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CLINICAL MANAGEMENT OF RECURRENT CANDIDIASIS: WHAT DOES THE EVIDENCE SAY?

Paulo Victor Santos Bezerra
Faculdade Pernambucana de Saúde
Recife, Pernambuco, Brazil
ORCID: 0009-0001-2868-5297

Gustavo Costa de Albuquerque Maranhão Neto
Faculdade Pernambucana de Saúde
Recife, Pernambuco, Brazil
ORCID:0009-0004-1632-8331
http://lattes.cnpq.br/4137640845408992

Caio Farias Pimentel
Faculdade Pernambucana de Saúde
Recife, Pernambuco, Brazil
ORCID: 0000-0003-1169-2770
https://lattes.cnpq.br/8760716033637106

Kênio Betmann-Azevêdo
Faculdade Pernambucana de Saúde
Recife, Pernambuco, Brazil
ORCID: 0009-0009-3249-2437
http://lattes.cnpq.br/1146702683153865

Julia Roffé de Vasconcelos Lins
Faculdade Pernambucana de Saúde
Recife, Pernambuco, Brazil
ORCID: 0009-0009-7336-4597
http://lattes.cnpq.br/5954011056237262

Beatriz Oliveira Gonçalves e Silva
Faculdade Pernambucana de Saúde
Recife, Pernambuco, Brazil
ORCID: 0009-0008-2024-8448
http://lattes.cnpq.br/1084938566222705

Pedro Henrique Bezerra de Menezes Amorim
Faculdade Pernambucana de Saúde
Recife, Pernambuco, Brazil
http://lattes.cnpq.br/4581630568589594

Matheus Marinho Gomes Correia
Faculdade Pernambucana de Saúde
Recife, Pernambuco
ORCID: 0009-0004-9050-9982
http://lattes.cnpq.br/4066746303867455

Maria Clara Azevedo Melo Patriota
Faculdade Pernambucana de Saúde
Recife, Pernambuco, Brazil
http://lattes.cnpq.br/4088488262136501

Manuelly Pereira de Morais Santos
Faculdade Pernambucana de Saúde
Recife, Pernambuco, Brazil
ORCID: 0000-0003-3255-0552
http://lattes.cnpq.br/6957775356692711

Luís Henrique Rufino Amaral Pinheiro
Faculdade Pernambucana de Saúde
Recife, Pernambuco, Brazil
ORCID: 0009-0008-8260-1737
https://lattes.cnpq.br/7859441845735257

Vinicyus Eduardo Melo Amorim
Faculdade Pernambucana de Saúde
Recife, Pernambuco, Brazil
http://lattes.cnpq.br/3530467921354204
ORCID: 0000-0003-4541-690X

Abstract: Recurrent vulvovaginal candidiasis (RVC) is a common condition affecting many women, characterized by frequent episodes of Candida infection. Although azoles are often prescribed as initial treatment, resistance to these drugs is becoming a growing concern. Furthermore, management of CVR can be challenging due to a lack of effective therapeutic options. Alternative strategies, such as immunotherapy and behavioral therapies, are being investigated but still lack conclusive evidence. The treatment approach should consider not only the eradication of acute infection, but also the prevention of recurrences through identification and elimination of underlying risk factors. An in-depth understanding of resistance mechanisms and host-pathogen interactions is essential for the development of new, more effective and safer therapeutic approaches for CVR.

Keywords: Candidiasis; Antifungals; Fluconazole

INTRODUCTION

Recurrent vulvovaginal candidiasis (RVC) is characterized by three or more episodes of symptomatic infection within a year, in contrast to the previous definition of four or more episodes annually.[1-4] It is crucial to perform vaginal cultures to confirm the diagnosis and identify possible species less common Candida. However, the effectiveness of molecular tests in the diagnosis and treatment of RVVC is not yet fully understood.

