Candidiasis (vulvovaginal)

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ABSTRACT

INTRODUCTION: Vulvovaginal candidiasis is estimated to be the second most common cause of vaginitis after bacterial vaginosis. Candida albicans accounts for 85% to 90% of cases. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of drug treatments for acute vulvovaginal candidiasis in non-pregnant symptomatic women? What are the effects of alternative or complementary treatments for acute vulvovaginal candidiasis in non-pregnant symptomatic women? What are the effects of treating asymptomatic non-pregnant women with a positive swab for candidiasis? We searched: Medline, Embase, The Cochrane Library, and other important databases up to October 2013 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 23 studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: alternative or complementary treatments; douching; drug treatments; garlic; intravaginal preparations (nystatin, imidazoles, tea tree oil); oral fluconazole; oral itraconazole; and yoghurt containing Lactobacillus acidophilus (oral or intravaginal).

QUESTIONS

INTERVENTIONS

Key points

- Vulvovaginal candidiasis is characterised by vulval itching and may also present with abnormal 'cheese-like' or watery vaginal discharge.

  Vulvovaginal candidiasis is estimated to be the second most common cause of vaginitis after bacterial vaginosis. *Candida albicans* accounts for 85% to 90% of cases.

  Risk factors include pregnancy (and other situations where oestrogen levels are increased), diabetes mellitus, immunosuppression, and systemic antibiotics. Incidence increases with the onset of sexual activity, but associations with different types of contraceptives are unclear.

- Intravaginal imidazoles seem to reduce symptoms of acute vulvovaginal candidiasis in non-pregnant symptomatic women.

  Intravaginal imidazoles (butoconazole, clotrimazole, miconazole) may reduce symptoms compared with placebo, and all seem to have similar efficacy compared with each other.

  Intravaginal imidazoles (clotrimazole, miconazole, and econazole) and oral imidazoles (fluconazole or itraconazole) may be equally effective at achieving clinical cure.

- Oral itraconazole seems to reduce persistent symptoms at 1 week compared with placebo, but we don't know whether it is more effective compared with oral fluconazole.

- Intravaginal nystatin seems to reduce symptoms compared with placebo, but we don't know how it compares with intravaginal imidazoles, oral fluconazole, or oral itraconazole.
- The benefits of other intravaginal treatments to treat acute attacks remain unclear, and some may be associated with serious adverse effects.

  We found no RCT evidence comparing intravaginal tea tree oil with other interventions listed in the review.

  We found no RCT evidence comparing garlic or yoghurt, used vaginally or orally, with other interventions listed in the review.

  We found no RCT evidence comparing douching with other interventions listed in the review, but observational studies suggest it is associated with serious adverse effects such as PID and infections, endometritis, and ectopic pregnancy.
- We found no RCT evidence comparing the effects of alternative or complementary treatments with other interventions listed in the review in asymptomatic non-pregnant women with a positive swab for candidiasis.
- We found no RCT evidence on the effects of drug treatments in asymptomatic non-pregnant women with a positive swab for candidiasis.

Clinical context

GENERAL BACKGROUND

Vulvovaginal candidiasis is a symptomatic vaginitis (inflammation of the vagina and/or vulva) caused by infection with a *Candida* yeast. Asymptomatic prevalence has been reported in 10% of women. This review looks at possible treatment options for acute vulvovaginal candidiasis in non-pregnant symptomatic women.

FOCUS OF THE REVIEW

This review includes evidence on the impact of commonly used treatments, including drug treatments and alternative or complementary treatments (garlic, douching, tea tree or yoghurt) over clinical cure rates and adverse effects in non-pregnant women with vulvovaginal candidiasis.

COMMENTS ON EVIDENCE

We found 23 studies that met our inclusion criteria. Most RCTs were heterogeneous, small, and many had weak methods (poorly described randomisation, inadequate concealment and blinding, and definitions of cure based on mycology results rather than symptoms), making difficult to draw definitive conclusions

SEARCH AND APPRAISAL SUMMARY

The update literature search for this review was carried out from the date of the last search, March 2009 to November 2013. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the review, please see the Methods section. Searching of electronic databases retrieved 75 studies. After deduplication and removal of conference abstracts, 36 records were screened for inclusion in the review. Appraisal of titles and abstracts led to the exclusion of 27 studies and the further review of nine full publications. Of the nine full articles evaluated, one RCT was added at this update, making a total of 23 studies included in this review.

ADDITIONAL INFORMATION

Oral and intravaginal imidazoles are secreted in maternal milk, therefore, they should not be administered to women who are breastfeeding. Intravaginal nystatin may be acceptable, as it is unlikely to be absorbed systemically. Before prescribing imidazoles, it is necessary to know the local resistance to these drugs, and to note that they may interact with other drugs (e.g., oral anticoagulants, phenytoin).

DEFINITION	Vulvovaginal candidiasis is defined as symptomatic vaginitis (inflammation of the vagina), which often involves the vulva (erythema and swelling), caused by infection with a *Candida* yeast. The predominant symptom is vulvar itching. Abnormal vaginal discharge (which may be minimal — a 'cheese-like' material or a watery secretion) may also be present. [1] Vulvar burning, soreness, and irritation are also common symptoms, and these may be accompanied by dysuria or dyspareunia, which worsen during the week prior to menses. [2] Differentiation from other forms of vaginitis requires the presence of yeast on microscopy of vaginal fluid.
INCIDENCE/ PREVALENCE	Vulvovaginal candidiasis is estimated to be the second most common cause of vaginitis after bacterial vaginosis. Estimates of its incidence are limited and often derived from women who attend hospital clinics. Asymptomatic prevalence has been reported in 10% of women, [3] so identification

of vulvovaginal *Candida* is not necessarily indicative of candidal disease. Self-reported history of at least one episode of vulvovaginal candidiasis has been as high as 72%. [4]

AETIOLOGY/ RISK FACTORS

Candida albicans accounts for 85% to 90% of cases of vulvovaginal candidiasis. [5] [6] *Candida glabrata* accounts for almost all of the remaining cases, [7] and treatment failure with azoles is common (around 50%) in patients with *C glabrata* vaginitis. [8] Development of symptomatic vulvovaginal candidiasis probably represents increased growth of yeast that previously colonised the vagina without causing symptoms. Risk factors for vulvovaginal candidiasis include pregnancy and other situations that increase oestrogen levels (e.g., contraceptive use and oestrogen therapy), diabetes mellitus, immunosuppression, [9] and systemic antibiotics. The evidence that different types of contraceptives are associated with risk factors is contradictory. The incidence of vulvovaginal candidiasis rises with initiation of sexual activity, but we found no direct evidence that vulvovaginal candidiasis is sexually transmitted. [10] [11] [12]

PROGNOSIS

We found few descriptions of the natural history of untreated vulvovaginal candidiasis. Discomfort is the main complication and can include pain while passing urine or during sexual intercourse.

AIMS OF INTERVENTION

To alleviate symptoms, with minimal adverse effects of treatment.

