Candidiasis (vulvovaginal)

Search date March 2009

Des Spence

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 a male sexual partner to resolve symptoms and prevent recurrence in non-pregnant women with symptomatic acute vulvovaginal candidiasis? What are the effects of alternative or complementary treatments for symptomatic recurrent vulvovaginal candidiasis in non-pregnant women? What are the effects of treating a male sexual partner in non-pregnant women with symptomatic recurrent vulvovaginal candidiasis? 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 March 2009 (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 61 systematic reviews, RCTs, or observational 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 (boric acid, nystatin, imidazoles, tea tree oil); oral fluconazole; oral itraconazole; treating a male sexual partner; and yoghurt containing Lactobacillus acidophilus (oral or vaginal).

QUESTIONS

INTERVENTIONS

DRUG TREATMENTS FOR ACUTE SYMPTOMATIC INFECTION

Beneficial

Likely to be beneficial

ALTERNATIVE TREATMENTS FOR ACUTE SYMPTOMATIC INFECTION

Unknown effectiveness

TREATING MALE SEXUAL PARTNER IN ACUTE SYMPTOMATIC INFECTION

Unlikely to be beneficial

DRUGS TO PREVENT RECURRENCE

Likely to be beneficial

Unknown effectiveness

ALTERNATIVE TREATMENTS TO PREVENT RECURRENCE

Unknown effectiveness

© BMJ Publishing Group Ltd 2010. All rights reserved.

Key points

- Vulvovaginal candidiasis is characterised by vulval itching and 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, diabetes mellitus, and systemic antibiotics. Incidence increases with the onset of sexual activity, but associations with different types of contraceptives are unclear.

  Recurrent symptoms are common, but are caused by candidiasis in only one third of cases.

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

  Intravaginal imidazoles (butoconazole, clotrimazole, miconazole) reduce symptoms compared with placebo and all seem to have similar efficacy compared with each other. RCTs suggest that single-dose regimens may be as effective as multiple-dose regimens.

  Intravaginal imidazoles and oral fluconazole or itraconazole seem equally effective in treating acute attacks.

- Intravaginal nystatin reduces symptoms compared with placebo, but we don't know how it compares with intravaginal imidazoles or oral fluconazole or itraconazole.

- The benefits of other intravaginal treatments, to treat acute attacks or prevent recurrence, remain unclear, and some may be associated with serious adverse effects.

  We found no RCT evidence assessing intravaginal boric acid or tea tree oil.

  We found no RCT evidence assessing garlic or yoghurt, used intravaginally or orally.

  We found no RCT evidence on efficacy of douching, but it is associated with serious adverse effects such as PID and infections, endometritis, and ectopic pregnancy.

  Oral fluconazole and itraconazole are likely to be beneficial in preventing recurrence of infection.

  Treating the woman's male sexual partner does not reduce symptoms or prevent recurrence in the woman.

DEFINITION

Vulvovaginal candidiasis is defined as symptomatic vaginitis (inflammation of the vagina), which often involves the vulva, caused by infection with a *Candida* yeast. Predominant symptoms are vulval itching and abnormal vaginal discharge (which may be minimal, a "cheese-like" material, or a watery secretion). [1] Differentiation from other forms of vaginitis requires the presence of yeast on microscopy of vaginal fluid. **Recurrent vulvovaginal candidiasis** is commonly defined as four or more symptomatic episodes a year. [2]

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] and self-reported history of at least one episode of vulvovaginal candidiasis has been as high as 72%. [4] Recurrent symptoms are common but are caused by candidiasis in only one third of cases. [5]

AETIOLOGY/ RISK FACTORS

Candida albicans accounts for 85% to 90% of cases of vulvovaginal candidiasis. [6] [7] 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, diabetes mellitus, 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. [8] [9] [10]

© BMJ Publishing Group Ltd 2010. All rights reserved.

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. Balanitis in male partners of women with vulvovaginal candidiasis can occur, but it is rare.

AIMS OF INTERVENTION To alleviate symptoms and prevent recurrence, with minimal adverse effects of treatment.

OUTCOMES **Acute vulvovaginal candidiasis:** Clinical cure rates, either measured in the short term (5–15 days) or medium term (3–6 weeks) after treatment; adverse effects of treatment. The definition of clinical cure varies among RCTs, but often includes both complete resolution of symptoms and culture negative for *Candida*. In the option on treating a male sexual partner, we also assessed symptomatic recurrence confirmed by positive culture. **Recurrent vulvovaginal candidiasis:** Symptomatic recurrence confirmed by positive culture, quality of life, and adverse effects of treatment.

METHODS *Clinical Evidence* search and appraisal March 2009. The following databases were used to identify studies for this review: Medline 1966 to March 2009, Embase 1980 to March 2009, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials, Issue 1, 2009. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, 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 required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We also searched for cohort studies on specific harms of named interventions. 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 from the target population (e.g., to answer the questions for non-pregnant women, we sought RCTs that excluded pregnant women, or RCTs in which pregnant women represented <20% of the participants). We excluded treatment trials where cure was defined solely on the basis of mycological results. We excluded studies of women with HIV infection. RCTs also excluded women with diabetes mellitus. For questions on symptomatic women, we included RCTs only if recruitment was restricted to women with both symptoms of vaginal candidiasis and laboratory confirmation of candidal infection. In the questions on treatment and preventing recurrence, we have searched for RCTs comparing all of the listed drug and non-drug interventions versus each other and reported all RCTs of sufficient quality. 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 38). 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 IMIDAZOLES (INTRAVAGINAL)

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 38 .
- Intravaginal imidazoles, p 3 reduce symptoms of acute vulvovaginal candidiasis in non-pregnant women.
- Intravaginal imidazoles (butoconazole, clotrimazole, miconazole) reduce symptoms compared with placebo and all seem to have similar efficacy compared with each other. RCTs suggest that single-dose regimens may be as effective as multiple-dose regimens.
- Intravaginal imidazoles and oral fluconazole or itraconazole seem equally effective in treating acute attacks.

© BMJ Publishing Group Ltd 2010. All rights reserved.

Benefits and harms

Intravaginal imidazoles versus placebo:

We found one systematic review (search date 1993 [Medline only], [11] 2 RCTs) [12] [13] and one additional RCT. [14] The systematic review did not perform a meta-analysis. [11] 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).

Clinical cure rates

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical cure rates					
[12] 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 [11] The remaining arms evaluated butoconazole 1% for 3 days and butoconazole 1% for 6 days.	**Persistent symptoms , 30 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 3 days 45/70 (64%) with placebo	P <0.03 for butoconazole 2% or miconazole *v* placebo	○○○	intravaginal imidazoles
[13] 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 about studies) In review [11]	**Persistent symptoms , 4 weeks** 8/48 (17%) with itraconazole 200 mg daily for 3 days 6/20 (30%) with clotrimazole 200 mg daily for 3 days 3/7 (43%) with placebo (oral)	Significance of difference between active treatment and placebo not reported		
[14] RCT	37 women with clinically and mycologically confirmed vulvovaginal candidiasis. Women in first trimester of pregnancy, with diabetes, or other vaginal infections and women using contraceptive foams or jellies excluded	**Persistent symptoms or mycological failure , 27 to 38 days** 4/18 (22%) with clotrimazole 500 mg for 1 day 19/19 (100%) with placebo	P <0.0001	○○○	intravaginal imidazoles

Adverse effects

© BMJ Publishing Group Ltd 2010. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] 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 [11] The remaining arms evaluated butoconazole 1% for 3 days and butoconazole 1% for 6 days.	**Adverse effects** with butoconazole 2% for 3 days with butoconazole 2% for 6 days with miconazole 2% for 3 days with placebo 2% of women in the trial withdrew due to vulvar and/or vaginal irritation (details of withdrawal not reported by treatment group)			
[13] 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 about studies) In review [11]	**Adverse effects** 17/50 (34%) with itraconazole 200 mg daily for 3 days 1/23 (4%) with clotrimazole 200 mg daily for 3 days 9/22 (41%) with placebo (oral) Adverse effects seen with oral placebo were mainly nausea and headache. Intravaginal itraconazole was associated with nausea, headache, dizziness, and bloating. There was an episode of irritation with clotrimazole.	Sgnificance not assessed		
[14] RCT	37 women with clinically and mycologically confirmed vulvovaginal candidiasis. Women in first trimester of pregnancy, with diabetes, or other vaginal infections and women using contraceptive foams or jellies excluded	**Adverse effects** with clotrimazole 500 mg for 1 day 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; [11] 9 RCTs) [12] [15] [16] [17] [18] [19] [20] [21] [22] and 13 additional RCTs. [23] [24] [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] [35] [36] Many of the RCTs were too small to detect clinically important differences in outcomes, and many did not use intention-to-treat analysis. The RCTs provided no evidence of any consistent difference in effectiveness among the different imidazoles.

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).

