Acute vulvovaginal candidiasis (VVC) is common and usually easily treated but some women develop chronic symptoms that do not respond to conventional anti-*Candida* treatment. Recently proposed diagnostic criteria may help clinicians identify women with chronic VVC. Evidence is mounting that it represents a hypersensitivity response to commensal *Candida* spp. It usually responds to long-term antifungal treatment.

### Key points
- **Vulvovaginal candidiasis (VVC)** covers a disease spectrum, from a single episode to chronic disease with unremitting symptoms.
- The concept of chronic VVC was recently described; it is a common cause of chronic nonerosive vulvovaginitis in women presenting at vulval disease clinics.
- Evidence suggests chronic VVC is a hypersensitivity response to commensal *Candida* spp.
- In healthy non-diabetic patients, chronic VVC, like acute VVC, occurs only in the presence of oestrogen.
- Chronic VVC may be diagnosed based on clinical features and a history that satisfies specific criteria; diagnosis is supported by, but does not require, a positive swab result for *Candida* spp. at presentation.
- Patients with chronic VVC respond well to oral antifungal therapy, which may be needed long term.
Furthermore, chronic VVC, like acute VVC, does not occur before menarche or after menopause unless the patient is taking hormone replacement therapy and, although it may commence at any stage of reproductive life, it is most common in young adults. It thus appears that oestrogen plays an essential permissive role and in healthy non-diabetic patients, no forms of VVC occur in the absence of oestrogen, whether endogenous or exogenous. The nature of this relationship with oestrogen has not been established.

VVC, including chronic VVC, imposes a significant burden on health resources and, like any chronic disease, has a large impact on quality of life, particularly as it occurs in an area of the body that many are too embarrassed to present to their doctor. Self-diagnosis and the availability of over-the-counter medication make it difficult to estimate this burden accurately; however, VVC has been estimated to cost one billion dollars per year in the USA.

A typical case of chronic VVC is described in Box 2.

### 1. DIAGNOSTIC CRITERIA FOR CHRONIC VULVOVAGINAL CANDIDIASIS

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
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<tr>
<td>Previous response, even if brief, to antifungal treatment</td>
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<tr>
<td>History of a positive vaginal swab for <em>Candida</em> spp. at any time while symptomatic</td>
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<td>Cyclical symptoms: build-up before menses, improvement during menses</td>
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<td>Discharge: usually nonoffensive, mucoid</td>
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<td>Exacerbation with antibiotics</td>
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<td>Dyspareunia</td>
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<td>Soreness</td>
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<td>Vulval oedema, including after coitus</td>
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**CLINICAL FEATURES**

The typical clinical features of recurrent VVC are well described in the medical literature as itch, variable discharge, soreness, irritation, burning, dyspareunia and dysuria with a premenstrual exacerbation. These are also features of chronic VVC (Box 1). Most patients report that their male partner has no symptoms, but postcoital penile erythema and irritation occurs in about 10% of men with a partner with untreated vaginal candidiasis. Examination reveals vaginal erythema, a nonoffensive mucoid discharge and erythema of the introitus and vulva. The dominant symptoms are pain, dyspareunia and itch with a definite but not cheesy discharge. Oral antibiotics are frequently associated with flares, and patients learn to avoid them. Single-dose antifungals bring only brief relief.

### 2. A TYPICAL CASE OF CHRONIC VULVOVAGINAL CANDIDIASIS

Jenna is a healthy 22-year-old woman who presents with vulvovaginitis. Her first attack occurred soon after she started taking the oral contraceptive pill (OCP) and concurrently became sexually active at the age of 18 years. She was too embarrassed to visit her family GP, who had known her all her life, but went instead to a pharmacist who provided her with a course of antifungal suppositories. Her symptoms improved rapidly but she had frequent recurrences, responsive to topical therapy.

