Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2015;24:5-7
doi: 10.15570/actaapa.2015.2

Treatment of vulvovaginal candidiasis: a review of the literature

Andraž Dovnik[1] ✉, Andrej Golle[2], Dušan Novak[2], Darja Arko[1], Iztok Takač[1, 3]

Abstract

Vulvovaginal candidiasis (VVC) affects around three-quarters of all women during their reproductive age, although the exact incidence of VVC is difficult to determine because many patients are self-treated. The infections are divided into complicated and uncomplicated. Uncomplicated VVC is most effectively treated with local azoles. Oral treatment with a single dose of fluconazole is also effective for treating uncomplicated VVC. Treatment of complicated VVC is prolonged and most commonly consists of multiple doses of oral fluconazole or at least 1 week of local azoles. The role of probiotics in treating VVC is still disputed. This article presents a review of the literature on the various treatment options for VVC. Treatment for the most common pathogens that cause complicated VVC is also discussed.

Keywords: fungal infection, vulva, vagina, local azoles, systemic treatment, probiotics

Received: 17 January 2015 | **Returned for modification:** 30 January 2015 | **Accepted:** 2 February 2015

Introduction

Fungal infection of the vulva and the vagina is estimated to be the second most common cause of inflammation after bacterial vaginosis (1). About three-quarters of women during their reproductive age have at least one episode of vulvovaginal candidiasis (VVC) and approximately half have two or more episodes (2). The most common pathogen is *Candida albicans*, which is isolated in 85 to 90% of all cases (3). Asymptomatic colonization with *Candida spp*. is also common. It can be found in about one-third of women without any symptoms and was identified in 70% of women during a 1-year observation period (4). In a study of 612 women, Bauters et al. found 20% overall colonization with *Candida spp*. and a 6.3% rate of clinical infection (5). Colonization with *Candida spp*. was also determined in 10 to 20% of women undergoing conization for cervical intraepithelial neoplasia (6).

VVC is divided into uncomplicated and complicated cases. Uncomplicated cases are sporadic episodes of mild infections caused by *C. albicans* (7). Complicated cases are cases of VVC caused by other species of *Candida*, cases of severe infection, VVC during pregnancy, or VVC associated with other medical conditions such as immunosuppression or diabetes. Recurrent VVC (RVVC) is also a form of complicated infection and is defined as four or more episodes of VVC per year (4, 8, 9). About 5 to 8% of VVC cases are recurrent, and *C. glabrata* and other non–*C. albicans* forms are isolated in 10 to 20% of these cases (2, 9). However, it is difficult to evaluate the exact incidence of VVC due to the high rate of self-treatment with over-the-counter medications. Moreover, the diagnosis is frequently based entirely on signs and symptoms without any tests to confirm the diagnosis (4).

Treatment depends on whether the infection is complicated or uncomplicated (10). This article presents a review of the literature on treating VVC.

Etiology

C. albicans, which most commonly causes VVC, is part of normal vaginal microflora (9). The second most common pathogen identified in women with VVC is *C. glabrata*, which is isolated in 7 to 16% of cases (4). Clinical inflammation occurs in cases of disturbed balance between the host and the colonizing microorganisms (4). Lactobacilli are an important element of vaginal microflora because their production of lactic acid keeps the vaginal pH low and prevents overgrowth of other pathogens (4, 11). Risk factors for VVC are pregnancy, diabetes, and behavioral risk factors such as the use of oral contraceptives with a high dose of estrogen, the use of condoms, spermicides, frequent oral sexual intercourse, and the use of tight synthetic underwear (12-14).

The use of antibiotics causes a change in vaginal microflora, which increases colonization with *Candida spp*. Colonization with *C. albicans* is increased from approximately 10% to 30%, and VVC is diagnosed in 28 to 33% of cases (15). Despite the role of lactobacilli, which help maintain the low vaginal pH and prevent other pathogenic species from growing disproportionately, it has not been proven that changes in the vaginal microflora in the absence of antibiotic use lead to VVC (16).

