

Review

Comprehensive review of conventional and non-conventional methods of management of recurrent vulvovaginal candidiasis

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Abstract

Recurrent vulvovaginal candidiasis (VVC) is a condition that causes women a great deal of discomfort, inconvenience, and sometimes has psychological sequelae.¹ This condition is notoriously difficult to manage. Conventional management is generally favoured by medical practitioners. Some practitioners prefer not to offer other options because of significant possible side-effects and the lack of research supporting alternative treatments.

There are many studies and much available information surrounding uncomplicated VVC, including two systematic reviews.^{2,3} In the area of recurrent VVC however, quality conclusive studies are scarce, and recurrent VVC is featured infrequently in randomised controlled trials (RCTs). Systematic reviews that strongly support a particular pharmacological method of conventional management of recurrent VVC over another are absent from medical literature. Recommendations are largely formed on the basis of scanty RCTs and expert opinion. There is even less conclusive evidence in the area of alternative therapies; yet despite this, anecdotally many practitioners (both alternative and mainstream) continue to advocate certain treatments in the absence of any reliable cure that can be confidently prescribed.

As the use of methods other than mainstream medicine becomes more widespread, it is important to be aware of both conventional and non-conventional management of recurrent vulvovaginal candidiasis. Practitioners need to ascertain their patient's preference and treatment history. It is difficult to find comprehensive literature assessing both approaches. Giving women the most up-to-date and relevant information, and different management options, is essential in allowing them to make informed decisions. This review critically assesses both mainstream and less conventional approaches in the management of recurrent VVC.

Key words: candidiasis, chronic disease, complementary therapies, recurrent, thrush.

Definitions

Most studies suggest that uncomplicated vulvovaginal candidiasis (VVC) affects 75% of women at least once during their life.^{3–5} Recurrent VVC affects up to 5% of premenopausal women.^{6,7}

Women with recurrent VVC often self-treat, and vulval irritation may result from long-term use of vaginal antifungal treatment. Accurate diagnosis of this condition is essential. A study by Nyirjesy *et al.*³ showed that only 28% of women who treated themselves for VVC had mycological evidence of this condition.

There are more than 100 different species of *Candida*, and more than 200 strains. The most common causative organism for VVC is *Candida albicans*.⁸ Recurrent, chronic and persistent VVC are terms that are often used interchangeably, although the presentation, course and management of these conditions can differ. Recurrent VVC most commonly occurs in women during their reproductive years, although it does occasionally occur in the postmenopausal woman, most

commonly those using exogenous oestrogen, or in women who are immunosuppressed.

Recurrent VVC

Recurrent VVC is commonly defined as four or more cases in 12 months or at least three episodes unrelated to antibiotic cover that occur within one year.^{3,9} There is generally a period of remission of symptoms between episodes. Suppression and maintenance therapy are often recommended for this condition. Late relapses (after three months) can be treated episodically.⁴

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Chronic or persistent VVC

The definition and treatment of chronic VVC remain controversial. For the purpose of this paper, chronic VVC is defined as an episode of VVC which does not respond to conventional antifungal therapy after two weeks. With this condition, sometimes symptoms are minimal with flare up at certain periods of time, especially at certain periods of the menstrual cycle.

A history of vulval itching and burning with premenstrual exacerbation has been reported. It may be worsened by courses of systemic antibiotics, and non-specific vulvitis may be present.¹⁰

Geller and Nelson⁸ suggest a test of cure following treatment to distinguish between recurrent VVC and chronic or persistent VVC, although this is perhaps questionable because of colonisation of candidiasis being present in many asymptomatic women. Prolonged therapy or treatment with a different agent can be indicated if colonisation persists in the asymptomatic patient. If vulval irritation results from long-term use of topical antifungals, an oral preparation may be more suitable.¹⁰

Precipitating factors of VVC

Many factors have been anecdotally associated with triggering episodes of VVC. Because of study design limitations, there is limited or conflicting evidence surrounding these factors. These include but are not limited to a diet high in sugar;⁹ use of sanitary pads; tight-fitting clothing and intrauterine devices.¹¹

Factors *likely* to be implicated in VVC include broad-spectrum antibiotics/systemic corticosteroids,⁷ allergies, especially allergic rhinitis,¹² high-dose oral contraceptives,¹³ spermicidal creams⁹ and some sexual practices including women receiving oral sex.^{14,15} It is uncertain whether these triggering factors are also significant in recurrent VVC.

Causes of recurrent VVC

The cause of recurrent VVC is complex and poorly understood. Host susceptibility factors and vaginal reinfection are currently thought to be responsible for recurrent VVC.¹⁶

Fidel and Sobel¹⁷ proposed that locally acquired mucosal immunity as well as cell-mediated immunity mechanisms may predispose a woman to recurrent VVC. A later work of Fidel *et al.*¹⁸ suggests that the presence of symptomatic infection appears to be more dependent on host factors than on properties of the organism.

Three theories have been proposed to explain recurrent VVC.

Intestinal reservoir

Intestinal reservoir theory has been largely refuted by trials which have shown that there is no difference between subjects and controls in the amount of yeast being harboured in the intestinal tract.¹⁹ O'Conner and Sobel²⁰ found that

despite recurrences after long-term treatment with ketoconazole, negative rectal cultures for yeast were present. Spinillo *et al.*²¹ concluded that intestinal reservoirs of *Candida* were an important source for re-infection in recurrent VVC. In this study, the rate of relapse was not influenced by the treatment of *Candida* colonisation of the female intestinal tract. The recurrence rate after treatment in the couples in which the man harboured yeast (oral cavity, penile coronal sulcus, seminal fluid) was significantly lower than that recorded in the couples without sexual partner involvement. Subsequently, a systematic review from an interdisciplinary and environmental medical point of view was undertaken and failed to reach conclusions about the pathogenetic significance of intestinal *Candida* colonisation.²² Thus, the role of intestinal colonisation in recurrent VVC remains contradictory.