OUTCOMES

Clinical cure rates, either measured in the short term (5–15 days) or in the medium term (3–6 weeks) after treatment; **adverse effects**. The definition of clinical cure varies among RCTs but often includes both complete resolution of symptoms and culture negative for *Candida*. As *Candida* may colonise the vagina asymptomatically, we have reported relief of symptoms preferentially where possible.

METHODS

Clinical Evidence search and appraisal October 2013. The following databases were used to identify studies for this review: Medline 1966 to October 2013, Embase 1980 to October 2013, and The Cochrane Database of Systematic Reviews 2013, issue 9 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published RCTs and systematic reviews, at least single-blinded and containing more than 20 individuals, of whom more than 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the review as required. Where a systematic review did not pool results for the RCTs that it included, we have only reported those RCTs that were of sufficient quality. We included only those RCTs in which most participants were non-pregnant women (e.g., we sought RCTs that excluded pregnant women, or RCTs in which pregnant women represented <20% of the participants). For the two questions on symptomatic non-pregnant women, we included RCTs only if recruitment was restricted to non-pregnant women with both symptoms of vaginal candidiasis and laboratory confirmation of candidal infection. We excluded treatment trials where cure was defined solely on the basis of mycological results. We excluded studies of women with HIV infection or trichomoniasis. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 23). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of drug treatments for acute vulvovaginal candidiasis in non-pregnant symptomatic women?**

OPTION **FLUCONAZOLE (ORAL)**

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 23 .
- Oral imidazoles (fluconazole or itraconazole) and intravaginal imidazoles (clotrimazole, miconazole, and econazole) may be equally effective at achieving clinical cure.
- We don't know whether oral fluconazole is more effective than oral itraconazole.
- We found no direct information from RCTs about how oral fluconazole compares to placebo, no treatment, or intravaginal nystatin.

Benefits and harms

Oral fluconazole versus placebo or no treatment:

We found no systematic review or RCTs.

Oral fluconazole versus intravaginal imidazoles:

See option on Intravaginal imidazoles, p 5 .

Oral fluconazole versus oral itraconazole:

We found one systematic review (search date 2006; 6 RCTs, 1092 women) comparing oral fluconazole with oral itraconazole, with follow-up of included studies ranging from 10 days to 8 weeks. [13]

Clinical cure rates

Oral fluconazole compared with oral itraconazole We don't know whether oral fluconazole is more effective than oral itraconazole at increasing rates of clinical cure or improvement at 1 to 8 weeks after treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical cure rates					
[13] Systematic review	1092 women 6 RCTs in this analysis	**Clinical cure or improvement , first scheduled visit assessment (1–4 weeks after treatment)** with fluconazole with itraconazole Absolute results not reported	OR 0.94 95% CI 0.6 to 1.48	⟷	Not significant
[13] Systematic review	1092 women 6 RCTs in this analysis	**Clinical cure or improvement , second scheduled visit assessment (4–8 weeks after treatment)** with fluconazole with itraconazole Absolute results not reported	OR 1.09 95% CI 0.68 to 1.75	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[13] Systematic review	206 women 3 RCTs in this analysis	**Withdrawal owing to serious adverse effects (not further defined)** with fluconazole with itraconazole Absolute results not reported	OR 0.72 95% CI 0.16 to 3.32	⟷	Not significant
[13] Systematic review	809 people 3 RCTs in this analysis	**Adverse effects of the nervous system** with fluconazole with itraconazole Absolute results not reported	OR 1.07 95% CI 0.42 to 2.73	⟷	Not significant
[13] Systematic review	759 women 3 RCTs in this analysis	**Adverse effects of the digestive system** with fluconazole with itraconazole Absolute results not reported	OR 1.84 95% CI 0.3 to 11.27	⟷	Not significant

Oral fluconazole versus intravaginal nystatin:

We found no systematic review or RCTs.

Further information on studies

[13] The review reported that all included trials were of low quality.

Comment: **Clinical guide**

Although studies show that adverse effects with single-dose oral fluconazole are infrequent, when deciding on a treatment it is important to note that fluconazole may interact with other drugs (e.g., oral anticoagulants, phenytoin). [14] One RCT [15] suggested that a single dose of oral fluconazole may be more effective than prolonged intravaginal clotrimazole (for 6 days) at clinical cure at 7 days. However, further research is required before any conclusions can be drawn.

OPTION IMIDAZOLES (INTRAVAGINAL)

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 23 .
- Intravaginal imidazoles seem to reduce symptoms of acute vulvovaginal candidiasis in non-pregnant symptomatic women.
- Intravaginal imidazoles (butoconazole, clotrimazole, miconazole) may reduce symptoms compared with placebo, and all seem to have similar efficacy compared with each other.
- Intravaginal imidazoles (including sertaconazole, econazole, and clotrimazole) may have similar rates of adverse effects (e.g., itching, burning, vaginitis, vulvitis, and delay in menstruation).
- Intravaginal imidazoles (clotrimazole, miconazole, and econazole) and oral imidazoles (fluconazole or itraconazole) may be equally effective at achieving clinical cure.
- We don’t know how intravaginal imidazoles and intravaginal nystatin compare at improving clinical cure rates.

Benefits and harms

Intravaginal imidazoles versus placebo:

We found two systematic reviews (search date 1993 [Medline only], [16] and 2006 [17]). The first systematic review found two RCTs. [18] [19] The second systematic review found one RCT, [19] which was also identified in the first systematic review, but the review did not report outcomes for the placebo arm of the RCT. We found one additional RCT. [20] The first systematic review did not perform a meta-analysis. [16] Most RCTs were small, and many had weak methods (poorly described randomisation, inadequate concealment and blinding, and definitions of cure based on mycology results rather than symptoms). There were high attrition rates for long-term outcomes, especially in the placebo arm.

Clinical cure rates

Intravaginal imidazoles compared with placebo Intravaginal imidazoles (butoconazole, clotrimazole, or miconazole) may be more effective at reducing persistent symptoms of vulvovaginal candidiasis at 4 to 5 weeks compared with placebo (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical cure rates					
[18] RCT **6-armed trial**	709 women with vulvovaginal candidiasis; analysis of 580 women, not by intention to treat (women with other vaginal infections excluded) In review [16]	**Persistent symptoms , 30 days** 31/95 (33%) with butoconazole 2% for 3 days (intravaginal cream) 31/96 (32%) with butoconazole 2% for 6 days (intravaginal cream) 34/95 (36%) with miconazole 2% for 3 days (intravaginal cream) 45/70 (64%) with placebo The remaining arms evaluated butoconazole 1% for 3 days and butoconazole 1% for 6 days	P <0.03 for butoconazole 2% or miconazole *v* placebo	○○○	intravaginal imidazoles
[19] RCT **3-armed trial**	95 women with clinically and mycologically confirmed vulvovaginal candidiasis; analysis of 90 women, not by intention to treat (see Further information on studies) In review [16]	**Persistent symptoms , 4 weeks** 6/20 (30%) with clotrimazole for 3 days (intravaginal tablets) 3/7 (43%) with placebo (oral) The remaining arm evaluated oral itraconazole for 3 days	Significance not reported		
[20] RCT	37 women with clinically and mycologically confirmed vulvovaginal candidiasis. Women in first trimester of pregnancy, women with diabetes or with other vaginal infections, and women using contraceptive foams or jellies were excluded	**Persistent symptoms or mycological failure , 27 to 38 days** 4/18 (22%) with clotrimazole for 1 day (intravaginal tablet) 19/19 (100%) with placebo	P <0.0001	○○○	intravaginal imidazoles

