the diagnosis and are important in describing any individual AFS patient, but are not used in making the diagnosis. Because this article was published, a group of patients with some, but not all, of the major or minor criteria have responded dramatically to the AFS treatment protocol. These patients, at present termed atypical AFS patients, most likely have the disease, but do not meet all the major criteria. It may be that the diagnostic criteria need to be revised to account for inclusion of these patients. This study is currently underway. It is also possible that different criteria are present at different times in the same patient and in some patients the IgE level may only fluctuate within the normal range as the disease stage changes.

Although there are no unique pathognomonic symptoms, some findings that raise the index of suspicion include unilateral nasal polyposis, young age, characteristic serpiginous sinus opacity on CT, and thick sticky yellow/green nasal or sinus mucus. Additionally, AFS may be suspected when a nasal polyp patient having no other known disease responds only to oral steroids. For example, one asthma patient who presented with chronic polypoid sinusitis unresponsive to medical management demonstrated this. She underwent bilateral functional endoscopic sinus surgery and 4 months later developed frontal recess polyposis, which cleared completely with 6 weeks of oral prednisone. She subsequently underwent
revision surgery to remove frontal recess cells and again developed frontal recess polyposis postoperatively, which responded to systemic steroid therapy. It was not until 18 months after the original operation that allergic mucin obtained from her sinuses grew out fungus, which established the diagnosis.

The prognosis and optimum treatment of AFS are not yet clear. Waxman et al.\textsuperscript{34} reported three groups of patients, those with immediate recurrence within a matter of months after treatment, delayed recurrence after a year or more, and cured patients who were free of symptoms with follow-up to 2 years. None of the patients were followed for longer than 2 years. He reserved oral steroids for those patients who recurred following surgery. The rationale for using oral steroids derives from the treatment of ABPA and the similarities between the two diseases. Their classification of cure after 2 years may be premature because cure for AFS has not yet been observed when patients treated only with surgery are followed over prolonged time periods (see below).

Kupferberg et al.\textsuperscript{21} refined the endoscopic follow-up into a staging system, which allows closer control of the mucosal response to medical management, that is, oral steroids: Stage 0—no mucosal edema or allergic mucin; Stage 1—mucosal edema with or without allergic mucin; Stage II—polypoid edema with or without allergic mucin; and Stage III—sinus polyps with fungal debris or allergic mucin (Table 1, Fig. 1). The difference between allergic mucin and fungal debris is a matter of degree and semantics. Allergic mucin is somewhat more thin and mucinous, whereas fungal debris is an inspissated, thick, sometimes gritty, putty-like material. The wording in the staging system was purposeful, not inadvertent, and was designed to match the progression of the stages of recurrence. This was planned to follow a logical progression of observed events gathered over 3 years. Kupferberg et al.\textsuperscript{21} reported on 24 patients with a 12-month average follow-up and found that 8 of 9 patients treated only with surgery recurred at stage II or higher. They also found no correlation between symptoms and recurrence, that is, recurrence may be silent for months. One patient was reported disease-free at 22 months, but nasal endoscopy had never been used in his follow-up. This patient recurred after publication of their report. The longest times before recurrence were 29 months (one patient), and 34 months (one patient). All patients who recurred in this group required reoperation to remove nasal polyps and allergic mucin load.

\textbf{Table 1. ENDOSCOPE MUCOSAL STAGING SYSTEM IN ALLERGIC Fungal Sinusitis}

<table>
<thead>
<tr>
<th>Stage</th>
<th>Endoscopic Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No mucosal edema or allergic mucin</td>
</tr>
<tr>
<td>I</td>
<td>Mucosal edema with or without allergic mucin</td>
</tr>
<tr>
<td>II</td>
<td>Polypoid edema with or without allergic mucin</td>
</tr>
<tr>
<td>III</td>
<td>Sinus polyps with fungal debris or allergic mucin</td>
</tr>
</tbody>
</table>
Figure 1. Endoscopic view showing mucosal staging system in allergic fungal sinusitis (AFS). (See Color Plate 1, Figure 5.)

SYSTEMIC STEROIDS

Waxman et al\textsuperscript{44} suggested the use of systemic corticosteroids postoperatively, based on the treatment modalities used in ABPA. Ten out of 26 of Kupferberg et al's\textsuperscript{21} patients, after surgery, received prednisone therapy starting with a prednisone burst, followed by a taper to lower doses. These patients had less endoscopically confirmed disease on follow-up. If the oral steroid dose was reduced too early in the course of therapy, the mucosal stage increased, that is, the disease became worse. This suggested that the mucosal stage and length of treatment were dose dependent and tied to some unknown factor, which responded to systemic steroids. They concluded that the mucosal stage was a reflection of disease activity.