Sexual transmission

There is some conflicting evidence around treatment of the male partner in recurrent VVC. One study found partner treatment to be helpful in reducing recurrences.² However, an earlier study by O'Conner and Sobel²⁰ found that 80% of women with recurrent VVC have partners with either no concurrent infection or *Candida* of a different species. Fong²³ found that treatment of the male sexual partner had no effect on recurrence rates of VVC for the woman. An inconsistency in this study was that the male partner was treated with 200 mg ketoconazole for five days, and the woman treated with 400 mg ketoconazole for seven days. It is unclear why the male partner received the lower dose, and whether the same dose would have altered results. A double-blind randomised controlled trial (RCT) by Bisschop *et al.*²⁴ showed no differences in recurrences between women whose partners had been treated with an oral azole and those whose partners were untreated. A possible weakness of this study was the definition of recurrences, which was the number of 'cured women' after three weeks. This cure was mycological and not symptomatic. As many women are asymptomatic carriers of candidiasis, this definition may not have been helpful when assessing recurrent VVC.

Reed *et al.*²⁵ concluded that sexual behaviours, rather than the presence of *Candida* species at various body locations of the male partner, are associated with recurrences of *C. albicans* vulvovaginitis. Cultures taken from various bodily parts of both the men and the women did not predict recurrence. They found that, in their study of 148 women and their male partners, female factors associated with recurrence included recent masturbating with saliva and cunnilingus. Male factors associated with recurrences in the woman included history of the male masturbating with saliva in the previous month and lower age at first intercourse.

Another possibility for the association between sexual intercourse and recurrent VVC has been proposed. White and Drake²⁶ suggest that epithelial damage caused by sexual intercourse may predispose a woman to VVC. Extra lubrication for women with recurrent VVC is advised, as is unhurried intercourse to reduce vaginal damage and possible recurrence of VVC.

Table 1 Comparative table of pharmacological treatment for recurrent vulvovaginal candidiasis (VVC)

| Drug (and class) | Benefits/advantages | Adverse affects/harms/disadvantages |
|--|---|---|
| <u>Suppression:</u> Clotrimazole (imidazole) 500 mg pessary 2 times a week for 2 weeks +/- clotrimazole 1% vaginal cream b.i.d. or clotrimazole 200 mg nocte 6–12 nights <u>Maintenance:</u> Clotrimazole 500 mg pessary/weekly | Generally well tolerated Inexpensive Simple and painless to use Approved for use in recurrent VVC OTC (S3) | Reduced patient preference/compliance Possible local effects eg vaginal burning, increased vaginal discharge Possible potential to damage to latex condoms and diaphragms More women prefer symptomatic treatment than prophylactic |
| <u>Suppression:</u> Fluconazole (triazole) 50 mg orally daily or 150 mg orally, 2–3 doses 3 days apart, for 1–2 weeks <u>Maintenance:</u> 150 mg–300 mg weekly for 6 months | Generally well tolerated Approved for use in recurrent VVC Single-dose available OTC (S3) | Expensive Systemic side-effects include headache, nausea and abdominal pain |
| <u>Suppression:</u> Nystatin (polyene) 100 000 units/5 g vaginal cream (1 applicatorful) or 100 000 units pessary intravaginally, daily for suppression <u>Maintenance:</u> dose as above, weekly | Generally well tolerated Inexpensive Approved for use in recurrent VVC OTC (S3) | Suppression therapy requires daily topical administration May cause yellow staining on underclothing Generally regarded as less effective than azoles |
| <u>Suppression:</u> Itraconazole (triazole) 100 mg daily <u>Maintenance:</u> 100–200 mg weekly | Some studies show good response Approved for use in recurrent VVC (S4) | Expensive Side-effects include dizziness, headache, diarrhoea, hepatic effects. LFTs required for therapy > 1 month. Rare effects: oedema, heart failure. Authority required |
| <u>Suppression:</u> Ketoconazole 100–200 mg orally daily | Available on authority for deep mycosis where other therapies have failed | Side-effects: itch, fatigue, dizziness, somnolence, gynaecomastia. Need baseline LFTs, then LFTs after 2 weeks, and then monthly if using for maintenance. Ketoconazole adverse effects include hepatotoxicity and hypoadrenalism |
| <u>Suppression:</u> Boric acid 600 mg in gelatin pessaries daily 2 weeks <u>Maintenance:</u> 600 mg weekly Flucytosine cream | Some studies show good response | Mostly used with resistant <i>C. glabrata</i> . Not available commercially in Victoria. Certain pharmacies prepare pessaries as required. Some skin irritation. Potential systemic toxicity Not available in Victoria. Used for <i>C. glabrata</i> with boric acid pessaries in the USA |

b.i.d., twice a day; LFT, liver function tests; OTC, over the counter.

during the luteal phase of menstruation (ie from day 20), when oestrogen and progesterone are elevated, women are more susceptible.⁴⁰ Another theory proposes that after day 14, a woman is most likely to have VVC.⁴¹ One study treated women on day 6 of menstruation,⁴² while another treated women postmenstrually.⁴³ Management may depend on the individual woman's susceptibility at a particular time of the menstrual cycle, but further studies investigating

the timing of the monthly prophylaxis may result in improved outcomes.

