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Local Treatment of Vulvovaginal Candidosis

General and Practical Considerations

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Abstract

Vulvovaginal candidosis is a common worldwide female medical problem, occurring mostly in women of childbearing age. Currently available options for the treatment of this condition include local and oral (systemic) therapy. Both alternatives have been considered equally effective in the treatment of uncomplicated vulvovaginal candidosis, although oral regimens are often preferred by physicians and women. However, local treatment presents several advantageous and unique features that may favour this therapeutic approach. The availability of numerous antifungal drugs and products for topical administration makes the selection quite challenging as this task is mostly based on personal experience or

anecdotal data. Also, recent advances have been made in topical antifungal formulations and there is an increasing availability of over-the-counter products. Therefore, a review of both general and practical considerations related to the local treatment of vulvovaginal candidosis is timely.

In summary, azoles and short-term regimens are usually recommended for the local treatment of vulvovaginal candidosis, with nystatin and boric acid considered as second-line alternatives. Unconventional approaches may also be regarded as suitable in patients refractory to usual treatments. In addition to the susceptibility of implicated *Candida* spp. to the antifungal agents, this choice should take into consideration other important issues such as particular situations (e.g. pregnancy, menopause, drug hypersensitivity), women's preferences, and the availability, particularities and cost of antifungal formulations.

Vulvovaginal candidosis is a mucocutaneous infection by yeasts of the genus *Candida* involving the vulva and vagina. It is a common worldwide problem, particularly in women of reproductive age.[1] Vulvovaginal candidosis is also frequently referred to as vulvovaginal candidiasis, thrush and, rarely, moniliasis. However, recent standardization trends suggest that the nomenclature of fungal diseases caused by specific pathogens should include the genus name followed by the suffix *-osis*. Although not considered a severely debilitating condition, its high prevalence and interference with daily activities and the well-being of women makes this disease an important medical condition. Various highly effective oral or local treatment regimens including different drugs (mostly azole antifungals), regimens, durations of treatment and pharmaceutical dosage forms have been proposed and routinely used in clinical practice. Recent reports on the comparative efficacy of local versus oral treatment of uncomplicated vulvovaginal candidosis found no significant differences, or at least no conclusive differences, between either treatment modalities.[2,3] In addition, treatment guidelines issued worldwide do not favour either local or oral therapy.

Even if only equally effective as oral therapy, local treatment of vulvovaginal candidosis may present several advantages when compared with oral therapy. However, physicians are not always aware of the benefits and limitations of both treatment modalities as they frequently prefer oral regimens when prescribing.[4] Moreover, the availability of several over-the-counter (OTC) vaginal products and their wide use increases the responsibility of non-physician healthcare providers to adequately respond to this situation. Therefore, it is important to review several general and practical considerations related to the local treatment of vulvovaginal candidosis in order to optimize its use in clinical practice.

1. Basic Concepts on Vulvovaginal Candidosis

The objective of this article is not to thoroughly review the subject of vulvovaginal candidosis because this has been recently addressed elsewhere by Sobel.[1] However, it is important to highlight several important aspects related to the epidemiology, classification, pathogenesis, clinical manifestations, diagnosis and risk factors implicated in this infection before discussing its local treatment. A brief overview is provided in the following sections.

1.1 Epidemiology

Vulvovaginal candidosis is one of the three most common vaginal infections among women in their fertile years and accounts for 20–30% of all cases.[5] Epidemiological studies indicate that approximately 75% of all women will have at least one episode of vulvovaginal candidosis throughout their lifetime, while 40–50% will experience one or more subsequent episodes. It is also noteworthy that the simple presence of *Candida* spp. in the vulvovaginal area does not necessarily mean infection. Approximately

10–20% of healthy women have vulvovaginal colonization by these yeasts without showing typical symptoms of vulvovaginal candidosis; in some women (e.g. HIV-positive or pregnant women), this rate may be higher.[6,7] Vulvovaginal candidosis is rarely associated with trichomoniasis or bacterial vaginosis, although mixed infections are possible.[8]

The frequency with which several *Candida* spp. are involved in vulvovaginal candidosis is relatively well known. *C. albicans* is the main species responsible and accounts for 80–90% of all infections, followed by *C. glabrata*, *C. tropicalis* and *C. krusei* with 5–10%, 5% and 1%, respectively.[9-11] Uncommonly, other non-*albicans Candida* spp. may also be responsible. However, non-*albicans Candida* spp. are more resistant to conventional antifungal therapies, making them important organisms in the prevalence of vulvovaginal candidosis. In fact, vulvovaginal candidosis caused by non-*albicans Candida* spp. has been increasing in recent years, a fact that may be related to the widespread and inadequate use of antifungal drugs, namely those available as OTC products.[12,13] It is thought that inadequate use of these drugs contributed to the elimination of azole-sensitive *C. albicans*, allowing the development of azole-resistant non-*albicans Candida* spp. However, a contradictory study that analysed the prevalence of non-*albicans Candida* strains among women before and after the introduction of OTC products seem to refute this claim.[14] It has been estimated that only approximately 50% of all cases of vulvovaginal candidosis caused by non-*albicans Candida* spp. respond to conventional oral or local therapy with azoles.

