Vulvovaginal Candidiasis

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Introduction

Vulvovaginal candidiasis (VVC) represents a spectrum of disease. Although there is a clear need for better use of diagnostic modalities and development of better treatment alternatives, most patients with VVC, even the complicated cases, at least have the perspective of achieving adequate control of their symptoms. Future advances, particularly in the area of home diagnostics, may help to optimize use of currently available medicines[1].

Although it is the second most common vaginal infection, VVC is a non notifiable disease and has been excluded from the ranks of sexually transmitted diseases. For many years clinicians categorized patients with vaginal candida into the following two groups Asymptomatic carriers of Candida (colonization) and Symptomatic disease (Candida vaginitis). More recently, the concept of "VVC" has replaced these distinct categories. This term was introduced to emphasize the "vulvar," often dominant component of symptomatic infection[2].

Clinical Classification

Uncomplicated

- Sporadic or infrequent VVC
- Mild-to-moderate VVC
- Likely to be C. albicans
- Normal, nonpregnant woman

A. Complicated

- Recurrent VVC
- Severe VVC
- Nonalbicans candidiasis
- Abnormal host (e.g., uncontrollable diabetes, debilitation, or immunosuppression). [2]

Etiologic Classification

Three broad categories

- Primary candidiasis,
- Antibiotic-induced candidiasis, and
- Systemically induced candidiasis[3].

Incidence

- By age 25, 50-72% of all women will have experienced at least one physician-diagnosed episode of VVC[2].
- Regrettably, VVC is routinely diagnosed without microscopy or culture, and in as many as half of the cases so diagnosed, the women may be uninfected or have other conditions.
- Furthermore, VVC is not a reportable disease, and prevalence estimates have relied mainly on self-reported history of physician diagnosis. This multiplies errors.

Microbiology

- Albicans is responsible for the majority of symptomatic episodes of VVC.
- Cases of sporadic and recurrent VVC caused by nonalbicans species of candida are increasing. Nearly, 10%-20% of cases are due to nonalbicans candida organisms. The dominant nonalbicans candida species reported is C. glabrata. Candida krusei is an uncommon cause of VVC.
- The possible reason for the apparent increase in nonalbicans Candida vulvovaginitis may be the increased use of antimycotics, which may be used inappropriately and frequently as a short, incomplete course of therapy, eliminating the more sensitive C. albicans and selecting for more azole-resistant nonalbicans candida species[4, 5].

Risk Factors

Age

It is extremely rare before menarche. Its annual incidence increases dramatically toward the end of the second decade of life[6] and peaks over the next two decades[4].

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Race

Among college women VVC was more common among black women than white women.

Hormonal Influence

- VVC is considered more common and difficult to eradicate during pregnancy; however, no recent studies have been performed and the original studies suffered methodologic flaws.
- The incidence of VVC in menopausal and postmenopausal women remains unstudied. Preliminary data suggest that women undergoing natural menopause who receive exogenous estrogen replacement therapy may be at higher risk of VVC[2].

Contraception

- Numerous studies have found a significantly higher risk of VVC in women who use oral contraceptives.
- The risk of infection may be greater with use of high-estrogen-containing, first generation oral contraceptives than with low-estrogen-containing oral contraceptives.
- Sexual intercourse with use of a diaphragm and spermicidal in the preceding 3 days was found to be associated with a marked increase in the rate of candidal colonization.
- An increase in the risk of infection is reported with the vaginal contraceptive sponge and the intrauterine contraceptive device[2].

Sexual Factors

- VVC is not considered to be a sexually transmitted disease because it occurs in celibate women, and because Candida is considered part of the normal vaginal flora.
- However, studies have confirmed the transmission of Candida organisms by vaginal sexual intercourse and other forms of sexual activity.
- A self-reported history of physician diagnosis indicates a marked increase in the frequency of VVC at the time most women begin regular sexual activity. Individual episodes do not appear to be related to lifetime numbers of sexual partners.
- The role of frequency of coitus as a risk factor for vaginitis remains controversial.
- Frequent oral-genital contact appears to increase risk[7].
- Sexual intercourse alone has not been shown to alter vaginal Candida colonization[2].