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[18] RCT **6-armed trial**	709 women with vulvovaginal candidiasis; analysis of 580 women, not by intention to treat (women with other vaginal infections excluded). In review [16]	**Adverse effects** with butoconazole 2% for 3 days (intravaginal cream) with butoconazole 2% for 6 days (intravaginal cream) with miconazole 2% for 3 days (intravaginal cream) with placebo The remaining arms evaluated butoconazole 1% for 3 days and butoconazole 1% for 6 days 2% of women in the trial withdrew due to vulvar and/or vaginal irritation (details of withdrawal not reported by treatment group)			
[19] RCT **3-armed trial**	95 women with clinically and mycologically confirmed vulvovaginal candidiasis; analysis of 90 women, not by intention to treat (see Further information on studies) In review [16]	**Adverse effects** 1/23 (4%) with clotrimazole for 3 days (intravaginal tablets) 9/22 (41%) with placebo (oral) The remaining arm evaluated oral itraconazole for 3 days Adverse effects seen with oral placebo were mainly nausea and headache There was an episode of irritation with clotrimazole	Significance not assessed		
[20] RCT	37 women with clinically and mycologically confirmed vulvovaginal candidiasis (women in first trimester of pregnancy, women with diabetes or with other vaginal infections, and women using contraceptive foams or jellies were excluded)	**Adverse effects** with clotrimazole for 1 day (intravaginal tablet) with placebo None of the women reported adverse effects associated with treatment			

Intravaginal imidazoles versus each other:

We found one systematic review (search date 1993; [16] 9 RCTs [18] [21] [22] [23] [24] [25] [26] [27] [28]) and 13 additional RCTs. [29] [30] [31] [32] [33] [34] [35] [36] [37] [38] [39] [40] [41] The systematic review did not perform a meta-analysis. [16] Many of the RCTs were too small to detect clinically important differences in outcomes, and many did not use intention-to-treat analysis.

