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Fungus and Chronic Rhinosinusitis: From Bench to Clinical Understanding

Donald C. Lanza, MD; Hun-Jong Dhong, MD; Pongsakorn Tantilipikorn, MD;
Jirayu Tanabodee, MD; Douglas M. Nadel, MD; David W. Kennedy, MD

Although fungus-related sinusitis has been described for at least 2 centuries, a more detailed pathologic description of the problem as it relates to eosinophilic disease was not detailed until 1983, when "allergic fungal sinusitis" was described histopathologically. Until then, most fungal sinus disease was perceived to occur in immunosuppressed diabetic patients with invasive fungus. It is now acknowledged that depending upon the immune status of the host, fungus-related sinus disease can take several forms. Interest in this subject matter was intensified in 1999, when it was suggested that fungi might be an important cause of most cases of chronic rhinosinusitis. This hypothesis remains controversial, and there is mounting evidence to support the multifactorial nature of chronic rhinosinusitis, which may include fungus. In fact, etiologic factors for all forms of fungus-related sinus disease are still poorly understood. The prevalence of the disease and the dominant fungal pathogen appear to vary in different geographic regions and probably are related to individual host conditions. Immunoglobulin E-mediated allergic reactions to mold appear to be associated with disease in some patients, but not in all. Although antifungal therapy is known to be lifesaving for invasive disease, its role in extramucosal disease is less well defined. Preliminary trials suggest that some systemic and topical antifungal agents are of clinical benefit in extramucosal disease. Since sinus fungi are rarely invasive in immunocompetent individuals, it is not clear whether the effects of the antifungal treatments are a result of the antifungal action itself, or due to additional properties these drugs possess. This review summarizes the available data and presents some of our clinical and experimental findings as to the role of fungus in chronic rhinosinusitis.

Key Words: *Alternaria*, antifungal therapy, antimycotic therapy, *Aspergillus*, Dematiaceae, *Dematium*, eosinophilia, fungal rhinosinusitis, fungal sinusitis.

INTRODUCTION

Chronic rhinosinusitis (CRS) is a debilitating disease that afflicts close to 30 million Americans, or 14% of the adult population.¹ It has most recently been defined as a chronic inflammatory disease of the nose and paranasal sinuses and can be divided into CRS with polyps and CRS without polyps.² Frequently, the cause is unknown, but it has been suggested that all CRS is caused by fungus. Although this generalization is debated, it is widely accepted that several types of sinus diseases have been attributed to the presence of fungal organisms in the nasal and sinus cavities. The causes of fungal-related rhinosinusitis are not fully understood, and many questions remain about its cause and appropriate treatment. Here we review the history of fungal sinus disease, the classification of fungal rhinosinusitis, current debates as they relate to CRS, and the role of antifungal therapy. Also, we present clinical and experimental data (not previously published) that were

gathered during the past 15 years at the University of Pennsylvania (Penn).

HISTORICAL PERSPECTIVE

The first reference in the literature to mycotic disease affecting the paranasal sinuses was in 1791, by Plaignaud,³ who described a 22-year-old soldier who complained of severe maxillary pain. Cautery of the area revealed a "fungus tumour" of the region. Many, however, credit Zarniko⁴ with reporting the first true case of sinus mycosis in a 50-year-old woman who had nasal obstruction treated with maxillary sinus lavage that produced a sticky brownish gray material. Culture grew out *Aspergillus* species. In 1913, Harmer⁵ reported the first patient with allergic symptoms treated with maxillary sinus lavage that produced a brown membrane and *Aspergillus fumigatus* on culture. Tilley⁶ reported a series of 5 patients with nasal obstruction, discharge, sneezing, headache, and pain around the eye. Pathologic ex-

From Division of Rhinology, Department of Otorhinolaryngology-Head and Neck Surgery, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania. Our bench research was made possible through research contributions provided by Elaine and Dan Sargent to the Rhinology Research Fund at the University of Pennsylvania.

