Evaluation and treatment of allergic fungal sinusitis. II. Treatment and follow-up

Mark S. Schubert, MD, PhD,[a] and David W. Goetz, MD, PhD[b] *Phoenix, Ariz, and Lackland AFB, Tex*

Background: Previous allergic fungal sinusitis case reports have speculated that oral corticosteroids might reduce the severity of disease and possibly forestall the high rate of recurrent sinus surgery.
Objectives: Our objective was to comprehensively review 67 consecutive cases of allergic fungal sinusitis for their response to treatment and the utility of monitoring patient serologies during clinical follow-up.
Methods: Allergic fungal sinusitis cases from a private practice were evaluated and treated with consistent diagnostic criteria and treatment paradigms. An 8-year retrospective review of serologic parameters and clinical response to treatment with or without oral corticosteroids is described.
Results: The total serum IgE was found to correlate with the clinical rhinosinusitis severity ($P = .0002$). The fungal-specific IgG also correlated with clinical rhinosinusitis severity but less rigorously ($P = .004$). An increase of 10% or more in total serum IgE during follow-up was found to have significant predictive value for recurrent surgical intervention, with a sensitivity of 79%, specificity of 77%, positive predictive value of 48%, and negative predictive value of 93% ($P < .0001$). With the use of a modified corticosteroid treatment regimen adapted from allergic bronchopulmonary aspergillosis, as little as 2 months of oral corticosteroids after surgery provided significant clinical improvement for up to 12 months ($P < .0001$), although patients taking 12 months of treatment fared the best clinically ($P = .03$). By survival analysis, oral corticosteroids prolonged the time between subsequent sinus surgeries ($P = .01$) in this highly recurrent disease. No significant side effects of oral corticosteroids were observed during treatment with this dosing regimen.
Conclusions: Postoperative oral corticosteroids appear to be an effective treatment option for allergic fungal sinusitis, and monitoring of total serum IgE can be helpful in the clinical follow-up of these patients. (J Allergy Clin Immunol 1998;102:395-402.)

Key words: *Allergic mucin; antibodies, fungal; diagnosis; Deuteromycetes; fungi; fungus diseases; hypersensitivity, type I; IgE; prednisone; serodiagnosis; spores, fungal; rhinosinusitis; sinusitis; treatment outcome*

Abbreviations used
ABPA: Allergic bronchopulmonary aspergillosis
AFS: Allergic fungal sinusitis
CT: Computed tomography
OCS: Oral corticosteroids
sIgE: Fungal-specific IgE
sIgG: Fungal-specific IgG

Allergic fungal sinusitis (AFS) is characterized by chronic hypertrophic rhinosinusitis with fungal hyphae growing within inspissated allergic mucin obstructing the sinus cavities. As described elsewhere and in Part I of this 2-part series, the fungal process involved in allergic fungal sinusitis is non–tissue invasive, representing an allergic, not infectious, disorder.[1-6] Dematiaceous fungi are the most common offending organisms, with *Bipolaris spicifera* found most often.

The immunologic basis for AFS is thought to involve a fungal-specific immediate hypersensitivity (IgE) reaction as well as other antibody responses to the fungus. AFS serologies have been suggested to be partly analogous to allergic bronchopulmonary aspergillosis (ABPA) and include fungal-specific IgG (sIgG) and fungal-specific IgE (sIgE).[2,7-9] However, there have been no clinical studies of AFS examining the presence and utility of monitoring such patient serologies.

Treatment options for AFS in the past have not been tested on any large scale for effectiveness. Surgery alone may not be curative because postsurgical recurrence rates are high.[2,8,10,11] Systemic antifungal drugs have not been shown to positively impact the need for recurrent surgery either[12-16]; they have been believed to be contraindicated by some,[4] which is not surprising because the fungus is extramucosal and does not represent a fungal infection per se. Long-term treatment with sinus irrigations containing topical antifungal drugs have been proposed but not studied.[17] Both nasal[18,19] and oral[7,11,20-22] corticosteroids (OCS) have been used in a few case reports with reported benefit. However, there have been no systematic studies with defined OCS dosing parameters designed to examine the role of OCS treatment in any large number of patients with AFS, and the total number of OCS-treated cases published are very few. Recently, a nonblinded study of fungal-specific allergen immunotherapy

From [a]the Allergy Asthma Clinic, Phoenix; and [b]Department of Allergy-Immunology, Wilford Hall Medical Center, Lackland AFB.
Supported in part by the US Air Force.
The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Defense or other Departments of the US Government.
Received for publication Aug 4, 1997; accepted for publication May 14, 1998.
Reprint requests: Mark S. Schubert, MD, PhD, Allergy Asthma Clinic, 31 W Camelback Road, Phoenix, AZ 85013.
1/1/91756

TABLE I. Clinical assessments: Criteria for judging clinical rhinosinusitis severity