© BMJ Publishing Group Ltd 2010. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical cure rates					
[15] RCT **3-armed trial**	900 women In review [11]	**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
[16] RCT **3-armed trial**	60 women In review [11]	**Persistent symptoms , 28 days** 7/20 (35%) with terconazole 240 mg for 1 day 4/17 (24%) with terconazole 80 mg for 3 days 5/23 (22%) with clotrimazole 200 mg for 3 days	Reported as not significant P value not reported	⟷	Not significant
[17] RCT	271 women In review [11]	**Persistent symptoms , 30 days** 22/100 (22%) with butoconazole 2% for 3 days 20/101 (20%) with miconazole 2% for 7 days	P = 0.996	⟷	Not significant
[18] RCT	274 women In review [11]	**Persistent symptoms , 30 days** 18% with butoconazole 2% for 3 days 26% with clotrimazole 200 mg for 3 days Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant
[19] RCT **3-armed trial**	140 women; 130 analysed, not by intention to treat In review [11]	**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
[20] RCT	63 women with mycologically confirmed vulvovaginal candidiasis In review [11]	**Less than a "very good" symptom response , 7 days** 47% with butoconazole 2% for 3 days 61% with clotrimazole 1% for 6 days Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant
[21] RCT	217 women; 185 analysed, not by intention to treat In review [11]	**Persistent symptoms , 30 days** 23% with butoconazole 100 mg for 3 days 31% with clotrimazole 200 mg for 3 days Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant
[12] RCT **6-armed trial**	483 women. Analysis not by intention to treat; women who did not have positive *Candida* swabs and did not	**Persistent symptoms , 30 days** 37/102 (36%) with butoconazole 1% for 3 days 41/95 (43%) with butoconazole 1% for 6 days	Reported as not significant P value not reported	⟷	Not significant

© BMJ Publishing Group Ltd 2010. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	adhere to protocols were excluded In review [11] The remaining arm evaluated placebo	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			
[23] RCT	60 women	**Symptoms , 4 weeks** 1/30 (3%) with clotrimazole 500 mg for 1 day 2/30 (7%) with econazole 150 mg for 1 day	Reported as not significant P value not reported	⟷	Not significant
[24] Pseudo-randomised trial	156 women	**Mycological failure and persistent symptoms , 14 days** 5/60 (8%) with clotrimazole 200 mg for 3 days 3/50 (6%) with econazole 150 mg for 3 days	Similar cure rates; significance of difference between groups not assessed		
[25] RCT	107 women; 101 analysed, not by intention to treat	**Mycological failure or persistent symptoms , 30 days** 2/48 (4%) with flutrimazole 1 g for 7 days 7/53 (13%) with clotrimazole 1 g for 7 days	Reported as not significant P value not reported	⟷	Not significant
[26] RCT	54 women (51 analysed)	**Mycological failure or persistent symptoms , 7 days** 1/26 (4%) with fenticonazole 2% for 7 days 2/30 (7%) with clotrimazole 1% for 7 days	Reported as not significant P value not reported	⟷	Not significant
[27] RCT	100 women; 86 analysed, not by intention to treat	**Moderate or severe symptoms , 7 to 10 days** 1/43 (2%) with miconazole tampons bd for 5 days 2/43 (5%) with clotrimazole 100 mg for 6 days	Reported as not significant P value not reported	⟷	Not significant
[29] RCT	223 women	**Persistent symptoms , 30 days** 10/84 (12%) with butoconazole 2% for 1 day 13/93 (14%) with miconazole 2% for 7 days	Reported as not significant P value not reported	⟷	Not significant
[30] 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 300 mg once 52/149 (35%) with econazole 150 mg once Interventions were repeated after 1 week if needed	Reported as not significant P value not reported	⟷	Not significant
[31] RCT	80 women	**Symptom failure or mycological failure , 4 weeks** 7/40 (17.5%) with fenticonazole 600 mg once 8/40 (20%) with clotrimazole 500 mg once	Reported as not significant P value not reported	⟷	Not significant

© BMJ Publishing Group Ltd 2010. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[32] RCT	78 women, 40 non-pregnant	**Persistent symptoms , 4 weeks** 1/20 (5%) with terconazole 20 mg for 7 days 4/20 (20%) with clotrimazole 50 mg for 7 days	Reported as not significant P value not reported	⟷	Not significant
[33] RCT	50 women	**Symptoms , 21 days** 5/17 (29%) with fenticonazole 600 mg once 4/15 (27%) with clotrimazole 500 mg once	Reported as not significant P value not reported	⟷	Not significant
[34] RCT	60 women	**Persistent symptoms , 1 month** 3/30 (10%) with clotrimazole 10% once 4/30 (13%) with econazole 150 mg once	Reported as not significant P value not reported	⟷	Not significant
[35] RCT	93 women with positive culture for *Candida* species	**Cure rates** with clotrimazole 1% for 7 days with miconazole 2% for 7 days Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant
[36] RCT	102 married women with positive culture for *Candida* species	**Symptoms , 28 days** 6/53 (11%) with econazole 150 mg for 2 days 8/49 (16%) with clotrimazole 100 mg for 6 days	P >0.05	⟷	Not significant
[37] RCT	196 women with positive culture for *Candida* species, about 30% with recurrent candidiasis	**Cure rate , 28 days** 64% with econazole 300 mg once 65% with isoconazole 600 mg once Absolute numbers not reported	P = 0.2	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[15] RCT	900 women In review [11]	**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			
[16] RCT **3-armed trial**	60 women In review [11]	**Adverse effects** with terconazole 240 mg for 1 day with terconazole 80 mg for 3 days with clotrimazole 200 mg for 3 days			

© BMJ Publishing Group Ltd 2010. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		One woman using terconazole had burning; no other adverse effects associated with treatment were found			
[17] RCT	271 women In review [11]	**Adverse effects** with butoconazole 2% for 3 days with miconazole 2% for 7 days 4/136 (3%) women using butoconazole and 2/135 (1.5%) using miconazole had vaginal irritation; two women using butoconazole and one woman using miconazole withdrew from the trial			
[18] RCT	274 women In review [11]	**Adverse effects** with butoconazole 2% for 3 days with clotrimazole 200 mg for 3 days 6/272 (2%) women (3 using butoconazole and 3 clotrimazole) had vaginal irritation; one woman using clotrimazole withdrew			
[19] RCT **3-armed trial**	140 women; 130 analysed, not by intention to treat In review [11]	**Adverse effects** with butoconazole 1% for 6 days with butoconazole 2% for 6 days with miconazole 2% for 6 days Four women using butoconazole at either dose had vaginal discharge and headache; two women using miconazole had headache, bleeding, and leakage of cream			
[38] RCT	63 women with mycologically confirmed vulvovaginal candidiasis In review [11]	**Adverse effects** with butoconazole 2% for 3 days with clotrimazole 1% for 6 days No adverse effects associated with treatment were reported			
[21] RCT	217 women; 185 analysed, not by intention to treat In review [11]	**Adverse effects** with butoconazole 100 mg for 3 days with clotrimazole 200 mg for 3 days Seven women (3%) in the trial had vulvovaginal irritation; three using butoconazole and four using clotrimazole were advised to discontinue treatment			
[23] RCT	60 women	**Adverse effects** with clotrimazole 500 mg for 1 day with econazole 150 mg for 1 day Six women using econazole had vaginal irritation			
[24] RCT	156 women	**Adverse effects** with clotrimazole 200 mg for 3 days			

© BMJ Publishing Group Ltd 2010. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with econazole 150 mg for 3 days One woman had difficulty in inserting pessary; no other adverse effects found			
[25] RCT	107 women; 101 analysed, not by intention to treat	**Adverse effects** with flutrimazole 1 g for 7 days with clotrimazole 1 g for 7 days One woman using flutrimazole had contact dermatitis and two woman using clotrimazole had pruritus			
[26] RCT	54 women (51 analysed)	**Adverse effects** with fenticonazole 2% for 7 days with clotrimazole 1% for 7 days No adverse effects associated with treatment were reported			
[27] RCT	100 women (86 analysed; not by intention to treat)	**Adverse effects** with miconazole tampons bd for 5 days with clotrimazole 100 mg for 6 days Four women in each group had mild burning or irritation associated with treatment			
[29] RCT	223 women	**Adverse effects** with butoconazole 2% for 1 day with miconazole 2% for 7 days Two women using butoconazole and two using miconazole had vulvovaginal irritation; one woman from each group withdrew from the trial			
[30] 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
[31] RCT	80 women	**Adverse effects** with fenticonazole 600 mg once with clotrimazole 500 mg once No adverse effects associated with treatment were reported			
[32] RCT	78 women, 40 non-pregnant	**Adverse effects** with terconazole 20 mg for 7 days with clotrimazole 50 mg for 7 days One woman using terconazole had burning			
[33] RCT	50 women	**Adverse effects** with fenticonazole 600 mg once with clotrimazole 500 mg once			

© BMJ Publishing Group Ltd 2010. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		One woman using fenticonazole had burning			
[34] RCT	60 women	**Adverse effects** with clotrimazole 10% once with econazole 150 mg once Information about adverse effects awaiting translation			
[36] RCT	102 married women with positive culture for *Candida* species	**Adverse effects** with econazole 150 mg for 2 days with clotrimazole 100 mg 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
[37] RCT	196 women with positive culture for *Candida* species, about 30% with recurrent candidiasis	**Adverse effects** with econazole 300 mg once with isoconazole 600 mg once Five women using isoconazole and two using econazole had vulval irritation			

No data from the following reference on this outcome. [12] [35]

Single- versus multiple-dose intravaginal imidazoles:

We found one systematic review (search date 1993; [11] 3 RCTs) [16] [39] [40] and four additional RCTs [41] [42] [43] [44] comparing single-dose intravaginal imidazole versus 2 to 3 days of treatment. The RCTs found no consistent difference between single and multiple doses in the proportion of women with persistent symptoms, but the trials were underpowered to detect a clinically important difference.

