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Topical azole treatments for otomycosis (Protocol)

Lee A, Tysome JR, Saeed SR

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Cochrane Database of Systematic Reviews 2011, Issue 9. Art. No.: CD009289.
DOI: 10.1002/14651858.CD009289.

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[Intervention Protocol]

Topical azole treatments for otomycosis

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Editorial group: Cochrane ENT Group.
Publication status and date: Edited (no change to conclusions), published in Issue 3, 2019.

Citation: Lee A, Tysome JR, Saeed SR. Topical azole treatments for otomycosis. *Cochrane Database of Systematic Reviews* 2011, Issue 9. Art. No.: CD009289. DOI: 10.1002/14651858.CD009289.

ABSTRACT

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

To assess the effects of topical azole treatments for otomycosis.

BACKGROUND

Description of the condition

Otomycosis is a term used to describe a superficial fungal infection of the external ear canal. It has a reported worldwide incidence of between 5% and 80% (Gharaghani 2015; Munguia 2008). It is common in tropical countries and patients typically present with localised pruritis (itchiness) of the ear canal. Ear pain, hearing loss and discharge can also occur. Symptoms can be exacerbated if the ear canal skin is manipulated. Otomycosis is often seen in patients who have been treated for bacterial otitis externa with multiple course of topical antibiotic ear drops.

The prevalence of otomycosis amongst those with pre-existing inflammatory conditions of the ear, such as eczema and psoriasis, ranges from 9% to 30.4% (Ho 2006; Kurnatowski 2001). It is seen in all age groups and amongst those who participate in aquatic sports. It is known to increase during the summer months (Rowlands 2001). More importantly, this disease has been linked to the extensive use of topical antibiotics for the treatment of otitis media and otitis externa (Munguia 2008). In a Nepalese cross-sectional study the prevalence of otomycosis was reported to be 23%. Of the 440 patients studied with otorrhoea, otalgia and canal pruritis, 100 showed positive fungal cultures (Pradhan 2003). Children with nutritional deficiency may be more susceptible to otomycosis (Enweani 1998).

Diagnosis of otomycosis is based on clinical grounds and should be suspected in patients with pruritic and/or discharging ear canals and fungal elements seen on otomicroscopy. However, while there are similarities in clinical presentation between otomycosis and acute otitis externa their treatments are different (Kaushik 2010). The prolonged usage of topical antibiotics alters the local flora of the ear canal leading to fungal proliferation and otomycosis. Patients with otomycosis often seek the advice of ENT specialists when their condition becomes unrelenting despite multiple courses of topical antibiotics. The role of the ENT specialist is to establish the correct diagnosis and prescribe the most appropriate treatment. This may include topical antifungals as well as suction clearance and dry mopping of debris. The recurrence rates of this disease vary according to the presence of the risk factors listed

above.

Both environmental and host factors may predispose people to otomycosis (Kaushik 2010; Munguia 2008). Environmental factors include moisture (leading to skin maceration, elevation of ear canal pH and diminution of cerumen, which protects the ear canal), trauma to the ear canal and high ambient temperatures. Host factors include open and wet mastoid cavities, the presence of excessive cerumen, an immunocompromised state, pregnancy, hearing aids with an occlusive mould, secondary bacterial otitis externa, increased use of topical antibiotics and swimming in pools. Many species of fungi have been identified as the cause of otomycosis. The two most common species are *Aspergillus niger* and *Candida albicans*. Controversy exists regarding the importance of identifying the causal agent(s) prior to treatment. While some clinicians believe it is good practice to use the appropriate treatment based on swab results to establish the sensitivity to antifungal agents (Bassiouny 1986), others advocate treatment based on the efficacy of the drug regardless of the causal agent (Blyth 2007).

In patients who are immunocompromised, an invasive and life-threatening form of fungal infection may develop, known as skull base osteomyelitis or malignant otitis externa (Blyth 2011). This results in destruction of the underlying bone of the external ear canal and spreads along the skull base to involve the lower cranial nerves. Symptoms may include intense ear pain, persistent discharge, facial palsy, deafness, hoarseness and dysphagia. This condition should be distinguished from otomycosis and is not the focus of our review.

