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Diagnosis and treatment of vulvovaginal candidiasis: a practical approach

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ABSTRACT

Candida infections are the second most common cause of vaginal infection, after bacterial vaginosis. The large majority of *Candida* spp. infections are caused by *C. albicans* (about 85-95%). The remaining part is caused by other pathogens such as *C. glabrata*, *C. parapsilosis*, *C. krusei* and *C. tropicalis*. Episodic vulvovaginal candidiasis (VVC) includes normal women with mild to moderate symptoms and no history of persistent or recurrent symptoms. Culture-dependent analysis and microscopic examination of vaginal fluid are recommended for episodic VVC diagnosis when the laboratory or clinical facilities are available. The current best test to diagnose *Candida* in women is microscopy. Complicated VVC may be defined as that which is recurrent (4 or more episodes in 12 months), associated with severe symptoms, the result of a non-albicans species, or present in a compromised host. This condition is more common in those with immunosuppression, diabetes, or both. Additional testing for HIV and diabetes may be warranted in these situations. When there is evidence of complicated VVC, collection of vaginal fluid for culture and yeast speciation may help to identify the therapy because, in such cases, there is an increased likelihood of non-albicans strains. All national and international guidelines include therapeutic options over-the-counter (OTC) or requiring medical prescription. Azoles topical single-use administration represents the therapy of choice of acute vaginal infection by *Candida*. The treatment with vaginal single dose of clotrimazole or isoconazole or fenticonazole has reported a cure rate of about 95-100% at 7 days and 50-90% at one month. In consideration of the high cure rate and the high

SOMMARIO

Le infezioni vulvo vaginali da *Candida* (VVC) sono la seconda causa più comune di infezione vaginale, dopo la vaginosi batterica. La grande maggioranza delle infezioni da *Candida* spp. sono causate da *C. albicans* (circa 85-95%). La parte rimanente è causata da altri agenti patogeni come *C. glabrata*, *C. parapsilosis*, *C. Krusei* e *C. tropicalis*. La VVC episodica include donne con sintomi da lievi a moderati e nessuna storia di sintomi persistenti o ricorrenti. Il test colturale e microscopico è raccomandato per VVC episodiche quando è possibile effettuarlo. La VVC complicata può essere definita come quella ricorrente (4 o più episodi in un periodo di 12 mesi), associata a sintomi intensi. Questa condizione è più comune in soggetti con immunosoppressione, diabete o entrambi. In caso di VVC complicata, l'esame colturale può aiutare a scegliere la terapia perché in tali casi esiste una maggiore probabilità di ceppi di *Candida* non-albicans. Tutte le linee guida nazionali e internazionali includono opzioni terapeutiche con o senza prescrizione medica. Allo stesso modo tutte le linee guida includono il trattamento con azoli topici in singola dose di un clotrimazolo o isoconazolo o fenticonazolo. In considerazione dell'alto tasso di cura e dell'elevata tollerabilità, il trattamento topico a dose singola può essere considerato trattamento di prima scelta della candidosi vaginale. La presenza di sintomi vulvari intensi può suggerire l'uso della crema da sola o in associazione alla capsula vaginale. Qualsiasi donna i cui sintomi persistono dopo aver utilizzato un preparato da banco o che ha una recidiva dei sintomi entro 2 mesi dopo il trattamento deve essere inviata al ginecologo. L'uso non

tolerability, topical single-dose treatment appear to be considered among the first-choice treatment of vaginal candidiasis. The presence of intense vulvar symptoms may suggest the use of cream alone or together to vaginal capsule according to the intensity of symptoms of complicated VVC. In general, the severity of individual episodes is based on clinical and not laboratory data. Severe disease may require more intensive treatment. Any woman whose symptoms persist after using an OTC preparation or who has a recurrence of symptoms within 2 months after treatment should be referred to a gynecologist. Unnecessary or inappropriate use of OTC preparations is common and can lead to a delay in the treatment of other vulvovaginitis etiologies. Key findings from the literature indicate that lactobacilli treated women after 3 months of follow-up showed a significant increase in vaginal lactobacilli count, a more stable restoration of physiologic pH value and a significant subjective improvement of symptomatic discomforts, such as burning or itching and a modest, but discernable, late effect on vaginal symptoms that could be related to the potential anti-inflammatory/immunomodulatory effects of some strains of lactobacilli. The efficacy of oral or vaginal *Lactobacillus* strains in lowering the risk of VVC recurrence has been shown in observational studies. These results emphasize the importance of defining new therapeutic plans capable of enhancing the effects of conventional antifungal therapy to preserve the *eubiosis* of the vaginal microbiota.