Recurrent disease usually occurs due to recurrence of a persistent vaginal reservoir of organisms or endogenous reinfection with identical strains of susceptible C. albicans; however, in rare cases, a new strain of Candida may be responsible for the infection.[5]

Estimating the incidence and prevalence of CVR is a challenging task due to the lack of symptoms unique to Candida infection, the self-medication of many individuals, and

the often-empirical treatment. In an internet research study of more than 7,000 women in seven countries, the estimated probability of CVR after a CVR episode at age 50 ranged from 14 to 28 percent, with an average of 23 percent.[6]

The vast majority of patients with CVR are healthy individuals, and the origin of this condition remains largely unknown. However, although the exact cause is unclear, some contributing factors have been identified, and several potential mechanisms are being studied. When it comes to the microbiology involved, longitudinal studies that analyzed DNA suggest that, in most cases, recurrence of the disease is due to the persistence of a vaginal reservoir of organisms or endogenous reinfection with the same strain of susceptible C. albicans.[5,7] In a smaller percentage of cases, the infection may be caused by another species of Candida, such as C. glabrata.[1]

Evidence has been gathered that establishes a link or associates recurrent episodes of symptomatic infection with immunological hyperreactivity in the vaginal mucosa in relation to the fungus.[8] This suggests that dysregulated immunological reactivity may occur in the pathogenesis of CVR.[9] Hyperreactivity in the vagina involves regulatory T cells that produce interleukin-22 (IL-22), IL-10 and IL-17.

The role of IL-17 in protecting against mucosal Candida infections has already been established.[10] It acts to control C. albicans infection by stimulating vaginal epithelial cells to produce antimicrobial peptides. Studies conducted in women with mucocutaneous candidiasis and CVR have confirmed the genetic basis for these infections. Different mutations and polymorphisms in genes related to innate immunity can alter the immune response of the vaginal mucosa against Candida.[11]

Furthermore, associations have been observed between CVR and specific genetic polymorphisms, such as variants in the alleles of genes such as mannose-binding lectin (LLM) and interleukin-4 (IL-4). Studies suggest that the prevalence of certain genetic variants, especially those related to LLM, is higher in women with CVR than in controls without the condition.[12,13] These genetic variants may compromise the body's ability to resist Candida infection, predisposing individuals affected by the recurrence of vulvovaginal candidiasis.[12,14-17]

RECURRENCE TREATMENT

Initially, studies point to a better outcome with the beginning of treatment based on azoles.[18-22] Although Oteseconazole is more effective in long-term treatments, it is more difficult to obtain and its cost is higher.[22,23]

For the treatment of vaginal candidiasis complicated with severe symptoms of vaginitis, oral fluconazole 150 mg every 72 hours in two or three doses can be used, depending on the severity. Alternatively, you can opt for topical antifungal therapy with azoles daily for 7 to 14 days. For symptomatic relief, a low-potency topical corticosteroid can be applied to the vulva for 48 hours until the antifungal takes effect.

In the case of recurrent vulvovaginal candidiasis, induction can be done with fluconazole 150 mg every 72 hours for three doses, followed by maintenance with fluconazole 150 mg once a week for six months. If fluconazole is not a viable option, other alternatives include 10 to 14 days of topical azole or alternative oral azole, followed by topical maintenance therapy for six months.

After stopping therapy, some patients experience prolonged remission, while up to 55% experience relapse.[20] In case of relapse confirmed with culture testing, reintroduction therapy with three doses of fluconazole is recommended, followed by weekly maintenance therapy with fluconazole for one

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year. Some patients, known as fluconazole dependent for CVR, may continue to have symptoms even with weekly fluconazole maintenance, requiring its use for months or even years.

Due to the safety profile of fluconazole at low doses, most experts do not recommend laboratory monitoring. However, if other oral imidazoles are used (such as ketoconazole, itraconazole), especially if taken daily, monitoring of liver function is recommended. Although there are reports of drug interactions between fluconazole and some oral agents (such as warfarin, rifampin), these interactions are extremely unlikely with the fluconazole maintenance regimen due to the low plasma concentrations resulting from the 150 mg weekly dose, therefore further testing is not necessary are necessary.

