Antifungal therapy in the treatment of chronic rhinosinusitis: A meta-analysis

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ABSTRACT

Background: *Chronic rhinosinusitis (CRS) is an inflammatory disorder of the nose and sinuses. Because fungi were postulated as a potential cause of CRS in the late 1990s, contrasting articles have advocated and refuted the use of antifungal agents in its management. Although good research shows an interaction of the immune system with fungus in CRS, e.g., allergic fungal sinusitis (AFS), this does not imply that fungi are the cause of CRS or that antifungals will be effective in management. This study was designed to assess the potential advantage of either topical or systemic antifungal therapy in the symptomatic treatment of CRS to aid physicians in making informed decisions about treating patients with CRS.*

Methods: *A systematic review of the literature was performed with meta-analysis. All studies obtained from searches were reviewed and trials meeting the eligibility criteria were selected. CRS was defined using either the European Position Paper on Rhinosinusitis and Nasal Polyps or American Academy of Otolaryngology–Head and Neck Surgery criteria. Authors were contacted and original data were used for data analysis.*

Results: *Five studies investigating topical antifungals and one investigating systemic antifungals met the inclusion criteria. All trials were double blinded and randomized. Pooled meta-analysis showed no statistically significant benefit of topical or systemic antifungals over placebo. Symptoms scores statistically favored the placebo group for this outcome. Adverse event reporting was higher in the antifungal group.*

Conclusion: *Reported side-effects of antifungal therapies may outweigh any potential benefits of treatment based on this meta-analysis and the authors therefore do not advocate the use antifungal treatment in the management of CRS.*

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Chronic rhinosinusitis (CRS) is an inflammatory disorder of the nose and sinuses, which is clinically defined as persistence of symptoms of nasal blockage, obstruction, congestion, or discharge for at least 12 weeks, combined with endoscopic abnormalities (polyps, mucopurulent discharge, and/or mucosal swelling) or an abnormal sinus computed tomography scan. Other symptoms may include facial pain or reduced sense of smell.[1] Allergic fungal sinusitis (AFS) is a well-recognized subgroup of CRS, in which a strong IgE-mediated hypersensitivity to fungal elements exacerbates and may be the dominant inflammatory process. In the past, fungi were thought to be important only in AFS, which was considered to be a less common distinct subset of CRS.[2]

It has now been proposed that fungal-related sinus disease is extremely common and accounts for the majority of CRS.[3] Ponikau *et al.* from the Mayo Clinic documented fungus as a potential cause of CRS and advocated the use of topical antifungals.[3] However, fungal colonization of the nose and paranasal sinuses have been found in both normal patients and in those with CRS.[4] Since then, there has been increasing controversy, and contrasting articles have both advocated and refuted the use of both topical and systemic antifungal agents in the management of these patients.[5]

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Although good research indicates an interaction of the immune system with fungus in CRS,[6] this does not necessarily imply that antifungals will be effective in managing the disease. Inappropriate immune activation may be the driving pathological mechanism and fungal elements only the innocent target of the process, and it is well known that fungi are ubiquitous in both our environment and sinuses.[4]

CRS has a significant impact on the quality of life and health burden within the adult population.[7] The impact of the disease on quality of life, as measured by short form 36 scores, is comparable with or worse than that of other chronic conditions such as chronic obstructive pulmonary disease, congestive heart failure, and back pain.[8] Systemic antifungals have significant side effects, particularly with regard to the hepatic and renal toxicity. Topical amphotericin is expensive and also associated with potential adverse events.[9] With the potential for fungus to be a common mediator of CRS, and a patient population of >60 million in the United States and European Union, it is essential that the need for and reported benefit and adverse effects of antifungals are well documented before broadly applying this form of therapy.[10]

METHODS

Criteria for Considering Studies for This Review

Types of Studies. Randomized placebo-controlled trials (RCTs), which fulfilled the criteria described previously, were included.

Types of Participants. Both adults and children with CRS as defined by either the European Position Paper on Rhinosinusitis and Nasal Polyps criteria[1,11] or by the American Academy of Otolaryngology–Head and Neck Surgery[10,12] were included. Fungus can be shown in almost all diseased and normal sinuses[4]; thus, associated fungus confirmed either histologically or on culture was not used as an inclusion criteria. The immunologic role of the fungus and the host is still an area of ongoing research. Patients with classic AFS satisfying the Bent-Kuhn criteria[13] for the diagnosis of AFS was used for subset analysis.