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INTRODUCTION

Candida vaginitis is a disease, whose symptoms are governed by the intersection of host physiology, fungal biology, and the immunological response (1).

Vaginal mycosis represents one of the most common female disorders affecting a large proportion of women throughout their life. Infection caused by *Candida spp.* affects 70 – 75% of women at least once during their lifetime. The most frequently affected age groups are young women of child-bearing age (2). About 40–50% of women will experience another episode and about 5–8% of adult women have recurrent episodes (four or more episodes each year) of *Candida* vaginal infection (3). Vulvovaginal candidiasis (VVC) is responsible for 15–30% of cases of symptomatic vulvovaginal

necessario o inappropriato di preparati da banco è comune e può portare a un ritardo nel trattamento di altre eziologie della vulvovaginite. I risultati principali della letteratura indicano che le donne trattate con lactobacilli dopo 3 mesi di follow-up mostrano un aumento significativo della densità di popolazione dei lactobacilli, un ripristino più stabile del pH fisiologico e un miglioramento soggettivo significativo dei sintomi come bruciore o prurito e un modesto ma un effetto tardivo rilevabile sui sintomi vaginali che potrebbe essere correlato ai potenziali effetti antinfiammatori/immunomodulatori di alcuni ceppi di lactobacilli. L'efficacia dei ceppi di lactobacilli, somministrati per via orale o vaginale, nel ridurre il rischio di recidiva di VVC è stata dimostrata in studi osservazionali. Questi risultati sottolineano l'importanza di definire nuovi piani terapeutici in grado di potenziare gli effetti della terapia antifungina convenzionale al fine di preservare l'eubiosi del microbiota vaginale.

Key words:

Candida infection; treatment; diagnosis.

infection (4, 5). *Candida* infections are the second most common cause of vaginal infection, after bacterial vaginosis (2). It has been estimated that worldwide, recurrent vulvovaginal candidiasis affects about 138 million women annually, with a global annual prevalence of 3871 per 100 000 women (6).

The large majority of *Candida spp.* infections are caused by *C. albicans* (about 85-95%). The remaining part is caused by other pathogens such as *C. glabrata*, *C. parapsilosis*, *C. Krusei* and *C. tropicalis* (7, 8).

Symptoms are thought to be caused by an overabundance of yeast and its penetration of vulvovaginal epithelial cells.

The premenstrual phase or the pregnancy represent moments of high vulnerability for women when the immune defenses are reduced so it is easier to

get infected. The causes are a modification of the vaginal ecosystem with a reduction of lactobacilli and an increase in local glycogen. A very important etiopathogenetic role is due to the estrogenic action that acts as a trigger to the development of mycoses, particularly in women with metabolic syndrome or diabetes where glucose metabolism is altered. Moreover, incorrect lifestyles such as a diet with an excess of simple carbohydrates and yeasts increase the risk of developing VVC.

The use of synthetic linens, panty liners, tight-fitting trousers and the use of internal vaginal swabs are additional factors favoring the development of candida through damage to the vaginal mucosa and alterations in pH (table I) (9).

The main reservoir for *Candida* species is the rectum, but also vaginal colonization is common.

Diagnostic criteria: how to identify a mycosis

Vaginal mycosis is delineated by the inflammation of vaginal wall due to the presence of opportunistic fungal pathogen *Candida* species that usually colonize the vagina without causing any kind of disturbance, until the vaginal mucosa, through the acidic pH, can regulate its development. The most common symptoms are intense itching, vulval fissuring irritation, vaginal burning, abundant milky vaginal secretions with a thick cottage-cheese-like discharge which can often be associated with urinary symptoms similar to cystitis.