It is important to emphasize that reducing gastrointestinal colonization by Candida through oral administration of nystatin does not prevent symptomatic recurrence of vaginal infection.[2]

Oteseconazole is an azole antifungal used in cases of CVR, being more effective against several species of Candida, including Candida glabrata, compared to fluconazole.[24-28] This medication is only indicated for adult women without reproductive potential, being contraindicated for those who may become pregnant, pregnant or lactating, due to concerns about fetal toxicity based on studies in rats that reported retinal abnormalities in offspring and due to its long half-life (138 days).[24] For better absorption, it is recommended take oteseconazole with food.

There are two dosage regimens available: single or double dose. The single-dose regimen consists of oteseconazole 600 mg orally on day 1, oteseconazole 450 mg orally on day 2, and, starting on day 14, oteseconazole 150 mg orally once a week for 11 weeks (i.e., weekly dose during weeks 2 to 12). Comparative studies showed that this regimen was associated with fewer culture-confirmed CVR infections compared with the fluconazole/placebo regimen.[24-26]

The double dose regimen involves initial treatment of the acute infection with fluconazole (150 mg orally administered on days 1, 4 and 7) followed by suppressive therapy with oteseconazole (150 mg orally once daily for seven days on days 14 to 20, followed by oteseconazole 150 mg orally once a week). This regimen has been shown to reduce the recurrence of RVVC and increase the recurrence-free time interval compared to placebo. The effectiveness of this regimen compared to long-term use of fluconazole has not yet been established.[26,29]

EVIDENCE FOR FLUCONAZOLE

A meta-analysis of 23 studies found that continuous antifungal treatment (oral or topical) was likely to reduce clinical recurrence at six months compared with placebo or no treatment (hazard ratio 0.36, 95% CI 0.21-0.63, number needed to treat = 2,607 participants). However, available data were limited to small trials with a high risk of bias due to insufficient blinding.[21]

Observational studies in non-pregnant women with CVR have reported that suppressive antifungal maintenance therapy, taken for six months after an initial induction regimen, resulted in negative cultures.[30,31] The most common option for this in non-pregnant people is fluconazole 150 mg orally, once a week, for six months.[32]

However, it is important to emphasize that maintenance therapy is only effective in preventing recurrent infections while the medication is being taken. A study of 387 women with CVR showed that those treated with fluconazole and subsequently randomly assigned to weekly doses of fluconazole or placebo for six months had a significantly

higher proportion of disease-free patients in the fluconazole group (91 versus 36 percent at 6 months)., 73 versus 28 percent at 9 months and 43 versus 22 percent at 12 months).[18]

Although the fluconazole maintenance regimen was convenient, safe, and as effective as other therapies, half of the patients studied did not achieve long-term cure of recurrent vulvovaginal candidiasis. Recurrent episodes of candidiasis resumed when maintenance therapy was discontinued.

TREATMENT IN INDIVIDUALS RESISTANT TO FLUCONAZOLE

In people with CVR, there is evidence that frequent and prolonged use of fluconazole may rarely select for resistance to fluconazole itself in previously susceptible strains of Candida albicans, which restricts the treatment options available to these individuals.

Assessing the drug's minimum inhibitory concentration (MIC) is a recommended approach in patients with refractory RVVC whose cultures remain positive for C. albicans. This test allows the sensitivity of various antifungals to be determined, using the broth microdilution method in accordance with the criteria established by the Clinical and Laboratory Standards Institution.[33]

Another strategy is to increase the azole dose based on the MIC. In a study involving 25 women with refractory Candida vaginitis and a C. albicans isolate with a fluconazole MIC ≥2 micrograms/mL, those with an MIC of 2 or 4 micrograms/mL were successfully treated by increasing the fluconazole dose to 200 mg. twice weekly.[34] However, higher doses of fluconazole may not be effective in patients with MIC ≥4 micrograms/mL, and in these cases, it may be necessary to evaluate cross-resistance to itraconazole and ketoconazole.