1.2 Classification

Although not a potentially fatal pathology, vulvovaginal candidosis is a common problem and includes all women with positive cultures for *Candida* spp., symptomatic or not.[1] Hence, this broad definition means that vulvovaginal candidosis can be classified according to various criteria, namely episode frequency (sporadic or recurrent), severity (complicated or uncomplicated), symptoms (asymptomatic, mild to moderate, or severely symptomatic) and duration of symptoms (acute or chronic).[8] Uncomplicated vulvovaginal candidosis is characterized by sporadic episodes with light to mild symptoms that are usually caused by *C. albicans*. This situation corresponds to the majority of all vulvovaginal candidosis cases as they are sensitive to almost all therapeutic regimens, including short-course regimens. In contrast, complicated vulvovaginal candidosis commonly refers to recurrent or severe cases that are usually caused by non-*albicans Candida* spp. Although recurrent vulvovaginal candidosis corresponds to approximately 6–8% of all cases in otherwise healthy women, this form of the disease presents as more preoccupant and is characterized by four or more confirmed episodes per year.[8] Recurrence seems to be related to the incomplete eradication of *Candida* spp. after symptomatic relief because of either yeast virulence or host factors (exacerbated immune response may play an important role).[15,16] Nonetheless, other factors may be implicated, namely the possibility of reinoculation from a persistent intestinal source. Vulvovaginal candidosis can also be classified as chronic when symptoms last for ≥6 months and is usually associated with azole-resistant non-*albicans Candida* spp.[17] Lastly, this vaginal infection is not considered a sexually transmitted disease (STD). However, vulvovaginal candidosis is usually considered in this group of infectious diseases, as it is often diagnosed in women being evaluated for a STD.

1.3 Pathogenesis

Although not entirely understood, vaginal immune and non-immune defences in healthy women are important in the pathophysiology of vulvovaginal candidosis. As stated in section 1.2, vulvovaginal colonization by *Candida* spp. does not necessarily mean symptomatic infection.

Indeed, several species are part of the normal vaginal flora but may become pathogens when the vaginal environment undergoes change, such as in the levels of lactobacilli (e.g. as a result of antibacterial therapy). These bacteria are capable of inhibiting the growth of a wide range of pathogens. In the

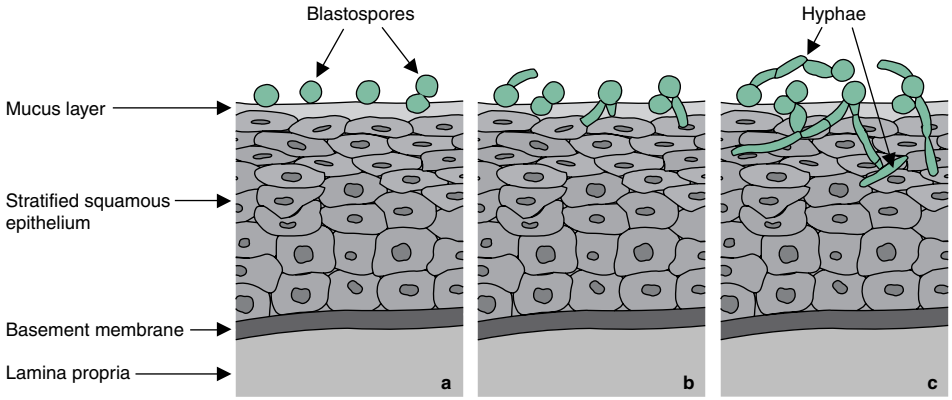

Fig. 1. Schematic drawing of the pathogenic mechanism of vaginal infection by *Candida albicans*. (**a**) Blastospores (budding yeast) are the dissemination and transmission form of *C. albicans*, and are associated with asymptomatic colonization of the vagina; (**b**) dimorphic transition to the filamentous form (hyphae) can be stimulated by various environmental conditions, resulting in increased adhesive properties to epithelial cells and production of lytic enzymes (mainly proteinases); (**c**) these enzymes facilitate epithelial invasion, resulting in vaginal wall damage and inflammation, responsible for symptom occurrence.

case of vulvovaginal candidosis, lactobacilli may prevent the adhesion and/or germination of *Candida* spp., thus providing a natural mechanism of defence against symptomatic infection.[18] However, a straightforward relationship between colonization with lactobacilli and the onset of vulvovaginal candidosis is unclear, as this pathology is also frequently observed in women with normal levels of lactobacilli.[19]

Reproductive hormones (estrogens and progestogens) also play an important role in local immunity as they are responsible for increased susceptibility to infection with *Candida* spp. when their levels are elevated. These hormones decrease both humoral and cellular immune response (and possibly chemotaxis) while augmenting glycogen deposition in epithelial cells. Taken together, these changes may induce growth, adhesion to the vaginal epithelium and germination of *Candida* spp.[15] A major indicator of the importance of these hormones on the pathogenesis of vulvovaginal candidosis is the low incidence of this condition in prepubertal and postmenopausal women as both ages are characterized by low levels of sexual hormones.