Types of Interventions. Studies involving both systemic and topical antifungal therapies were considered. Systemic antifungals can be given orally or i.v. Topical therapy may be administered by douching,

nebulization, atomization, inhalations, irrigation, spray, drops, or powder insufflations.

Types of Outcome Measures

Primary Outcomes

- Symptom improvement as defined by
  - Collated symptom scores (visual analog scales or Likert severity categories)
  - Validated disease-specific quality-of-life questionnaires, such as the 31-item Rhinosinusitis Outcome Measure, 20-Item Sino-Nasal Outcome Test,[14] Rhinosinusitis Disability Index, or Chronic Sinusitis Survey

Secondary Outcomes

- Adverse events associated with treatment
- Surrogate outcoes
  - Endoscopic scores
  - Radiographic scores (*i.e.*, Lund-Mackay)

Data Collection and Analysis

Electronic systematic searches for RCTs were conducted with no language, publication year, or publication status restrictions. A search strategy was used with a combination of medical subject headings terms and key words in collaboration with the Cochrane Ear, Nose, and Throat Disorders Group. The Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; mRCT; and additional sources were searched for published and unpublished trials.

The reference lists of identified publications for additional trials were scanned and where necessary, authors were contacted. One review author (PS) reviewed and selected trials and evaluated them against the inclusion criteria. In cases where PS was unsure as to whether the trial was relevant, a second review author (RJH) was consulted.

A structured data collection form was used. The review authors (PS and RJH) conducted the data extraction and assessed the quality of the method used in each included trial. If necessary, authors of studies were contacted for clarification.

We considered

- Number of participants
- Age of participants
- Characteristics of trial such, *e.g.*, duration of trial
- Method of randomization
- Method of blinding
- Whether an intention-to-treat analysis was conducted
- Exclusion criteria
- Diagnostic criteria
- Duration of treatment
- Outcomes
- Duration of illness
- Severity of illness
- Adverse effects
- Other medicines being used

Assessment of risk of bias was conducted in accordance with the Cochrane Collaboration tool for assessing risk of bias.[15] This tool deals with sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. In trials lacking details of randomization and other characteristics, authors of the studies were contacted to obtain further information.

Standardized mean differences (SMDs) were obtained from the reported results to compare trials using different scales as outcome scales. Raw data were extracted from graphs and tables. For SD results for the mean changes that were not available from the articles, authors were contacted to provide original data. Where this was not possible, SDs were imputed from studies using similar scales and methods. Dichotomous data were collected for adverse events.

Assessment of Heterogeneity

Clinical Heterogeneity. All included studies were considered and where issues appeared that might have added to clinical heterogeneity, these were noted and considered in the analysis.

Statistical. Forest plots were visually inspected to investigate statistical heterogeneity. Heterogeneity between studies was investigated using the I^2 statistic,[15] which provides an estimate of the percentage of variation observed in results that is unlikely to be caused by chance. A value of ≥50% was taken to indicate heterogeneity.

RESULTS

Description of Studies

Results of the Search. A total of 374 references (324 from the search conducted in December 2009 and 50 from the search conducted in June 2010) from the searches were received: 269 of these were removed in first-level screening (*i.e.*, removal of duplicates and clearly irrelevant references), leaving 105 references for further consideration. A flowchart of study selection is provided in Fig. 1. There were six studies that met the inclusion criteria. Characteristics of the included studies can be found in Table 1.

Excluded Studies. Of the majority of the 374 abstracts retrieved from the searches 302 were not in the scope of our review. Seventy-two trials were identified. Forty-seven of these trials did not focus on the use of topical or systemic antifungal therapy in the treatment of CRS or AFS. We consulted the full-text articles of 25 trials. Four[4] were repeat data.[9,16–18] Seven[7] trials were not randomized or controlled.[19–25] One[1] study was discontinued and the unpublished data were not made available by the authors.[26] One[1] trial did not have a relevant intervention, rather considering combination therapy.[27] One[1] trial did not have relevant participants, focusing on patients with acute rhinosinusitis.[28] Two[2] trials did not have relevant outcomes.[29,30] These trials considered levels of proinflammatory cytokines, chemokines, and growth factors. Three[3] studies did not have information available beyond that which was in the abstract; full-text manuscripts were not made available by the authors.[31–33]

