

Vulvovaginal candidosis

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Despite therapeutic advances, vulvovaginal candidosis remains a common problem worldwide, affecting all strata of society. Understanding of anti-candida host defence mechanisms in the vagina has developed slowly and, despite a growing list of recognised risk factors, a fundamental grasp of pathogenic mechanisms continues to elude us. The absence of rapid, simple, and inexpensive diagnostic tests continues to result in both overdiagnosis and underdiagnosis of vulvovaginal candidosis. I review the epidemiology and pathogenesis of this infection, and also discuss management strategies.

Epidemiology

Information on the incidence of vulvovaginal candidosis is incomplete, since the disease is not a reportable entity and data collection is hampered by inaccuracies of diagnosis and the use of non-representative study populations. The infection—caused by *Candida* spp—affects 70–75% of women at least once during their lives, most frequently young women of childbearing age. 40–50% of women will experience a recurrence.¹ 5–8% of adult women have recurrent vulvovaginal candidosis, defined as four or more episodes every year.² In one study,³ almost 30% of the women with symptoms of vulvovaginitis had yeast isolated, confirming the diagnosis of vulvovaginal candidosis. Other authors indicate that vulvovaginal candidosis is responsible for 15–30% of vulvovaginal symptoms.^{4,5} Unfortunately, the availability of over-the-counter antimycotics will further limit the ability to measure asymptomatic candida carriage and vulvovaginal candidosis. Point-prevalence studies indicate that *Candida* spp can be isolated from the vagina of about 20% (range 10–80%) of asymptomatic healthy women.^{6–8} Higher cumulative incidence of candida colonisation is reported.⁹

Diagnosis and treatment of vulvovaginal candidosis, together with lost productivity, result in an estimated cost of US\$1 billion per year in the USA,¹⁰ where vulvovaginal candidosis is the second most common cause of vaginal infections, after bacterial vaginosis.^{11,12} The number of prescriptions written to treat yeast infections between 1980 and 1990 indicate that the incidence of vulvovaginal candidosis almost doubled during that time; about 13 million prescriptions were written in 1990.

Microbiology

Between 85% and 95% of yeast strains isolated from the vagina belong to the species *Candida albicans*.^{8,12–14} The remainder are non-albicans *Candida* spp, the most common of which is *Candida glabrata*. In many parts of the world, non-albicans isolates—notably *C glabrata*—affect 10–20% of women.^{15–17} Vaginitis is infrequently caused by *Candida parapsilosis*, *Candida tropicalis*, and *Candida krusei*, although most species of candida have been associated with the condition.^{18,19} Vaginitis induced by non-albicans species is clinically indistinguishable from that caused by *C albicans*; moreover, such species are often more resistant to

treatment.^{8,12,20–22} Non-albicans *Candida* spp—especially *C glabrata*—often cause recurrent vulvovaginal candidosis.

The incidence of vulvovaginal candidosis caused by non-albicans strains is thought to be increasing²³ because of single-dose treatment, low-dosage azole maintenance regimens, and the use of over-the-counter antimycotics. However, several multicentre studies in the USA failed to confirm any increase in the prevalence of vulvovaginal candidosis caused by such species.^{24,25}

Typing of vaginal *C albicans* isolates failed to identify strains with tropism for the vagina.²⁶ Similarly, there was no evidence of vaginopathic strains that showed enhanced virulence, which could have explained why some women remain entirely asymptomatic despite being heavily colonised with *Candida* spp.²⁷ However, the notion of yeast vaginopathogenicity is not without merit and could be the result of switching phenotypic and virulence properties after gene activation.²⁸ Yeast genetic adaptation could facilitate persistence and survival in the vagina.

Yeast blastospores (blastoconidia) represent the phenotypic form responsible for vaginal transmission and asymptomatic colonisation of the vagina. Germinated yeast, which have produced mycelia (hyphae), are found most commonly in symptomatic vaginitis.

Candida virulence factors

Colonisation of the vagina requires yeast adherence to vaginal epithelial cells. *C albicans* adheres in significantly higher numbers to such cells than do non-albicans species.²⁹ All *C albicans* strains seem to adhere equally well to both exfoliated vaginal and buccal epithelial cells.³⁰ By contrast, there is considerable person-to-person variation in in-vitro vaginal epithelial cell receptivity to

Lancet 2007; 369: 1961–71

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Search strategy and selection criteria

Databases including PubMed (Medline), Current Contents, and the Cochrane Library were searched with the terms “candida vaginitis”, “fungal vaginitis”, “vulvovaginal candidiasis”, “vaginal candidiasis” and crossed with “epidemiology”, “pathogenesis”, “diagnosis”, and “therapy”. References were largely selected from the past 5 years; older references from my personal files were used for historical perspective or relevance. There were no language restrictions.

