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Cochrane Database of Systematic Reviews 2011, Issue 5. Art. No.: CD009151.
DOI: 10.1002/14651858.CD009151.

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[Intervention Protocol]

Treatment for recurrent vulvovaginal candidiasis (thrush)

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Editorial group: Cochrane HIV/AIDS Group.
Publication status and date: New, published in Issue 5, 2011.

Citation: Cooke G, Watson C, Smith J, Pirotta M, van Driel ML. Treatment for recurrent vulvovaginal candidiasis (thrush). *Cochrane Database of Systematic Reviews* 2011, Issue 5. Art. No.: CD009151. DOI: 10.1002/14651858.CD009151.

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

The primary objective of this systematic review is to assess the relative efficacy of pharmacological and non-pharmacological treatments for recurrent vulvovaginal candidiasis. The secondary objectives of the review are to assess the safety and patient preference of these treatment options.

BACKGROUND

Description of the condition

Candida is a yeast that is commonly found in the vagina as part of normal flora, without causing symptoms. For reasons that are largely unknown, *Candida* changes from being a commensal organism (that is, it can live in the environment without causing problems for the host) to a pathogenic one, which causes symptoms of vulvovaginal candidiasis (commonly named thrush). Uncomplicated vulvovaginal candidiasis affects up to 75% of women at some time during their reproductive years (Sobel 2007). Predisposing factors have been identified for uncomplicated vulvovaginal candidiasis (Patel 2004), and include the use of antibiotics, pregnancy, diabetes mellitus, genetic factors and behavioural factors (Sobel 2006).

Up to 5% of women suffer from recurrent vulvovaginal candidiasis (RVVC), which is commonly defined as four or more episodes of VVC in a 12 month period (Sobel 2007). The role of factors predisposing for uncomplicated vulvovaginal candidiasis is not certain in RVVC. In approximately half of women with RVVC, no risk factors can be identified (Nyirjesy 2008).

The aetiology of RVVC is unclear. Most cases (85-95%) of uncomplicated vulvovaginal candidiasis are caused by *Candida albicans. However in RVVC* less common candidal species such as *Candida glabrata* may be implicated. These tend to be more resistant to treatment (Sobel 2007). Many theories, such as maladaptive immune response, remain controversial (Fidel 1998; Sobel 2007), and the role of individual susceptibility has not yet been defined (Sobel 2007).

For women suffering from RVVC, the effects on their intimate relationships and daily living can be significant (Ehrstrom 2007). The major impact of the physical symptoms, including discharge, itchiness, pain and psychological effects, are often unrecognised (Chapple 2000). It has been suggested that chronic irritation, as occurs in RVVC, can be a factor in conditions such as vulval vestibulitis and dermatitis (Metts 1999).

Description of the intervention

Management of uncomplicated vulvovaginal candidiasis usually consists of topical or oral anti-fungal treatments with frequency ranging from a single dose to short term treatment for up to 14 days. However, treatment of RVVC is notoriously difficult and often involves long term or multiple treatments.

Topical anti-fungal agents are applied to the vaginal mucosa, and are delivered in the form of creams or pessaries. Oral anti-fungal treatment is in the form of tablets or capsules. The current consensus-based recommended treatment for RVVC aims for suppression of the condition. Initially high doses of oral or topical anti-fungal agents are taken to induce suppression of symptoms, which usually takes around two weeks, but may take up to six months (Sobel 2004). This suppression period is followed by long term regular (weekly or monthly) treatment to maintain remission of symptoms.

A previous Cochrane review aimed to compare the clinical cure rates of topical versus oral treatment for uncomplicated vulvovaginal candidiasis (Nurbhai 2007) and detected no difference in the efficacy of oral and vaginal treatment, but found that women generally prefer oral treatment.

The recommended treatment regimen for complicated vulvovaginal such as RVVC as outlined in clinical guidelines (Therapeutic Guidelines Limited 2006; Pappas 2009), whether oral or topical, is not effective for all women (Shahid 2009). Many experience side effects including headache, abdominal pain and nausea for oral treatment (Sobel 1995; Stein 1993) and dyspareunia or irritation with vaginal treatment (Stein 1993). Additionally, long term treatment is expensive, and approximately 50% of women experience recurrence of symptoms within months of finishing treatment (Sobel 2004).