The budding form of *C. albicans* is associated with asymptomatic colonization and the need to convert to their filamentous form (germination) to become pathogenic and invade the epithelium (figure 1). This morphological conversion is dependent on multiple factors, namely vaginal pH, and humoral and cellular immune status.[20] Factors that enhance or facilitate germination (e.g. estrogen therapy, pregnancy) tend to precipitate symptomatic vulvovaginal candidosis, whereas others that inhibit this dimorphic change (e.g. bacterial flora) may prevent acute symptoms in women who are asymptomatic carriers. In addition, virulence of *Candida* spp. is related to their capacity for adhesion to epithelial cells, which is a complex process that is not yet fully understood, and their increased proteolytic activity.[21,22]

1.4 Clinical Findings and Diagnosis

Clinical manifestations of vulvovaginal candidosis are often inconclusive and unspecific for this condition, making its recognition intricate and not always readily available (figure 2).[1,23-25] The ability of women to recognize this condition is frequently unreliable, and it is estimated that only about one-third of self-diagnosed cases are indeed confirmed by clinical examination and laboratory testing.[13] This fact is particularly worrying if we consider the increasing number of women who use OTC antifungal products (up to nine of ten) without consulting a physician or other licensed healthcare provider.[26,27] Although important, diagnosis should

not be based solely on a patient's clinical history, pelvic examination and symptomatic assessment, as only microscopic observation (10% potassium hydroxide) or mycological culture can accurately diagnose vulvovaginal candidosis.[28] The Whiff test and pH determination are also useful tools, particularly in office-based practice.[29] Vaginal pH associated with vulvovaginal candidosis is similar to that observed in otherwise healthy women during their fertile years (approximately 3.5–4.5), which contrasts with increased values associated with bacterial vaginosis, trichomoniasis or mixed infections.[5] The main symptom of vulvovaginal candidosis is pruritus, which can be accompanied by burning sensation, pain, dysuria and dyspareunia. These symptoms frequently emerge 1 week before menses and disappear with the onset of menstruation. Vaginal discharge may be present or not, with variable amounts and physicochemical properties (usually without pronounced odour). Possible vulval symptoms also include erythema, oedema and swelling, particularly near the introitus.[1,8] The cervix is usually unaffected, while the vaginal mucosa presents erythema and white plaques, this last feature being typical in women with vulvovaginal candidosis during pregnancy.[28]

1.5 Risk Factors

Several risk factors have been described for vulvovaginal candidosis,[30-41] even if most affected