	Mechanism	Comments
Innate		
Vaginal epithelial cells	Inhibit candida growth in vitro, cell contact required. ⁴⁵⁻⁴⁷ No endocytosis.	Protective role in vivo unknown. Decreased anti-candida activity in women with recurrent vulvovaginal candidosis. ⁴⁶
Mannose-binding lectin	Epithelial-cell associated. Binds to candida surface mannan. ^{48,49} Activates complement. Inhibits candida growth.	Genetically determined. Might provide individual host susceptibility to vaginal colonisation and vulvovaginal candidosis. ⁵⁰
Activated lactoferrin	Fungistatic and fungicidal activity. ⁵¹	Natural peptides in cervico-vaginal secretions (role unproven).
Vaginal bacterial flora	<i>Lactobacillus</i> spp favoured. Competition for nutrients. Bacteriocins and hydrogen peroxide inhibits yeast growth/germination. ^{52,53}	Protective role controversial. ⁵⁴
Phagocytic systems/polymononuclear leucocytes, mononuclear cells, complement	Phagocytosis and intracellular killing decreases fungal load and prevents mucosal invasion. ^{55,56} Mainly found in lamina propria in experimental vaginitis. ^{47,52} Nitric oxide has anti-candida activity.	Protective role controversial. Polymorphonuclear cells not prominent in vaginal secretions. ⁵⁷
Adaptive		
Humoral-immunoglobulin (S-IgA, IgM, IgG)	Following vulvovaginal candidosis systemic immune response (IgM, IgG, and local IgA). ⁵⁷ Experimental candida vaginitis some but not all investigators show protective role by active and passive local immunisation. ⁵⁸⁻⁶¹	Protective role not proven. Women with recurrent vulvovaginal candidosis have high titres of vaginal anti-candida IgG, IgA. ^{62,63} Anti-candida IgE could contribute to symptoms. ⁶⁴
Cell-mediated immunity T-cell response	Compartmentalisation of vaginal cell-mediated response from systemic cell-mediated immunity. ⁶⁵ Experimental studies: minimal role of systemic cell-mediated immunity but protection induced with local immunisation. Hypothesis: protective role of Th1 cytokine profile and Th2 profile contributes to recurrent vulvovaginal candidosis. ⁶⁵	Role is extremely controversial. Failure to detect Th2 cytokines in women with recurrent vulvovaginal candidosis. ⁶⁶ Interleukin 4 (Th2) inhibits anti-candida activity of nitric oxide and protective pro-inflammatory Th1 cytokines. ^{50,67}

Table 1: Vaginal defence mechanisms against *Candida* spp

candida organisms in adherence assays.³⁰ However, no increased receptivity has been reported in women with recurrent infections.³¹ Yeast surface mannoprotein serves as adhesins.

Germination of candida cells enhances colonisation and facilitates tissue invasion.^{32,33} By use of a mutant strain of *C albicans* that failed to germinate at 37°C, my colleagues and I have shown that non-germinating mutants are incapable of inducing experimental vulvovaginal candidosis in vivo.³² Factors that enhance or facilitate germination promote symptomatic vaginitis, whereas inhibition of germination could prevent vaginitis in asymptomatic yeast carriers.

Virulence is enhanced by proteolytic enzymes, toxins, and phospholipase elaborated by yeast. Secreted aspartyl proteinases elaborated by pathogenic *Candida* spp have been identified in vaginal secretions in women with symptomatic vaginitis but not in those with asymptomatic colonisation.^{33,34} These proteolytic enzymes, with broad substrate specificity, destroy free and cell-bound proteins that impair fungal colonisation and invasion. Several genes that govern proteinase production (SAP1, SAP2, and SAP3) have been cloned, and a strong correlation exists both in vitro and in experimental vaginitis between gene expression, aspartyl proteinase secretion, and the ability to cause disease.³⁵⁻³⁷ Mycotoxin—including a gliotoxin identified in the vagina—could act to inhibit phagocytic activity or suppress the local immune system.³⁸ Iron binding by candida organisms has also been reported to facilitate yeast virulence.³⁹

