

## The Diagnosis and Incidence of Allergic Fungal Sinusitis

JENS U. PONIKAU, MD; DAVID A. SHERRIS, MD; EUGENE B. KERN, MD; HENRY A. HOMBURGER, MD; EVANGELOS FRIGAS, MD; THOMAS A. GAFFEY, MD; AND GLENN D. ROBERTS, PhD

• **Objective:** To reevaluate the current criteria for diagnosing allergic fungal sinusitis (AFS) and determine the incidence of AFS in patients with chronic rhinosinusitis (CRS).

• **Methods:** This prospective study evaluated the incidence of AFS in 210 consecutive patients with CRS with or without polyposis, of whom 101 were treated surgically. Collecting and culturing fungi from nasal mucus require special handling, and novel methods are described. Surgical specimen handling emphasizes histologic examination to visualize fungi and eosinophils in the mucin. The value of allergy testing in the diagnosis of AFS is examined.

• **Results:** Fungal cultures of nasal secretions were positive in 202 (96%) of 210 consecutive CRS patients. Allergic mucin was found in 97 (96%) of 101 consecutive surgical cases of CRS. Allergic fungal sinusitis was diagnosed in 94

(93%) of 101 consecutive surgical cases with CRS, based on histopathologic findings and culture results. Immunoglobulin E-mediated hypersensitivity to fungal allergens was not evident in the majority of AFS patients.

• **Conclusion:** The data presented indicate that the diagnostic criteria for AFS are present in the majority of patients with CRS with or without polyposis. Since the presence of eosinophils in the allergic mucin, and not a type I hypersensitivity, is likely the common denominator in the pathophysiology of AFS, we propose a change in terminology from AFS to eosinophilic fungal rhinosinusitis.

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AFS = allergic fungal sinusitis; CRS = chronic rhinosinusitis; CT = computed tomographic; IgE = immunoglobulin E; RAST = radioallergosorbent test

In 1983, Katzenstein et al<sup>1</sup> described allergic *Aspergillus* sinusitis as a newly recognized form of sinusitis. The diagnosis was made based on the histologic triad of (1) clumps or sheets of necrotic eosinophils; (2) Charcot-Leyden crystals (from degraded eosinophils); and (3) noninvasive fungal hyphae with morphology consistent with *Aspergillus* species within the nasal mucus. In 1989, Robson et al<sup>2</sup> introduced the term *allergic fungal sinusitis* (AFS) because they identified a number of fungi thought to cause the same disorder. In 1990, Ence et al<sup>3</sup> identified 5 different organisms responsible for AFS. Cody et al<sup>4</sup> reported that *Aspergillus* species were responsible for only about 15% of cases of AFS in a large retrospective study. The incidence of AFS in cases of chronic rhinosinusitis (CRS) treated surgically has been approximately 6% to

7%.<sup>1,4</sup> Nasal polyps were found in 75% and asthma was found in 65% of the AFS cases described.<sup>5</sup>

Based on the clinical findings in 16 patients, Bent and Kuhn<sup>6</sup> proposed 5 criteria for the diagnosis of AFS: (1) nasal polyposis; (2) allergic mucin; (3) computed tomographic (CT) scan findings consistent with CRS; (4) positive fungal histology or culture; and (5) type I hypersensitivity (atopy) diagnosed by history, positive skin test, or serology. Recently, deShazo and Swain<sup>7</sup> described 7 patients with AFS in whom they applied similar diagnostic criteria, with the exception of atopy. The reason they excluded atopy as a diagnostic criterion for AFS was their review of the literature in which they found that only two thirds of patients tested had a positive skin test result to the fungi cultured. In addition, 1 of their 7 patients with the histologic diagnosis of AFS had no evidence of atopy. Cody et al<sup>4</sup> also stated that the sensitivity and specificity of total and specific immunoglobulin E (IgE) and immunoglobulin G in AFS are unknown, and the usefulness of those tests in determining prognosis or efficiency of treatment is unknown. Both type I and type III hypersensitivity reactions (Gell and Coombs classification) have been postulated to play an instrumental role in the development of AFS. This hypothesis arose from the correlation of AFS with the pulmonary disorder termed *allergic bronchopulmonary aspergillosis*. Some of the reported cases of AFS demonstrated an elevated level of IgE antibodies specific for fungi. No other evidence, beyond speculation, exists

From the Department of Otorhinolaryngology (J.U.P., D.A.S., E.B.K.), Department of Laboratory Medicine and Pathology (H.A.H., T.A.G., G.D.R.), and Division of Allergy and Outpatient Infectious Disease and Internal Medicine (E.F.), Mayo Clinic Rochester, Rochester, Minn.