1. None
   (a) None to mild intermittent allergic rhinitis without purulent nasal discharge or perceived sinus involvement.
2. Mild rhinosinusitis
   (a) Mild to moderate allergic rhinitis.
   (b) Can have mild limited patchy sinus mucosal edema (as seen on rhinoscopy or CT scan) if this information is available.
   (c) Intermittent scant purulent nasal discharge.
   (d) Without large sinus mucosal edema, systemic sinus disease, anatomic nasal or sinus mucosal disease (such as polyps), or symptoms such as headache or any other systemic symptoms.
3. Moderate rhinosinusitis
   (a) Moderate to severe allergic rhinitis with perceived sinus involvement.
   (b) Mucosal edema in more than 1 sinus as seen on either rhinoscopy or CT scan if information available. No complete obstructing anatomic mucosal disease seen, but partial anatomic obstruction may be present.
   (c) Intermittent but significant purulent nasal discharge.
   (d) No evidence for fungal involvement or systemic symptoms other than headache, which may be intermittent but frequent and associated with purulent nasal discharge and congestion.
4. Severe rhinosinusitis
   (a) Severe allergic rhinitis, rhinosinusitis.
   (b) With chronic mucopurulent nasal discharge.
   (c) Often with nasal cast production.
   (d) With obstructing hypertrophic sinonasal disease in 1 or more sinuses on rhinoscopy or CT scan.
   (e) With or without hyperattenuating inspissated sinus material on CT scan.
   (f) Often constitutional symptoms such as headache, fatigue.

has been shown to have had a positive impact on clinical symptoms.[23]

To more fully explore the frequency and relevance of positive serologies in AFS, 67 consecutive cases of patients who satisfied all criteria for the diagnosis of AFS as described in Part I of this 2-part series were retrospectively reviewed for changes in postoperative serologic and clinical parameters as a function of the treatment option that had been chosen. Although the resulting review is not blinded or randomized, those patients who elected to take OCS after surgery were treated with a consistent treatment paradigm as described below. Clinical assessments were scored from the temporal history, physical examination, and any relevant ancillary clinical information (separate from patient serologies or other blood work) that had been obtained from patient follow-up visits. This report of the largest series of AFS cases published examines the impact of OCS treatment on clinical rhinosinusitis, surgical recurrence rates, and changes in serologic parameters.

METHODS

AFS treatment protocol

The patient population treated for AFS was described in Part I of this 2-part series. Once the diagnosis of AFS had been made, the potential risks and benefits of various treatment options were discussed with each patient or his or her parent in detail. All patients available for follow-up were placed on a combination of antiinflammatory nasal sprays, antihistamines with or without decongestants, and allergen immunotherapy to the relevant outdoor seasonal and indoor perennial aeroallergens to which they were found to be allergic by skin testing. *Bipolaris*, *Exserohilum*, and *Curvularia* dematiaceous fungi involved as the causative AFS agent were not available commercially for use as immunotherapy. After discussion of risks and benefits, some patients elected to start OCS in an attempt to both reduce symptoms and potentially reduce the need for recurrent surgery. Roughly half of all patients with AFS elected to start OCS. All of these patients underwent ophthalmologic screening examinations for cataracts and intraocular hypertension both before and at intervals no longer than 1 year during treatment with OCS.

The standard clinic approach for dosing OCS was as follows: OCS were started perioperatively at a dose of 0.5 mg prednisone/kg given once daily in the morning. This daily dose of prednisone was maintained for 14 days, then decreased to 0.5 mg/kg every other day and gradually tapered according to clinical assessment severity. In all cases, the prednisone dose was decreased to 5 to 7.5 mg every other day within 3 months, then maintained on 5 mg every other day for the duration of treatment. Only 1 case was treated with methylprednisolone, but the equivalent dosing to prednisone was used. Intercurrent respiratory infections were generally treated with a short "burst" of prednisone to 20 or 30 mg daily for 4 to 7 days, with a rapid taper back to 5 mg on alternate days within a week. Antibiotics and other supportive therapy were used as clinically judged to be indicated. No patients were treated with parenteral or prolonged (>2 weeks) oral antibiotics at any one time. The total duration of treatment with OCS was individually determined, and some patients stopped taking OCS for periods of time during follow-up but usually restarted within the context of a subsequent surgery. If the patient underwent a subsequent surgery for recurrent sinus disease, OCS were restarted according to the original protocol at 0.5 mg/kg daily and tapered as before.

AFS serologies and total serum IgE

At their initial evaluation and during follow-up, patients' periodic serologic measurements of total serum IgE, *B spicifera* precipitins, and *B spicifera* sIgG and sIgE were performed as outlined in Part I. Serum was drawn for serologies during the initial workup (time 0), which was in the immediate perioperative period, then at 2 months and 6 months after surgery. Once out beyond 6 months, serologies were obtained at yearly intervals. If another surgery for recurrent AFS occurred, serologies were then obtained at the time of surgery (time 0), 2 months, 6 months, and yearly thereafter again. This pattern was always repeated for subsequent surgeries.

Clinical assessments

Patients were seen for follow-up visits as clinically deemed appropriate, usually every 1 to 2 months, sometimes more often. Specific clinical assessments for analysis and postoperative serologies were those at 2 months, 6 months, 12 months, and yearly, at which times postoperative serologies were also drawn. Each clinical assessment used the temporally appropriate history, physical examination, and ancillary testing information (eg, recent repeat sinus computed tomography [CT] in some cases, and information from concurrent otolaryngologic evaluation if performed). If a subsequent sinus surgical recurrence intervened, then clinical assessments were reset to the time of surgery (time 0), 2 months, 6 months, and so on. Patients were graded as having no, mild, moderate, or severe clinical rhinosinusitis according to the scheme as shown in Table I. Clinical assessments were always made from the clinical information charted before obtaining the results of any of the serologies.