Risk of Bias in Included Studies

Risk of bias was assessed using the Cochrane Collaboration Tool for Assessing Risk of Bias.[15] In cases where information regarding methods was not provided, we consulted the authors for further information. The Jadad Composite scale[34] was also used. In this system, 1 point was allocated if the study was described as being randomized with an additional point awarded if the method of randomization was described. One point was allocated if the study was described as blinded to patients and assessors with an additional point given if the method of double-blinding was described. The final point was allocated to follow-up regarding patient withdrawal. Studies with 2 points or less are considered to be low-quality studies, whereas studies with at least 3 points are considered to be of high quality. Four trials (66.7%) had a total score of 5.[35–38] One (16.7%) trial had a total score of 4[39] and one (16.7%) trial had a total score of 3.[40]

Four trials (66.7%) had both adequate sequence generation and allocation concealment as ascertained from the articles or by correspondence.[35–38] One trial (16.7%) had adequate sequence generation but no information was given regarding the method of allocation concealment and we received no reply from the author.[39] One trial (16.7%) gave no information regarding sequence generation or allocation concealment.[40] All trials were reported to be doubled blinded. Four trials (66.7%) explicitly stated the method of blinding either in the article or by correspondence.[35–38] All trials addressed dropout and loss to follow-up population. All trials were free of selective reporting. All but one trial[39] provided an allocation table or otherwise stated

