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Vulvovaginal candidiasis

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Abstract

Vulvovaginal candidiasis (VVC) is one of the most frequent infections of the female genital tract; 75% of women of reproductive age will have one episode, and 5% of these will have recurring episodes (>3 a year). Symptoms can be quite unpleasant and impact the quality of life. World incidence is difficult to estimate accurately, for notification is not mandatory. Nonetheless, population estimates range from 5% to 25%.

The fungi exist as saprophytes in the genital tract, but when local defense mechanisms fail, they proliferate and symptoms appear. The mechanisms determining such a transition are still unclear. The most frequent species, *Candida albicans*, accounts for 85% to 95% of the cases, and other species (*C. glabrata, C. krusei, C. paratropicalis, C. guilhermondi,* etc.), for the remainder.

Although some factors are thought to predispose to VVC (diabetes mellitus, pregnancy, high-dosage contraceptives)**,** it is impaired local immunity which seems to underlie recurring phenomena. The most frequent symptom is itching, usually accompanied by white vaginal discharge, dysuria, and dyspareunia. Examination reveals signs of vulva inflammation often with fissures and lacerations in severe cases and a white content, in moderate or abundant quantity, adhered to the vaginal walls. Diagnosis should be confirmed by microscopy with 10% saline or KOH solution. In cases of clinical suspicion and negative microscopy, a culture should be carried out to enable identification of the fungal species and sensitivity tests applied in recurring cases.
For treatment, azoles delivered systemically or vaginally or polyenes via the vaginal route produce good results in sporadic episodes. During pregnancy, only the vaginal route should be used. Recurring episodes may be treated with 3 doses of 150 mg of fluconazole at 72-hour intervals, followed by a once-a-week use of the medication for 6 months. Treatment does not eradicate the fungus completely; recurrences occur in nearly 42.5% of women six months after therapy. The non-albicans strains do not usually respond well to azoles; amphotericin B or 600 mg boric acid ovules can be used instead. In refractory cases, 17% flucytosine is recommended. There is no vaccine for vulvovaginal candidiasis yet.

Keywords: vulvovaginal candidiasis, candida, pregnancy, immunity, diagnosis, treatment

Summary of recommendations

1. The clinical diagnosis of candidiasis based on signs and symptoms should always be confirmed by fungal identification through microscopy of fresh vaginal smear or culture when signs and symptoms are present but microscopy is negative.
2. Sporadic episodes can be treated with azoles administered orally or vaginally or with polyenes via the vaginal route.
3. For recurring candidiasis, the treatment is long term and consists of azoles given after the acute phase treatment.
4. Non-*albicans* strains of *Candida* generally do not respond well to azoles; amphotericin B or 600 mg boric acid ovules for 14 days are recommended instead. In refractory cases, the recommendation is for 17% flucytosine. *Candida krusei* has shown resistance to fluconazole and flucytosine; it responds to local treatment with clotrimazole, other imidazoles, and boric acid.

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1 Introduction

Vulvovaginal candidiasis (VVC) is one of the most frequent infections of the female genital tract, and as such it is an important public health problem. It is estimated that approximately 75% of all women of reproductive age will experience at least one episode in their lifetime [1]. Most of these will have infrequent episodes, many of which prompted by triggering factors such as diabetes, pregnancy, a state of immunosuppression, use of antibiotics, etc. [2]. However, 5% of them will have recurrent episodes despite adequate response to antifungal therapy during the acute phase of the disease and absence of classical factors predisposing to new episodes [3].

Candidiasis symptoms are highly frequent and may be severe and at times extremely disagreeable, impacting the sexual as well as the personal and professional lives of the affected women, particularly in recurrent episodes. Infection is most frequent in menacme, the most productive phase in a woman's lifetime. The inflammatory process attendant on infection and the changes in genital tract skin and mucosa may facilitate the acquisition or transmission of other sexually transmitted infections, including HIV. During pregnancy, if the inflammatory process is severe, there may be greater predisposition towards early rupture of the membranes and preterm delivery. Furthermore, some studies suggest a potential vertical and horizontal transmission of *Candida*, primarily in low-weight newborns [4], [5].