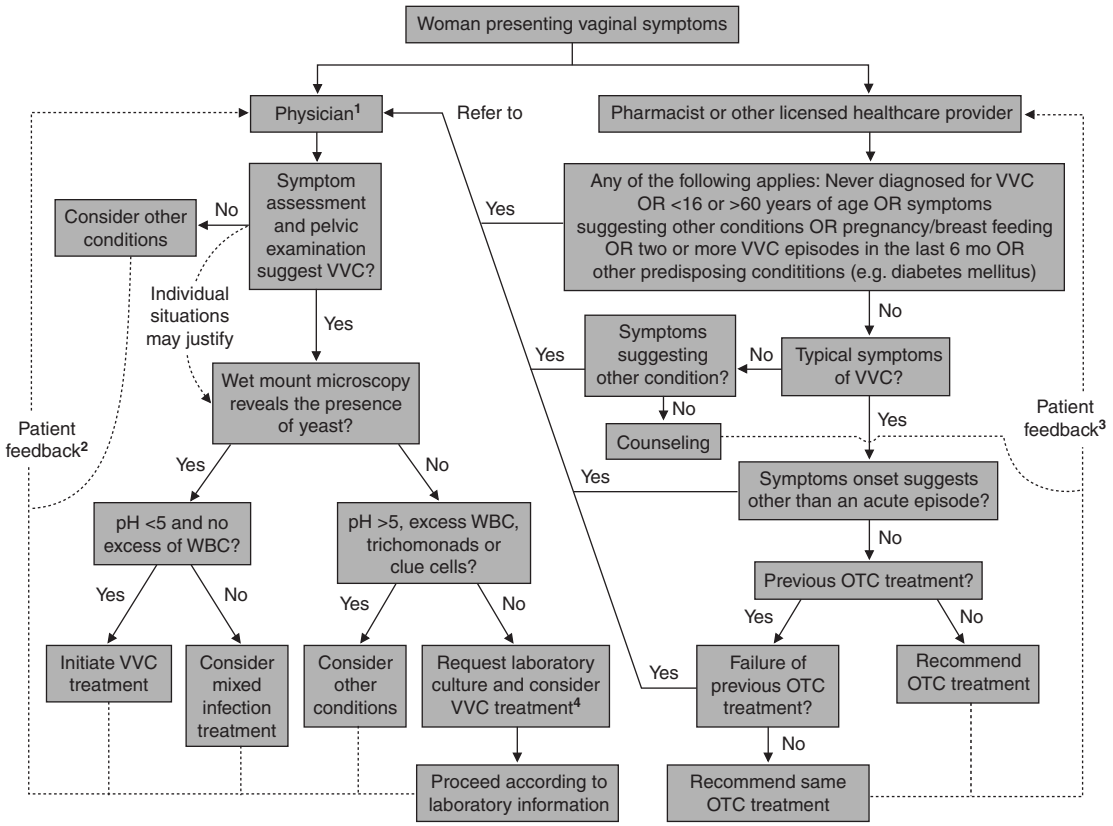

Fig. 2. Combined algorithm for office-based and over-the-counter (OTC) management of women presenting vaginal symptoms allegedly due to vulvovaginal candidosis (VVC).[1,23-25] **1** Complicated cases may require reference to an experienced gynaecologist and/or infectious disease specialist. **2** In cases of treatment failure or short-term relapse consider possible drug-resistant or recurrent VVC, respectively. **3** In cases of treatment failure or relapse refer to physician. **4** Laboratory culture may also be required in other cases (e.g. chronic, recurrent or presumably azole-resistant cases). **WBC** = white blood cells.

women may not present any of these. Table I presents a synopsis of the most important predisposing factors to vulvovaginal infection by *Candida* spp.

2. Treatment of Vulvovaginal Candidosis: General Considerations

General guidelines for the management of vulvovaginal candidosis have been issued by several groups and organizations worldwide.[42-46] The main goal of vulvovaginal candidosis treatment is to achieve rapid and complete relief of signs and symptoms of vulvovaginal inflammation after 48–72 hours, and mycological cure following 4–7 days.[43] Prevention of recurrence is also sought. Main therapeutic regimens include azoles (imidazoles or triazoles), although others can be used. The selection of individual drugs for vulvovaginal candidosis therapy (oral or local) should be based upon their pharmacology and implicated *Candida* spp. susceptibility. In general, the sensitivity of several *Candida* spp. to antifungal drugs is documented,[43] but individual isolates may not always fit this pattern. Thus, laboratory susceptibility tests should be performed whenever empirical therapy does not produce a response.

Table I. Risk factors contributing for vulvovaginal candidosis occurrence[30-41]

Hormonal factors	Increased levels of endogenous estrogens (mainly during pregnancy) Use of exogenous estrogens (oral contraceptives or hormonal replacement therapy) Increased levels of progesterone (?)
Immune factors	Decreased cellular immunity Immunosuppressed patients High predisposition for atopia, allergic and hypersensitivity reactions HIV infection (?)
Antibacterial use	Broad-spectrum antibacterials (systemic or local; mostly during prolonged treatments)
Diabetes mellitus	Particularly in patients with type 1 diabetes or in whom diabetes is not well controlled
Others	Obesity Dietary (?) Debilitating conditions Heat, moisture and occlusive underwear Intrauterine contraceptive device Contraceptive sponges or irritating vaginal products [e.g. containing nonoxynol-9] (?) Corticosteroids (?) Nappy or diaper dermatitis or sexual abuse in children Sexual activity [namely orogenital or high frequency intercourse] (?) Stress factors

(?) = role in the occurrence of vulvovaginal candidosis remains controversial.

2.1 Local versus Oral Therapy

As mentioned in the introduction, efficacy of both oral and local therapy has been shown to be equivalent.[2,3] However, there are several other issues that may favour one therapeutic approach over the other.

Local treatment presents several advantages. Antifungal products administered in the vagina are usually designed to avoid extensive drug absorption, with blood concentrations frequently being negligible. The incidence of adverse effects, particularly due to prolonged systemic exposure to antifungals, may therefore be decreased with local therapy.[47,48] Drug interactions frequently observed during oral administration are uncommon when using topical antifungals, with this fact being an important advantage over oral regimens. Nonetheless, their occurrence should not be ignored since some reports indicate that these interactions might also be observed during local treatment, e.g. between topical azoles and oral anticoagulants.[49,50] Oral azoles are contraindicated or, at least, should be avoided during pregnancy and breast feeding because of safety issues to the fetus or baby, with local therapy usually being recommended.[51,52] For the same reasons, it is also prudent to choose local therapy when treating women who are not using reliable birth control methods or who are planning to become pregnant.

Vaginal administration of antifungals also presents some disadvantages. Women's preferences do not favour local therapy. A review study in the early 1990s found that approximately 50% of women favoured oral antifungal therapy, while only 5% preferred local therapy; the remaining women showed no preferences.[53] A study published in 2001 corroborated these results; among 1348 women, 58% preferred oral treatment, while 36% and 8% favoured vaginal suppositories and vaginal tablets,

respectively.[54] However, these results may be changing towards local therapy as a result of the advances in the formulation of vaginal products and decrease of genitalia related taboos.[55] Antifungals used for local treatment may cause local reactions, namely burning or irritation. Although mild and somewhat occasional, these symptoms may cause women to discontinue treatment or may even be misinterpreted by healthcare providers as being caused by fungal persistence and lead to inadequate continuation of local therapy.

Another relevant aspect when comparing both treatment modalities is their cost. Affordability is, in fact, a critical issue related to treatment compliance and should not be disregarded by clinicians. A rapid analysis of US and UK markets reveals a wide range of prices among oral and local treatment options; this variability is observed between different drugs, dosage regimens or even formulations (see table II for prices of local therapy regimens). A typical example of an oral regimen is that of fluconazole (150 mg, single dose), which costs approximately $US26 or £12.50 (2008 costings). Also, patients' healthcare plan financing and worldwide price variability may substantially influence treatment affordability. Hence, general comparison between oral and local regimen costs and specific recommendations on the subject are hard to perform. The golden rule should always be 'the best treatment at the best price'.