Description of the intervention

There are at least six main classes of drugs for the treatment of fungal infections: azoles, polyenes, nucleoside analogues, echinocandins, antiseptics and hydroxyquinolones (Munguia 2008). In this review we are focusing on topical azoles due to their wide availability, low risk of ototoxicity and low rates of antifungal drug resistance. Examples include clotrimazole, fluconazole and ketoconazole. Clotrimazole is the most widely used topical azole. It can be dispensed as a 1% lotion or a topical cream, with the duration of treatment ranging from a few days to four weeks. Side effects are often localised and limited to skin redness and burning. Clotrimazole has a reported rate of effectiveness in otomycosis that ranges from 50% to 100% (Jackman 2005; Jadhav 2003). Topical azoles can also be used in cases of perforated ear drums (Vennewald 2010).

During treatment for otomycosis it is also common practice to remove the debris from the ear canal. This is known as aural toileting and it is administered with microsuction or dry mopping just prior to application of the topical remedy. It is considered to be standard therapy in most ENT outpatient clinics and an important adjunctive treatment (Mofatteh 2018). In this review we plan to explore the effects of aural toileting in subgroup analysis.

How the intervention might work

Azole antifungal drugs (with the exception of abafungin) inhibit the enzyme lanosterol 14 α-demethylase, which is the enzyme necessary to convert lanosterol to ergosterol. Depletion of ergosterol in the fungal membrane disrupts the structure and many of its functions leading to inhibition of fungal growth (Sheehan 1999). It has been shown to have a potent in vitro broad-spectrum fungicidal activity including against *Aspergillus* and *Candida* species, which are common agents in otomycosis (Stern 1988).

Although there is no general consensus as to the duration of topical azole therapy, two weeks appears to be common (Khan 2013).

Why it is important to do this review

Otomycosis is a common condition with a significant health and financial burden. An intervention found to be effective based on good evidence could have an impact globally. Although many treatment options are available clinicians continue to struggle with the most appropriate treatment option (Munguia 2008). Evidence from Denmark has shown that there is wide variation in how this condition is treated by ENT consultants (Arndal 2016). Many cohort studies have been published that investigate the usage of clotrimazole in otomycosis, the majority of which have found it to be safe and effective (Hamza 2011; Khan 2013).

A Cochrane Review has examined a number of interventions for otitis externa but its focus was on bacterial infections of the ear canal and not otomycosis specifically (Kaushik 2010). A set of guidelines published by the Infectious Disease Society of America has examined the treatment of aspergillosis, but this is a condition that is prevalent amongst the immunocompromised population and is most often disseminated with a high risk of morbidity and mortality, which is vastly different to otomycosis (Walsh 2008). A recent systematic review compared the efficacy of clotrimazole versus flumethasone pivalate 0.02% and clioquinol 1% (Locacorten Vioform) for otomycosis and concluded that there was insufficient evidence to support either therapy (Herasym 2016).

It is important that an effective treatment is found for otomycosis due to its worldwide prevalence and the accompanying disease burden. A few randomised controlled trials have been conducted, however performing a meta-analysis may be difficult because the interventions assessed vary in each study. We are aware of studies that have compared clotrimazole with 3% boric acid, with an experimental compound known as G328 and with eberconazole (Cota 2018; NCT01547221; NCT01993823).

Topical azoles are widely available on prescription in many countries and they are thought to be well tolerated with few side effects (Bassiouny 1986). A systematic review of the current evidence to assess their effects in the treatment of otomycosis is therefore warranted.

OBJECTIVES

To assess the effects of topical azole treatments for otomycosis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials with a minimum follow-up duration of two weeks from the start of treatment.
We will exclude the following study designs:

- Cross-over studies (because uncomplicated otomycosis is a self-limiting condition). Furthermore, it is anticipated that the carry-over effect of clotrimazole treatment may be prolonged as this drug is typically administered for over two weeks.
- Cluster-randomised studies.
- Within-patient controlled studies (where the unit of randomisation is the ear) because it is difficult to determine with confidence whether the outcomes of interest can clearly be attributed to one side as reported by either the participant or the study investigator.

Types of participants

Participants over the age of 16 with a diagnosis of otomycosis.
Diagnosis of otomycosis will be based on presentation with symptoms including: ear pain, itchiness, discharge, fullness or hearing impairment with findings of ear discharge. Studies should describe the mycological criteria for confirmation using either direct microscopy or culture showing fungal spores or hyphae.
We will exclude studies that focus primarily on otitis externa (see Subgroup analysis and investigation of heterogeneity) and those with skull base osteomyelitis (also known as malignant otitis externa).

Types of interventions

Intervention

Topical azole antifungals.

Control

Placebo or no intervention.

Adjunctive treatment

Aural toileting is considered routine in the treatment of discharging ears in an outpatient clinic. It may consist of dry mopping, syringing or microsuction.
The main comparisons will be:

- topical azoles versus placebo;
- topical azoles versus no treatment;
- one type of topical azole versus another type of topical azole.