Statistical analysis

When comparing clinical serologies, rhinosinusitis severities, and treatment outcomes during patient episodes of rhinosinusitis, each episode was considered to be independent. This was strictly true for most episodes because most patients were evaluated during only 1 episode of rhinosinusitis. However, the simplifying and statistically conservative assumption of independence was also applied to those patients who contributed more than 1 clinical episode to the analysis (ie, relapsed and underwent another sinus surgery with subsequent evaluation and follow-up) to provide a comprehensive and clinically useful analysis of the data.

Statistical analyses were performed with the use of a nonparametric contingency table analysis, a factorial (nonrepeated measures) ANOVA, or a Kaplan-Meier survival analysis. When ANOVA showed significant differences, specific comparisons among means were made by using the Fisher's protected least significant difference test. The Tarone-Ware rank test of significance was used for comparison between groups in survival analyses. Two-tailed tests with significance level $\alpha = .05$ were used in all comparisons.

RESULTS

AFS is a highly recurrent disease. Surgeries are commonly repeated to remove both reaccumulated inspissated allergic mucin containing fungal hyphae as well as any recurrent hypertrophic sinus mucosa that is sinus obstructive. In this review of patients with AFS, the total serum IgE was analyzed retrospectively as a possible prognosticator of the need for recurrent surgery during clinical follow-up. Fig 1 shows the correlation of a change of 10% or more in total serum IgE with the requirement for recurrent sinus surgery ($P < .0001$). As a test for recurrent sinus disease, the sensitivity for this change in total IgE was 79%, the specificity was 77%, the positive predictive value was 48%, and the negative predictive value was 93%. Taken together, these findings showed that a change of 10% or more in IgE may have occurred at times other than when recurring sinus disease required surgery, but if AFS did recur, the concurrent IgE virtually always had increased by at least 10% over samplings before recurrence. Of the 34 recurrent surgeries for which data were available, the mean concurrent increase in total IgE was 118.5 ± 34.2 IU/mL (mean ± SEM).

In Fig 2, the clinical rhinosinusitis severities at all time points were compared with their respective measured

		Recurrent Sinus Surgery	
		YES	NO
Increase in IgE ≥ 10%	YES	27	29
	NO	7	97

FIG 1. Requirement for repeat sinus surgery during follow-up of AFS is significantly correlated with increase of 10% or more in total IgE. If increase of 10% or more in total serum IgE is used as a test for recurrent sinus disease that requires additional surgical intervention, test sensitivity is 79%, specificity is 77%, positive predictive value is 48%, and negative predictive value is 93% ($P < .0001$).

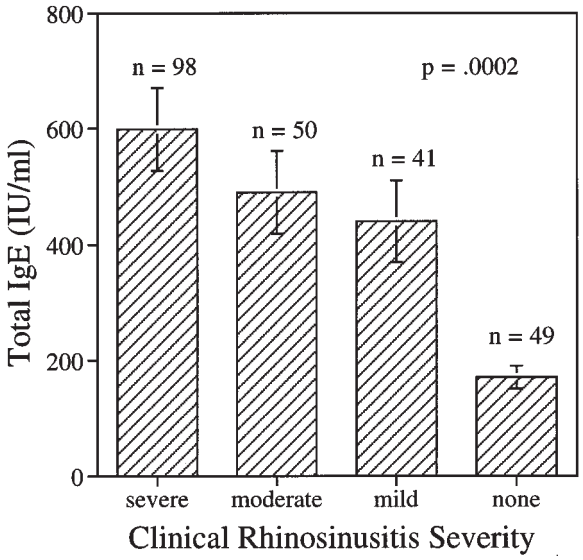

FIG 2. Severity of clinical rhinosinusitis at any time during clinical course of AFS is significantly associated with concurrent total serum IgE. Total serum IgE (IU/mL) is shown as mean ± SEM. Number of clinical data points *(n)* for each rhinosinusitis severity is shown. Individual comparisons were significant for none versus severe ($P < .0001$), moderate ($P = .004$), and mild rhinosinusitis ($P = .02$); overall $P = .0002$.

total serum IgE levels (these laboratory results were not available at the time of clinical assessment). There was a statistically significant relation between the clinical severity and IgE; increased severity was associated with higher IgE levels ($P < .02$ for clinical rhinosinusitis severity "none" compared with all other severity levels). Additionally, if the clinical severity improved, the mean total serum IgE dropped; if the clinical severity worsened, the total serum IgE rose (Fig 3, $P < .0001$). If there was no change in clinical severity, the total serum IgE generally did not change. Clinical rhinosinusitis severity in *B spicifera* AFS also directly correlated with the sIgG (Fig 4, $P = .004$) but did not correlate with sIgE (data not