At the age of 21 years, Jenna had an appendectomy and was treated with intravenous antibiotics. While in hospital, she developed severe vulvovaginitis. She again self-medicated with topical antifungals but this time without a response. At this point she consulted her GP. A vaginal swab was negative for *Candida* spp. but showed group B streptococci. At a loss to explain her problem, her GP prescribed a course of amoxicillin. Her symptoms of itch, dyspareunia and discharge worsened and she was then empirically treated with two single doses of fluconazole 150 mg. After each dose, her symptoms remitted but rapidly returned.

Each month Jenna noted a premenstrual flare of symptoms, and the only time she felt well was while menstruating. Stopping the OCP made no difference to her symptoms and extensive investigations for sexually transmitted infections, iron deficiency and impaired glucose tolerance gave negative results. A referral to an immunologist did not reveal anything to suggest immunodeficiency.

Examination revealed nonspecific vulvovaginal erythema extending to the labia minora and the sulcus between the labia minora and majora, accompanied by a nonoffensive mucoid discharge. A repeat vaginal swab revealed no abnormality.

Jenna was referred to a vulval disease clinic, where she was diagnosed with chronic VVC. She gradually became asymptomatic over a three-month course of continuous treatment with oral fluconazole.

**Commentary**

This young woman’s story is typical of the history and evolution of chronic VVC over time. Many similar patients present at vulval dermatology clinics. Patients are usually aged in their late teens to early 20s and at symptom onset have recently become sexually active. They are otherwise healthy with no factors to suggest immunodeficiency. Because sexual activity often coincides with commencing the OCP, the latter is usually implicated, but patients find no change in symptom severity whether they are taking or not taking the OCP.

Attacks are initially sporadic and readily treated with antifungal medication. With time, they become progressively more frequent, treatment resistant and finally chronic with a premenstrual flare. The typical appearance of acute candidiasis is replaced by a low-grade chronic erythema involving the vagina, introitus and vulva. The dominant symptoms are pain, dyspareunia and itch with a definite but not cheesy discharge. Oral antibiotics are frequently associated with flares, and patients learn to avoid them. Single-dose antifungals bring only brief relief.
labia minora and majora, perineum and sometimes perianal skin, which may be complicated by oedema and painful fissuring (Figures 1 to 3).

Patients with chronic VVC are typically systemically well. They show no evidence of immunosuppression, and oral and oesophageal involvement is the exception. The latter do occur in individuals with VVC who are immunosuppressed or have diabetes, but this group appears distinct from the otherwise healthy women who have chronic VVC.

It is not uncommon for patients with chronic VVC to have a negative vaginal swab for Candida at presentation. There are several possible causes of false negatives. They are most likely the result of self-medication with over-the-counter antifungals, but sampling errors and the limitations of current detection methods may also be implicated. Patients with this condition find that common skin conditions causing burning can sometimes coexist, and if a patient has not responded to antifungal therapy then these should be considered.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of VVC includes a range of conditions that cause persistent erythematous vulvovaginitis (Box 3). Of these many conditions, VVC is the only one that is causally related to Candida albicans and the only one that responds to antifungal medication alone. It is an important practice point that common skin conditions causing vulvitis such as dermatitis and psoriasis are not associated with a vaginitis but may resemble VVC externally and may coexist with it. Patients with psoriasis or dermatitis may have signs of these conditions on other parts of their skin and it is always worth scanning patients for such evidence on first examination. Patients who have a dermatosis, rather than chronic VVC, generally give a very different history that does not include a previous good response to antifungal treatment, discharge, dyspareunia or a premenstrual flare.

Although burning as a symptom is certainly seen in chronic VVC, it is rarely the only symptom. Nevertheless, chronic pain syndromes that can cause burning can occur concurrently, and if a patient has not responded to antifungal therapy then these should be considered.
• Recurrent vulvovaginal candidiasis (VVC)
• Recurrent bacterial vaginosis

Uncommon
• Desquamative inflammatory vaginitis
• Intravaginal foreign body (e.g. retained tampon)
• Chronic fixed drug eruption
• Allergy: contact dermatitis to intravaginal substance

Rare
• Mucosal lichen planus
• Oestrogen hypersensitivity vulvovaginitis

Very rare
• Crohn’s disease
• Immuno bullous disease
• Graft versus host disease


3. CAUSES OF CHRONIC VULVOVAGINITIS

Common

• Recurrent vulvovaginal candidiasis (VVC)
• Recurrent bacterial vaginosis

Uncommon

• Desquamative inflammatory vaginitis
• Intravaginal foreign body (e.g. retained tampon)
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Very rare

• Crohn’s disease
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presentation. In these patients it is necessary to rely on clinical judgement irrespective of whether there is a positive culture result.

