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 fungi 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. 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.

It has now been proposed that fungal-related sinus disease is extremely common and accounts for the majority of CRS. Fonikau et al. from the Mayo Clinic documented fungi as a potential cause of CRS and advocated the use of topical antifungals. However, fungal colonization of the nose and paranasal sinuses have been found in both normal patients and in those with CRS. 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.

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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,13 Rhinosinusitis Disability Index, or Chronic Sinusitis Survey

Secondary Outcomes
- Adverse events associated with treatment
- Surrogate outcomes
- 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 I² 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. Four4 were repeat data.9,16-18 Seven7 trials were not randomized or controlled.19-25 One1 study was discontinued and the unpublished data were not made available by the authors.26 One1 trial did not have a relevant intervention, rather considering combination therapy.27 One1 trial did not have relevant participants, focusing on patients with acute rhinosinusitis.28 Two2 trials did not have relevant outcomes.29 30 These trials considered levels of proinflammatory cytokines, chemokines, and growth factors. Three3 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 scale15 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 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.29 One trial (16.7%) gave no information regarding sequence generation or allocation concealment.40 All trials were reported to be double 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 trial39 provided an allocation table or otherwise stated
that the two groups were similar at baseline. It was noted that the Mayo Clinic is a collaborative partner with Accentia Biopharmaceuticals, a company that holds the worldwide, exclusive commercial rights to SinuNase (topical amphotericin B, Accentia Biopharmaceuticals, Tampa, FL), and that Ponikau holds a patent for this product.

**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. 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 I² statistic was 45%, which represents acceptable homogeneity (χ² = 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 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 I² statistic was 10%, with good homogeneity (χ² = 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, with a total of 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 I² statistic was 62%, representing substantial heterogeneity (χ² = 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 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 I² statistic was 88%, representing considerable heterogeneity (χ² = 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. This trial reported radiographic scores and...
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.\(^4\) 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.
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 trials38 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 trials40,42–44 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 irrigation35,37,38 and two trials used nasal sprays36,40 to administer the antifungal or placebo. Patients who had endoscopic sinus surgery...
(ESS) were reported heterogeneously. Some trials required patients to have had previous ESS before administration of the antifungal or placebo and other trials had some patients who had not had previous ESSs. In one trial, previous ESS was part of the exclusion criteria and therefore no patients had previous ESSs. 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.

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. Two trials used amphotericin B at concentrations of 100 µg/mL. 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. Some imputation and transformation was performed but original data provided limited this to only one study.

The results of this meta-analysis confirms the conclusion from a previous non-systematic review conducted by Lim et al., 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. Three more trials were included in this review. No meta-analysis was performed in the study by Lim et al. 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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Table 3: Adverse events with systemic therapy

| Report | Antifungal Group n (%) | Placebo Group n (%) | Complaints in total Population | Comments |
|--------|------------------------|---------------------|-------------------------------|----------|
| Kennedy 2005 | 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.
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