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# Antifungal therapy for chronic rhinosinusitis: the controversy persists

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## Abstract

**Purpose of review—**Chronic rhinosinusitis is a debilitating disease seen frequently by allergist–immunologists. Recent research examining the pathophysiological mechanisms and treatment options for chronic rhinosinusitis have yielded contradicting results, particularly in regard to the role of fungi and antifungal therapies.

**Recent findings—**Recent studies using antifungal therapies for chronic rhinosinusitis will be critically evaluated with careful attention to sample selection, length of the intervention, drug delivery system, drug stability and handling, assessment of compliance to study medications, and choice of outcome measures with attention to study power (both primary and secondary). Using this framework to evaluate currently available studies reveals limitations in studies showing a benefit for antifungal therapy and in studies showing no benefit (or harm).

**Summary—**Limitations in studies that either support or refute the benefit of antifungal therapy for chronic rhinosinusitis prevent any firm conclusions about its efficacy.

### Keywords

amphotericin B; antifungal; sinusitis

## Introduction

The purpose of this review is to critically evaluate recent studies involving antifungal therapies for chronic rhinosinusitis (CRS). Several different trials have contributed to the accumulating body of literature that examines the efficacy of antifungal treatments for CRS. We will examine each of these trials (focusing on the most recent studies) in an attempt to resolve their differences and draw conclusions about the role of antifungal therapies in CRS.

## Challenges in chronic rhinosinusitis clinical research

Chronic rhinosinusitis affects approximately 35 million patients yearly in the USA and its incidence appears to be rising [1]. Due a paucity of controlled studies examining medical treatments for CRS, there are currently no FDA-approved medical treatments for CRS. Three key factors contribute to the challenges associated with CRS treatment studies: the difficulty in establishing a unified definition for CRS, a limited understanding of the underlying pathophysiology of CRS, and the lack of useful clinical and laboratory markers to assess response to therapy.



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Recently, several organizations have proposed definitions for CRS and have described a specific set of symptoms that must be present for at least 8–12 weeks (symptoms include nasal congestion, facial pain/pressure/fullness, anterior or posterior nasal drainage, and hyposmia/ anosmia) [2,3,4•]. Additional aids for establishing a CRS diagnosis include rhinoscopic findings of polyps, mucopurulent secretions, or edema and radiographic confirmation of mucosal changes or obstruction of the ostiomeatal complexes. Establishing universally accepted definitions of CRS will allow better comparisons among future studies.

The term chronic rhinosinusitis has gained favor over chronic sinusitis given that nasal inflammation nearly always accompanies sinus inflammation [2,3,4•]. However, draft guidance from the FDA on designing clinical development programs of nonantimicrobial drugs to treat sinusitis emphasizes the need to distinguish the effects of study medications on sinusitis and rhinitis [5••]. Therefore, drug treatments must demonstrate clearly that their effect is not limited to improving rhinitis but also clearly has an effect on sinusitis. The lack of robust, sensitive, and specific laboratory and clinical markers to monitor the severity of CRS further hampers efforts to evaluate the efficacy of treatment.

The difficulty in establishing consensus definitions in CRS likely is because of the heterogeneity of the disease and because of the limited understanding of the pathophysiological processes that drive the inflammation of the sinus mucosa. Several different causative factors have been suggested: bacterial infection (including biofilm development and supertoxins), viral infection, fungal allergy (allergic fungal sinusitis), fungal infection (invasive), ubiquitous fungi leading to an inappropriate immune response, humoral immunodeficiency, and allergic and nonallergic rhinitis. For these reasons – difficulty establishing definitions for study enrollment in what appears to be a heterogenous disease, the lack of adequate laboratory and clinical markers to assess treatment outcomes, and a limited understanding of the underlying pathophysiology of the disease – medical providers have meager evidence to support the treatment choices for their patients suffering with CRS.

