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[Intervention Protocol]

Topical and systemic antifungal therapy for chronic rhinosinusitis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of systemic and topical antifungal agents in people with chronic rhinosinusitis, including those with allergic fungal rhinosinusitis (AFRS) and, if possible, AFRS exclusively.

The review will exclude patients in the immediate post-surgical period (within six weeks of sinus surgery).

BACKGROUND

Description of the condition

This review will update and replace the previously published review 'Topical and systemic antifungal therapy for the symptomatic treatment of chronic rhinosinusitis' (Sacks 2011).

Chronic rhinosinusitis is defined as inflammation of the nose and paranasal sinuses. It is characterised by two or more symptoms, one of which must be nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) and one of facial pain/pressure and/or reduction or loss of sense of smell. Symptoms must have continued for at least 12 weeks. In addition, people must have either mucosal changes within the ostiomeatal complex or sinuses (or both) as evidenced by a computerised tomography (CT) scan and/or endoscopic signs of at least one of the following: nasal polyps, mucopurulent discharge primarily from the middle

meatus or oedema/mucosal obstruction primarily in the middle meatus (EPOS 2012).

Two major phenotypes of chronic rhinosinusitis have been identified based on the presence or absence of nasal polyps on examination. Nasal polyps are tumour-like hyperplastic swellings of the nasal mucosa, most commonly originating from within the ostiomeatal complex (Larsen 2004). Chronic rhinosinusitis with nasal polyps (CRSwNP) is diagnosed when polyps are seen (on direct or endoscopic examination) bilaterally in the middle meatus. The acronym CRSsNP is used for the condition in which no polyps are present.

Although the aetiology of chronic rhinosinusitis is not fully understood, it may involve abnormalities in the host response to irritants, commensal and pathogenic organisms and allergens, obstruction of sinus drainage pathways, abnormalities of normal mucociliary function, loss of the normal mucosal barrier or infection. Two typical profiles may be observed with respect to inflammatory

mediators; in eosinophilic chronic rhinosinusitis, which is typically associated with nasal polyps, high levels of eosinophils, immunoglobulin E (IgE) and interleukin (IL)-5 may be found, while in neutrophilic chronic rhinosinusitis, more often associated with chronic rhinosinusitis without polyps, neutrophils predominate, with elevated interferon (IFN) gamma, IL-8 and tumour necrosis factor (TNF) (EPOS 2012).

While treatment decisions should be made based on an understanding of the patient's chronic rhinosinusitis phenotype and likely aetiology, in practice treatment may be initiated without knowledge of the polyp status, particularly in primary care. This review (and most of its companion reviews) consider patients with and without polyps together in the initial evaluation of treatment effects. However, subgroup analyses explore potential differences between them.

There is much debate regarding the role of fungus in the aetiology of chronic rhinosinusitis. Intranasal fungus can be demonstrated in nearly all diseased and normal sinuses (Braun 2003; Lackner 2005; Ponikau 1999). The definition and categorisation of fungal rhinosinusitis is still controversial but the most commonly accepted system divides the condition into two: invasive and non-invasive disease, based on histopathological evidence of tissue invasion by fungi (Chakrabarti 2009). Invasive fungal disease is a unique entity and represents angioinvasive fungal propagation in the immunocompromised host setting. This is not the common presentation of chronic rhinosinusitis experienced by the vast majority of chronic sinusitis patients. Treatments usually include surgery followed by medical treatment (EPOS 2012).

Non-invasive fungal rhinosinusitis can be divided into two categories: a fungus ball (also known as mycetoma) and allergic fungal rhinosinusitis (AFRS). A fungus ball is a fungal collection in an abnormal sinus that usually produces only mild symptoms and can be surgically removed. Patients with fungus balls will not be included in this review.

AFRS is a well-recognised subgroup of chronic rhinosinusitis, in which an IgE mediated hypersensitivity to fungal elements drives the inflammatory process. Allergic fungal rhinosinusitis is generally diagnosed using the Bent-Kuhn criteria (Bent 1994): type I hypersensitivity confirmed by history, skin tests or serology; nasal polyposis; characteristic CT scan (double density sign); eosinophilic mucus without fungal invasion into sinus tissue; positive fungal stain of sinus contents removed intraoperatively or during office endoscopy.

In addition to AFRS, there is some research to suggest that a much broader group of patients with chronic rhinosinusitis with an eosinophilic inflammation may be mediated by fungal elements and a subsequent cascade of immune effects through non-classical pathways (Sok 2006). Furthermore, since Bent and Kuhn defined their subgroup of AFRS, further parallel groups have been defined including eosinophilic fungal rhinosinusitis (EFRS) and eosinophilic mucinous rhinosinusitis (EMRS). Patients with eosinophilic fungal rhinosinusitis have been defined as those who

meet the Bent-Kuhn criteria for AFRS except for the IgE mediated hypersensitivity to a fungal allergen. Patients with eosinophilic mucinous rhinosinusitis are defined as those who meet the Bent-Kuhn criteria for AFRS except that they have no positive fungal culture or smear. The Bent and Kuhn definition has been modified to include immunocompetence, which replaces type 1 hypersensitivity as a requirement (Philpott 2011).

Chronic rhinosinusitis represents a common source of ill health; 11% of UK adults reported chronic rhinosinusitis symptoms in a worldwide population study (Hastan 2011). Symptoms have a major impact on quality of life, reportedly greater in several domains of the SF-36 than angina or chronic respiratory disease (Gliklich 1995). Acute exacerbations, inadequate symptom control and respiratory disease exacerbation are common. Complications are rare, but may include visual impairment, bone erosion and expansion, and intracranial infection (EPOS 2012). Chronic rhinosinusitis affects an increasing proportion of the adult population until the sixth decade of life and then declines (Chen 2003).

The most commonly used interventions for chronic rhinosinusitis are used either topically (sprayed into the nose) or systemically (by mouth) and include steroids, antibiotics and saline. In the late 1990s some centres advocated the use of topical antifungals in chronic rhinosinusitis patients (Ponikau 1999). Since then there has been increasing controversy and contrasting papers have both advocated and refuted the use of both topical and systemic antifungal agents in the management of these patients (Ebbens 2007).

Description of the intervention

Antifungal agents can be used as systemic medications (orally or intravenously) or as topical preparations delivered directly to the sinuses. Topical treatments can be given using different delivery systems such as douching, nebulisation, atomisation, inhalation, irrigation, spray, drops or powder insufflations.

We will include all antifungals used in the management of inflammatory disease of the paranasal sinuses, both systemic and topical. Examples of antifungal agents include amphotericin B, glucanazole, itraconazole, voriconazole and ketoconazole. These agents may be fungistatic or fungicidal depending on the drug concentration and the susceptibility of the fungus.

How the intervention might work

Antifungal agents work in one of two ways, either as fungicides that kill the fungus cells, or as fungistatics that inhibit the growth and reproduction of the fungal cells. Although good research demonstrates an interaction of the immune system with fungus in chronic rhinosinusitis (Ponikau 2007), this does not necessarily imply that antifungals will be effective in managing the disease. In analogy, there is little plausibility in using anti-dust mite agents in managing house dust mite allergic rhinitis. It is well-established that

dust mite allergen can stimulate the same response in these patients. Similarly, in chronic rhinosinusitis the inappropriate immune activation may be the driving pathologic mechanism and fungal elements only the innocent target of the process. Fungus is ubiquitous in both our environment and sinuses (Lackner 2005). When taken orally (systemic) certain classes of antifungals, such as the azoles, have the potential for adverse events such as gastrointestinal disturbances and they have also been associated with serious adverse events, particularly with regard to hepatic and renal toxicity. Topical amphotericin is expensive and also associated with potential adverse events such as headache and local irritations (Ebbens 2006).

Why it is important to do this review

The previous Cochrane Review and other more recent systematic reviews have concluded that there is no convincing evidence to support the use of antifungals in chronic rhinosinusitis (Mistry 2014; Sacks 2011). However, the authors of these reviews have commented on the clinical diversity of the included populations within the trials, particularly with regard to diagnosis. Often the population includes patients with both chronic rhinosinusitis and AFRS, as this distinction is ambiguous in some trials. It is important to understand whether there is a difference in treatment effect between these two populations. Similarly, the existing reviews include a heterogeneous population of people with respect to sinus surgery prior to the start of the trial. We will not include studies designed to evaluate interventions in the immediate peri-surgical period, which are focused on assessing the impact of the intervention on the surgical procedure or on modifying the post-surgical results (preventing recurrence of chronic rhinosinusitis symptoms).