Douching and Feminine Hygiene Products

- Studies have failed to establish an association between douching and VVC.
- Douching as a risk factor in women who are predisposed to recurrent bouts of VVC caused by Candida glabrata.
- Similarly, the use of menstrual protection (e.g., sanitary napkins or tampons) has not been shown to increase risk.
- The role of tight-fitting clothing in precipitating episodes of VVC remains unproved[2].

Antibiotics

- Antibiotics have been identified as a risk factor for VVC in some women; however, the exact mechanism for this association has not been adequately studied[8].
- This complication may also follow topical iodine solutions and topical formulations of metronidazole and clindamycin.
- Only a minority of women taking antibiotics subsequently have VVC.
- A prerequisite for infection appears to be vaginal colonization by Candida organisms.
- An association between lack or loss of vaginal lactobacilli, hydrogen peroxide production, and susceptibility to VVC has not been established in women in whom infection develops while they are taking antibiotics[5,2].

Dietary Factors

- Most studies have failed to show that dietary excesses or deficiencies play a major role in the etiology of sporadic or recurrent VVC.
- Occasional patients report an excess of unrefined sugars as a factor in the pathogenesis of infection.
- Some women who have recurrent VVC may be tempted to follow a variety of highly restrictive diets that are defined as yeast free; these diets are very difficult to follow and have not been shown to be of benefit[9].

Diabetes

Vaginal colonization and infection are also more common among women with diabetes mellitus[2].

Diagnosis

- The clinical signs and symptoms of VVC include vulvovaginal pruritus, irritation, soreness, dyspareunia, burning on micturition, and whitish, cheesy discharge[4].
- None of these symptoms, either individually or collectively, is pathognomonic; a reliable diagnosis therefore cannot be made on the basis of the history and physical examination without the corroborative evidence of laboratory tests[4].
- Unfortunately, VVC is diagnosed daily in thousands of women on the basis of a telephone conversation or non-inclusive physical examination. A countless infectious and noninfectious factors may cause identical signs and symptoms, hence the need for laboratory confirmation. Self-diagnosis is the usual basis for purchase of antimycotics, although the reliability of self-diagnosis is considered to be poor[4].
- Vaginal pH remains normal in VVC. This simple and inexpensive test has been greatly underused in cases of suspected VVC.
- Microscopy with the use of saline solution detects the presence of yeast blastospores or pseudohyphae in approximately 30% to 50% of patients with symptomatic VVC.
- Although the sensitivity of the 10% potassium hydroxide examination is higher, at least one third of patients with symptomatic VVC will have negative findings with potassium hydroxide microscopy. Blastospores of nonalbicans strains that do not form hyphae or pseudohyphae are more difficult to recognize.
- Nevertheless, these two tests in combination with a normal vaginal pH are valuable in confirming the diagnosis of VVC and excluding other causes. They are inexpensive and rapid and provide the physician with an additional opportunity to evaluate the patient's genital flora, establish whether an inflammatory process exists, and detect hormone deficiency.
- Vaginal cultures are extremely valuable, but are not routinely required, in the diagnosis of VVC. Accordingly, in a patient with a compatible clinical syndrome, who has a normal vaginal pH and in whom yeast is identified microscopically, a culture is not required unless there is suspicion of a resistant organism. On the other hand, in a patient with a suggestive clinical picture, in whom the pH is normal but microscopy is negative for yeast and another cause for the clinical syndrome has not been identified, a yeast culture should be obtained. Antifungal therapy may then be prescribed before the availability of the culture results. Not infrequently, mixed infections occur in which two simultaneous pathologic processes (e.g., bacterial plus candidal) coexist. The true frequency of mixed infections is estimated to be 10%[10, 11, 12].

Therapy

The characteristics of the ideal antimycotic agent include the following[9, 12, 13:]

- It is easy to administer and compliance enhancing. Several studies have shown women's preference for oral therapy, citing the advantage of convenience.
- It is effective in a short course of therapy.
- It is fungicidal. None of the available antimycotic agents is fungicidal.
- It provides immediate symptomatic relief. None of the available oral therapies results in a dramatic improvement in symptoms within 12 to 24 hours. Much of the relief that is achieved initially with topical agents is a function of the vehicle rather than the antifungal agent itself.
- It lacks systemic and local side effects.
- It is safe in pregnancy. Currently, no oral agents are approved or recommended for use during pregnancy. For many years there was a general recommendation that even topical azoles should be avoided in the first trimester of pregnancy; infections were usually treated with topical nystatin. Recent guidelines issued by the Centers for Disease Control and Prevention suggest that topical azoles may be used in the first trimester of pregnancy.
- It prevents recurrent infection.