Not only should personal cost and loss of productivity be considered, but also the financial costs involving consultations, diagnosis, and treatment. In the United States of America, where the disease is the second most common vaginal infection after bacterial vaginosis, such costs surpass one billion dollars a year [6]. Antifungals are among the most sold medications in the USA; the number of prescriptions doubled between 1980 and 1990, reaching 13 million prescriptions [7].

2 Method

This literature review was carried out using the Medline primary database and accessing it with the MeSH terms 'Candidiasis, Vulvovaginal'. The studies available in Portuguese, English, Italian, French, and Spanish were included regardless of the year of publication. Using such criteria, the search yielded 3,195 articles. These were sorted out per topic relevance based on evaluation of titles, abstracts, and full text reading. Thus, **40 Reports** were selected for this review.

3 Epidemiology

Conducting epidemiology studies for assessing factual incidence of candidiasis worldwide is extremely difficult. About 30% of healthy women are colonized, but not infected. Infection, even when confirmed clinically by inflammation and microbiologically, does not have been reported by health professionals; diagnosis is often inaccurate for lack of laboratory exams; and many women self-diagnose themselves and do not seek any medical help because they can easily purchase antifungals without a doctor's prescription.

Epidemiology studies have been conducted in the public health clinics for sexually transmitted diseases, family planning, and teens, while the private clinics with large number of patients, certainly providers of relevant epidemiological data, have been ignored.

Hoffman and collaborators conducted a study in the USA to assess the prevalence of *Candida* in postmenopausal women. These received a swab for self-collection and the material was subsequently evaluated on Gram-stained slides. *Candida* detection totaled 5% [8]. Goldacre and collaborators studied the vaginal flora of 1,498 women, outpatients at family planning services, also through Gram staining. Fungi were present in 21% of the women; no statistically significant differences were detected between users and nonusers of oral contraceptives [9]. Bauters and collaborators found that *Candida* colonization tested positive in 20.1% of women at a gynecology outpatient clinic [10]. Tibaldi and collaborators, when assessing 4904 symptomatic and asymptomatic women, found an 18% colonization rate but no differences between women with and without genital complaints [11]. Mucci and collaborators in a study conducted in Argentina with pregnant women detected fungi in 25% of them, and *Candida albicans* comprised 80.7% of that total [12].

4 Microbiology

Fungi occur in nature as saprophytes of human beings and animals. However, when defense mechanisms are impaired, the fungi may proliferate and cause infection. The mechanisms regulating the

transition from vaginal colonization to infection and manifestation of symptomatic candidiasis are still unclear, but they seem to be related mainly to the immune system of the genital tract [13].

The blastopores of Candida sp. migrate from the lower gastrointestinal tract to the vagina and its vestibule, following a similar route to that of Lactobacillus sp. Colonization occurs in a small volume upon adhesion of the fungi to the vaginal epithelial cells.

Colonization mechanisms are still little known and appear to be directly dependent on an environment influenced by estrogen action. They start after menarche and decline considerably after menopause. In healthy women, asymptomatic colonization may persist for years since the fungus establishes a symbiotic relationship with the host. The infection process manifests when the relationship becomes unbalanced, thereby triggering excessive growth or a significant decrease in the body's defense mechanisms and thus diminishing the tolerance of the vaginal mucosa to the fungus and causing the symptoms initiated by the inflammatory process [14].

Among the 150 existing species of *Candida,* only a few are capable of infecting humans: *Candida albicans, C. tropicalis, C. glabrata, C. krusei, C. paratropicalis, C. guilhermondi, C. rugosa, C. lipolytica, C. lusitaniae, C. briglis,* and *C. kefyr* [15]. *Candida albicans* is the most frequent species and accounts for nearly 85% to 95% of the VVC cases. *Candida glabrata* and *C. tropicalis* are associated with 5% to 10% of the cases, whereas the other species rarely appear [7].