This review is one of a suite of Cochrane Reviews looking at common management options for patients with chronic rhinosinusitis (Chong 2016a; Chong 2016b; Chong 2016c; Head 2016a; Head 2016b; Head 2016c), and we will use the same methods and outcome measures as have been used across these reviews.

This systematic review will aim to look at the balance of benefits and harms for both systemic and topical antifungal agents in the treatment of people with chronic rhinosinusitis.

OBJECTIVES

To assess the effects of systemic and topical antifungal agents in people with chronic rhinosinusitis, including those with allergic fungal rhinosinusitis (AFRS) and, if possible, AFRS exclusively.

The review will exclude patients in the immediate post-surgical period (within six weeks of sinus surgery).

METHODS

Criteria for considering studies for this review

Types of studies

We will **include** studies with the following design characteristics:

- randomised controlled trials, including cluster-randomised trials and quasi-randomised trials (cross-over trials will only be included if the data from the first phase are available); and
- patients were followed up for at least two weeks.

We will **exclude** studies with the following design characteristics:

- randomised patients by side of nose (within-patient controlled) because it is difficult to ensure that the effects of any of the interventions considered can be localised; or
- perioperative studies, where the sole purpose of the study was to investigate the effect of the intervention on surgical outcome.

Types of participants

People (adults and children) with chronic rhinosinusitis, whether with polyps or without polyps. This includes the subgroups of people with a diagnosis of allergic fungal rhinosinusitis (AFRS), eosinophilic fungal rhinosinusitis (EFRS) or eosinophilic mucinous rhinosinusitis (EMRS).

We will exclude studies that included a majority of patients with:

- cystic fibrosis;
- aspirin-exacerbated respiratory disease (aka Samter's triad);
- antrochoanal polyps (benign polyps originating from the mucosa of the maxillary sinus);
- malignant polyps and inverted papilloma;
- primary ciliary dyskinesia;
- invasive fungal disease in the sinuses;
- fungus ball;
- a history of surgery for nasal polyps within six weeks of entry to the study.

Fungus can be demonstrated in almost all diseased and normal sinuses (Lackner 2005), thus we will not set associated fungus confirmed either histologically or on culture as an inclusion criteria. The immunological role of the fungus and the host is still an area of ongoing research.

Patients with chronic rhinosinusitis will be included if they fulfil the criteria defined by EPOS (EPOS 2012).

In order to identify patients with AFRS for subgroup analysis, we will use the modified Bent-Kuhn criteria (Philpott 2011), where a patient must fulfil the following criteria:

- type I hypersensitivity confirmed by history, skin tests or serology OR immunocompromise;
- nasal polyposis;

- characteristic CT scan (double density sign);
- eosinophilic mucus without fungal invasion into sinus tissue;
- positive fungal stain of sinus contents removed intraoperatively or during office endoscopy.

We will identify patients with EFRS for subgroup analysis if they meet the criteria for AFRS (above) except for the presence of hypersensitivity to a fungal allergen.

We will identify patients with EMRS for subgroup analysis if they meet the criteria for AFRS (above) except that they do not have a positive fungal culture/smear.

Types of interventions

We will include the following groups of topical or systemic antifungals:

- polyene antifungals (e.g. amphotericin);
- imidazole, triazole and thiazole antifungals (e.g. itraconazole);
- allylamines;
- echinocandins.

We will include both topically applied and systemic antifungals in the review. We will include any dose and delivery method. The minimum duration of treatment is 28 days.

Comparisons

The comparators are:

- placebo or no intervention;
- another class of antifungals;
- the same type of antifungal, which is either:
 - given for a different duration;
 - given at a different dose;
- other treatments for chronic rhinosinusitis, including:
 - intranasal corticosteroids;
 - oral/systemic steroids;
 - antibiotics;
 - nasal saline irrigation.

Concurrent treatments will be allowed if they are used in both treatment arms; they include, for example:

- nasal saline irrigation only;
- intranasal corticosteroids only;
- intranasal corticosteroids *plus* antibiotics;
- intranasal corticosteroids *plus* nasal irrigation *plus* oral steroids;
- other combinations.

Comparison pairs

There will be multiple possible comparison pairs due to the large number of interventions allowed.

The main comparison pairs of interest will be:

- topical antifungals *versus* no antifungal intervention or placebo;
- systemic antifungals *versus* no antifungal intervention or placebo;
- topical antifungals *versus* no intervention or placebo *alongside* intranasal steroids or other standard treatment in all arms of the trial.

Other possible comparison pairs will include:

- antifungals *versus* intranasal steroids;
- antifungals *versus* oral/systemic steroids;
- antifungals class A *versus* antifungals class B;
- antifungal A with duration of treatment X *versus* antifungal A with duration of treatment Y;
- antifungal A at dose X *versus* antifungal A at dose Y.

Types of outcome measures

We will analyse the following outcomes in the review, but we will not use them as a basis for including or excluding studies.

Primary outcomes

- Health-related quality of life, using **disease-specific** health-related quality of life scores, such as the Sino-Nasal Outcome Test-22 (SNOT-22), Rhinosinusitis Outcome Measures-31 (RSOM-31) and SNOT-20.
 - Disease severity, as measured by patient-reported symptom score (such as the Chronic Sinusitis Survey (CSS) questionnaire and visual analogue scales). In the absence of validated symptom score data, patient-reported individual symptom scores will be reported for the following symptoms: nasal obstruction/blockage/congestion, nasal discharge (rhinorrhoea), facial pressure/pain, loss of sense of smell (adults) and cough (children).
 - Significant adverse effects: hepatic toxicity (systemic antifungals).

Secondary outcomes

- Health-related quality of life, using **generic** quality of life scores, such as the SF-36, EQ-5D and other well-validated instruments.
 - Other adverse effects: gastrointestinal disturbances, allergic reactions (systemic antifungals).
 - Other adverse effects: epistaxis, headache, local discomfort (e.g. itching, mild burning) (topical antifungals).
 - Endoscopic score (depending on population, either nasal polyps size score or endoscopy score, e.g. Lund-Mackay/Lund-Kennedy).
 - Computerised tomography (CT) scan score (e.g. Lund-Mackay).

Both short-term (at the end of treatment) and long-term effects are important therefore we will evaluate outcomes at the end of treatment or within four weeks, at four weeks to six months, six to 12 months and more than 12 months. For adverse events we will analyse data from the longest time periods.

Search methods for identification of studies

The Cochrane ENT Information Specialist will conduct systematic searches for randomised controlled trials and controlled clinical trials. There will be no language, publication year or publication status restrictions. We may contact original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers where necessary.

Electronic searches

Published, unpublished and ongoing studies will be identified by searching the following databases from their inception:

- the Cochrane ENT Trials Register;
- the Cochrane Register of Studies Online;
- Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R);
- Ovid Embase;
- Ovid CAB Abstracts;
- EBSCO CINAHL;
- LILACS, lilacs.bvsalud.org;
- KoreaMed;
- IndMed, www.indmed.nic.in;
- PakMediNet, www.pakmedinet.com;
- Web of Knowledge, Web of Science;
- ClinicalTrials.gov;
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), www.who.int/ictpr;
- ISRCTN, www.isrctn.com;
- Google Scholar, scholar.google.co.uk;
- Google, www.google.com.

The subject strategies for databases will be modelled on the search strategy designed for CENTRAL ([Appendix 1](#)). Where appropriate, these will be combined with subject strategy adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. ([Handbook 2011](#))).

Searching other resources

We will scan the reference lists of identified publications for additional trials and contact trial authors if necessary. In addition, the Information Specialist will search Ovid MEDLINE, the *Cochrane*

Library and Google to retrieve existing systematic reviews relevant to this systematic review, so that we can scan their reference lists for additional trials.

Data collection and analysis

Selection of studies

At least two review authors (KH, PLS, LYC) will independently screen all titles and abstracts of the studies obtained from the database searches to identify potentially relevant studies. At least two review authors (KH, PLS, LYC) will evaluate the full text of each potentially relevant study to determine whether it meets the inclusion and exclusion criteria for this review.

We will resolve any differences by discussion and consensus, with the involvement of a third author for clinical and methodological input where necessary.