High-frequency heritable switching occurs in colony morphology of most *Candida* spp grown on aminoacid-rich agar at 24°C.⁴⁰ The variant phenotypes show a varying capacity to form mycelia spontaneously and express other virulence factors, including drug

resistance and adherence. There is insufficient evidence that phenotypic switching occurs in vivo at 37°C; however, this is an attractive hypothesis to explain spontaneous in-vivo transformation from asymptomatic colonisation to symptomatic vaginitis. Fresh clinical vaginal isolates obtained during acute vaginitis have been found to be in a high-frequency mode of switching. These multiple phenotypes are derived from the same or related genetic strains.^{28,41,42} In one patient with recurrent vulvovaginal candidosis, Soll and colleagues²⁸ observed colony phenotype switch with each recurrence of infection, even though DNA genotyping remained identical. Schroppel and co-workers⁴³ showed that a certain degree of yeast genetic instability exists long term and is associated with repeated courses of antifungal treatment.⁴³

Pathogenesis

Candida organisms gain access to the vaginal lumen and secretions mainly from the adjacent perianal area.⁴⁴ Effective anti-candida defence mechanisms in the vagina allow long-term persistence of candida organisms as vaginal commensals in an avirulent phase (table 1).

Most, if not all women carry candida in the vagina at some point in their lives, yet without symptoms or signs of vaginitis and usually with a low concentration of yeast organisms.⁹ *Candida* can be either a commensal organism or a pathogen in the vagina, and dogma dictates that changes in the host vaginal environment are necessary before the organism induces pathological effects.

Predisposing factors

Although vulvovaginal candidosis is monomicrobial, causation is multifactorial. Recurrent vulvovaginal candidosis can be idiopathic or caused by several different

mechanisms (figure 1). Factors that predispose to vaginal colonisation can differ from those that facilitate transformation from asymptomatic colonisation to symptomatic vaginitis.

Genetic

Anecdotal reports of familial susceptibility to vulvovaginal candidosis and studies that indicate increased prevalence of vulvovaginal candidosis in African-American women⁶⁸ and people with blood group ABO-Lewis non-secretor phenotype all suggest that there could be genetic factors that predispose individuals to colonisation or vaginitis.⁶⁹ Recently, in-vivo polymorphism studies involving mannose-binding lectin and experimental vaginitis in inbred and outbred mice further suggest that some individuals could have a genetic susceptibility to candida colonisation or vaginitis.^{50,70}

Pregnancy

A higher prevalence of vaginal colonisation and symptomatic vaginitis is more often seen in pregnant women than in those who are not pregnant;^{71,72} recurrences are more common and therapeutic response is reduced compared with women who are not pregnant.⁵³ High concentrations of reproductive hormones—which increase the glycogen content in the vaginal tissue—provide a carbon source for candida organisms.^{73,74} Oestrogen also enhances adherence of yeast to vaginal epithelial cells. A cytosol receptor or binding system for female reproductive hormones has been documented in *C albicans*, resulting in enhanced mycelial formation.⁷⁵

Contraceptives

Many small, poorly controlled studies of the effect of contraceptives on predisposition to vulvovaginal candidosis have produced conflicting data. Some studies indicate increased vaginal colonisation with candida after the use of oral contraceptives with high oestrogen content.^{8,76-78} Contradictory results from studies of women using low-oestrogen oral contraceptives have been reported.^{8,79} Nevertheless, most investigators believe that oral contraceptives predispose women to recurrent vulvovaginal candidosis. Increased carriage of yeast is reported in users of intrauterine contraceptive devices, contraceptive sponges, diaphragms, and condoms, with or without spermicides.^{79,80} However, an extensive study in college students did not show an increase in the risk of symptomatic vulvovaginal candidosis in users of oral contraceptives, diaphragms, condoms, or spermicides.⁷⁷

Diabetes mellitus

Vaginal colonisation with candida is more frequent in diabetic women than in non-diabetics. Women with type 2 diabetes are more prone to colonisation with *C glabrata*.^{81,82} Although uncontrolled diabetes predisposes to symptomatic vaginitis, the prevalence of vulvovaginal