Clinical cure rates

Single compared with multiple doses Single dose and multiple doses of intravaginal imidazoles seem equally effective at reducing the proportion of women with persistent symptoms (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical cure rates					
[16] RCT **3-armed trial**	60 women In review [11] The remaining arm evaluated clotrimazole 200 mg for 3 days	**Persistent symptoms , 4 weeks** 1/17 (6%) with terconazole 80 mg for 3 days 7/20 (35%) with terconazole 240 mg for 1 day	Reported as not significant P value not reported	⟷	Not significant
[39] RCT	39 women with clinically and mycologically confirmed candidiasis In review [11]	**Symptoms or mycological failure , 14 days** 8/18 (44%) with clotrimazole 500 mg for 1 day 2/18 (11%) with clotrimazole 500 mg for 1 day plus 100 mg 2 days	P = 0.06	⟷	Not significant

© BMJ Publishing Group Ltd 2010. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[40] RCT	103 women with clinically and mycologically confirmed vulvovaginal candidiasis (95 analysed) In review [11]	**Symptoms or mycological failure , 27 days** 12/48 (25%) with clotrimazole 500 mg for 1 day 13/47 (28%) with clotrimazole 100 mg for 3 days	Reported as not significant P value not reported	⟷	Not significant
[41] RCT	29 women (27 analysed)	**Persistent symptoms , 4 weeks** 2/14 (14%) with clotrimazole 500 mg for 1 day 2/13 (15%) with clotrimazole 100 mg for 3 day	P = 1.00	⟷	Not significant
[42] RCT	72 women	**Persistent symptoms , 4 weeks** 14% with clotrimazole 500 mg for 1 day 10% with clotrimazole 100 mg for 3 days Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant
[43] RCT	40 women	**Persistent symptoms , 4 weeks** 5% with clotrimazole 500 mg for 1 day 20% with clotrimazole 100 mg for 3 days Absolute numbers not reported	Significance not assessed		
[44] RCT	558 women (2 RCTs)	**Persistent symptoms , 4 weeks** 18% with miconazole 1200 mg for 1 day 19% with miconazole 100 mg for 7 days Absolute numbers not reported Results from first RCT: number of women in this analysis unclear	Reported as not significant P value not reported	⟷	Not significant
[44] RCT	558 women (2 RCTs)	**Persistent symptoms , 4 weeks** 31% with miconazole 1200 mg for 1 day 30% with miconazole 100 mg for 7 days Absolute numbers not reported Results from second RCT: Number of women in this analysis unclear	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					
[39] RCT	39 women with clinically and mycologically confirmed candidiasis In review [11]	**Adverse effects** with clotrimazole 500 mg for 1 day with clotrimazole 500 mg for 1 day plus 100 mg 2 days			

© BMJ Publishing Group Ltd 2010. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		One woman having 3-day treatment had severe perianal rash			
[40] RCT	103 women with clinically and mycologically confirmed vulvovaginal candidiasis (95 analysed) In review [11]	**Adverse effects** with clotrimazole 500 mg for 1 day with clotrimazole 100 mg for 3 days One woman having 3-day treatment had vulval oedema			
[41] RCT	29 women (27 analysed)	**Adverse effects** with clotrimazole 500 mg for 1 day with clotrimazole 100 mg for 3 day No adverse effects associated with treatment reported			
[45] RCT	72 women	**Adverse effects** with clotrimazole 500 mg for 1 day with clotrimazole 100 mg for 3 days No adverse effects associated with treatment reported			
[43] RCT	40 women	**Adverse effects** with clotrimazole 500 mg for 1 day with clotrimazole 100 mg for 3 days One woman had burning			
[46] RCT	558 women (2 RCTs)	**Adverse effects** with miconazole 1200 mg for 1 day with miconazole 100 mg for 7 days Miconazole associated with vulval irritation, pruritus, and headache No significant difference between groups Reported as not significant P values not reported			

No data from the following reference on this outcome. [16]

Different durations of multiple-dose regimen of intravaginal imidazoles:

We found one systematic review (search date 1993; [11] 5 RCTs) [12] [16] [47] [48] [49] and one additional RCT [50] comparing different durations (between 3 and 14 days) of the same intravaginal imidazole against each other. The RCTs found no consistent difference between regimens in the proportion of women with persistent symptoms, but were probably underpowered to detect a clinically important difference.

© BMJ Publishing Group Ltd 2010. All rights reserved.

Clinical cure rates

Different doses of multiple-dose regimens compared with each other We don't know how different durations (3–14 days) of multiple-dose regimens 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					
[12] RCT **4-armed trial**	709 women with vulvovaginal candidiasis (analysis of 580 women; not by intention to treat; women who did not have positive *Candida* swabs and did not adhere to protocols were excluded) In review [11]	**Persistent symptoms , 30 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 3 days 45/70 (64%) with placebo	No significant difference among active treatment groups Reported as not significant P value not reported	⟷	Not significant
[47] RCT **3-armed trial**	150 women (open label, 117/150 [78%] women analysed; not by intention to treat) In review [11]	**Symptom or mycological failure , 28 days** 12% with clotrimazole 100 mg vaginal tablet for 7 days 16% with clotrimazole 100 mg vaginal tablet for 14 days 22% with miconazole vaginal cream for 14 days Absolute numbers not reported	P = 0.50	⟷	Not significant
[16] RCT **3-armed trial**	60 women In review [11] The remaining arm evaluated terconazole 240 mg for 1 day	**Persistent symptoms , 4 weeks** 1/17 (6%) with terconazole 80 mg for 3 days 5/23 (22%) with clotrimazole 200 mg for 3 days	Reported as not significant P value not reported	⟷	Not significant
[48] RCT	130 women with mycologically confirmed vulvovaginal candidiasis (110 analysed) In review [11]	**Persistent symptoms , 4 weeks** 8/54 (15%) with clotrimazole 200 mg for 3 days 15/56 (27%) with clotrimazole 100 mg for 7 days	Reported as not significant P value not reported	⟷	Not significant
[49] RCT	63 women (54 analysed) In review [11]	**Persistent symptoms , 4 weeks** 3/26 (11%) with clotrimazole 200 mg for 3 days 6/28 (21%) with clotrimazole 100 mg for 7 days	Reported as not significant P value not reported	⟷	Not significant
[50] RCT	138 women (127 analysed)	**Persistent symptoms , 2 days after treatment** 47% with clotrimazole 200 mg for 3 days 40% with clotrimazole 100 mg for 6 days	Reported as not significant P value not reported	⟷	Not significant

Adverse effects

© BMJ Publishing Group Ltd 2010. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] RCT **4-armed trial**	709 women with vulvovaginal candidiasis (analysis of 580 women; not by intention to treat; women who did not have positive *Candida* swabs and did not adhere to protocols were excluded) In review [11]	**Adverse effects** with butoconazole 2% for 3 days with butoconazole 2% for 6 days with miconazole 2% for 3 days with placebo 2% of women in the trial withdrew due to vulvar and/or vaginal irritation (details of withdrawals not reported by treatment group)			
[47] RCT **3-armed trial**	150 women (open label, 117/150 [78%] women analysed; not by intention to treat) In review [11]	**Adverse effects** with clotrimazole 100 mg vaginal tablet for 7 days with clotrimazole 100 mg vaginal tablet for 14 days with miconazole vaginal cream for 14 days One woman using clotrimazole for 7 days withdrew due to abdominal pain and one using clotrimazole for 14 days withdrew due to vulval irritation			
[48] RCT	130 women with mycologically confirmed vulvovaginal candidiasis (110 analysed) In review [11]	**Adverse effects** with clotrimazole 200 mg for 3 days with clotrimazole 100 mg for 7 days One woman using 7-day treatment had vulval irritation			
[49] RCT	63 women (54 analysed) In review [11]	**Adverse effects** with clotrimazole 200 mg for 3 days with clotrimazole 100 mg for 7 days One woman having 3-day treatment had vulval irritation; two women having 7-day treatment had adverse effects; one had bloating, the other had burning, cramping, and bleeding			
[50] RCT	138 women (127 analysed)	**Adverse effects** with clotrimazole 200 mg for 3 days with clotrimazole 100 mg for 6 days Absolute numbers not reported One woman had a tingling sensation and one felt overheated			

No data from the following reference on this outcome. [16]

© BMJ Publishing Group Ltd 2010. All rights reserved.