The use of hydrocortisone 1% cream topically two to three times daily may also be recommended for itching. Combination cream clotrimazole 1% and hydrocortisone 1% 30 g is available as S3.¹⁰

The comparison between pharmacological methods of management of recurrent VVC is presented in Tables 1 and 2.

Table 2 Comparative cost of treatment (approximate Australian \$)

| Drug | Weekly maintenance dose | Approximate cost per prescription | Cost per six months |
|----------------|--|--|---------------------|
| Clotrimazole | 500 mg pessary | \$13–17 | \$312–408 |
| Clotrimazole | 1% cream (can be used with above) | \$12–16 | \$288–384 |
| Fluconazole | 150 mg orally | \$25–30 | \$600–720 |
| Nystatin | 100 000 units/5 g vaginal cream | Cream and pessary: 15 doses | \$15 |
| intravaginally | (1 applicatorful) or 100 000 units pessary | \$9.50 | |
| Itraconazole | 100 mg | 100 mg (60s) authority PBS/RPBS: \$345; 100 mg (28s) \$157 | \$150–250 |
| Boric acid | 600 mg (in gelatine capsule) | Not available commercially. Varies between centres. Approx. \$30 per 15 capsules | \$60 approx. |

Prices obtained from MIMS Online (2006), and Schedule of Pharmaceutical Benefits August 2006. Prices vary between different pharmacies. PBS, pharmaceutical benefits scheme; RPBS, repatriation pharmaceutical benefits scheme.

Pharmacological treatment of *Candida glabrata* or other *Candida* species

Non-albicans species, most commonly *Candida glabrata*, are said to be responsible for up to 33% of recurrent cases of vulvovaginal candidiasis.⁶ *C. glabrata* is less susceptible to azole antifungals than *C. albicans*. Most non-albicans species have higher minimum inhibitory concentrations to azoles than the albicans species. Most, however, remain susceptible. Since topical azoles achieve vaginal therapeutic levels in excess of minimum inhibitory concentrations after local application, a course of adequate duration of topical antifungals is recommended, avoiding short courses.¹³ Fluconazole resistance has been reported in some case studies, particularly in systemic cases and in those immunologically suppressed, and is not recommended as first line treatment.⁴⁴

In clinically resistant infection, boric acid and flucytosine cream have been shown to be effective.⁴⁴ Boric acid vaginal suppositories and flucytosine cream not currently available commercially in Australia. However, some pharmacies prepare boric acid suppositories, made up as 600-mg suppositories (extemporaneously prepared in a gelatin capsule), which can be given intravaginally daily for ten to 14 days. One study suggests that although boric acid therapy appears valid, like many antifungal treatments for recurrent VVC, its efficacy ceases with suspension of treatment.⁴⁵ Repeated treatment or long-term maintenance therapy may be needed.¹⁰ Another option for management is nystatin vaginal pessary 100 000 U/s daily for 14 days -6 months. There is however, no evidence that the efficacy of this treatment is superior to boric acid.^{4,46}

Non-conventional management

A summary of alternative methods of management of recurrent vulvovaginal candidiasis can be found in Table 3.

Complementary and alternative medicines

Forty-two per cent of Australians use complementary and alternative medicines (CAM), and this figure is on the increase. It will continue to pose a challenge to conventional medicine. Over half of the users decline to tell their doctor.⁴⁷ Many women with recurrent VVC seek alternative solutions when conventional therapies are unsuccessful. It is in both the patient's and each practitioner's best interest to become familiar with CAM. It is suggested that establishing whether a patient is or plans to use different treatments, and establishing referral patterns for CAM practitioners where requested, will assist with therapies and approaches to achieve patients' health-care goals.⁴⁷

History of allergies

Those with a history of allergies who are unsuccessfully treated with standard antifungal therapy may respond to treatment with antihistamines, or to the combination of antihistamine and antifungal treatment.^{12,31}

Therapeutic vaccination and antibody-mediated immunotherapy

Therapeutic vaccination and antibody-mediated immunotherapy have been emerging as possible alternative approaches to management of this condition, and further studies may result in successful alternatives for some patients being available.⁴⁸

Depot medroxyprogesterone acetate (Depo-Provera™ [DMPA], Pfizer) is not in the category of CAM. However, as it is a non-conventional method of treating recurrent VVC, it is included in this section.

It is widely believed that *C. albicans* proliferates in an oestrogen-rich environment.^{7,11} Inducing a slightly atrophic environment in the vagina provides a less attractive environment for the *Candidal* species to proliferate.⁴⁹ In 1979, a study by

Topozada *et al.* suggested that those using DMPA had reduced incidence of candidal vaginal cultures compared with those not using it, and the incidence of vaginal candidiasis reduced even further with long-term users.⁵⁰

The use of DMPA with recurrent VVC has not been published in an RCT. Dennerstein's interest in this area resulted in an observational study that followed a group of 15 women with recurrent VVC who used DMPA for contraception for up to seven years.⁵¹ All were observed for recurrences of VVC. All but two patients did not have VVC during the time of treatment. Those that did have clinical recurrences despite the use of DMPA alone requested to remain on the drug because they believed it was responsible for their longest remissions.

This study had many design faults, and the author himself suggested that it be viewed as a pilot. It involved a small sample size. There was no control group, and the treatment differed (three months to seven years), with three of the women receiving exogenous oestrogen that could have confounded the results.

Many women would not be comfortable using DMPA for recurrent VVC, because of concerns about its anti-oestrogenic effect and side-effects that can include weight gain, menstrual spotting and irregularity (usually only in the first few months), amenorrhoea and delay in return to fertility.⁵² In the early years of its use, there was a concern about bone density and the use of additional oestrogen was prescribed. Later studies have found that although the bone density is reduced in DMPA users,⁵³ some studies suggesting up to a 5% loss over two years in hip and spine,⁵³ this effect is reversible once the medication is ceased.⁵⁴ For those not contemplating conception within the next two years and with a history of unsuccessful treatments using other conventional methods, the use of DMPA may be beneficial.