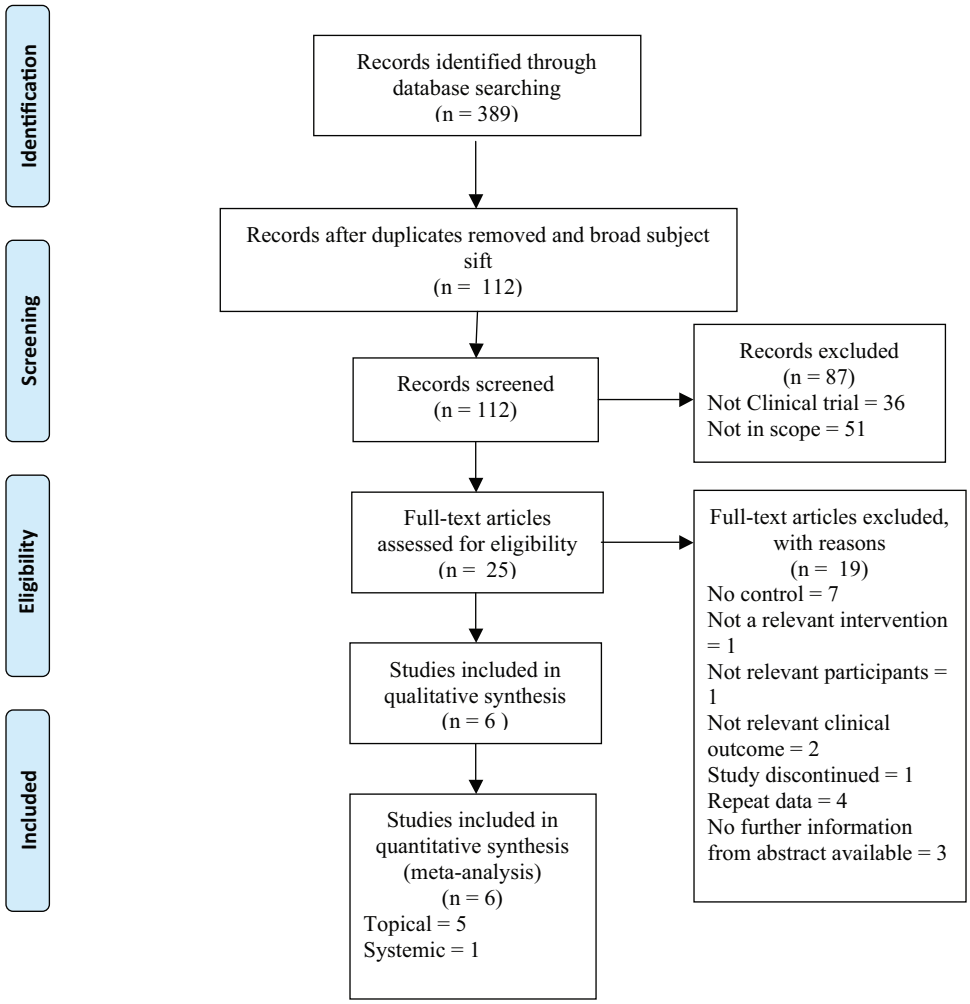

Figure 1. *Flowchart illustrating study selection process.*

that the two groups were similar at baseline. It was noted that the Mayo Clinic is a collaborative partner with Accentia Biopharmeuticals, a company that holds the worldwide, exclusive commercial rights to SinuNase (topical amphotericin B, Accentia Biopharmaceuticals, Tampa, FL),[26] and that Ponikau holds a patent for this product.[41]

Effects of Interventions

We considered topical and systemic antifungal therapies separately for meta-analysis. There was a considerable range of tools used for outcome assessment, with few trials using the same questionnaires or scales. SMDs were assessed for the different outcome measures.

Summary

Topical Antifungal Therapy versus Placebo

Symptom Scores. Symptom scores were collected from three trials for meta-analysis.[35,36,40] There were a total of 101 patients allocated to the topical amphotericin B group and 105 allocated to the placebo group. Liang *et al.* and Ponikau *et al.* did not consider symptom scores in their outcomes.

Pooled results favored the control (SMD = 0.35 [0.07, 0.62]; p =0 .01). The I^2 statistic was 45%, which represents acceptable homogeneity (χ^2 = 3.64; df = 2; p = 0.16). A forest plot illustrating this outcome is provided in Fig. 2.

Disease-Specific Quality-of-Life Scores. Five trials were pooled for meta-analysis regarding the outcome of disease-specific quality-of-life scores,[35–38,40] with a total of 143 and 151 patients for the antifungal group and the placebo group, respectively.

Pooled results showed no statistically significant benefit for topical amphotericin B over placebo (SMD = 0.18 [−0.05, 0.42]; p = 0.12). The I^2 statistic was 10%, with good homogeneity (χ^2 = 4.46; df = 4; p = 0.35). A forest plot illustrating this outcome is provided in Fig. 3.

Nasal Endoscopy Scores. For nasal endoscopy scores, data from four trials were pooled for meta-analysis,[35–38] with 101 patients allocated to topical antifungals and 103 patients allocated to placebo. Weschta *et al.* did not consider endoscopy scores in their outcomes.

Pooled results did not show any statistically significant benefit over placebo (SMD = −0.00 [−0.26, 0.26]; p = 0.98). The I^2 statistic was 62%, representing substantial heterogeneity (χ^2 = 7.93; df = 3; p = 0.05}. A forest plot illustrating this outcome is provided in Fig. 4.

Radiographic Scores. Three trials were pooled for meta-analysis for radiographic scores,[36,38,40] with Ebbens *et al.* and Gerlinger *et al.* not considering radiographic scores as an outcome in their respective trials. A total of 52 patients were allocated to the intervention group and 62 patients were allocated to placebo.

Pooled data did not show any statistically significant results (SMD = 0.02 [−0.36, 0.41]; p = 0.90}. The I^2 statistic was 88%, representing considerable heterogeneity (χ^2 = 17.03; df = 2; p = 0.0002). A forest plot illustrating this outcome is provided in Fig. 5.

Systemic Antifungal Therapy versus Placebo. Only one trial was identified with available data that investigated the efficacy of a systemic antifungal therapy versus a placebo.[39] This trial reported radiographic scores and