Clinical cure rates

Intravaginal imidazoles compared with each other We don't know how intravaginal imidazoles compare with each other at reducing the proportion of women with persistent symptoms (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical cure rates					
[18] RCT **6-armed trial**	483 women; analysis not by intention to treat; women who did not have positive *Candida* swabs and did not adhere to protocols were excluded In review [16]	**Persistent symptoms , 30 days** 37/102 (36%) with butoconazole 1% for 3 days 41/95 (43%) with butoconazole 1% for 6 days 31/95 (33%) with butoconazole 2% for 3 days 31/96 (32%) with butoconazole 2% for 6 days 34/95 (36%) with miconazole 2% for 6 days The remaining arm evaluated placebo	Reported as not significant P value not reported	⟷	Not significant
[21] RCT **3-armed trial**	900 women In review [16]	**Symptom or mycological failure , 7 days** 12% with terconazole 0.4% 16% with terconazole 0.8% 19% with miconazole 2% Absolute numbers not reported The duration of treatment was 7 days	Reported as not significant P value not reported	⟷	Not significant
[22] RCT **3-armed trial**	60 women In review [16]	**Persistent symptoms , 28 days** 7/20 (35%) with high-dose terconazole for 1 day 4/17 (24%) with low-dose terconazole for 3 days 5/23 (22%) with clotrimazole for 3 days High dose for terconazole was 240 mg (for 1 day); low dose was 80 mg (for 3 days)	Reported as not significant P value not reported	⟷	Not significant
[23] RCT	271 women In review [16]	**Persistent symptoms , 30 days** 22/100 (22%) with butoconazole for 3 days 20/101 (20%) with miconazole for 7 days	P = 0.996	⟷	Not significant
[24] RCT	274 women In review [16]	**Persistent symptoms , 30 days** 18% with butoconazole for 3 days 26% with clotrimazole for 3 days Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant
[25] RCT **3-armed trial**	140 women; 130 analysed, not by intention to treat In review [16]	**Persistent symptoms , 35 days** 15/44 (34%) with butoconazole 1% for 6 days 12/45 (27%) with butoconazole 2% for 6 days 14/41 (34%) with miconazole 2% for 6 days	Reported as not significant P value not reported	⟷	Not significant
[26] RCT	63 women with mycologically confirmed vulvovaginal candidiasis In review [16]	**Less than a 'very good' symptom response , 7 days** 47% with butoconazole for 3 days 61% with clotrimazole for 6 days	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute numbers not reported			
[27] RCT	217 women; 185 analysed, not by intention to treat In review [16]	**Persistent symptoms , 30 days** 23% with butoconazole for 3 days 31% with clotrimazole for 3 days Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant
[29] RCT	60 women	**Symptoms , 4 weeks** 1/30 (3%) with clotrimazole for 1 day 2/30 (7%) with econazole for 1 day	Reported as not significant P value not reported	⟷	Not significant
[30] RCT	107 women; 101 analysed, not by intention to treat	**Mycological failure or persistent symptoms , 30 days** 2/48 (4%) with flutrimazole for 7 days 7/53 (13%) with clotrimazole for 7 days	Reported as not significant P value not reported	⟷	Not significant
[31] RCT	54 women (51 analysed)	**Mycological failure or persistent symptoms , 7 days** 1/26 (4%) with fenticonazole for 7 days 2/30 (7%) with clotrimazole for 7 days	Reported as not significant P value not reported	⟷	Not significant
[32] RCT	100 women; 86 analysed, not by intention to treat	**Moderate or severe symptoms , 7 to 10 days** 1/43 (2%) with miconazole for 5 days 2/43 (5%) with clotrimazole for 6 days	Reported as not significant P value not reported	⟷	Not significant
[33] RCT	196 women with positive culture for *Candida* species, about 30% with recurrent candidiasis	**Cure rate , 28 days** 64% with econazole once 65% with isoconazole once Absolute numbers not reported	P = 0.2	⟷	Not significant
[34] RCT	223 women	**Persistent symptoms , 30 days** 10/84 (12%) with butoconazole for 1 day 13/93 (14%) with miconazole for 7 days	Reported as not significant P value not reported	⟷	Not significant
[35] RCT	369 women (310 analysed; women without positive swab for candidiasis excluded from analysis; not by intention to treat)	**Persistent symptoms , 1 month** 48/139 (35%) with sertaconazole once 52/149 (35%) with econazole once Interventions were repeated after 1 week if needed	Reported as not significant P value not reported	⟷	Not significant
[36] RCT	80 women	**Symptom failure or mycological failure , 4 weeks** 7/40 (17.5%) with fenticonazole once 8/40 (20.0%) with clotrimazole once	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[37] RCT	50 women	**Symptoms , 21 days** 5/17 (29%) with fenticonazole once 4/15 (27%) with clotrimazole once	Reported as not significant P value not reported	⟷	Not significant
[38] RCT	60 women	**Persistent symptoms , 1 month** 3/30 (10%) with clotrimazole once 4/30 (13%) with econazole once	Reported as not significant P value not reported	⟷	Not significant
[39] RCT	93 women with positive culture for *Candida* species	**Cure rates** with clotrimazole for 7 days with miconazole for 7 days Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant
[40] RCT	102 married women with positive culture for *Candida* species	**Symptoms , 28 days** 6/53 (11%) with econazole for 2 days 8/49 (16%) with clotrimazole for 6 days	P >0.05	⟷	Not significant
[41] RCT	78 women, 40 non-pregnant	**Persistent symptoms , 4 weeks** 1/20 (5%) with terconazole for 7 days 4/20 (20%) with clotrimazole for 7 days	Reported as not significant P value not reported	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] RCT	900 women In review [16]	**Adverse effects** with terconazole 0.4% with terconazole 0.8% with miconazole 2% The most frequently reported adverse effect was headache (no significant difference reported among groups) All treatments were associated with pruritus and burning			
[22] RCT **3-armed trial**	60 women In review [16]	**Adverse effects** with terconazole 240 mg for 1 day with terconazole 80 mg for 3 days with clotrimazole 200 mg for 3 days One woman using terconazole had burning; no other adverse effects associated with treatment were found			
[23] RCT	271 women In review [16]	**Adverse effects** with butoconazole for 3 days with miconazole for 7 days			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		4/136 (3%) women using butoconazole and 2/135 (1.5%) using miconazole had vaginal irritation; 2 women using butoconazole and 1 woman using miconazole withdrew from the trial			
[24] RCT	274 women In review [16]	**Adverse effects** with butoconazole for 3 days with clotrimazole for 3 days 6/272 (2%) women (3 using butoconazole and 3 clotrimazole) had vaginal irritation; 1 woman using clotrimazole withdrew			
[25] RCT **3-armed trial**	140 women; 130 analysed, not by intention to treat In review [16]	**Adverse effects** with butoconazole 1% for 6 days with butoconazole 2% for 6 days with miconazole 2% for 6 days 4 women using butoconazole at either dose had vaginal discharge and headache; 2 women using miconazole had headache, bleeding, and leakage of cream			
[26] RCT	63 women with mycologically confirmed vulvovaginal candidiasis In review [16]	**Adverse effects** with butoconazole for 3 days with clotrimazole for 6 days No adverse effects associated with treatment were reported			
[27] RCT	217 women; 185 analysed, not by intention to treat In review [16]	**Adverse effects** with butoconazole for 3 days with clotrimazole for 3 days 7 women (3%) in the trial had vulvovaginal irritation; 3 using butoconazole and 4 using clotrimazole were advised to discontinue treatment			
[29] RCT	60 women	**Adverse effects** with clotrimazole for 1 day with econazole for 1 day 6 women using econazole had vaginal irritation			
[30] RCT	107 women; 101 analysed, not by intention to treat	**Adverse effects** with flutrimazole for 7 days with clotrimazole for 7 days 1 woman using flutrimazole had contact dermatitis and 2 women using clotrimazole had pruritus			
[31] RCT	54 women (51 analysed)	**Adverse effects** with fenticonazole for 7 days with clotrimazole for 7 days No adverse effects associated with treatment were reported			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[32] RCT	100 women; 86 analysed, not by intention to treat	**Adverse effects** with miconazole for 5 days with clotrimazole for 6 days 4 women in each group had mild burning or irritation associated with treatment			
[33] RCT	196 women with positive culture for *Candida* species, about 30% with recurrent candidiasis	**Adverse effects** with econazole once with isoconazole once 5 women using isoconazole and 2 using econazole had vulvar irritation			
[34] RCT	223 women	**Adverse effects** with butoconazole for 1 day with miconazole for 7 days 2 women using butoconazole and 2 using miconazole had vulvovaginal irritation; 1 woman from each group withdrew from the trial			
[35] RCT	369 women (310 analysed; women without positive swab for candidiasis excluded from analysis; not by intention to treat)	**Itching and burning** 9% with sertaconazole 13% with econazole Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant
[36] RCT	80 women	**Adverse effects** with fenticonazole once with clotrimazole once No adverse effects associated with treatment were reported			
[37] RCT	50 women	**Adverse effects** with fenticonazole once with clotrimazole once 1 woman using fenticonazole had burning			
[38] RCT	60 women	**Adverse effects** with clotrimazole once with econazole once Information about adverse effects awaiting translation			
[40] RCT	102 married women with positive culture for *Candida* species	**Adverse effects** with econazole for 2 days with clotrimazole for 6 days No significant difference between groups in adverse effects, including itching, burning, vaginitis, vulvitis, and delay in menstruation (P value not reported)		⟷	Not significant
[41] RCT	78 women, 40 non-pregnant	**Adverse effects** with terconazole for 7 days with clotrimazole for 7 days			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		1 woman using terconazole had burning			

No data from the following reference on this outcome. [18] [39]

Intravaginal imidazoles versus oral fluconazole or oral itraconazole:

We found one systematic review (search date 2006; 19 RCTs, 2579 women) comparing intravaginal imidazoles (clotrimazole, miconazole, econazole, and butoconazole) with oral fluconazole or oral itraconazole. [17] We found one subsequent RCT comparing intravaginal clotrimazole versus oral fluconazole. [15]

Clinical cure rates

Intravaginal imidazoles compared with oral fluconazole or oral itraconazole Intravaginal imidazoles (clotrimazole, miconazole, and econazole) and oral imidazoles (fluconazole or itraconazole) may be equally effective at achieving clinical cure at up to 12 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical cure rates					
[17] Systematic review	Number of randomised women unclear 12 RCTs in this analysis	**Clinical cure , short-term follow-up (5−15 days)** 673/924 (73%) with intravaginal imidazoles 627/849 (74%) with oral fluconazole or oral itraconazole	OR 0.94 95% CI 0.75 to 1.17 P = 0.57 (See Further information on studies)	⟷	Not significant
[17] Systematic review	Number of randomised women unclear 9 RCTs in this analysis	**Clinical cure , long-term follow-up (2−12 weeks)** 553/723 (76%) with intravaginal imidazoles 467/585 (81%) with oral fluconazole or oral itraconazole	OR 1.07 95% CI 0.82 to 1.41 P = 0.61 (See Further information on studies)	⟷	Not significant
[15] RCT	142 women aged >15 years with acute clinical and mycologically confirmed vulvovaginal candidiasis	**Complete clinical cure , at 7 days** 53/72 (73.6%) with oral fluconazole single dose 41/70 (58.6%) with intravaginal clotrimazole daily for 7 days Unclear method of randomisation, allocation concealment, and blinding See Further information on studies	OR 1.9 95% CI 1.1 to 9.3 P = 0.001	●○○	oral fluconazole