Data extraction and management

At least two review authors (KH, PLS, LYC) will independently extract data from each study using a standardised data collection form (see [Appendix 2](#)). Whenever a study has more than one publication, we will retrieve all publications to ensure complete extraction of data. Where there are discrepancies in the data extracted by different review authors, we will check these against the original reports and will resolve differences by discussion and consensus, with the involvement of a third author or a methodologist where appropriate. We will contact the original study authors for clarification or for missing data whenever possible. If differences are found between publications of a study, we will contact the original authors for clarification. We will use data from the main paper(s) if no further information is found.

We will include key characteristics of the studies, such as study design, setting, sample size, population and how outcomes were defined or collected in the studies. In addition, we will also collect baseline information on prognostic factors or effect modifiers. For this review, this will include:

- presence or absence of allergic fungal rhinosinusitis (AFRS), eosinophilic fungal rhinosinusitis (EFRS) and eosinophilic mucinous rhinosinusitis (EMRS);
- presence or absence of nasal polyps and baseline nasal polyp score where appropriate;
- presence of eosinophilic chronic rhinosinusitis;
- whether the patient has had previous sinus surgery.

We will also note down whether studies only selected patients with known AFRS and how this was identified.

For the outcomes of interest to the review, we will extract the findings of the studies on an available case analysis basis; i.e. we will include data from all patients available at the time points

based on the treatment randomised whenever possible, irrespective of compliance or whether patients had received the treatment as planned.

In addition to extracting pre-specified information about study characteristics and aspects of methodology relevant to risk of bias, we will extract the following summary statistics for each trial and each outcome:

- For continuous data: the mean values, standard deviations and number of patients for each treatment group. Where endpoint data are not available, we will extract the values for change from baseline. We will analyse data from measurement scales such as SNOT-22 and EQ-5D as continuous data.
- For binary data: the numbers of participants experiencing an event and the number of patients assessed at the time point.
- For ordinal scale data: if the data appear to be approximately normally distributed or if the analysis that the investigators performed suggested parametric tests were appropriate, then we will treat the outcome measures as continuous data. Alternatively, if data are available, we plan to convert into binary data.

We have prespecified the time points of interest for the outcomes in this review. While studies may have reported data at multiple time points, we will only extract the longest available data within the time points of interest. For example, for 'short' follow-up periods, our time point is defined as 'three to six months' post-randomisation. If a study reports data at three, four and six months, we will only extract and analyse the data for the six-month follow-up.

Extracting data from figures

Where values for primary or secondary outcomes are shown as figures within the paper we will contact the study authors to try to obtain the raw values. When the raw values are not provided, we will extract information from the graphs using an online data extraction tool (<http://arohatgi.info/WebPlotDigitizer/app/>), using the best quality version of the relevant figures available.

Assessment of risk of bias in included studies

At least two review authors (KH, PLS, LYC) will independently assess the risk of bias of each included study. We will follow the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011), and we will use the Cochrane 'Risk of bias' tool. With this tool we will assess the risk of bias as 'low', 'high' or 'unclear' for each of the following six domains:

- sequence generation;
- allocation concealment;
- blinding of participants, personnel and outcome assessment;
- incomplete outcome data;
- selective reporting;
- other sources of bias.

Measures of treatment effect

We will summarise the effects of dichotomous outcomes (e.g. proportion of patients with symptom resolution) as risk ratios (RR) with CIs. For the key outcomes that we will present in the 'Summary of findings' table, we will also express the results as absolute numbers based on the pooled results and compared to the assumed risk. We also plan to calculate the number needed to treat to benefit (NNTB) using the pooled results. The assumed baseline risk will typically be either (a) the median of the risks of the control groups in the included studies, this being used to represent a 'medium risk population' or, alternatively, (b) the average risk of the control groups in the included studies is used as the 'study population' (Handbook 2011). If a large number of studies are available, and where appropriate, we also plan to present additional data based on the assumed baseline risk in (c) a low-risk population and (d) a high-risk population.

For continuous outcomes, we will express treatment effects as a mean difference (MD) with standard deviation (SD). If different scales are used to measure the same outcome we will use the standardised mean difference (SMD), and we will provide a clinical interpretation of the SMD values.

Unit of analysis issues

This review will not use data from phase II of cross-over studies or from studies where the patient is not the unit of randomisation, i.e. studies where the side (right versus left) was randomised. If we find cluster-randomised trials, we will analyse these according to the methods in section 16.3.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011).

Dealing with missing data

We will contact study authors via email whenever the outcome of interest is not reported, if the methods of the study suggest that the outcome had been measured. We will do the same if not all data required for meta-analysis are reported, unless the missing data are standard deviations. If standard deviation data are not available, we will approximate these using the standard estimation methods from P values, standard errors or 95% CIs if these are reported, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). Where it is impossible to estimate these, we will contact the study authors.

Apart from imputations for missing standard deviations, we will not conduct any other imputations. However, we will complete calculations relating to disease severity (measured by patient-reported symptom scores) as some studies may measure individual symptoms rather than using validated instruments (see 'Imputing total symptom scores' below). We will extract and analyse data for all outcomes using the available case analysis method.

Imputing total symptom scores

Where a paper does not present information for the total disease severity in terms of patient-reported symptom scores but presents data for the results of individual symptoms, we will use the symptoms covering the important domains of the EPOS chronic rhinosinusitis diagnosis criteria (EPOS 2012), to calculate a total symptom score. The EPOS 2012 criteria for chronic rhinosinusitis require at least two symptoms. One of the symptoms must be either nasal blockage or nasal discharge; other symptoms can include facial pressure/pain, loss of sense of smell (for adults) or cough (for children). Where mean final values or changes from baseline are presented in the paper for the individual symptoms we will sum these to calculate a 'total symptom score'. We will calculate standard deviations for the total symptom score as if the symptoms were independent, random variables that were normally distributed. We acknowledge that there is likely to be a degree of correlation between the individual symptoms, however we will use this process as the magnitude of correlation between the individual symptoms is not currently well understood (no evidence found). If the correlation is high, the summation of variables as discrete variables is likely to give a conservative estimate of the total variance of the summed final score. If the correlation is low, this method of calculation will underestimate the standard deviation of the total score. However, the average patient-reported symptom scores have a correlation coefficient of about 0.5; if this is also applicable to chronic rhinosinusitis symptoms, the method used should have minimal impact (Balk 2012). As this method of calculation does not take into account weighting of different symptoms (no evidence found), we will downgrade all the disease severity outcomes in GRADE for lack of use of validated scales where this occurs.

Assessment of heterogeneity

We will assess clinical heterogeneity (which may be present even in the absence of statistical heterogeneity) by examining the included trials for potential differences between studies in the types of participants recruited, interventions or controls used and the outcomes measured.

We will assess statistical heterogeneity by visually inspecting the forest plots and by considering the Chi² test (with a significance level set at P value < 0.10) and the I² statistic, which calculates the percentage of variability that is due to heterogeneity rather than chance, with I² values over 50% suggesting substantial heterogeneity (Handbook 2011).

Assessment of reporting biases

We will assess reporting bias as between-study publication bias and within-study outcome reporting bias.

Outcome reporting bias (within-study reporting bias)

We will assess within-study reporting bias by comparing the outcomes reported in the published report against the study protocol, whenever this can be obtained. If the protocol is not available, we will compare the outcomes reported to those listed in the methods section. If results are mentioned but not reported adequately in a way that allows analysis (e.g. the report only mentions whether the results were statistically significant or not), bias in a meta-analysis is likely to occur. We will try to find further information from the study authors. If no further information can be obtained, we will note this as being a high risk of bias. Where there is insufficient information to judge the risk of bias, we will note this as an unclear risk of bias (Handbook 2011).

Publication bias (between-study reporting bias)

We plan to create funnel plots if sufficient trials (more than 10) are available for an outcome. If we observe asymmetry of the funnel plot, we plan to conduct more formal investigation using the methods proposed by Egger 1997.

Data synthesis

We will conduct all meta-analyses using Review Manager 5.3 (RevMan 2014). For dichotomous data, we plan to analyse treatment differences as a risk ratio (RR) calculated using the Mantel-Haenszel methods. We plan to analyse time-to-event data using the generic inverse variance method.

For continuous outcomes, if all the data are from the same scale, we plan to pool mean values obtained at follow-up with change outcomes and report this as a MD. However, if the SMD has to be used as an effect measure, we will not pool change and endpoint data.

When statistical heterogeneity is low, random-effects versus fixed-effect methods yield trivial differences in treatment effects. However, when statistical heterogeneity is high, the random-effects method provides a more conservative estimate of the difference.