Conditions such as diabetes mellitus, pregnancy, and use of high-dosage oral contraceptives are classically associated with a greater predisposition towards the infection. The use of antibiotics, probably due to the consequent reduction in the quantity of *Lactobacilli,* also facilitates the transition from asymptomatic colonization to infection [16].

More recently, investigation of the vaginal microbiome has added new elements for understanding the pathophysiology, diagnosis, and treatment of female genital tract infections. However, analysis of the microbiome in women with VVC has shown conflicting results. In China, Liu and collaborators, using advanced molecular techniques for identifying microorganisms, were unable to detect vaginal microbial communities characteristic of candidiasis. The microorganisms were like those found in the flora of healthy women with a high prevalence of *Lactobacilli* and, in some cases, like those found in bacterial vaginosis, with the presence of *Gardnerella, Atopobium,* and *Prevotella species* [17]. In the USA, Zhou and collaborators, comparing the vaginal microbiome of women with VVC and that of healthy women, found no differences between the two groups either. Both vaginal communities were dominated by species of *Lactobacilli.* Hence, there was no evidence to demonstrate an altered vaginal microflora or unusual bacterial communities in women with frequent episodes of VVC when contrasted with healthy women. According to the authors, parasitic bacteria are unlikely to prevent the transition from colonization to infection [18].

5 Immunology

As with other microbial infections, immune response to *Candida* has been studied in animal models and in vitro and ex vivo, using reconstituted human vaginal epithelium. Vaginitis by *Candida* has been widely researched in rat and mouse experimental infections and both models have provided useful knowledge. But the differences between the infection caused by *Candida* in humans and that in animals are relevant, particularly in the relapse process. Although estrogen dependence is similar, the human vagina is colonized by fungi, present as parasites, but such is not the case with animals. Hence, there is previous immunity to *Candida* in the human vagina, but not in the vagina of female rats or mice. Therefore, in some situations, such immunity becomes ineffective or less effective, allowing the fungi to proliferate and the symptoms to appear [19]. Another difference is that the source of infection in women is generally endogenous – in the intestines, the cervicovaginal region, or the skin – whereas the infection in animals requires the introduction of a large quantity of exogenous microorganisms. This leads to a marked inflammatory process in estrogenized animals [20]. In women, symptoms are independent of quantity, for they can be pronounced with low concentrations of fungi or better tolerated with higher concentrations. A primary infection protects animals but not women against subsequent infections; women are thus susceptible to recurrences or reinfections [21].

Increasing knowledge of immune system components has made it possible to better understand the mechanisms involved in the protection against fungal infections. A component of the innate immune system, mannose-binding lectin is a protein secreted by the liver and is present in the serum and other biological fluids like vaginal secretion. It can bind to monosaccharide residues on the surface of diverse microorganisms, including *Candida.* Such binding can promote opsonization and complement cascade activation with the attendant destruction of the microorganism [22]. The gene encoding the mannose-binding lectin is polymorphic; consequently, protein concentration is lower or the formed protein is

unstable, incapable of playing its protective role. Women carrying the polymorphism have been shown to be more prone to recurrent vulvovaginal candidiasis. This tendency provides a genetic explanation for recurring phenomena [13].

Other components of the innate immune system are the toll-like receptors, molecules present on the surface of phagocytes and which react with specific molecular patterns on the surface of microorganisms. Such binding stimulates the phagocytosis mechanisms and induces cell-mediated immunity. Over ten different types of TLR have been identified. Two of them, TLR2 and TLR4, recognize and bind to molecular patterns of *Candida* [23].

Like innate immunity action, cell immunity action also protects against fungi. Phagocytic activity is encouraged by the production of proinflammatory cytokines which, in turn, activate cell immunity in their Th1 and Th17 lymphocyte response pathways. Induction of Th1 immunity protects against candidiasis, while the prevalence of the Th2 response, involving anti-inflammatory cytokines, is associated with increased susceptibility to infection [24].