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[17] Systematic review	2579 women	**Adverse events** with intravaginal imidazoles			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with oral fluconazole or oral itraconazole The review did not directly compare adverse effects of intravaginal imidazoles with oral fluconazole or oral itraconazole			
[15] RCT	142 women aged >15 years with acute clinical and mycologically confirmed vulvovaginal candidiasis	**Adverse effects , at 7 days** 5/72 (6.9%) with oral fluconazole single dose 3/70 (4.3%) with intravaginal clotrimazole daily for 7 days The major adverse effect in the oral fluconazole group was headache, and in the intravaginal clotrimazole group it was pelvic pain See Further information on studies	OR 1.8 95% CI 0.4 to 3.3 P = 0.4	⟷	Not significant

Intravaginal imidazoles versus intravaginal nystatin:

We found no systematic review comparing intravaginal imidazoles versus intravaginal nystatin, but we found one RCT. [42]

Clinical cure rates

Intravaginal imidazoles compared with intravaginal nystatin We don't know how intravaginal clotrimazole and intravaginal nystatin compare at improving the composite outcome of symptoms or mycological failure at 4 weeks of follow-up (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical cure rates					
[42] RCT	70 women with vulvovaginal candidiasis (open label)	**Symptoms or mycological failure , 4 weeks** 1/37 (3%) with intravaginal clotrimazole (for 14 days) 1/33 (3%) with nystatin vaginal cream (once daily for 7 days)	Significance not reported (See Further information on studies)		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[42] RCT	70 women with vulvovaginal candidiasis (open label)	**Adverse effects** with intravaginal clotrimazole (for 14 days) with nystatin vaginal cream (once daily for 7 days) No adverse effects associated with treatment reported			

Further information on studies

[17] Allocation concealment was unclear in all studies, and four studies also had no blinding of outcomes assessors, a possible source of performance bias for the outcome of clinical cure. Around half the studies in the analysis had loss to follow-up of greater than 20% or unclear loss to follow-up. The review noted that of the 19 studies in the entire review, seven trials reported pharmaceutical industry support. It is possible that the remaining 12 trials had some pharmaceutical industry involvement.

[19] Five women were excluded from analysis as negative culture for *Candida albicans*; analysis not by intention to treat. Pregnant women, and women with diabetes, immunosuppression, receiving antifungal chemotherapy, or with other vaginal infections were excluded.

[42] The RCT is likely to have been underpowered to detect clinically important differences between groups.

Comment: Trials in women who obtain intravaginal imidazoles over the counter are needed.

A case report of an unplanned pregnancy after treatment with intravaginal miconazole raises concerns that vaginal medicines have the potential to damage rubber condoms and diaphragms because of the fatty excipients used as therapeutic vehicles. [43]

Clinical guide

Clinical heterogeneity among RCTs (e.g., differences in treatment duration, dose, and administration [i.e., before or after menstruation]) makes it difficult to draw definitive conclusions on the effectiveness of specific regimens of intravaginal imidazoles in treating vulvovaginal candidiasis. The subsequent RCT [15] suggests that a single dose of oral fluconazole may be more effective than prolonged intravaginal clotrimazole (for 6 days) at clinical cure at 7 days. However, further research is required.

Oral and intravaginal imidazoles are secreted in maternal milk; therefore, they should not be administered to women who are breastfeeding. Intravaginal nystatin may be acceptable as it is unlikely to be absorbed systemically. Furthermore, before prescribing imidazoles, it is necessary to know the local resistance to these drugs.

OPTION ITRACONAZOLE (ORAL)

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 23 .
- Oral itraconazole seems to be more effective at increasing clinical cure at 1 week compared to placebo, but we don't know whether it is more effective compared to oral fluconazole.
- Oral imidazoles (fluconazole or itraconazole) and intravaginal imidazoles (clotrimazole, miconazole, and econazole) may be equally effective at achieving clinical cure over longer periods up to 12 weeks.
- We found no direct information from RCTs about how oral itraconazole compares to intravaginal nystatin.

Benefits and harms

Oral itraconazole versus placebo:

We found one systematic review (search date 2006), [17] which identified one RCT (95 women) comparing three interventions: oral itraconazole, intravaginal clotrimazole, and placebo. [19]

Clinical cure rates

Oral itraconazole compared with placebo Oral itraconazole seems to be more effective than placebo at increasing clinical cure in women with persistent symptoms of vulvovaginal candidiasis at 1 week (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical cure rates					
[19] RCT **3-armed trial**	95 women with clinically and mycologically confirmed vulvovaginal candidiasis; analysis of 90 women, not by intention to treat (see Further information on studies) In review [17]	**Clinical cure , 1 week** 35/48 (73%) with oral itraconazole (for 3 days) 10/22 (45%) with placebo The remaining arm evaluated intravaginal clotrimazole for 3 days	P <0.05	○○○	oral itraconazole

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[19] RCT **3-armed trial**	95 women with clinically and mycologically confirmed vulvovaginal candidiasis; analysis of 90 women, not by intention to treat (see Further information on studies) In review [17]	**Adverse effects** 17/50 (34%) with oral itraconazole (for 3 days) 9/22 (41%) with placebo The remaining arm evaluated intravaginal clotrimazole for 3 days Adverse effects seen with placebo were mainly nausea and headache. The adverse effects seen with oral itraconazole with increased frequency were nausea (14%), headache (12%), dizziness (6%), and bloating (6%)	Significance not reported		

Oral itraconazole versus intravaginal imidazoles:

See option on Intravaginal imidazoles, p 5 .

Oral itraconazole versus oral fluconazole:

See option on Oral fluconazole, p 4 .

Oral itraconazole versus intravaginal nystatin:

We found no systematic review or RCTs.

Further information on studies

[19] Five women were excluded from analysis as they had a negative culture for *Candida albicans*; analysis not by intention to treat. Pregnant women and women with diabetes, immunosuppression, receiving antifungal chemotherapy, or with other vaginal infections, were also excluded from the study.

Comment: **Clinical guide**
When deciding on a treatment, it is important to note that oral itraconazole may interact with other drugs (e.g., ritonavir, levacetylmethadol). Furthermore, women of childbearing potential should take effective contraception during treatment with itraconazole, and this should continue until the next menstrual period after the end of treatment.

OPTION NYSTATIN (INTRAVAGINAL)

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 23 .
- Intravaginal nystatin seems to reduce symptoms compared with placebo, but we don't know how it compares with intravaginal imidazoles, oral fluconazole, or oral itraconazole.

Benefits and harms

Intravaginal nystatin versus placebo:

We found no systematic review, but found one small RCT comparing intravaginal nystatin with placebo. [44]

Clinical cure rates

Intravaginal nystatin compared with placebo Intravaginal nystatin seems to be more effective than placebo at reducing the proportion of women with a poor symptomatic response at 14 days' treatment; however, this is based on one small study involving 50 women (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical cure rates					
[44] RCT	50 women	**Proportion of women with a symptomatic response categorised as 'poor' , 14 days** 2/25 (8%) with intravaginal nystatin (for 14 days) 10/25 (40%) with placebo	ARR 32% 95% CI 8% to 56% OR 0.18 95% CI 0.05 to 0.65 NNT 3 95% CI 2 to 12	●○○	intravaginal nystatin

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[44] RCT	50 women	**Adverse effects** with intravaginal nystatin (for 14 days) with placebo The RCT reported no adverse effects among 50 women who used intravaginal nystatin			

Intravaginal nystatin versus intravaginal imidazoles:

See option on Intravaginal imidazoles, p 5 .