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Address reprint requests and correspondence to Jens U. Ponikau, MD, Department of Otorhinolaryngology, Mayo Clinic Rochester, 200 First St SW, Rochester, MN 55905.

that IgE-mediated type I hypersensitivity is involved in the pathophysiology of AFS. Thus, the unrefuted diagnostic criteria for AFS are (1) CRS; (2) the presence of allergic mucin (clusters of eosinophils and their by-products, eg, Charcot-Leyden crystals and major basic protein); and (3) the presence of fungal organisms within that mucin, confirmed by histology, culture, or both.<sup>4,7,8</sup>

There remains a group of patients with "AFS-like" disease described by previous authors; these cases do not fit the criteria for AFS in that fungi are not found on culture or histology despite the presence of allergic mucin.<sup>4,8,9</sup> We pose the question: Were those cases caused by fungus that was simply missed in the diagnostic process, or is an AFS-like syndrome a different clinical condition?

Most authors agree that AFS is an underdiagnosed entity and that only an increased awareness among physicians to look for fungal involvement will increase the accuracy of diagnosing AFS. Unfortunately, previous diagnostic methods seem to lack sensitivity. For example, in the past, even when fungal hyphae were clearly identified in histologic specimens, only 60% of the cultures were positive for fungi.<sup>4,5</sup> Some investigators approached this problem with other diagnostic methods directed at identifying the fungi, such as *in situ* hybridization.<sup>10</sup> Although *in situ* hybridization appears to be an intriguing and precise method to determine the species of organisms seen histologically, it seems to be impractical for screening. Each DNA probe is specific only for the complementary recombinant RNA of the preselected species. A complete catalog of DNA probes does not exist, and the method is both cumbersome and expensive.

Radiologically, patients with AFS frequently have areas of high attenuation within soft tissue masses of the affected sinuses on noncontrast CT scan.<sup>11-13</sup> These areas are void on T<sub>2</sub>-weighted magnetic resonance imaging. The hypodense areas on CT scan seem to correspond well with the surgically proven areas of allergic mucin. Yet, as we know from head and neck studies, CT scans are insensitive to subtle structural differences smaller than 1 cm (eg, lymph nodes). Thus, the CT sinus examination may not be sensitive or specific enough to identify small areas of allergic mucin.

In studying CRS and AFS, we set out to improve the sensitivity of standard tests used to diagnose AFS, namely, mucus sample collection, nasal secretion culture, surgical specimen handling, and histologic evaluation of surgical specimens. The role of IgE-mediated hypersensitivity was prospectively evaluated with various standard methods. Applying the improved test methods in a prospective, consecutive fashion to all CRS patients with or without nasal polyposis allowed us to better estimate the incidence of AFS in the general CRS population.

## METHODS AND MATERIALS

### Collection and Culture Technique

Awareness that fungi are colonizing the mucus prompted development of a simple noninvasive procedure to obtain as much mucus as possible for testing. Two puffs of phenylephrine hydrochloride 1% are sprayed into each nostril to produce vasoconstriction. The spray also increases the nasal lumen and consequently the yield from nasal lavage. After approximately 2 minutes each nostril is flushed with 20 mL of sterile saline using a sterile syringe with a sterile curved blunt needle (Figure 1, A). The patient takes a deep inspiratory breath and holds it before the injection of saline. The patient then forcefully exhales through the nose during the flushing. The return is collected in a sterile pan (Figure 1, B).

The collected fluid is placed into centrifuge tubes and sent directly to the mycology laboratory where the specimen is processed under a laminar flow hood to prevent contamination. One vial (10 mL) of sterile dithiothreitol is diluted with 90 mL of sterile water. The collected specimen is suspended with an equal volume of diluted dithiothreitol and vortexed for 30 seconds. The mixture is allowed to stand at room temperature for 15 minutes while the dithiothreitol breaks apart the disulfide bonds, thus liquefying the mucus. The mixture is then centrifuged at 3000g in a 50-mL tube for 10 minutes. The supernatant is discarded, and the sediment is vortexed for 30 seconds. One-half milliliter of the prepared sediment is inoculated onto an inhibitory mold agar plate containing chloramphenicol (125 µg/mL); inhibitory mold agar containing ciprofloxacin (5 µg/mL); brain-heart infusion agar containing 5% sheep blood, gentamicin (5 µg/mL), and chloramphenicol (15 µg/mL); and brain-heart infusion agar containing 5% chloramphenicol (15 µg/mL), gentamicin (5 µg/mL), and cycloheximide (5 mg/mL). The plates are incubated at 30°C and allowed to grow for 30 days. The plates are examined at 2-day intervals, and all cultures are identified.

