Review article

Recurrent vulvovaginal candidiasis and drug resistance

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Introduction

Vulvovaginal candidiasis (VVC) is one of the most common vaginal diseases among women in the reproductive age group. It is the second most common condition that causes a pathological vaginal discharge after bacterial vaginosis (BV)[1]. It is estimated that at least 75% of women encounter this condition at some point during their reproductive age, and up to 50% of women experience at least one recurrence[2]. Vulvovaginal candidiasis is commonly seen in pregnancy, where the vaginal epithelium is under estrogenic influence[3]. It is uncommon before menarche and after menopause[3].

The exact incidence of the condition is unknown as it is usually diagnosed clinically and treated empirically[4]. The condition is most commonly caused by a yeast, *Candida albicans* and hence initially termed vaginal candidiasis and commonly called vaginal thrush. However, to incorporate a wider spectrum of symptoms and wider anatomical definition it was termed vulvovaginal candidiasis[5].

Recurrent VVC is defined as four or more symptomatic episodes during 12 months. It affects up to nine percent of women of reproductive age[6]. RVVC affects the quality of life as it causes not only physical symptoms such as troublesome vaginal discharge, vulval soreness, dyspareunia, and dysuria, but also psychological symptoms of anxiety, depression, and low mood[7]. Although the commonest organism that accounts for RVVC is *C. albicans*, other yeasts such as *C. glabrata*, *C. krusei*, *C. tropicals*, and *C. parapsilosis* have been identified in cases of RVVC[8]. Some non-*albicans Candida* infections can be treatment-resistant and hence are associated with RVVC. RVVC is known to be associated with the usage of oral contraceptive pills, diabetes mellitus, tampons, douching, sexual transmission, and immunocompromisation. Recent evidence suggests heterogeneity of mannose-binding lectin (MBL2) allele causes as much as fourfold increased risk for RVVC[9]. However, the exact mechanism of RVVC is yet to be determined. Besides the increasing use of hormone replacement therapy, especially vaginal oestrogens therapy, an increasing number of post-menopausal women are now encountering RVVC.

The widely accepted treatment for RVVC includes induction therapy with antifungal drugs and prolonged maintenance therapy. However, a wide variation

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of drugs and treatment regimens exist in current practice[10,11]. Controversies remain in the areas of treatment of non-*albicans Candida* infections and asymptomatic infections. Evidence suggests that vaginal probiotics, especially *Lactobacillus* species support symptomatic relief of RVVC and help restore the balance of healthy vaginal flora and reduce recurrent episodes[12,13].

Healthy vaginal microbiome

A healthy vaginal microbiome is one of the key factors preventing vaginal infections. In the reproductive age group, the predominant microorganism in healthy vaginal flora is *Lactobacillus* species which produces lactic acid and makes healthy vaginal pH less than 4.5. *Candida* species also may take part in normal healthy vaginal flora. It is demonstrated that up to 20% of healthy women have *Candida* species as a part of their normal vaginal flora essentially in its yeast form[2]. Acidic pH due to lactic acid and various compounds such as hydrogen peroxide and bacteriocins secreted by *Lactobacillus* aids *Candida* species to maintain their non-pathogenic yeast form and not transform into its pathogenic hyphal form.

Microbiology of RVVC

VVC is a mucocutaneous manifestation of candidiasis. *Candida* are eukaryotic, unicellular organisms. Their pathogenesis is aided by the ability to form biofilms. They are found as commensals on healthy skin, as well as mucous membranes on the gastrointestinal, respiratory, and female genitourinary tracts. Although there are many *Candida* species, human infections are caused by around twenty species, of which *C. albicans* is the commonest so far, causing 80-89% of VVC cases. The remainder is caused by *C. tropicalis, C. glabrata, C. parapsilosis, C. krusei* and *Saccharomyces cerevisiae*[14].