Intravaginal nystatin versus oral fluconazole or oral itraconazole:

We found no systematic review or RCTs.

Comment: A case report of an unplanned pregnancy after treatment with intravaginal miconazole raises concerns that vaginal medicines may damage rubber condoms and diaphragms because of the fatty excipients used as therapeutic vehicles. [43]

Clinical guide
Intravaginal nystatin is not available in all countries. Adverse effects that have been reported with nystatin include irritation and sensitisation, diarrhoea, nausea, vomiting, dyspepsia, rash, hives, and Stevens-Johnson syndrome. Intravaginal nystatin may be considered for women who are breastfeeding as it is unlikely to be absorbed systemically.

QUESTION What are the effects of alternative or complementary treatments for acute vulvovaginal candidiasis in non-pregnant symptomatic women?

OPTION DOUCHING

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 23 .
- We found no direct information from RCTs about douching in the treatment of women with acute vulvovaginal candidiasis.
- Observational studies have found douching to be associated with serious sequelae, including PID, endometritis, ectopic pregnancy, gonorrhoea, and chlamydia.

Benefits and harms

Douching versus other interventions listed in the review:

We found two systematic reviews (search dates 2002), [45] [46] which identified no RCTs.

Comment: Adverse effects: Case control studies identified by the reviews found that douching was associated with serious sequelae, although there are limited data on the frequency of adverse events. Serious sequelae included PID (douching 3 or more times/month increased the risk of PID >3 times/month compared with not douching), endometritis, ectopic pregnancy, gonorrhoea, and chlamydia. [45] [46] Large, well-designed studies are necessary to explore further the frequency of serious outcomes and the suspected dose-response relationship between douching and its adverse effects. [46]

OPTION GARLIC (ORAL OR INTRAVAGINAL)

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 23 .
- We found no RCT evidence comparing garlic with other interventions listed in the review for the treatment of women with acute vulvovaginal candidiasis.
- Observational studies have shown that garlic taken orally may cause heartburn, nausea, diarrhoea, flatulence, bloating, and an offensive body odour. Prolonged topical use of garlic can lead to allergic reactions or chemical burns.

Benefits and harms

Garlic versus other interventions listed in the review:

We found one systematic review (search date 2002), [45] which identified no RCTs.

Comment: Adverse effects: The one systematic review we found stated that garlic taken orally may cause heartburn, nausea, diarrhoea, flatulence, bloating, and an offensive body odour. [45] Prolonged topical use of garlic can lead to allergic reactions or chemical burns.

Clinical guide
Although there is a lack of good-quality evidence for garlic in treating vulvovaginal candidiasis, it is a cheap and easily available intervention.

OPTION TEA TREE OIL (INTRAVAGINAL)

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 23 .
- We found no RCT evidence comparing intravaginal tea tree oil with other interventions listed in the review for the treatment of women with acute vulvovaginal candidiasis.
- Observational studies have shown that topical tea tree oil can cause skin irritation and a severe allergic rash, or even systematic hypersensitivity reaction.

Benefits and harms

Tea tree oil (intravaginal) versus other interventions listed in the review:

We found one systematic review (search date 2002), [45] which identified no RCTs.

Comment: Adverse effects: The one systematic review we found stated that topical tea tree oil can cause skin irritation and a severe allergic rash. [45] One case report found that topical tea tree oil was associated with systematic hypersensitivity reaction. [47]

Clinical guide
Intravaginal tea tree oil may be difficult to obtain. Some women may find it difficult to apply.

OPTION YOGHURT CONTAINING LACTOBACILLUS ACIDOPHILUS (ORAL OR INTRAVAGINAL)

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 23 .
- We found no RCT evidence comparing yoghurt containing *Lactobacillus acidophilus* with other interventions listed in the review for the treatment of women with acute vulvovaginal candidiasis.

Benefits and harms

Yoghurt containing *Lactobacillus acidophilus* (oral or intravaginal) versus other interventions listed in the review:

We found two systematic reviews (search date 2002; [45] and 2007 [48]), both of which identified no RCTs.

Comment: We found one RCT (55 women) that compared oral *L acidophilus* with placebo at 1 month when given after a single dose of oral fluconazole (150 mg). [49] The RCT found that oral *L acidophilus* decreased vaginal discharge compared with placebo (3/29 [10%] with oral *L acidophilus v* 9/26 [35%] with placebo; P = 0.03). The RCT also found that oral *L acidophilus* reduced the presence of yeast detected by culture compared with placebo (3/29 [10%] with oral *L acidophilus v* 10/26 [39%] with placebo; P = 0.01).

Adverse effects: One of the systematic reviews we found stated that oral yoghurt may cause gastrointestinal disturbance in people with lactose intolerance. [45]

Clinical guide
For some women, it can be embarrassing and uncomfortable applying yoghurt intravaginally. Although different yoghurts can be purchased easily, the composition of yoghurts varies and, therefore, their effects may differ. Furthermore, we do not know the effects of alterations in vaginal pH that may occur with intravaginal yoghurt use.

QUESTION **What are the effects of treating asymptomatic non-pregnant women with a positive swab for candidiasis?**

OPTION **ALTERNATIVE OR COMPLEMENTARY TREATMENTS (YOGHURT CONTAINING LACTOBACILLUS ACIDOPHILUS, DOUCHING, GARLIC, OR INTRAVAGINAL TEA-TREE OIL)**

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 23 .
- We found no RCT evidence comparing the effects of yoghurt containing *Lactobacillus acidophilus*, douching, garlic, or intravaginal tea tree oil versus other interventions listed in the review in asymptomatic non-pregnant women with a positive swab for candidiasis.

Benefits and harms

Alternative or complementary treatments versus other interventions listed in the review:

We found no systematic review or RCTs comparing the effects of alternative or complementary treatments versus other interventions listed in the review in asymptomatic non-pregnant women with a positive swab for candidiasis.

Comment: Asymptomatic vulvovaginal candidiasis has been reported in 10% of women [3] and is a common incidental finding on routine swabs. We found no evidence about the effects of treating asymptomatic women, and treatments may be associated with potential harms.

Clinical guide
For women with asymptomatic vulvovaginal candidiasis, treatment is not recommended by some guidelines. [50] [51] [52]

OPTION **DRUG TREATMENTS (INTRAVAGINAL IMIDAZOLES [BUTOCONAZOLE, CLOTRIMAZOLE, MICONAZOLE, FENTICONAZOLE, TERCONAZOLE, TIOCONAZOLE, ECONAZOLE], ORAL FLUCONAZOLE, ORAL ITRACONAZOLE, OR INTRAVAGINAL NYSTATIN)**

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 23 .
- We found no direct information from RCTs on the effects of intravaginal imidazoles (butoconazole, clotrimazole, miconazole, fenticonazole, terconazole, tioconazole, econazole), oral fluconazole, oral itraconazole, or intravaginal nystatin in asymptomatic non-pregnant women with a positive swab for candidiasis.