### Patients

Two hundred ten consecutive patients with the clinical diagnosis of CRS with or without nasal polyposis had lavage specimens collected for culture. The clinical diagnosis of CRS was established with a history of recurrent upper respiratory tract infections lasting longer than 3 months and inflammatory mucosal thickening seen on endoscopic examination and confirmed with a coronal CT scan.<sup>14</sup> Fourteen volunteers with no history of nasal or paranasal sinus disease, with no symptoms of inhalant allergy, and with normal-appearing mucosa confirmed by nasal endoscopy served as controls.

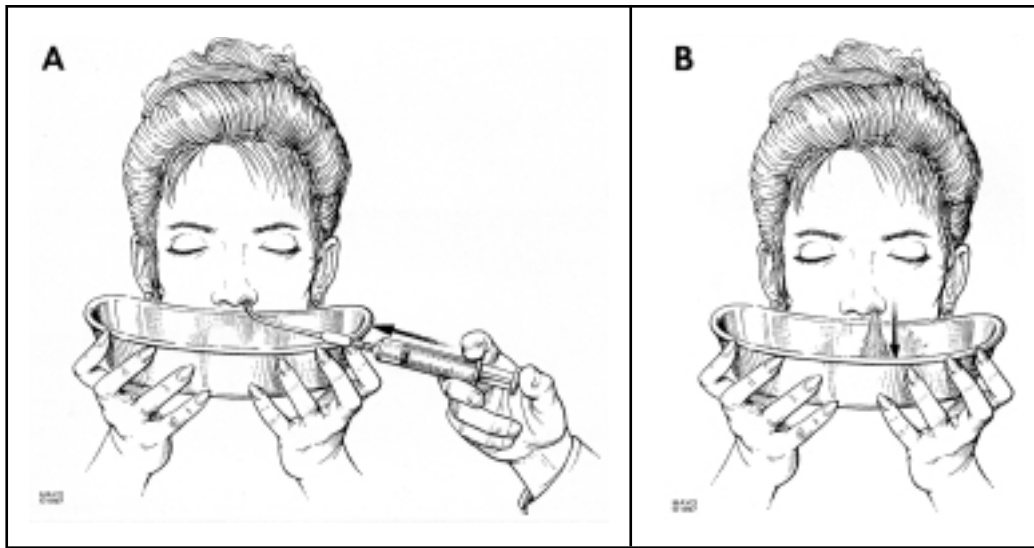


Figure 1. A, Saline is instilled forcefully into the patient's nostril. B, The patient exhales saline and mucus into a sterile pan.

**Collection of Surgical Specimens and Histologic Examination**

The principle of maximum mucus preservation was adhered to during the acquisition of surgical specimens. This enabled the assigned pathologist to find allergic mucin and fungal elements within the mucus. All the surgical procedures were performed without a power microdébrider to ensure maximal mucin collection. In addition, use of suction devices was limited. The mucus was manually removed together with inflamed tissue and placed on a saline-moistened nonstick sheet (Figure 2). Specimens were not placed directly on a surgical towel or on gauze because these carriers absorb a large amount of the mucus (Figure 3). Frozen sections were not performed except to exclude inverted papilloma, malignancy, or other disor-

ders. The specimen was then processed routinely. Multiple serial sections of different specimens from each patient were stained with hematoxylin and eosin and with Gomori methenamine silver. The pathologists were alerted to pay special attention to the mucin. Of the 210 CRS patients from whom specimens were collected, 101 underwent sinus surgery and thus provided material for histologic analysis.

**Immunologic Work-up**

A total blood IgE level was determined in 179 of the 210 patients who had cultures done. In all 179, a specially designed skin test was used to screen for IgE-mediated hypersensitivity. A battery of 18 commercially available fungal extracts was used to perform a skin-prick test and an



Figure 2. A nonstick sheet protects the mucus on the removed polypoid tissue from being absorbed.



Figure 3. A nasal polyp is placed directly on a towel. Note the large amount of mucus that has been absorbed by the towel.