Unfortunately, mycologic recurrence rates remain high, owing to the lack of fungicidal agents.
- There is no alteration of host vaginal flora.
- Its cost is low.
- It has broad-spectrum activity.

Uncomplicated Vulvovaginal Candidiasis

- The majority of episodes of VVC are uncomplicated.
- All forms of antimycotic therapy (topical and oral depicted in Table 1) are highly effective against acute uncomplicated VVC, and cure rates of 80% can be expected.
- There is clinical and mycologic equivalence between single-dose fluconazole, single-day itraconazole, and multidose conventional topical azole therapy.
- A critical issue pertains to the importance of duration of therapy versus total dose of the antimycotic agents. Duration of therapy is of little significance in treating uncomplicated VVC.
- Topical. No difference exists in overall in vitro activity and clinical efficacy of the various azole topical agents in the treatment of uncomplicated VVC.
- Oral. These agents include fluconazole, a 150 mg single dose; ketoconazole, 400 mg daily for 5 days; and itraconazole, 200 mg twice in a single day or 200 mg daily for 3 days.
- Although antimycotic agents do achieve fungal killing, the rate of killing is not sufficient to meet the definition of a fungicidal agent. Accordingly, whereas vaginal cultures may be negative on completion of therapy, it cannot be assumed that the organisms have been eradicated. The number of viable organisms usually drops below the level of detection, and a negative culture is reported in spite of the fact that a residual yeast population may exist. Within 6 weeks of the completion of a course of therapy, between 25% and 40% of women who do not have symptoms will have positive cultures with the identical strain of Candida that was responsible for the previous symptomatic episode.

Complicated Vulvovaginal Candidiasis

Severe Vulvovaginal Candidiasis

- Infection severity affects the therapeutic outcome, but duration of symptoms does not.
- Conventional 7-day topical azole therapy was shown to be superior to single-dose therapy with fluconazole in the presence of severe disease.
- Topical azole therapy may fail to adequately relieve the extensive vulvar inflammation and may, in fact, exacerbate the burning sensation in patients.
- Oral azole therapy fails to provide immediate relief of vulvar burning, soreness, and itching.
- Low-potency topical corticosteroids often achieve a more rapid relief of symptoms. High-potency corticosteroids, however, may actually induce or exacerbate burning.
- Some of the older topical antifungal preparations, such as nystatin cream, and a variety of household remedies, including Sitz baths with sodium bicarbonate, often offer the best immediate relief.
- All the azole medications, both topical and oral, are associated with dramatic symptom relief after the first 24 to 48 hours[1].

Recurrent Vulvovaginal Candidiasis

- Definition: four or more episodes of proved infection during a 12-month period. It is a form of complicated VVC. Recurrent episodes occur in 40-50% of cases[14,15].
- Many women in whom recurrent yeast infections are diagnosed have been misdiagnosed. Misdiagnosis by clinicians inevitably results in incorrect self-diagnosis by patients. Among the many reasons for incorrect diagnosis is that an initial Candida vaginitis may perpetuate itself as nonmycotic topical contact dermatitis. Hyper-sensitivity reactions and chemical or allergic reactions to antimycotic therapy frequently result in continuation of symptoms that are incorrectly thought to be caused by fungi, resulting in inappropriate additional antimycotic therapy[16,17].