Benefits and harms

Drug treatments:

We found no systematic review or RCTs on the effects of drug treatments in asymptomatic non-pregnant women with a positive swab for candidiasis.

Comment: Asymptomatic vulvovaginal candidiasis has been reported in 10% of women [3] and is a common incidental finding on routine swabs. We found no evidence about the effects of treating asymptomatic women, and treatments may be associated with potential harms.

Clinical guide
For women with asymptomatic vulvovaginal candidiasis, treatment is not recommended by some guidelines. [50] [51] [52]

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

SUBSTANTIVE CHANGES

Fluconazole (oral) One RCT added comparing oral fluconazole versus intravaginal clotrimazole. [15] Categorisation unchanged (beneficial).

Imidazoles (intravaginal) One RCT added comparing intravaginal clotrimazole versus oral fluconazole. [15] Categorisation unchanged (beneficial).

REFERENCES

1. Anderson MR, Klink K, Cohrssen A. Evaluation of vaginal complaints. *JAMA* 2004;291:1368–1379.[PubMed]
2. Eckert LO, Hawes SE, Stevens CE, et al. Vulvovaginal candidiasis: clinical manifestations, risk factors, management algorithm. *Obstet Gynecol* 1998;92:757–765.[PubMed]
3. de Oliveira JM, Cruz AS, Fonseca AF, et al. Prevalence of *Candida albicans* in vaginal fluid of asymptomatic Portuguese women. *J Reprod Med* 1993;38:41–42.[PubMed]
4. Sobel JD, Faro S, Force RW, et al. Vulvovaginal candidiasis: epidemiologic, diagnostic, and therapeutic considerations. *Am J Obstet Gynecol* 1998;178:203–211.[PubMed]
5. Sobel JD. Vaginitis. *N Engl J Med* 1997;337:1896–1903.[PubMed]
6. Horowitz BJ, Giaquinta D, Ito S. Evolving pathogens in vulvovaginal candidiasis: implications for patient care. *J Clin Pharmacol* 1992;32:248–255.[PubMed]
7. Sobel JD. Vulvovaginal candidosis. *Lancet* 2007;369:1961–1971.[PubMed]
8. Sobel JD, Chaim W. Treatment of Torulopsis glabrata vaginitis: retrospective review of boric acid therapy. *Clin Infect Dis* 1997;24:649–652.[PubMed]
9. Duerr A, Heilig CM, Meikle SF, et al. Incident and persistent vulvovaginal candidiasis among human immunodeficiency virus-infected women: risk factors and severity. *Obstet Gynecol* 2003;101:548–556.[PubMed]
10. Foxman B. The epidemiology of vulvovaginal candidiasis: risk factors. *Am J Public Health* 1990;80:329–331.[PubMed]
11. Geiger AM, Foxman B, Sobel JD. Chronic vulvovaginal candidiasis: characteristics of women with *Candida albicans*, *C glabrata* and no *Candida*. *Genitourin Med* 1995;71:304–307.[PubMed]
12. Geiger AM, Foxman B, Gillespie BW. The epidemiology of vulvovaginal candidiasis among university students. *Am J Public Health* 1995;85:1146–1148.[PubMed]
13. Pitsouni E, Iavazzo C, Falagas ME. Itraconazole vs fluconazole for the treatment of uncomplicated acute vaginal and vulvovaginal candidiasis in nonpregnant women: a metaanalysis of randomized controlled trials. *Am J Obstet Gynecol* 2008;198:153–160.[PubMed]
14. Houang ET, Chappatte O, Byrne D, et al. Fluconazole levels in plasma and vaginal secretions of patients after a 150-milligram single oral dose and rate of eradication of infection in vaginal candidiasis. *Antimicrob Agents Chemother* 1990;34:909–910.[PubMed]
15. Sekhavat L, Tabatabaii A, Tezerjani FZ. Oral fluconazole 150 mg single dose versus intra-vaginal clotrimazole treatment of acute vulvovaginal candidiasis. *J Infect Public Health* 2011;4:195–199.[PubMed]
16. Reef SE, Levine WC, McNeil MM, et al. Treatment options for vulvovaginal candidiasis, 1993. *Clin Infect Dis* 1995;20:S80–S90.[PubMed]
17. Nurbhai M, Grimshaw J, Watson M, et al. Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush). In: The Cochrane Library, Issue 9, 2013. Chichester, UK: John Wiley & Sons, Ltd.[PubMed]
18. Brown D Jr, Henzl MR, LePage ME, et al. Butoconazole vaginal cream in the treatment of vulvovaginal candidiasis: comparison with miconazole nitrate and placebo. *J Reprod Med* 1986;31:1045–1048.[PubMed]
19. Stein GE, Mummaw N. Placebo-controlled trial of itraconazole for treatment of acute vaginal candidiasis. *Antimicrob Agents Chemother* 1993;37:89–92.[PubMed]
20. Fleury F, Hodgson C. Single-dose treatment of vulvovaginal candidiasis with a new 500 mg clotrimazole vaginal tablet. *Adv Ther* 1984;1:349–356.
21. Corson SL, Kapikian RR, Nehring R. Terconazole and miconazole cream for treating vulvovaginal candidiasis. A comparison. *J Reprod Med* 1991;36:561–567.[PubMed]
22. Kjaeldgaard A. Comparison of terconazole and clotrimazole vaginal tablets in the treatment of vulvovaginal candidosis. *Pharmatherapeutica* 1986;4:525–531.[PubMed]
23. Kaufman RH, Henzl MR, Brown D Jr, et al. Comparison of three-day butoconazole treatment with seven-day miconazole treatment for vulvovaginal candidiasis. *J Reprod Med* 1989;34:479–483.[PubMed]
24. Droegemueller W, Adamson DG, Brown D. Three-day treatment with butoconazole nitrate for vulvovaginal candidiasis. *Obstet Gynecol* 1984;64:530–534.[PubMed]
25. Jacobson JB, Hajman AJ, Wiese J. A new vaginal antifungal agent – butoconazole nitrate. *Acta Obstet Gynecol Scand* 1985;64:241–244.[PubMed]
26. Hajman AJ. Vulvovaginal candidosis: comparison of 3-day treatment with 2% butoconazole nitrate cream and 6-day treatment of 1% clotrimazole cream. *J Int Med Res* 1988;16:367–375.[PubMed]
27. Adamson GD, Brown D Jr, Standard JV, et al. Three-day treatment with butoconazole vaginal suppositories for vulvovaginal candidiasis. *J Reprod Med* 1986;31:131–132.[PubMed]
28. Bradbeer CS, Mayhew SR, Barlow D. Butaconazole and miconazole in treating vaginal candidiasis. *Genitourin Med* 1985;61:270–272.[PubMed]
29. Glasser A. Single-dose treatment of vaginal mycoses. Effectiveness of clotrimazole and econazole. *Fortschr Med* 1986;104:259–262. [In German][PubMed]
30. Amrouni B, Pereiro M, Florez A, et al. A Phase III comparative study of the efficacies of flutrimazole versus clotrimazole for the treatment of vulvovaginal candidiasis. *J Mycol Med* 2000;10:62–65.
31. Brewster E, Preti PM, Ruffmann R, et al. Effect of fenticonazole in vaginal candidiasis: a double-blind clinical trial versus clotrimazole. *J Int Med Res* 1986;14:306–310.[PubMed]
32. Balsdon MJ. Comparison of miconazole-coated tampons with clotrimazole vaginal tablets in the treatment of vaginal candidosis. *Br J Vener Dis* 1981;57:275–278.[PubMed]
33. Bradbeer CS, Thin RN. Comparison of econazole and isoconazole as single-dose treatment for vaginal candidosis. *Genitourin Med* 1985;61:396–398.[PubMed]
34. Brown D, Henzl MR, Kaufman RH, et al. Butoconazole nitrate 2% for vulvovaginal candidiasis. New, single-dose vaginal cream formulation vs. seven-day treatment with miconazole nitrate. Gynazole 1 Study Group. *J Reprod Med* 1999;44:933–938.[PubMed]
35. Dellenbach P, Thomas J-L, Guerin V, et al. Topical treatment of vaginal candidosis with sertaconazole and econazole sustained-release suppositories. *Int J Gynecol Obstet* 2000;71:S47–S52.[PubMed]
36. Wiest W, Azzollini E, Ruffmann R. Comparison of single administration with an ovule of 600 mg fenticonazole versus a 500 mg clotrimazole vaginal pessary in the treatment of vaginal candidiasis. *J Int Med Res* 1989;17:369–372.[PubMed]
37. Studd JW, Dooley MM, Welch CC, et al. Comparative clinical trial of fenticonazole ovule (600 mg) versus clotrimazole vaginal tablet (500 mg) in the treatment of symptomatic vaginal candidiasis. *Curr Med Res Opin* 1989;11:477–484.[PubMed]
38. Herbold H. Comparative studies to the clinical efficacy of two 1-dose-therapies of vaginal candidosis. *Med Welt* 1985;36:255–257.
39. Lebherz TB, Goldman L, Wiesmeier E, et al. A comparison of the efficacy of two vaginal creams for vulvovaginal candidiasis, and correlations with the presence of *Candida* species in the perianal area and oral contraceptive use. *Clin Ther* 1983;5:409–416.[PubMed]
40. Perera J, Seneviratne HR. Econazole and clotrimazole in the treatment of vaginal candidiasis: a double blind comparative study. *Ceylon Med J* 1994;39:132–134.[PubMed]
41. Del Palacio-Hernanz A, Sanz-Sanz F, Rodriquez-Noriega A. Double-blind investigation of R-42470 (terconazole cream 0.4%) and clotrimazole (cream 1%) for the topical treatment of mycotic vaginitis. *Chemioterapia* 1984;3:192−195.[PubMed]
42. Cassar NL. High-potency nystatin cream in the treatment of vulvovaginal candidiasis. *Curr Ther Res* 1983;34:305–310.
43. Meyboom RH, Havinga JS, Lastdrager CJ, et al. Damage to condoms caused by vaginally administered drug. *Ned Tijdschr Geneeskd* 1995;139:1602–1605. [In Dutch][PubMed]
44. Isaacs JH. Nystatin vaginal cream in monilial vaginitis. *Illinois Med J* 1973;3:240–241.[PubMed]
45. Van Kessel K, Assefi N, Marrazzo J, et al. Common complementary and alternative therapies for yeast vaginitis and bacterial vaginosis: a systematic review. *Obstet Gynecol Surv* 2003;58:351–358.[PubMed]
46. Martino JL, Vermund SH. Vaginal douching: evidence for risks or benefits to women's health *Epidemiol Rev* 2002;24:109–124.[PubMed]
47. Mozelsio NB, Harris KE, McGrath KG, et al. Immediate systemic hypersensitivity reaction associated with topical application of Australian tea tree oil. *Allergy Asthma Proc* 2003;24:73–75.[PubMed]
48. Abad CL, Safdar N. The role of Lactobacillus probiotics in the treatment or prevention of urogenital infections: a systematic review. *J Chemother* 2009;21:243–252.[PubMed]
49. Martinez RC, Franceschini SA, Patta MC, et al. Improved treatment of vulvovaginal candidiasis with fluconazole plus probiotic Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14. *Lett App Microbiol* 2009;48:269–274.
50. American College of Obstetricians and Gynecologists (ACOG). Vaginitis (ACOG practice bulletin no. 72). May 2006. Available at http://www.guideline.gov/content.aspx?id=10925 (last accessed 12 November 2014).
51. British Association for Sexual Health and HIV. United Kingdom national guideline on the management of vulvovaginal candidiasis. 2007. Available at http://www.bashh.org/documents/1798.pdf (last accessed 12 November 2014).
52. Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases: treatment guidelines, 2010. *MMWR Recomm Rep* 2010;59:1–110.[PubMed]