A rise in prostaglandin E2 in the vaginal environment may lead to inhibition of cell immunity and promote adequate conditions for *Candida* to proliferate and symptoms to manifest. Thus, factors which prompt an increase in PE2, such as local or systemic allergic processes, may facilitate infection. Allergens may be present in products or medications of local use, systemically ingested medications, and food; as for the partner, semen may contain allergenic products in its natural components. Thus, reactions of vaginal hypersensitivity ease manifestation of symptomatic candidiasis and recurrences [25].

6 Clinical conditions and diagnosis

The most frequent symptom in VVC is itching, found in approximately 90% of the patients [15]. Depending on the intensity of the inflammatory process, there may be complaints of dysuria and dyspareunia. Symptoms are generally more distressing prior to menstruation, when vaginal pH is more acid; they can be severe enough to seriously compromise the quality of life, especially in recurrent episodes, often associated with depression and anxiety [26].

Examination of the external genitalia performed before insertion of the speculum may, once again depending on the intensity of the condition, show vulvar erythema and edema occasionally with skin and mucosal fissures and excoriations. Also, it generally reveals vaginal content, whitish or yellowish, flocculent or fluid, externalizing through the introitus [27]. Clinical signs, however, are not pathognomonic of candidiasis. William J Ledger and collaborators in the USA demonstrated that only half of the patients clinically diagnosed by gynecologists as VVC carriers had the infection confirmed by laboratory exams [28].

During the speculum examination, vaginal pH is measured with an appropriate indicator strip and material is collected with a spatula for microscopic examination of two slides, one with saline solution and the other with 10% potassium hydroxide. With candidiasis, the vaginal pH is usually within the normal range of 4.0 to 4.5 or more acid. Factors such as light source or speculum lubricated with liquid petroleum jelly or even water may interfere with the procedure leading to erroneous interpretations [23]. Microscopy with saline solution or 10% potassium hydroxide (10% KOH) in most cases shows the presence of leukocytes, hyphae or fungal spores and leukocytes at a 100-fold and a 400-fold magnification. Potassium hydroxide causes the cell elements to separate making it easier to identify the fungi. Phase-contrast microscopy renders details more precise. When immediate microscopy is unfeasible, the vaginal content can be placed on a slide and allowed to dry, then stained by the Gram, Giemsa, or even Papanicolaou method [15]. If strongly attached to epithelial cells, hyphae are hard to detect. When only spores are present, visualization is more difficult, rendering a culture necessary. Unfortunately, microscopy is little used in clinical practice, probably owing to the gynecologists' lack of training and the cost of a microscope. When symptoms and/or signs are present but microscopy is negative, a culture for fungi in specific media is indicated; the Sabouraud medium is the most used. In recurrent cases, culture will allow the identification of the fungal species and the testing of sensitivity to antifungals. Although molecular biology methods like PCR can detect the fungus in clinical samples, they have been limited to research.

Clinical diagnosis of candidiasis is not always easy, since other conditions may show the same symptoms of itching and/or genital discharge. Vulva disorders, such as lichen sclerosus, dermatitides, and allergic conditions, may cause the itchiness. Cytolytic vaginosis and allergic vulvovaginitides may have white discharge in moderate or abundant amount and itching as symptoms. In cytolytic vaginosis, there is a massive increase in *Lactobacilli* and cell lysis and no inflammatory process. In Gram stain microscopy, naked nuclei, cell debris, excessive *Lactobacilli*, and rare leukocytes or none can be seen. In allergic vulvovaginitis, findings are nonspecific: white discharge and itching. The patient's or the partner's

allergy history is relevant to diagnosis and so is the increase in IgE in vaginal fluid. Some women may develop allergies to the very antigens of *Candida.* In lactobacillosis, the stained smears show extremely long *Lactobacilli*. All of these situations can be confused with VVC; a carefully done medical history and a fungi culture testing negative are important.