The mycotic agent generally responsible for these infections in normal women is *Candida albicans* while in diabetics the pathogens are *C. glabrata* and *C. krusei*.

The vaginal secretions of VVC have a pH < 4.5, and budding yeast and pseudohyphae may be seen on wet mount (10, 11).

Table I. Risk factors for vaginal candidiasis.

Pregnancy
Oral contraceptives, local estrogen administration, hormone replacement therapy
Antibiotics
Immunosuppression
Diabetes
Poor personal hygiene
Sexual habits
Clothing and hygienic habits
Diet and irritable bowel syndrome (IBS)
Host factors: local defence mechanisms, gene polymorphisms, allergies, psycho-social stress Vestibulodynia in premenopausal women.

The physical examination highlights the signs of inflammation characterized by intense edema and redness of the vaginal mucosa with the presence of white vaginal discharge. Erythema and edema of vulvar and vaginal tissues, in conjunction with thick, white clumped vaginal discharge, are supportive of the diagnosis.

Episodic VVC includes normal women with mild to moderate symptoms and no history of persistent or recurrent symptoms. Culture-dependent analysis and microscopic examination of vaginal fluid are recommended for episodic VVC when the laboratory or clinical facilities are available. According to the 2018 European (IUSTI/WHO) International Union against sexually transmitted infections (IUSTI) World Health Organization (WHO) guideline on the management of vaginal discharge, the current best test to diagnose *Candida* in women is microscopy (strength of recommendation: Grade 1, quality of evidence: Grade B) (12).

Complicated VVC may be defined as that which is recurrent (4 or more episodes in 12 months), associated with severe symptoms, the result of a non-albicans specie, or present in a compromised host. This condition is more common in those with immunosuppression, diabetes, or both. Additional testing for HIV and diabetes may be warranted in these situations.

When there is evidence of complicated VVC, collection of vaginal fluid for culture and yeast speciation may help direct therapy because there is an increased likelihood of non-albicans strains in such cases.

TREATMENT

The goal of a symptomatic treatment is to obtain a fast resolution of symptoms. This approach may be useful to quickly improve the quality of life of the woman. However, to lower the risk of recurrent infection we need to obtain a healing of infection. Thus, in symptomatic women treatment may include symptomatic treatment (such as intravaginal boric acid) and healing ones. Treatment based on symptoms alone is a common clinical practice, but results in the overtreatment of a large number of women.

Symptomatic treatment can be administered together with the healing treatment.

We should always consider that incorrect (or inadequate) treatments of VVC increase the risk of relapse. Among women without infectious vagini-

tis, return visits for vaginitis symptoms are more common among women treated empirically (13). Treatment is clearly indicated for symptomatic women who are microscopy positive and/or those who are culture positive.

Healing treatments for vaginal candidiasis

Azoles represents the therapy of choice of acute vaginal infection by *Candida*. Numerous topical and oral azoles are available in a variety of formulations for the treatment of acute VVC infection (**table II**).

Evidence suggests that the use of different drugs or formulation is not associated with different cure rates. A review of the literature published by the Cochran Collaboration in 2007 (14), that assessed the effect of antifungal treatments on vulvovaginal candidiasis, showed similar efficacy of oral or vaginal treatments.

Oral azoles have a potential systemic toxicity effect that may limit the use of ketoconazole.

Topical azoles are safe and well tolerated, although patients may report a burning sensation. There has also been a growing tendency to use shorter treatments.

All national and international guidelines (15-19) include therapeutic options OTC or requiring med-

ical prescription. Similarly, all guidelines include treatment with azoles topical single-use administration. The treatment with vaginal single dose of clotrimazole or isoconazole or fenticonazole have reported a cure rate of about 95-100% at 7 days and 50-90% at one month (20, 21)

Intravaginal azoles reduce symptoms compared with placebo and all seem to have similar efficacy compared with each other. Randomized control trials suggest that single-dose regimens may be as effective as multiple-dose regimens. Intravaginal azoles and oral fluconazole seem equally effective in treating acute attacks (18).