Furthermore, in situations of azole resistance, as reported in non-albicans Candida infections, people with severe CVR infection and high azole resistance may have no treatment options other than topical boric acid or nystatin suppositories.[35, 36] These alternatives can be considered when other therapeutic options prove to be ineffective.

LONG-TERM TREATMENT WITH TRITERTENOIDS

Long-term use of ibrexafungerp, an oral triterpenoid medication, is an alternative for the suppression of recurrent vulvovaginal candidiasis (CVVR). In a phase 3 clinical trial evaluating patients with CVR initially treated with fluconazole followed by ibrexafungerp or placebo, more patients in the group receiving ibrexafungerp remained free of evidence of CVR (65.4% versus 53.1%, respectively) in the trial. The healing performed at week 24 of the study. A total of 37 Patients received oral fluconazole 150 mg every 72 hours for a total of three doses, followed by oral ibrexafungerp (300 mg twice daily for one day every four weeks for one total of six doses) or placebo with the same dosing regimen.[38,39]

However, the long-term benefit of treating CVR caused by C. albicans is still unclear, as follow-up was limited to three months after stopping ibrexafungerp rather than the typical six months. Furthermore, because the majority of study participants had C. albicans infections, it is unknown whether patients with non-albicans Candida isolates, which represent 10 to 15% of usual isolates, will experience similar benefits from prophylaxis.[22]

Common side effects included headaches and gastrointestinal upsets such as diarrhea and nausea. Although it offers a treatment option for patients who do not respond to azoles or have infections resistant to them, the cost of treatment with ibrexafungerp can be prohibitive. Additionally, pregnant or breastfeeding women should not use ibrexafungerp.

DOES GENTIAN VIOLET STILL HAVE ANY APPLICATIONS?

Topical gentian violet was commonly used before the availability of intravaginal azole antifungal creams and suppositories. However, its use was largely abandoned due to the greater effectiveness of azole antimycotics and the inconvenience caused by gentian violet, which permanently stains clothes. Despite this, it is still useful as a vulvar antipruritic and for occasional cases of vulvovaginal candidiasis refractory to azoles. The medicine is applied to the affected areas of the vulva and vagina daily for 10 to 14 days.[40]

APPLICABILITY OF BORIC ACID

Vaginal boric acid is not indicated for the treatment of recurrent vulvovaginitis caused by C. albicans unless laboratory tests confirm resistance to azoles. Its prolonged use does not have established safety data and can cause significant local irritation and even toxicity if accidentally ingested, which can lead to death.[1]

In rare cases of proven azole-resistant infection or RVVC not caused by C. albicans, a course of boric acid, usually administered as 600 mg vaginal suppositories daily for two weeks, may be considered. However, it is important to note that sexual partners exposed to vaginal boric acid may develop irritation or dermatitis in the affected area, although the duration of this risk is not well known.[41,42]

Local vaginal sensitivity to C. albicans has been suggested as a possible cause of recurrent infections in some women. Immunotherapy for Candida vaginitis, both for prevention and treatment, is being investigated as a therapeutic approach. A prophylactic vaccine would need to stimulate a host immune response against features of fungal virulence without disturbing the tolerance/inflammation balance of the vaginal environment. On the other hand, a therapeutic vaccine for women with CVR could help correct or increase this imbalance. Currently, two vaccines are in the development process.[43-45]

IMPORTANCE OF BEHAVIORAL CHANGES

Although there is no randomized trial data, making changes to one or more behaviors (such as avoiding panty liners, pantyhose, cranberry juice, and topical lubricants) to see if there is improvement may be beneficial in rare cases.[46] If there are present risks, such as inadequate glycemic control or use of oral contraceptives with high doses of estrogen, efforts should be made to eliminate or reduce them. It is important to also address the sexual dysfunction and marital problems that often accompany chronic vaginitis.