7 Treatment

Addressing VVC includes orienting the medical history towards the condition and focusing on risk factors (use of antibiotics, state of immunosuppression, use of corticosteroids, diabetes mellitus, use of high-dosage oral contraceptives, chronic or high-stress levels, previous episodes of candidiasis, inadequate hygiene habits) [29]. Before treatment, the clinical diagnosis of the infection should be confirmed through microscopy with saline and 10% KOH and specific fungal culture if necessary, because microscopy may be negative in 50% of the cases despite the presence of symptoms [30]. Furthermore, as previously mentioned, culture allows for the identification of the fungal species causing the clinical condition and the performance of antifungal susceptibility tests, advisable actions in recurrences.

Simple or uncomplicated candidiasis is that which affects healthy women, whose symptoms are sporadic and infrequent. It occurs at least once a year and responds satisfactorily to conventional antifungal therapy. In the vast majority of cases, the etiological agent is *Candida albicans* and the cure rates are high, around 90%.

On the other hand, complicated candidiasis is that which includes one or more of the following factors: severe signs and/or symptoms, recurrence (≥3 episodes a year), the host's inadequate immune response to yeast (often non-*albicans*), diabetes mellitus, pregnancy, or states of immunosuppression [31], [32].

The therapeutic arsenal comprises the azole drugs, which inhibit the transformation of lanosterol into ergosterol in fungal cell membranes, and the polyenes, which form complexes with ergosterol, changing the permeability of the membrane. These drugs are fungistatic; the eukaryotic structure of the fungus (complex cell structure with membranes and a well-compartmentalized interior with metabolic functions between the organelles, namely endoplasmic reticula, mitochondria, the Golgi complex, and lysosomes) hinders the development of harmless fungal drugs [15].

In simple candidiasis, the local and systemic routes are used and they are statistically the same. Recommendations by the Centers for Disease Control and Prevention include [31], [32].

Over-the-counter intravaginal agents

- Clotrimazole cream 1% intravaginal 5 g – 7 to 4 days
- Clotrimazole cream 2% intravaginal 5 g – 3 days
- Miconazole cream 2% intravaginal 5 g – 7 days
- Miconazole cream 4% intravaginal 5 g – 3 days
- Miconazole vaginal suppository 100 mg – 7 days
- Miconazole vaginal suppository 200 mg – 3 days
- Miconazole vaginal suppository 1,200 mg – 1 day
- Tioconazole cream 6.5% intravaginal 5 g – single dose

Prescription intravaginal agents

- Butoconazole cream 2% (bioadhesive) 5 g – single dose
- Terconazole cream 0.4% 5 g – 7 days
- Terconazole cream 0.8% 5 g – 3 days
- Terconazole suppository 80 mg – 3 days

Below are other agents for oral or vaginal use as cream or suppositories:

- Itraconazole 200 mg 2 x a day – 1 day or 200 mg a day – 3 days

- Ketoconazole 200 mg 2 x a day – 5 days
- Nystatin 100,000 units per ovule – single daily application for 14 days [15], [22].

The treatment for complicated VVC has some peculiarities. The non-*albicans Candida* strains respond well to azole agents; the recommendation is for vaginal ovules with 600 mg of boric acid for 14 days [33]. Other authors recommend amphotericin B ovules [34]. In refractory cases, Sobel indicates topical 17% flucytosine; his success rate was 90% [33]. When flucytosine is not commercially available, it can be compounded. However, fungal drug resistance limits its use.

In some countries, the use of boric acid is forbidden and flucytosine is not available for vaginal use. Mendling and Seebacher suggest 800 mg of fluconazole for 2 to 3 weeks, depending on resistance tests [35]. Vaginitis by *Candida krusei* resists treatment with fluconazole and flucytosine, but it responds adequately to local treatment with clotrimazole, other imidazoles, and boric acid [36]. Given the low frequency of infections by non-albicans strains, there are no controlled randomized studies addressing the therapy.