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) versus oral fluconazole or itraconazole. [51]

Clinical cure rates

Intravaginal imidazoles compared with oral fluconazole or oral itraconazole Intravaginal imidazoles (clotrimazole, miconazole, and econazole) and oral fluconazole or itraconazole are equally effective at reducing persistent symptoms at short-term follow-up; however, intravaginal imidazoles are less effective than oral fluconazole or itraconazole at reducing persistent symptoms at long-term follow-up (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical cure rates					
[51] Systematic review	2579 women 12 RCTs in this analysis	**Clinical cure , short-term follow-up (time frame not specified)** 673/924 (73%) with intravaginal imidazoles 627/849 (74%) with oral fluconazole or itraconazole	P = 0.57	⟷	Not significant
[51] Systematic review	2579 women 9 RCTs in this analysis	**Clinical cure , long-term follow-up (time frame not specified)** 553/723 (76%) with intravaginal imidazoles 467/585 (81%) with oral fluconazole or itraconazole	OR 1.07 95% CI 0.82 to 1.41 P = 0.61	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[51] Systematic review	2579 women	**Adverse events** with intravaginal imidazoles with oral fluconazole or itraconazole The review did not directly compare adverse effects of intravaginal imidazoles versus oral fluconazole or oral itraconazole			

Intravaginal imidazoles versus intravaginal nystatin:

We found no systematic review. We found one RCT. [52]

Clinical cure rates

Intravaginal imidazoles compared with intravaginal nystatin Intravaginal imidazoles may be more effective at improving the composite outcome of symptoms or mycological failure at 4 weeks (low-quality evidence).

© BMJ Publishing Group Ltd 2010. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical cure rates					
[52] RCT	70 women with vulvovaginal candidiasis (open label)	**Symptoms or mycological failure , 4 weeks** 1/37 (3%) with clotrimazole (100 mg for 14 days) 1/33 (3%) with nystatin vaginal cream (1 million IU, once daily for 7 days)	Significance not reported		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[52] RCT	70 women with vulvovaginal candidiasis (open label)	**Adverse effects** with clotrimazole (100 mg for 14 days) with nystatin vaginal cream (1 million IU, once daily for 7 days) No adverse effects associated with treatment reported			

No data from the following reference on this outcome. [53]

Further information on studies

[13] 5 women excluded from analysis as negative culture for *Candida albicans;* analysis not by intention to treat. Pregnant women, women with diabetes, immunosuppression, receiving antifungal chemotherapy, or with other vaginal infections excluded.

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

[53] It should be noted that the comparator groups were very different in size (80 people in the intravaginal miconazole alone group, 31 people in the intravaginal miconazole plus oral nystatin group, and 45 people in the intravaginal nystatin alone group).

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. [54]

OPTION FLUCONAZOLE (ORAL)

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 38 .
- Intravaginal imidazoles and oral fluconazole or itraconazole seem equally effective in treating acute attacks.
- We found no direct information from RCTs about whether oral fluconazole is better than no active treatment, no treatment, or intravaginal nystatin.

© BMJ Publishing Group Ltd 2010. All rights reserved.

Benefits and harms

Oral fluconazole versus placebo:

We found no systematic review or RCTs.

Oral fluconazole versus intravaginal imidazoles:

See benefits and harms of intravaginal imidazoles, p 3 .

Oral fluconazole versus oral itraconazole:

We found one systematic review (search date 2006; 6 RCTs, 1092 women) comparing oral fluconazole versus oral itraconazole with follow-up of included studies, ranging from 10 days to 8 weeks. [55]

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 or mycological cure at 10 days to 8 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical cure rates					
[55] 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
[55] 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					
[55] Systematic review	206 women 3 RCTs in this analysis	**Withdrawal owing to 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
[55] 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

© BMJ Publishing Group Ltd 2010. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[55] 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

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

Comment: **Oral fluconazole versus intravaginal treatments:**
See comment on intravaginal nystatin, p 20 .

OPTION ITRACONAZOLE (ORAL)

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 38 .
- Intravaginal imidazoles and oral fluconazole or itraconazole seem equally effective in treating acute attacks.

Benefits and harms

Oral itraconazole versus placebo:

We found one systematic review (search date 2000), [56] which identified one RCT (90 women) comparing three interventions: oral itraconazole, intravaginal clotrimazole, and placebo. [13]

Clinical cure rates

Oral itraconazole compared with placebo Oral itraconazole is more effective at reducing the proportion of 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					
[13] RCT **3-armed trial**	90 women In review [56] The remaining arm evaluated intravaginal clotrimazole	**Persistent symptoms , 1 week** 13/48 (27%) with oral itraconazole (200 mg/day for 3 days) 12/22 (55%) with placebo	P <0.05	○○○	oral itraconazole

Adverse effects

© BMJ Publishing Group Ltd 2010. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[13] RCT **3-armed trial**	90 women In review [56] The remaining arm evaluated intravaginal clotrimazole	**Adverse effects** 17/50 (34%) with oral itraconazole (200 mg/day for 3 days) 1/23 (4%) with intravaginal clotrimazole The adverse effects with increased frequency were nausea (14%), headache (12%), dizziness (6%), and bloating (6%)	OR 4.83 95% CI 1.55 to 15.1	●●○	intravaginal clotrimazole

Oral itraconazole versus intravaginal imidazoles:

See option on intravaginal imidazoles, p 3 .

Oral itraconazole versus oral fluconazole:

See option on oral fluconazole, p 17 .

Oral itraconazole versus intravaginal nystatin:

We found no systematic review or RCTs.

Further information on studies

Comment: **Oral itraconazole versus intravaginal treatments:**

See comment on intravaginal nystatin, p 20 .

OPTION NYSTATIN (INTRAVAGINAL)

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 38 .
- Intravaginal nystatin, p 20 reduces symptoms compared with placebo, but we don't know how it compares with intravaginal imidazoles or oral fluconazole or itraconazole.

Benefits and harms

Intravaginal nystatin versus placebo:

We found no systematic review, but found one RCT comparing intravaginal nystatin versus placebo. [57]

Clinical cure rates

Intravaginal nystatin compared with placebo Intravaginal nystatin is more effective at reducing the proportion of women with a poor symptomatic response at 14 days' treatment (high-quality evidence).

© BMJ Publishing Group Ltd 2010. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical cure rates					
[57] RCT	50 women	**Proportion of women with a symptomatic response categorised as "poor" , 14 days** 2/25 (8%) with intravaginal nystatin (500,000 IU twice daily 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					
[57] RCT	50 women	**Adverse effects** with intravaginal nystatin (500,000 IU twice daily for 14 days) with placebo The RCT reported no adverse effects among 50 women who used intravaginal nystatin			

Intravaginal nystatin versus intravaginal imidazoles:

See benefits and harms of intravaginal imidazoles, p 3 .

Intravaginal nystatin versus oral fluconazole or itraconazole :

We found no systematic review or RCTs.

Intravaginal nystatin versus intravaginal boric acid :

See benefits of intravaginal boric acid, p 22 .

Further information on studies

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. [54]

© BMJ Publishing Group Ltd 2010. All rights reserved.

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 38 .
- We found no direct information from RCTs about douching in the treatment of women with acute vulvovaginal candidiasis.
- Douching has been associated with serious sequelae, including PID, endometritis, ectopic pregnancy, gonorrhoea, and chlamydia.

Benefits and harms

Douching:

We found two systematic reviews (search dates 2002), which identified no RCTs. [58] [59]

Further information on studies

Comment: **Harms**

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. [58] [59] 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. [59]

OPTION GARLIC

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 38 .
- We found no direct information from RCTs about garlic in the treatment of women with acute vulvovaginal candidiasis.

Benefits and harms

Garlic:

We found one systematic review (search date 2002), which identified no RCTs. [58]

Further information on studies

Comment: **Harms**

The review stated that garlic taken orally may cause heartburn, nausea, diarrhoea, flatulence, bloating, and an offensive body odour. [58] Prolonged topical use of garlic can lead to allergic reactions or chemical burns.

OPTION BORIC ACID (INTRAVAGINAL)

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 38 .
- Intravaginal boric acid is more effective at increasing clinical cure rates at 4 weeks (moderate-quality evidence).

© BMJ Publishing Group Ltd 2010. All rights reserved.

- Intravaginal boric acid has been associated with skin irritation.