The risk factors for complicated VVC are the same as in uncomplicated VVC. Recurrent cases of VVC can be associated with coexistent dermatological diseases, such as lichen sclerosus, and with immunosuppression, such as in HIV infection (2).

Clinical presentation and diagnosis

The most common symptoms are burning pain and pruritus of the vulva with discomfort that can lead to dysuria and dyspareunia in more severe cases (17). Clinical signs of VVC are edema and erythema of the vulva and the vagina accompanied by an abnormal vaginal discharge that may be watery, cheese-like, or minimal (17). The vaginal discharge typically resembles cottage cheese (8).

The diagnosis is most frequently made clinically (8). Microscopic examination of the discharge is also helpful. Mycelia can be seen under microscopy in 50 to 80% of cases. The whiff test, in which 10% potassium hydroxide is added to the vaginal discharge, is used to distinguish between VVC and bacterial vaginosis. In bacterial vaginosis, an amine-like odor is released following this reaction. The test is negative in cases of VVC (8). The vaginal

[1]University Clinical Department of Gynecology and Perinatology, Maribor University Clinical Centre, Maribor, Slovenia. [2]Department of Medical Microbiology, Medical Microbiology Center, National Laboratory of Health, Environment, and Food, Maribor, Slovenia. [3]Department of Gynecology and Perinatology, University of Maribor Faculty of Medicine, Maribor, Slovenia. ✉ **Corresponding author: andrazdovnik@gmail.com**

pH in women with VVC is usually less than 4.5, and in cases of infection with *Trichomonas vaginalis* the pH is more than 4.5 (4). A fungal culture is recommended to confirm the diagnosis. When no fungal elements are identified under microscopy and no typical clinical signs are present, a woman is not likely to have VVC. Empirical treatment should not be started in this case except in cases of positive culture (8).

Treatment of vulvovaginal candidiasis

Treatment of VVC depends on whether the patient has uncomplicated or complicated VVC (10).

Treatment of uncomplicated vulvovaginal candidiasis

Short-term local therapy or single-dose oral treatment is effective for treating 90% of uncomplicated cases. It is not clear whether oral or local agents are more appropriate for treating uncomplicated VVC, and no single agent seems to be clearly superior to others (4, 10). The most easily available are local azoles. Short-term therapy of up to 3 days with local azoles is recommended and the symptoms usually disappear after 2 to 3 days. This treatment is effective in 80 to 90% of cases (8). Various local agents with similar effects are available, including clotrimazole, butoconazole, and miconazole (1). Agents that are used in short-term regimens contain higher doses of antifungal medicine, allowing higher concentrations for longer-lasting inhibitory effect (8). Topical azoles are more efficient than local nystatin in treating uncomplicated VVC (18). Recently, Mendling et al. performed a comparative study on 160 patients with VVC in which they compared treatment with clotrimazole vaginal suppositories alone and a combination of 2% clotrimazole cream for external use and clotrimazole vaginal suppositories. They concluded that the combination of both was better than the suppositories alone (19).

An alternative to local therapy of uncomplicated VVC is oral treatment with single-dose 150 mg fluconazole. The efficiency of single-dose fluconazole for treating acute VVC was evaluated in a prospective trial by Sekhavat et al. (20). They compared 1 week of clotrimazole vaginal suppositories and a single dose of 150 mg oral fluconazole. Clinical and mycological results in both groups were comparable and oral fluconazole proved to be effective in treating acute VVC (20). The Infectious Diseases Society of America made no preference and recommends both local azoles and oral fluconazole (10). However, the patients should be warned that the symptoms may last up to 3 days following the oral dose (8).

Treatment of complicated vulvovaginal candidiasis and recurrent vulvovaginal candidiasis

Complicated cases of VVC require prolonged treatment. Oral fluconazole can be given three times with a gap of 72 hours or local azoles applied daily for at least 1 week (4). Sobel et al. compared single-dose and two-dose regimens of fluconazole in women with complicated VVC. The two-dose regimen was shown to achieve higher mycological and clinical response rates (21).