Diet

A consensus statement by clinical experts states that the role of dietary factors in management of recurrent VVC is limited.¹³ They reported cases where patients noticed that an excess of unrefined sugars caused exacerbation of symptoms. One study reporting the multivariate analysis of female factors associated with recurrent VVC found that the ingestion of two or more servings of (yeast) bread each day may be implicated.²⁵ This reached statistical significance ($P < 0.05$).

Lactobacillus recolonisation

Lactobacillus recolonisation (via yogurt or capsules) shows potential for alternative treatment of vulvovaginal candidiasis with little potential for harm. A study of 27 subjects concluded that vaginal inserts of *Lactobacillus acidophilus*, strain NAS (hydrogen peroxide positive) capsules, with or without oral probiotic capsules, may significantly reduce the incidence of recurrent VVC.⁵⁵ Application of these results, although promising, may be difficult. This regimen requires women to use the lactobacillus vaginal inserts (+/- oral

probiotics) three times a week. That less than half of the patients in the treatment arm of the study completed in six months is not encouraging. Studies have shown that patients generally prefer oral to intravaginal treatment for VVC, so compliance may be an issue.³⁸

Another study concluded that a daily ingestion of 125 g of yoghurt containing lactobacillus decreased both *Candida* colonisation and infection.⁵⁶ Other commercially available products such as ThreeLac™ claim to be beneficial but no RCTs are available to validate these claims, and the expense of such products may be prohibitive. No studies were found using intravaginal yoghurt, which is a treatment sometimes recommended to women.

A recent review of probiotics for recurrent VVC concluded that despite the current limited evidence for the benefits of probiotics, they can be recommended to women as the adverse effects are rare.⁵⁷ The unproven usefulness needs to be outlined.

Garlic

In vitro studies have shown that garlic has fungistatic properties at temperatures below 37°C and fungicidal properties at 37°C.⁵⁸ Recommended dosing is one clove of garlic wrapped in unbleached gauze, then crushed just prior to vaginal insertion, used nocte for six nights. Potential side-effects include offensive odour. Prolonged topical use can lead to allergic reactions or chemical burns.⁵⁹ No studies were found that examined the use of preparations of odourless garlic, either oral or intravaginal.

Gentian violet

Gentian violet has been used with less frequency in recent years, possibly because of the availability of less messy and more convenient treatments. It is said to possess antifungal and antihelmintic activity, as well as bactericidal and bacteriostatic activities against gram-positive bacteria.^{60,61}

A 1985 study reported the link between gentian violet and cancer, particularly liver cancer.⁶² In this study, however, the rats ingested between 100 mg/kg and 500 mg/kg of their body weight each week for up to 18 months, thus its relevance with topical vaginal use of 1% gentian violet is questionable.

No RCTs were found investigating the use of gentian violet. Jovanic *et al.*⁶³ observed patients treated unsuccessfully with 12 days of gentian violet tampons, but the dilutions were not specified. Diehl⁶¹ suggests that gentian violet is still effective for vulvovaginal candidiasis, having antifungal and antibacterial properties. It can, however, irritate the skin and stain clothing.

Haefner⁶⁴ described the benefit of the use of gentian violet with resistant thrush. He suggested 0.25% or 0.5% aqueous solution applied at home daily, or 1% solution applied in doctor's surgery up to three times a week. Geller and Nelson⁸ propose that gentian violet affects chitin production on the yeast's cell wall and suggest that application of gentian violet to the vaginal vault and affected

Table 3 Alternative methods of management of recurrent vulvovaginal candidiasis (RVVC)

| Evaluation criteria | DMPA | <i>Lactobacillus</i> | Gentian violet | Tea tree oil (TTO) |
|-----------------------------|---|--|--|---|
| Rationale for use | <i>Candida albicans</i> proliferates in oestrogen-rich environment. ^{7,11} Reducing the amount of serum oestrogen and inducing a slightly atrophic environment in the vagina should provide less attractive environment for the candidal species | <i>Lactobacillus acidophilus</i> is able to restore the acidic vaginal pH and encourage growth of normal vaginal flora ⁵⁹ | Gentian violet affects chitin production on the yeast's cell wall ⁸ Antifungal and antibacterial actions ⁶¹ | TTO is an excellent antifungal and antibacterial herb agent. ⁵⁵ Terpinen-4-ol is responsible for the rupture of fungal cell walls ⁵⁹ |
| Known side-effects or harms | Not approved for use with RVVC. Anti-oestrogenic effect; weight gain; menstrual spotting and irregularity (usually only in the first few months); amenorrhoea; delay in return to fertility. ⁵² Possible bone density effects: recent studies: the bone density in long term users is minimally reduced (5% loss over two years with hip and spine) ⁵³ but this effect is reversible once DMPA ceased ⁵⁴ | Use of lactobacillus in products such as yoghurt is not recommended for those who are lactose intolerant | Caution: different strengths available Skin irritation Stains clothing | Anecdotal reports of severe allergic reaction Allergic dermatitis Caution: different strengths and preparations are available Vaginal irritation |
| Cost | \$16 per dose every 3 months | Eg ThreeLac™ \$65 for 15 days; yoghurt \$0.60/day | Not available commercially | TTO vaginal cream \$16–20/50 g. Vaginal pessaries no longer available commercially |
| Method of administration | Depomedroxyprogesterone 150 mg i.m. 12 weekly | 250-mg <i>Lactobacillus</i> -containing yoghurt daily; oral probiotics; unflavoured lactobacillus yoghurt applied vaginally daily | 0.25% or 0.5% aqueous solution applied at home daily, or 1% solution applied in clinic up to 3 times a week ⁶⁴ Gentian violet to the vaginal vault and affected areas on the labia can be combined with topical antifungal cream nocte. Incomplete response: treat for 7 days afterwards | 1 or 2 drops of TTO placed in gelatin capsule and rest of capsule filled with calendula oil, vegetable oil or water. Two capsules inserted into vagina nocte for 6 nights. A few drops of TTO added to the bath Intravaginal pessaries and gels Tampon dipped in 1 cup of water with 5 drops TTO |