Correspondence: Donald C. Lanza, MD, Sinus & Nasal Institute of Florida, PA, Carillon Outpatient Center, Suite 200, 900 Carillon Parkway, St Petersburg, FL 33716.

CLASSIFICATION OF FUNGAL RHINOSINUSITIS

Extramucosal Fungal	Invasive
Superficial sinonasal mycosis (Fig 1)	Chronic invasive fungal rhinosinusitis (Fig 3)
Fungal ball	Granulomatous invasive fungal rhinosinusitis (eg, Aspergilloma)
Fungus-related eosinophilic rhinosinusitis (Fig 2)	Acute (fulminant) fungal rhinosinusitis
Allergic fungal rhinosinusitis	

amination revealed a soft, jelly-like membrane, identified on mycology as *Aspergillus* sp.⁶

The first use of the term "aspergilloma" to describe an *Aspergillus* granuloma was by Miloshev et al⁷ in 1966. This was an invasive condition in which the fungus was identified within the granulation tissue. This was not an extramucosal condition and should not be confused with a fungal ball. A histopathologic triad of eosinophils, Charcot-Leyden crystals, and fungal forms was first described by Katzenstein et al⁸ in 1983 in a group of patients with a clinically distinct form of CRS. This disease was first called "allergic *Aspergillus* sinusitis." In addition to the presence of eosinophilic mucin, the disease was associated with recurrent nasal polyps, asthma and/or atopy, sinus involvement, poor response to medical treatment, and multiple surgical procedures.⁹ In 1984, Stammberger et al¹⁰ acknowledged the incidence of chronic noninvasive fungal infections in Graz, Austria, and advocated the use of surgery and topical antifungal therapy in certain patients. In 1999, Ponikau et al¹¹ identified mold in nearly all surgical patients and 100% of normal individuals with CRS. Ponikau et al¹¹ have made stunning observations at the cellular level that have shed

light on an important area for research in CRS that previously was underappreciated. Additionally, they have developed specialized diagnostic techniques (specimen collection methods and chitin) that go beyond the in situ hybridization methods used to identify *Aspergillus* that had been previously described at Penn.¹² Ponikau et al¹¹ proposed renaming CRS as "eosinophilic fungal rhinosinusitis" to reflect their assertion that fungus is its cause. In 2006, this term has not been adopted, and the assertion that fungus is the sole driver for CRS remains unproven. Many physician researchers continue to find evidence for alternative mechanisms related to CRS (see discussion below).

TERMINOLOGY IN FUNGAL RHINOSINUSITIS

Some extramucosal conditions in fungal rhinosinusitis are superficial (noninvasive) sinonasal mycoses (see Table and Fig 1). For the purposes of this discussion, we introduce the term "fungus-related eosinophilic rhinosinusitis" (FRER). If the term is to be useful, more research is needed to precisely define inflammatory mechanisms in which fungus is related to CRS. Suffice it to say for this discussion that FRER is a chronic condition in which fungal organisms are at least partially responsible for attracting eosinophils to the luminal surface of the sinonasal mucosa and promoting inflammation. Figure 2 depicts the computed tomographic (CT) scan of a middle-aged man who had multiple prior operations; his cultures grew gram-negative enteric bacteria, and he was negative for mold allergy by skin and radioallergosorbent test methods within 1 year of these images. His nasal discharge was partially opaque yellow and had beads or clumps within it, and although the mucopus was thick, it was not clinically the same as the dense accumulations seen in fully developed fungal rhinosinusitis. Figure 2B, of this patient's nasal mucopus, clearly identifies eosinophils clustering adjacent to fungal hyphae. In patients with CRS who have the additional risk factor of mold allergy, the noninvasive disease is referred to as allergic fungal rhinosinusitis (AFRS).^{13,14} Indeed, AFRS could be a subset of the more general condition FRER, or a separate entity altogether. Importantly, Ferguson¹⁵ has described a distinct form of CRS, "eosinophilic mucin rhinosinusitis" (EMRS), that is different from AFRS. She found her