Another American study assessed the effectiveness of fluconazole maintenance therapy for treating recurrent VVC (22). A total of 387 patients were randomized into two groups. After initial treatment with three 150 mg doses of fluconazole every 72 hours, the first group of participants received weekly doses of 150 mg fluconazole for 6 months and the second group received a weekly placebo for 6 months. After 6 months of maintenance treatment, 90.8% of the women remained disease-free, compared to 35.9% in the placebo group. The time to recurrence was statistically significantly shorter in the placebo group compared to the fluconazole group (4.0 months vs. 10.2 months; $p < 0.001$). No proof of superinfection with *C. glabrata* and other non-*C. albicans* isolates was obtained and there was no evidence of *C. albicans* species developing resistance to fluconazole (22).

A comparison of vaginal nystatin and oral fluconazole for treating RVVC was performed in a recent study on 293 patients by a Chinese research group (23). Standard oral fluconazole regimens for treating RVVC were compared with 2 weeks of vaginal nystatin every month. The results showed that both oral fluconazole and vaginal nystatin are effective in treating RVVC and that in cases of fluconazole-resistant *C. albicans* or *C. glabrata* RVVC nystatin can also be efficient (23).

The location of *C. albicans* persistence in patients with RVVC was evaluated by Beikert et al. (24). Swabs of 139 patients with an episode of microbiologically confirmed RVVC were taken from the interlabial sulcus on the vulva and from the vagina. This was followed by a combined 20-day treatment with topical Ciclopirox Olamin cream and 100 mg oral fluconazole. About three-quarters of the patients had at least one positive vulvar culture identifying *C. albicans* on one of the four follow-up visits. They concluded that the origin of reinfection in patients with RVVC seems to be the external vulva (24).

Witt et al. compared standard homeopathy and monthly itraconazole for treating RVVC in a prospective study of 150 patients (25). Patients treated with classic homeopathy experienced earlier recurrences. Almost 90% of patients treated with itraconazole had no Candida detected in the culture at the first follow-up visit compared to 47% in the standard homeopathy group (25). Maintenance therapy with 100 mg ketoconazole also proved effective, but it is not favored for treating RVVC due to its hepatotoxicity (26, 27).

Therapy with azoles is less effective in treating non–*C. albicans* VVC. All preparations used for treating non–*C. albicans* VVC have to be made in the pharmacy (4). Phillips studied the effectiveness of vaginal amphotericin B in women with non–*C. albicans* VVC that did not respond to the usual antimycotics. A 2-week regimen with 50 mg amphotericin B intravaginally was effective in 70% of cases (28). In a retrospective review, Sobel et al. evaluated the efficiency of topical treatment of *C. glabrata* VVC with flucytosine and boric acid (29). Topical boric acid was used in a dose of 600 mg and was administered intravaginally for 14 to 21 days. In the two groups of patients with C. glabrata VVC, boric acid was effective in 64 to 71% of patients. When the patients did not respond to boric acid, flucytosine was used and was effective in 90% (29).

The role of probiotics in treating recurrent vulvovaginal candidiasis

Probiotics are living microorganisms that, in appropriate amounts, are beneficial for the health of the host (30). Studies evaluating the effectiveness of probiotics in preventing RVVC have shown conflicting results. In a review by Falagas et al., some studies supported the effectiveness of oral or local lactobacilli, particularly *Lactobacillus rhamnosus* GR-1, *Lactobacillus fermentum* RC-14, and *Lactobacillus acidophilus*, whereas other studies did not prove the effectiveness of lactobacilli. The authors emphasized

the methodological difficulties of the studies reviewed. The majority of studies evaluated a small sample of participants with no placebo group. In addition, different strains of probiotics that have various effects on *Candida* were tested in the various trials included in the review with variable duration and dosage (30). A recent Croatian study evaluated the effectiveness of probiotics in restitution of normal vaginal microflora after vaginal infection (31). The study comprised patients diagnosed with vaginal infection containing VVC. They were randomized into two groups. The first group received a placebo containing capsules for 6 weeks and the second group received capsules containing the probiotics *Lactobacillus reuteri* RC-14 and *Lactobacillus rhamnosus* GR-1 for 6 weeks. The first follow-up visit was performed 6 weeks after the end of the treatment. Compared to 61.5% in the probiotics group, 26.9% of the participants in the placebo group had normal vaginal microflora at the first follow-up visit (31).