It is not known why so many women with significant long-term symptoms present with a negative result for Candida on culture and even polymerase chain reaction (PCR) testing. Nevertheless, in my experience, most patients relate if questioned that culture has been positive for Candida at some stage while they were symptomatic in the past.

Biopsy shows only nonspecific inflammatory changes and usually does not demonstrate the presence of yeast in the epidermis. Microscopy is time-consuming and difficult for practitioners and, as stated above, is not always positive. The pH of vaginal discharge, which is normal in VVC, serves only to differentiate VVC from bacterial vaginosis.

As there is no definitive diagnostic test for chronic VVC, the diagnosis rests on:
- a history
- nonerosive vulvovaginitis seen on examination (although this can be nonspecific and vary with the menstrual cycle) and
- a convincing objective return to a normal vulvovaginal appearance and self-reported symptomatic response to antifungal therapy.

Previous studies have demonstrated the unreliability of clinical diagnosis, but diagnostic accuracy can be improved by ensuring that patients satisfy at least five of the diagnostic criteria listed in Box 1.

A vaginal swab positive for C. albicans or a non-albicans Candida species supports the diagnosis but does not confirm it, and a negative swab does not rule it out.

WHY DO HEALTHY PATIENTS DEVELOP CHRONIC VVC?

Candida is a dimorphic yeast, a commensal of the genital and gastrointestinal tracts. Many studies have shown it is responsible for VVC and that in approximately 85 to 95% of cases, C. albicans is isolated on culture. In the other 5 to 15% of cases, other Candida species are isolated, with the most frequent being Candida glabrata. In certain geographic areas, non-albicans species are isolated at higher rates than 5 to 15% but this is not true of the Australian population.

An important practice point is that non-albicans species are azole-resistant, although susceptible to topical boric acid and to oral voriconazole, an antifungal drug that recently became available. The prevalence of non-albicans strains appears to be increasing.

Most diseases caused by commensal organisms occur in patients who are immunosuppressed or have diabetes, so it is of great interest that chronic VVC is an exception. The role of the organism itself has been studied; virulence factors are not relevant, which possibly explains the rarity of drug resistance.

Many studies have attempted to discover an immune deficiency underlying VVC but none have been successful. Why or how a commensal organism that is tolerated by most individuals evolves to cause severe symptoms in a few otherwise healthy women is unknown. Our understanding of pathogenesis involving organisms of the normal microbiota (the community of organisms making up a tissue microbiome) is in its infancy. As tissue microorganisms become better understood some of the paradoxes of this condition may be better explained.

Symptom severity and signs of inflammation in VVC appear to be unrelated to the severity of infection. Some patients who are heavily colonised by Candida remain asymptomatic, while others with low or negative colony counts may display severe symptoms.

Predisposing and trigger factors

Although there is much we do not know about the cause of VVC, there are factors that have been shown to play a role, others that may play a role and some that have been shown not to play a role (summarised in Box 4).

Recent evidence points to two aetiological factors that appear to be the most important in susceptibility to chronic VVC: host immune response and oestrogen. Other factors that are well recognised to predispose to or trigger attacks include antibiotics and sexual activity, although the condition is not sexually transmitted and treating the male partner does not enhance treatment response. After menopause, hormone replacement therapy can trigger VVC but studies have not shown that the OCP has any effect on it. There are reports implicating progesterone-releasing intrauterine devices, and my experience corroborates this.

Host immune response

Cell-mediated and humoral immunity

In the past, Candida-specific cell-mediated immunity has been considered to be the most likely host defence mechanism against mucosal Candida infection. However, studies using mouse models as well as cross-sectional clinical studies have convincingly ruled out a role for either local or adaptive immunity in VVC. Humoral immunity similarly has not been shown to...
play a role. No study has been able to demonstrate a difference in total or Candida-specific antibodies in sera or vaginal secretions between women with recurrent VVC and control women.