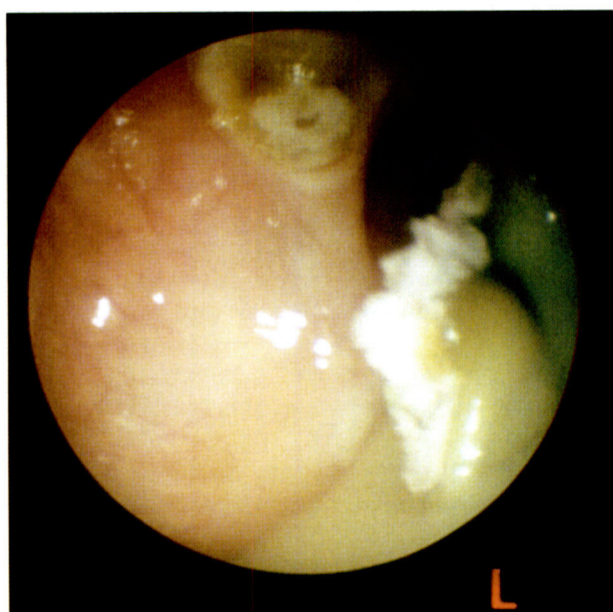


Fig 1. Endoscopic view of superficial (noninvasive) mycosis in left maxillary sinus. Note crusting adherent to mucosa, possibly representing type of biofilm.

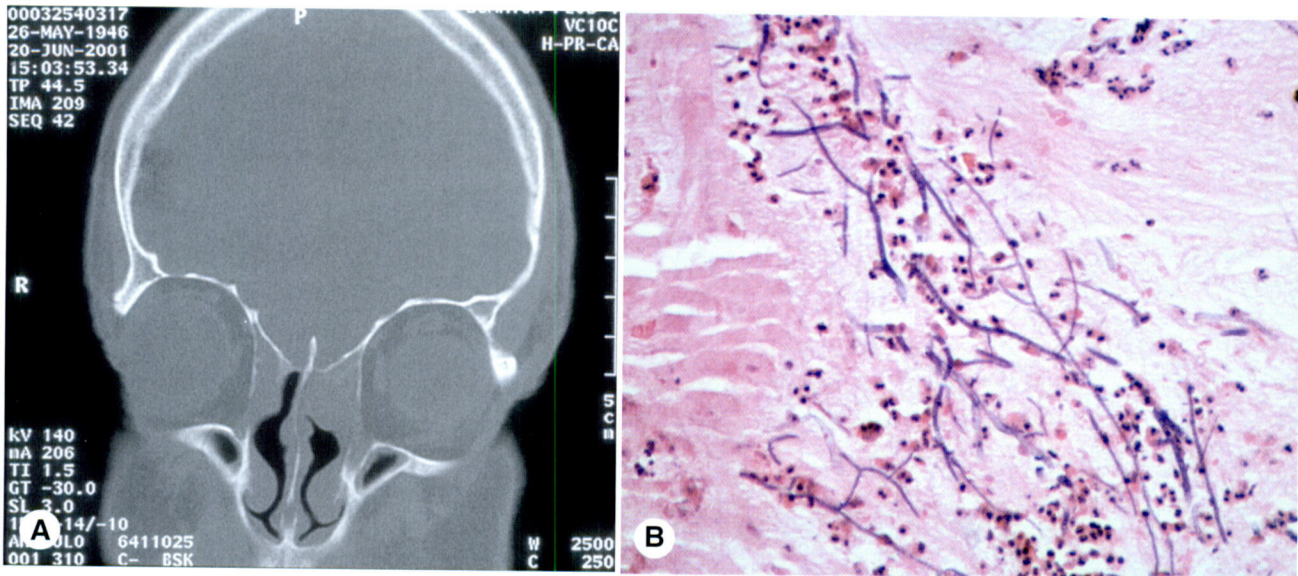


Fig 2. Nonallergic male patient. **A)** Coronal computed tomogram. **B)** Microscopy demonstrates fungal hyphae in mucin, with eosinophils clustering adjacent to hyphae.