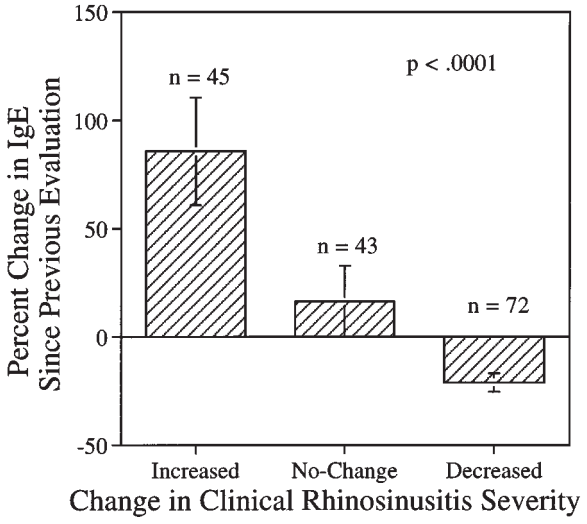

FIG 3. Change in clinical rhinosinusitis severity between evaluations is significantly associated with concurrent change in total serum IgE. Percent change in total serum IgE (mean ± SEM) and number of clinical data points *(n)* are shown for each change in clinical rhinosinusitis severity. Individual comparisons were significant for decrease versus increase in severity ($P < .0001$) and for no change versus increase in severity ($P = .003$); overall $P < .0001$.

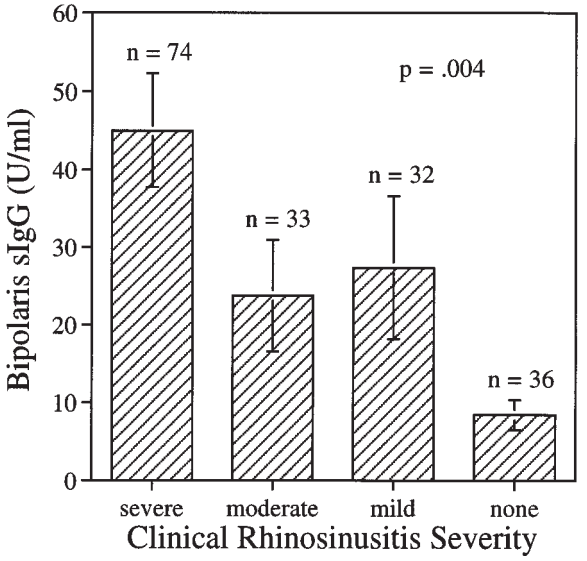

FIG 4. Severity of clinical rhinosinusitis at any time during the clinical course of AFS is significantly associated with the concurrent *B spicifera* specific–IgG. Specific IgG (U/mL) is shown as mean ± SEM. Number of clinical data points *(n)* for each rhinosinusitis severity is shown. Individual comparisons were significant for none versus severe ($P = .0004$) and moderate versus severe rhinosinusitis ($P = .04$); overall $P = .004$.

shown). Overall, these data showed that the values for total serum IgE (for all patients with AFS) and, to some extent, sIgG (for patients with *B spicifera* AFS) reflected the clinical rhinosinusitis disease activity.

When clinical rhinosinusitis severity for patients during a treatment period in which they received OCS was compared with not receiving OCS, a superior improvement in severity was seen with OCS therapy. As early as 2 months after surgery, patients demonstrated lower clinical rhinosinusitis severity when treated with OCS (Fig 5, $P < .0001$). Approximately 50% of all clinical assessments from patients on OCS at 2 months after surgery were rated as lacking any evidence for active rhinosinusitis ("none"), as compared with 22% of assessments from patients when not receiving OCS. Roughly 43% of 2-month assessments from patients receiving OCS were judged to be clinically mild, as compared with only approximately 15% of 2-month assessments from patients when not receiving OCS. Approximately 35% of 2-month assessments from patients not receiving OCS were judged clinically severe as compared with no clinically severe patients on OCS. Overall, 98% of patients improved from 0 to 2 months after surgery when receiving OCS compared with 59% of patients when not receiving OCS ($P < .0001$) (data not shown). Although treatment with OCS was not blinded, every attempt was made to exclude any conscious treatment bias and to make objective clinical assessments of all patients.

Some patients continued treatment with OCS for 12 months or more after surgery. Other patients started OCS but elected to discontinue them before 12 months; most took OCS for at least 2 months. When 12-month outcomes were assessed, there was a direct correlation between lower clinical rhinosinusitis severity and 12 months of treatment with OCS (Fig 6, $P = .03$). At the end of 12 months, approximately 62% of patients who received OCS for 12 months showed no evidence of clinical rhinosinusitis, whereas only 29% of patients when not receiving OCS for 12 months had a clinical rhinosinusitis score of "none"; alternatively, no patients receiving OCS for 12 months were judged to be clinically severe as compared with approximately 36% of patients when not receiving OCS. Of patients who took OCS for less than 12 months, the 18% of those with no evidence for clinical rhinosinusitis at 12 months of follow-up was intermediate between those with 12 months or no OCS therapy; none of these patients were clinically severe by 12 months. By 12 months of follow-up, 100% of patients who had taken OCS for the entire follow-up period were clinically improved as compared with 81% of those who took OCS for less than 12 months, and 64% of those who never took OCS ($P = .04$) (data not shown).