It is now accepted, therefore, that systemic immunity is not relevant and the problem is specific to the vagina. This is supported by the observation that women with recurrent VVC are almost never susceptible to oral candidiasis, and conversely that immunosuppressed women with HIV disease are susceptible to oral but not vaginal candidiasis.

Local immunoregulatory mechanisms

Data suggest that host-specific innate immunoregulatory mechanisms play a role in susceptibility to VVC. The concept that symptoms are the result of an allergic reaction mediated by Candida-specific IgE has been explored by a number of researchers and does appear relevant in a small number of patients. Interestingly, atopy has been shown to be more prevalent in this group than in the general population.

Much of our data come from murine experiments, but in 2004 a breakthrough study used an intravaginal challenge with C. albicans in healthy human volunteers. This study demonstrated that, counter-intuitively at first, susceptibility to acute symptomatic candidiasis was associated with a brisk inflammatory leukocyte response, while protection from symptoms was associated with lack of inflammation. Patients with a previous history of candidiasis were more susceptible than those without. Vaginal lavage fluid from women with symptomatic infection had the ability to stimulate neutrophil migration in vitro.

This same study demonstrated that inoculation of Candida into the vagina was much more likely to result in colonisation in women with a previous history of recurrent attacks of candidiasis than in those without such a history, thus suggesting an individual, possibly genetic susceptibility.

Vaginal cells in these patients both lacked anti-Candida activity and were highly intolerant to the presence of Candida, generating an exaggerated immune response triggered by very low numbers of the organism.

A study that evaluated vaginal epithelial cell anti-Candida activity prior to intravaginal challenge showed that cells in women who develop symptoms have significantly lower activity compared with those in women who do not develop symptoms. This suggests an inherent but as yet not elucidated protective mechanism at the level of the vaginal epithelial cell.

T cells can be demonstrated in large numbers in the vagina in candidiasis and appear to migrate in response to local antigenic stimuli or inflammatory chemokines. Their exact role in VVC is unclear.

A study examining immune mediators found elevated levels of prostaglandin as well as Candida-specific intravaginal IgE. This study also postulated a hypersensitivity response.

It thus appears that VVC is associated with signals following interactions between Candida and vaginal epithelial cells that promote a nonprotective inflammatory response, which results in symptoms. Resistance to disease is associated with a lack of these signals. Vaginal cells in VVC patients have a low tolerance for even small numbers of organisms (theoretically so small in some cases that they are not able to be cultured) and signal an inflammatory response. The threshold above which this signalling takes place varies from patient to patient. It is possible also that, given the numbers of women with significant symptoms despite negative culture, the inflammatory response continues after initiation in the absence of detectable antigen.

These studies raise a paradigm for understanding chronic VVC, suggesting a host-mediated individual genetic susceptibility to a commensal organism that is tolerated by most women. This may explain the paradoxes that have so far confounded investigators, including lack of local or systemic immune deficiency, the fact that chronic VVC is no more common in HIV-infected patients than in healthy patients, the lack of oral involvement and irrelevance of infection of the male partner.

This may also explain why continuous suppression is required in patients with chronic VVC to keep the levels of Candida in the vagina below the threshold for inflammation and why some patients need more suppression than others. It is of interest here to compare chronic VVC with autoimmune conditions where the antigenic stimulus is not known. In these conditions, treatment requires nonspecific suppression of the immune system. In chronic VVC we need to suppress only the known antigen.

Oestrogen

The role of oestrogen appears obvious but is largely unexplored. Chronic VVC is usually characterised clinically by oestrogen-related cyclicity. Most patients report that symptoms worsen after ovulation when...
Chronic Vulvovaginal Candidiasis Continued

Figure 4. Even when patients are treated and become asymptomatic, they may retain some erythema in the sulcus between the labia minora and majora.