Table 3 Continued

| Evaluation criteria | Dietary changes | Allergy Therapy | Garlic | Nuva-Ring |
|-----------------------------|---|--|---|---|
| Rationale for use | A nutritious and healthy diet can assist with overall health and immune response Oral yeasts may promote the growth of systemic candidiasis (although limited evidence that this promotes vaginal candidiasis) Women with poorly controlled diabetes mellitus often have recurrent VVC Anecdotally some patients have reported an excess of unrefined sugars as a factor in RVVC ¹³ | Women who are prone to recurrent vulvovaginal candidiasis may have deficient cell-mediated immunity ⁹ RVVC is commonly linked to allergic rhinitis ²⁹ Strong association between atopy and RVVC ³⁰ Locally acquired mucosal immunity is an important host defence at the vaginal mucosa; changes in local cell-mediated immunity mechanism(s) may predispose to RVVC ¹⁷ | Allicin, the active form of garlic, has antimicrobial effects <i>in vitro</i> against many fungi ⁵⁹ | Nuva-Ring may improve counts of normal vaginal flora and increase hydrogen peroxide-producing lactobacillus |
| Known side-effects or harms | Oral yoghurt may cause gastrointestinal disturbance in people with lactose intolerance | In one study ²⁹ 11 patients showed no improvement and one worsened | Oral garlic: heartburn, nausea, diarrhoea, flatulence, bloating and offensive body odour Topical: allergic reactions and chemical burns | Not approved for use for RVVC. Increase in vaginal wetness, vaginal irritation, headache, weight gain, nausea, breakthrough bleeding URTI and sinusitis have been quoted as occurring in the studies although they have been considered not related to ring use |
| Cost | Variable | Variable | Fresh: \$1 per day. Odourless capsules: approx. \$16 per 200. | Approx. \$25 per month |
| Method of administration | Omit yeast, breads, sugar, alcohol, include natural yoghurt; some advocate avoiding dairy, nuts and dried fruit | Oral/i.m. allergy therapy i.m. allergenic extract Combination oral/intravaginal antifungals with allergy therapy | 1 clove of garlic wrapped in unbleached gauze crushed prior to vaginal insertion t.d.s. for 6 days Oral odourless capsules daily Some advocate adding half a cup of white vinegar to the bath in addition to garlic use | Continuous: Inserted intravaginally for 3 weeks with a 1-week break |

DMPA, depot medroxyprogesterone acetate; t.d.s., three times a day; URTI, upper respiratory tract infection.

areas on the labia can be combined with topical antifungal cream at night. Incomplete response can be treated seven days afterwards. Difficulties with use include permanent purple staining on clothing, and some patients develop a vulvar irritation after application of gentian violet.

A case study describing three cases of complicated VVC was retrieved.⁶⁵ In this study, one patient did not respond to a prolonged course of oral itraconazole in combination with vaginal and oral nystatin, oral medroxyprogesterone or intravaginal boric acid. Eradication of *C. glabrata* was finally achieved by local application of 1% gentian violet.

Tea tree oil

There have been claims that tea tree oil (TTO) is an excellent antifungal and antibacterial herb agent.⁶⁶ Suggested route of administration is by adding a few drops of TTO to the bath, or tea tree pessaries. Intravaginal pessaries and gels are available from health food shops. Anecdotally, severe vaginal irritation following use of intravaginal TTO has been reported, although no studies to date have documented this adverse reaction.

One difficulty of using TTO is that different strengths and preparations are available. In one study, the oil was analysed for exact determination of single constituents.⁶⁷ Terpinen-4-ol and 1,8-cineole were used as positive markers. There is no guarantee that commercially available products would meet these standards, although commercially available TTO products demonstrated similar fungicidal activity to non-formulated TTO.⁶⁸ One difficulty with this trial was that recurrences were analysed on day 21, which may have omitted later recurrences. In this study, the efficacy of the TTO was partly determined by the pH of the vaginal fluid. In a more acidic environment, the efficacy was higher. This variable could also have confounding effects when using it in human subjects.

Ernst and Huntley⁶⁹ conducted a systematic review of TTO and located four trials. They concluded that there is no compelling evidence that TTO is efficacious in any dermatological condition, but that it deserves to be studied more closely in view of promising findings. They found that adverse reactions were mainly mild and transient allergic reactions.

Other lifestyle measures: Clothing and douches

Although vinegar has been found to be inhibitory against candidiasis, no RCTs were found for the use of vinegar in water 1:4 perineal wash-downs. Additionally, vaginal douches have been found to be harmful and are not recommended.⁷⁰

The link between clothing and candidiasis remains controversial. The use of panty liners or pantyhose have been found to be associated with symptomatic VVC.⁷¹ Another study failed to establish any link between tight-fitting clothing, synthetic underwear and increased recurrences of VVC.⁷² Common sense and comfort would suggest that cotton underwear would reduce vulvovaginal irritation but this has not been scientifically established.

