**Recurrent vulvovaginal candidiasis**

Natalie Schellack, BCut, BPharm, PhD
Senior Lecturer, Department of Pharmacy, Faculty of Health Sciences, University of Limpopo (Medunsa Campus)

Correspondence to: Natalie Schellack, e-mail: nschellack@gmail.com

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**Abstract**

Vulvovaginal candidiasis (VVC) is part of a group of infections termed the superficial fungal infections. These can be classified as complicated or uncomplicated, sporadic or recurrent. Some patients are difficult to diagnose, and may not respond to standard therapies. These patients suffer from recurrent or chronic VVC. Recurrent VVC is defined as more than four episodes of VVC within a 12-month period. Patients normally present with a white, cheesy discharge and vulvovaginal itching. Clinical findings (itching or a cheesy discharge) or laboratory tests (potassium hydroxide, Gram stains and vaginal pH) are not sensitive or specific predictors of Candida vaginitis. Treating recurrent VVC requires an aggressive treatment plan using two stages, namely an induction and a maintenance stage. A high incidence of recurrent VVC requires a thorough understanding of the epidemiology and pathophysiology of the condition. Treatment with azole antifungals and nystatin derivatives may provide relief if given for an adequate period of time.

**Introduction**

Vaginal infections in women, with or without positive vaginal cultures for Candida spp., are termed vulvovaginal candidiasis (VVC). Clinical symptoms are defined by a vaginal yeast count which is ≥ 10⁶ CfU/ml of vaginal fluids. Episodes of Candida vaginitis vary in severity, microbial aetiology, host risk factors and the likelihood of early and late post-treatment relapse.

VVC can be classified as sporadic or recurrent based on the episodic frequency, and can further be classified as uncomplicated or complicated (Table 1). The classification is based on the response to antifungal therapy. Uncomplicated VVC refers to sporadic infections that are susceptible to all forms of antifungal therapy. Treatment of complicated VVC has to take into consideration factors that affect the host, the microorganisms and the pharmacotherapy. Recurrent VVC is defined as more than four episodes in a single year.

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<thead>
<tr>
<th>Feature</th>
<th>Uncomplicated</th>
<th>Complicated</th>
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<tr>
<td>Severity</td>
<td>Mild or moderate</td>
<td>Severe</td>
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<tr>
<td>Frequency</td>
<td>Sporadic</td>
<td>Recurrent</td>
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<tr>
<td>Organism</td>
<td>Candida albicans</td>
<td>Candida spp., except C. albicans</td>
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<tr>
<td>Host</td>
<td>Normal</td>
<td>Abnormal, e.g. uncontrolled diabetes mellitus</td>
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Vaginal candidiasis is a common problem in healthy women with an immunocompetent status. It is estimated that by the age of 25 years, 54.7% of women would have had at least one presumed C. vaginitis infection. This figure highlights the need for a better understanding of the epidemiology and pathophysiology of the condition. It is important to develop a more accurate, rapid method of diagnosing candidiasis and treating it effectively.

C. albicans is the most common cause (> 90%) of vaginitis, and it has been found that up to 75% of women have experienced symptomatic vaginal candidiasis at least once. Of these infections, the minority is caused by non-C. albicans spp. (< 10 %), including C. glabrata, C. krusei, C. parapsilosis and C. tropicalis. The Candida spp. that are not C. albicans are nonpathogenic and rarely require treatment which is fortunate as most normally prescribed antifungals are ineffective, due to resistance. Genitourinary infections caused by yeasts that are not Candida spp. (Saccharomyces cerevisiae) are uncommon, but have been described in the literature.

Using vaginal swabs and vulvular biopsies may be useful when differentiating between different causative organisms and disease types. Biotyping of C. albicans can assist in identifying individual strains. However, all strains are capable of colonising the vagina, and can cause vaginitis.