EMRS patients to be older; more likely to have bilateral disease, asthma, aspirin sensitivity, and immunoglobulin (Ig) G1 deficiency; and less likely to have IgE-mediated allergy than those with AFRS. The fact that none of these patients had identified fungal hyphae suggests that multiple pathways can produce similar clinical results relative to CRS.¹⁵

Invasive fungal rhinosinusitis may be expressed as either chronic (Fig 3) or acute (fulminant) fungal rhinosinusitis.^{16,17} It is important to note that patients with AFRS who have become severely immunocompromised have then gone on to develop acute fungal rhinosinusitis. Recommendations to prevent

such a catastrophe have been made previously.¹⁸

RISK FACTORS FOR FUNGUS-RELATED RHINOSINUSITIS

The mechanisms underlying this condition are not yet understood. There are multiple risk factors for all forms of fungal rhinosinusitis that, briefly stated, may include mechanisms that alter certain aspects of acquired and/or innate immunity, mucociliary clearance, and those factors that promote mucous stasis and tissue edema. Risk factors could theoretically include concurrent or preceding viral or bacterial infection, immune response elicited by superantigens produced by microorganisms, biofilm formation, allergy, topical steroid therapy, antibiotic therapy, and the concentration of ambient mold.

GEOGRAPHIC DIFFERENCES IN PREVALENCE AND DOMINANT FUNGAL PATHOGEN

With regard to AFRS, there appear to be geographic variations in frequency and organisms.¹⁹ Previously, we reviewed the mycology of fungal rhinosinusitis at our clinic in Philadelphia between 1994 and 1998. Of 127 consecutive fungal cultures, 32 patients (25%) had positive cultures, and 50% of those positive cultures had *Aspergillus*. *Aspergillus fumigatus* was the most prevalent species (22%). Many other organisms were found, including *Alternaria* and *Fusarium*. In another review of our experience at Penn in 92 consecutive surgical patients, 23 (25%) had manifestations of fungal rhinosinusitis, including tissue eosinophilia, and positive mycology (using standard techniques) or pathologic examination for fungus. They also had a constellation

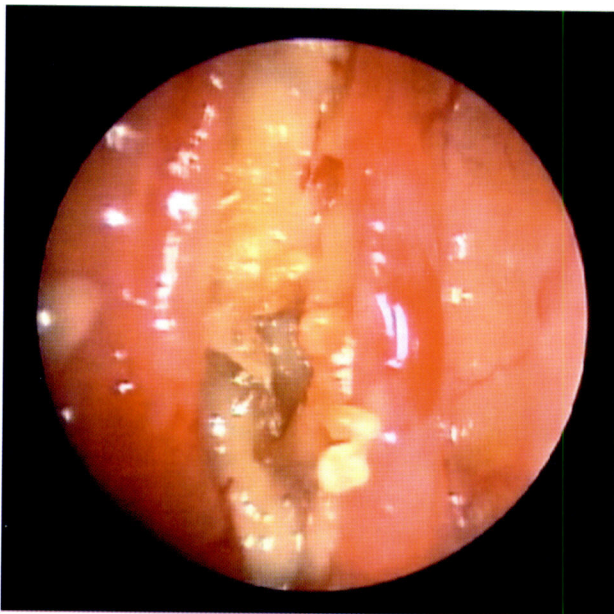


Fig 3. Endoscopic view of chronic invasive *Fusarium* along cribriform plate in immunocompetent host.