Either due to these limitations in current treatments or patient preference, many women seek treatment alternatives. Complementary and alternative medicine (CAM) is highly acceptable to women and widely used in managing this condition (Nyirjesy 2001). In one study it was found that up to 40% of women use CAM to treat or prevent vulvovaginal candidiasis despite wide availability of conventional anti-fungal agents (Pirotta 2003). Examples of CAM used are herbal preparations such as tea tree oil, probiotics such as lactobacillus, use of vaginal acidifying agents. Other treatment options include changing contraceptive, partner treatment and use of topical gentian violet. Evaluation of the use of CAM for vulvovaginal candidiasis in the literature has been limited.

How the intervention might work

The mode of action of antifungal agents is generally fungistatic, that is, they induce breakdown of the fungal cell wall (Wildfeuer 1997). Alteration of the host environment so that it is less favourable for the proliferation of *Candida* is the underlying theory supporting use of other therapies such as probiotics, gels used to restore vaginal acid balance, and treatments such as depomedroxyprogesterone (Falagas 2006; Miller 2000). Efficacy for these treatments has been questioned by some studies (Pirotta 2004) and the lack of supporting evidence highlighted by others (Van Kessel 2003). Some treatments less commonly used such as immunotherapy promote the restoration of the immune system (Moraes 2000).

Why it is important to do this review

Currently there is no systematic review of treatment options for RVVC. Available guidelines are based on consensus only. RVVC is a common condition and can have a severe impact on women and their partners, both physically and psychologically. Many treatments are expensive and for many, the evidence for their efficacy has not been systematically researched. Evaluation of the many therapies used to manage this condition is essential to provide information so that women and their health care practitioners are able to make informed decisions about management of RVVC.

OBJECTIVES

The primary objective of this systematic review is to assess the relative efficacy of pharmacological and non-pharmacological treatments for recurrent vulvovaginal candidiasis. The secondary objectives of the review are to assess the safety and patient preference of these treatment options.

METHODS

Criteria for considering studies for this review

Types of studies

All published and unpublished assessor-blinded randomised controlled trials evaluating treatments for RVVC in immunocompetent women will be considered for inclusion.

Types of participants

All women with 4 or more symptomatic episodes of vulvovaginal candidiasis in the past year will be included. Women with immunosuppressive disorders or taking immunosuppressant medication will be excluded. However women with diabetes mellitus and pregnant women will be included in the review (and included in separate subgroup analyses). Diagnosis of RVVC will confirmed by the presence of symptoms and a positive culture or symptoms and positive microscopy.

All settings (such as family medicine clinic, gynaecology outpatient clinic, sexually transmitted disease or family planning clinic) will be included.

Types of interventions

Interventions to be considered will be antifungal treatments: anti-fungal drugs administered intra-vaginally (e.g. butoconazole, clotrimazole, econazole, fenticonazole, isoconazole, miconazole, omoconazole, oxiconazole, , terconazole, tioconazole, natamycin, sertaconazole, , and amphotericin) or oral anti-fungals (e.g. fluconazole, ketoconazole,itraconazole, posaconazole, and voriconazole) or polyenes (nystatin).

Other treatments for candida vulvovaginitis will also be included, for example probiotics, gentian violet, acidifying agents (including cider vinegar, boric acid, and vaginal gels), fermented whey concentrate, partner treatment, tea tree oil, douching, garlic and dietary modification.

The following comparisons will be made:

- Any treatment versus placebo
- Short duration of treatment vs longer duration of treatment
- Systemic versus local treatment
- Partner treatment versus placebo
- Comparison of two different classes of drugs
- Comparison of different doses of the same agent

Types of outcome measures

Primary outcomes

- Number of clinical recurrences per patient per year (recurrence defined as clinical features and positive culture or microscopy)
- Proportion of participants with at least one clinical recurrence during the treatment and follow up period

Secondary outcomes

- Time to first recurrence
- Number of symptomatic days per year
- Number of mycological recurrences per patient per year
- Proportion of participants with at least one mycological recurrence during the treatment and follow up period
- Duration of symptoms after treatment initiation
- Complications
- Adverse events
- Patient preference

Search methods for identification of studies

We will attempt to identify as many published and unpublished trials as possible which evaluate interventions for recurrent vulvovaginal candidiasis. We will use both electronic searching of bibliographic databases and handsearching, as described in the Cochrane Collaboration Handbook. No language restrictions will be used.