Table 1. Number of Organisms (in Alphabetical Order) Recovered From Patients With Chronic Rhinosinusitis (N=210) and Percentage of Patients Colonized With the Species

<i>Acremonium</i>	5 (2.4%)
<i>Alternaria</i>	93 (44.3%)
<i>Arachniotus citrinus</i>	3 (1.4%)
<i>Arthrographis kalrae</i>	1 (0.5%)
<i>Aspergillus</i>	62 (29.5%)
<i>A flavus</i>	8
<i>A fumigatus</i>	17
<i>A glaucus</i>	6
<i>A nidulans</i>	1
<i>A niger</i>	5
<i>A terreus</i>	2
<i>A versicolor</i>	15
<i>A versiforme</i>	1
<i>Aspergillus</i> species*	7
<i>Aureobasidium</i>	8 (3.8%)
<i>Beauveria</i>	2 (1.0%)
<i>Bipolaris</i>	2 (1.0%)
<i>Candida</i>	45 (21.4%)
<i>C albicans</i>	31
<i>C krusei</i>	1
<i>C lipolytica</i>	1
<i>C lusitaniae</i>	1
<i>C parapsilosis</i>	9
<i>C tropicalis</i>	1
<i>Candida</i> species*	1
<i>Chaetomium</i>	3 (1.4%)
<i>Chryso sporium</i>	2 (1.0%)
<i>Cladosporium</i>	82 (39.0%)
<i>Cryptococcus</i>	4 (1.9%)
<i>C albidus</i>	1
<i>C laurentii</i>	2
<i>Cryptococcus</i> species*	1
<i>Curvularia</i>	2 (1.0%)
<i>Epicoccum</i>	12 (5.7%)
<i>Exophiala jeanselmei</i>	2 (1.0%)
<i>Fusarium</i>	34 (16.2%)
<i>Geotrichum</i>	10 (4.8%)
<i>Gliomastix</i>	1 (0.5%)
<i>Monilia</i>	3 (1.4%)
<i>Mucor</i>	4 (1.9%)
<i>Nigrospora</i>	1 (0.5%)
<i>Oidiiodendron</i>	1 (0.5%)
<i>Paecilomyces</i>	5 (2.4%)
<i>Papularia</i>	4 (1.9%)
<i>Penicillium</i>	91 (43.3%)
<i>Phoma</i>	2 (1.0%)
<i>Pithomyces</i>	14 (6.7%)
<i>Pseudallescheria boydii</i>	1 (0.5%)
<i>Rhino cladiella</i>	3 (1.4%)
<i>Rhizopus</i>	5 (2.4%)
<i>Rhodotorula</i>	4 (1.9%)
<i>R minuta</i>	2
<i>Rhodotorula</i> species*	2
<i>Saccharomyces cerevisiae</i>	1 (0.5%)
<i>Sagrahamala</i>	1 (0.5%)
<i>Scolecobasidium</i>	1 (0.5%)
<i>Scopulariopsis</i>	3 (1.4%)
<i>S brumptii</i>	1
<i>Scopulariopsis</i> species*	2
<i>Trichoderma</i>	8 (3.8%)
<i>Trichophyton</i>	2 (1.0%)
<i>T rubrum</i>	1
<i>Trichophyton</i> species*	1
<i>Trichosporon beigelii</i>	1 (0.5%)
<i>Ustilago</i>	13 (6.2%)
Total No. of organisms	541

\*Subclasses not available.

Table 2. Number of Organisms (in Alphabetical Order) Recovered From Healthy Control Subjects (N=14) and Percentage of Volunteers Colonized With the Species

<i>Acremonium</i>	1 (7.1%)
<i>Alternaria</i>	7 (50.0%)
<i>Aspergillus</i>	6 (42.9%)
<i>A clavatus</i>	1
<i>A flavus</i>	1
<i>A fumigatus</i>	2
<i>A niger</i>	1
<i>Aspergillus</i> species*	1
<i>Candida albicans</i>	1 (7.1%)
<i>Cladosporium</i>	8 (57.1%)
<i>Geotrichum</i>	4 (28.6%)
<i>Penicillium</i>	3 (21.4%)
<i>Pithomyces</i>	1 (7.1%)
Total No. of organisms	31

\* Subclasses not available.

intradermal test (dilution 1:100). A 48-hour reading was done looking for delayed type IV hypersensitivity.

Serum samples from 95 of the 179 skin-tested patients were screened with the radioallergosorbent test (RAST) method using 23 mold allergen assays. Total and fungus-specific IgE blood levels were determined and the fungus-specific skin tests were performed in the 14 normal subjects serving as the control group.

## RESULTS

The novel collection and culturing method resulted in cultures positive for fungus in 202 (96%) of 210 consecutive patients with CRS. A total of 541 positive cultures grew, with an average of 2.7 organisms per patient and a maximum of 8 different organisms per patient. A total of 40 different genera of fungi were identified (Table 1). Thirty-one species have not been associated with or described in AFS before to our knowledge. Interestingly, the control group of normal, healthy volunteers was 100% culture positive for fungi. Thirty-one fungus-positive cultures grew, with an average of 2.3 different organisms per volunteer, and a maximum of 4 different organisms per subject. Eight genera were identified (Table 2). The organisms grown from the controls were not markedly different than those from the CRS patients.