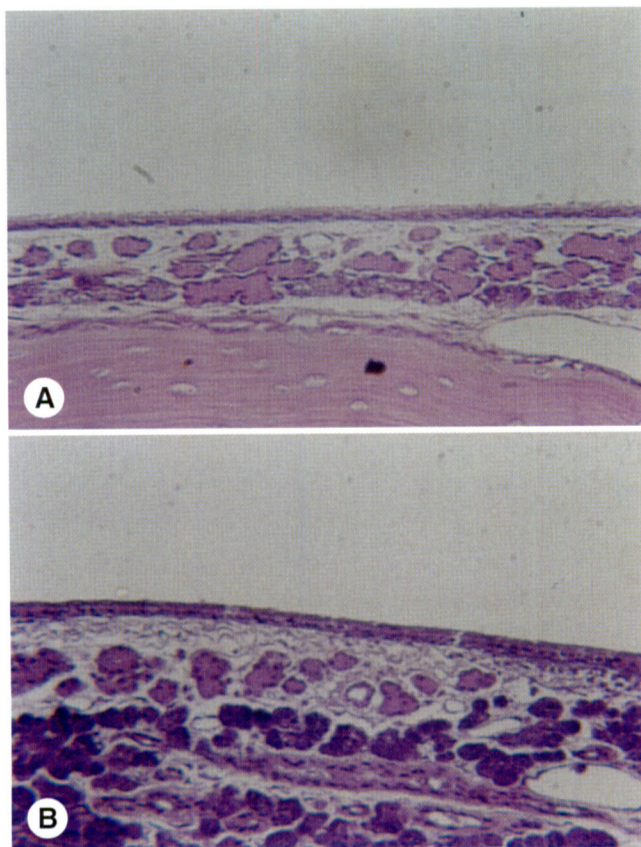


Fig 4. Reactions to inoculations of *Aspergillus fumigatus* in maxillary sinus of New Zealand white rabbits. **A)** Normal rabbit sinus mucosa. **B)** Inflammatory response to *A fumigatus* in allergic rabbit. **C)** Inflammatory response to *A fumigatus* in allergic rabbit with surgical obstruction of maxillary sinus. Eosinophils are not readily distinguished, in rabbits, from more prevalent heterophil (which also contains eosinophilic granules). Progressive tissue edema and glandular hyperplasia are evident.

of clinical features suggestive of AFRS, including recurrent nasal polyposis, asthma, multiple sinus involvement, medicinal recalcitrance, multiple surgical procedures, and thick, "peanut butter" mucus. Of these 23 patients, 100% had prior medical treatment, 74% had prior surgery, 35% had mold allergy, 14% had elevated serum eosinophil levels, 57% had elevated levels of eosinophils in the tissue, 35% had positive fungus cultures, and 13% had gross quantities of allergic mucin.

In the United States, AFRS is observed most frequently in the Southeast and the Mississippi basin. A survey of 20 otolaryngology practices throughout the United States found that 23% of all patients in a Memphis, Tennessee, practice who were referred for endoscopic sinus procedures had a diagnosis of AFRS. Practices in Alabama, Georgia, and Texas reported a frequency of at least 10%, as well. In contrast, the AFRS frequencies in the Northern locations ranged from 0% to 4%.¹⁹ It should be noted that there are difficulties in accurately estimating the frequency of AFRS or even FRER, since the results depend on the diagnostic criteria and histologic techniques selected.

EXPLORING ROLE OF ALLERGIES IN FRER AND AFRS

It has been known for some time that polyp tis-

sue IgE is elevated. In 1985, allergen-specific IgE was detected in polyp fluid in 19 of 24 patients. Ten patients had specific IgE locally in polyp tissue that could not be detected systemically.²⁰ Subsequent work demonstrated that a high proportion of patients with AFRS had allergies to common environmental molds and elevated serum IgE levels.^{21,22} Consequently, clinician-researchers in Texas administered immunotherapy to diminish the IgE-mediated response. Theoretically speaking, this was considered dangerous because of the possibility of eliciting an exaggerated immune response. However, because the antigenic load was diminished through sinus surgery before immunotherapy, it was reasonably safe to explore. Two small studies suggest that immunotherapy might be of clinical benefit in AFRS.^{22,23} In the only controlled study,²³ postoperative patients who underwent immunotherapy had significantly lower rates of revision surgery relative to controls (11% versus 33%; $p < .01$). The number of office visits per patient requiring treatment decreased significantly, as well (3.17 and 4.79 visits, respectively; $p < .05$).