Oestrogen levels are highest, peak in the premenstrual week and rapidly decrease during menstruation. Similarly, clinical appearance varies over the menstrual cycle and is often near to normal during menstruation and for a few days after.

A 2001 study suggested that postmenopausal women could become susceptible to candidiasis as a result of hormone replacement therapy.11 Among 339 consecutive patients aged 55 years or over presenting to a dermatogynaecology clinic, 26% of women using oestrogen had a positive vaginal swab for C. albicans as opposed to 4% in the group not using oestrogen.

A more recent study supports these findings. It demonstrated that after menopause, VVC occurs almost exclusively in women using oestrogen (but not progesterone) replacement therapy and that most of these patients were susceptible to it before menopause, thus demonstrating the importance of oestrogen in the aetiology of chronic VVC.7

Healthy patients with chronic VVC typically do not have oral or oesophageal involvement, in contrast to immunosuppressed and diabetic individuals who often do. This fact may support the contention that the pathology of VVC is particular to the vaginal microenvironment and that the pathogenesis in healthy people differs from that in those who are immunocompromised. The difference may be related to the density or type of oestrogen receptors.

**Current Recommended Management of Chronic VVC**

There is a paucity of grade A evidence for treatment of chronic VVC. A recent systematic review identified only two studies suitable for meta-analysis in the past 10 years.25 Both these trials examined long-term maintenance therapy with fluconazole 150 mg per week. However, my experience is that weekly regimens often fail in patients with chronic VVC, a point that was not addressed in the review. Long-term treatment regimens have all tended to recommend oral azoles, because long-term use of pessaries is difficult to comply with and often causes irritant skin reactions that complicate the assessment of treatment response.

**Principles of treatment**

The principles of treating chronic VVC are as follows.

- Commence therapy with an induction course, usually with an oral antifungal medication such as fluconazole or itraconazole taken daily. Continue until the patient is asymptomatic and vulval appearance on examination is essentially normal, other than erythema of the sulcus between the labia minora and majora. The usual dose is fluconazole 50 to 100 mg daily or itraconazole 100 mg daily.

- Where C. glabrata is found and the patient fits the diagnostic criteria, boric acid suppositories 600 mg daily are used. If patients are unable to tolerate boric acid then oral voriconazole is an alternative although this drug has potential toxicities not shared by fluconazole or itraconazole.

- For the next six months after symptom remission is achieved, maintenance therapy should be undertaken as about 50% of patients relapse soon after the induction course is ceased. The dose required differs between patients. For most, a twice weekly dose of fluconazole 50 to 100 mg or itraconazole 100 mg is adequate, but some cannot reduce from daily dosing without a relapse of symptoms.

- If relapse occurs after maintenance therapy is ceased, long-term maintenance may be needed. Signs and symptoms usually resolve with these regimens, so much so that response becomes a diagnostic test in itself. Once symptoms have resolved there is usually an objective improvement, but some degree of persistent erythema in the sulcus between the labia minora and majora is common (Figure 4). Although patients taking these medications almost always have negative cultures while on treatment, relapse is common after the medications are ceased. Relapse appears not to be caused by drug resistance as re-treatment is usually effective.

**Oral antifungal agents**

The antifungal agents itraconazole and fluconazole are well tolerated with low rates of side effects. Unlike ketoconazole, which has been associated with drug-induced hepatitis in 10% of patients, itraconazole and fluconazole very rarely affect the liver and are safe to take orally long term. Neither drug is supported by the PBS for the indication of chronic VVC, but the cost of fluconazole has reduced significantly recently and the cost–benefit ratio is good. In general, antifungal resistance is rare although recently reported.26

**Natural therapies**

Patients often request ‘natural therapies’ for treatment of candidiasis, which have been reviewed recently.27 The role of diet and probiotics is as yet undetermined. In my experience, although many women express reservations about long-term antifungal therapy with fluconazole and itraconazole, fuelled largely by unsubstantiated reports of liver toxicity, they are sufficiently frustrated with other treatment options to embark on it and happy to remain on it once they realise its efficacy.