A 4-year follow-up study of 11 AFS patients by Kuhn and Javer demonstrated a reduction in mucosal stage and IgE level postoperatively while the patients were on systemic steroids.\textsuperscript{16} Initially in 1996 a prednisone treatment protocol was designed to keep the patient at endoscopic mucosal Stage 0 for 4 months before discontinuation of systemic steroids. This was ultimately extended to 6 months because of significant recurrence after only 4 months at Stage 0. Eight out of the 11 patients had a recurrence of disease with average time to recurrence being 10.6 months (range 2 to 27 months) after prednisone discontinuation. One patient died
free of disease at 36 months postsurgery (28 months after discontinuation of prednisone), 1 patient remained disease free at 56 months, and 1 remained disease free at 60 months after discontinuation of prednisone.

Systemic steroids are not without adverse effects, many of which are not appreciated until several years later. These include accelerated osteoporosis, cataracts, glaucoma, and avascular necrosis of the hip. Kupperberg and Bent cautioned that systemic corticosteroids should be weaned aggressively in children with AFS to minimize possible long-term growth retardation. Acutely, systemic corticosteroids frequently are associated with personality changes ranging from euphoria to psychosis and may complicate the treatment of diabetes and hypertension and lead to recrudescence of peptic ulcer disease in predisposed individuals.

Preoperative steroids also may confuse the diagnosis of allergic fungal sinusitis, causing resolution of the typical allergic mucin required for histopathologic diagnosis of the disease. Graham and Ballas describe a 39-year-old male with a history of nasal polyps and allergy with unilateral disease who was treated with a 5-day course of 60 mg of prednisone per day. At surgery, thick pasty material was removed from the sphenoid and histology revealed fungal hyphae; however, neither eosinophils nor allergic mucin were present. It was assumed the patient had a sphenoid fungus ball and no further treatment was planned. Two weeks later, however, the patient noted a rapid recurrence of symptoms. Endoscopic examination revealed polypoid recurrence and allergic mucin. This allergic mucin was examined histopathologically, and hyphae and characteristic allergic mucin consisting of eosinophils and Charcot-Leyden crystals were found. The diagnosis of AFS was made and the patient responded to subsequent steroid treatment.

ANTIFUNGALS

Topical and systemic antifungal therapy for AFS has been studied by Kuhn and colleagues with mixed to poor results. Twenty-two fungal cultures obtained from 15 AFS patients were studied for in vitro susceptibility to five common antifungal agents: ketoconazole, amphotericin B, itraconazole, nystatin, and fluconazole. They demonstrated that ketoconazole and amphotericin B were the most effective agents in vitro. Results from an in vivo placebo controlled study are pending. Few studies showing the effect of systemic antifungals for AFS have been published, mainly because preliminary experience with antifungals has proven disappointing. In general, even patients whose symptoms, endoscopy, and CT scans completely cleared after systemic antifungal therapy experienced a recurrence immediately after antifungal therapy was discontinued. This is exemplified by an 81-year-old diabetic female patient treated with itraconazole for 19 months until her residual sphenoid disease cleared on CT. Her medication was discontinued and the disease recurred within 2 months.
Mabry and colleagues have made a considerable effort investigating immunotherapy for AFS. Allergic individuals, including those with allergic rhinitis or AFS, are injected, usually subcutaneously, with small, graded doses of allergens against which they are reactive. The effectiveness of therapy and the level of increased IgG obtained are dose-dependent, so it is desirable to reach a high dose of antigen. Of 11 relevant fungal antigens used for testing and immunotherapy, all patients with AFS displayed sensitivity to multiple fungal antigens. They stated that immunotherapy produced a decreased amount of crusting and polyposis as well as a reduction in the need for systemic and topical corticosteroids in these patients. The initial Mabry et al study, however, did not have a control group for comparison. A more recent follow-up study with a control group showed that immunotherapy reduced reliance on systemic and nasal corticosteroid therapy to control disease when compared with patients not receiving immunotherapy after both groups had been treated with surgery followed by systemic steroid therapy. Mabry et al recently have presented data on eight patients who have discontinued immunotherapy after 3 or more years. They found no evidence of recurrence in an early 17-month follow-up study. As noted previously, a longer follow-up is necessary when dealing with AFS patients. A retrospective review by Ferguson of seven AFS patients who received immunotherapy without adequate surgical and medical management indicated that five patients did not improve or worsened with immunotherapy. Concerns have existed about the use of immunotherapy for AFS because allergen-specific IgG produced by immunotherapy theoretically could incite a Gell and Coombs Type III Arthus reaction with immune complex mediated tissue damage. This has not been borne out in clinical studies completed so far. Another concern about immunotherapy is the possible worsening of disease with the introduction of extraneous fungal antigens to patients with AFS. A third difficulty hindering the use of immunotherapy is that antigens of many common allergenic fungal species are not available commercially (e.g. Bipolaris and some species of Aspergillus and Penicillium). Laboratories capable of measuring fungal specific serum IgE levels for all fungi are not readily available.