Diagnosis

Diagnosis of VVC is clinical, based on the presence of typical symptoms and signs, aided by laboratory confirmation. Vaginal pH is normal in VVC and elevated pH hints at an alternative diagnosis[14]. A high vaginal swab of the discharge is collected, and dispatched for a wet smear and/or Gram staining. The visualization of yeast cells, along with pseudohyphae and neutrophils is indicative of infection. The presence of neutrophils in vaginal secretions suggests the presence of inflammation but is not specific to VVC[14]. Hence, interpreting culture results must be done cautiously, as asymptomatic vaginal colonization is common. Up to 20% of women in the reproductive age group can have vaginal colonization with *Candida* species but require no treatment[14]. A positive culture result, but with the absence of neutrophils in the direct smear is deemed colonization. Additionally, quantification of yeast growth in culture could also be misleading, as transport delays may lead to fungal overgrowth[15].

Any fungal growth should be identified and speciated in RVVC, and antifungal sensitivity should be done for fluconazole. It is worthwhile remembering that mixed infections with two or more *Candida* species can occur and should be processed and identification and antifungal sensitivities done[14].

Pathogenesis

C. albicans, the commonest yeast to cause RVVC, has the ability to exist both as a commensal and as an opportunistic pathogen. This is due to its ability to change morphology from yeast to hyphal form, depending on environmental stressors, and thus contributes to its pathogenicity. In its yeast form, the organism is tolerated by the host in low numbers on the vaginal epithelium. However, when the tolerance mechanisms become deficient, the organism morphs into hyphal form and forms a biofilm on the vaginal epithelium, facilitating its invasion[16]. It is thought that the source of *Candida* in the vagina is from the lower gastrointestinal tract. Estrogenic influence of vaginal epithelium helps *Candida* colonization whereas deprivation of oestrogen inhibits it. VVC results in overgrowth of *Candida* which can be due to alterations of host defence mechanisms that prevent candida overgrowth.

Vaginal local defence mechanisms are the initial barrier against *Candida albicans* overgrowth. Cell wall components such as phospholipomannan, *O*-linked mannans and zymosan in *Candida* cell wall are recognized by the local immune system and trigger pro-inflammatory markers to induce an inflammatory response[17,18].

Treatment

The key concern for treatment of RVVC is its recurrent nature. Achieving symptomatic control is usually possible with each episode but the relapsing nature of the condition is challenging to the physician and frustrating to the patient. Treatment is indicated only

when it is symptomatic and asymptomatic patients with positive culture/microscopy should not be treated. Treatment for RVVC consists of intense induction with an antifungal agent and then maintenance therapy aimed to prevent relapses, whereas in simple vaginal candidiasis, short-term local therapy usually cures the disease or spontaneous resolution occurs with the resolution of any provoking factors.

Once the diagnosis is made and the *Candida* species responsible for the disease is identified, predisposing factors must be sought (Table 1).

Table 1. Predisposing factors for RVVC

- Diabetes mellitus
- Oral contraceptive pills (OCP)
- Intrauterine contraceptive device (IUCD)
- Hormonal replacement therapy (HRT)
- Tampons
- Prolonged antibiotic use
- Douching
- Immunocompromisation
- HIV infection
- Multiple sexual partners
- Oral sexual practice
- Poor vulval hygiene
- Heterogeneity of MBL2 gene

However routine screening for HIV and diabetes is not recommended. If it is associated with prolonged antibiotic use, adding fluconazole 150 mg daily with the onset of antibiotic regime and then every 3-4 days during the period of antibiotic therapy has shown to be beneficial[19]. If a causative factor is not identified as in the majority of the cases species-specific treatment can then be initiated. For idiopathic RVVC oral fluconazole is preferred for both induction and maintenance therapy[20]. During maintenance, treatment relapses are rare. However, one of the major challenges is recurrent episodes of VVC after completing the maintenance period. Up to 40% of women will have long-term remission following treatment[20]. However, in these instances, *Candida* species identified were usually sensitive to fluconazole and essentially the same species for which treatment was initiated. Treatment for relapses also includes induction therapy followed by maintenance treatment. A list of commonly practiced drug regimens is shown in Table 2.

Non-*albicans Candida* species

Non-*albicans Candida* species such as *C. glabrata* and *C. krusei* have high resistance to azoles and may be the main reason that they are found in RVVC[19]. Studies are lacking with RVVC with such species. Therefore, alternative treatment options like vaginal Boric acid and nystatin alone or in combination can be tried[21]. Evidence for long-term maintenance therapy is lacking for non-*albicans Candida* species. Uncontrolled diabetes is one of the commonly identified predisposing factors of non-*albicans Candida* causing RVVC[19].