Subgroup analysis and investigation of heterogeneity

We plan to conduct some subgroup analyses regardless of whether statistical heterogeneity is observed, as these are widely suspected to be potential effect modifiers. For this review, this includes:

- Presence of allergic fungal rhinosinusitis (as defined by the modified Bent-Kuhn criteria; see [Types of participants](#)), EFRS and EMRS. People with AFRS may respond differently to antifungal agents as in AFRS an IgE mediated hypersensitivity to fungal elements drives the inflammatory process.
- Phenotype of patients: whether patients have chronic rhinosinusitis without nasal polyps, chronic rhinosinusitis with nasal polyps, a mixed group or the status of polyps is not known or not reported. We planned to undertake the subgroup analysis

as although there appears to be a considerable overlap between the two forms of chronic rhinosinusitis with regards to inflammatory profile, clinical presentation and effect of treatment (Cho 2012; DeMarcanonio 2011; Ebbens 2010; Fokkens 2007; Ragab 2004; Ragab 2010; van Druenen 2009), there is some evidence pointing to differences in the respective inflammatory profiles (Kern 2008; Keswani 2012; Tan 2011; Tomassen 2011; Zhang 2008; Zhang 2009), and potentially even differences in treatment outcome (Ebbens 2011). The role of fungi in the pathology is also unclear and this makes it uncertain whether antifungals will have similar effects.

- Eosinophilic versus non-eosinophilic chronic rhinosinusitis. Some researchers hypothesise that patients with eosinophilic chronic rhinosinusitis will form an eosinophilic reaction towards the fungi present in their sinonasal mucin. It is proposed that this reaction will subsequently be involved in the inflammatory response (Ponikau 1999).

We plan to present the main analyses of this review according to the subgroups of presence of AFRS. We intend to present all other subgroup analysis results in tables.

When studies have a mixed group of patients, we plan to analyse the study as one of the subgroups (rather than as a mixed group) if more than 80% of patients belong to one category. For example, if 81% of patients have AFRS, we will analyse the study as that subgroup.

In addition to the subgroups above, we plan to conduct the following subgroup analyses in the presence of statistical heterogeneity:

- patient age (children versus adults);
- dose;
- duration of treatment;
- method of delivery;
- class of antifungal agent.

Sensitivity analysis

We plan to carry out sensitivity analyses to determine whether the findings are robust to the decisions made in the course of identifying, screening and analysing the trials. We plan to conduct sensitivity analysis for the following factors, whenever possible:

- impact of model chosen: fixed-effect versus random-effects model;
- risk of bias of included studies: excluding studies with high risk of bias (we will define these as studies that have a high risk of allocation concealment bias and a high risk of attrition bias (overall loss to follow-up of 20%, differential follow-up observed));
- how outcomes were measured: we plan to investigate the impact of including data where the validity of the measurement

was unclear.

If any of these investigations find a difference in the size of the effect or heterogeneity, we will mention this in the 'Effects of interventions' section.

GRADE and 'Summary of findings' table

Using the GRADE approach, at least two review authors (KH, PLS, LYC) will independently rate the overall quality of evidence using the GDT tool (<http://www.guidelinedevelopment.org/>) for the *main comparison pairs* listed in the [Types of interventions](#) section. The quality of evidence reflects the extent to which we are confident that an estimate of effect is correct and we will apply this in the interpretation of results. There are four possible ratings: 'high', 'moderate', 'low' and 'very low'. A rating of 'high' quality evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of 'very low' quality implies that any estimate of effect obtained is very uncertain.

The GRADE approach rates evidence from RCTs that do not have serious limitations as high quality. However, several factors can lead to the downgrading of the evidence to moderate, low or very low. The degree of downgrading is determined by the seriousness of these factors:

- study limitations (risk of bias);
- inconsistency;
- indirectness of evidence;
- imprecision;
- publication bias.

The 'Summary of findings' tables will present only the top priority outcomes (disease-specific health-related quality of life, disease severity score, adverse effects and generic quality of life score). We will not include the outcomes endoscopic score or CT scan score in the 'Summary of findings' tables.

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* Indicates the major publication for the study

APPENDICES

Appendix I. CENTRAL search strategy

CRSO	MEDLINE (Ovid)	Embase (Ovid)	Web of Science (Web of Knowledge)
#1 MESH DESCRIPTOR Rhinitis EXPLODE ALL TREES #2 MESH DESCRIPTOR Paranasal Sinus Diseases EXPLODE All TREES #3 MESH DESCRIPTOR Paranasal Sinuses EXPLODE All TREES #4 (rhinosinusitis or nasosinusitis or pansinusitis or ethmoiditis or sphenoiditis):TI, AB, KY #5 (kartagener* near syndrome*):TI, AB, KY #6 (inflamm* near sinus*):TI, AB, KY #7 ((maxilla* or frontal*) near sinus*):TI, AB, KY #8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 #9 MESH DESCRIPTOR Chronic Disease EXPLODE All TREES #10 MESH DESCRIPTOR Recurrence EXPLODE All TREES #11 MESH DESCRIPTOR Fungi EXPLODE All TREES #12 MESH DESCRIPTOR Mycetoma EXPLODE All TREES #13 (chronic or persis* or recurrent* or fung* or eosinophil* or mycetoma* or Maduromycos* or Actinomycetoma* or Eumycetoma*):TI, AB, KY #14 #9 OR #10 OR #11 OR #12 OR #13 #15 #8 AND #14 #16 (CRSsNP or AFS or AFRS):TI, AB, KY	1 exp Rhinitis/ 2 exp Paranasal Sinuses/ 3 exp Paranasal Sinus Diseases/ 4 (rhinosinusitis or nasosinusitis or pansinusitis or ethmoiditis or sphenoiditis).ab,ti 5 (kartagener* adj3 syndrome*) .ab,ti. 6 (inflamm* adj3 sinus*).ab,ti. 7 ((maxilla* or frontal*) adj3 sinus*).ab,ti. 8 1 or 2 or 3 or 4 or 5 or 6 or 7 9 exp Chronic Disease/ 10 exp Recurrence/ 11 exp Fungi/ 12 exp Mycetoma/ 13 (chronic or persis* or recurrent* or fung* or eosinophil* or mycetoma* or Maduromycos* or Actinomycetoma* or Eumycetoma*).ab,ti 14 9 or 10 or 11 or 12 or 13 15 8 and 14 16 (CRSsNP or AFS or AFRS) .ab,ti. 17 ((sinusitis or rhinitis) adj3 (chronic or persis* or recurrent* or fung*)).ab,ti 18 15 or 16 or 17 19 exp Nasal Polyps/ 20 exp Paranasal Sinus Diseases/mi [Microbiology] 21 exp rhinitis/mi [Microbiology] 22 exp Nasal Mucosa/mi [Microbiology] 23 exp Paranasal Sinuses/mi [Microbiology] 24 exp Nose/ 25 exp Nose Diseases/ 26 24 or 25	1 exp rhinitis/ 2 exp Paranasal Sinuses/ 3 exp Paranasal Sinus Diseases/ 4 (rhinosinusitis or nasosinusitis or pansinusitis or ethmoiditis or sphenoiditis).ab,ti 5 (kartagener* adj3 syndrome*) .ab,ti. 6 (inflamm* adj3 sinus*).ab,ti. 7 ((maxilla* or frontal*) adj3 sinus*).ab,ti. 8 1 or 2 or 3 or 4 or 5 or 6 or 7 9 exp Chronic Disease/ 10 exp Recurrence/ 11 exp Fungi/ 12 exp Mycetoma/ 13 (chronic or persis* or recurrent* or fung* or eosinophil* or mycetoma* or Maduromycos* or Actinomycetoma* or Eumycetoma*).ab,ti 14 9 or 10 or 11 or 12 or 13 15 8 and 14 16 (CRSsNP or AFS or AFRS) .ab,ti. 17 ((sinusitis or rhinitis) adj3 (chronic or persis* or recurrent* or fung*)).ab,ti 18 15 or 16 or 17 19 exp Nasal Polyps/ 20 exp Nose/ 21 exp Nose Diseases/ 22 20 or 21 23 exp Polyps/ 24 22 and 23 25 ((nose or nasal or rhino* or rhinitis or sinus* or sinonasal) adj3 (papilloma* or polyp* or fung*)).ab,ti 26 (rhinopolyp* or CRSwNP).	S1 TOPIC: ((rhinosinusitis or nasosinusitis or pansinusitis or ethmoiditis or sphenoiditis)) S2 TOPIC: ((kartagener* near/3 syndrome*)) S3 TOPIC: ((inflamm* near/3 sinus*)) S4 TOPIC: ((maxilla* near/3 sinus*)) S5 TOPIC: ((frontal* near/3 sinus*)) S6 #5 OR #4 OR #3 OR #2 OR #1 S7 TOPIC: ((chronic or persis* or recurrent* or fung* or eosinophil* or mycetoma* or Maduromycos* or Actinomycetoma* or Eumycetoma*)) S8 #7 AND #6 S9 TOPIC: (CRSsNP or AFS or AFRS) S10 TOPIC: (sinusitis near/3 chronic) S11 TOPIC: (sinusitis near/3 persis*) S12 TOPIC: (sinusitis near/3 recurrent*) S13 TOPIC: (sinusitis near/3 fung*) S14 TOPIC: (rhinitis near/3 fung*) S15 TOPIC: (rhinitis near/3 recurrent*) S16 TOPIC: (rhinitis near/3 persis*) S17 TOPIC: (rhinitis near/3 chronic) S18 #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8