Of the 101 surgical cases, fungal elements (hyphae, destroyed hyphae, conidia, and spores) were found in 82 histologic specimens (81%) (Figure 4, A). The allergic mucin, containing clusters (or sheets) of degenerating eosinophils and their by-products (Figure 4, B), was found in 97 (96%) of 101 consecutive surgical cases. Interestingly, in the remaining 4 cases in which the allergic mucin was absent, the eosinophils were also almost completely absent in the harvested nasal mucosa and polyps. The possibility exists that preoperative steroids given to these patients explain the absence of eosinophils. Two of these

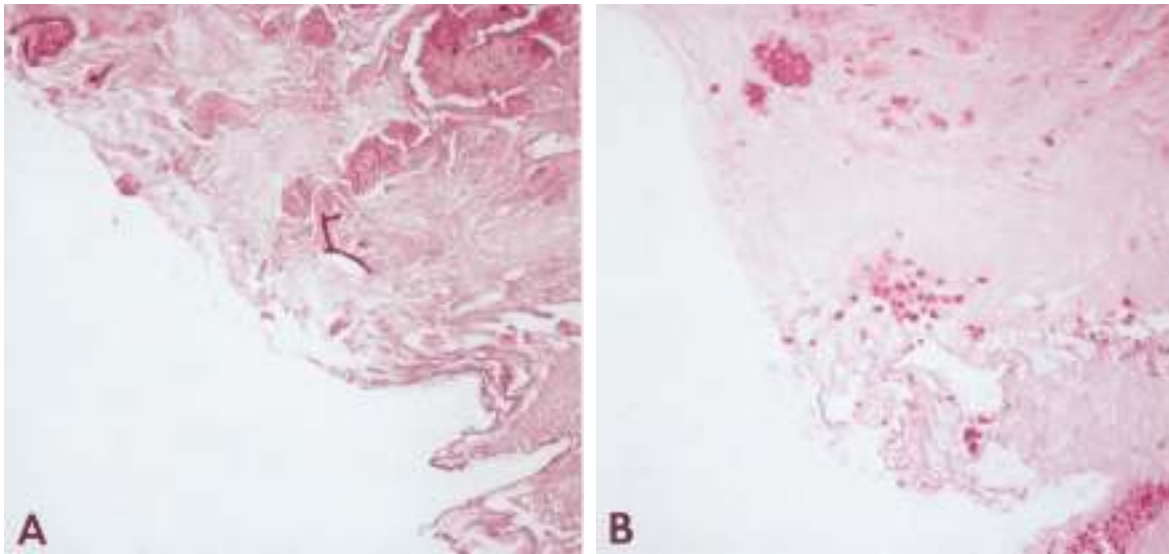


Figure 4. A, Scattered fungal elements (hyphae) within the eosinophilic (allergic) mucin (Gomori methenamine silver stain, original magnification x200). B, Serial section from A shows eosinophilic mucin with typical sheets and clusters of degenerating eosinophils (hematoxylin and eosin stain, original magnification x200).

patients also had an acute bacterial onset with neutrophil predominance.

Tissue from 4 healthy controls had absent tissue eosinophilia, which confirms similar findings by other authors.<sup>15</sup>

Sometimes the mucus filled the entire sinus, and sometimes there were only small pockets of thick mucin between the polypoid material or only a thin layer coating the inflamed mucosa. High-attenuation areas, reflecting the

allergic mucin precisely where we have found it during surgery, were noted on CT scan in most cases of CRS (Figure 5). Because of the small size of the mucus pockets, we felt that the histologic examination was more sensitive and specific than the CT scans.

Overall, the diagnostic criteria for AFS were met in 94 (93%) of 101 patients with CRS. All patients had a broad spectrum of inflammatory mucosal thickening