Table 1 **Characteristics of included studies**

	Methods	Participants	Interventions	Outcomes	Jadad Score
Ebbens 2006[35]	RCT over 13 wk	116 adult patients with CRS	Topical amphotericin B (100 μg/mL) nasal lavage (25 mL twice daily); total daily dose = 10 mg	Total VAS, RSOM-31, and nasal endoscopy score	5
Gerlinger 2009[36]	RCT over 52 wk	33 adult patients with CRS with nasal polyps	Topical amphotericin B (5 mg/mL) nasal spray (100 μL twice daily) Total daily dose = 4 mg	SNAQ-11, Quality-of-Life Questionnaire, CT score (modified Lund-Mackay), and endoscopy score	5
Kennedy 2005[39]	RCT over 6 wk	53 adult patients with CRS	625 mg of oral terbinafine	CT score, changes from baseline in patient/physician Evaluation and RSDI scores	4
Liang 2008[37]	RCT over 4 wk	70 adults and children with CRS without nasal polyps	Topical amphotericin B (5 mg/mL) nasal irrigation (60 mL); total daily dose = 20 mg	CRSOM-31 and endoscopy score	5
Ponikau 2005[38]	RCT over 24 wk	30 adult patients with CRS	Topical amphotericin B (250 μg/mL) bulb syringe (20 mL twice daily); total daily dose = 20 mg	SNOT-20, CT score, endoscopy score, inflammatory mediators, *Alternaria* protein, and blood eosinophilia	5
Weschta 2004[40]	RCT over 8 wk	78 adult patients with CRS with nasal polyps	Topical amphotericin B (3 mg/mL) nasal spray (200 μL four times daily); total daily dose = 4.8 mg	VAS, rhinosinusitis Quality-of-life score, CT score, and endoscopy score	3

RCT = randomized controlled trial; CRS = chronic rhinosinusitis; VAS = visual analog scale; RSOM-31 = 31-item rhinosinusitis outcome measure; CT = computed tomography; SNAQ-11 = Sino-Nasal Assessment Questionnaire; RDSI = rhinosinusitis disability index; CRSOM-31 = Chinese Rhinosinusitis Outcome Measure; SNOT-20 = Sino-Nasal Outcome Test.

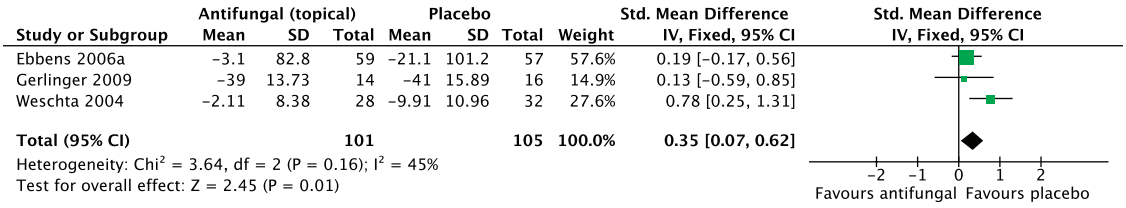

Figure 2. *Forest plot illustrating standardized mean differences for symptom scores.*

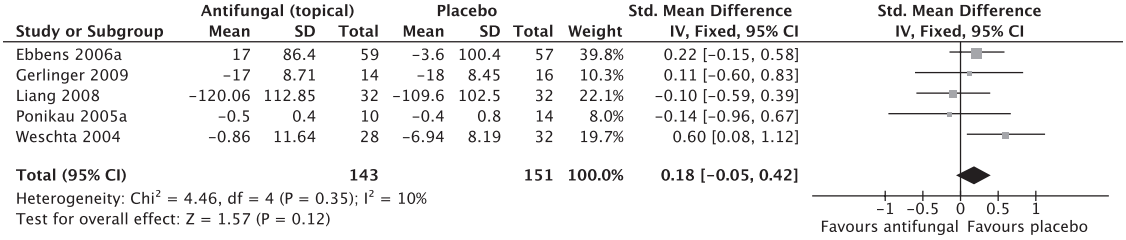

Figure 3. *Forest plot illustrating standardized mean differences for disease-specific quality-of-life scores.*

symptom scores as outcomes. There were a total of 23 patients allocated to the antifungal group and 26 patients allocated to the placebo group.

For symptom scores, there was no significant benefit of terbinafine over placebo (SMD = −0.07 [−0.64, 0.51]; $p = 0.82$). Similarly, for radiographic, there was no significant benefit of terbinafine over placebo (SMD = −0.14 [−19.22, 18.94]; $p = 0.99$).