Immunotherapy research may be a promising direction in which to develop a supplemental treatment option for surgery and steroid therapy of this difficult disease. A lack of availability of the specific fungal antigens would appear to be a major obstacle to progress from an immunotherapeutic point of view. Additionally, precise fungal identification may be necessary to accurately use this treatment method. Crossover from one fungal antigen to another, however, if proven, might solve the problem.

**TREATMENT PROTOCOL**

At the Georgia Nasal and Sinus Institute all patients that have been positively diagnosed for AFS with the criteria established by Bent and
Kuhn undergo functional endoscopic sinus surgery. This reduces the fungal and allergic mucin load (decreasing the eosinophilic inflammatory mediators) and creates adequate drainage, restoring physiologic mucociliary clearance pathways for the sinuses. Serum is drawn for total IgE levels and saved at -70°C for later fungal specific IgE and other studies, as they become available. The allergic mucin obtained at surgery is sent immediately to the microbiology laboratory for culture. Cultures then are forwarded for final identification to the Biology Department at Georgia State University. With the objective of keeping the mucous membrane at Stage 0, oral prednisone therapy is started within 48 hours of surgery. This early intervention takes advantage of the decreased edema caused by surgical removal of the fungal burden and allergic mucin.

The authors' recommendation is to begin oral prednisone in a dose of 0.4 mg/kg (~40 mg) per day for 4 days. The dose is then decreased by 0.1 mg/kg per day in cycles of 4 days until a dose of 20 mg/day, or 0.2 mg/kg/day, whichever is greater, is reached. This is continued until the 1-month postoperative visit, when it is adjusted to 0.2 mg/kg/day. This dose then is maintained and the patient is followed monthly with both nasal endoscopy and total serum IgE levels. The patient's weight and prednisone dose are recorded at each visit. The condition of the nasal and sinus mucous membrane is endoscopically staged according to Kupferberg et al. The prednisone dose then is adjusted based on maintenance of Stage 0. All pertinent information is recorded on an AFS patient encounter form (Fig. 2).

Each patient's total serum IgE level, prednisone dose and clinical stage are plotted monthly on a graph (Fig. 3). After maintaining normal mucosa (Stage 0) for 4 consecutive months while receiving a dose of 0.2 mg prednisone/kg/day, the prednisone is reduced to 0.1 mg/kg/day. Intranasal steroid powder spray is simultaneously started at triple the allergic rhinitis dose (one spray in each nostril 3 times daily, as opposed to once daily). If the patient stays at Stage 0 for 2 additional months, the prednisone is tapered to zero and the intranasal steroid spray is continued for at least 1 year. Endoscopy and serum IgE level determinations are continued monthly for 6 months and then bimonthly for 3 to 5 years. Patients need to be followed for up to 5 years after the prednisone therapy because the authors' longest time to recurrence after surgery and without postoperative oral prednisone treatment has been 34 months.

DISCUSSION

At the present state of knowledge, all patients appear to need surgical debridement with removal of fungi and obstructing polyps in an attempt to restore mucociliary clearance. Why AFS occurs or why it recurs following surgery or termination of medical treatment remains unknown, making this a fertile area for research. There is some preliminary data on one mechanism, to be discussed later, that may explain late recurrence.

At present the etiology of AFS is understood to be mucosal hypersensitivity directed against fungal antigens deposited on sinus mucosa.
Removing the allergen should reduce the allergic response and reduce edema. These may be incorrect assumptions, however, and the improvement simply may be a result of removing eosinophilic inflammatory mediators, which in turn reduces the inflammatory reaction and edema.