Electronic searches

A comprehensive search of electronic databases will be performed. Specifically, we will search:

1. MEDLINE from 1966 to present
2. The Cochrane Controlled Trials Register (CENTRAL)
3. EMBASE
4. CINAHL
5. Conference paper abstracts
6. Ovid's Dissertation Abstracts

Searching other resources

We will attempt to identify all unpublished trials by using the following methods:

- hand-searching reference lists of trials identified in database searches
- contacting authors of identified trials
- contacting manufacturers producing products for vulvovaginal candidiasis
- searching clinical trials databases (www.trialscentral.org ; www.controlled-trials.com)

Data collection and analysis

Selection of studies

Two review authors (GC and CW) will independently assess eligibility for inclusion of the trials identified by the search. Disagreements will be resolved by discussion, involving input from a third author (author to be named [TBN]). Trial authors will be contacted if more information is required before deciding on inclusion.

Data extraction and management

Data will be extracted using a paper-based data extraction form. This will be assessed independently by two authors (GC and CW). Again, discrepancies will be resolved by discussion, involving input from a third author (author TBN). Authors will be contacted if more information is required. When appropriate, data analysis will be carried out using the RevMan software.

Assessment of risk of bias in included studies

The risk of bias in eligible trials will be evaluated as described in the Cochrane Collaboration Handbook (Higgins 2009), including assessment of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias.

This will be assessed independently by two authors (JS and author TBN). Discrepancies will be resolved by discussion, involving input from a third author (MVD). Authors will be contacted if more information is required.

Measures of treatment effect

For dichotomous data, we will report the results as risk ratios (odds ratios) with 95% confidence intervals. For continuous data, we will report mean difference of pre and post measurements or weighted mean difference if different scales were used. We will also report standard deviations.

Unit of analysis issues

The unit of analysis in meta-analysis is the patient. If the patient is not the unit of randomisation, such as is the case in cluster randomised trials, adjustments for clustering will be made following the guidelines in the Cochrane Reviewers Handbook (Higgins 2009). Cross-over trials will not be included in the review.

Dealing with missing data

We will attempt to obtain information on missing data from authors. If this is not successful we will perform intention to treat analysis (ITT), which considers all missing data as treatment failures. We will perform on treatment analysis as well and discuss discrepancies in the findings in the discussion of our review. We will follow the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2009) to perform a sensitivity analysis to explore the impact of studies with high amounts of missing data.

Assessment of heterogeneity

We will assess heterogeneity in two ways. First, we will explore face value heterogeneity (populations, interventions etc). If there is obvious heterogeneity we will not pool the studies. Second, we will perform a Chi^2 test, using $P < 0.1$ as the cut off for statistical heterogeneity. In addition we will calculate the Higgins I^2 statistic and consider a cut off point of 50% as significant heterogeneity (Higgins 2009).

Assessment of reporting biases

Where reporting bias is suspected, we will contact the authors, asking for missing data. We will include this information in the discussion.

Data synthesis

We will use Review Manager software (RevMan 2010) to perform the statistical analysis. Where the trial populations, methods and outcome measures are judged to be similar, and in the absence of statistical heterogeneity, we will pool the data using a fixed effects model (Higgins 2009). In case statistical heterogeneity is present, we will either not pool or use a random effects model (Higgins 2009).

We will attempt to calculate a number needed to treat (NNT) and a number needed to harm (NNH) where data are available and outcomes are statistically significant.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses:

1. Sexually active women versus non-sexually active women
2. Pregnant versus non-pregnant women
3. Women with diabetes mellitus versus non-diabetic women
4. Intervention - duration: short versus long treatment
5. Route of administration: topical versus systemic
6. Candida albicans v non-albicans RVVC

Sensitivity analysis

We will perform sensitivity analyses to assess the effect of risk of bias on the overall estimate of the meta-analysis by first pooling studies with a low risk of bias and then gradually adding the studies assessed as having a high risk of bias.

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* *Indicates the major publication for the study*

CONTRIBUTIONS OF AUTHORS

Cathy Watson and Georga Cooke wrote the protocol. Mieke Van Driel, Marie Pirotta and Jane Smith provided comment and advice on the protocol. All authors approved the final version.

DECLARATIONS OF INTEREST

The authors have no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- No financial support was received for this review, Australia.

External sources

- No external financial support was provided for this review, Australia.