Benefits and harms

Intravaginal boric acid versus intravaginal nystatin:

We found one systematic review (search date 2002), [58] which identified one RCT (108 women) comparing intravaginal boric acid 600 mg daily versus intravaginal nystatin 100,000 IU daily for 14 days. [60]

Clinical cure rates

Intravaginal boric acid compared with intravaginal nystatin Intravaginal boric acid is more effective at increasing clinical cure rates at 4 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical cure rates					
[60] RCT	108 women In review [58]	**Clinical cure , 4 weeks** 36/50 (72%) with boric acid 26/52 (50%) with nystatin	P = 0.02	◌◌◌	nystatin

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[60] RCT	108 women In review [58]	**Adverse effects** with boric acid with nystatin The review stated that intravaginal boric acid can cause skin irritation. The RCT gave no information on the adverse effects of boric acid compared with intravaginal nystatin. It stated that it found "no evidence of toxicity" associated with boric acid, but it was too small to exclude clinically important adverse effects			

Further information on studies

Comment: A case series of oral ingestion of boric acid has raised concerns about toxicity because it is associated with vomiting, abdominal pain, diarrhoea, lethargy, headache, and dizziness, but serious complications are rare. [61]

OPTION TEA TREE OIL (INTRAVAGINAL)

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 38 .
- We found no direct information from RCTs about intravaginal tea tree oil in the treatment of women with acute vulvovaginal candidiasis.

© BMJ Publishing Group Ltd 2010. All rights reserved.

Benefits and harms

Tea tree oil (intravaginal):

We found one systematic review (search date 2002), which identified no RCTs. [58]

Further information on studies

Comment: The review stated that topical tea tree oil can cause skin irritation and a severe allergic rash. [58] One case report found that topical tea tree oil was associated with systematic hypersensitivity reaction. [62]

OPTION YOGHURT CONTAINING LACTOBACILLUS ACIDOPHILUS (ORAL OR VAGINAL)

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 38 .
- Yoghurt containing Lactobacillus maybe more effective at reducing the rate of vaginal discharge associated with thrush symptoms and lowering the rate of yeast detected by culture.

Benefits and harms

Yoghurt containing *Lactobacillus acidophilus* (oral or vaginal) versus placebo:

We found one systematic review (search date 2002), which identified no RCTs. [58] We found one additional RCT (55 women) comparing oral *lactobacillus* versus placebo at 1 month used following a single dose of oral fluconazole (150 mg) to all participants. [63]

Clinical cure rates

Yoghurt containing Lactobacillus compared with placebo Yoghurt containing Lactobacillus maybe more effective at reducing the rate of vaginal discharge associated with thrush symptoms and lowering the rate of yeast detected by culture (low-quality evidence)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical cure rates					
[63] RCT	55 women	**Persistent symptoms , 1 month** 3/29 (10%) with lactobacillus 9/36 (35%) with placebo	P = 0.03 and also significantly lowered the rate of yeast detection by culture (3/29 [10%] with *lactobacillus v*10/26 [39%] with placebo; P = 0.01) at 1 month	○○○	lactobacillus

Adverse effects

No data from the following reference on this outcome. [63]

Further information on studies

© BMJ Publishing Group Ltd 2010. All rights reserved.

Comment: **Harms**
The review stated that oral yoghurt may cause gastrointestinal disturbance in people with lactose intolerance. [58]

QUESTION **What are the effects of treating a male sexual partner to resolve symptoms and prevent recurrence in non-pregnant women with symptomatic acute vulvovaginal candidiasis?**

OPTION **TREATING A MALE SEXUAL PARTNER IN WOMEN WITH ACUTE VULVOVAGINAL CANDIDIASIS**

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 38 .
- Treating the women's male sexual partner does not reduce symptoms or prevent recurrence of candidiasis in the woman.

Benefits and harms

Oral itraconazole versus placebo:

We found no systematic review but found one RCT. [64] In the RCT (40 women with acute vulvovaginal candidiasis and their male partners), all of the women received oral itraconazole 100 mg daily for 5 days. Their male partners were randomised to receive oral itraconazole 100 mg daily for 5 days or placebo. [64]

Clinical cure rates

Oral itraconazole compared with placebo Treating a woman's male sexual partner is no more effective at reducing the proportion of women with persistent symptoms at 30 days (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical cure rates					
[64] RCT	40 women with acute vulvovaginal candidiasis and their male partners	**Persistent symptoms , 30 days** 2/19 (11%) with partners who received itraconazole 4/18 (22%) with partners who received placebo	OR 0.43 95% CI 0.08 to 2.43	⟷	Not significant

Recurrence rates

No data from the following reference on this outcome. [64]

Adverse effects

No data from the following reference on this outcome. [64]

Topical natamycin versus placebo:

We found no systematic review but found one RCT. [65] In the RCT (42 women with acute vulvovaginal candidiasis and their male partners), all the women received topical natamycin for 10 days. Their partners were randomised to receive topical natamycin for 10 days or placebo. [65]

Clinical cure rates

Topical natamycin compared with placebo Treating a male sexual partner with topical natamycin may be no more effective at reducing symptoms at 8 days (low-quality evidence).

© BMJ Publishing Group Ltd 2010. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical cure rates					
[65] RCT	42 women with acute vulvovaginal candidiasis and their male partners	**Symptoms , 8 days** 1/16 (6%) with partners receiving topical natamycin 2/17 (12%) with partners receiving placebo	Reported as not significant P value not reported	⟷	Not significant

Recurrence rates

Topical natamycin compared with placebo Treating a male sexual partner with topical natamycin may be no more effective at preventing symptomatic relapses at 39 days (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence rates					
[65] RCT	42 women with acute vulvovaginal candidiasis and their male partners	**Symptomatic relapse , 39 days** 1/16 (6%) with partners receiving topical natamycin 2/17 (12%) with partners receiving placebo	Reported as not significant P value not reported	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [65]

Further information on studies

Comment: **Topical natamycin versus placebo:**
A case report of an unplanned pregnancy after treatment with intravaginal miconazole raises concerns that topical medicines may damage rubber condoms and diaphragms because of the fatty excipients used as therapeutic vehicles. [54]

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

OPTION **FLUCONAZOLE (ORAL)**

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 38 .
- Oral fluconazole, p 17 is likely to be beneficial in preventing recurrence of infection.

Benefits and harms

Oral fluconazole versus placebo:

We found no systematic review. We found one RCT (387 women with recurrent vulvovaginal candidiasis) comparing the effects of fluconazole versus placebo on maintenance of clinical remission. [66]

© BMJ Publishing Group Ltd 2010. All rights reserved.

Recurrence rates

Oral fluconazole compared with placebo Oral fluconazole is more effective at increasing symptomatic remission at 6 months (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence rates					
[66] RCT	387 women with recurrent vulvovaginal candidiasis	**Symptomatic remission , 6 months** 128/141 (91%) with oral fluconazole (150 mg/week) 51/142 (36%) with placebo	2.53 95% CI 2.02 to 3.17	●●○	fluconazole

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[66] RCT	387 women with recurrent vulvovaginal candidiasis	**Withdrawal , 12 months** 3% with oral fluconazole (150 mg/week) 1% with placebo Absolute numbers not reported Reasons for withdrawal included unintended pregnancy (3 with fluconazole *v* 1 with placebo) and adverse effects (headache and vestibulitis)	Significance not reported		
[66] RCT	387 women with recurrent vulvovaginal candidiasis	**Adverse effects** with oral fluconazole (150 mg/week) with placebo One person had elevated aminotransferase levels but did not withdraw from the study (treatment group not reported)			

Regular prophylaxis versus as-required treatment:

We found no systematic review or RCTs.

Further information on studies

[66] Only 75% of people in the RCT were available for follow-up at 12 months.

Comment: None.

OPTION ITRACONAZOLE (ORAL)

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 38 .

© BMJ Publishing Group Ltd 2010. All rights reserved.

- Oral itraconazole, p 19 is likely to be beneficial in preventing recurrence of infection.

Benefits and harms

Oral itraconazole versus placebo:

We found no systematic review. We found one RCT (single blind; 114 women with recurrent vulvovaginal candidiasis), which compared oral itraconazole (400 mg monthly) versus placebo. [67]

Clinical cure rates

No data from the following reference on this outcome. [67]

Recurrence rates

Oral itraconazole compared with placebo Oral itraconazole (monthly prophylaxis for 6 months) is more effective at reducing recurrence of symptoms of vulvovaginal candidiasis for duration of prophylaxis (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence rates					
[67] RCT	114 women with recurrent vulvovaginal candidiasis	**Recurrence of symptoms , 6 months** 20/55 (36%) with itraconazole 34/53 (64%) with placebo	ARR 28% 95% CI 9% to 47% OR 0.32 95% CI 0.14 to 0.70 NNT 4 95% CI 3 to 11	●○○	itraconazole

Adverse effects

No data from the following reference on this outcome. [67]

Oral itraconazole versus intravaginal imidazoles:

We found no systematic review. We found one RCT (open label; 44 women) comparing oral itraconazole (200 mg twice weekly) versus intravaginal clotrimazole (200 mg twice weekly) for 6 months. [68] One woman withdrew from itraconazole treatment and five withdrew from clotrimazole treatment.