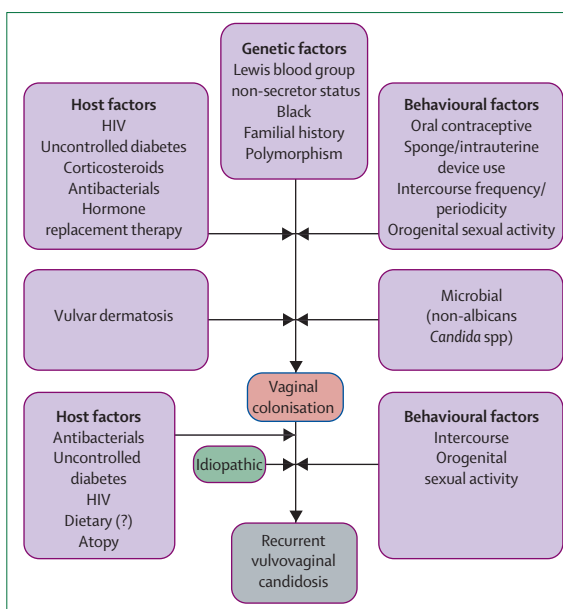


Figure 1: Risk factors for recurrent vulvovaginal candidosis

candidosis is not increased in individuals with well-controlled diabetes.⁸³ Although a glucose tolerance test is often recommended in women with recurrent vulvovaginal candidosis, the likelihood of finding an abnormal glucose tolerance test is extremely low, and testing is not justified in premenopausal women. Occasionally, non-diabetic women with recurrent vulvovaginal candidosis describe an association between binges of sugary confectionery and exacerbation of symptomatic vulvovaginal candidosis. Donders and colleagues⁸⁴ did glucose tolerance tests on women with recurrent vulvovaginal candidosis. Although there was no increased frequency of abnormal test results compatible with diabetes or prediabetes, and plasma glucose concentrations were within the normal range, such concentrations were still substantially higher than in control individuals, suggesting that a diet high in refined sugars could contribute to the risk of vulvovaginal candidosis.⁸⁴

Antibiotics

Symptomatic vulvovaginal candidosis frequently follows use of vaginal or systemic antibiotics.^{85,86} All antimicrobials seem to exert this effect. Estimates of how frequently vulvovaginal candidosis follows antibiotic use range from 28% to 33%;^{87,88} vaginal colonisation rates increase from about 10% to 30%.⁸⁹ Antibiotics are thought to predispose women to vulvovaginal candidosis by eliminating the protective bacterial flora, thus allowing candida overgrowth in the gastrointestinal tract, vagina, or both.⁹⁰ In particular, *Lactobacillus* spp could provide colonisation resistance and prevent germination, maintaining low numbers of yeast. Auger and Joly⁵² found low numbers of lactobacilli in vaginal cultures

obtained from women with symptomatic vulvovaginal candidosis. Lactobacilli and yeast cells can interact in several ways, including competition for nutrients, stearic interference with candida adherence, and elaboration of hydrogen peroxide and inhibitory bacteriocins by lactobacilli. Studying adult mice, Pultz and colleagues⁹⁰ reported that antibiotics that inhibit intestinal anaerobes promote *C glabrata* gut colonisation.

Some studies have failed to show a link between the occurrence of vulvovaginal candidosis and antibiotic treatment.⁹¹ Most women who receive antibiotics do not develop symptomatic vulvovaginal candidosis; moreover, most women with acute vulvovaginal candidosis have not been recent recipients of antibiotics. Only those women who are already colonised with candida are at risk of vaginitis following antimicrobial treatment.⁹²

Behavioural factors

The role of sexual behaviour in causing symptomatic, often recurrent, vulvovaginal candidosis has been underestimated.^{8,68,79} Although women who are not sexually active often develop vulvovaginal candidosis, the incidence of the disease increases dramatically in the second decade of life, corresponding with the onset of sexual activity.² Occurrence peaks in the third decade of life, declining in women older than 40 years, until the permissive effect of oestrogen replacement therapy becomes apparent. Sexual transmission of candida organisms can occur during vaginal intercourse.⁷⁸ There is some evidence to suggest that the frequency/periodicity of sexual intercourse is associated with acute vaginitis.^{78,79} In terms of sexual practices, receptive orogenital sexual intercourse consistently emerges as a risk factor.^{93,94}