Candidiasis (vulvovaginal)

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Competing interests: JEML declares that she has no competing interests.
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Disclaimer

GRADE **Evaluation of interventions for Candidiasis (vulvovaginal).**

Important outcomes					Clinical cure rates				
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of drug treatments for acute vulvovaginal candidiasis in non-pregnant symptomatic women?									
6 (1092) [13]	Clinical cure rates	Oral fluconazole versus oral itraconazole	4	−2	0	0	0	Low	Quality point deducted for weak methods and incomplete reporting of results
3 (712) [16] [20]	Clinical cure rates	Intravaginal imidazoles versus placebo	4	−1	0	−1	0	Low	Quality point deducted for no ITT analysis; directness point deducted for high rates of attrition, especially in the placebo arm
22 (at least 790 women) [16] [27] [29] [30] [31] [32] [33] [34] [35] [36] [37] [38] [39] [40] [41]	Clinical cure rates	Intravaginal imidazoles versus each other	4	−2	0	0	0	Low	Quality points deducted for no ITT analysis and for incomplete reporting
20 (at least 2721) [17] [15]	Clinical cure rates	Intravaginal imidazoles versus oral fluconazole or oral itraconazole	4	−1	0	−1	0	Low	Quality point deducted for lack of allocation concealment; directness point deducted for not reporting results of comparisons versus oral fluconazole and oral itraconazole separately
1 (70) [42]	Clinical cure rates	Intravaginal imidazoles versus intravaginal nystatin	4	−2	0	0	0	Low	Quality points deducted for lack of blinding and incomplete reporting of results
1 (95) [19]	Clinical cure rates	Oral itraconazole versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
1 (50) [44]	Clinical cure rates	Intravaginal nystatin versus placebo	4	−1	0	−1	+1	Moderate	Quality point deducted for sparse data. Directness point deducted for uncertainty about definition of outcome. Effect-size point added for OR <0.2

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.