



Recurrent vulvovaginal candidiasis



Belinda Sheary, BMed, is a general practice registrar, Scone, New South Wales.
bsheary@hotmail.com

Linda Dayan, BMedSc, MBBS, MM (SexHlth), DipRAOG, MRCMA, FACSHP, is Director, Sexual Health Services, Northern Sydney Health, Head, Sexual Health Department, Royal North Shore Hospital, Clinical Lecturer, Department of Public Health and Community Medicine, University of Sydney, and is in private practice, Darlinghurst, New South Wales.



BACKGROUND

Recurrent vulvovaginal candidiasis affects up to 5% of premenopausal women. It is often associated with significant morbidity and may be difficult to manage.

OBJECTIVE

This article discusses the pathogenesis, investigations and management of recurrent vulvovaginal candidiasis.

DISCUSSION

Recurrent vulvovaginal candidiasis may be misdiagnosed as presenting signs and symptoms are not specific. Examination and microbial testing are required to confirm the diagnosis. Some women appear to have an abnormal host response to the presence of candida species in the vagina, making them susceptible to recurrent episodes of symptomatic infection. Women with recurrent vulvovaginal candidiasis generally respond to a course of suppressive treatment, but many relapse after ceasing therapy.

Recurrent vulvovaginal candidiasis is defined as four or more proven episodes of vulvovaginal candidiasis in a 12 month period.¹ Classically, vulvovaginal candidiasis is described as consisting of a white 'cottage cheese' discharge with associated vulval and vaginal inflammation. This inflammation can present as vulval pruritus, a burning sensation and/or dysuria. In a typical infection, signs include vulval erythema, oedema, excoriations and fissures. Women can present with one or all of these symptoms. Alternatively, women can test positive for candida, eg. on a routine Pap test with no clinical evidence of infection. Asymptomatic carriage is present in more than 20% of healthy women.^{2,3}

Epidemiology and aetiology

Approximately 75% of women will experience at least one episode of vulvovaginal candidiasis^{2,4} and up to 5% of these women will have recurrent infections meeting the definition of recurrent vulvovaginal candidiasis.⁴ The incidence of vulvovaginal candidiasis is highest for women aged 20–40 years.^{1,4} It is rare in prepubertal,¹ and postmenopausal women.⁴

Higher oestrogen levels are thought to make women more susceptible to vulvovagi-

nal candidiasis. This is seen with an increased incidence in pregnant women⁵ and postmenopausal women on hormone therapy.^{1,6} A study showed that while women on the combined oral contraceptive were no more likely than controls to have vulvovaginal candidiasis, women on high dose oestrogen oral contraceptives had higher rates of candida colonisation.⁶ Oestrogen increases the glycogen content of the vagina, has a direct effect on candida growth and increases its adherence to the vaginal epithelium.^{4,6}

Vulvovaginal candidiasis is most often caused by *Candida albicans*. *Candida glabrata* is the most commonly reported 'nonalbicans' species.¹ In two studies looking at symptomatic women, *C. albicans* was isolated in 86.6%⁷ (American) and 77.1%⁸ (Italian) of the positive cultures.

Pathogenesis

In primary vulvovaginal candidiasis, no aetiological or precipitating factors are identified. The host response to the presence of candida in the vagina determines whether or not a woman is symptomatic.^{1,9} In a paper published in 1991, Witkin¹⁰ proposed some women with recurrent vulvovaginal candidiasis have a

localised vaginal allergic response due to an underlying disorder of immunoregulation. In 1996, Fidel and Sobel¹¹ hypothesised women with recurrent vulvovaginal candidiasis have an impaired host organism interaction in the vagina – an organ specific, antigen specific abnormality. A recent intravaginal candida challenge study has cast doubt on this theory. Fidel et al⁹ now propose that symptoms relating to the presence of candida in the vagina are due to an infiltration of polymorphonuclear neutrophils. That is, symptoms of candidal infection are not the result of a failing by the woman's immune system, but rather 'an aggressive innate response'.⁹

Two theories have been proposed to explain the recurrence of vulvovaginal candidiasis post-treatment – relapse and reinfection. Relapse is the favoured hypothesis by those that have shown sequential episodes of recurrent vulvovaginal candidiasis are caused by an identical strain type of *C. albicans*. Vazquez et al,¹² in a retrospective review, found eight out of 10 women with recurrent vulvovaginal candidiasis over a mean of 3.1 years consistently demonstrated the same *C. albican* strain.