**Antifungal pessaries**

In theory, antifungal pessaries containing azoles such as miconazole and clotrimazole, nystatin or boric acid may be used with once-daily dosing. Indeed, where swabs...
have demonstrated atypical candidiasis, caused most commonly by *C. glabrata*, boric acid suppositories 600 mg daily are indicated as this organism is generally resistant to azoles. The problem with long-term use of pessaries is poor adherence.

**Ancillary treatments**
Ancillary treatment, including topical corticosteroids and avoidance of soap and irritants (including pads, liners, perfumed sprays and G-string underwear) is helpful, particularly in patients who have a concurrent atopic or psoriatic tendency and may have a concurrent dermatosis.

**WHAT TO DO IF TREATMENT FAILS**
If the diagnosis is correct then there is usually a rapid and pleasing response with significant improvement in quality of life score by three months of treatment. If treatment fails then the possibilities are as follows.
- The diagnosis was incorrect, and other possibilities should be considered (see Box 3).
- The diagnosis was correct but comorbidities such as pain syndromes, pelvic floor spasm or dermatoses have prevented a complete symptom response. Patients are usually much improved but still have residual complaints.
- The patient is not absorbing the medication. This may indicate coeliac disease, although not invariably.
- The organism is either resistant to the medication or has an unusually high minimum inhibitory concentration, and a higher dose is required.
- The patient is postmenopausal and taking oestrogen replacement therapy and has not ceased it during the induction course.
- The patient has a progesterone-releasing intrauterine device in situ.
  In these situations, specialist referral is suggested.

**PRACTICE POINTS FOR CLINICIANS**
At present, the diagnosis of chronic VVC is not defined. I suggest, based on the criteria presented in Box 1, the following guide to diagnosis.
- Patients who have a nonerosive chronic vulvovaginitis that worsens premenstrually and also with antibiotic treatment, who have had a positive culture result for *Candida* at any time while they were symptomatic and who have a history of a positive response to antifungal medication are likely to have chronic VVC.
- These patients are likely to benefit from a trial of oral antifungal medication. The optimum duration and frequency of treatment are yet to be determined, but the guidelines outlined above are a good starting point. My practice is to initiate treatment with a minimum of three months of continuous oral antifungal medication, continued until the patient is completely asymptomatic and objectively appears close to normal (many patients always retain slight erythema in the sulcus between the labia minora and majora).
- Fluconazole is significantly cheaper than itraconazole and has less potential for drug interactions. If swabs show *C. glabrata* then boric acid pessaries should be used instead. Most patients given a choice indicate they would rather take oral medication than use pessaries. *C. glabrata* is sensitive to voriconazole but this drug is potentially more toxic than fluconazole and itraconazole.
- Maintenance therapy is then continued for a minimum of six months, using a reduced dose usually twice a week. Some patients require continued maintenance therapy for many years.

There are no data at present on how many patients are able to completely withdraw from therapy without relapse in the long term. A study suggested 50% can do so, but follow up was of short duration. The safety of maintenance therapy appears high despite the requirement for long-term oral antifungal medication using either fluconazole and itraconazole, akin to long-term antiviral therapy for genital herpes. To date no more effective treatment has been identified.

**CONCLUSION**
There is still much that we do not know about chronic VVC. Research suggests it is an oestrogen-related hypersensitivity response, which may be genetic, and which appears to best explain the clinical features. As none of the clinical features of chronic VVC are highly specific or sensitive, diagnosis has required the development of a set of diagnostic criteria. Recently, our research group proposed a definition and diagnostic criteria for chronic VVC. Over the past 10 years there have been only two well-controlled trials to determine the best evidence-based treatment regimen. Using our criteria, the probable response to a trial of oral antifungal treatment can be predicted, even when a vaginal swab on presentation is not positive for *Candida*. In most cases, oral antifungal treatment is effective and safe but may need to be prolonged, and a significant although undetermined number of patients require ongoing maintenance therapy, in some cases until menopause.

**REFERENCES**
A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

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Coping with chronic vulvovaginal candidiasis

GAYLE FISCHER MB BS, MD, FACD

REFERENCES