One study investigated the effectiveness of microwaving fabric against *C. albicans*.⁷³ Samples of *Candida*-impregnated cotton underpants were subjected to domestic microwaving at the high setting for up to 30 min. It was found that if the fabric was moistened, sterilisation occurred within five minutes. Conclusion drawn was that microwaving wet, freshly laundered cotton underpants should sterilise residual *Candida* and reduce the risk of reinfection.

No studies were found that investigated whether fungal spores on underpants are responsible for reinfection. Further studies testing these theories are needed before this can be confidently recommended as a strategy to manage recurrent VVC.

Available patient information

Currently, there is no Australian quality written patient information adequately addressing both conventional and non-conventional management of recurrent VVC. The available information is scanty, and concentrates largely on uncomplicated vulvovaginal candidiasis. The good quality information available focuses on pharmacological methods, and does not attempt to address the complex issues facing the patient or provide many other options of management.

Conclusion

A variety of alternatives are available for the treatment of recurrent VVC. Currently, management is aimed at control rather than cure of this condition. What is successful for one patient does not guarantee success for another. The clinician needs to be aware of the range of options for the patient, and the patient's preference needs to be considered when making recommendations. Patients should to be given accurate information regarding the evidence or lack thereof underpinning all options.

Well-designed RCTs are lacking in the literature surrounding the management of recurrent VVC, and further research is recommended. It will be important to address this deficit so that patients are able to make an informed decision about the management of this condition using both conventional and less conventional methods. There are some promising alternative treatments emerging in the area of recurrent VVC, offering hope for the patient who does not respond to conventional treatment, or to those who prefer alternative or complementary methods of health care. The use of immunotherapy for this condition is gaining recognition. However, there is no current treatment for this condition, whether conventional or non-mainstream, that can guarantee success.

References

- 1 Reef SE, Levine WC, Mcneil MM *et al.* Treatment options for vulvovaginal candidiasis. *Clin Infect Dis* 1995; 20 (Suppl. 1): S80–S90.