Rhinosinusitis treated with OCS after surgery for 2 months or longer ("with steroid treatment") was compared with no OCS treatment after surgery ("without steroid treatment") by survival analysis of the time to any further surgery for recurrent hypertrophic rhinosinusitis (Fig 7). The decision to operate again for recurrent hypertrophic disease was made independently by the patient and his or her otolaryngologist. Each patient had his or her own otolaryngologist, with a number of different independent otolaryngologists represented overall. All patients had AFS diagnosed through surgery at entry

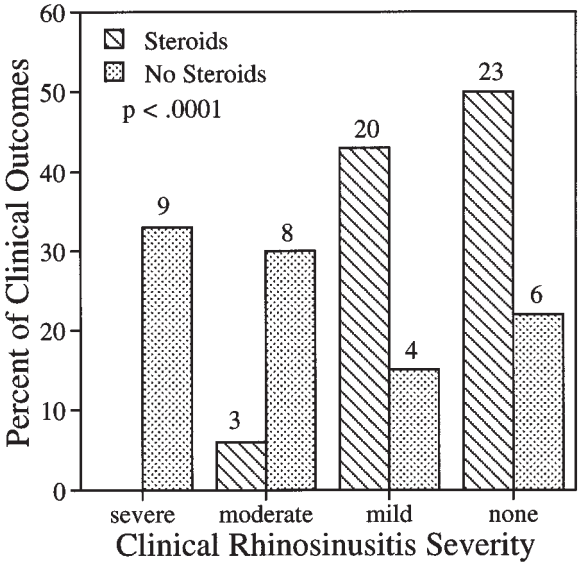

FIG 5. Rhinosinusitis severity 2 months after surgical intervention was significantly superior when patients were treated with OCS compared with not receiving OCS. Number of clinical data points is shown above each bar ($P < .0001$).

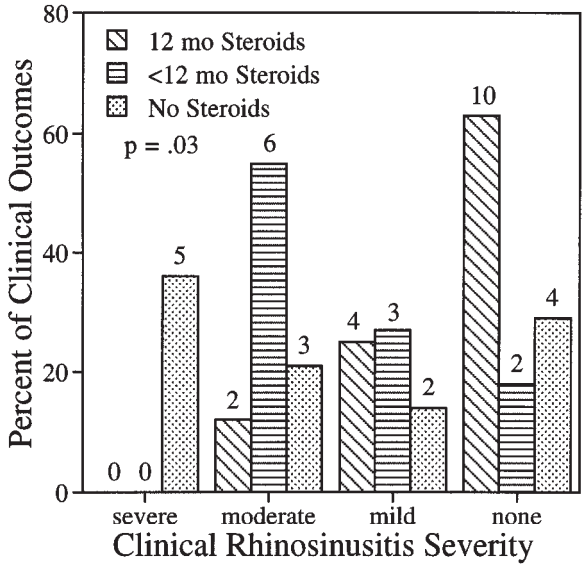

FIG 6. Rhinosinusitis severity 12 months after surgical intervention was significantly superior when patients were treated with OCS for 12 months compared with treatment with OCS for less than 12 months and with no OCS during the 12 months. Number of clinical data points is shown above each bar ($P = .03$).

("occurrence 1"), but recurrent rhinosinusitis requiring surgery may have revealed either AFS or only hypertrophic sinus disease. All such follow-up surgeries, whether found to be AFS or hypertrophic disease only, were considered additional surgical occurrences (occurrences 2, 3, and so on). After any recurrent surgery the patient was offered OCS, as they had been offered at entry. As shown in Fig 7, when receiving at least 2 months of OCS, patients underwent additional surgeries at significantly longer times to recurrence compared with not being treated with OCS ($P = .01$). A steep rise in the frequency of recurrent surgery appeared in approximately 2 months if patients were not treated with OCS. Although OCS increased the time to a recurrent surgery, the difference in survival without surgical recurrence between those treated with or without OCS had narrowed considerably by the end of 2 years, perhaps in part because of OCS discontinuations between 2 months and 2 years. Of the 23 recurrent surgeries in the OCS-treated patients, 16 (70%) were still receiving treatment at the time of recurrence, whereas 7 (30%) had discontinued therapy at some time between 2 months and the time of the recurrence. Another view of the propensity to discontinue OCS therapy once started can be seen in the 12-month follow-up data, in which 41% of those treated with OCS discontinued therapy before 12 months (Fig 6). Patients who dropped out of OCS treatment did so for personal reasons rather than OCS side effects, as significant OCS side effects were not observed in any treated patient.

Not all surgical recurrences for chronic rhinosinusitis met the pathologic requirements for description as AFS, possibly because of sampling error. In some

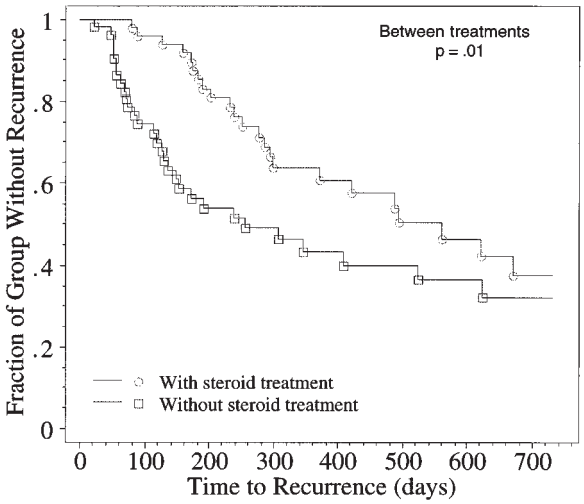

FIG 7. Survival analysis describing time to recurrence of rhinosinusitis surgical intervention in all patients with AFS entered into study. If patients received at least 2 months of OCS treatment, time to recurrence was significantly longer than if OCS were not given ($P = .01$).

cases with several surgeries, AFS criteria were met at multiple but nonsequential recurrences. Whether recurrent disease met the criteria of AFS or only hypertrophic sinus disease, patients were always offered OCS as part of their subsequent treatment. Comparing the 2 forms of recurrent disease over 1 year of follow-up, survival analysis showed no qualitative or statistical difference in the response to treatment regardless of

whether the surgical recurrence was AFS or only hypertrophic disease (data not shown).