In secondary vulvovaginal candidiasis, either host or microbial factors are considered the causative factor for the condition. Host factors include use of antibacterials or systemic corticosteroids and conditions affecting a patient's immunologic status, eg. uncontrolled diabetes, lupus, thyroid disease and human immunodeficiency virus (HIV). Microbial factors chiefly consist of nonalbicans candida species, most commonly *C. glabrata*. Resistant *C. albicans* is uncommon.¹

Behavioural factors hypothesised to trigger episodes of vulvovaginal candidiasis include sexual practices, clothing habits, and diet. Conflicting results have been reported and it is difficult to design a study that can demonstrate behavioural factors contributing to vulvovaginal candidiasis. In a recent study where several behavioural factors were associated with recurrence of symptoms in women with recurrent vulvovaginal candidiasis, the authors advised caution in extrapolating the results due to study design limitations.¹³

Diagnosis

Women and doctors often make the diagnosis of vulvovaginal candidiasis on clinical grounds alone, however, the presentation of vulvovaginal candidiasis is not specific and misdiagnosis can occur. A study examining women's ability to self diagnose vulvovaginal candidiasis on the basis of a classic case history found less than half were correct and many would use over-the-counter preparations for symptoms more likely to be attributed to pelvic inflammatory disease, bacterial vaginosis and urinary tract infection.¹⁴

Examining women with suspected vulvovaginal candidiasis will occasionally suggest another diagnosis, eg. genital herpes. *Table 1* lists potential differential diagnoses. Confirming candidiasis with culture is especially important in women with recurrent symptoms to ensure appropriate treatment is instituted. It is suggested two consecutive negative cultures for candida during symptomatic periods are adequate to exclude recurrent vulvovaginal candidiasis.¹⁵

Investigations

Vulvovaginal candidiasis is usually diagnosed by culture and/or direct microscopy. Culture

is done on Sabourand dextrose agar and a high vaginal specimen is placed into conventional bacterial transport mediums. Light microscopic examination of high vaginal secretions may show spores and pseudohyphae. Note that no diagnostic method appears to be a 'gold standard' investigation, as false negatives have been shown to occur with culture, microscopy and polymerase chain reaction.¹⁶

Treatment

Uncomplicated vulvovaginal candidiasis

Uncomplicated vulvovaginal candidiasis is defined as sporadic vaginitis caused by strains of *C. albicans* which is responsive to all types of antifungal therapy.¹ *Table 2* lists the available treatments. Uncomplicated cases of

Table 1. Differential diagnosis of vulvovaginal symptoms

- vulval dermatitis – allergic and irritant
- genital herpes
- bacterial vaginosis
- lichen sclerosis
- urinary tract infection
- vestibulitis

Table 2. Treatments for vulvovaginal candidiasis

Polyenes

- nystatin, topical

Azoles

- imidazoles
 - clotriamazole, topical
 - miconazole, topical
 - ketoconazole*, oral
- triazoles
 - fluconazole**, oral

Other

- boric acid intravaginal capsules
- flucytosine, topical

* Authority script required. Approved indication: symptomatic vulvovaginal candidiasis after treatment of at least two episodes with topical therapy. Note hepatotoxicity has been reported with ketoconazole and it is recommended patients on long term treatment have their liver function tests checked monthly²

** Patients taking fluconazole long term are recommended to have liver function tests after 6 months²

vulvovaginal candidiasis respond to azole treatments at least 80% of the time.¹⁴ Topical imidazole creams occasionally cause local side effects such as vaginal burning or irritation.^{2,5} Fluconazole is an oral treatment available over-the-counter and is taken as a single statim dose. Nausea and vomiting are infrequent side effects.² Topical hydrocortisone cream may be used in addition for symptomatic relief of vulval symptoms.

Non-*Candida albicans* vulvovaginal candidiasis

Non-*C. albicans* species may be resistant to standard azole therapy.¹⁵ Species identification and azole sensitivity can be requested on culture. *C. glabrata* is the most commonly found 'nonalbican' species.¹ Figure 1 lists

management. As *C. glabrata* has a poor in vitro response to fluconazole, Fidel et al¹⁷ recommend against using it as a first line treatment. In addition, as the minimum inhibitory concentration for azoles against *C. glabrata* are higher than that for *C. albicans* isolates, they advise against short courses of azole therapy.¹⁷

Recurrent vulvovaginal candidiasis

Recurrent vulvovaginal candidiasis may be more difficult to treat than uncomplicated vulvovaginal candidiasis episodes. Sobel et al¹⁷ showed the clinical cure rates for women with a history of four or more episodes of vulvovaginal candidiasis in the previous 12 months were significantly lower than that seen in the women with three or fewer

episodes (54.1 vs. 75.1%). Therefore it is important that the current infection is treated effectively. It is recommended women with recurrent vulvovaginal candidiasis are prescribed a longer course of azole therapy.¹⁴

A suppressive course of treatment is then commenced. There are differing opinions on how aggressive suppressive treatment should be – weekly or monthly treatments. Sobel¹⁵ recommends weekly doses of oral fluconazole as this will achieve therapeutic concentrations in the vagina for 3–5 days and reduce the attack rate by more than 90%. Ketoconazole is another oral therapy used for suppressive treatment. Hepatotoxicity is a known complication of both fluconazole and ketoconazole and this becomes more important with prolonged treatment. Another option would be 500 mg of clotrimazole intravaginally weekly.^{2,4} Maintenance therapy needs to continue for at least 6 months. During this time, 90% of patients can expect to be symptom free.¹ On ceasing maintenance therapy, 60–70% of women will experience recurrence of symptoms within 1–2 months.¹⁵ This can initially be treated as simple vulvovaginal candidiasis with the usual treatment. However, if infections continue, the patient should again repeat the treatment process.¹⁴ Sobel recommends continuing the suppressive treatment in these cases for 12 months.¹⁵