In spite of anecdotal evidence, there is no evidence to suggest that female hygiene habits are risk factors for vulvovaginal candidosis.⁷⁷ The use of well-ventilated clothing and cotton underwear could be of value in preventing infection. However, no increased risk for vulvovaginal candidosis has been found among wearers of tight clothing or non-cotton underwear.⁷⁷

Other factors

There is no evidence to suggest that iron deficiency predisposes an individual to infection. Chemical contact, atopy, local allergy, or hypersensitivity reactions could alter the vaginal milieu and facilitate transformation from asymptomatic colonisation to symptomatic vaginitis.⁹⁵

Source of infection

Intestinal reservoir

Although the gut could well be the initial source of vaginal colonisation by candida organisms, there is some controversy with regard to the role of the intestinal tract as a source of reinfection in women with recurrent vulvovaginal candidosis. Candida isolated from rectal cultures of women with recurrent vulvovaginal

candidosis were found to be identical to candida isolated from vaginal cultures,⁹⁶ suggesting that there is a persistent intestinal reservoir of yeast. Re-inoculation of the vagina might occur from the persistent rectal focus following apparent eradication of vaginal yeast by topical treatments. However, other studies have found much lower concordance between rectal and vaginal cultures in patients with recurrent vulvovaginal candidosis. The high rate of anorectal cultures in some studies could be indicative of perianal contamination from the vaginal discharge. Controlled studies with oral nystatin, which reduces intestinal yeast carriage, failed to prevent symptomatic recurrence of vulvovaginal candidosis.¹²

Sexual transmission

Asymptomatic colonisation of the male genitalia with candida is four times more common in the sexual partners of infected women than in those of non-infected women.⁹⁷ About 20% of the partners of women with recurrent vulvovaginal candidosis have candida organisms on their penises.¹² Candida organisms are more commonly found in uncircumcised men than in those who are circumcised. Infected partners usually carry identical strains; however, the contribution of sexual transmission to the pathogenesis of infection remains unknown. From the prevalence of positive penile and urethral cultures, penile-vaginal transmission probably occurs in only a few cases. Epidemiological evidence suggests that anogenital and particularly orogenital contact transmits yeast.^{78,94}

Vaginal relapse

20–25% of women who test negative for candida immediately after antimycotic treatment for vulvovaginal candidosis subsequently test positive at 30 days, indicating the persistence of some strains of yeast and hence a vaginal rather than intestinal reservoir. Strains isolated before and after treatment are identical in more than two-thirds of recurrences.^{12,42} Some microorganisms persist within the vaginal lumen, generally in numbers too small to be detected by conventional vaginal cultures, only to re-emerge some weeks or months later.⁹⁸

Transformation to symptomatic vaginitis

The mechanism by which candida organisms induce vulvovaginal inflammation is still obscure. Yeast cells are capable of producing extracellular proteases and phospholipase. The absence of phagocytic cells in the vaginal discharge is probably due to chemotactic substances not being elaborated. Both blastoconidia and pseudohyphae are capable of destroying superficial cells by direct invasion.¹²

Pseudohyphae and hyphae appear during a symptomatic episode. Hyphal elements enhance colonisation and, although they represent the dominant invasive form that is capable of penetrating intact epithelial cells, only the

very superficial layers are involved.¹² Although symptoms are not always related to yeast load, vulvovaginal candidosis is associated with greater numbers of candida organisms and with hyphal elements.⁹⁹

The clinical spectrum of symptomatic vaginitis varies from an acute florid exudative form with copious white vaginal discharge and large numbers of germinated yeast cells, to the other extreme of absent or little discharge, fewer organisms, and yet severe pruritus. Accordingly, more than one pathogenic mechanism probably exists. Host hypersensitivity or immune mechanisms are probably involved when pruritus is evident. Indeed, vulvovaginal candidosis is more common in women with atopy and allergic diseases.^{65,95} Although clinical signs and symptoms are indistinguishable in infections caused by different *Candida* spp, *C glabrata* and *C parapsilosis* tend to be associated with milder—often absent—symptoms.^{18,81} Occasionally, male partners of asymptomatic female carriers of candida develop transient postcoital penile erythema and pruritus, suggesting that inflammation is due to hypersensitivity mechanisms. Much remains to be elucidated as to the role of the host versus microorganisms in inducing vulvovaginal inflammation.