DISCUSSION

This clinical series represents an open-label analysis of serologic and clinical data from the largest consecutive retrospective series of AFS cases published to date, in which patients were uniformly evaluated, treated, and followed. As reported in Part I of this 2-part series, the total serum IgE was generally elevated in patients with AFS at presentation. A drop in total serum IgE was usually seen after AFS surgical debulking (data not shown). Following the changes in total serum IgE at intervals after surgery was found to have significant predictive value in prognosticating the need for a subsequent sinus surgery for recurrent sinus disease (Fig 1). In this retrospective analysis, if patients had required recurrent sinus surgery, their total serum IgE was most likely to have increased by at least 10% from their most recent previous level. Therefore trending of the total serum IgE upward may be used prognostically, indicating possible recurrent AFS. A statistically more powerful conclusion can be drawn from the lack of at least 10% IgE trending between subsequent follow-up visits, as recurrent surgery was virtually never required under these circumstances.

In drawing conclusions from the changes in the IgE data, the potential was small for a treatment bias confounding the conclusion because (1) the IgE values were neither available nor of interest to the otolaryngologists at the time that surgical treatment decisions were made, and (2) no patient was operated on without compelling clinical reasons as determined by the patient's independent otolaryngologist and the patient and family. The otolaryngologists independently assessed the need for recurrent sinus surgery by using their own clinical evaluation, sinus CT scanning, and often flexible fiberoptic rhinoscopy. Similarly, the potential for bias in the assignment of a rhinosinusitis severity grade was minimal because the clinical information to which the grading (Table I) was applied had been charted before obtaining the results of any of the serologies. Although treatment was not blinded or randomized, every attempt was made to exclude bias in the clinical assessments of all patients.

The total serum IgE was additionally found to be helpful in evaluating the clinical status of patients with AFS after surgery. As shown in Figs 2 and 3, there was a direct correlation between the total serum IgE and the clinical rhinosinusitis severity. These data demonstrated that both the total serum IgE value and the upward or downward trending of the total serum IgE over time can be used as independent measures to help assess the overall clinical status and, to some extent, prognosis for AFS during postoperative follow-up visits.

Like total serum IgE, sIgG levels have been shown to be helpful in monitoring the analogous pulmonary disorder ABPA.[2,7-9] In the current clinical series, all clinical assessments of patients with *B spicifera* AFS were compared with their corresponding sIgG levels, as shown in Fig 4. There was a direct correlation between the sIgG level and the clinical rhinosinusitis severity. Worse rhinosinusitis was associated with greater values of sIgG but not as strongly as with total serum IgE (Fig 2). Taken together, all of the serologic data support the utility of monitoring total serum IgE and sIgG as aids in the clinical follow-up of patients with AFS over time, similar to their utility in ABPA, but the value of monitoring sIgG (when available for the specific mold) is more limited. As seen in ABPA,[24] total serum IgE acts as an "allergic acute phase reactant," making it useful during the assessment of changes in the immediate clinical status of patients with AFS.

Surgical resection of inspissated allergic mucin and obstructing hypertrophic mucosal disease has been the primary mode of treatment for AFS in the past. However, most previous reports have not adequately distinguished between AFS and other forms of fungal sinusitis, making potential treatment comparisons difficult. Some individual case reports have treated AFS with systemic antifungal drugs,[12-16] others with topical nasal steroids[18-19] or OCS.[7,11,20-22] The generally high recurrence rates for AFS after surgery, lack of data supporting a positive benefit with systemic antifungals, and the encouraging response to treatment with OCS in individual case reports have made the use of OCS the most viable option for treatment, although significant experience with OCS has been lacking.

Lending support for the use of OCS in treating AFS is the acceptance of OCS treatment for ABPA, the analogous pulmonary disorder. OCS and not antifungal drugs[25] are the mainstay of ABPA treatment. Sinus surgery with removal of inspissated allergic mucin and reventilation of obstructed sinuses in AFS could be considered the surgical equivalent of bronchoscopic suctioning to relieve obstructive atelectasis in ABPA. In our patients, OCS were offered after surgery to control clinical rhinosinusitis severity and to potentially affect the surgical recurrence rate. All patients with AFS in our retrospective case review were offered OCS if they did not have a medical contraindication for its use, for example, untreated positive purified protein derivative (1 patient), type I diabetes mellitus (1 patient), or mixed fungal sinusitis (2 patients). The dosing of OCS followed a modified ABPA protocol. Roughly half of all patients with AFS elected to take postoperative OCS for periods of time up to several years after surgery, with the majority of dosing at 5 mg of prednisone on alternate days. OCS were terminated on an individual basis when the patient was believed to be clinically quiescent for an extended period of time without evidence of rhinosinusitis activity or if the patient wanted to stop OCS by his or her own decision. Several patients were followed over multiple years in which their surgical recurrences were treated sometimes with and sometimes without OCS, allowing them to contribute both treated and nontreated data to the comparisons. No significant OCS-related side effects were seen, and ophthalmologic follow-up never reported OCS-induced lenticular cataracts or intraocular hypertension. There was no difference between the OCS-

treated and nontreated patients in the numbers who elected to start conventional treatment with antihistamines as required, antiinflammatory nasal sprays (either cromolyn or topical steroids), and relevant aeroallergen immunotherapy. The AFS organism was not used for allergen immunotherapy.