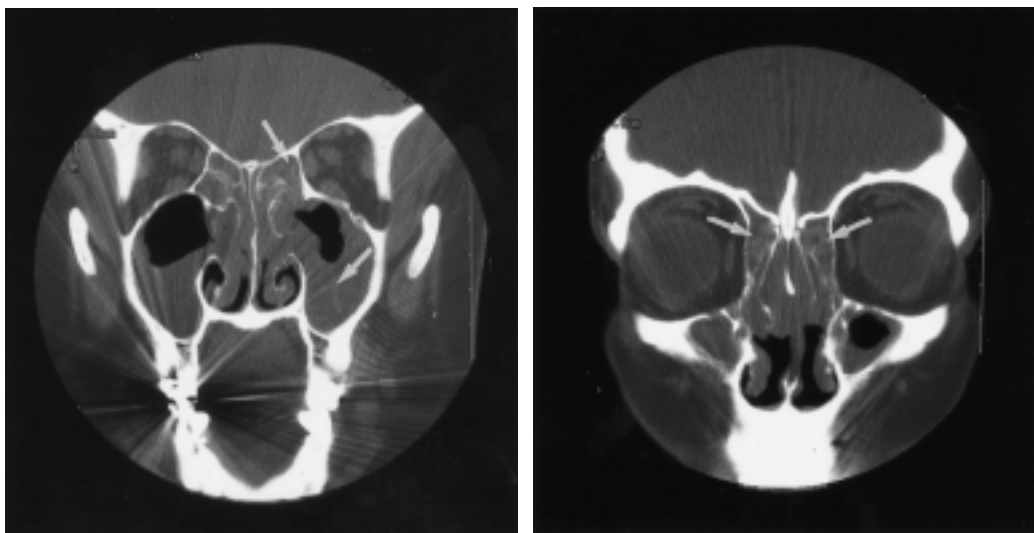


Figure 5. Coronal computed tomographic scans from 2 different patients with chronic rhinosinusitis showing moderate inflammatory thickening and typical small areas of high attenuation (arrows) correlating with the intraoperative finding of eosinophilic (allergic) mucin.

ranging from minimal polypoid changes to massive polyposis.

In 59 (33%) of 179 patients evaluated, the total IgE level was higher than 128 KU/L (the second SD); in 61 (34%) of 179 patients, it was between 41 and 128 KU/L (the first and second SDs), and in 43 (24%) of 179 patients, it was between 13.2 and 41 KU/L (the mean value for the atopic control population and the first SD, respectively). Interestingly, 16 (9%) of 179 patients had a total IgE level of less than the normal value, and 2 of these patients' values were less than the laboratory's detection level (2 KU/L). Clear evidence of allergic mucin and fungi was present (on histology as well as culture) in each of these cases.

The specific IgE levels in the blood were elevated for at least 1 fungal species in 27 (28%) of 95 patients. In 12 (44%) of 27 patients with an elevated specific IgE level, the total IgE level was not higher than 128 KU/L. The lowest total IgE level we have noted in a patient with elevated specific IgE for multiple molds was about 30 KU/L.

Allergy skin tests by the skin-prick and intradermal methods showed similar results. With the skin-prick method, 45 (25%) of 179 patients had a positive reaction to at least 1 fungal allergen. An additional 30 patients (17%) who had negative skin-prick test results were positive to at least 1 species by the intradermal method. A delayed type IV hypersensitivity reaction was noted in 9 (5%) of 179 patients.

The immunologic evaluation of the control group resulted in elevated total IgE levels in 4 (29%) of 14 controls. Three of these 4 volunteers had an elevated specific IgE level and a positive skin-prick test result to at least 1 fungal allergen. In 2 of these 3 volunteers the organisms growing on culture correlated with the elevated specific IgE level and the positive skin test finding. Overall, the differences in the specific and total IgE values were not significant between the patient group and the control group.

## DISCUSSION

With fewer than 250 cases reported in the literature to date, AFS has been considered rare. With heightened awareness of the disease, an increased number of reports have been published more recently.<sup>4,5,16</sup> Suggestions regarding the criteria for clinical diagnosis, pathophysiologic mechanisms involved, and treatment regimens have appeared in the literature.<sup>3,4,6,9,10,16</sup> The diagnostic criteria of AFS include (1) CRS (confirmed by CT scan); (2) the presence of allergic mucin (predominantly eosinophils and their degenerated by-products); and (3) the presence of fungal organisms within that mucin confirmed by histology or culture. We believe this is the first prospective report to demonstrate, using these diagnostic criteria, the incidence of AFS in CRS patients. The 93% incidence of AFS in CRS is considerably higher than

the incidence reported in previous retrospective reviews.<sup>1,4,5</sup> Undoubtedly, the biggest problem facing previous investigators has been the inability to demonstrate fungal organisms in the nasal mucin. Naturally, most clinicians concluded from a negative culture or a negative pathology report that fungi were not present in the mucus, and therefore the disease could not be AFS. They probably ignored the possibility that the methods used to collect mucus were inadequate to identify the fungi. Because fungi colonize within the nasal mucus, the more mucus that is collected for culture and histologic examination, the greater the chance of a positive fungal yield. Thus, we developed a novel method to collect the mucus in an office setting. The forceful injection of physiologic saline into the nostril of the patient followed by forceful exhalation loosens the mucus and increases the amount of mucus collected. During surgery, the mucus can be removed manually with forceps, directly with a suction trap, or by instilling saline in the nose and/or the sinuses and capturing it within a suction trap.