- 2 Calderon-Marquez JJ. Itraconazole in the treatment of vaginal candidosis and the effect of treatment of the sexual partner. *Rev Infect Dis* 1987; 9: S143–S145.
- 3 Nyirjesy P, Weitz M, Grody MH, Lorber B. Over-the-counter and alternative medicines in the treatment of chronic vaginal symptoms. *Obstet Gynecol* 1997; 90: 50–53.
- 4 Adis Data Information BV. Maintenance suppressive azole antifungal regimens are a major advance in controlling recurrent vulvovaginal candidiasis. *Drugs Ther Perspect* 2004; 20: 7–11.
- 5 Saporiti AM, Gomez D, Levalle S *et al*. Vaginal candidiasis: Etiology and sensitivity profile to antifungal agents in clinical use. *Rev Argent Microbiol* 2001; 33: 217–222.
- 6 Nyirjesy P. Chronic vulvovaginal candidiasis. *Am Fam Physician* 2001; 63: 697–702.
- 7 Sheary B, Dayan L. Clinical practice. Recurrent vulvovaginal candidiasis. *Aust Fam Physician* 2005; 34: 147–150.
- 8 Geller ML, Nelson AL. Bacterial vaginosis and vulvovaginal candidiasis. *Women's Health Prim Pract* 2003; 6: 537–548.
- 9 Ringdahl EN. Treatment of recurrent vulvovaginal candidiasis. *Am Fam Physician* 2000; 61: 3306–3312, 3317.
- 10 Therapeutic Goods Administration. Therapeutic Guidelines Ltd. Antibiotic, Version 13. eTG complete. Melbourne, Vic.: Therapeutic Guidelines Limited, 2006 January. [Accessed 18 October 2006.] Available from <http://www.tg.com.au/ip/complete/>.
- 11 Prodigy Knowledge. The Management of Genital Thrush (Vulvo-Vaginal Candidiasis) in Women. Candida-Female Genital. 2005. Crown Copyright, Department of Health 1998–2004. [Accessed 2 November 2006.] Available from http://www.prodigy.nhs.uk/candida_female_genital.
- 12 White DJ, Vanthuyne A, Wood PM, Ayres JG. Zafirlukast for severe recurrent vulvovaginal candidiasis: An open label pilot study. *Sex Transm Infect* 2004; 80: 219–222.
- 13 Sobel JD, Faro S, Force RW *et al*. Vulvovaginal candidiasis: Epidemiologic, diagnostic, and therapeutic considerations. *Am J Obstet Gynecol* 1998; 178: 203–211.
- 14 Clinical Effectiveness Group (CEG). *National Guideline on the Management of Vulvovaginal Candidiasis*. 2002. London, UK: ECG, University of London. [Accessed 10 October 2006.] Available from http://www.bashh.org/guidelines/2002/candida_0601.pdf.
- 15 Mardh PA, Novikova N, Stukalova E. Colonisation of extragenital sites by candida in women with recurrent vulvovaginal candidosis. *BjOG* 2003; 110: 934–937.
- 16 Sobel JD. Pathogenesis and treatment of recurrent vulvovaginal candidiasis. *Clin Infect Dis* 1992; 14 (Suppl. 1): S148–S153.
- 17 Fidel PL, Sobel JD. Immunopathogenesis of recurrent vulvovaginal candidiasis. *Clin Microbiol Rev* 1996; 9: 335–348.
- 18 Fidel PL Jr, Barousse M, Espinosa T *et al*. *Infect Immun* 2004; 72: 2939–2946.
- 19 Fong IW. The rectal carriage of yeast in patients with vaginal candidiasis. *Clin Invest Med* 1994; 17: 426–431.
- 20 O'Conner MI, Sobel JD. Epidemiology of recurrent vulvovaginal candidiasis: Identification and strain differentiation of *Candida albicans*. *J Infect Dis* 1986; 154: 358–363.
- 21 Spinillo A, Carratta L, Pizzoli G *et al*. Recurrent vaginal candidiasis. Results of a cohort study of sexual transmission and intestinal reservoir. *J Reprod Med* 1992; 37: 343–347.
- 22 Lacour M, Zunder T, Huber R, Sander A, Daschner F, Frank U. The pathogenetic significance of intestinal *Candida* colonization: A systematic review from an interdisciplinary and environmental medical point of view. *Int J Hyg Environ Health* 2002; 205: 257–268.
- 23 Fong IW. The value of treating the sexual partners of women with recurrent vulvovaginal candidiasis with ketoconazole. *Genitourin Med* 1992; 68: 174–176.
- 24 Bisschop MP, Merkus JM, Scheygrond H, Van Cutsem J. Co-treatment of the male partner in vaginal candidosis: A double-blind randomized control study. *Br J Obstet Gynaecol* 1986; 93: 79–81.
- 25 Reed BD, Zazove P, Pierson CL, Gorenflo DW, Horrocks J. *Candida* transmission and sexual behaviors as risks for a repeat episode of candida vulvovaginitis. *J Womens Health (Larchmt)* 2003; 12: 979–989.
- 26 White DJ, Drake SM. Management of genital candidiasis. *BMJ* 1995; 311: 629.
- 27 Tasic S, Tasic N, Tasic A, Mitrovic A. Recurrent genital candidosis of women; consequence of reinfection of relapse. *Med Biol* 2002; 9: 217–222.
- 28 Dennerstein GJ. The treatment of candida vaginitis and vulvitis. *Aust Prescr* 2001; 24: 62–64.
- 29 Moraes PS. Recurrent vaginal candidiasis and allergic rhinitis: A common association. *Ann Allergy Asthma Immunol* 1998; 81: 165–169.
- 30 Neves NA, Carvalho LP, De Oliveira M *et al*. Association between atopy and recurrent vaginal candidiasis. *Clin Exp Immunol* 2005; 142: 167–171.
- 31 Neves NA, Carvalho LP, Lucas P, Lopes AC, Cruz A, Carvalho E. Successful treatment of refractory recurrent vaginal candidiasis with cetirizine plus fluconazole. *J Low Genit Tract Dis* 2005; 9: 167–170.
- 32 Macneill C, Carey JC. Recurrent vulvovaginal candidiasis. *Curr Women Health Rep* 2001; 1: 31–35.
- 33 El-Din S, Reynolds M, Ashbee H, Barton R, Evans E. An investigation into the pathogenesis of vulvo-vaginal candidosis. *Sex Transm Infect* 2001; 77: 179–183.
- 34 Spence D. Candidiasis (vulvovaginal). In: Godlee F, ed. *Clinical Evidence* [online book]. London: BMJ Publishing Group Pty Ltd, 2005.
- 35 Sobel JD, Schmitt C, Meriwether C. Clotrimazole treatment of recurrent and chronic candida vulvovaginitis. *Obstet Gynecol* 1989; 73: 330–334.
- 36 Sobel JD, Schmitt C, Stein G, Mummaw N, Christensen S, Meriwether C. Initial management of recurrent vulvovaginal candidiasis with oral ketoconazole and topical clotrimazole. *J Reprod Med* 1994; 39: 517–520.
- 37 Sobel JD, Wiesenfeld HC, Martens M *et al*. Maintenance fluconazole therapy for recurrent vulvovaginal candidiasis. *N Eng J Med* 2004; 351: 876–883.
- 38 Watson MC, Grimshaw JM, Bond CM, Mollison J, Ludbrook A. Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush). *Cochrane Database Syst Rev* 2006, Issue 3. Art. No.:CD002845. DOI: 10.1002/14651.
- 39 Eschenbach DA, Thwin SS, Patton DL *et al*. Influence of the normal menstrual cycle on vaginal tissue, discharge, and microflora. *Clin Infect Dis* 2000; 30: 901–907.
- 40 Kozel TR, Fidel PL, Cutright J, Stelle C. Effects of reproductive