Antifungal drug resistance

Based on available data, *C. albicans* causing RVVC is usually sensitive to azoles and thus treatable with the first-line agents. However, risk factors causing RVVC should be controlled or removed for a successful outcome. In the instance of infection with a non-*albicans* species of *Candida*, resistance to azoles may be expected to occur[16].

However, in recent years, data on resistant *C. albicans* infections causing RVVC have begun to emerge. This occurs through the repetitive administration of short courses of fluconazole for suspected fungal infections such as *Candida* vaginitis, and the prolonged courses of antifungals used as maintenance therapy for RVVC. Drug resistance should be suspected when the patient doesn't improve symptomatically to therapeutic doses of antifungal agents and has persistently positive vaginal microscopy/fungal cultures, despite controlling the risk factors[22].

A study in Argentina estimated that the percentage of fluconazole resistance to *C. albicans* isolated from females with vaginal discharge is about 6.6% in 1996-2000, which increased exponentially to 45.4% in 2011-2017[23].

Another study in Detroit, USA aimed to analyse the antifungal susceptibility trends in 250 *C.albicans* isolates from vaginal discharges between 1986 to 2008 concluded that although a clinically significant increase in resistance was not documented, the minimum inhibitory concentrations for fluconazole had increased over time[24].

Table 2. Treatment options for RVVC[19]

***Candida* species**	**Oral regimes**	**Local regimes**
Candida albicans *C tropicalis* *C parapsilosis*	1. Induction with Fluconazole 150mg daily for 3 days and Maintenance of Fluconazole weekly for 150mg 6 months.	Induction with either Clotrimazole 1% vaginal cream for 7 nights OR Clotrimazole 2% vaginal cream for 3 nights OR Miconazole 2% vaginal cream for 7 nights OR Miconazole 4% vaginal cream for 3 nights Maintenance with Miconazole 1.2g suppository weekly for 6 months
C glabrata		Induction with Nystatin vaginal pessary 100000 U daily for 14 days and maintenance with the same dose for another 14 days
C krusei		Any regimen described above. Avoid fluconazole.
Azole-resistant *Candida* species		Induction with either Nystatin as described above OR Boric acid vaginal suppository/capsule 600mg daily for 14 days. Maintenance with the same regime for 14 more days.

During pregnancy, local treatment should be used. Treating the partner is not indicated in RVVC.

Similarly, a study in Peshawar, Pakistan which involved pregnant women with vulvovaginal candidiasis found that out of the 108 Candida isolates, 58.3% were non-*albicans* species. It was elucidated that 62% of all the isolates were resistant to fluconazole, while 58.3% were resistant to nystatin[25].

Role of probiotics

Lactobacillus predominance offers protection against the overgrowth of *Candida* species in a healthy vaginal environment. It also renders a good local immunity to the vaginal mucosa. Probiotics aim to replenish *Lactobacillus* species volume which has been depleted

by exogenous or endogenous activities[19]. Therefore, probiotics have been long used in the treatment of vaginal candidiasis. However good evidence is lacking in favor of probiotics in the treatment of RVVC. Hence it is not recommended in the majority of guidelines[19].

Conclusion

Recurrent vulvovaginal candidiasis (RVVC) is a debilitating illness among women in the reproductive age group. The Exact mechanism of RVVC is unknown. The most common pathogen responsible for RVVC is *Candida albicans*, however non-*albicans Candida* species can also cause RVVC. *Candida albicans* can be a commensal in normal vaginal flora, however, in VVC it acts as an opportunistic pathogen. Diagnosis is mainly clinical and aided by microscopy and culture. There are known predisposing factors for RVVC that must be addressed before treatment. The majority of RVVC are fluconazole sensitive and fluconazole resistance can be seen mainly in non-*albicans Candida* related RVVC. Various treatment regimens are available for fluconazole-resistant cases. The role of probiotics in the treatment of RVVC is uncertain.

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Conflicts of interest

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