3. Local Treatment of Vulvovaginal Candidosis

3.1 General Considerations

Several local drug regimens have been recommended and used in clinical practice (table II).[42-46] Azoles are recommended as first-line treatment unless a confirmed or suspected azole-resistant *Candida* strain is involved. Other situations may also contraindicate azole therapy (e.g. hypersensitivity to these agents) in which nystatin or boric acid should be used. Uncomplicated vulvovaginal candidosis usually responds quite rapidly to any empirical short-course local regimen (up to 3 days of treatment), with symptomatic and mycological cure being achieved in approximately 80–90% of patients who have completed the treatment. Prolonged therapy (>7 days) is necessary for complicated or non-*albicans Candida* infections; after a symptomatic cure, a maintenance regimen may be initiated and prolonged for 6 months (oral regimens) or intermittently (local therapy).[42,43] Some experts recommend clotrimazole 200 mg twice weekly, clotrimazole 500 mg once weekly, nystatin 100 000 units every other day or boric acid 600 mg every other day (then twice weekly) as examples of local intermittent therapy.[59] Even if considered effective, maintenance therapy does not guarantee a cure, with 30–50% or 50–70% of women experiencing relapses in the following month or following 2 months after treatment cessation, respectively.[48] This can be explained by the fungistatic action of the drugs that are used and immunopathogenesis of the disease. In these patients with relapsing infections, subsequent maintenance therapy regimens may be considered. It is also important to further consider relevant factors related to the patient (e.g. identification and control of risk factors, tolerability to the antifungal regimen), disease-causing *Candida* spp. (particularly antifungal drug resistance), drug and drug formulation (e.g. safety profile).

Special populations may have specific requirements. In pregnant women, it is advisable to duplicate the treatment period. In this particular group, miconazole, clotrimazole, butoconazole and terconazole are generally considered the most effective drugs.[46] Alongside oral antifungals, several other drugs have been considered unsafe during pregnancy (either locally or systemically), namely flucytosine and potassium iodide.[60] Boric acid use also seems contraindicated in pregnant women.[61] HIV-positive women are usually treated for vulvovaginal candidosis in the same way as HIV-negative women, although their vaginal colonization rates with *Candida* spp. are usually higher.[42] Postmenopausal women should also be treated as younger fertile women, although several age-related aspects should be taken into consideration (e.g. higher incidence of type 2 diabetes mellitus, higher

Table II. Some drug regimens recommended for the local treatment of vulvovaginal candidosis[42-46]

Drugs	Dosage regimens	Commercially available formulations[a]	Cost[b]
Butoconazole	100 mg, single dose	2% cream[c]	$US60–65.70
	100 mg × 3 d	2% cream[d]	NA
Clotrimazole	500 mg, single dose	Vaginal suppository[e], 10% cream[e]	£4.50–7.50, £5.13
	100 mg, bid × 3 d	1% cream[d,e], vaginal tablet, vaginal suppository[e]	$US9.60–14.25, $US19.20, NA
	200 mg × 3 d	Vaginal suppository	£3.63
	100 mg × 7 d	1% cream[d,e], vaginal tablet, vaginal suppository[e]	$US8.20–9.95, $US19.20, NA
	50 mg × 7–14 d	1% cream[d,e]	$US8.20 (7 d)
Econazole	150 mg, single dose	Vaginal suppository[c]	£3.10–4.35
	150 mg × 3 d	Vaginal suppository	£2.95–3.35
Fenticonazole	600 mg, single dose	Vaginal suppository	NA
	200 mg × 3 d	Vaginal suppository	NA
Isoconazole	600 mg, single dose	Vaginal tablet	NA
Miconazole	1.2 g, single dose	Vaginal suppository[c,d]	$US17–20.65/£3.12
	200 mg × 3 d	4% cream, vaginal suppository[d]	$US13–16.70, $US14-19
	100 mg × 7–14 d	2% cream[d], vaginal suppository[d]	$US9.95–15.40 (7 d), NA
Tioconazole	325 mg, single dose	6.5% ointment[d]	$US14.90–17.55
Terconazole	40 mg × 3 d	0.8% cream	$US52–57.20
	80 mg × 3 d	Vaginal suppository	$US52–57.20
	20 mg × 7 d	0.4% cream	$US52–57.20
Nystatin	100 000 units × 14 d	Vaginal tablet, cream, vaginal suppository	$US57.40–60.85, $US11/£2.58, NA
Boric acid	600 mg × 7–14 d	Vaginal gelatin capsules[f]	$US5.60–14 (7 d)[g]

a Availability is country dependent.

b Price or price ranges (depending on brand or product particularities) are per treatment course and merely orientative; from Drugstore.com[56] for US available products ($US), and British National Formulary 55[57] and Clinical Knowledge Summaries[58] for UK available products (£) [2008 costings].

c Prolonged-release formulation.

d Available over the counter in the US.

e Available over the counter in the UK.