We include studies using aural toileting if this adjunctive treatment is administered equally in both the intervention and comparator groups.
We will exclude other agents used for treating otomycosis as a comparison as we expect that the majority of these studies would use a heterogeneous mixture of agents and concentrations. Pooling of data under these circumstances would be problematic.
We will record details of the interventions including treatment concentration, mode of administration (cream, drops, powder), dose (milligrams, millilitres or other) and number of administrations per day. We will include studies using an azole dosage of 1% with a minimal duration of therapy of 14 days.

Types of outcome measures

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

Primary outcomes

- Clinical resolution as measured by the proportion of participants with complete resolution, however defined by the authors of the studies.
- Significant adverse events: severe topical allergic reaction.

Secondary outcomes

- Mycological resolution: eradication of pathogenic ear canal fungi as determined by mycological means (e.g. KOH smear or fungal culture).
- Other adverse effects: local irritation, hearing loss, mild allergic reaction.

The time point for outcome assessment will be final follow-up, as defined by the study authors.

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 Register of Studies ENT Trials Register (search to date);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (search via Cochrane Register of Studies to date);
- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to present);
- Ovid Embase (1974 to date);
- EBSCO CINAHL (1982 to date);
- LILACS (search to date);
- KoreaMed (search via Google Scholar to date);
- IndMed (search to date);
- PakMediNet (search to date);
- Web of Knowledge, Web of Science (1945 to date);
- CNKI (searched via Google Scholar to date);
- ClinicalTrials.gov, www.clinicaltrials.gov (search via the Cochrane Register of Studies to date);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (search to date).

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 Cochrane 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 to retrieve existing systematic reviews relevant to this systematic review, so that we can scan their reference lists for additional trials. The Information Specialist will also run non-systematic searches of Google Scholar to retrieve grey literature and other sources of potential trials.

Data collection and analysis

Selection of studies

Two independent review authors (AL and JT) will assess all titles and abstracts from the search and eliminate studies that clearly do not satisfy the inclusion criteria. For studies that appear to meet the inclusion criteria we will obtain the full-text report to confirm eligibility. In the event of a disagreement, the third author (SS) will act as an adjudicator. We will list the reasons for exclusion in the 'Characteristics of excluded studies' table. We will use a study flow diagram (PRISMA) to illustrate the process for selection of studies (Handbook 2011).

Data extraction and management

AL and JT will independently extract data from each study report using specifically designed data extraction forms. We will check any discrepancies in the data extracted against the original reports and resolve any differences by consensus. We will contact the original study authors for clarification or missing data whenever possible.

We will record the following data from each of the included studies: general characteristics (type of study, citation data, number of patients included and their baseline characteristics and risk factors), potential sources of bias, fungal types, procedures (type of randomisation, inclusion criteria, protocol for follow-up and assessment, protocol for therapy and control, and number of patients who dropped out of the study), outcome data (clinical signs and symptoms, adverse events, microbiological data) and authors' conclusions. If information or data are missing, we will attempt to contact the study authors.

Where possible we will extract data to allow an intention-to-treat analysis (i.e. the analysis should include all the participants in the groups to which they were randomly assigned 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 binary data: the number 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 suggests parametric tests were appropriate, then we will treat the outcome measures as continuous data. Alternatively, if data are available, we will to convert into binary data.

Assessment of risk of bias in included studies

AL and TJ will independently undertake assessment of the risk of bias of the included trials as guided by the*Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011):

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

We will use the Cochrane 'Risk of bias' tool in RevMan 5.3 (RevMan 2014), which involves describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry: low, high or unclear risk of bias. We will provide evidence to support our assessments in 'Risk of bias' tables.

Measures of treatment effect

We will summarise the effects of dichotomous outcomes (e.g. proportion of patients with symptom resolution) as risk ratios (RR). For each of the key outcomes that we present in the 'Summary of findings' table, we will also express the results as corresponding risk based on the pooled results and compared to the assumed risk as odds ratios with CIs. The assumed baseline risk is typically 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).

Unit of analysis issues

The unit of randomisation will be the individual participant (we will exclude within-patient controlled studies and cluster-randomised trials).

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 suggested that the outcome had been measured. We will do the same if not all data required for meta-analysis have been 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 were reported as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). If it is impossible to estimate these, we will contact the study authors.

We will undertake imputation for missing standard deviations, but otherwise we do not plan to conduct other imputation. We will extract and analyse all data using the available case analysis method.