(Continued)

<p>#17 ((sinusitis or rhinitis) near (chronic or persis* or recurrent* or fung*)):TI,AB,KY #18 #15 OR #16 OR #17 #19 MESH DESCRIPTOR Nasal Polyps EXPLODE ALL TREES #20 MESH DESCRIPTOR Paranasal Sinus Diseases EXPLODE ALL TREES WITH QUALIFIERS MI #21 MESH DESCRIPTOR Rhinitis EXPLODE ALL TREES WITH QUALIFIERS MI #22 MESH DESCRIPTOR Paranasal Sinuses EXPLODE ALL TREES WITH QUALIFIERS MI #23 MESH DESCRIPTOR Nasal Mucosa EXPLODE ALL TREES WITH QUALIFIERS MI #24 MESH DESCRIPTOR Nose EXPLODE ALL TREES #25 MESH DESCRIPTOR Nose Diseases EXPLODE ALL TREES #26 #24 OR #25 #27 MESH DESCRIPTOR Polyps EXPLODE ALL TREES #28 #26 AND #27 #29 (rhinopolyp* or CRSwNP):TI,AB,KY #30 ((nose or nasal or rhino* or rhinitis or sinus* or sinonasal) near (papilloma* or polyp* or fung*)):TI,AB,KY #31 #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #28 OR #29 OR #30 #32 MESH DESCRIPTOR Antifungal Agents EXPLODE ALL TREES #33 (antifung* or "anti fung*" or fungastic or fungicidal or Fungizone or Amphocil or Zonal or Diflucan or Triflucan</p>	<p>27 exp Polyps/ 28 26 and 27 29 ((nose or nasal or rhino* or rhinitis or sinus* or sinonasal) adj3 (papilloma* or polyp* or fung*)).ab,ti 30 (rhinopolyp* or CRSwNP).ab,ti. 31 18 or 19 or 20 or 21 or 22 or 23 or 28 or 29 or 30 32 exp Antifungal Agents/ or exp Amphotericin B/ or exp Antimycin A/ or exp Azaserine/ or exp Benzoates/ or exp Brefeldin A/ or exp Candidin/ or exp Cerulenin/ or exp Clotrimazole/ or exp Cycloheximide/ or exp Cyclosporine/ or exp Dichlorophen/ or exp Echinocandins/ or exp Econazole/ or exp Filipin/ or exp Fluconazole/ or exp Flucytosine/ or exp Griseofulvin/ or exp Hexetidine/ or exp Itraconazole/ or exp Ketoconazole/ or exp Lucensomycin/ or exp Mepartricin/ or exp Miconazole/ or exp Monensin/ or exp Mycobacillin/ or exp Natamycin/ or exp Nifuratel/ or exp Nystatin/ or exp Pentamidine/ or exp Rutamycin/ or exp Salicylic Acid/ or exp Sirolimus/ or exp Sodium Benzoate/ or exp Thymol/ or exp Tomatine/ or exp Tolnaftate/ or exp Triacetin/ or exp Trimetrexate/ or exp Venturicidins/ 33 exp Mycoses/dt, th [Drug Therapy, Therapy] 34 (acivicin or ajoene or amorolfin or Amphotericin or anidulafungin or Antimycin or artemether or aureobasidin or Azaserine or bafilomycin or Benzoates or bifonazole or blasticidin or Brefeldin or butenafine or butoconazole).ab,ti,</p>	<p>ab,ti. 27 18 or 19 or 24 or 25 or 26 28 exp Antifungal Agents/ 29 exp Amphotericin B/ 30 exp Antimycin A/ 31 exp Azaserine/ 32 exp Benzoates/ 33 exp Brefeldin A/ 34 exp Candidin/ 35 exp Cerulenin/ 36 exp Clotrimazole/ 37 exp Cycloheximide/ 38 exp Cyclosporine/ 39 exp Dichlorophen/ 40 exp Echinocandins/ 41 exp Econazole/ 42 exp Filipin/ 43 exp Fluconazole/ 44 exp Flucytosine/ 45 exp Griseofulvin/ 46 exp Hexetidine/ 47 exp Itraconazole/ 48 exp Ketoconazole/ 49 exp Lucensomycin/ 50 exp Mepartricin/ 51 exp Miconazole/ 52 exp Monensin/ 53 exp Mycobacillin/ 54 exp Natamycin/ 55 exp Nifuratel/ 56 exp Nystatin/ 57 exp Pentamidine/ 58 exp Rutamycin/ 59 exp Salicylic Acid/ 60 exp Sirolimus/ 61 exp Sodium Benzoate/ 62 exp Thymol/ 63 exp Tomatine/ 64 exp Tolnaftate/ 65 exp Triacetin/ 66 exp Trimetrexate/ 67 exp Venturicidins/ 68 exp mycosis/dt, th [Drug Therapy, Therapy] 69 (acivicin or ajoene or amorolfin or Amphotericin or anidulafungin or Antimycin or artemether or aureobasidin or</p>	<p>S19 TOPIC: (nose near/3 papilloma*) S20 TOPIC: (nose near/3 polyp*) S21 TOPIC: (nose near/3 fung*) S22 TOPIC: (nasal near/3 fung*) S23 TOPIC: (nasal near/3 polyp*) S24 TOPIC: (nasal near/3 papilloma*) S25 TOPIC: (rhino* near/3 papilloma*) S26 TOPIC: (rhino* near/3 polyp*) S27 TOPIC: (rhino* near/3 fung*) S28 TOPIC: (rhinitis near/3 fung*) S29 TOPIC: (rhinitis near/3 polyp*) S30 TOPIC: (rhinitis near/3 papilloma*) S31 TOPIC: (sinus* near/3 papilloma*) S32 TOPIC: (sinus* near/3 polyp*) S33 TOPIC: (sinus* near/3 fung*) S34 TOPIC: (sinonasal near/3 fung*) S35 TOPIC: (sinonasal near/3 polyp*) S36 TOPIC: (sinonasal near/3 papilloma*) S37 TOPIC: (rhinopolyp* or CRSwNP) S38 #37 OR #36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 S39 TOPIC: (acivicin or ajoene or amorolfin or Amphotericin or anidulafungin or Antimycin</p>
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(Continued)

or hexal or Fluco* or Flunazul or Fungata or Lavisa or Loitin or Neofomiral or oxifungol or Solacap or 49858 of BĒagyne or 51211 or Sporanox or Orungal)
:TI,AB,KY
#34 MESH DESCRIPTOR Mycoses EXPLODE ALL TREES WITH QUALIFIERS DT,TH
#35 MESH DESCRIPTOR Venturicidins EXPLODE ALL TREES
#36 MESH DESCRIPTOR Trimetrexate EXPLODE ALL TREES
#37 MESH DESCRIPTOR Triacetin EXPLODE ALL TREES
#38 MESH DESCRIPTOR Tolnaftate EXPLODE All TREES
#39 MESH DESCRIPTOR Tomatine EXPLODE All TREES
#40 MESH DESCRIPTOR Thymol EXPLODE All TREES
#41 MESH DESCRIPTOR Sodium Benzoate EXPLODE All TREES
#42 MESH DESCRIPTOR Sirolimus EXPLODE All TREES
#43 MESH DESCRIPTOR Salicylic Acid EXPLODE All TREES
#44 MESH DESCRIPTOR Pentamidine EXPLODE All TREES
#45 MESH DESCRIPTOR Nystatin EXPLODE All TREES
#46 MESH DESCRIPTOR Nifuratel EXPLODE All TREES
#47 MESH DESCRIPTOR Natamycin EXPLODE All TREES