- The role of sexual transmission and hence reinfection in causing repeated episodes remains unclear; most studies have failed to document that treatment of the male partner puts an end to recurrent VVC. In one study there has been a reduction in the recurrence of candidal vaginitis in women whose culture-positive partners were treated with antimycotics. Most experts do not recommend the routine evaluation or treatment of sexual partners. Repeated episodes are not the result of more frequent introduction of the organism into the lower genital tract (i.e., by sexual transmission) or a more virulent organism but, rather, are caused by host factors[16,17].
- After confirmation of the diagnosis by at least 10% potassium hydroxide examination and, where any doubt exists, by mycologic culture, every effort should be made to correct any exogenous factors that may be contributing to recurrence. Measures include Control of diabetes mellitus and avoidance of systemic corticosteroids[16].
- Unfortunately, recognizable and reversible exogenous factors are infrequently found.
- Recurrent VVC is best managed by judicious use of antimycotic therapy. An initial regimen of oral therapy is recommended and continued for approximately 14 days so as to ensure clinical remission and a negative fungal culture[18].
- Immediately after achievement of these treatment goals, a maintenance regimen is indicated. Several possible regimens to consider include ketoconazole, 100 mg daily for 6 months, itraconazole, 50 to 100 mg daily for 6 months, and fluconazole, 100 mg once weekly for 6 months. One topical regimen that is useful is clotrimazole, 500 mg vaginal suppositories, administered once weekly.
- During maintenance therapy, which should last at least 6 months, 90% of patients are protected from symptomatic recurrences.
- Recurrences of VVC are common in a high percentage of women immediately after cessation of the 6-month regimen.
- If recurrences are infrequent, each episode should be treated independently. Once the repetitive pattern of VVC recurs, however, it is essential to return to the induction and maintenance regimens to control infection.
- A small percentage of women may require maintenance azole regimens for several years.
- The role of dietary and behavioral changes in curing recurrent VVC is minimal. One center reported success in a limited number of women with recurrent disease who used yogurt as Lactobacillus oral therapy[16].

Nonalbicans Candidiasis

- Most nonalbicans Candida species tend to have higher minimum inhibitory concentrations to available azole agents.
- The majority of patients with VVC caused by C. glabrata will respond to therapy with azoles provided that there is adequate duration of therapy.
- Glabrata vaginitis may be unresponsive, partially responsive, or recurs immediately after a course of azole therapy. Therapy with topical boric acid (prescribed as a 600 mg gelatin capsule inserted into the vagina daily for 14 days) or topical flucytosine has been encouraging. The safety of these regimens has not been established[19].

Antifungal Resistance

- Resistance should be suspected in compliant patients with failure to respond to therapy and persistently positive yeast cultures.
- Rarely, nonalbicans Candida sp. e.g. C krusei and C glabrata, demonstrate intrinsic resistance to a number of antifungal agents.
- Resistant C. albicans strains has received attention in recent years, particularly in patients who are human immunodeficiency virus positive and have in vitro and clinically resistant oropharyngeal and esophageal candidiasis caused by highly resistant C. albicans.
- Azole-resistant infections should be treated with nystatin, boric acid, or flucytosine.
- Given the rarity of VVC caused by resistant C. albicans strains, susceptibility testing is rarely indicated

Table 1. Antimycotic Drugs & Formulation

Drug	Formulation
Topical	
Butoconazole	2% cream, 5 g for 3 days
Clotrimazole	1% cream, 5 g for 7-14 days
Miconazole	2% cream, 5 g for 7 days 100 mg vaginal suppository, 1 suppository for 7 days 200 mg vaginal suppository, 1 suppository for 3 days 1200 mg vaginal suppository, 1 suppository single dose
Econazole	150 mg vaginal tablet, 1 tablet for 3 days
Fenticonazole	2% cream, 5 g for 7 days
Tioconazole	2% cream, 5 g for 3 days 6.5% cream, 5 g single dose
Terconazole	0.8% cream, 5 gm for 3 days 80 mg vaginal suppository, 1 suppository for 3 days
Nystatin	100,000 units vaginal tablet, 1 tablet for 14 days
Oral	
Ketoconazole	200 mg bid for 5 days
Itraconzole	200 mg bid for 1 day
Fluconazole	150 mg single dose

Other Considerations

- Prophylactic antimycotic therapy. A small percentage of women, who take oral antibacterial drugs, develop symptomatic VVC. For the patient who has had confirmed antibiotic-induced VVC episodes in the past, it is reasonable to prescribe prophylactic antimycotic therapy along with antibiotics[1].
- Vaginal colonization. Because vaginal colonization is predictably found in 15% to 20% of nonpregnant women, routine treatment of asymptomatic colonization is not recommended[1].
- Inappropriate use of antimycotics:
  - Abuse of antimycotics is considerable and the majority of women using antimycotics for vulvovaginal symptoms do so without actually having a definitive diagnosis of VVC[20].
  - The lack of availability of home diagnostic tests is a major disadvantage.
  - The abuse of antimycotics is not only costly but suspected of precipitating allergic, vaginal and vulvar reactions, including contact dermatitis and chronic vulvitis.