Assessment of heterogeneity

We will visually inspect the forest plots in conjunction with the Chi^2 test, using a 5% level of statistical significance, and the I^2 statistic to assess the levels of heterogeneity. The I^2 statistic describes the percentage of variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value greater than 50% usually suggests substantial heterogeneity (Handbook 2011). If sufficient studies are available for meta-analysis we will explore this using *either* a fixed-effect or a random-effects model. If there is substantial clinical or methodological heterogeneity in the methodology of the different studies within a comparison, or the statistical heterogeneity is substantial, we will choose a random-effects model (Handbook 2011).

Assessment of reporting biases

We plan to create funnel plots if sufficient studies (more than 10) are available for an outcome.

Data synthesis

AL will enter data into Review Manager 5.3 (RevMan 2014).

If there are sufficient data we will undertake a quantitative analysis and present the data in forest plots.

We anticipate that trialists will usually have determined their outcome measures on more than one occasion. In general, these assessment visits will fall into the following categories: early (e.g. halfway through treatment), end-of-therapy (a day or so after the cessation of treatment), test-of-cure (around a week after treatment) or test-of-recurrence (a few weeks after treatment has finished). Trialists may vary in the number and timing of visits they choose. In order to make a fair comparison between trials it is important to compare outcome measures taken at similar times. We have therefore decided a priori that we will only perform pooling of data from different studies (meta-analysis) for outcome measures taken at similar times.

We also plan to calculate the number needed to treat to benefit (NNTB) with 95% CIs using the methods outlined by Cook and Sackett (Cook 1995). We do not intend to calculate the number needed to treat to harm (NNTH) because we anticipate the risk of significant side effects from topical azoles to be very low.

Subgroup analysis and investigation of heterogeneity

If we identify studies with a mixed group of patients (consisting of otitis externa and otomycosis) we will analyse them providing that they have more than 80% of patients with otomycosis.

If the data allow, we plan to explore the effects of aural toileting as an adjunctive treatment in subgroup analysis.

We do not intend to perform subgroup analyses based on dosage because azole antifungals are a topical medication applied over a very small surface area. Hence, we do not believe that this variation is clinically important.

Sensitivity analysis

We plan to carry out sensitivity analysis for the follow factors to determine whether the findings are robust to the decisions made in the course of identifying, screening and analysing the trials:

- risk of bias of included studies: excluding studies with high risk of bias, defined as a high risk of allocation concealment bias

and a high risk of attrition bias (overall loss to follow-up of over 20%);

- how outcomes were measured: we plan to investigate the impact of including data when the validity of the measurement is unclear.

If any of these investigations finds 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, two review authors (AL and JT) will independently rate the overall quality of evidence using the GDT tool (http://www.guidelinedevelopment.org/) for the following comparisons:

- topical azoles versus placebo;
- topical azoles versus no treatment;
- one type of topical azole versus another type of topical azole.

The quality of evidence reflects the extent to which we are confident that an estimate of effect is correct and we applied this in the interpretation of results. There are four possible ratings: high, moderate, low and very low. A rating of high quality of 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; and
- publication bias.

We will include 'Summary of findings' tables for each comparison, constructed according to the recommendations described in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). The outcomes selected for GRADE assessment will be: clinical resolution as measured by the proportion of participants with complete resolution, significant adverse events (severe topical allergic reaction), mycological resolution and other adverse effects (local irritation, hearing loss, mild allergic reaction).

ACKNOWLEDGEMENTS

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure, Cochrane Programme Grant or Cochrane Incentive funding to Cochrane ENT. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL search strategy