f Prepared by compounding pharmacies.

g Price range obtained from three compounding pharmacies.

bid = twice daily; **NA** = not available.

drug usage and vaginal dryness).[62] The treatment of male sexual partners is usually not considered, except in women with recurrent vulvovaginal candidosis or when partners present with genital symptoms.[42] In this situation, topical application of nystatin or clotrimazole, lotion or cream, twice daily for 7 days may be useful.[46]

Alongside antifungal therapy, several other local therapeutic approaches may be helpful, namely in the relief of vulval dermatitis or intense pruritus. These measures may include the utilization of corticosteroids (e.g. 1% hydrocortisone ointment) and applying cold compresses on the affected areas.[63] Corticosteroids should only be considered in severe cases and used with caution as rebound effects may be observed. Use of non-irritating moisturizers, implementation of adequate hygiene practices and avoidance of soap-containing cleansers are equally important in the prevention and exacerbation of these symptoms.

3.2 Antifungal Drugs for Local Treatment

A considerable number of antifungal agents for the local treatment of vulvovaginal candidosis are currently available. However, a thorough discussion of in-depth pharmacological, chemical or pharmaceutical aspects for each drug is beyond the scope of this review. Interested readers are referred to more extensive and specialized review literature;[64] a general overview of antifungal drugs used in the local treatment of vulvovaginal candidosis is presented in table III.[65-79]

3.3 Other Potential Local Therapeutic Options

Although current vulvovaginal candidosis drug therapy provides high efficacy and safety, the recent emergence of complicated infections and drug resistance has led to the development and research of new oral and local therapeutic options. Alongside existing antifungal agents, innovative and improved drugs are reaching the market such as second-generation azoles (e.g. voriconazole, posaconazole) and echinocandins (e.g. caspofungin, micafungin). Although their use is still reserved for severe systemic

Table III. General overview of antifungal drugs used in the local treatment of vulvovaginal candidosis (VVC)[65-79]

Drug	Advantages	Limitations	Comments
Azoles	Relative broad spectrum Convenient dose regimens Limited toxicity	Relevant drug-drug interactions and adverse effects may occur Emergence of azole-resistant strains	Mostly imidazoles (see table II for examples) Preferential drugs for the treatment of VVC
Boric acid	Effective in acute, recurrent and chronic azole-resistant non-*albicans Candida* spp. infections Local adverse effects are uncommon	Unable to prevent relapse in recurrent VVC	Needs to be prepared by compounding pharmacies
Polyenes	Effective in azole-resistant non-*albicans Candida* spp. infections	Considered less effective than azoles Mucocutaneous reactions may occur	Mostly nystatin (see table II) Other examples include amphotericin B and natamycin
Flucytosine	Effective in azole-resistant non-*albicans Candida* spp. infections Local adverse effects are uncommon	Prolonged use is discouraged because of risk of systemic toxicity	Association with amphotericin B may be helpful in azole-resistant non-*albicans Candida* spp.
Ciclopirox	As effective and safe as azoles	Local adverse effects	Used in some countries outside the US and the UK
Antiseptics	May be helpful in azole-resistant acute infections	Local adverse effects	Examples include chlorhexidine, gentian violet, octenidine, dequalinium chloride, phenoxyethanol and povidone iodide (used alone or in association)

conditions, these drugs may find in the future a place in the therapy of complicated vulvovaginal candidosis. The use of drugs with different mechanisms of action may also be an interesting strategy. *In vitro* and animal data show synergistic effects between commonly used azoles and other substances showing antifungal activity.[80] In addition, limited clinical case reports using flucytosine and amphotericin B seem to point in this direction.[75] However, further studies are required to test the possibility of synergistic drug use.

Probiotic local therapy with products containing lactobacilli has been proposed as an alternative option for the prevention of vulvovaginal candidosis, particularly for recurrent cases. A relatively common practice recommended by some gynaecologists has been the administration of yogurt containing lactobacilli into the vagina. Nevertheless, available clinical data fail to clearly demonstrate the beneficial outcome of this strategy.[81,82] Immunotherapy is also being investigated, particularly in the field of vaccine, antibody and cytokine development.[83,84] The purpose of this strategy is to induce or regulate the local immune response against infection by *Candida* spp., either by passive or active immunization. Findings from a recent review of preclinical data seems to support that the vaginal administration of diverse immunomodulatory compounds (e.g. antibodies) can kill *Candida* spp. or inhibit its germination and epithelial adhesion, thus reducing symptomatic infection; reduction of inflammatory humoral and cellular response associated with vulvovaginal candidosis also seems to be possible.[85] Although immunotherapy is considered very promising, several important issues related to the correlation between disease, success and protection of this therapeutic approach still have to be resolved before translation to clinical practice is possible. Natural products have also shown antifungal activity *in vitro* against *Candida* spp., with their use being a potential option for the treatment of vulvovaginal candidosis in the future.[86] For example, *Thymus* spp. essential oil (thyme oil),[87] a commonly used food spice, and *Melaleuca alternifolia* essential oil (tea tree oil)[88] demonstrated high antifungal activity *in vitro* against *Candida* spp. commonly involved in vulvovaginal candidosis. An interesting feature of these natural products is their similar activity against both azole-sensitive and -resistant *Candida* spp.