Witt et al. also studied the effect of added probiotics to itraconazole in treating RVVC. Local lactobacilli were added for 6 days to monthly 200 mg itraconazole maintenance therapy following treatment of an acute episode of VVC. The lactobacilli did not offer any advantage in treating RVVC (25). Martinez et al. evaluated the additional value of 4-week therapy with probiotics that were added to a single dose of 150 mg fluconazole in treating culture-positive VVC. After 4 weeks of treatment, 38.5% of participants in the probiotics group were culture-free compared to 10.3% of patients that received only fluconazole (32). A recent report by De Seta et al. evaluated the effectiveness of local *Lactobacillus plantarum* P17630. One group of patients received the standard treatment with local clotrimazole for 3 days and the other group had additional probiotic capsules applied intravaginally for 6 days and then once weekly for 4 weeks. They concluded that local *Lactobacillus plantarum* P17630 offers potential benefit for resolution of vaginal discomfort (33).

Conclusion

Vulvovaginal candidiasis is not a reportable disease and, due to the high degree of self-treatment and available over-the-counter agents, it is not possible to evaluate the exact incidence of this infection. Preventing VVC is as important as treating this condition. Treatment should be individual and depends on whether the patient has complicated or uncomplicated VVC.

References

1. Spence D. Candidiasis (vulvovaginal). Clin Evid [Internet]. c2010. [cited 2014 Dec 27]. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2907618/.
2. Mitchell H. Vaginal discharge–causes, diagnosis, and treatment. BMJ. 2004; 328:1306-8.
3. Sobel JD. Vaginitis. N Engl J Med. 1997;337:1896-903.
4. Achkar JM, Fries BC. Candida infections of the genitourinary tract. Clin Microbiol Rev. 2010;23:253-73.
5. Bauters TG, Dhont MA, Temmerman MI, Nelis HJ. Prevalence of vulvovaginal candidiasis and susceptibility to fluconazole in women. Am J Obstet Gynecol. 2002;187:569-74.
6. Takač I. The frequency of bacterial and yeast infection in women with different grades of cervical intraepithelial neoplasia (CIN). Eur J Obstet Gyn Reprod Biol. 1998;80:231-4.
7. Sobel JD, Faro S, Force RW, Foxman B, Ledger WJ, Nyirjesy PR, et al. Vulvovaginal candidiasis: epidemiologic, diagnostic, and therapeutic considerations. Am J Obstet Gynecol. 1998;178:203-11.
8. Berek JS. Berek & Novak's gynecology. 15th ed. Philadelphia: Lipincott, Williams & Wilkins; c2012. Chapter 18, Genitourinary infections and sexually transmitted diseases; p. 557-74.
9. Peters BM, Yano J, Noverr MC, Fidel PR Jr. Candida vaginitis: when opportunism knocks, the host responds. PLoS Pathog. 2014;10:e1003965.
10. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;48:503-35.
11. Ronnqvist PD, Forsgren-Brusk UB, Grahn-Hakansson EE. Lactobacilli in the female genital tract in relation to other genital microbes and vaginal pH. Acta Obstet. 2006;85:726-35.
12. Foxman B. 1990. The epidemiology of vulvovaginal candidiasis: risk factors. Am J Public Health. 1990;80:329-31.
13. Cetin M, Ocak S, Gungoren A, Hakverdi AU. Distribution of Candida species in women with vulvovaginal symptoms and their association with different ages and contraceptive methods. Scand J Infect Dis. 2007;39:584-8.
14. Geiger AM, Foxman B. Risk factors for vulvovaginal candidiasis: a case-control study among university students. Epidemiology. 1996;7:182-7.