Adverse Events. Adverse events are described in Tables 2 and 3. A meta-analysis of adverse events was performed and found no statistically significant difference between the amphotericin and placebo groups (risk ratio, 3.36; 95% CI, 0.86–13.0; $p = 0.08$). Adverse events were reported inconsistently throughout the various trials. Weschta *et al.*[40] reported a significant difference between placebo and antifungal groups with the antifungal group reporting more adverse events. The main side effect reported in trials investigating topical antifungals was local irritation, which was not deemed by the authors to be a serious adverse event.

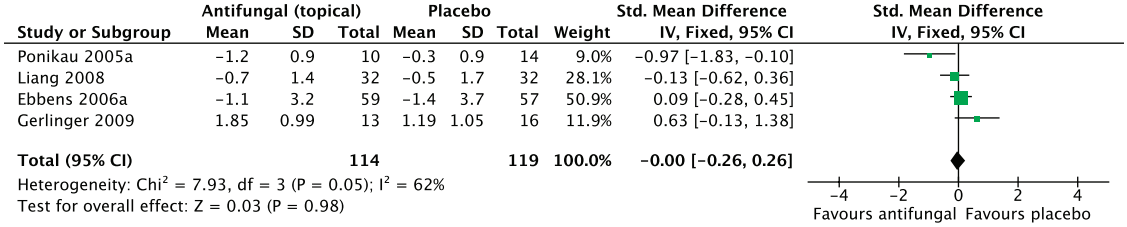

Figure 4. *Forest plot illustrating standardized mean differences for nasal endoscopy scores.*

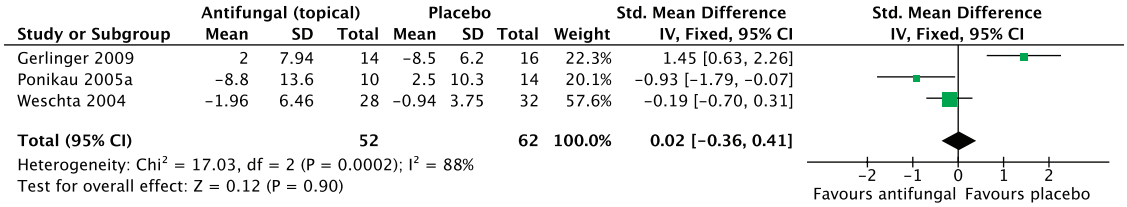

Figure 5. *Forest plot illustrating standardized mean differences for computed tomography scores.*

Table 2 **Adverse events with topical therapy**

	Report	Antifungal Group *n* (%)	Placebo Group *n* (%)	Complaints in Total Population	Comments
Ebbens 2006[35]	Yes	39 (66)	35 (61)	Multiple symptoms including rhinological (*e.g.* facial pain, increased congestion and/or rhinorrhea), respiratory (*e.g.* asthma, bronchitis, and cough), and systemic symptoms (*e.g.* skin rash, cystitis, and muscle ache)	Quote: The proportion of patients experiencing a serious adverse event, as judged by the investigators, was higher in the amphotericin B group than in the placebo group: 5 (9%) of 59 vs 0 (0%) of 57, respectively; there was only one serious adverse event reported as drug-related (asthma attack)
Gerlinger 2009[36]	Yes	6 (37.5)	1 (5.9)	Short-term nasal burning, dryness of the nasal mucous, bleeding	The therapy did not have to be interrupted because of side-effects in any of the cases
Liang 2008[37]	Yes	1 (2.9)	0 (0)	Skin itching	Information regarding adverse effects was only provided for patients that discontinued the study
Ponikau 2005[38]	Yes	2 (13.3)	0 (0)	Nasal burning	The two patients that had adverse effects discontinued the study
Weschta 2004[40]	Yes	7 (25)	1 (0.03)	Acute exacerbation of CRS	Information regarding adverse effects was only provided for patients that discontinued the study Quote: "The patients in the AMB group reported nasal burning ($p < 0.005$) ans nasal blockage ($p < 0.05$) more frequently than the patients in the control group; serious adverse effects were not observed."
Summary		55 (38.5)	37 (24.5)		

AMB = amphotericin B; CRS = chronic rhinosinusitis.