There are also few randomized double-blind controlled clinical trials of recurrent VVC (RVVC). Sobel and collaborators [37], when studying 343 women with the condition, used 3 doses of 150 mg of fluconazole administered at 72-hour intervals for symptoms to go into remission. The patients were subsequently randomized to receive a weekly dose of 150 mg of fluconazole or placebo for 6 months. After the treatment, they were followed up for the same period of time. The percentage of women who remained free from symptoms and whose culture tested negative for fungus at 6, 9, and 12 months was 90.8%, 73.2%, and 42.9%, respectively, in the fluconazole group, and 35.9%, 27.8%, and 21.9%, respectively, in the placebo group ($p<0.001$). Median recurrence time for women using fluconazole was 10.2 months and for those using placebo, 4 months ($p<0.001$). Thus, long-term use of fluconazole reduced symptomatic VVC recurrences. Nevertheless, recurrence in 42.9% of the women 6 months after therapy shows the difficulty in attaining a definitive cure of the disease [37].

Boulori and collaborators [38], in a controlled double-blind randomized clinical trial in Iran with 64 patients with RVVC, also adopted the method proposed by Sobel and assessed the patients at the end of the treatment and 3 and 6 months thereafter. At 6 months, the fungal culture tested positive in 25% of the fluconazole group and in 62.5% of the placebo group ($p=0.05$). However, 6 months after the treatment, there were no differences in symptoms or in positive outcomes between the two groups [38].

Other studies, though nonrandomized, show potential alternative treatments for RVVC. Fan and collaborators [39] used nystatin vaginally for 14 days a month versus the standard regimens with fluconazole (n=293 patients). Assessment after the initial therapy showed mycological cure in 78.3% and 73.8% of the nystatin and fluconazole groups, respectively ($p<0.05$). At the end of the maintenance therapy, culture remained negative in 80.7% and 72.7% of the groups, respectively ($p<0.05$). After 6 months without treatment, culture continued to test negative, with a mycological cure of 81.25% and 82.19% ($p<0.05$). The culture with *Candida albicans* was negative in 84.0% and 81.8% of the nystatin and fluconazole groups, respectively. However, the mycological cure for RVVC by *Candida glabrata* was 64.3% in the nystatin group and only 12.5% in the fluconazole group. Both groups contained fluconazole-resistant strains of *Candida albicans*. The authors concluded that both nystatin and fluconazole effectively treated RVVC and that nystatin could be efficacious when the etiological agent was *Candida glabrata* and when *Candida albicans* was resistant to fluconazole [39].

Hence, it is obvious that new double-blind randomized studies should be conducted for further assessment of RVVC treatment protocols, using different medications and alternative dosages.

Additionally, probiotics as treatment adjuvants still yield controversial results due to differences in product composition and scarcity of controlled randomized studies with an adequate number of patients [40].

Certainly, pathophysiology-oriented therapy and the strengthening of the host's immune response would be important resources in controlling RVVC. Cassone has been conducting important experimental studies with the virulent factors of *Candida albicans*. It is hoped that vaccines will soon be offered for use to gynecologists [21].

8 Further research

The continuation of collaborative research between clinical investigators, immunologists and microbiologists will hopefully lead to new insights about the mechanisms leading to *Candida* colonization in some women but not in others and to the factors facilitating its conversion from a harmless commensal to a vulvovaginal pathogen. The research clearly must encompass an examination of host responses as

well as a delineation of microbial characteristics that lead to pathology. Investigations in women will most likely be the most fruitful. While studies in animal models help us gain further insight into potential mechanisms, these studies must be viewed with caution since there are significant differences between artificially induced vulvovaginal candidiasis in animals and clinical disease in women. There also remains an unmet need to identify mechanisms to totally eradicate *Candida* from the genital tract. Current treatments are *Candida*-static and not *Candida*-cidal. Whether an antibiotic alone, or an antibiotic coupled with a probiotic or some other adjuvant can best accomplish this remains to be explored. Finally, further studies on the vaginal microbiome will hopefully bring new insights about its contribution to Candida colonization and pathogenesis and suggest development of novel protocols to prevent this infection.

9 Conclusions

Far from being a trivial and non-significant problem, vulvovaginal candidiasis significantly affects the health and well-being of many women. Despite years of research and advances in our understanding of the involved mechanisms as well as improvements in treatment strategies, vulvovaginal candidiasis remains one of the most common disorders affected women. New prevention and treatment strategies remain to be developed to more effectively deal with this most common disorder.

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