Clinical manifestations

Although acute pruritus and vaginal discharge are the usual presenting complaints associated with vulvovaginal candidosis, neither is specific to this infection.^{100,101} Vaginal discharge is present only variably and is often negligible. Although described as typically cottage-cheese-like, the discharge can vary from watery to homogeneously thick. Vaginal soreness, irritation, vulvar burning, dyspareunia, and external dysuria are common. Odour, if present, is slight and inoffensive. Examination reveals erythema and swelling of the labia and vulva, often with fissures and pustulopapular peripheral lesions. The cervix is normal, and vaginal erythema is present together with an adherent off-white discharge. Characteristically, symptoms are exacerbated in the week before menses. Several surveys indicate the unreliability of patient self-diagnosis.

Diagnosis

Since the symptoms and signs of vulvovaginal candidosis are not specific to the infection, diagnosis cannot be made solely on the basis of history and physical examination.^{4,5,14,101} The most specific symptom in vulvovaginal candidosis is pruritus, and even this criterion correctly predicted vulvovaginal candidosis in only 38% of patients.¹⁰¹

Most patients with symptomatic vaginitis can be readily diagnosed by microscopic examination of vaginal secretions. A wet mount or saline preparation should be done routinely to identify the presence of yeast cells and mycelia but also to exclude the presence of so-called clue cells indicative of bacterial vaginosis and motile trichomonads. A 10% potassium hydroxide preparation is more sensitive than a saline preparation in identifying yeast or hyphae (65–85% sensitivity; figure 2). Vaginal



Figure 2: Wet-mount examination of vaginal discharge from a woman with vulvovaginal candidosis

(A) *C albicans* hyphae, 10× magnification. (B) Budding *C glabrata*, 40× magnification.

pH is normal (4.0–4.5) in vulvovaginal candidosis, and pH in excess of 4.7 usually indicates bacterial vaginosis, trichomoniasis, or a mixed infection.

Unfortunately, up to 50% of patients with culture-positive symptomatic vulvovaginal candidosis will have negative microscopy.⁵ Thus, although routine cultures are not necessary if microscopy is positive, vaginal culture should be done in symptomatic women with negative microscopy and a normal pH (figure 3).^{5,102} The pap smear, although specific, is insensitive, being positive in only about 25% of patients with culture-positive symptomatic vulvovaginal candidosis. There is no difference in using Sabouraud agar, Nickerson's medium, or Microstix-candida medium for culture.

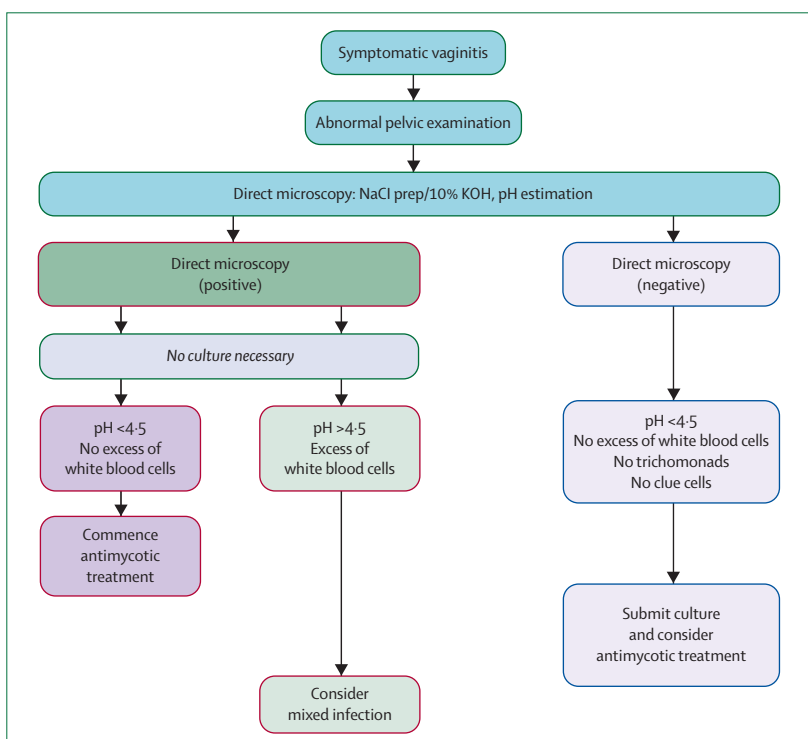


Figure 3: Algorithm for diagnosis and treatment of vulvovaginal candidosis

A positive culture alone does not necessarily indicate that the yeast so identified are responsible for vaginal symptoms, since 10–15% of asymptomatic women are colonised with candida and hence are culture positive.⁷ Diagnosis of vulvovaginal candidosis requires a correlation of clinical findings, microscopic examination, and vaginal culture.