## Research leads to fungi-immunological response hypothesis

Research into the potential underlying mechanisms driving CRS led to the discovery that eosinophils appear to release their toxic mediators in the presence of fungi [6]. Fungi were ubiquitous in nasal secretions in both patients with CRS and healthy controls [6]. Further research demonstrated an aberrant Th2-like immune response to fungi in peripheral blood mononuclear cells from patients with CRS compared to controls [7]. This research formed the basis for the proposed medical intervention of antifungal therapy: eradication of fungi will lead to an abrogation of the aberrant immune response involving IL-5 production, eosinophil accumulation and activation, and the toxic effects from release of eosinophil mediators such as eosinophil major basic protein.

## Controlled trials of intranasal antifungal agents for chronic rhinosinusitis

A literature search was performed for clinical trials involving antifungal therapies and sinusitis, including the key words for specific antifungal therapies such as amphotericin B and itraconazole. Four randomized controlled trials of intranasal amphotericin B were identified; two were published in the past 18 months and will be the focus of this review. One additional controlled trial of treatment with systemic antifungal (terbinafine) was identified. A search of clinicaltrials.gov for medical trials for CRS revealed eight trials actively recruiting, two active but not yet recruiting, and two completed. Two of these trials pertain to this review: a completed trial of intranasal amphotericin B and a trial currently recruiting that will examine nasal itraconazole levels [8] (see Tables 1 and 2 for summaries of these studies).

## Key components for sinusitis studies

Both the FDA and a group, which included several subspecialty societies (AAAAI, AAOA, AAO-HNS, ACAAI, ARS), have published guidelines for sinusitis research [2,5••]. Several key components mentioned in these articles will be summarized here and will be used to analyze specific CRS antifungal trials. The FDA guidance draft suggests that outcome measurements must combine subjective and objective endpoints. Subjective symptom data should be collected 7–10 days before study initiation to establish a baseline and then at least twice daily during the study period [5••]. The FDA draft suggests using composite scores that include facial pain/ pressure, purulent draining (anterior or posterior), and nasal congestion. The subspecialty society consensus statement emphasizes the need to include quality of life measurements [3]. Imaging (CT or MRI scan) is the preferred objective measurement for CRS medication trials, although endoscopy and microbiological assessment are also options depending on study design and outcomes [5••]. Controlling for potentially confounding treatments is recommended, either by discouraging use of medications that may affect nasal symptoms (such as intranasal corticosteroid, antihistamine, nasal decongestants) or by recording their use during the study period [5••]. Lastly, the FDA draft recommends at least two confirmatory studies to support efficacy claims.

## Analysis of recent randomized controlled trials of antifungals for chronic rhinosinusitis

Two recent controlled trials address the use of antifungals for CRS in slightly different CRS patient populations.

### Randomized trial of antifungal therapy for chronic rhinosinusitis without nasal polyps

The most recent trial evaluated 64 patients with CRS without nasal polyps using a randomized, placebo-controlled, double-blind study design [9•]. This trial was the first to study antifungal treatment in a population that excludes those with nasal polyps. Patients were included if they had 12 weeks of nasal symptoms, rhinoscopy that showed mucosal swelling or purulent discharge, and findings on sinus roentgenogram suggestive of sinusitis. Patients were excluded if nasal polyps were found. Amphotericin was mixed in sterile water and delivered via a pulsatile irrigator; patients were instructed to keep the medication refrigerated. Placebo was a similar yellow-colored solution. The total dose of amphotericin B was 20 mg in 4 ml of solution once daily for 4 weeks. Patients were instructed not to take antibiotics, oral antifungal agents, oral steroids, or oral antihistamines. The study outcomes were the Rhinosinusitis Outcome Measures-31 (CRSOM-31) and rhinoscopy (scored by the Lund system) at 2 and 4 weeks after enrollment. There was no description of how the study was powered in the statistical description section. The CRSOM-31 scores were significantly lower at 2 weeks (but not 4 weeks) for the amphotericin B-treated patients compared with patients assigned the placebo group. There were no significant differences in the endoscopic scores between the two groups. Sixty-six percent of nasal lavage specimens grew fungi before treatment and 55% grew fungi afterward in the treatment group, suggesting that the amphotericin B treatment did not eradicate the fungi in the study.