If the allergic response is being reduced, then the question arises as to why edema recurs so quickly following surgery (within 2 to 3 months) in the absence of any recolonization with fungus detectable by endoscopy, smears, and culture. Other questions that arise are: (1) What should the proper objective of treatment be? (2) Is the correct objective to maintain the mucosa in a normal state long enough for the mucociliary clearance to fully empty the sinus of reproducible fungal elements? (3) If the disease is extramucosal, how long does it take the cilia to sweep the remaining fungal elements out of the sinus? (4) Are areas of mucosal invasion going
undetected for lack of sufficient biopsies?; (5) Can undetected incidence of mucosal invasion explain why AFS recurs so frequently?; (6) Are patients perhaps reinfected or reinoculated from continuing environmental exposure? Another question about AFS is whether or not it represents a true allergic state or is it a local inflammatory response induced by the fungus attracting eosinophils to the sinus? Some investigators have started using the term eosinophilic fungal sinusitis to denote a local inflammatory response as the primary physiologic pathway in AFS.30 A recent article refutes the presence of allergy in AFS. These authors state that the only unrefuted diagnostic criteria for AFS are chronic sinusitis, the presence of allergic mucin, and fungal organisms; however, they do not define allergic mucin. They state that the reason AFS remains underdiagnosed is because fungus was missed in the diagnostic process. Interestingly, they cultured fungus in all 14 of their control non-AFS patients. The presence of fungus alone may not be important and may even be a weak criterion for the diagnosis of AFS. Accepting only two diagnostic criteria (presence of fungus and allergic mucin) in chronic sinusitis patients allows for a massive overdiagnosis of AFS.30

Does AFS have an autoimmune component directed against the sinus mucus membrane? This question is supported by the identification of 35- to 50-kd proteins most closely resembling human epithelial protein in the
allergic mucin from 10 of 11 patients with AFS. The allergic mucin also contained mucosal epithelial cellular debris. Because sera recognized proteins in this molecular weight range in a skin epithelial extract, the question arises as to whether a human antigen, an autoallergen, is in some way involved in the pathogenesis of AFS. This would explain why medical management of patients with AFS after surgery consistently requires chronic oral corticosteroid therapy. Chrzanowski et al also identified an 18-kd protein in the sera of AFS patients, which was present in allergic mucin and commercial fungal extracts. The identity of the 18-kd protein is unknown, but its low molecular weight and ubiquitous nature suggests that it might be a fungal panallergen. Further characterization of this protein is warranted as a potential marker for AFS.

Recently, Noble et al have focused on the patients’ environment. Possibly these AFS patients are being cured only to return to their original environment, where they are reinoculated. Metal surfaces, air filters, and insulation materials present in residential and commercial buildings can serve as foci of fungal growth and the dissemination of airborne conidia (spores) associated with the agents of AFS. Noble et al showed that 15 of the predominant fungi recovered from air samples of selected patients’ residences included the same species isolated from their mucin. Air samples from the residences in 8 out of 9 patients yielded exactly the same species recovered from the mucin of the corresponding patients’ sinuses. What immunologic differences occur between the patient and their families who inhabit the same environment? What factors determine which family members exposed to the same home environment develop AFS? Clearly, there is ample opportunity for studying the genetic control of immune responses in AFS patients’ families. Whatever the answers to these questions may be, patients need medical treatment in addition to surgery until more specific, targeted therapy, including immunotherapy, becomes available.

In the authors’ experience, if the mucous membrane appears to be improving, and the steroid dose is decreased too early in the treatment regimen, the disease worsens, as indicated by an increased mucosal stage and total serum IgE level at subsequent follow-up visits.

Serologic Markers

An important advance in the clinical follow-up of these patients would be to have a serologic marker of disease activity at the cellular and molecular level that may foreshadow flare-ups of disease. To this end the authors have attempted to follow several serum markers, notably eosinophil cationic protein (ECP), total serum IgE, and fungal-specific serum IgE levels. A correlation between clinical findings and serum ECP was not demonstrable and ECP levels have not proven to be a satisfactory marker for AFS. Serologic tests for antibodies are not available for all fungi implicated in AFS. Serum is collected and banked at −70°C to retrospectively evaluate these sera when fungal specific IgE tests become available.
Clearly, there is a need for molecular immunologists to develop more specific tests for fungal antibodies and for inflammatory mediators.