4. Selection of Topical Antifungal Drug Formulations

4.1 General Considerations

As well as choosing an effective drug, an adequate antifungal product must be selected or even sometimes compounded in order to fulfil a treatment regimen. This task should not be neglected as inadequate vaginal drug delivery systems may lead to poor clinical outcomes. Features related to the anatomy, histology and physiology of the vulva and vagina (figure 3) should be taken into account when choosing a topical antifungal formulation for local treatment of vulvovaginal candidosis.[89,90] Also, it is occasionally necessary to compound antifungal formulations in pharmacies when products are not commercially available (e.g. boric acid capsules, amphotericin B vaginal suppositories). Whenever possible, these compounded formulations should be fully characterized and optimized for their biopharmaceutical and pharmacotechnological features, as vehicles are recognized to dramatically influence the release, *in loco* residence, and rate and extent of drug penetration into the mucosa. This last feature is particularly important, as inadequate mucosal penetration of antifungal drugs may lead to toxicity (with excessive penetration) or poor cure rates (with poor penetration). Although antifungal products are administered topically, their action is not merely on the mucosal surface or vaginal lumen; these agents need to penetrate deep into the epithelium to reach invasive *Candida* hyphae (figure 1) and exert a local antifungal action there. Moreover, other important issues should not be disregarded such as women's preferences, their ability to fully comply with the treatment (e.g. correct use of vaginal applicators) and treatment affordability.

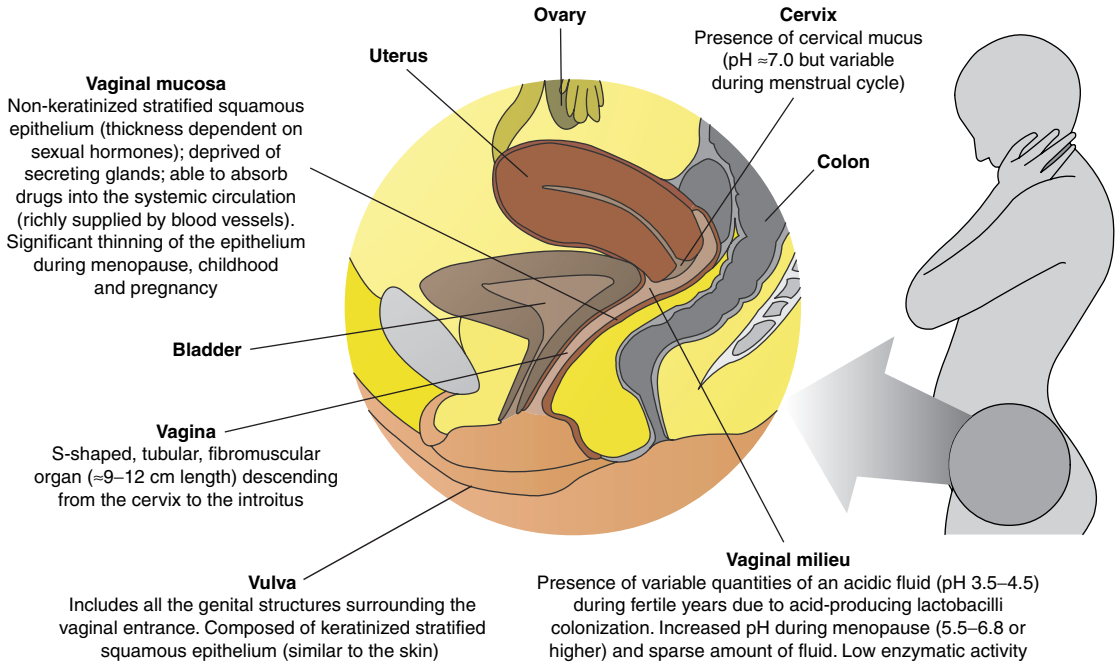

Fig. 3. Some of the most important features of the anatomy, histology and physiology of the vulva and vagina related to the administration of antifungal drugs.

4.2 Conventional and Novel Antifungal Formulations

Current antifungal products are mostly formulated as ointments, creams or vaginal suppositories, capsules and tablets. However, these products do not reliably control the release of active drugs, with the release and presence in the vagina of the drug frequently depending on the properties of the drug. This results in longer treatment regimens and exposure to higher amounts of the active drug, which can lead to increased toxicity. Another negative aspect of these traditional formulations is associated with the leakage and messiness of products; in order to alleviate these problems, women are usually recommended to administer antifungal products at bedtime. Taken together, most available products can lead to poor compliance and, ultimately, poor clinical outcomes.[91]

Efforts have been made in the past few years to optimize the retention of antifungal products in the vagina and allow prolonged action of active drugs. The main strategies used to achieve these goals include mucoadhesive and controlled-release formulations. Some products have already reached the market and offer new and valuable options for shorter and highly acceptable therapeutic regimens. An example is the Site Release® [1] (SR) vaginal delivery system, which is based on a water-in-oil cream comprising a highly concentrated, drug-loaded internal phase.[91] This technology is characterized by high mucoadhesiveness (improves product residence in the vagina by adhering to the mucosa for up to 6 days) and the possibility of prolonged release of active drugs (reduces the number of administrations and total amount of drug exposure). Prolonged release is achieved by controlling drug diffusion through the outer hydrophobic phase.[92] A product based on SR technology, Gynazole-1® (2% butoconazole) is available in the US as a single-dose treatment for vulvovaginal candidosis. Results from