Regarding probiotics and dietary changes, there is no evidence that women with CVR have a vaginal flora deficient in lactobacilli, so the use of probiotics containing lactobacilli is recommended.[19,47,48] Although many people believe that consuming yogurt or other products with live lactobacilli may reduce Candida colonization and symptomatic recurrences, studies in this area have methodological flaws and inconclusive results.[49-53] Administration of live lactobacilli to women with recurrent infection has been refuted in some studies, and this approach is considered unproven.[54] Furthermore, the quality of probiotics may vary and their use may not be safe for immunocompromised patients.[55]

Regarding diet, there is no specific recommendation, as there are no controlled studies that evaluate its role in preventing and controlling Candida vaginitis. Some patients report that the consumption of beer or refined sugar products can precipitate episodes of vaginitis, and in these cases, avoiding these foods may be prudent, but is often not enough to resolve the symptoms.

TREATMENT FOR NON-ALBICANS CANDIDA

For non-albicans Candida vaginitis, treatment varies depending on the species identified. For C. glabrata, intravaginal boric acid 600 mg per day can be used for 14 days. In case of failure, topical flucytosine 16% cream, 5 g at night for 14 days, can be used. For C. krusei, clotrimazole, miconazole or terconazole can be used intravaginally for 7 to 14 days. For all other species, fluconazole can be used in a conventional dose of 150 mg.

In cases of compromised host status, such as poorly controlled diabetes or immunosuppression, and isolation of azole-susceptible Candida, oral or topical therapy for 7 to 14 days is recommended. During pregnancy, you can opt for topical clotrimazole or miconazole for 7 days. It is important to note that boric acid capsules and flucytosine cream are not commercially available, but can be manufactured in a compounding pharmacy.

REFERENCES

Workowski KA, Bachmann LH, Chan PA, et al. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep 2021; 70:1.

Sobel JD. Epidemiology and pathogenesis of recurrent vulvovaginal candidiasis. Am J Obstet Gynecol 1985; 152:924.

Sobel JD. Recurrent vulvovaginal candidiasis. Am J Obstet Gynecol 2016; 214:15.

Nyirjesy P, Brookhart C, Lazenby G, et al. Vulvovaginal Candidiasis: A Review of the Evidence for the 2021 Centers for Disease Control and Prevention of Sexually Transmitted Infections Treatment Guidelines. Clin Infect Dis 2022; 74:S162.

Vazquez JA, Sobel JD, Demitriou R, et al. Karyotyping of Candida albicans isolates obtained longitudinally in women with recurrent vulvovaginal candidiasis. J Infect Dis 1994; 170:1566.

Blostein F, Levin-Sparenberg E, Wagner J, Foxman B. Recurrent vulvovaginal candidiasis. Ann Epidemiol 2017; 27:575.

Lockhart SR, Reed BD, Pierson CL, Soll DR. Most frequent scenario for recurrent Candida vaginitis is strain maintenance with "substrain shuffling": demonstration by sequential DNA fingerprinting with probes Ca3, C1, and CARE2. J Clin Microbiol 1996; 34:767.

Yano J, Noverr MC, Fidel PL Jr. Cytokines in the host response to Candida vaginitis: Identifying a role for non-classical immune mediators, S100 alarmins. Cytokine 2012; 58:118.

De Luca A, Carvalho A, Cunha C, et al. IL-22 and IDO1 affect immunity and tolerance to murine and human vaginal candidiasis. PLoS Pathog 2013; 9:e1003486.

Mengesha BG, Conti HR. The Role of IL-17 in Protection against Mucosal Candida Infections. J Fungi (Basel) 2017; 3.

Jaeger M, Plantinga TS, Joosten LA, et al. Genetic basis for recurrent vulvo-vaginal candidiasis. Curr Infect Dis Rep 2013; 15:136.

Liu F, Liao Q, Liu Z. Mannose-binding lectin and vulvovaginal candidiasis. Int J Gynaecol Obstet 2006; 92:43.