During the culturing of nasal secretions, fungi must be extracted from the mucus before being placed on the growth medium (Figure 6, A). We use dithiothreitol, a mucolytic agent, to liquefy the mucus. The fungi are separated from the mucus by centrifugation and placed on the growth media (Figure 6, B). During the incubation period no single temperature setting seems to be perfectly suited for all fungal species; however, 30°C is optimal for most fungal organisms. A minimum incubation time of 30 days seems necessary for complete recovery.

The maxim "more is better" also applies to collection of surgical specimens for histologic evaluation. Suction devices and power microdebriders decrease the amount of recovered mucus. The use of suction traps should always be considered. The handling of specimens sent to the pathologist is also crucial. Placing specimens on absorbent material (eg, towels, cotton sheets) results in a significant reduction of collected mucus, and use of nonabsorbent sheets is preferable. Technicians processing the specimens are instructed to preserve the attached mucus because it is essential for histologic diagnosis. Multiple sections from different areas of the nose and paranasal cavities must be prepared since fungi are frequently scattered. The sections must be routinely stained with Gomori methenamine silver to identify the fungi and hematoxylin and eosin to identify the eosinophils in the mucus.

Pathologists must be informed about the nature of the disease so they can focus their study on the mucus. They must be aware of the different morphologic features, sizes, and shapes of the common fungi. In addition, the pathologist needs to understand that the eosinophils may present in various stages of cell degeneration, depending on the different stages of the disease. Sometimes the eosinophils in

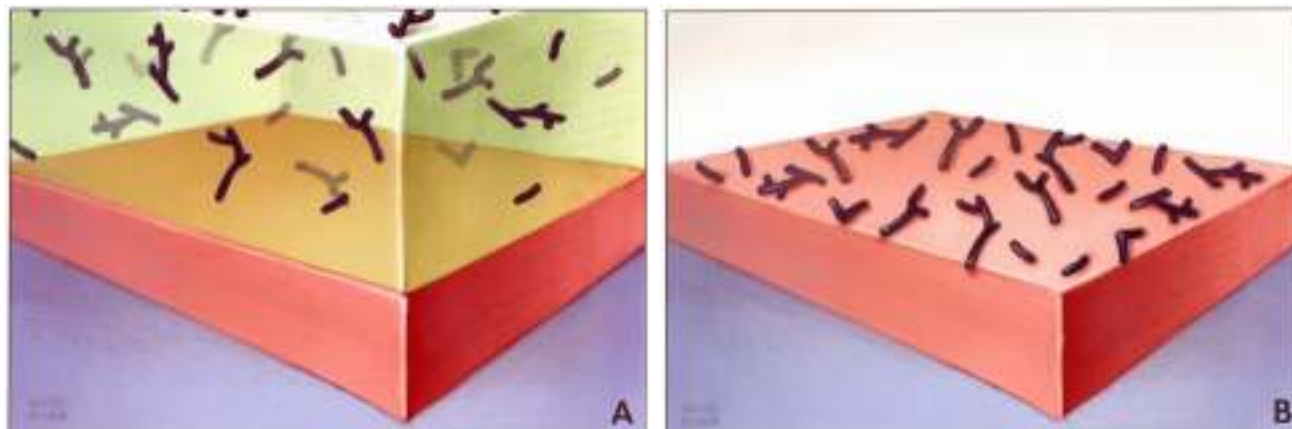


Figure 6. A, Fungi are entrapped in the mucus during incubation if a mucolytic agent is not used in the culturing process. B, Fungal elements are released from the mucus by a mucolytic agent and contact the growth medium.

the clusters are still intact with few Charcot-Leyden crystals present. At the other end of the spectrum, only the remnants of eosinophils are found in the form of cellular debris and crystals. The crystals are a product of degenerating eosinophils and common in other diseases with eosinophil involvement. The presence of Charcot-Leyden crystals alone is not specific for AFS and therefore should not be used as a diagnostic criterion. All that the presence of crystals implies is that eosinophils have died. Other markers more specific for eosinophil degranulation (eg, major basic protein) may be more useful histologic markers, although this concept needs further study.