1 The use of trade names is for product identification only and does not imply any kind of endorsement.

clinical trials demonstrated that treatment with SR cream is as safe and effective as 7-day treatment with conventional 2% miconazole cream or oral fluconazole, with the advantage of allowing faster relief of symptoms.[93,94] Clinical data also suggest that SR technology may be used for the vaginal administration of other antifungal agents (e.g. flutrimazole).[95] Another currently commercially available prolonged-release product in the US is Monistat-1® (1.2 g miconazole); in the UK it is commercialized as Gyno-Daktarin® 1200 mg vaginal capsule. This ovule-shaped insert is comprised of miconazole suspended in an ointment base (mineral oil, white petrolatum and lecithin), which is covered by a soft gelatin hydrogel layer that controls drug release. Single-dose Monistat-1® was shown to be as effective as 7-day treatment with conventional 2% miconazole cream and achieved symptom relief faster.[96] Moreover, it demonstrated the convenient feature of equal efficacy either with daytime or bedtime use.[97] The same product is available in combination with a 2% miconazole cream to be applied in the vulva for symptomatic relief (Monistat-1® Combination Pack). Similar single-dose, prolonged-release vaginal products are also available worldwide that contain econazole 150 mg (Ecostatin-1® E.R. and Gyno-Pevaryl® LP) or sertaconazole 300 mg (Monazol®), and have been shown to be effective and well tolerated in vulvovaginal candidosis.[98]

4.3 Potential and Investigational Antifungal Delivery Systems

Recent investigations in drug delivery have opened the way for some new and interesting approaches for the vaginal administration of antifungals. Key objectives remain the same: to improve *in loco* residence and achieve prolonged drug release. The development of user-acceptable products is also desirable. For example, drugs for *Candida* infections may benefit from innovative drug dose forms, such as mucoadhesive gels, foams or vaginal rings.[89] These dosage forms, which are already commercially available for the management of other conditions, may be particularly advantageous when prolonged drug release is valuable (e.g. maintenance therapy for recurrent vulvovaginal candidosis). Other interesting drug delivery approaches have also been proposed. Chang et al.[99] and Bilensoy et al.[100] designed thermosensitive formulations that are able to release clotrimazole in a controlled fashion. Besides allowing longer administration intervals than conventional products, the fact that these formulations are liquids at room temperature and mucoadhesive semisolid gels at body temperature facilitates their administration while guaranteeing good retention in the vagina.

Nanocarriers, such as liposomes,[101] proliposomes[102] or niosomes,[103] may also play a future role in the treatment of vulvovaginal candidosis. These spherical vesicles have been shown to effectively deliver antifungals (e.g. clotrimazole) deeply into the vaginal epithelium and provide prolonged drug release without being submitted to the natural vaginal cleansing mechanism responsible for leakage of conventional products.

4.4 Safety Issues

Safety concerns with antifungal products are not exclusively related to the toxic effects of active drugs. Excipients commonly present in antifungal products administered in the vulvovaginal area may be responsible for adverse effects, particularly local ones. For example, local irritation or allergic reaction has been attributed to propylene glycol,[104] polysorbates[105] and benzyl alcohol.[106] Thus, it is important to assess the patient's hypersensitivity history to the ingredients of antifungal formulations. Conversely, some excipients (acidic polymers or moisturizers) may contribute to the re-establishment of a healthy vaginal milieu.[107,108] Women should also be informed that the use of vaginal antifungal products may damage condoms or other vaginal contraceptive devices (e.g. diaphragms); when applicable, a 3-day break is usually recommended before using condoms or contraceptive devices. In all cases, information about individual products should be checked before prescribing and/or dispensing.

5. Conclusions

In addition to equivalent efficacy, local treatment of vulvovaginal candidosis presents several advantageous features when compared with oral therapy. These include a low rate of adverse events (particularly systemic ones), safe utilization during pregnancy and breast feeding, and the availability of several efficacious agents against azole-resistant *Candida* spp. However, the wide variety of antifungal drugs, regimens and products that is currently available for the local treatment of vulvovaginal candidosis requires an adequate choice of therapeutic approach that is based on a systematic assessment of diverse aspects related to the women, and *Candida* spp. responsible for episode. Azoles and short-course regimens are used as first-line treatment, with nystatin and boric acid usually considered as alternative agents. However, particular situations may benefit from other drugs and regimens when previous therapy has failed. Choosing a convenient antifungal drug formulation should not be neglected as they can facilitate or complicate the clinical outcome; recent advances in vaginal drug delivery have brought interesting and convenient options for the local treatment of vulvovaginal candidosis. Additionally, non-physician healthcare providers must be made aware of the main features of vulvovaginal candidosis in order to correctly counsel women about OTC antifungal products, or effectively identify those patients who require a physician's attention.

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