Between 1993 and 1995 we conducted Institutional Review Board–approved animal experiments at Penn in white New Zealand *Pasteurella*-free rabbits to determine the effect of both *A fumigatus* and sinus obstruction on the sinus mucosa. This research ex-

perience was not previously published. *Aspergillus fumigatus* was injected intraperitoneally and then subcutaneously for a fixed period to induce allergy. The rabbits were later tested for passive cutaneous anaphylaxis to demonstrate that they had developed an allergic reaction. All rabbits underwent surgery: either a sham operation or a unilateral obstruction of the maxillary sinus. The sinus was injected twice with *A. fumigatus*. Animals were euthanized at fixed time intervals after surgery to observe differences in mucosal healing and inflammation. The contralateral side served as a control. The normal sinus mucosa can be seen in Fig 4A. In rabbits with *A. fumigatus* allergy but no sinus obstruction, there was a moderate degree of inflammation and no positive cultures for *A. fumigatus* (Fig 4B). In comparison, in the rabbits with both antigen sensitivity and sinus obstruction, the inflammation was substantially more intense. All rabbits from this group were culture-positive (Fig 4C). In rabbits with an obstructed sinus but no antigen sensitivity, the inflammatory response was less intense. Only some of these nonallergic rabbits were culture-positive (not shown) for *Aspergillus* at the time of sacrifice. This evidence suggested that the allergic sensitivity and the sinus obstruction had an additive effect. This finding supports the hypothesis that mold allergy could heighten the disease state of a given individual in whom FRER had already developed.

Collins et al²⁴ demonstrated in humans that local fungal-specific IgE may be demonstrated in sinus mucin. It was significantly associated with systemic fungal allergy and may play a role in a minority of patients with fungal sinusitis in the absence of systemic fungal allergy.²⁴ Additionally, this group from the University of Adelaide found that serum elevations of fungal-specific IgG,³ and not fungal-specific IgE, distinguished the EMRS subgroups from control groups. Their work challenges the presumption of a unique pathogenic role of IgE-mediated allergy in "allergic fungal sinusitis."²⁵

EOSINOPHILS, CHRONIC RHINOSINUSITIS, AND FUNGUS

The precise relationship between AFRS and CRS associated with eosinophilic disease is unclear. Nonetheless, it has been recognized for more than a decade that non-IgE-related mechanisms exist for eosinophil chemotaxis to certain fungi. In 1994, it was demonstrated that interleukin-5 (IL-5) was produced and released from the site of a granuloma (in Kimura's disease) and lymph nodes after stimulation with *Candida* antigen.²⁶ Additionally, interactions between blood eosinophils and nasal mucin and/or tissue have been observed in vitro. A concentration-

dependent increase in migration of eosinophils in the presence of both nasal mucin and nasal tissue extract is described. The percentage of migration was significantly higher with eosinophils harvested from the blood of CRS patients than with those harvested from that of healthy controls ($p = .033$).²⁷ These results suggest that the nasal tissue and nasal mucin have secretions that act as chemoattractants for eosinophils. Separately, it is also interesting to note that the peripheral eosinophil count in CRS is elevated compared with control groups,²⁸ and that a relatively strong correlation exists between CT scan stage and tissue eosinophilia in CRS.²⁹