Recurrence rates

Oral itraconazole compared with intravaginal imidazoles We don't know whether oral itraconazole is more effective at increasing the proportion of women with symptomatic recurrences at 6 months (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence rates					
[68] RCT **Crossover design**	44 women	**Recurrence of symptoms , 6 months** 7/21 (33%) with oral itraconazole 0/17 (0%) with intravaginal clotrimazole	P = 0.02	○○○	intravaginal clotrimazole

© BMJ Publishing Group Ltd 2010. All rights reserved.

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[68] RCT **Crossover design**	44 women	**Adverse effects** 7/22 (32%) with oral itraconazole 0/22 (0%) with intravaginal clotrimazole Adverse effects reported included nausea, diarrhoea, headache, and dizziness	P = 0.02	○○○	intravaginal clotrimazole

Regular prophylaxis versus as-required treatment:

We found no systematic review or RCTs.

Further information on studies

[68] The results of the RCT are difficult to interpret because it was open label, and the unbalanced withdrawal from the RCT could explain the observed difference between groups.

Comment: See comment on intravaginal nystatin, p 20 .

OPTION IMIDAZOLES (INTRAVAGINAL)

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 38 .
- We don't know whether monthly prophylaxis (for 6 months) with intravaginal imidazoles is more effective than placebo at reducing the proportion of women with symptomatic recurrences at 6 months.
- Regular prophylaxis and as-required intravaginal clotrimazole seem equally effective at reducing the proportion of women who have symptomatic episodes of vaginitis at 6 months.

Benefits and harms

Intravaginal imidazoles versus placebo:

We found one systematic review (search date 1993; [11] 2 RCTs, [69] [70] 89 women with recurrent vulvovaginal candidiasis) comparing intravaginal clotrimazole 500 mg monthly versus intravaginal placebo monthly for 6 months.

Recurrence rates

Intravaginal imidazoles compared with placebo We don't know whether monthly prophylaxis (for 6 months) with intravaginal imidazoles is more effective at reducing the proportion of women with symptomatic recurrences at 6 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence rates					
[69] RCT	62 women In review [11]	**Symptomatic recurrence , 6 months** 30% with intravaginal clotrimazole	P <0.001	○○○	intravaginal clotrimazole

© BMJ Publishing Group Ltd 2010. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		79% with placebo Absolute numbers not reported			
[70] RCT	42 women In review [11]	**Symptomatic recurrence , 6 months** 53% with intravaginal clotrimazole 67% with placebo Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [69] [70]

Regular prophylaxis versus as-required treatment:

We found no systematic review. We found one crossover RCT (open label; 23 women with recurrent vaginal candidiasis) comparing regular prophylactic intravaginal clotrimazole 500 mg each month versus intravaginal clotrimazole 500 mg at the onset of symptoms for 12 months. [71]

Recurrence rates

Regular prophylaxis compared with as-required treatment Regular prophylaxis and as-required intravaginal clotrimazole seem equally effective at reducing the proportion of women who have symptomatic episodes of vaginitis at 6 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence rates					
[71] RCT **Crossover design**	23 women with recurrent vaginal candidiasis	**Number of symptomatic episodes per woman , 6 months** 2.2 with regular clotrimazole 3.7 with as-required clotrimazole	P = 0.05	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [71]

Intravaginal imidazoles versus oral itraconazole:

See benefits and harms of oral itraconazole, p 27 .

© BMJ Publishing Group Ltd 2010. All rights reserved.

Further information on studies

[71] The RCT may have been underpowered to detect a clinically important difference. It found that significantly more women preferred treatment as required compared with prophylactic treatment (17/23 [74%] with regular clotrimazole *v* 4/23 [17%] with as-required clotrimazole; P = 0.001).

Comment: See comment on intravaginal nystatin, p 20 .

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

OPTION DOUCHING

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 38 .
- We found no direct information from RCTs about the effects of douching in preventing recurrent vulvovaginal candidiasis. Douching has been associated with serious sequelae, including PID, endometritis, ectopic pregnancy, gonorrhoea, and chlamydia.

Benefits and harms

Douching:

We found two systematic reviews (search dates 2002), which identified no RCTs. [58] [59]

Further information on studies

Comment: **Harms**

See harms of douching under alternative or complementary treatments for acute vulvovaginal candidiasis, p 22 . One RCT (1827 women aged 18–34 years who were regular douche users, treated recently for a sexually transmitted bacterial infection or bacterial vaginosis, with no current indication of PID) compared a commercial douche versus a cloth towel. [72] It found no significant difference in risk of PID between treatments (RR 1.05, 95% CI 0.57 to 1.90). [72]

OPTION GARLIC

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 38 .
- We found no direct information from RCTs about the effects of garlic in preventing recurrent vulvovaginal candidiasis.

Benefits and harms

Garlic:

We found one systematic review (search date 2002), which identified no RCTs. [58]

Further information on studies

[58] The review stated 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.

© BMJ Publishing Group Ltd 2010. All rights reserved.

Comment: None.

OPTION BORIC ACID (INTRAVAGINAL)

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 38 .
- We found no direct information from RCTs about the effects of intravaginal boric acid in preventing recurrent vulvovaginal candidiasis.

Benefits and harms

Boric acid (intravaginal):

We found one systematic review (search date 2002), which identified no RCTs. [58]

Further information on studies

[58] The review stated that intravaginal boric acid can cause skin irritation.

Comment: Oral ingestion has raised concerns about toxicity because it is associated with vomiting, abdominal pain, diarrhoea, lethargy, headache, and dizziness, but serious complications are rare. [61]

OPTION TEA TREE OIL (INTRAVAGINAL)

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 38 .
- We found no direct information from RCTs about the effects of intravaginal tea tree oil in preventing recurrent vulvovaginal candidiasis.

Benefits and harms

Tea tree oil (intravaginal):

We found one systematic review (search date 2002), which identified no RCTs. [58]

Further information on studies

[58] The review stated that topical tea tree oil can cause skin irritation and a severe allergic rash.

Comment: One case report found that topical tea tree oil was associated with systematic hypersensitivity reaction. [62]

OPTION YOGHURT CONTAINING LACTOBACILLUS ACIDOPHILUS (ORAL OR VAGINAL)

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 38 .
- We don't know whether a diet containing oral lactobacillus yoghurt is more effective at reducing symptomatic recurrences at 6 months in women with recurrent vulvovaginal candidiasis.
- Oral yoghurt may cause gastrointestinal disturbance in people with lactose intolerance.

© BMJ Publishing Group Ltd 2010. All rights reserved.

Benefits and harms

Yoghurt containing *Lactobacillus acidophilus* (oral or vaginal):

We found one systematic review (search date 2002), [58] which identified two crossover RCTs of oral yoghurt. [73] [74] The first RCT (33 women) compared a diet containing 200 g of oral *lactobacillus* yoghurt daily versus a diet containing no yoghurt for 6 months. [73] The second RCT (46 women; 18 with recurrent vulvovaginal candidiasis, 20 with bacterial vaginosis, 8 with both infections) compared *lactobacillus* yoghurt 150 mL daily versus pasteurised yoghurt 150 mL daily for 2 months' treatment in a crossover design with a 2-month washout. [74]

Recurrence rates

Oral lactobacillus yoghurt compared with lactobacillus-free yoghurt We don't know whether a diet containing oral lactobacillus yoghurt is more effective at reducing symptomatic recurrences at 6 months in women with recurrent vulvovaginal candidiasis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptomatic recurrence					
[73] RCT **Crossover design**	33 women In review [58]	**Mean number of infections , 1 year** 0.38 with yoghurt 2.54 with no yoghurt High loss-to-follow-up; for full details, see further information about studies	P = 0.001	○○○	yoghurt
[74] RCT **Crossover design**	46 women; 18 with recurrent vulvovaginal candidiasis, 20 with bacterial vaginosis, eight with both infections In review [58]	**Number of infections over 14 visits , 6 months** 3 with oral *lactobacillus* yoghurt 5 with pasteurised yoghurt Underpowered; for full details, see further information about studies	P = 0.67	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[58] Systematic review	79 women	**Adverse effects** with yoghurt with no yoghurt The review stated that oral yoghurt may cause gastrointestinal disturbance in people with lactose intolerance			

Further information on studies

[73] The results of the first RCT should be treated with caution because it did not provide results before crossover and 20/33 (61%) women did not complete the trial.

[74] The second RCT was underpowered to detect a clinically important difference between groups because it did not assess results before crossover and 39/46 (85%) women did not complete the trial.

© BMJ Publishing Group Ltd 2010. All rights reserved.

Comment: None.

QUESTION **What are the effects of treating a male sexual partner in non-pregnant women with symptomatic recurrent vulvovaginal candidiasis?**

OPTION **TREATING A MALE SEXUAL PARTNER IN NON-PREGNANT WOMEN WITH SYMPTOMATIC RECURRENT VULVOVAGINAL CANDIDIASIS**

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 38 .
- Treating the woman's male sexual partner, p 25 does not reduce symptoms or prevent recurrence in the woman.

Benefits and harms

Treating a male sexual partner to resolve symptoms and prevent recurrence in women with symptomatic recurrent vulvovaginal candidiasis:

We found no systematic review or RCTs.