There is no reliable serological or antigen detection technique available for the diagnosis of vulvovaginal candidosis. Because most clinicians are unable or unwilling to measure vaginal pH and do microscopy, most women with vulvovaginal symptoms remain incorrectly diagnosed and treated. PCR detection of *Candida* spp in vaginal samples is possible but is not

available as a diagnostic test and might not prove to be a clinically useful test.¹⁰³

Treatment

Asymptomatic carriage

Whether individuals who are asymptomatic carriers of candida should receive treatment is controversial. In otherwise healthy women, treatment with an antifungal is not advised. The benefits of treating asymptomatic HIV-positive women who are colonised with candida have not been established.

Acute symptomatic vaginitis

Treatment of acute vulvovaginal candidosis should be assessed on an individual basis, and a classification of vulvovaginal candidosis is available that determines selection and duration of antifungal therapy (panel). According to this classification, women with severe vulvovaginal candidosis do not respond adequately to single dose and short-course treatment, requiring treatment for 5–7 days.¹⁰⁴

Several effective topical azole agents are available in a variety of formulations (table 2).¹⁰⁵ Topical azoles are remarkably safe and well tolerated, although patients may report a burning sensation. No evidence exists to suggest that any one formulation results in better cure rates, nor is there any evidence of any specific azole being better than any other.¹⁰⁵ Overall cure rates for topical azoles range from 80% to 90%. Oral azole agents achieve comparable or marginally higher cure rates than do topical agents. Indeed, in a meta-analysis of 17 trials that assessed the effect of antifungal treatments on uncomplicated vulvovaginal candidosis, treatment was similarly effective when administered by either the oral or vaginal route.¹⁰⁶ Most patients prefer the convenience of oral administration, which eliminates local side-effects and messiness.¹⁰⁷ However, oral azoles have a potential side-effect of systemic toxicity, which has dramatically restricted the use of ketoconazole. One should note that azoles are poorly effective in vaginitis caused by *C glabrata*.⁸¹

There has been a growing tendency to use shorter courses of topical (eg, miconazole 1200 mg suppository) and oral agents.^{105,108} Single-dose therapy by any route is effective in mild to moderate disease. Vaginal clotrimazole (500 mg suppository), butoconazole as a bioadhesive, and oral fluconazole (150 mg)¹⁰⁹ possess pharmacokinetic properties that achieve therapeutic concentrations in the vagina for up to 5 days after the administration of a single dose.^{109,110} During pregnancy, topical azoles are more effective than nystatin and achieve acceptable cure rates; however, treatment for 7 days might be necessary.¹¹¹

Management of recurrent vulvovaginal candidosis

Every effort should be made to eliminate factors that predispose an individual to vulvovaginal candidosis. No correctable causal factors are apparent in most women; moreover, recurrent vulvovaginal candidosis is multi-

Panel: Classification for vulvovaginal candidosis

Uncomplicated

- Mild to moderate severity AND fewer than four episodes per year AND pseudohyphae or hyphae on microscopy AND a healthy, non-gravid host
- Treated with any short-course antimycotic

Complicated

- Moderate to severe disease OR four or more episodes per year OR only budding yeast visible on microscopy OR adverse factors (eg, pregnancy, diabetes, immunocompromised) in the host
- Treated with intensive regimens, avoid short-course treatment

	Formulation	Dosage
Butoconazole	2% cream	5 g per day for 3 days
	2% cream (bioadhesive)	Single dose
Clotrimazole	1% cream	5 g per day for 7–14 days
	10% cream	5 g single application
	100 mg vaginal tablet	One tablet per day for 7 days
	100 mg vaginal tablet	Two tablets per day for 3 days
	500 mg vaginal tablet	One tablet once
Miconazole	2% cream	5 g per day for 7 days
	100 mg vaginal suppository	One suppository per day for 7 days
	200 mg vaginal suppository	One suppository per day for 3 days
	1200 mg vaginal suppository	One suppository once
Econazole	150 mg vaginal tablet	One tablet per day for 3 days
	150 mg vaginal suppository	Single dose
Fenticonazole	2% cream	5 g per day for 7 days
Sertaconazole	300 mg suppository	Single dose
Ticonazole (Vagistat, Novartis)	2% cream	5 g per day for 3 days
	6.5% cream	5 g single application
Terconazole (Terazol, Jansen Pharmaceutica)	0.4% cream	5 g per day for 7 days
	0.8% cream	5 g per day for 3 days
	80 mg vaginal suppository	One suppository per day for 3 days
Fluconazole	150 mg tablet	Single dose
Ketoconazole	200 mg tablet	Two tablets per day for 5 days
Itraconazole	100 mg tablet	Two tablets per day for 3 days

