

Is topical antifungal therapy effective in the treatment of chronic rhinosinusitis?

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Chronic rhinosinusitis (CRS) has been defined as a disease of the nasal and paranasal sinus mucosa present for greater than 3 months with mucosal changes ranging from inflammatory thickening to gross nasal polyps.^{1,2} CRS is a common clinical condition and presents a vexing clinical problem for the treating physician. In large part, this is because the etiology and pathophysiology of CRS are poorly understood.

What is known is that CRS is associated with eosinophilic inflammation in the tissues.³ The cytokine IL-5 may be an important factor in the generation of this inflammatory response.⁴ In addition, histologic detection of fungi within the mucus occurs in 80% to 100% of surgical specimens from patients with CRS.^{3,5-7}

The investigators at the Mayo Clinic hypothesize that immune responses to the fungi, particularly *Alternaria alternata*, play an important role in the pathogenesis of CRS. This hypothesis is based on the evidence that new culture/histologic techniques confirm the presence of this common and other airborne fungi in the mucus of the nasal cavities and sinuses in nearly every patient with CRS.^{5,6} However, it should be noted that similar techniques demonstrate the presence of these fungi in healthy controls as well. Of particular interest is the immune response to these fungi in patients with CRS. Recent observations suggest that PBMCs from as many as 90% of patients with CRS produced IL-5 and IL-13 when exposed to *Alternaria* extracts *in vitro*, whereas those from normal controls did not.⁸ Interestingly, less than 30% of these patients had specific IgE antibodies to *A alternata*. Increased levels of serum IgG antibodies to *Alternaria* and *Cladosporium* were also increased in the patients with CRS compared with normal individuals, and the presence of IgG-specific antibodies correlated with the increased cellular IL-5 production.⁸

On the basis of these observations, Ponikau et al⁹ have suggested that intranasal treatment with an antifungal agent (amphotericin B) is an appropriate treatment for patients with CRS. In 2 uncontrolled trials, such therapy was reported as successful.^{9,10} However, when subjected to a randomized, double-blind, placebo-controlled trial that involved 60 subjects, there was no significant benefit from the amphotericin B nasal spray over the course of an 8-week study. In fact, symptom scores were distinctly worse after amphotericin B treatment.¹¹ Similarly, the study by Ricchetti et al¹⁰ did not demonstrate any improvement in patients who had severe obstructive polyposis treated for less than 8 weeks.

In the current report by Ponikau et al,¹² 24 patients completed a 6-month placebo-controlled, double-blind trial of the use of intranasal amphotericin B 250 µg/mL or placebo twice daily. The primary outcome was the reduction in inflammatory mucosal thickening of the maxillary sinuses on computerized tomography of a standardized coronal cut. Other outcomes measured were endoscopic scores, patient symptom scores, and levels of *Alternaria* protein, IL-5, and eosinophil-derived neurotoxin. Individual patients receiving amphotericin B showed a mean decrease of 8.8% in the mucosal thickening on computerized tomography scanning, whereas the placebo group had an increase of 2.5% ($P = .03$; 11.3% between-group comparison; 95% CI, 1.2-21.4). On the basis of a single observer's evaluation by endoscopic criteria, 70% of the patients receiving amphotericin B showed endoscopic improvement, versus no change in the placebo group ($P = .047$ at 3 months; $P = .38$ at 6 months). *Alternaria* concentration in the mucus was significantly decreased in the amphotericin group (median change, -15.7 µg/mL vs $+6.3$ µg/mL; $P = .046$ in the placebo group). No statistical decrease in IL-5 or peripheral blood eosinophil counts was found in the placebo-treated group. After 6 months, 90% of the amphotericin group (9 of 10) improved their SNOT-20 (Sinus Nasal Outcome Test) scores compared with 64% (9 of 14) of the placebo group, but overall, there was no statistical difference. Two patients in the amphotericin group experienced nasal burning and discontinued the treatment.

The results of this study indicate a small but statistically significant difference between amphotericin-treated subjects and placebo-treated subjects. The overall clinical significance of this improvement, however, is not clear. The number of patients involved in the study was low, and

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therefore, it should be judged as a pilot study. The role of topical amphotericin treatment for chronic rhinosinusitis can be established only when large-scale, multicenter, placebo-controlled, double-blind studies are performed. It should be noted that the benefit of this treatment did not extend to the frontal posterior ethmoid or sphenoid sinuses because delivery of the treatment to these areas is limited.

In addition to the avenues being explored by the Mayo investigators in terms of immune responses to fungi as a potential etiology for chronic rhinosinusitis, other investigators are pursuing interesting concepts such as the upregulation of specific genes that contribute to cellular hyperplasia observed in patients with chronic nasal polyposis. Specifically, the observations by Fritz et al¹³ indicate that nasal polyposis involves deregulated cell growth using genes acting in ways similar to neoplasia.

Much remains to be learned about the etiology and pathogenesis of chronic rhinosinusitis/nasal polyposis. Exciting new approaches to the basic mechanisms and treatment of chronic rhinosinusitis are being used, and further investigation should lead to improvements in treatment for this difficult clinical problem.

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