The strengths of the Liang *et al.* [9•] study are the drug dosage (on the higher end), drug stability (refrigeration plan and re-making of the solution every 2 weeks), the placebo-matching, the attempt to deliver a lower volume of irrigation to separate out the effect of irrigation, and the attempts to control confounding medications. The study limitations are the short length of treatment, the lack of descriptive methods to evaluate compliance to therapy, the possibility of inadequate power to detect a difference between groups and that

fungi were not eradicated in the treatment group. Additionally, given the relationship in previous studies associating eosinophilia, fungi, and nasal polyps, the selected patient sample may be less likely to respond to antifungal therapy. Although this study demonstrates some benefits for antifungal therapy in CRS, its limitations prevent reaching any firm conclusions.

### Randomized trial of antifungal therapy for chronic rhinosinusitis with or without polyps

The next most recent trial evaluated 116 patients with CRS with or without polyps and employed a double-blind, placebo-controlled, multicenter study design [10]. This is the largest trial to date examining the role of intranasal amphotericin for CRS. Patients were included if they were more than 18 years old, had clinical signs and symptoms consistent with CRS, had rhinoscopic signs of CRS and/or nasal polyp, a sinus CT more than five per the Lund-Mackay scoring system, and previously had undergone functional endoscopic sinus surgery. Patients with allergic fungal sinusitis were excluded, although the definition used for exclusion was not stated. Intranasal steroids were allowed, antibiotics were allowed for exacerbation, and systemic corticosteroids were allowed for diseases other than sinusitis. Total dose of amphotericin was 10 mg/day, delivered twice daily in 25 ml (sterile water containing 2.5% glucose) using the Emcur nasal douching device; solutions were freshly made every month for 3 months. Placebo solutions were prepared with an appearance similar to the active drug. Outcome measures were change in symptoms (with visual analog scale) and mucosal disease as assessed by rhinoscopy. Standardized questionnaires including RSOM-31 and SF-36 were administered. The sample size calculation was based on a 25% expected improvement compared with placebo; 83% of the patients completed the trial. There were no differences between the treatment and placebo groups for their tested outcomes. Less than 20% of patients used antibiotics or systemic corticosteroids during the study, and these were equally dispersed between the study groups.

The strengths of the Ebbens *et al.* [10] study include the sample size, the incorporation of a visual analog scale of key symptoms, the inclusion of quality of life questionnaires, the delivery system and stability of the study medication, and the attempts to control confounding medication use. The limitations of the study are the lack of information about either drug delivery to the disease site or fungal cultures to indicate eradication or reduction, exclusion of patients with allergic fungal sinusitis using an unknown definition (potentially a sampling error leading to exclusion of patients with nasal polyps and eosinophilia most likely to respond to antifungal therapy), the lack of descriptive methods to evaluate compliance to therapy, the 3-month study period, which may not be long enough to detect a difference, and not including imaging as an objective measurement. Thus, a well designed study that used several important endpoints did not demonstrate benefit for antifungal therapy. In addition, it was unclear if fungal load was reduced or eradicated; this prevents drawing a firm conclusion about the hypothesis that elimination of fungi will reduce the purported aberrant Th2-like response and resultant disease.

## Summary of previous controlled trials of antifungals for chronic rhinosinusitis

There are three controlled trials that were reported prior to our review period that are important when considering the role of antifungal therapy in CRS.

### Pilot study of antifungal therapy in chronic rhinosinusitis

The randomized, placebo-controlled, double-blind pilot trial of 24 patients compared intranasal amphotericin B rinse with similarly colored placebo solution for 6 months [11]. Inclusion criteria were based on symptoms, CT scan, and rhinoscopy findings. A total of 20