Shin et al³⁰ have identified *Alternaria* as a prime target of research in that it may be more likely than other molds to induce the eosinophilic migration in CRS. They found that in patients with CRS there were exaggerated humoral and cellular responses, of both Th1 and Th2 types, to *Alternaria*. Peripheral blood mononuclear cells from approximately 90% of the patients with CRS, but not those from normal individuals, produced both IL-5 and IL-13 when exposed to *Alternaria*. Interleukin-5 and IL-13 are involved in eosinophil chemotaxis.³⁰ A 2004 study provided additional support for the fungal causation of CRS when fungal DNA from *Alternaria* was detected in 100% of tissue samples from CRS patients, but not from healthy controls.³¹ Interestingly, *Alternaria* has a unique group of mycotoxins that are cytotoxic to cultured human cell lines in vitro.³²

Confounding the research suggesting that fungus is the sole driver for all CRS and nasal polypsis is the work of Zhang et al.³³ Their studies have demonstrated a strong local up-regulation of the IgE synthesis with the formation of specific IgE to *Staphylococcus aureus* enterotoxins, suggesting a possible role of superantigens in these pathologic processes.³³ Interesting, and possibly supportive of this superantigen hypothesis, is the work of Clement et al³⁴ with confocal laser microscopy and special staining that shows *S. aureus* actually residing within the sinus tissue. This finding is consistent with prior in situ hybridization data on CRS published by colleagues at Penn who were looking at bone inflammation.³⁵

ROLE OF ANTIFUNGAL THERAPY IN FRER AND AFRS

Currently there are no medications that are approved by the US Food and Drug Administration for the treatment of CRS, yet many agents, including antibiotics and systemic steroids, have brought many CRS patients symptomatic relief. Additionally, debate over the role of antifungal agents in the treat-

ment of FRER is significant, as the very existence of FRER has been hotly contested. If the inflammation is a result of an immune reaction to mold (Fig 2B), then it stands to reason that antifungal therapy could temporarily reduce the presence of an inflammatory trigger in CRS. This could disrupt the cycle of eosinophil chemotaxis and degranulation. To support this hypothesis, there are reports that systemic and topical antimycotic therapies give temporary relief of sinus inflammation and polyps in patients with AFRS,³⁶ as well as in those with nasal polyposis.³⁷ There are no reports of long-term cure of CRS, nasal polyposis, or AFRS with antifungal therapy.

Concerns over antifungal therapy are related to its efficacy, cost, availability, pharmacologic stability, direct tissue effects, possibilities of inducing greater fungal resistance, and life-threatening side effects. It needs to be acknowledged that not all fungi are susceptible to amphotericin B and that resistance can develop in sensitive fungi. The existence of fungal resistance to antimycotic agents is widely reported, especially for *Candida* and *Mucor*. It is hypothesized that antimicrobial resistance may occur more gradually in fungal organisms than in bacteria, because of their generally slower reproductive rate. Should antifungal therapy be an appropriate treatment choice, the antimycotic agent used should be based upon existing knowledge of sensitivities to the involved fungus (if it can be identified). In vitro testing in most microbiology laboratories is either unavailable or inconsistent.

Two small, open-label trials have demonstrated a therapeutic effect of topical intranasal applications of amphotericin B.^{37,38} In 1 study of 74 patients with nasal polyposis, the nasal polyposis disappeared completely in 29 patients (39%), and there was an overall decrease in severity in those with remaining polyposis.³⁷ In a second study, which was a randomized, placebo-controlled, double-blind, single-center trial, amphotericin B was used to treat 30 randomly selected patients with CRS. The patients were instructed to instill 20 mL amphotericin B (250 µg/mL) or placebo into each nostril twice daily for 6 months. The patients who received amphotericin B achieved a relative reduction in the percentage of mucosal thickening on CT scans ($n = 10$; -8.8%) in comparison with the placebo group ($n = 14$; $+2.5\%$; $p = .030$). Likewise, the endoscopic scores improved in the amphotericin B group as compared with the placebo group ($p = .038$).³⁸ Unfortunately, similar trials with conflicting results have been reported at recent international meetings.