- hormones on experimental vaginal candidiasis. *Infect Immun* 2000; **68**: 651–657.
- 41 Eckert LO, Hawes SE, Stevens CE, Koutsky LA, Esenbach DA, Holmes K. Vulvovaginal candidiasis: Clinical manifestations, risk factors, management algorithm. *Obstet Gynecol* 1998; **92**: 757–765.
- 42 Lopez-Olmos J, Lerma E. Treatment of recurring vulvo-vaginal candidiasis: A comparative prospective study during six months of three anti-mycotic preparations of a single dose. *Clin Invest Gynecol Obstet* 2000; **27**: 366–375.
- 43 Roth AC, Milsom I, Forssman L, Wahlen P. Intermittent prophylactic treatment of recurrent vaginal candidiasis by postmenstrual application of a 500 mg clotrimazole vaginal tablet. *Genitourin Med* 1990; **66**: 357–360.
- 44 Sobel JD. Management of patients with recurrent vulvovaginal candidiasis. *Drugs* 2003; **63**: 1059–1066.
- 45 Guaschino S, De Seta F, Sartore A *et al.* Efficacy of maintenance therapy with boric acid in comparison with oral itraconazole in the treatment of recurrent vulvovaginal candidiasis. *Am J Obstet Gynecol* 2001; **184**: 598–602.
- 46 NHS. An update on vulvovaginal candidiasis (thrush). *MeReC Bulletin* 2004; **14**; MeReC Publications. NICS.
- 47 Coulter ID, Willis EM. The rise and rise of complementary and alternative medicine: A sociological perspective. *MJA* 2004; **180**: 587–589.
- 48 Magliani W, Conti S, Salati A *et al.* New strategies for treatment of *Candida* vaginal infections. *Rev Iberoam Micol* 2002; **19**: 144–148.
- 49 Miller L, Patton D, Meier A *et al.* Depomedroxyprogesterone-induced hypoestrogenism and changes in vaginal flora and epithelium. *Obstet Gynecol Surv* 2000; **96**: 431–439.
- 50 Toppozada M, Onsy F, Fares E, Amir S, Shaala S. The protective influence of progestogen only contraception against vaginal moniliasis. *Contraception* 1979; **20**: 99–103.
- 51 Dennerstein G. Depo-Provera in the treatment of recurrent vulvovaginal candidiasis. *J Reprod Med* 1986; **31**: 801–803.
- 52 Kaunitz A. Injectable depot medroxyprogesterone acetate contraception: An update for U.S. clinicians. *Int J Fertil Womens Med* 1998; **43**: 73–83.
- 53 Clark MK, Sowers M, Nichols S, Levy B. Bone mineral density changes over two years in first-time users of depot medroxyprogesterone acetate. *Fertil Steril* 2004; **82**: 1580–1586.
- 54 Gbolade B, Ellis S, Murby B, Randal S, Kirkman R. Bone density in long term users of depot medroxyprogesterone acetate. *Br J Obstet Gynaecol* 1998; **105**: 790–794.
- 55 Metts J, Famula T, Tenev N, Clemens R. *Lactobacillus acidophilus*, strain NAS (H2O2 positive), in reduction of recurrent candidal vulvovaginitis. *J Appl Res* 2003; **3**: 340–348.
- 56 Hilton E, Isenberg HD, Alperstein P, France K, Borenstein MT. Ingestion of yoghurt containing acidophilus as prophylaxis for candidal vaginitis. *Ann Intern Med* 1992; **116**: 353–357.
- 57 Falagas ME, Betsi GI, Athanasiou S. Probiotics for prevention of recurrent vulvovaginal candidiasis: A review. *J Antimicrob Chemother* 2006; **58**: 266–272.
- 58 Moore GS, Atkins RD. The fungicidal and fungistatic properties of an aqueous garlic extract on the medically important yeast-like fungi. *Mycologia* 1977; **69**: 341–348.
- 59 Van Kessel K, Assefi N, Marrazzo J, Eckert L. Common complementary and alternative therapies for yeast vaginitis and bacterial vaginosis: A systematic review. *Obstet Gynecol Surv* 2003; **58**: 351–358.
- 60 Thompson Healthcare Inc. DRUGDEX® Drug Point Gentian Violet. *MICROMEDIX*. 1974–2006. Micromedex® Healthcare Series [Internet database]. Greenwood Village, CO: Thomson Micromedex. Updated periodically. [Accessed 23 October 2006.] Available from Clinician's Health Channel.
- 61 Diehl KB. Topical antifungal agents: An update. *Am Fam Physician* 1996; **54**: 1687–1693.
- 62 Littlefield NA, Blackwell BN, Hewitt CC, Gaylor DW. Chronic toxicity and carcinogenicity studies of Gentian violet in mice. *Fundamental Appl Toxicol* 1985; **5**: 902–912.
- 63 Jovanovic R, Congema R, Nguyen H. Antifungal agents vs Boric Acid for treating chronic myotic vulvovaginitis. *J Reprod Med* 1991; **36**: 593–597.
- 64 Haefner HK. Current evaluation and management of vulvovaginitis. *Clin Obstet Gynecol* 1999; **42**: 184–195.
- 65 White DJ, Johnson EM, Warnock DW. Management of persistent vulvo vaginal candidosis due to azole-resistant *Candida glabrata*. *Genitourin Med* 1993; **69**: 112–114.
- 66 Glenville M. *Thrush, Vaginal. The Natural Health Website for Women*. 2001–2006. UK. [Accessed 12 September 2006.] Available from <http://www.marilynglenville.com/>.
- 67 Mondello F, De Bernardis F, Girolamo A, Salvatore G, Cassone A. In vitro and in vivo activity of tea tree oil against azole-susceptible and -resistant human pathogenic yeasts. *J Antimicrob Chemother* 2003; **51**: 1223–1229.
- 68 Hammer KA, Carson CF, Riley TV. In-vitro activity of essential oils, in particular *Melaleuca alternifolia* (tea tree) oil and tea tree oil products, against *Candida* spp. *J Antimicrob Chemother* 1998; **42**: 591–595.
- 69 Ernst E, Huntley A. Tea tree oil: A systematic review of randomised clinical trials. *Forsch Komplementarmed, Klass Naturheilked (Research in Complementary Medicine)* 2000; **7**: 17–20.
- 70 Martino JL, Vermund SH. Vaginal douching: Evidence for risks or benefits to women's health. *Epidemiol Rev* 2002; **24**: 109–124.
- 71 Patel DA, Gillespie B, Sobel JD *et al.* Risk factors for recurrent vulvovaginal candidiasis in women receiving maintenance antifungal therapy: Results of a prospective cohort study. *Am J Obstet Gynecol* 2004; **190**: 644–653.
- 72 Mardh PA, Novikova N, Stukalova E. Colonisation of extragenital sites by *Candida* in women with recurrent vulvovaginal candidosis. *BJOG* 2003; **110**: 934–937.
- 73 Friedrich EG Jr, Phillips LE. Microwave sterilization of *Candida* on underwear fabric. *J Reprod Med* 1988; **33**: 421–422.