Several lines of evidence support the conclusion that postoperative OCS given according to the ABPA-like protocol were of significant benefit in the treatment of AFS. First, when clinical rhinosinusitis severity was compared for treatment with or without OCS (Figs 5 and 6), we found that at least 2 months of postoperative OCS was required to give significant clinical improvement over 12 months of follow-up, suggesting the immediate postoperative period is the most critical time to use OCS. Patients taking OCS over 12 months fared the best clinically, with the least severe clinical outcome overall. Second, the time to recurrent sinus surgery was significantly increased when postoperative OCS were taken (Fig 7). Despite the fact that many patients discontinued OCS during their follow-up, postoperative OCS treatment both attenuated and forestalled by several months the abrupt rise in recurrent surgical disease seen in untreated patients at about 2 months.

The mechanism of action of OCS in this disorder presumably relates to its ability to suppress most of the immunobiology of the AFS hypersensitivity response and to interfere with the inflammatory components of the "sinusitis cycle,"[26] thus slowing the progression of AFS-driven hypertrophic sinonasal disease. We speculate that once the AFS is cleared surgically, the primary role of OCS is to slow the development of recurrent allergic hypertrophic rhinosinusitis predisposing to AFS relapse. No patient was believed to worsen clinically as the result of treatment with OCS, and no OCS-treated patient developed fungal invasive disease from treatment with this dosing protocol.

One possible explanation for the generally high incidence of AFS recurrence in our patients with AFS might relate to the relatively smaller degree of sinus mucosal resection more common to functional endoscopic sinus surgery compared with older, more mucosal tissue–destructive techniques such as the Caldwell-Luc procedure. Functional endoscopic sinus surgery has become the most prevalent surgical approach to chronic sinus disease because it preserves the natural placement of the osteomeatal complex high in the maxillary sinus. It has been believed that reestablishing sinus ventilation pathways through this more physiologic osteoplasty will lead to proper drainage, with resolution of chronic infection without extensive mucosal resection.[27] One published report of a series of patients with fungal sinusitis treated with endoscopic sinus surgery described a high success rate,[28] but no distinction between the 4 categories of fungal sinusitis was made making it unclear whether any of the patients actually had AFS. In fact, despite the successes of modern tissue-sparing functional endoscopic sinus surgery in the treatment of many forms of sinusitis, it might actually potentiate the high recurrence rate of AFS when residual mucosal disease is left.

More tissue-destructive surgeries are used less frequently now, but in the past sinus mucosal stripping provided extensive removal of diseased hypertrophic sinus mucosa. One potential disadvantage of relatively mucosa-sparing sinus surgery in the AFS patient is that significant amounts of residual nonobstructing hypertrophic sinus mucosa may in some way predispose the patient to rapid AFS recurrence. Although sinuses are usually debulked of all gross inspissated allergic mucin at the time of AFS surgery, occult microscopic allergic mucin containing fungal hyphae could potentially be contiguous with the residual hypertrophic mucosa, leading to continuation and perpetuation of the AFS allergic response with gradual return of surgical AFS. If this is true, then the more complete the removal of all hypertrophic sinus mucosa at the time of surgery, the greater the chance that OCS could eliminate the potential for AFS recurrence. Having followed these patients through many surgeries with different otolaryngologist and surgical techniques, we believe that in general, this concept may be true. We speculate that another reason for the generally high AFS recurrence rate in the southwestern United States is that the intermittently high *Bipolaris* spp mold spore counts seen in Phoenix (see Part I) lead to significant reintroduction of this nasophilic mold to the respiratory tract, creating a high risk for recurrent AFS. Further analysis of both of these issues will have to await coordinated trials of different surgical approaches to AFS with and without OCS in different parts of the country where different AFS mold ecologies exist.

In conclusion, our retrospective clinical series suggests that recurrent surgical sinusitis is part of the natural history of AFS disease. This natural history could be positively affected when OCS were taken for at least 2 months after surgery. Maximum clinical benefit was seen with 12 months of OCS treatment. An increased time to surgical recurrence was also seen with the use of OCS after surgery. Additionally, the total serum IgE was found to follow the patient's clinical status and to be prognostic for recurrent AFS, acting as an acute phase reactant similar to its role in ABPA but with overall lower values. Fungal-specific IgG was a less useful diagnostic test. Controlled studies with OCS under defined surgical conditions will now be needed to more fully explore the optimum medical/surgical treatment modality for this challenging new allergic disorder.

We wish to acknowledge the assistance and laboratory skills of Bonnie Whisman, MS, and Mary Fust, LPN. We additionally thank all of the Arizona Otolaryngologists and Allergists who referred patients with AFS for treatment and follow-up. Finally, we thank all of our patients with AFS for their sustaining hope and confidence.