The only serum marker that currently is followed is total serum IgE. IgE levels fluctuate with mucosal stage and are tracked in all the authors' patients, demonstrating a correlation between total serum IgE levels and clinical disease stage. IgE levels decrease over time in response to oral steroid treatment, but do not always return to normal. This was demonstrated in the authors' 4-year follow-up study that demonstrated a drop in total IgE from 1070 to 569.4 while on the steroid treatment protocol. The mean total IgE at recurrence of disease was significantly elevated at 1258.6. Another question that arises then is whether the IgE level determined at the end of prednisone therapy has value for predicting recurrence in the future.

Fungal specific IgE determinations would potentially be more helpful. Unfortunately, it is not available for important allergenic fungal species in the genera Bipolaris, Aspergillus, and Penicillium. A study carried out at the Georgia Nasal and Sinus Institute on 10 patients who had fungal specific IgE levels followed over several years showed a moderate correlation between total IgE, clinical stage, and fungal specific IgE (see Fig. 3). The major weakness in using fungal specific IgE level as a marker is the inability to obtain fungal specific antigens for all fungi cultured, as well as the inability to definitively identify the causative fungus/fungi. An average of 3.5 fungi per patient were isolated from the authors' group of 10 patients with a range of 1 to 10 fungi per patient. There was no definitive way of separating contaminant from pathogenic fungi in this cohort.

At present the most helpful clinical tool is nasal endoscopy coupled with the mucosal staging system (see Fig. 1). If any anatomic site in the sinuses qualifies for a given clinical stage, the patient is staged as such even if other areas, such as the middle meatal antrostomy, middle turbinate, or ethmoid cavity are at Stage 0. It is important to realize that the most complete functional endoscopic surgery with good visualization of all sinuses is essential for adequate follow-up of these patients. Sinus obliteration is contraindicated for AFS patients because it is not possible to know that all fungal elements have been removed from the sinus. If they are not all removed, obliteration is not safe. Obliteration also makes it impossible to follow these patients radiographically for later recurrence of disease.

It is important to note that intercurrent bacterial infection quickly may change a normal Stage 0 sinus into a Stage II (polypoid mucosal edema) with purulent discharge or even allergic mucin. An endoscopically guided culture should be performed for bacteria and fungi and appropriate antibiotics prescribed on the basis of culture results. Fungi often are cultured in addition to bacteria. These fungi, however, disappear when the bacterial infection is treated appropriately. The patient should be re-examined, recultured, and restaged 2 weeks after final antibiotic selection. If the patient's stage returns to his or her prebacterial infection stage, this aberration in the clinical stage should be noted, but not considered in
determining length of medical treatment. Generally, the IgE level does not increase when intercurrent bacterial infection masquerades as recurrent AFS.

CONCLUSION

If AFS is truly not invasive and is an immunologic reaction to fungal allergens, complete fungal removal should lead to a cure. Complete surgical removal, however, is probably unattainable. Consequently, normal mucociliary clearance must be restored so that sinus mucosa can sweep out the remaining fungal elements. A major question, then, is how long must the sinus remain normal before discontinuing prednisone? Assuming that normal appearing mucosa functions normally while the patient is on prednisone, a 4-month period at Stage 0 was arbitrarily picked as a starting point for studying the effect of tapering prednisone therapy in AFS patients. The time interval ultimately was extended to 6 months because of significant recurrence after only 4 months at Stage 0.16,18

Because the etiology of the disease and the factors leading to its recurrence are unknown, one does not know whether patients become reinfected in their environment or if residual fungal elements release chemotactic agents that in turn reattract eosinophils to the sinus. These eosinophils then may release their inflammatory mediators (ECP, eosinophil peroxidase, eosinophil derived neurotoxin and major basic protein), which incite the production of edema, polyps, and allergic mucin. If it is principally inflammatory, why then does the fungus proliferate so rapidly and why does the IgE level go up?

In conclusion, AFS plays a prominent role in patients suffering from symptoms of chronic rhinosinusitis. It accounts for up to 7% of the diagnosis in all chronic sinusitis patients that are operated upon.7,8,17 This number may be higher in the southeastern United States. AFS is an intriguing disease, the nature of which is only beginning to be understood. Several diagnostic and therapeutic aspects need further investigation from several different fields of study. The future holds exciting possibilities for investigation and treatment; however, this disease may be chronic without a cure.

References


Address reprint requests to
Frederick A. Kuhn, MD, FACS
Georgia Nasal & Sinus Institute
Suite 112, 4750 Waters Avenue
PO Box 23357
Savannah, Georgia 31403-3357