Further information on studies

Comment: None.

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

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

- For GRADE evaluation of interventions for Candidiasis (vulvovaginal), see table, p 38 .
- We found no direct information from RCTs on the effects of yoghurt containing lactobacillus acidophilus, douching, garlic, tea tree oil, or intravaginal boric acid in asymptomatic non-pregnant women with a positive swab for candidiasis.

Benefits and harms

Alternative or complementary treatments:

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

Further information on studies

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.

© BMJ Publishing Group Ltd 2010. All rights reserved.

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 38 .
- 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.

Further information on studies

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.

GLOSSARY

Balanitis is inflammation of the glans penis. The foreskin is often involved (balanoposthitis).

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

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.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Fluconazole (oral): One systematic review added comparing oral fluconazole versus oral itraconazole. [55] The review found no significant difference between groups for clinical or mycological cure with follow-up of the included studies, ranging from 10 days to 8 weeks. [55] Categorisation unchanged (Beneficial).

Imidazoles (intravaginal): One systematic review added comparing intravaginal imidazoles versus oral fluconazole or itraconazole. [51] The review found no significant difference between intravaginal treatment and oral treatment in clinical cure at short- and long-term follow-up, or mycological cure at short-term follow-up. However, intravaginal imidazoles were less effective than oral treatment with fluconazole or itraconazole for achieving long-term mycological cure. [51] Categorisation of intravaginal imidazoles unchanged (Beneficial).

Yoghurt containing *Lactobacillus acidophilus*: One RCT added comparing *lactobacillus* versus placebo after one dose of fluconazole (150 mg) at 1 month. [63] The RCT found that *lactobacillus* decreased vaginal discharge and the presence of yeast detected by culture compared with placebo. [63] Categorisation unchanged (Unknown effectiveness).

REFERENCES

1. Anderson MR, Klink K, Cohrssen A. Evaluation of vaginal complaints. *JAMA* 2004;291:1368–1379.[PubMed]
2. Sobel JD. Vulvovaginal candidiasis. In: Holmes KK MP-A, Sparling PF, Lemon SM, et al, eds. *Sexually transmitted diseases*. New York: McGraw-Hill, 1999:629–639.
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. Weissenbacher S, Witkin SS, Tolbert V, et al. Value of *Candida* polymerase chain reaction and vaginal cytokine analysis for the differential diagnosis of women with recurrent vulvovaginitis. *Infect Dis Obstet Gynecol* 2000;8:244–247.[PubMed]
6. Sobel JD. Vaginitis. *N Engl J Med* 1997;337:1896–1903.[PubMed]
7. Horowitz BJ, Giaquinta D, Ito S. Evolving pathogens in vulvovaginal candidiasis: implications for patient care. *J Clin Pharmacol* 1992;32:248–255.[PubMed]
8. Foxman B. The epidemiology of vulvovaginal candidiasis: risk factors. *Am J Public Health* 1990;80:329–331.[PubMed]
9. 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]

© BMJ Publishing Group Ltd 2010. All rights reserved.

10. Geiger AM, Foxman B, Gillespie BW. The epidemiology of vulvovaginal candidiasis among university students. *Am J Public Health* 1995;85:1146–1148.[PubMed]
11. Reef SE, Levine WC, McNeil MM, et al. Treatment options for vulvovaginal candidiasis, 1993. *Clin Infect Dis* 1995;20:S80–S90. Search date 1993.[PubMed]
12. 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]
13. Stein GE, Mummaw N. Placebo-controlled trial of itraconazole for treatment of acute vaginal candidiasis. *Antimicrob Agents Chemother* 1993;37:89–92.[PubMed]
14. Fleury F, Hodgson C. Single-dose treatment of vulvovaginal candidiasis with a new 500 mg clotrimazole vaginal tablet. *Adv Ther* 1984;1:349–356.
15. Corson SL, Kapikian RR, Nehring R. Terconazole and miconazole cream for treating vulvovaginal candidiasis. *J Reprod Med* 1991;36:561–567.[PubMed]
16. Kjaeldgaard A. Comparison of terconazole and clotrimazole vaginal tablets in the treatment of vulvovaginal candidosis. *Pharmatherapeutica* 1986;4:525–531.[PubMed]
17. 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]
18. Droegemueller W, Adamson DG, Brown D. Three-day treatment with butoconazole nitrate for vulvovaginal candidiasis. *Obstet Gynecol* 1984;64:530–534.[PubMed]
19. Jacobson JB, Hajman AJ, Wiese J. A new vaginal antifungal agent — butoconazole nitrate. *Acta Obstet Gynecol Scand* 1985;64:241–244. [PubMed]
20. 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]
21. Adamson GD, Brown D Jr, Standard JV, et al. Three-day treatment with butoconazole vaginal suppositories for vulvovaginal candidiasis. *J Reprod Med Obstet Gynecol* 1986;31:131–132.[PubMed]
22. Bradbeer CS, Mayhew SR, Barlow D. Butaconazole and miconazole in treating vaginal candidiasis. *Genitourin Med* 1985;61:270–272.[PubMed]
23. Glasser A. Single-dose treatment of vaginal mycoses. Effectiveness of clotrimazole and econazole. *Fortschr Med* 1986;104:259–262.[PubMed]
24. Gabriel G, Thin RN. Clotrimazole and econazole in the treatment of vaginal candidosis. A single-blind comparison. *Br J Vener Dis* 1983;59:56–58.[PubMed]
25. 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.
26. 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]
27. Balsdon M-J. Comparison of miconazole-coated tampons with clotrimazole vaginal tablets in the treatment of vaginal candidosis. *Br J Vener Dis* 1981;57:275–278.[PubMed]
28. Bradbeer CS, Thin RN. Comparison of econazole and isoconazole as single dose treatment for vaginal candidosis. *Genitourin Med* 1985;61:396–398.[PubMed]
29. Brown D, Henzl MR, Kaufman RH, et al. Butoconazole nitrate 2% for vulvovaginal candidiasis. *J Reprod Med* 1999;44:933–938.[PubMed]
30. 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]
31. 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]
32. Adamson GD, Brown D Jr, Standard JV, et al. Three-day treatment with butoconazole vaginal suppositories for vulvovaginal candidiasis. *J Reprod Med Obstet Gynecol* 1986;31:131–132.
33. 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]
34. Herbold H. Comparative studies to the clinical efficacy of two 1-dose-therapies of vaginal candidosis. *Med Welt* 1985;36:255–257.
35. 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]
36. 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]
37. Bradbeer CS, Thin RN. Comparison of econazole and isoconazole as single dose treatment for vaginal candidosis. *Genitourin Med* 1985;61:396–398.
38. 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.
39. Wolfson N, Samuels B, Hodgson C, et al. One-day management of vulvovaginal candidiasis. *J La State Med Soc* 1987;139:27–29.
40. Fleury F, Hughes D, Floyd R. Therapeutic results obtained in vaginal mycoses after single-dose treatment with 500 mg clotrimazole vaginal tablets. *Am J Obstet Gynecol* 1985;152:968–970.[PubMed]
41. Hughes D, Kriedman T, Hodgson C. Treatment of vulvovaginal candidiasis with a single 500-mg clotrimazole vaginal tablet compared with two 100-mg tablets daily for three days. *Curr Ther Res Clin Exp* 1986;39:773–777.
42. Milsom I, Forssman L. Treatment of vaginal candidosis with a single 500-mg clotrimazole pessary. *Br J Vener Dis* 1982;58:124–126.[PubMed]
43. Westphal J. Treatment of *Candida mycoses* of the vulva and vagina with clotrimazole. Comparison of single-dose and six-day therapy. *Fortschr Med* 1988;106:445–448. [PubMed]
44. Upmalis DH, Cone FL, Lamia CA, et al. Single-dose miconazole nitrate vaginal ovule in the treatment of vulvovaginal candidiasis: two single-blind, controlled studies versus miconazole nitrate 100 mg cream for 7 days. *J Womens Health Gend Based Med* 2000;9:421–429.[PubMed]
45. Milsom I, Forssman L. Treatment of vaginal candidosis with a single 500-mg clotrimazole pessary. *Br J Vener Dis* 1982;58:124–126.
46. Upmalis DH, Cone FL, Lamia CA, et al. Single-dose miconazole nitrate vaginal ovule in the treatment of vulvovaginal candidiasis: two single-blind, controlled studies versus miconazole nitrate 100 mg cream for 7 days. *J Womens Health Gend Based Med* 2000;9:421–429.
47. Franklin R. Seven-day clotrimazole therapy for vulvovaginal candidiasis. *South Med J* 1978;71:141–143.[PubMed]
48. Wolfson N, Samuels B, Riley J. A three-day treatment regimen for vulvovaginal candidiasis. *J La State Med Soc* 1982;134:28–31.[PubMed]
49. Lebherz TB, Ford LC, Kleinkopf V. A comparison of a three-day and seven-day clotrimazole regimen for vulvovaginal candidiasis. *Clin Ther* 1981;3:344–348.[PubMed]
50. Mizuno S, Cho N. Clinical evaluation of three-day treatment of vaginal mycosis with clotrimazole vaginal tablets. *J Int Med Res* 1983;11:179–185.[PubMed]
51. 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 4, 2007. Chichester, UK: John Wiley & Sons, Ltd.[PubMed]
52. Cassar NL. High-potency nystatin cream in the treatment of vulvovaginal candidiasis. *Curr Ther Res* 1983;34:305–310.
53. Dennerstein GJ, Langley R. Vulvovaginal candidiasis: treatment and recurrence. *Aust N Z J Obstet Gynaecol* 1982;22:231–233.[PubMed]
54. 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]
55. 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]
56. Watson MC, Grimshaw JM, Bond CM, et al. Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush). In: The Cochrane Library, Issue 3, 2005. Oxford: Update Software. Search date 2000; date of most recent substantive amendment: 28 May 2001.
57. Isaacs JH. Nystatin vaginal cream in monilial vaginitis. *Illinois Med J* 1973;3:240–241.[PubMed]
58. 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. Search date 2002.[PubMed]
59. Martino JL, Vermund SH. Vaginal douching: evidence for risks or benefits to women's health *Epidemiol Rev* 2002;24:109–124. Search date 2002.[PubMed]
60. Van Slyke K, Michel VP, Rein M. Treatment of vulvovaginal candidiasis with boric acid powder *Am J Obstet Gynecol* 1981;141:145–148.[PubMed]
61. Litovitz TL, Klein-Schwartz W, Oderda GM, et al. Clinical manifestations of toxicity in a series of 784 boric acid ingestions. *Am J Emerg Med* 1988;6:209–213.[PubMed]
62. 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]
63. 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.
64. Calderon-Marquez JJ. Itraconazole in the treatment of vaginal candidosis and the effect of treatment of the sexual partner. *Rev Inf Dis* 1987;9:S143–S145.[PubMed]
65. Buch A, Skytte Christensen E. Treatment of vaginal candidosis with natamycin and effect of treating the partner at the same time. *Acta Obstet Gynecol Scand* 1982;61:393–396.[PubMed]
66. Sobel JD, Wiesenfeld HC, Martens M, et al. Maintenance fluconazole therapy for recurrent vulvovaginal candidiasis. *N Engl J Med* 2004;351:876–883.[PubMed]
67. Spinillo A, Colonna L, Piazzi G, et al. Managing recurrent vulvovaginal candidiasis. Intermittent prevention with itraconazole. *J Reprod Med* 1997;42:83–87.[PubMed]
68. Fong IW. The value of chronic suppressive therapy with itraconazole versus clotrimazole in women with recurrent vaginal candidiasis. *Genitourin Med* 1992;68:374–377.[PubMed]
69. Roth AC, Milsom I, Forssman L, et al. Intermittent prophylactic treatment of recurrent vaginal candidiasis by postmenstrual application of a 500 mg clotrimazole vaginal tablet. *Genitourin Med* 1990;66:357–360.[PubMed]
70. Sobel JD. Clotrimazole treatment of recurrent and chronic and chronic *candida* vulvovaginitis. *Obstet Gynecol* 1989;73:330–334.[PubMed]
71. Fong IW. The value of prophylactic (monthly) clotrimazole versus empiric self-treatment in recurrent vaginal candidiasis. *Genitourin Med* 1994;70:124–126.[PubMed]
72. Rothman KJ, Funch DP, Alfredson T, et al. Randomized field trial of vaginal douching, pelvic inflammatory disease and pregnancy. *Epidemiology* 2003;14:340–348.[PubMed]
73. Hilton E, Isenberg HD, Alperstein P, et al. Ingestion of yoghurt containing *Lactobacillus acidophilus* as prophylaxis for candidal vaginitis. *Ann Intern Med* 1992;116:353–357.[PubMed]
74. Shalev E, Battino S, Weiner E, et al. Ingestion of yoghurt containing *Lactobacillus acidophilus* as prophylaxis for recurrent candidal vaginitis and bacterial vaginosis. *Arch Fam Med* 1996;5:593–596.[PubMed]