REFERENCES

1. Katzenstein AA, Sale SR, Greenberger PA. Allergic Aspergillus sinusitis: a newly recognized form of sinusitis. J Allergy Clin Immunol 1983;72:89-93.
2. Gourley DS, Whisman BA, Jorgensen NL, Martin ME, Reid MJ. Aller-

gic Bipolaris sinusitis: clinical and immunopathologic characteristics. J Allergy Clin Immunol 1990;85:582-91.
3. Manning SC, Mabry RL, Schaefer SD, Close LG. Evidence of IgE-mediated hypersensitivity in allergic fungal sinusitis. Laryngoscope 1993;103:717-21.
4. Bent JP III, Kuhn FA. Diagnosis of allergic fungal sinusitis. Otolaryngol Head Neck Surg 1994;111:580-8.
5. Mabry RL, Manning S. Radioallergosorbent microscreen and total immunoglobulin E in allergic fungal sinusitis. Otolaryngol Head Neck Surg 1995;113:721-3.
6. deShazo RD, Swain RE. Diagnostic criteria for allergic fungal sinusitis. J Allergy Clin Immunol 1995;96:24-35.
7. Goldstein MF, Atkins PC, Cogen FC, Kornstein MJ, Levine RS, Zweiman B. Allergic Aspergillus sinusitis. J Allergy Clin Immunol 1985;76:515-24.
8. Waxman JE, Spector JG, Sale SR, Katzenstein AA. Allergic Aspergillus sinusitis: concepts in diagnosis and treatment of a new clinical entity. Laryngoscope 1987;97:261-6.
9. Wickern GM. Pediatric allergic fungai sinusitis: another "great masquerader." Pediatr Asthma Allergy Immunol 1993;7:147-56.
10. Torres C, Ro JY, El-Naggar AK, Sim SJ, Weber RS, Ayala AG. Allergic fungal sinusitis: a clinicopathologic study of 16 cases. Hum Pathol 1996;27:793-9.
11. Kinsella JB, Bradfield JJ, Gourley WK, Calhoun KH, Rassekh CH. Allergic fungal sinusitis. Clin Otolaryngol 1996;21:389-92.
12. Frenkel L, Kuhls TL, Nitta K, Clancy M, Howard DH, Ward P, et al. Recurrent Bipolaris sinusitis following surgical and antifungal therapy. Pediatr Infect Dis J 1987;6:1130-2.
13. Washburn RG, Kennedy DW, Begley MG, Henderson DK, Bennett JE. Chronic fungal sinusitis in apparently normal hosts. Medicine 1988;67:231-47.
14. Corey JP, Delsuphene KG, Ferguson BJ. Allergic fungal sinusitis: allergic, infectious, or both? Otolaryngol Head Neck Surg 1995;113:110-9.
15. Bent JP III, Kuhn FA. Allergic fungal sinusitis/polyposis. Allergy Asthma Proc 1996;17:259-68.
16. Morpeth JF, Rupp NT, Dolen WK, Bent JP, Kuhn FA. Fungal sinusitis: an update. Ann Allergy Asthma Immunol 1996;76:128-40.
17. Bent JP III, Kuhn FA. Antifungal activity against allergic fungal sinusitis organisms. Laryngoscope 1996;106:1331-4.
18. Jonathan D, Lund V, Milroy C. Allergic aspergillus sinusitis: an overlooked diagnosis? J Laryngol Otol 1989;103:1181-3.
19. Manning SC, Vuitch F, Weinberg AG, Brown OE. Allergic aspergillosis: a newly recognized form of sinusitis in the pediatric population. Laryngoscope 1989;99:681-5.
20. Cleveland CH, Fisher RH. Allergic Curvularia sinusitis. Pediatr Asthma Allergy Immunol 1992;6:189-95.
21. Roth M. Should oral steroids be the primary treatment for allergic fungal sinusitis? Ear Nose Throat J 1994;73:928-30.
22. Kupferberg SB, Bent JP. Allergic fungal sinusitis in the pediatric population. Arch Otolaryngol Head Neck Surg 1996;122:1381-4.
23. Mabry RL, Manning SC, Mabry CS. Immunotherapy in the treatment of allergic fungal sinusitis. Otolaryngol Head Neck Surg 1997;116:31-5.
24. Patterson H, Rosenberg M, Roberts M. Evidence that Aspergillus fumigatus growing in the airway of man can be a potent stimulus of specific and nonspecific IgE formation. Am J Med 1977;63:257-61.
25. Greenberger PA. Allergic bronchopulmonary aspergillosis. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yuninger JW, Busse WW, editors. Allergy, principles and practice. 4th ed. St Louis, Mo: Mosby-Year Book; 1993.
26. Reilly JS. The sinusitis cycle. Otolaryngol Head Neck Surg 1990;103(suppl):856-61.
27. Kennedy DW, Zinreich SJ, Rosenbaum AE, Johns ME. Functional endoscopic sinus surgery: theory and diagnostic evaluation. Arch Otolaryngol 1985;111:576-82.
28. Stammberger H. Endoscopic surgery for mycotic and chronic recurring sinusitis. Ann Otol Rhinol Laryngol 1985;94(suppl 119):1-10.