Précis and Key messages

- Vaginal candidiasis affects about 50-72% of women, 40-50% having recurrent episodes.
- Candida albicans accounts for about 80-90% of infections
- Pruritus vulvae and vaginal discharge are the cardinal symptoms.
- The majority of episodes of VVC are uncomplicated. All forms of antimycotic therapy (topical and oral) are highly effective against acute uncomplicated VVC, and cure rates of 80% can be expected
- G. Glabrata may be unresponsive, partially responsive, or recurs immediately after a course of azole therapy. Candida krusei has an intrinsic resistance to fluconazole.
- Many women in whom recurrent yeast infections are diagnosed have been misdiagnosed. Recurrent episodes require clinical examination, culture of swabs, and consideration of underlying disease.

References

1. Nyirjesy P., Sobel J. Vulvovaginal candidiasis. *Obstet Gynecol Clin North Am*. 2003; **30(4):**671-84.
2. Sobel J., Faro S., Force R., et al. Vulvovaginal candidiasis: epidemiologic, diagnostic, and therapeutic considerations. *Am. J. Obstet. Gynecol.* 1998; **178(2):**203-11.
3. Monif G. Classification and pathogenesis of vulvovaginal candidiasis. *Am. J. Obstet. Gynecol.* 1985; **152(7 Pt 2):**935-39.
4. Marrazzo J. Vulvovaginal candidiasis. *B.M.J.* 2003; **326(7397):**993-94.
5. Dennerstein G. Pathogenesis and treatment of genital candidiasis. *Aust. Fam. Physician.* 1998; **27(5):**363-69.
6. Syed T., Braverman P. Vaginitis in adolescents. *Adolesc. Med. Clin.* 2004; **15(2):**235-51.
7. White D., Radcliffe K. Oral sex and recurrent vaginal candidiasis. *Genitourin. Med.* 1992; **68(3):**199.
8. Glover D., Larsen B. Relationship of fungal vaginitis therapy to prior antibiotic exposure. *Infect. Dis. Obstet. Gynecol.* 2003; **11(3):**157-60.
9. Sobel J. Vulvovaginitis. When Candida becomes a problem. *Dermatol. Clin.* 1998; **16(4):**763-8, xii.
10. Omar A. Gram stain versus culture in the diagnosis of vulvovaginal candidiasis. East *Mediterr. Health. J.* 2001; **7(6):**925-34.
11. Cleveland A. Vaginitis: finding the cause prevents treatment failure. *Cleve. Clin. J. Med.* 2000; **67(9):**634, 637-42, 645-6.
12. Greer P. Vaginal thrush: diagnosis and treatment options. *Nurs. Times*. 1998; **94(4):**50-2.
13. Tanaka D. Management of vaginal candidiasis: a review. *Pediatr. Infect. Dis. J.* 1998; **17(8):**746-47.
14. Mardh P., Rodrigues A., Genc M., et al. Facts and myths on recurrent vulvovaginal candidosis--a review on epidemiology, clinical manifestations, diagnosis, pathogenesis and therapy. *Int. J. STD. AIDS.* 2002; **13(8):**522-39.
15. MacNeill C., Carey J. Recurrent vulvovaginal candidiasis. *Curr. Womens. Health. Rep.* 2001; **1(1):**31-5.
16. Sobel J. Management of patients with recurrent vulvovaginal *candidiasis. Drugs.* 2003; **63(11):**1059-66.
17. Nyirjesy P. Chronic vulvovaginal candidiasis. *Am. Fam. Physician.* 2001; **63(4):**697-702.
18. Ringdahl E. Treatment of recurrent vulvovaginal candidiasis. *Am. Fam. Physician.* 2000; **61(11):**3306-12, 3317.
19. Shann S., Wilson J. Treatment of Candida glabrata using topical amphotericin B and flucytosine. *Sex. Transm. Infect.* 2003; **79(3):**265-66.
20. Roy S., Caillouette J., Faden J., et al. Improving appropriate use of antifungal medications: the role of an over-the-counter vaginal pH self-test device. *Infect. Dis. Obstet. Gynecol.* 2003; **11(4):**209-16.