mg/day (20 ml twice daily) of amphotericin B was instilled in the treatment group. Patients were specifically instructed to point the tip of the bulb syringe to the middle meatus region while bending their heads laterally. The primary outcome measurement was the percentage of inflammatory mucosal thickening, as assessed by CT scan, and the secondary endpoints were a rhinoscopy grading system and symptom scores using the Sinus Nasal Outcome Study 20 (SNOT-20). Additionally, IL-5, eosinophil-derived neurotoxin (EDN), and *Alternaria* levels were measured in the nasal mucosa. The treatment group had a reduction in CT scan mucosal thickening and improvement in endoscopic scoring compared to the placebo group. Symptom scores (per the SNOT-20) were not significantly different between treatment and placebo groups. Additionally, EDN levels, but not IL-5 levels, were reduced in the treatment group. *Alternaria* levels were not different between treatment and placebo groups. The strengths of this pilot study are that the intranasal amphotericin B rinses improved CT scan scores (considered an important objective endpoint), reduced EDN levels, and that the dosage and delivery of the study medication were substantial. The limitations include the lack of improvement in patient symptoms, the lack of descriptive methods to evaluate compliance to therapy, and the inability to demonstrate a decreased load of *Alternaria* after treatment.

### High-dose oral antifungal therapy for chronic rhinosinusitis

The first double-blind, placebo-controlled study on systemic antifungal therapy for CRS was reported in 2005 in 53 adult patients [12]. This 6-week study compared terbinafine with placebo and included patients with symptoms and CT scan evidence of CRS. The primary outcome was change in CT opacification score. Secondary outcome measures were physician's overall assessment and total score for Rhinosinusitis Disability Index (RSDI). Additionally, fungal cultures were collected in all patients and terbinafine concentrations were evaluated in a limited number of nasal mucosal samples obtained at the conclusion of the study. The sample size of the study was not based on an expected statistical outcome. There were no differences between study groups in total opacification score, eradication of fungi, RSDI, or in physician's overall assessment. The limited sample size that examined the presence of terbinafine in the nasal mucosa makes these results inconclusive. Strengths of the study were the use of an imaging endpoint (CT scan) and the novel concept of using an oral antifungal agent. Shortcomings of the study included the short study period, the lack of descriptive methods to evaluate compliance to therapy, finding that the fungi load was not different between treatment and placebo group, and the risk for type II error given the sample size was not based on a power calculation. This pilot study suggests that oral terbinafine may not be effective for patients with CRS, although its limitations prevent any firm conclusions.

### Randomized trial of antifungal therapy for chronic rhinosinusitis with nasal polyps

The first randomized controlled trial of antifungal agents for CRS studied 78 patients for 8 weeks and used a nasal spray delivery system that resulted in a total dose of 4.8 mg/day (eight sprays per day of 100 μl each with an amphotericin concentration of 3 mg/ml) [13]. The nasal spray device was used to avoid the possible confounding effects of nasal lavages, which alone might be therapeutic. Patients were included on the basis of symptom scores, rhinoscopy, and CT scan score. Those with a 'clinical suspicion' of allergic fungal sinusitis were excluded. Study medication was refrigerated and refreshed every 2 weeks. Compliance to the study medications was assessed by regular questioning and also collection of spray containers every 2 weeks. Change in grade of CT scan, using the Lund-Mackay system, was the primary outcome measurement. The study was powered to find a 50% reduction in the pretreatment CT scan score. Quality of life and rhinoscopy scores were secondary outcome measures. Fungal culture and PCR were performed. There were no differences between treatment and control groups in CT scan scores or quality of life scores. Symptom scores

were significantly worse in the treatment group. Evaluation of patients in four subgroups (fungal elements before and after treatment, fungal elements before treatment only, fungal elements after treatment only, fungal elements not detected before or after treatment) were analyzed for response to amphotericin B. These four groups were not different in terms of CT scan scores, quality of life scores, or rhinoscopy scores. Strengths of this study were its use of several outcome measures including imaging and quality of life and its attempt to monitor adherence to the study medication. Limitations include the use of a spray delivery system, exclusion of patients with allergic fungal sinusitis using an unclear definition, short study length, the lack of fungal load elimination in most patients, and the small sample size of patients ($n$ = 11) that had fungal eradication that were analyzed.