© BMJ Publishing Group Ltd 2010. All rights reserved.

Candidiasis (vulvovaginal)

Des Spence
General Practice
Glasgow University
Glasgow
Scotland

Competing interests: DS declares that he has no competing interests.

Disclaimer

The information contained in this publication is intended for medical professionals. Categories presented in Clinical Evidence indicate a judgement about the strength of the evidence available to our contributors prior to publication and the relevant importance of benefit and harms. We rely on our contributors to confirm the accuracy of the information presented and to adhere to describe accepted practices. Readers should be aware that professionals in the field may have different opinions. Because of this and regular advances in medical research we strongly recommend that readers' independently verify specified treatments and drugs including manufacturers' guidance. Also, the categories do not indicate whether a particular treatment is generally appropriate or whether it is suitable for a particular individual. Ultimately it is the readers' responsibility to make their own professional judgements, so to appropriately advise and treat their patients. To the fullest extent permitted by law, BMJ Publishing Group Limited and its editors are not responsible for any losses, injury or damage caused to any person or property (including under contract, by negligence, products liability or otherwise) whether they be direct or indirect, special, incidental or consequential, resulting from the application of the information in this publication.

© BMJ Publishing Group Ltd 2010. All rights reserved.

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

Important outcomes			, Clinical cure rates, Recurrence 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?									
3 (712) [11] [14]	Clinical cure rates	Intravaginal imidazoles versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for no ITT analysis
22 (at least 900 women) [11] [23] [24] [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] [35] [36]	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
7 (901) [11] [41] [42] [43] [44]	Clinical cure rates	Single- versus multiple-dose intravaginal imidazoles	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
6 (1048) [11] [50]	Clinical cure rates	Different durations of multiple-dose regimen of intravaginal imidazoles	4	–2	0	0	0	Low	Quality points deducted for no ITT analysis and for incomplete reporting
19 (2579) [51]	Clinical cure rates	Intravaginal imidazoles versus oral fluconazole or oral itraconazole	4	0	0	−1	0	Moderate	Directness point deducted for not reporting results of comparisons versus oral fluconazole and oral itraconazole separately
1 (70) [52]	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.
6 (1092) [55]	Clinical cure rates	Oral fluconazole versus oral itraconazole	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (90) [13]	Clinical cure rates	Oral itraconazole versus placebo	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
1 (50) [57]	Clinical cure rates	Intravaginal nystatin versus placebo	4	−1	0	−1	+2	Unset	Quality point deducted for sparse data. Directness point deducted for uncertainty about definition of outcome. Effect-size points added for OR <2
What are the effects of alternative or complementary treatments for acute vulvovaginal candidiasis in non-pregnant symptomatic women?									
1 (108) [60]	Clinical cure rates	Intravaginal boric acid versus intravaginal nystatin	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
1 (55) [63]	Clinical cure rates	Yoghurt containing *Lactobacillus acidophilus* (oral or vaginal) versus placebo	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for use of co-intervention.
What are the effects of treating a male sexual partner to resolve symptoms and prevent recurrence in non-pregnant women with symptomatic acute vulvovaginal candidiasis?									
1 (40) [64]	Clinical cure rates	Oral itraconazole versus placebo	4	−1	0	0	+1	High	Quality point deducted for sparse data. Effect-size point added for OR 0.5–0. 2

© BMJ Publishing Group Ltd 2010. All rights reserved.

Important outcomes			, Clinical cure rates, Recurrence rates						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (42) [65]	Clinical cure rates	Topical natamycin versus placebo	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (42) [65]	Recurrence rates	Topical natamycin versus placebo	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
What are the effects of drug treatments for recurrent vulvovaginal candidiasis in non-pregnant symptomatic women?									
1 (283) [66]	Recurrence rates	Oral fluconazole versus placebo	4	0	0	0	+1	High	Effect-size point added for RR 2–5
1 (114) [67]	Recurrence rates	Oral itraconazole versus placebo	4	−1	0	0	+1	High	Quality point deducted for sparse data. Effect-size point added for OR 2–5
1 (44) [68]	Recurrence rates	Oral itraconazole versus intravaginal imidazoles	4	−3	0	0	0	Very low	Quality points deducted for sparse data, lack of blinding, and for differences in follow-up between groups
2 (89) [69] [70]	Recurrence rates	Intravaginal imidazoles versus placebo	4	−1	−1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results
1 (23) [71]	Recurrence rates	Regular prophylaxis versus as-required treatment	4	−2	0	0	0	Low	Quality points deducted for sparse data and for lack of blinding
What are the effects of alternative or complementary treatments for symptomatic recurrent vulvovaginal candidiasis in non-pregnant women?									
2 (79) [73] [74]	Recurrence rates	Yoghurt containing *Lactobacillus acidophilus* (oral or vaginal)	4	−3	−1	−1	0	Very low	Quality points deducted for sparse data, poor follow-up, and incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for including women without recurrent vulvovaginal candidiasis

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.

© BMJ Publishing Group Ltd 2010. All rights reserved.