nm
35 (Candicidin or candidin or captax or caspofungin or Cerulenin or ciclopirox or cilofungin or Clotrimazole or compactin or cordycepin or cryptocophycin or Cycloheximide or Cyclosporine or (decanoic adj3 acid) or (diallyl adj3 trisulfide) or Dichlorophen or diucifon or echinocandin or Echinocandins or Econazole or Ethonium or fenticonazole or ferroin or Filipin or Fluconazole or Flucytosine or glyphosate or Griseofulvin or hamycin or Hexetidine or hydroxyitraconazole or (ICI adj3 “195739”) or isoconazole or Itraconazole or iturin or jasplakinolide or Ketoconazole or lactoferricin or lapachol or lawsone or leptomycin or Lucensomycin or Mepartricin or methylamphotericin or micafungin or Miconazole or miltefosine or Monensin or monorden or mucidin or mucionaldehyde or Mycobacillin or myxothiazol or n-hexanal or naftifine or Natamycin or Nifuratel or nikkomycin or nitroxoline or Nystatin or oxiconazole or papulacandin or (pelargonic adj3 acid) or Pentamidine or polygodial or (polyoxin adj3 D) or posaconazole or (potassium adj3 iodate) or pradimicin or protegrin-1 or purothionin or pyochelin or pyrithione or Pyrrolnitrin or rhizoxin or Rutamycin or (salicylhydroxamic adj3 acid) or (Salicylic adj3 Acid) or saperconazole or (Sch adj3 “39304”) or sertaconazole or sinefungin or Sirolimus or (Sodium adj3 Benzoate) or squalastatin or sulconazole or terbinafine or ter-

Azaserine or bafilomycin or Benzoates or bifonazole or blasticidin or Brefeldin or butenafine or butoconazole).tw
70 (Candicidin or candidin or captax or caspofungin or Cerulenin or ciclopirox or cilofungin or Clotrimazole or compactin or cordycepin or cryptocophycin or Cycloheximide or Cyclosporine or (decanoic adj3 acid) or (diallyl adj3 trisulfide) or Dichlorophen or diucifon or echinocandin or Echinocandins or Econazole or Ethonium or fenticonazole or ferroin or Filipin or Fluconazole or Flucytosine or glyphosate or Griseofulvin or hamycin or Hexetidine or hydroxyitraconazole or (ICI adj3 “195739”) or isoconazole or Itraconazole or iturin or jasplakinolide or Ketoconazole or lactoferricin or lapachol or lawsone or leptomycin or Lucensomycin or Mepartricin or methylamphotericin or micafungin or Miconazole or miltefosine or Monensin or monorden or mucidin or mucionaldehyde or Mycobacillin or myxothiazol or n-hexanal or naftifine or Natamycin or Nifuratel or nikkomycin or nitroxoline or Nystatin or oxiconazole or papulacandin or (pelargonic adj3 acid) or Pentamidine or polygodial or (polyoxin adj3 D) or posaconazole or (potassium adj3 iodate) or pradimicin or protegrin-1 or purothionin or pyochelin or pyrithione or Pyrrolnitrin or rhizoxin or Rutamycin or (salicylhydroxamic adj3 acid) or (Salicylic adj3 Acid) or saperconazole or (Sch adj3 “39304”) or sertaconazole or sinefungin

or artemether or aureobasidin or Azaserine or bafilomycin or Benzoates or bifonazole or blasticidin or Brefeldin or butenafine or butoconazole)
S40 TOPIC: (Candicidin or candidin or captax or caspofungin or Cerulenin or ciclopirox or cilofungin or Clotrimazole or compactin or cordycepin or cryptocophycin or Cycloheximide or Cyclosporine)
S41 TOPIC: (decanoic near/3 acid)
S42 TOPIC: (diallyl near/3 trisulfide)
S43 TOPIC: (Dichlorophen or diucifon or echinocandin or Echinocandins or Econazole or Ethonium or fenticonazole or ferroin or Filipin or Fluconazole or Flucytosine or glyphosate or Griseofulvin or hamycin or Hexetidine or hydroxyitraconazole)
S44 TOPIC: (ICI near/3 “195739”)
S45 TOPIC: (isoconazole or Itraconazole or iturin or jasplakinolide or Ketoconazole or lactoferricin or lapachol or lawsone or leptomycin or Lucensomycin or Mepartricin or methylamphotericin or micafungin or Miconazole or miltefosine or Monensin or monorden or mucidin or mucionaldehyde or Mycobacillin or myxothiazol or n-hexanal or naftifine or Natamycin or Nifuratel or nikkomycin or nitroxoline or Nystatin or oxiconazole or papulacandin)
S46 TOPIC: (pelargonic near/3 acid)
S47 TOPIC: (Pentamidine or polygodia)

(Continued)

#48 MESH DESCRIPTOR Mycobacillin EXPLODE All TREES	conazole or thermozyomicidin or Thymol or tioconazole or Tolnaftate or Tomatine or Triacetin or trichostatin or Trime-trexate or troclosenone or (usnic adj3 acid) or Venturicidins or vibunazole or voriconazole or wortmannin).ab,ti,nm	or Sirolimus or (Sodium adj3 Benzoate) or squalestatin or sul-conazole or terbinafine or ter-conazole or thermozyomicidin or Thymol or tioconazole or Tolnaftate or Tomatine or Triacetin or trichostatin or Trime-trexate or troclosenone or (usnic adj3 acid) or Venturicidins or vibunazole or voriconazole or wortmannin).tw	S48 TOPIC: (polyoxin near/3 "D")
#49 MESH DESCRIPTOR Monensin EXPLODE All TREES	36 (antifung* or "anti fung*" or fungastic or fungicidal or Fun-gizone or Amphocil or Zonal or Diflucan or Triflucan or hexal or Fluco* or Flunazul or Fun-gata or Lavisia or Loitin or Ne-ofomiral or oxifungol or Sola-cap or 49858 of Beagyne or "51211" or Sporanox or Orun-gal).ab,ti,nm	71 (antifung* or "anti fung*" or fungastic or fungicidal or Fun-gizone or Amphocil or Zonal or Diflucan or Triflucan or hexal or Fluco* or Flunazul or Fun-gata or Lavisia or Loitin or Ne-ofomiral or oxifungol or Sola-cap or 49858 of Beagyne or "51211" or Sporanox or Orun-gal).tw	S49 TOPIC: (potassium near/3 iodate)
#50 MESH DESCRIPTOR Miconazole EXPLODE All TREES	37 32 or 33 or 34 or 35 or 36 38 31 and 37	72 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71	S50 TOPIC: (posaconazole or pradimicin or protegrin-1 or purothionin or pyochelin or pyrithione or Pyrrolnitrin or rhizoxin or Rutamycin)
#51 MESH DESCRIPTOR Mepartricin EXPLODE All TREES		73 27 and 72	S51 TOPIC: (salicylhydrox-amic near/3 acid)
#52 MESH DESCRIPTOR Lucensomycin EXPLODE All TREES			S52 TOPIC: (Salicylic near/3 Acid)
#53 MESH DESCRIPTOR Ketoconazole EXPLODE All TREES			S53 TOPIC: (Sch near/3 "39304")
#54 MESH DESCRIPTOR Itraconazole EXPLODE All TREES			S54 TOPIC: (saperconazole or sertaconazole or sinefungin or Sirolimus)
#55 MESH DESCRIPTOR Hexe-tidine EXPLODE All TREES			S55 TOPIC: (Sodium near/3 Benzoate)
#56 MESH DESCRIPTOR Griseofulvin EXPLODE All TREES			S56 TOPIC: (squalestatin or sulconazole or terbinafine or terconazole or thermozyo-micidin or Thymol or tiocona-zole or Tolnaftate or Tomatine or Triacetin or trichostatin or Trimetrexate or troclosenone)
#57 MESH DESCRIPTOR Flucy-tosine EXPLODE All TREES			S57 TOPIC: (usnic near/3 acid)
#58 MESH DESCRIPTOR Fluconazole EXPLODE All TREES			S58 TOPIC: (Venturicidins or vibunazole or voriconazole or wortmannin)
#59 MESH DESCRIPTOR Econazole EXPLODE All TREES			S59 TOPIC: (antifung* or "anti fung*" or fungastic or fungici-dal or Fungizone or Amphocil or Zonal or Diflucan or Triflu-can or hexal or Fluco* or Flu-nazul or Fungata or Lavisia or Loitin or Neofomiral or oxi-fungol or Solacap or 49858 of Beagyne or "51211" or Spora-nox or Orungal)
#60 MESH DESCRIPTOR Echinocandins EXPLODE All TREES			S60 #59 OR #58 OR #57 OR #56 OR #55 OR #54 OR #53 OR #52 OR #51 OR #50 OR #49 OR #48 OR #47 OR #46 OR #45 OR #44 OR #43 OR
#61 MESH DESCRIPTOR Dichlorophen EXPLODE All TREES			
#62 MESH DESCRIPTOR Cyclosporine EXPLODE All TREES			
#63 MESH DESCRIPTOR Cycloheximide EXPLODE All TREES			
#64 MESH DESCRIPTOR			