Donders GG, Babula O, Bellen G, et al. Mannose-binding lectin gene polymorphism and resistance to therapy in women with recurrent vulvovaginal candidiasis. BJOG 2008; 115:1225.

Babula O, Lazdāne G, Kroica J, et al. Frequency of interleukin-4 (IL-4) -589 gene polymorphism and vaginal concentrations of IL-4, nitric oxide, and mannose-binding lectin in women with recurrent vulvovaginal candidiasis. Clin Infect Dis 2005; 40:1258.

Ip WK, Lau YL. Role of mannose-binding lectin in the innate defense against Candida albicans: enhancement of complement activation, but lack of opsonic function, in phagocytosis by human dendritic cells. J Infect Dis 2004; 190:632.

Lillegard JB, Sim RB, Thorkildson P, et al. Recognition of Candida albicans by mannan-binding lectin in vitro and in vivo. J Infect Dis 2006; 193:1589.

Giraldo PC, Babula O, Gonçalves AK, et al. Mannose-binding lectin gene polymorphism, vulvovaginal candidiasis, and bacterial vaginosis. Obstet Gynecol 2007; 109:1123.

Sobel JD, Wiesenfeld HC, Martens M, et al. Maintenance fluconazole therapy for recurrent vulvovaginal candidiasis. N Engl J Med 2004; 351:876.

Vaginitis in Nonpregnant Patients: ACOG Practice Bulletin, Number 215. Obstet Gynecol 2020; 135:e1. Reaffirmed 2022.

Collins LM, Moore R, Sobel JD. Prognosis and Long-Term Outcome of Women With Idiopathic Recurrent Vulvovaginal Candidiasis Caused by Candida albicans. J Low Genit Tract Dis 2020; 24:48.

Cooke G, Watson C, Deckx L, et al. Treatment for recurrent vulvovaginal candidiasis (thrush). Cochrane Database Syst Rev 2022; 1:CD009151.

Sobel J, Wayne State University School of Medicine, 2022, personal communication.

Martens MG, Maximos B, Degenhardt T, et al. Phase 3 study evaluating the safety and efficacy of oteseconazole in the treatment of recurrent vulvovaginal candidiasis and acute vulvovaginal candidiasis infections. Am J Obstet Gynecol 2022; 227:880.e1.

Sobel J, Wayne State University School of Medicine, 2022, personal communication.

Martens MG, Maximos B, Degenhardt T, et al. Phase 3 study evaluating the safety and efficacy of oteseconazole in the treatment of recurrent vulvovaginal candidiasis and acute vulvovaginal candidiasis infections. Am J Obstet Gynecol 2022; 227:880.e1.

VIVJOA (oteseconazole) [package insert]. Durham, NC: Mycovia Pharmaceuticals Inc, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215888s000lbl.pdf (Accessed on April 29, 2022).

Sobel JD, Nyirjesy P. Oteseconazole: an advance in treatment of recurrent vulvovaginal candidiasis. Future Microbiol 2021; 16:1453.

Brand SR, Sobel JD, Nyirjesy P, et al. A Randomized Phase 2 Study of VT-1161 for the Treatment of Acute Vulvovaginal Candidiasis. Clin Infect Dis 2021; 73:e1518.

Sobel JD, Donders G, Degenhardt T, et al. Efficacy and Safety of Oteseconazole in Recurrent Vulvovaginal Candidiasis. NEJM Evid 2022.

Reef SE, Levine WC, McNeil MM, et al. Treatment options for vulvovaginal candidiasis, 1993. Clin Infect Dis 1995; 20 Suppl 1:S80.

Donders G, Bellen G, Byttebier G, et al. Individualized decreasing-dose maintenance fluconazole regimen for recurrent vulvovaginal candidiasis (ReCiDiF trial). Am J Obstet Gynecol 2008; 199:613.e1.

Pappas PG, Kauffman CA, Andes D, 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.