DISCUSSION

Proponents of antifungals for the treatment of CRS and AFS argue that in CRS, fungi in sinonasal mucosa cause the activation of sensitized patients' immune systems, thereby driving the eosinophilic inflammation. Consequently, eliminating fungus in the sinus and nasal cavity through the use of antifungals would potentially reduce this inflammatory response.[3]

There is no evidence of any benefit of topical antifungals from the included studies. Topical antifungal therapy reported beneficial effects in only one of five trials[38] for radiographic and endoscopic scores, but not for symptoms. There was substantial heterogeneity in these two outcomes, possibly because of differences in patient populations and disease factors. The control groups were favored in one of five trials[40,42–44] for symptom scores and disease-specific quality-of-life scores. The pooled results showed significant symptom improvement in the placebo group across those studies reporting this outcome.

The five studies differed in methodology. Delivery volume and surgical state are established factors influencing the effectiveness to topical delivery to the sinuses.[42–44] Three trials used nasal irrigation[35,37,38] and two trials used nasal sprays[36,40] to administer the antifungal or placebo. Patients who had endoscopic sinus surgery

Table 3 **Adverse events with systemic therapy**

	Report	Antifungal Group *n* (%)	Placebo Group *n* (%)	Complaints in total Population	Comments
Kennedy 2005[39]	Yes	9 (36.0)	16 (57.1)	Multiple symptoms including infections, nervous system, respiratory, and ophthalmic disorders	Quote: One ADR in placebo (chest pain) and one ADR in terbinafine (pregnancy) were classified as serious ADRs, but again, neither was suspected to be related to study medication; no clinically significant difference between treatment groups was observed in liver function tests at wks 3 or 6

ADR = adverse drug reaction.

(ESS) were reported heterogeneously. Some trials required patients to have had previous ESS before administration of the antifungal or placebo[35,36] and other trials had some patients who had not had previous ESSs.[38,40] In one trial, previous ESS was part of the exclusion criteria and therefore no patients had previous ESSs.[37] Although traditional concepts of ESS is aimed at relieving obstruction and improving ventilation, ESS has been shown to allow effective delivery of topical therapies to the mucosa of the sinuses compared with the preoperative state.[42,43]

The concentrations of the antifungal differed among studies. This may influence the proposed action because fungal growth may not be impeded at a concentration of 100 μg/mL *in vitro* compared with convincing inhibition at 200 and 300 μg/mL.[45] Two trials used amphotericin B at concentrations of 100 μg/mL.[35,36] There is currently some controversy surrounding both the optimum dosage and the preparation of the antifungal treatment, which may influence the ultimate outcome of treatment.

Systemic antifungal therapy reported no benefits over placebo for symptom scores or radiographic scores. Because there was only one trial that fit our inclusion criteria for systemic antifungals, there is no heterogeneity of approach.

Although it is well known that fungi are both ubiquitous in the sinuses and the environment and can therefore be found in normal sinuses, there are certain phenotypes of the disease process that may more readily yield positive culture or behave differently with regard to antifungal therapy. These situations might, in fact, represent a process where the fungi are causative and these specific situations may call for antifungal therapy to be used.

Although there was incomplete reporting of data in the published literature of the included studies, authors of four of the five topical antifungal RCTs provided original data to allow a meta-analysis.[35,37,38,40] Some imputation and transformation was performed but original data provided limited this to only one study.[36]

The results of this meta-analysis confirms the conclusion from a previous nonsystematic review conducted by Lim *et al.*,[46] which states that "no definite conclusions could be made regarding the use of antifungals." Lim *et al.* found 14 studies that fulfilled their inclusion criteria; however, only 7 studies were controlled trials and only 5 were double-blind randomized trials. Two of their RCTs were excluded in this review because they did not deal with antifungals as an intervention.[47,48] Three more trials were included in this review.[36,37,39] No meta-analysis was performed in the study by Lim *et al.*[46] Rather, it was purely qualitative.

CONCLUSION

Based on this meta-analysis, the authors do not advocate the use of either topical or systemic antifungal treatment in the routine management of CRS. Although there appears to be considerable evidence against the use of topical and systemic antifungals in the treatment of CRS, clinical diversity in the surgical state of patients, delivery volume, and concentrations of antifungals in included studies may bring about heterogeneity of treatment effect and are factors that should be considered for any topical therapy trial in CRS. It is therefore advised that antifungal therapy should only be considered in specific instances or situations where clinical features may suggest a possible benefit from treatment.

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