In consideration of the high cure rate and the high tolerability topical single-dose treatment appear to be considered among the first choice treatment of vaginal candidiasis.

Unnecessary or inappropriate use of OTC preparations is common and can lead to a delay in the treatment of other vulvovaginitis etiologies. When itch is a significant symptom, the use of a hydrocortisone-containing topical preparation may provide rapid symptomatic relief.

For *C. glabrata* vulvovaginitis, topical intravaginal boric acid (administered in a gelatin capsule, 600 mg daily, for 14 days), nystatin intravaginal suppositories (100.000 units daily for 14 days) and topical 17% flucytosine cream alone or in combination with 3% AmB cream administered daily for 14 days, have been suggested as alternative treatments. However, the quality of evidences is low (22).

Recurrent VVC is reported in literature as a major issue. Recurrent VVC is a difficult-to-manage condition that affects 5-8% of women of reproductive age. Current treatment regimens have high relapse rates, resulting in poor quality of life for the women affected. Current international guidelines for recurrent VVC are consistent in terms of definition of the condition, diagnostic techniques and induction and maintenance therapy as treatment of choice. However, the regimen suggested by most guidelines (fluconazole weekly for six months) is not particularly effective; only 42.9% of patients are disease free after 12 months. An alternative regimen put forward by one of the guidelines cites a 77% cure rate after 12 months. Most guidelines lacked specific recommendations for the induction and maintenance treatment. (23)

In case of recurrent infection (4 or more episodes in 12 months), the therapy includes an induction regimen to ensure clinical remission, followed immediately by a maintenance regimen. **Table III** shows

Table II. The recommended treatment regimens according to the CDC in Atlanta. Centers for Disease Control and Prevention (15).

Intravaginal agents:		
Butoconazole 2% cream	5 g intravaginally	for 3 days
Clotrimazole 1% cream	5 g intravaginally	for 7-14 days
Clotrimazole 2% cream	5 g intravaginally	for 3 days
Miconazole 2% cream	5 g intravaginally	for 7 days
Miconazole 4% cream	5 g intravaginally	for 3 days
Miconazole	100 mg vaginal suppository	one suppository for 7 days
Miconazole	200 mg vaginal suppository	one suppository for 3 days
Miconazole	1,200 mg vaginal suppository	one suppository for 1 day
Tioconazole 6.5% ointment	5 g intravaginally	in a single application
Butoconazole 2% cream (single dose bioadhesive product)	5 g intravaginally	for 1 day
Nystatin	100,000-unit vaginal tablet	one tablet for 14 days
Terconazole 0.4% cream	5 g intravaginally	for 7 days
Terconazole 0.8% cream	5 g intravaginally	for 3 days
Terconazole	80 mg vaginal suppository	one suppository for 3 days
Oral drugs:		
Fluconazole	150 mg oral tablet	one tablet in single dose

Table III. Recommended treatment regimens for maintenance treatment.

DRUG	DOSAGE REGIMEN ^o
Intravaginal treatments	
Clotrimazole	500 mg once a week
Fluconazole*	50 mg daily
Itraconazole*	50–100 mg daily
Ketoconazole*	100 mg daily
Oral treatments	
Fluconazole*	150 mg once a week

^ofor 6 months. *Avoid in pregnancy/risk of pregnancy and breastfeeding.

the recommended treatment regimens for maintenance treatment.

Boric acid has been suggested in the prevention of relapses of recurrent vulvovaginal candidiasis, but its efficacy ends with the suspension of the therapy (24).

Role of lactobacilli in the treatment of acute vaginal infection and prevention of recurrent disease

The vagina can be considered as one of the most complete and interesting model for the study of the relationships between host and resident microbial population.