Drug resistance

An increasing incidence of nonalbican vulvovaginal candidiasis, and a correspondingly higher incidence of drug resistance, has been debated in the literature. Increased use and possible misuse of over-the-counter antimycotics is cited as a concern. It is proposed that frequent short courses of therapy may eliminate the more sensitive *C. albicans*, selecting for more azole resistant nonalbican candida species.¹ However, the evidence for these theories is inconclusive. A retrospective United Kingdom review found that in HIV negative women, there was no change in the proportion of vulvovaginal candidiasis cases being attributed to non-*C. albicans* species over the 6 year period between 1993–1998.¹⁸ A study by Sobel et al¹⁷ published in 1995,

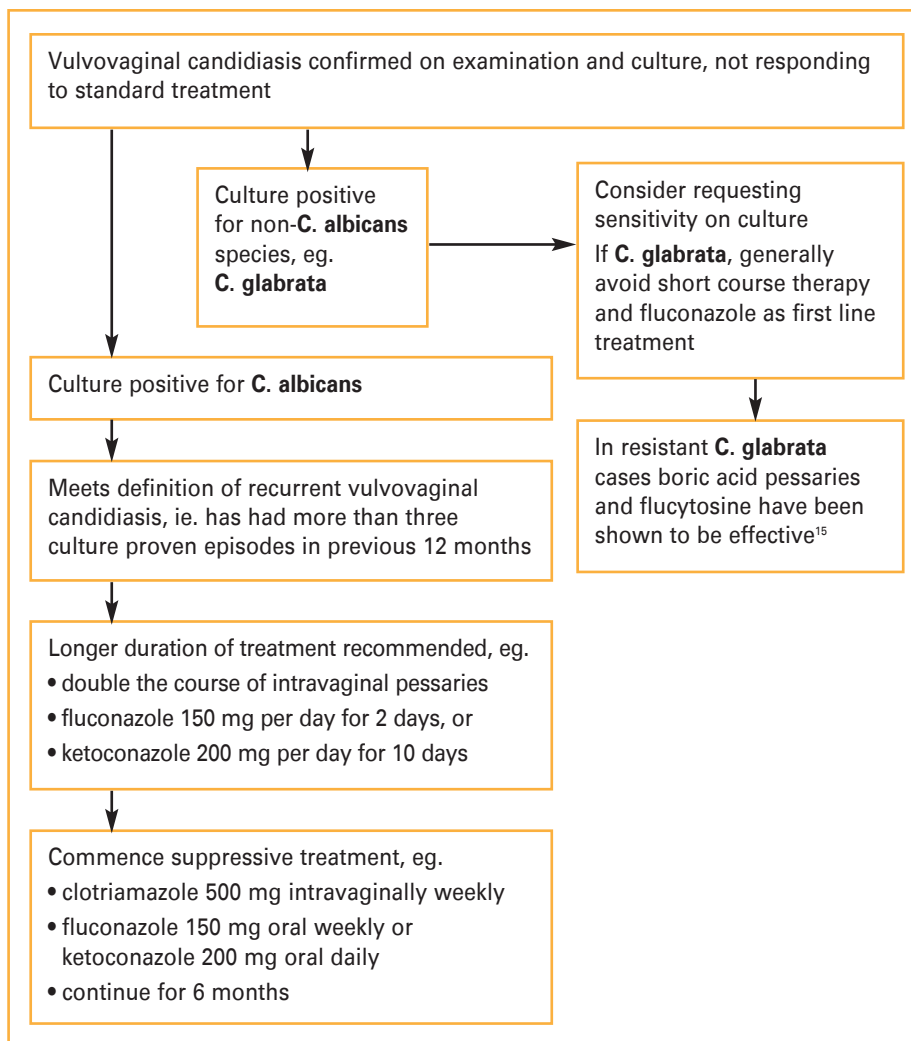


Figure 1. Management of vulvovaginal candidiasis not responsive to standard therapy

found that in 182 fluconazole treated patients there was a 94% clinical response rate. A more recent Belgium study found 21% of yeast isolates were resistant to fluconazole with in vitro testing. However, when they re-tested eight samples they were all were susceptible to fluconazole.⁹

Conclusion

It is important the diagnosis of vulvovaginal candidiasis is confirmed by examination and culture. For women with recurrent vulvovaginal candidiasis, adequate treatment for the initial infection may involve doubling the standard treatment. Maintenance therapy can then be commenced and continued for at least 6 months. Cure can be difficult to achieve, and a significant proportion of women will relapse after ceasing therapy.

Conflict of interest: none declared.

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AFP

Correspondence

Email: afp@racgp.org.au