(Continued)

Clotrimazole EXPLODE All TREES #65 MESH DESCRIPTOR Filipin EXPLODE All TREES #66 MESH DESCRIPTOR Cerulenin EXPLODE All TREES #67 MESH DESCRIPTOR Candicidin EXPLODE All TREES #68 MESH DESCRIPTOR Brefeldin A EXPLODE All TREES #69 MESH DESCRIPTOR Benzoates EXPLODE All TREES #70 MESH DESCRIPTOR Azaserine EXPLODE All TREES #71 MESH DESCRIPTOR Antimycin A EXPLODE All TREES #72 MESH DESCRIPTOR Amphotericin B EXPLODE All TREES #73 (acivicin or ajoene or amorolfin or Amphotericin or anidulafungin or Antimycin or artemether or aureobasidin or Azaserine or bafilomycin or Benzoates or bifonazole or blastidicin or Brefeldin or butenafine or butoconazole):TI,AB, KY #74 (Candicidin or candidin or captax or caspofungin or Cerulenin or ciclopirox or cilofungin or Clotrimazole or compactin or cordycepin or cryptophycin or Cycloheximide or Cyclosporine or (decanoic near acid) or (diallyl near trisulfide) or Dichlorophen or diucifon or echinocandin or Echinocandins or Econazole or Ethonium):TI, AB,KY #75 (fenticonazole or ferroin or Filipin or Flucytosine or glyphosate or Griseofulvin or			#42 OR #41 OR #40 OR #39 S61 #60 AND #38
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hamycin or Hexetidine or hydroxyitraconazole or (ICI near "195739") or isoconazole or Itraconazole or iturin or jaspakinolide or Ketoconazole or lactoferricin or lapachol or lawsonone or leptomycin or Lucensomycin):TI,AB,KY

#76 (Mepartricin or methylamphotericin or micafungin or Miconazole or miltefosine or Monensin or monorden or mucidin or muconaldehyde or Mycobacillin or myxothiazol or n-hexanal or naftifine or Natamycin or Nifuratel or nikkomyacin or nitroxoline or Nystatin or oxiconazole or papulacandin or (pelargonic near acid) or Pentamidine or polygodial or (polyoxin near D) or posaconazole or (potassium near iodate) or pradimicin or protegri-1 or purothionin or pyochelin or pyrithione or Pyrrolnitrin):TI,AB,KY

#77 (rhizoxin or Rutamycin or (salicylhydroxamic near acid) or (Salicylic near Acid) or saperconazole or (Sch near "39304") or sertaconazole or sinefungin or Sirolimus or (Sodium near Benzoate) or squalestatin or sulconazole or terbinafine or terconazole or thermozytocidin or Thymol or tioconazole or Tolnaftate or Tomatine or Triacetin or trichostatin or Trimetrexate or troclosesene or (usnic near acid) or Venturicidins or vibunazole or voriconazole or wortmannin):TI,AB,KY

#78 #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR

(Continued)

#56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 #79 #31 AND #78			
CINAHL (EBSCO)	ICTRP	ClinicalTrials.gov	LILACS
S36 S29 AND S35 S35 S30 OR S31 OR S32 OR S33 OR S34 S34 TX (antifung* or “anti fung*” or fungastic or fungici- dal or Fungizone or Amphocil or Zonal or Diflucan or Triflu- can or hexal or Fluco* or Flu- nazul or Fungata or Lavisal or Loitin or Neofomiral or oxifun- gol or Solacap or 49858 of Beagyne or “51211” or Spora- nox or Orungal) S33 TX (Candididin or can- didin or captax or caspofun- gin or Cerulenin or ciclopirox or cilofungin or Clotrimazole or compactin or cordycepin or cryptophycin or Cyclohex- imide or Cyclosporine or (de- canoic N3 acid) or (diallyl N3 trisulfide) or Dichlorophen or diucifon or echinocandin or Echinocandins or Econa- zole or Ethonium or fenti- conazole or ferroin or Fil- ipin or Fluconazole or Flucy- tosine or glyphosate or Grise- ofulvin or hamycin or Hexeti- dine or hydroxyitraconazole or (ICI N3 “195739”) or isocona- zole or Itraconazole or iturin or jasplakinolide or Ketocona- zole or lactoferricin or lapa- chol or lawsone or leptomycin or Lucensomycin or Mepar- tricin or methylamphotericin or micafungin or Miconazole	rhinitis AND fungal OR rhini- tis AND antifungal OR sinusi- tis AND fungal OR sinusitis AND antifungal or CRS AND fungal OR CRS AND antifun- gal OR AFRS AND antifun- gal OR AFRS AND fungal OR rhinosinusitis AND fungal OR rhinosinusitis AND antifungal	(rhinitis OR sinusitis OR rhinosinusitis OR (nose AND polyps) OR (nasal AND polyps) OR CRSsNP OR CRSwNP OR CRS OR AFRS) AND (fungal OR fungastic OR fungicidal OR Fungizone OR antifungal OR Amphotericin)	TW:rhinit* OR TW: sinusit* OR TW:rhinosinusitis OR TW:rinit* OR (TW:nose AND TW:polyp*) OR (TW: nasal AND TW:polyp*) OR (TW: polipos AND TW:nasa*) OR TW:CRSsNP OR TW: CRSwNP OR TW:CRS OR TW:AFRS

(Continued)

or miltefosine or Monensin or monorden or mucidin or mucinaldehyde or Mycobacillin or myxothiazol or n-hexanal or naftifine or Natamycin or Nifuratel or nikkomycin or nitroxoline or Nystatin or oxiconazole or papulacandin or (pelargonic N3 acid) or Pentamidine or polygodial or (polyoxin N3 D) or posaconazole or (potassium N3 iodate) or pradimicin or protegrin-1 or purothionin or pyochelin or pyrithione or Pyrrolnitrin or rhizoxin or Rutamycin or (salicylhydroxamic N3 acid) or (Salicylic N3 Acid) or saperconazole or (Sch N3 “39304”) or sertaconazole or sinefungin or Sirolimus or (Sodium N3 Benzoate) or squalestatin or sulconazole or terbinafine or terconazole or thermozyomicidin or Thymol or tioconazole or Tolnaftate or Tomatine or Triacetin or trichostatin or Trime-trexate or troclosene or (usnic N3 acid) or Venturicidins or vibunazole or voriconazole or wortmannin)

S32 TX (acivicin or ajoene or amorolfin or Amphotericin or anidulafungin or Antimycin or artemether or aureobasidin or Azaserine or bafilomycin or Benzoates or bifonazole or blas-ticidin or Brefeldin or bute-nafine or butoconazole)

S31 (MH “Mycoses/DT/TH”)

S30
(MH “Antifungal Agents+”) or (MH “Amphotericin B+”) or (MH “Antimycin A+”) or (MH “Azaserine+”) or (MH “Ben-zoates+”) or (MH “Brefeldin A+”) or (MH “Candididin+”) or (MH “Cerulenin+”) or (MH “Clotrimazole+”) or (MH “Cy-