## Future directions

Advances in the understanding of the pathophysiology of CRS will lead to improved definitions of CRS, robust clinical and laboratory markers to judge severity and responsiveness to treatment, and ultimately to more effective treatment options for patients. Heterogeneity (in severity, triggers, immune cells involved, etc.) among CRS patients provides both challenges and opportunities. Perhaps similar to patients suffering from asthma who have different clinical phenotypes (eosinophilic, neutrophilic, atopic, etc.), patients with CRS will likely respond differently to therapies depending on the underlying disease mechanism. At present, results from a complete multicenter trial will likely contribute substantially to our understanding of how antifungal therapy fits into CRS treatment.

## Conclusion

Five controlled trials have addressed the role of antifungals in CRS therapy, each contributing important data to our overall understanding of the potential benefits and limitations of antifungal therapy. Two randomized controlled trials have demonstrated a benefit of topical antifungal therapies, whereas two have not. The FDA draft guide suggests at least two confirmatory studies to support efficacy claims. The reviewed studies that support efficacy claims [7,9•] both have significant flaws (one demonstrated imaging improvement but not symptom improvement, whereas the other demonstrated symptom improvement at one time point but did not use sensitive imaging techniques). Therefore, the controversy over antifungal therapy for CRS persists, at least until the results from the recently completed multicenter trial are analyzed and published.

## Acknowledgments

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## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 84).

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**Table 1**

Antifungal therapy for chronic rhinosinusitis: summary of randomized trial design

| Study | Selection criteria | Length of study | Dose | Placebo matching | Drug delivery system | Drug stability | Compliance assessment | Outcomes |
|---|---|---|---|---|---|---|---|---|
| Liang *et al.* [9•] | Symptoms, rhinoscopy, X-ray | 4 weeks | 20 mg/day in 4 ml | Yes | Pulsatile irrigator | Refrigerated | None stated | Primary: symptoms, rhinoscopy |
| Ebbens *et al.* [10] | Rhinoscopy, CT scan, previous FESS | 12 weeks | 10 mg/day in 25 ml | Yes | Emcur nasal douching device | Refrigerated and remade every month | None stated | Primary: symptoms, rhinoscopy |
| Ponikau *et al.* [11] | Symptoms, rhinoscopy, CT scan | 24 weeks | 20 mg/day in 40 ml | Yes | Bulb syringe | Refrigerated and remade every 2 weeks | None stated | Primary: CT scan Secondary: symptoms, rhinoscopy |
| Kennedy *et al.* [12] | Symptoms, CT scan | 6 weeks | 625 mg/day | Yes | Oral tablet | Not applicable | None stated | Primary: CT scan Secondary: symptoms |
| Weschta *et al.* [13] | Symptoms, rhinoscopy, CT scan | 8 weeks | 4.8 mg/day | Yes | Nasal spray | Refrigerated and remade every 2 weeks | Collected spray bottles, patient questionnaire | Primary: CT scan Secondary: symptoms, rhinoscopy |

**Table 2**

Antifungal therapy for chronic rhinosinusitis: summary of randomized trial results

| Study | Sample size | Symptoms | Imaging | Rhinoscopy | Fungi assessment |
|---|---|---|---|---|---|
| Liang *et al*. [9•] | 64 | Treatment group improved at 2 weeks but no difference at 4 weeks | Not assessed | No difference between treatment and placebo | 66% fungal growth before treatment, 55% fungal growth after treatment |
| Ebbens *et al.* [10] | 116 | No difference between treatment and placebo | Not assessed | No difference between treatment and placebo | Not assessed |
| Ponikau *et al*. [11] | 24 | No difference between treatment and placebo | Treatment group improved significantly relative to placebo | Treatment group improved significantly relative to placebo | No difference in *Alternaria* growth between treatment and placebo |
| Kennedy *et al*. [12] | 53 | No difference between treatment and placebo | No difference between treatment and placebo | Not assessed | No difference in fungal growth between treatment and placebo |
| Weschta *et al.* [13] | 78 | Treatment group with worse symptoms that placebo | No difference between treatment and placebo | No difference between treatment and placebo | Only 11 patients with fungal eradication |