1 MESH DESCRIPTOR Otomycosis EXPLODE ALL AND CENTRAL:TARGET
2 (otomyco*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
3 ((singapore NEXT ear) OR (ear NEXT simgapore)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
4 #1 OR #2 OR #3 AND CENTRAL:TARGET
5 MESH DESCRIPTOR Ear, External EXPLODE ALL AND CENTRAL:TARGET
6 MESH DESCRIPTOR Otitis Externa EXPLODE ALL AND CENTRAL:TARGET
7 ((outer OR extern*) NEXT (ear OR otitis)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
8 ((ear OR otitis) NEXT (outer OR extern*)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
9 ((pruritis OR itch*) AND ear):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
10 ((external AND auditory AND canal)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
11 #5 OR #6 OR #7 OR #8 OR #9 OR #10 AND CENTRAL:TARGET7
12 MESH DESCRIPTOR Mycoses EXPLODE ALL AND CENTRAL:TARGET
13 MESH DESCRIPTOR Microbiology EXPLODE ALL AND CENTRAL:TARGET
14 MESH DESCRIPTOR Fungi EXPLODE ALL AND CENTRAL:TARGET
15 (mycos* OR fung* OR Candida or candidias* or aspergill*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
16 MESH DESCRIPTOR Antifungal Agents EXPLODE ALL AND CENTRAL:TARGET
17 MESH DESCRIPTOR azoles EXPLODE ALL AND CENTRAL:TARGET
18 (azole* or triazole* or antifunag*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
19 (Imidazole* OR imidazolidinone OR Aminoimidazole* OR Antazoline OR Biotin OR Carbimazole* OR Cimetidine OR Clotrimazole* OR Creatinine OR Dacarbazine OR Dexmedetomidine OR Econazole* OR Enoximone OR Etimizol OR Etomidate OR Fadrozole* OR Fluspirilene OR Histamine OR Histidinol OR Idazoxan OR Imidazolidine* OR Imidazoline* OR Impromidine OR Levamisole* OR Losartan OR Medetomidine OR Methimazole* OR Miconazole* OR Naphazoline OR Niridazole* OR Nitroimidazole* OR Olmesartan Medoxomil OR Ondansetron OR Oxymetazoline OR Phentolamine OR Tetramisole* OR Trimethaphan OR Urocanic Acid OR Vardenafil Dihydrochloride OR Isoxazole* OR isoxazolepropionic Acid OR Cycloserine OR Ibotenic Acid OR Isocarboxazid OR Paliperidone Palmitate OR Oxazole* OR Aminorex OR Dimethadione OR Fura-2 OR Muscimol OR Oxadiazole* OR Oxazolidinone* OR Oxazolone* OR Pemoline OR Trimethadione OR Pyrazole* OR Betazole* OR Celecoxib OR Epirizole* OR Indazole* OR Muzolimine OR Oxypurinol OR Pyrazolone* OR Sulfaphenazole* OR Pyrrole* OR Atorvastatin Calcium OR Cromakalim OR Maleimide* OR Porphobilinogen OR Prodigiosin OR Pyrrolnitrin OR Ryanodine OR Tetrapyrrole* OR Tolmetin OR Tetrazole* OR Cefotetan OR Losartan OR Olmesartan Medoxomil OR Tetrazolium Salt* OR Valsartan OR Thiazole* OR Benzothiazole* OR Chlormethiazole* OR Cobicistat OR Dasatinib OR Famotidine OR FANFT OR Febuxostat OR Firefly Luciferin OR Levamisole* OR Lurasidone Hydrochloride OR Niridazole* OR Nizatidine OR Oxythiamine OR Rhodanine OR Ritonavir OR Sulfathiazole* OR Tetramisole* OR Thiabendazole* OR Thiadiazole* OR Thiamine OR Thiazolidinedione* OR Triazole* OR Amitrole* OR Fluconazole* OR Guanazole* OR Itraconazole* OR Sitagliptin Phosphate OR Trapidil OR Voriconazole*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
20 MESH DESCRIPTOR Ketoconazole EXPLODE ALL AND CENTRAL:TARGET
21 (Klotrimazole* OR Mycelex OR Lotrimin OR Canesten OR Kanesten OR Zonal* OR Béagyne OR Diflucan OR Fluc Hexal OR Flucobeta OR FlucoLich OR Fluconazol* OR Flunazul OR Fungata OR Lavisa OR Loitin OR Neofomiral OR Oxifungol OR Solacap OR Triflucan OR Ketoconazole* OR Nizoral OR Miconasil* OR Monistat OR Brentan OR Dactarin OR Ekonazole* OR GynoPevaril OR (Gyno AND Pevaril) OR (Gyno AND Pervaryl)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
22 (Castellani OR (otic AND powder)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
23 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #21 OR #20 OR #22 AND CENTRAL:TARGET
24 #11 AND #23 AND CENTRAL:TARGET
25 #24 OR #4 AND CENTRAL:TARGET

WHAT'S NEW

Date	Event	Description
22 March 2019	Amended	Protocol revision.

CONTRIBUTIONS OF AUTHORS

Ambrose Lee (lead author): original concept, obtaining the papers, writing the early drafts, protocol development, risk of bias assessment, analysis and interpretation of data, writing of review.

James Tysome: protocol development, risk of bias assessment, analysis and interpretation of data, writing of review.

Shakeel Saeed: clinical, methodological and editorial input and advice.

DECLARATIONS OF INTEREST

Ambrose Lee: none known.

James Tysome: none known.

Shakeel Saeed: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

Infrastructure funding for Cochrane ENT