The vaginal microbiota in *eubiosis* conditions consists mainly of lactobacilli, known as Doderlain's flora. Among these, the most commonly species found in homeostasis conditions are: *Lactobacillus salivarius*, *Lactobacillus jensenii*, *Lactobacillus crispatus*, *Lactobacillus rhamnosus*, *Lactobacillus gasseri*, *Lactobacillus acidophilus*, *Lactobacillus fermentum*, *Lactobacillus plantarum*, and *Lactobacillus brevis*. The mutual symbiosis between host and lactobacillary flora is the aspect that characterizes the vaginal ecosystem and can be considered as the main factor in the defense against the onset of infections of the lower genital tract in women.

The vaginal mucosa under the estrogenic effect produces glycogen, which acts as nourishment for lactobacilli. These settle on the mucosa carrying out a protective effect.

Vaginal microflora is altered by:

- particular pharmacological or therapeutic treatments (iatrogenic dysbiosis);
- hormonal changes (contraceptive use, menstrual cycle, menopause);
- pregnancy;
- incorrect behavioral habits (sexual, food, hygiene, smoking, stress, use of synthetic linen, interior absorbents, etc.).

The lactobacilli used for the prevention and/or treatment of urogenital infections are now commonly used in clinical practice to maintain a balance of the vaginal ecosystem. Lactobacilli produce high quantities of lactic acid, antimicrobial substances such as hydrogen peroxide, bacteriocins and biosurfactants. Lactobacilli are also able to inhibit the development of pathogens through competition for both nutrients and receptor sites present on the mucosal tissues, as well as through the co-aggregation with the pathogens. The ability of the lactobacilli ascribed to the species *Lactobacillus rhamnosus*, *Lactobacillus reuteri* and *Lactobacillus plantarum*, to maintain a normal urogenital flora is known, with a dose-dependent effect. In particular, the *L. plantarum* P 17630 strain showed, in an *in vitro* study, to have a more marked adhesion capacity on vaginal epithelial cells (17).

An increasing number of studies suggest that lactobacilli use may improve clinical outcomes or lower the likelihood of recurrence.

Key findings from the literature indicate that lactobacilli treated women after 3 months of follow-up showed a significant increase in vaginal lactobacilli count, a more stable restoration of physiologic pH value and a significant subjective improvement of symptomatic discomforts such as burning or itching and a modest but discernable late effect on vaginal symptoms that could be related to the potential anti-inflammatory/immunomodulatory effects of some strains of lactobacilli (25).

These findings have been confirmed in a recent meta-analysis including 2000 non-pregnant women. Compared with conventional antifungal drugs used alone, probiotics as adjuvant therapy could enhance their effectiveness in improving the rate of short-term (within five to 10 days) clinical cure, short-term mycological cure (no abnormal laboratory results) and relapse at one month (recurrence of problems). Less clear was the effect on the rate of long-term (within one to three months) clinical cure, long-term mycological cure, serious and non-serious side events (26). However, the efficacy of oral or vaginal administration of lactobacilli in lowering the risk of VVC recurrence has been shown in observational studies. In a study conducted by Davar and co-workers (27), 7.2% of probiotic and 35.5% of placebo groups presented with a recurrence of complicated VVC within 6 months.

Carriero et al. (28) conducted a multicenter observational study on 476 patients with *Candida albicans* infection, demonstrating that co-administration of *Lactobacillus plantarum* to antifungal therapy (Fluconazole 150mg per os, one-shot) enhanced thera-

peutic efficacy of the antimycotic reducing relapses at 4 weeks and 4 months.

These results emphasize the importance of defining new therapeutic plans capable of enhancing the effects of conventional antifungal therapy to preserve the eubiosis of the vaginal microbiota.

FINAL REMARKS

Vaginal candidiasis is a common condition requiring correct clinical approach:

- treatment based on symptoms alone should be avoided resulting in the overtreatment of a large number of women;

- correct diagnosis should be always made before treatment;
- incorrect (or inadequate) treatments of VVC increase the risk of relapse;
- only treatments included in the national and international guidelines should be considered;
- in case of recurrent VVC maintenance therapy must be considered according to national and international guidelines.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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