(Continued)

cloheximide+) or (MH "Cyclosporine+")
or (MH "Dichlorophen+") or
(MH "Echinocandins+") or
(MH "Econazole+") or (MH
"Filipin+") or (MH "Fluconazole+")
or (MH "Flucytosine+") or
(MH "Griseofulvin+") or (MH
"Hexetidine+") or (MH "Itraconazole+") or (MH "Ketoconazole+") or (MH "Lucensomycin+") or (MH "Mepartricin+") or (MH "Miconazole+") or (MH "Monensin+") or (MH "Mycobacillin+") or (MH "Natamycin+") or (MH "Nifuratel+")
or (MH "Nystatin+") or (MH "Pentamidine+") or (MH "Rutamycin+") or (MH "Salicylic Acid+") or (MH "Sirolimus+") or (MH "Sodium Benzoate+") or (MH "Thymol+") or (MH "Tomatine+") or (MH "Tolnafate+") or (MH "Triacetin+") or (MH "Trimetrexate+") or (MH "Venturicidins+")
S29 S18 OR S19 OR S20 OR
S21 OR S26 OR S27 OR S28
S28 TX (rhinopolyp* or CR-SwNP)
S27 TX ((nose or nasal or rhino* or rhinitis or sinus* or sinonasal) N3 (papilloma* or polyp* or fung*))
S26 S24 AND S25
S25 (MH "Polyps+")
S24 S22 OR S23
S23 (MH "Nose Diseases+")
S22 (MH "Nose+")
S21 (MH "Rhinitis+/MI") OR (MH "Nasal Mucosa+/MI")
S20 (MH "Paranasal Sinus Diseases+/MI") OR (MH "Paranasal Sinuses+/MI")
S19 (MH "Nasal Polyps+")
S18 S15 OR S16 OR S17
S17 TX ((sinusitis or rhinitis)

(Continued)

n3 (chronic or persis* or recurrent* or fung*)
S16 TX (CRSsNP or AFS or AFRS)
S15 S8 AND S14
S14 S9 OR S10 OR S11 OR S12 OR S13
S13 TX (chronic or persis* or recurrent* or fung* or eosinophil* or mycetoma* or Maduromycos* or Actinomycetoma* or Eumycetoma*)
S12 (MH "Mycetoma+")
S11 (MH "Fungi+")
S10 (MH "Chronic Disease+")
S9 (MH "Recurrence+")
S8 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7
S7 TX ((maxilla* or frontal*) n3 sinus*)
S6 TX (inflamm* n3 sinus*)
S5 TX kartagener* n3 syndrome*
S4 TX rhinosinusitis or nasosinusitis or pansinusitis or ethmoiditis or sphenoiditis
S3 (MH "Paranasal Sinus Diseases+")
S2 (MH "Paranasal Sinuses+")
S1 (MH "Rhinitis+")

Appendix 2. Data extraction form

REF ID:	Study title:
Date of extraction:	Extracted by:

General comments/notes (internal for discussion):

Flow chart of trial

	Group A (Intervention)	Group B (Comparison)
No. of people screened		
No. of participants randomised - all		
No. randomised to each group		
No. receiving treatment as allocated		
No. not receiving treatment as allocated - Reason 1 - Reason 2		
No. dropped out (no follow-up data for any outcome available)		
No. excluded from analysis ¹ (for all outcomes) - Reason 1 - Reason 2		

¹This should be the people who received the treatment and were therefore not considered 'drop-outs' but were excluded from all analyses (e.g. because the data could not be interpreted or the outcome was not recorded for some reason)

Information to go into 'Characteristics of included studies' table

Methods	X arm, double/single/non-blinded, [multicentre] parallel-group/cross-over/cluster-RCT, with x duration of treatment and x duration of follow-up
Participants	<p>Location: country, no of sites etc.</p> <p>Setting of recruitment and treatment:</p> <p>Sample size:</p> <ul style="list-style-type: none"> ● Number randomised: x in intervention, y in comparison ● Number completed: x in intervention, y in comparison <p>Participant (baseline) characteristics:</p> <ul style="list-style-type: none"> ● Age: ● Gender:

(Continued)

	<ul style="list-style-type: none"> • Main diagnosis: <i>[as stated in paper]</i> • Polyps status: x % with polyps/no information <i>[add info on mean polyps score if available]</i> • Presence of allergic fungal rhinosinusitis: x% with AFRS <i>[add info if available]</i> • Presence of eosinophilic CRS: x% with eosinophilic CRS <i>[add info if available]</i> • Previous sinus surgery status: <i>[x% with previous surgery]</i> • Other important effect modifiers, if applicable (e.g. aspirin sensitivity, comorbidities of asthma): <p>Inclusion criteria: <i>[state diagnostic criteria used for CRS, polyps score if available]</i></p> <p>Exclusion criteria:</p>
Interventions	<p>Intervention (n = x): drug name, method of administration, dose per day/frequency of administration, duration of treatment</p> <p>Comparator group (n = y):</p> <p>Use of additional interventions (common to both treatment arms):</p>
Outcomes	<p>Outcomes of interest in the review:</p> <p>Primary outcomes:</p> <ul style="list-style-type: none"> • Health-related quality of life, disease-specific • Disease severity symptom score • Significant adverse effects (systemic antifungals): hepatic toxicity <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Health-related quality of life, generic • Adverse effects (topical antifungals): epistaxis, headache, local discomfort (mild burning, itching) • Adverse effects (systemic antifungals): gastrointestinal disturbances, allergic reactions. • Endoscopy (polyps size or overall score) • CT scan <p>Other outcomes reported by the study:</p> <ul style="list-style-type: none"> • <i>[List outcomes reported but not of interest to the review]</i>
Funding sources	'No information provided'/'None declared'/'State source of funding
Declarations of interest	'No information provided'/'None declared'/'State conflict
Notes	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)		Quote: "..." Comment:
Allocation concealment (selection bias)		Quote: "..." Comment:
Blinding of participants and personnel (performance bias)		Quote: "..." Comment:
Blinding of outcome assessment (detection bias)		Quote: "..." Comment:
Incomplete outcome data (attrition bias)		Quote: "..." Comment:
Selective reporting (reporting bias)		Quote: "..." Comment:
Other bias (see section 8.15) Insensitive/non-validated instrument?		Quote: "..." Comment:
Other bias (see section 8.15)		Quote: "..." Comment:

Findings of study: continuous outcomes

Results (continuous data table)

Outcome	Group A			Group B			Other summary stats/Notes
	Mean	SD	N	Mean	SD	N	
Disease-specific HRQL (<i>instrument name/range</i>) Time point:							Mean difference (95% CI), P values etc.
Generic HRQL (<i>instrument name/range</i>) Time point:							

(Continued)

Symptom score (overall) (<i>instrument name/range</i>) Time point:									
Added total - if scores reported separately for each symptom (<i>range</i>) Time point:									
Nasal blockage/obstruction/congestion (<i>instrument name/range</i>)									
Nasal discharge (<i>instrument name/range</i>)									
Facial pain/pressure (<i>instrument name/range</i>)									
Smell (reduction) (<i>instrument name/range</i>)									
Headache (<i>instrument name/range</i>)									
Cough (in children) (<i>instrument name/range</i>)									
Polyp size (<i>instrument name/range</i>)									

(Continued)

CT score (instrument name/range)										
Comments:										

Results (dichotomous data table)										
Outcome	Ap- plicable review/ intervention	Group A		Group B		Other summary stats/notes				
		No. of people with events	No. of people analysed	No. of people with events	No. of people analysed	P values, RR (95% CI), OR (95% CI)				
Renal/hepatic toxicity	Systemic antifungals									
Headache	Topical antifungals									
Gastrointestinal disturbances (diarrhoea, nausea, vomiting, stomach irritation)	Topical antifungals Systemic antifungals									
Epistaxis	Topical antifungals									
Local discomfort	Topical antifungals									
Anaphylaxis or other serious allergic reactions	Systemic antifungals									
Comments:										

CONTRIBUTIONS OF AUTHORS

Karen Head wrote the protocol with the help of the other authors.

Peta-Lee Sacks, Lee Yee Chong, Claire Hopkins and Carl Philpott reviewed and edited the protocol.

DECLARATIONS OF INTEREST

Karen Head: none known

Peta-Lee Sacks: none known

Lee Yee Chong: none known

Claire Hopkins: I have received financial support from several companies involved in producing instruments for sinus surgery: Acclarent, Sinusys, Cryolife and Medtronic.

Carl Philpott: I have previously received consultancy fees from the companies Acclarent, Navigant, Aerin Medical and Entellus, and am a trustee of the patient charity Fifth Sense.

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Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.
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NOTES

This review will update and replace the previously published review 'Topical and systemic antifungal therapy for the symptomatic treatment of chronic rhinosinusitis' ([Sacks 2011](#)).