Additionally, it is not clear whether the clinical benefits of amphotericin B resulted from its antifun-

gal action or from other direct tissue effects of the drug on the mucosa. It has been shown that amphotericin B disrupts the integrity of epithelial monolayers derived from nasal polyp cells, resulting in cell death, reduction in transepithelial resistance, and loss of tight junctions.³⁹ These are possible mechanisms for the clinical effect of amphotericin B that are independent of its antifungal role.

Systemic itraconazole therapy was evaluated retrospectively in 139 patients with AFRS.³⁶ There was an average follow-up of 31.4 months. Rains and Mineck³⁶ believed that a medical regimen that included itraconazole might help avoid reoperation. They advocated the use of itraconazole, short-burst, low-dose oral corticosteroids, and topical corticosteroids, in conjunction with endoscopic surgery, as relatively safe and clinically effective for AFRS. There were no serious adverse effects attributed to itraconazole over the 36,000 doses prescribed.³⁶ Whether the steroid-sparing effect is a major part of this apparent effectiveness of itraconazole in AFRS is unclear. Steroids are known to stabilize membranes, decrease eosinophil recruitment and chemotaxis, and increase eosinophil apoptosis.

In a multicenter, double-blind trial based at Penn, treatment with high-dose (650 mg/d) systemic terbinafine hydrochloride failed to improve the symptoms or radiographic appearance of CRS in comparison with the control group, even when nasal irrigation samples were positive for fungus on culture. One consideration is that the fungi isolated were not a major pathologic factor in this cohort. It is also possible that even at high doses, terbinafine may not have maintained therapeutic levels in the nasal secretions.⁴⁰ The commonly identified fungal species in this study were those that are typically very sensitive to this drug in vitro.

Hepatic failure remains a concern with systemic antifungal use. Congestive heart failure has resulted in death with itraconazole (Sporanox).⁴¹ Web sites exist that promote legal advice for complications related to this drug. Transient visual changes are common with voriconazole (VFEND),⁴² and it may carry a risk of permanent change, but to our knowledge this has not been reported. Should systemic antifungal treatment appear appropriate, pretreatment blood work and possibly vision checks are good safety precautions. Follow-up blood work every 1 to 2 months is indicated, along with patient understanding of the risks, benefits, and alternatives.

CONCLUSIONS

Fungus can cause a variety of different conditions

inside the nose and paranasal sinuses, the severity of which is, in part, related to the competency of the host's immune system. Over the past 2 decades, a fungus-related rhinosinusitis that is characterized by eosinophilic mucin and tissue eosinophilia has been typically considered to be related to IgE-mediated sensitivity to mold. Whether that relationship is critical to the majority of extramucosal fungal diseases has been thrown into question. Evidence suggests that eosinophil chemotaxis can be altered by the presence of certain molds (eg, *Alternaria*) and that they can participate in sustaining some forms of CRS. Additionally, there is some bench experience to support the hypothesis that *A fumigatus* allergy plus sinus obstruction can have at least an additive adverse effect on the intensity of experimentally induced rhinosinusitis. Confounding this direction of thinking is important research analyzing the role of

S aureus superantigen.

Currently, there are more questions than answers concerning the cause of CRS and the role of fungus in CRS (eg, FRER). Most likely, there are multiple pathways involved, including the effects of viruses, bacteria, and fungi. There are many mechanisms by which fungi can exert an effect on sinuses of susceptible individuals. A better understanding of the underlying mechanisms may, in turn, improve our understanding of how best to identify and treat patients with this condition. Antimycotic therapy appears to be beneficial for selected patients with FRER and AFRR, but the effects are not permanent, nor is the therapy without risk. Additional, controlled clinical trials are needed to establish the role and mechanism of action of antifungal agents in the treatment of FRER.

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