Clinical and Laboratory Standards Institute. Performance standards for antimibrobial susceptibility testing. Nineteenth informational supplement. Approved standard M100–S19. Wayne (PA): Clinical and Laboratory Standards Institute; 2009.

Marchaim D, Lemanek L, Bheemreddy S, et al. Fluconazole-resistant Candida albicans vulvovaginitis. Obstet Gynecol 2012; 120:1407.

Guidelines for the Prevention and Treatment of opportunistic Infections in Adults and Adolescents with HIV. U.S Department of Health and Human Services. May 2020.

Danby CS, Boikov D, Rautemaa-Richardson R, Sobel JD. Effect of pH on in vitro susceptibility of Candida glabrata and Candida albicans to 11 antifungal agents and implications for clinical use. Antimicrob Agents Chemother 2012; 56:1403.

Drugs@FDA: FDA-Approved Drugs. Brexafemme. 2022. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (Accessed on December 20, 2022).

Phase 3 Study of Oral Ibrexafungerp (SCY-078) Vs. Placebo in Subjects With Recurrent Vulvovaginal Candidiasis (VVC) (CANDLE). ClinicalTrials.gov Identifier: NCT04029116. https://clinicaltrials.gov/ct2/show/NCT04029116.

BREXAFEMME (ibrexafungerp tablets). US FDA approved product information; Jersey City, NJ: SCYNEXIS; November 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214900s002lbl.pdf.

White DJ, Johnson EM, Warnock DW. Management of persistent vulvo vaginal candidosis due to azole-resistant Candida glabrata. Genitourin Med 1993; 69:112.

Guidelines for the Prevention and Treatment of opportunistic Infections in Adults and Adolescents with HIV. U.S Department of Health and Human Services. May 2020. https://aidsinfo.nih.gov/guidelines

Iavazzo C, Gkegkes ID, Zarkada IM, Falagas ME. Boric acid for recurrent vulvovaginal candidiasis: The clinical evidence. J Womens Health (Larchmt) 2011; 20:1245.

Rigg D, Miller MM, Metzger WJ. Recurrent allergic vulvovaginitis: Treatment with Candida albicans allergen immunotherapy. Am J Obstet Gynecol 1990; 162:332.

Magliani W, Conti S, Cassone A, et al. New immunotherapeutic strategies to control vaginal candidiasis. Trends Mol Med 2002; 8:121.

Cassone A. Vulvovaginal Candida albicans infections: Pathogenesis, immunity and vaccine prospects. BJOG 2015; 122:785.

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.

Sobel JD, Chaim W. Vaginal microbiology of women with acute recurrent vulvovaginal candidiasis. J Clin Microbiol 1996; 34:2497.

McClelland RS, Richardson BA, Hassan WM, et al. Prospective study of vaginal bacterial flora and other risk factors for vulvovaginal candidiasis. J Infect Dis 2009; 199:1883.

Hilton E, Isenberg HD, Alperstein P, et al. Ingestion of yogurt containing Lactobacillus acidophilus as prophylaxis for candidal vaginitis. Ann Intern Med 1992; 116:353.

Shalev E, Battino S, Weiner E, et al. Ingestion of yogurt containing Lactobacillus acidophilus compared with pasteurized yogurt as prophylaxis for recurrent candidal vaginitis and bacterial vaginosis. Arch Fam Med 1996; 5:593.

Collins EB, Hardt P. Inhibition of Candida albicans by Lactobacillus acidophilus. J Dairy Sci 1980; 63:830.

Falagas ME, Betsi GI, Athanasiou S. Probiotics for prevention of recurrent vulvovaginal candidiasis: A review. J Antimicrob Chemother 2006; 58:266.

Martinez RC, Franceschini SA, Patta MC, 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.

Witt A, Kaufmann U, Bitschnau M, et al. Monthly itraconazole versus classic homeopathy for the treatment of recurrent vulvovaginal candidiasis: A randomised trial. BJOG 2009; 116:1499.

US Food and Drug Administration. MedWatch safety alerts for human medical products. Available at: https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/