The histologic markers of CRS are the striking numbers of eosinophils in CRS, in contrast to the near absence of eosinophils in healthy controls.<sup>17</sup> Our findings demonstrate that eosinophils, when present in high numbers in the tissue in CRS, are also invariably present in the mucus, mostly in the form of cell clusters. The conclusion we draw from this observation is that the eosinophils are only in transit through the tissue toward the mucus. Our observation is that eosinophils actually migrate intact through the epithelium and degranulate within the mucus. Hypothesizing that the eosinophils are more than role players in a general inflammatory response, we think that the eosinophils play an immunologic defensive role in CRS, and their target is located in the mucus. In other words, the fungal organisms in the mucus could be the target for the eosinophils, but this hypothesis needs further validation.

Confusion exists about the role of IgE-mediated allergy in AFS. Some investigators insist that an IgE-mediated type I hypersensitivity to fungi plays a central role in the pathogenesis of AFS.<sup>3,6,10,16,18</sup> To support their contention, they found a history of atopy or an elevated total serum IgE level in their cases. In addition, they occasionally noted elevated fungus-

specific IgE levels that correlated with the species found in the positive fungal cultures from the nasal mucus.

Further evidence supporting the type I hypersensitivity theory was the postoperative finding of a decrease of total and specific IgE levels after surgery in some cases, probably as a result of a reduction of the fungal antigenic load. Consequently, Mabry et al<sup>19</sup> championed a postoperative immunotherapy approach to AFS. They observed that those AFS patients responding to immunotherapy had less need for systemic steroids. In a follow-up article, Mabry and Mabry<sup>20</sup> reported that the mold-specific IgE levels do not decrease in AFS patients responding well to immunotherapy, with normal-appearing nasal mucosa. Thus, the effect of the immunotherapy is unlikely to be IgE mediated.

Our IgE data and other observations seem to challenge the thinking that IgE might drive the inflammatory changes seen in AFS. For example, we found elevated total IgE levels in fewer than 33% of our patients diagnosed as having AFS. Only 42% of the patients had a detectable type I hypersensitivity by skin test, and only 30% had an elevated fungus-specific IgE level by RAST. Thus, more than half (58%) of our patients showed no evidence of increased IgE levels to fungi. While more than half of our patients were not allergic to fungi, the clinical and histopathologic findings were the same as in those with allergy to fungi. The possibility exists that local IgE production in the nasal mucosa could explain the fact that 58% of our patients with AFS showed no evidence of elevated blood IgE levels to fungi.<sup>21</sup> Even with an elevated local IgE production, an IgE-mediated type I hypersensitivity reaction to fungi requires mast cell degranulation. But mast cells are not increased in the nasal mucosal tissue or in the nasal mucus itself in CRS or AFS patients.<sup>22</sup> Another compelling piece of evidence against the type I hypersensitivity mechanism

in AFS is that antihistamines neither relieve nor reverse patients' symptoms. Finally, 2 subjects from our control group who had elevated IgE levels to fungi, which were cultured from their nasal mucus, had no evidence of chronic nasal mucosal inflammation or symptoms of AFS or CRS.

The findings of fungi in the mucus and elevated specific IgE level to fungi without mucosal inflammation are exactly what occurs in patients with rhinitis caused by allergic reaction to molds. It is obvious that some patients have both AFS and allergic rhinitis (especially to molds) as comorbid diseases. Both share major symptoms, such as nasal obstruction and nasal congestion, and patients with active allergic rhinitis and AFS may be the most symptomatic.

Our data reveal that many different fungi colonize everyone's nasal secretions. Some people even have allergic rhinitis to molds with elevated specific IgE levels to these fungi but do not have nasal mucosal inflammatory changes with AFS-associated tissue damage. If IgE mediation is the primary pathophysiologic mechanism, how can these patients be explained?

We view the increased fungus-specific IgE levels found in some AFS patients merely as a recognition by the immune system of fungi and not the cause of disease. Since AFS clearly exists independently from elevated fungus-specific or total IgE levels or positive skin test results, atopy should not be a diagnostic criterion.

For all the above reasons, we conclude that a role for IgE in either the etiology or the pathophysiology of AFS is unlikely. The mere presence of eosinophils in the mucus does not necessarily mean an allergic (IgE-mediated) origin alone. In fact, the clinical finding that eosinophil migration and influx occur independently from IgE was recently demonstrated in a murine model.<sup>23,24</sup> The term *allergic mucin* is thus a misnomer and is confusing. We prefer the term *eosinophilic mucin*, since it is clear and descriptive and does not imply an IgE-mediated type I hypersensitivity. Consequently, the term *allergic fungal sinusitis* is also inaccurate for this disease and should be altered. We propose the term *eosinophilic fungal rhinosinusitis* to reflect the striking role of the eosinophils in this disease, which we hypothesize are triggered by the extramucosal fungi.

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