15. Sobel JD. Vulvovaginal candidosis. Lancet. 2007;369:1961-71.
16. Sobel JD, Chaim W. Vaginal microbiology of women with acute recurrent vulvovaginal candidiasis. J Clin Microbiol. 1996;34:2497-9.
17. Anderson MR, Klink K, Cohrssen A. Evaluation of vaginal complaints. JAMA. 2004;291:1368-79.
18. Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. MMWR Recommend Rep. 2006;55:1-94.
19. Mendling W, Schlegelmilch R. Three-day combination treatment for vulvovaginal vandidosis with 200 mg clotrimazol vaginal suppositories and clotrimazol cream for the vulva is significantly better than treatment with vaginal suppositories alone–an earlier, multi-centre, placebo-controlled double blind study. Geburtshilfe Frauenheilkd. 2014;74:355-60.
20. Sekhavat L, Tabatabaii A, Tezerjani FZ. Oral fluconazole 150 mg single dose versus intra-vaginal clotrimazole treatment of acute vulvovaginal candidiasis. J Infect Public Health. 2011;4:195-9.
21. Sobel JD, Kapernick PS, Zervos M, Reed BD, Hooton T, Soper D, et al. Treatment of complicated Candida vaginitis: comparison of single and sequential doses of fluconazole. Am J Obstet Gynecol. 2001;185:363-9.
22. Sobel JD, Wiesenfeld HC, Martens M, Danna P, Hooton TM, Rompalo A, et al. Maintenance fluconazole therapy for recurrent vulvovaginal candidiasis. N Engl J Med. 2004;351:876-83.
23. Fan S, Liu X, Wu C, Xu L, Li J. Vaginal nystatin versus oral fluconazole for the treatment for recurrent vulvovaginal candidiasis. Mycopathologia. 2014 Nov 22. [Epub ahead of print].
24. Beikert FC, Le MT, Koeninger A, Technau K, Clad A. Recurrent vulvovaginal candidosis: focus on the vulva. Mycoses. 2011;54:e807-10.
25. Witt A, Kaufmann U, Bitschnau M, Tempfer C, Ozbal A, Haytouglu E, et al. Monthly itraconazole versus classic homeopathy for the treatment of recurrent vulvovaginal candidiasis: a randomised trial. BJOG. 2009;116:1499-505.
26. Sobel JD. Management of recurrent vulvovaginal candidiasis with intermittent ketoconazole prophylaxis. Obstet Gynecol. 1985;65:435-40.
27. Lewis JH, Zimmerman HJ, Benson GD, Ishak KG. Hepatic injury associated with ketoconazole therapy. Analysis of 33 cases. Gastroenterology. 1984;86:503-13.
28. Phillips AJ. Treatment of non-albicans Candida vaginitis with amphotericin B vaginal suppositories. Am J Obstet Gynecol. 2005;192:2009-13.
29. Sobel JD, Chaim W, Nagappan V, Leaman D. Treatment of vaginitis caused by Candida glabrata: use of topical boric acid and flucytosine. Am J Obstet Gynecol. 2003;189:1297-300.
30. Falagas ME, Betsi GI, Athanasiou S. Probiotics for prevention of recurrent vulvovaginal candidiasis: a review. J Antimicrob Chemother. 2006;58:266-72.
31. Vujic G, Jajac Knez A, Despot Stefanovic V, Kuzmic Vrbanovic V. Efficacy of orally applied probiotic capsules for bacterial vaginosis and other vaginal infections: a double-blind, randomized, placebo-controlled study. Eur J Obstet Gynecol Reprod Biol. 2013;168:75-9.
32. Martinez RC, Franceschini SA, Patta MC, Quintana SM, Candido RC, Ferreira JC, et al. Improved treatment of vulvovaginal candidiasis with fluconazole plus probiotic Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14. Lett Appl Microbiol. 2009;48:269-74.
33. De Seta F, Parazzini F, De Leo R, Banco R, Maso GP, De Santo D, et al. Lactobacillus plantarum P17630 for preventing Candida vaginitis recurrence: a retrospective comparative study. Eur J Obstet Gynecol Reprod Biol. 2014;182:136-9.