Candida spp. are dimorphic fungi and can be found in humans in different phenotypic phases.
Pathophysiology

Normally, women with vaginal candidiasis require only relatively superficial evaluation and are easily treated. However, in some patients it may be difficult to diagnose and may not respond to treatment.9 Women who suffer from recurrent or complicated vaginitis do not always have the obvious predisposing factors, i.e. their menstrual cycle in the luteal phase, the use of oral contraceptives, wearing tight-fitting clothing such as hosiery and undergarments, and taking broad-spectrum antibiotics. Their glucose tolerance tests may also be normal. This implies that it may be attributed to fungal reinoculation of the vagina by various sources and mechanisms.9

Table II differentiates between the source and mechanisms involved in the pathogenesis of recurrent VVC.

Complicated VVC includes recurrent VVC, severe disease, involvement of Candida spp., other than C. albicans, and host factors that predispose the patient to recurrent candidiasis, including diabetes mellitus, immunosuppression and pregnancy.2

<table>
<thead>
<tr>
<th>Source</th>
<th>Mechanism</th>
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<td>More frequent vaginal inoculation or re-infection:</td>
<td>Enhanced Candido virulence Host dependent:</td>
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<tr>
<td>- Intestinal reservoir theory</td>
<td>- Depressed mucosal immunity</td>
</tr>
<tr>
<td>- Sexual transmission</td>
<td>- Immediate hypersensitivity reactivity (immunoglobulin E)</td>
</tr>
<tr>
<td>- Vaginal relapse</td>
<td>- Loss of bacterial &quot;colonisation resistance&quot;</td>
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Intestinal reservoir

The intestinal reservoir theory is based on Candida spp. recovery from the rectal culture in patients who are diagnosed with acute candidiasis.5,9 Cultures obtained from rectal and vaginal biotyping indicate similar strains.5,9 Contradictory to this theory is that some women persistently carry yeast without any vaginal colonisation.5,9

Sexual transmission

It has not been conclusively shown that candidiasis can be transmitted sexually, as treatment for men did not prevent recurrence in women.4,5,9 However, it has been shown that anogenital and orogenital contact can transmit the disease.4,5,9

Vaginal relapse

Women suffering from recurrent vaginitis differ from those who have infrequent episodes of candidiasis. The main difference is that women who experience recurrent vaginitis seem to be unable to tolerate small numbers of Candida spp.9 Recurrent VVC is rarely caused by polyene or azole drug resistance, but the pathogenesis involved may include a deficiency in the normal protective vaginal bacterial flora that permits unsuppressed growth and the proliferation and germination of colonising yeast microorganisms.

Women with AIDS seem to suffer from recurrent VVC. It seems to be the most common opportunistic mucosal infection in this patient population. Conversely, there is an association with an increased rate of transmission of sexually transmitted infections, including HIV, in women with symptomatic VVC.3,9

Clinical manifestations

A reliable diagnosis cannot be made from the signs and symptoms alone, and the sensitivity and specificity for self-diagnosis are 35% and 89% respectively.4 The presenting symptoms of acute pruritus and vaginal discharge are not specific to VVC, and a reliable diagnosis cannot be made without laboratory findings.3,9 Vulvar pruritus is the most frequent symptom in all symptomatic patients, but vaginal discharge is not always present, and the amount is usually minimal.9 The discharge is usually cottage cheese-like in character, and it may range from watery to homogenously thick.

Other signs and symptoms include:

- Vaginal soreness
- Irritation
- Vulvar burning
- Dyspareunia
- External dysuria
- Odour, which is minimal and not offensive.

On examination of the patient, erythema and swelling of the labia and vulva are seen. The cervix appears normal.1,9 Vaginal mucosal erythema is present with adherent whitish discharge.1,9 The symptoms worsen the week before the onset of menstruation. There is some relief after the onset of menstrual flow.1,9

As stated earlier, relying on the patient’s own symptomatic assessment is not dependable. Positive vaginal cultures may reflect colonisation only, and cannot be used as the sole basis for the diagnosis.1,4,9

Patients who present with symptomatic vaginitis can be diagnosed using a simple microscopical examination of their vaginal secretions.7 A wet mount with saline preparation can be used to diagnose the presence of yeast and mycelia, and also to exclude other conditions.7 A 10% potassium hydroxide preparation is more sensitive with regard to diagnosing the presence of germinated yeast.9 The pH is normal in vaginal candidiasis, but in bacterial vaginosis, trichomoniasis and a mixed infection, the pH would be in excess of 4.7.1,9 Candida cultures should not be requested unless classic symptoms and signs with a normal vaginal pH and other microscopy parameters are inconclusive, or a recurrence is suspected.1,9

Treatment

General principles of treatment would be to obtain a complete resolution of symptoms. Antifungal agents have a slow killing rate.9 At the end of therapy, the number of viable cells will be undetectable in most patients. However, after six weeks of therapy, a number of patients will have complicated or recurrent VVC,
and they will require a more aggressive approach and treatment plan.\textsuperscript{1,5,7}

Co-morbidities in these patients, such as their immunocompromised state or uncontrolled diabetes mellitus, should be factored into the treatment plan. When treating these patients, a number of parameters should be taken into consideration (Figure 1).

The importance of educating the patient on personal care during treatment cannot be underestimated, and is of great value when the pharmacist counsels the patient appropriately.\textsuperscript{7} The epithelium is hypersensitive to chemical and physical trauma. Therefore, normal saline is considered to be safe for washing purposes.\textsuperscript{7} Advice to the patient should include avoiding soap and other cleansing agents, and bathing the infected area with normal saline. At home, this may be prepared with table salt and water, by mixing two teaspoons to the litre. The solution should be applied with cotton wool. The infected area should be gently patted dry with a soft, clean towel.\textsuperscript{7} Patients should also be advised to avoid home remedies and other over-the-counter medications, and if the patient is sexually active, to avoid artificial lubricants.\textsuperscript{7}

Daily ingestion of yoghurt containing \textit{Lactobacillus acidophilus} decreases colonisation and can be useful in women with recurrent VVC.\textsuperscript{1,11}

\textbf{Induction therapy} +  \textbf{Maintenance therapy}  

\textbf{Remission} \textsuperscript{1}

The most well-tolerated regimen is: Oral fluconazole at a dose of 150 mg \textbf{OR} if fluconazole is not tolerated Topical clotrimazole (200 mg twice weekly) \textbf{OR} Clotrimazole (500 mg vaginal suppository once weekly)

\textbf{Figure 1:} Treatment plan for recurrent vulvovaginal candidiasis

\textbf{Figure 2:} Treatment of recurrent vulvovaginal candidiasis \textsuperscript{1}
After managing contributing factors such as diabetes, induction therapy can be initiated with 10-14 days of a topical or oral azole, followed by suppressive therapy for six months. Patients who are HIV positive should be treated with the same regimen as HIV-negative patients.5

The vaginal environment can also be altered by changing the contraception to depot medroxyprogesterone acetate (oestrogen-free ovulation suppression). A lower dose of oestrogen may be used in women taking hormone replacement therapy.7 Infections that are antifungal resistant, with persistent positive yeast cultures, and which fail to respond to therapy despite adequate patient adherence, can be treated with boric acid or 5-flucytocine.13 Boric acid is especially useful in infections caused by C. glabrata, with a cure rate of 81% and a mycological eradication rate of 77%.13

Conclusion

Candida spp. are the most common cause of vaginitis and recurrent VVC. Recurrent vaginitis may present with chronic dyspareunia, discharge, irritation and vulval burning, as well as other signs and symptoms. Education should be provided to women on early identification of related symptoms for prompt and timely treatment. This may reduce the prevalence of candidiasis and other sexually transmitted diseases, including HIV. Part of the treatment for chronic or recurrent VVC is reassurance, support and counselling. Nearly all cases of VVC can be adequately treated, if not cured.

References