Table 2: Azole therapy of vaginal candidosis

factorial in terms of cause. A small subgroup of women seem to benefit from restricting dietary intake of refined sugars.⁸⁵ Before therapy, mycological culture should be obtained to confirm diagnosis and to identify the specific *Candida* spp involved.

Successful therapy requires an induction course of either oral or topical azole, continued until the patient is asymptomatic and culture negative (7–14 days). In recurrent vulvovaginal candidosis, failure to initiate a maintenance regimen results in clinical relapse in 50% of patients within 3 months.^{12,25} Maintenance-suppressive regimens include ketoconazole (100 mg daily) and once-weekly regimens of either 500 mg clotrimazole suppositories or 150 mg fluconazole orally. All three regimens are effective in preventing breakthrough vaginitis;^{12,25,112} however, the better safety of fluconazole and clotrimazole means that ketoconazole is rarely used for maintenance suppression. One should note that, no matter what maintenance regimen is chosen, symptomatic relapse is seen in half the women within a short time of cessation of treatment.^{12,25}

There is some evidence to suggest that suppression of recurrence is possible with other agents. Dennerstein reported a reduced rate of recurrence in 15 patients with recurrent vulvovaginal candidosis when treated with depo-medroxyprogesterone acetate for 3 months.¹¹³ In a small study using patients as their own controls, Hilton reported fewer episodes of vulvovaginal candidosis in women who ate live yoghurt daily.¹¹⁴ However, in view of the small number of patients and absence of controls in this unblinded study, the role of yoghurt in preventing candida vaginitis remains questionable. Occasionally, women on fluconazole with persistent pruritus benefit from addition of antihistamines.⁶⁵ Several studies have shown that treatment of male sexual partners is of no benefit.¹¹⁵

An infrequently used alternative approach to maintenance antifungals is the use of systemic candida antigen hyposensitisation via the cutaneous route. Two small studies achieved encouraging results.^{116,117} This approach might be particularly useful in women who are unable to tolerate maintenance azole suppressive therapy.

Resistant and non-albicans candida vaginitis

By contrast with oral candidosis, vaginitis—including recurrent vulvovaginal candidosis—caused by azole-resistant strains of *C albicans* is rare.^{22,118,119} Nonetheless, isolation from the vagina of *C albicans* strains with higher minimum inhibitory concentrations (MIC) to fluconazole than in isolates obtained before exposure to weekly maintenance fluconazole is not rare.^{120,121} In general, peak vaginal concentrations of fluconazole do not exceed 4–8 µg/mL, therefore, isolates with a fluconazole MIC over 8 µg/mL should be clinically resistant to conventional doses of fluconazole. In-vitro susceptibility testing has not been validated and is not reliable in predicting clinical response in vaginitis. This

lack of validation is by sharp contrast with systemic and oral candidosis. These results could be explained in part by the in-vivo synergy between fluconazole and organic acids (eg, acetic acid) normally found in the vagina.¹²² The addition of acetic acid to a mixture of yeast and fluconazole in vitro makes fluconazole fungicidal, rather than just fungistatic.¹²²

About half of *C glabrata* strains isolated from cases of recurrent vulvovaginal candidosis show reduced sensitivity to fluconazole compared with *C albicans*.^{21,22,120} Vaginal boric acid (600 mg daily) in a gelatin capsule for 14 days or amphotericin B suppositories are effective (70%) for refractory infection.^{123,124} When a patient's history suggests recurrent vulvovaginal candidosis, a maintenance regimen of boric acid on alternate days and then twice weekly should be considered. The long-term safety of intravaginal boric acid has not been confirmed and it should not be used during pregnancy. In patients in whom boric acid fails, a success rate of more than 90% was achieved with a 2-week course of topical 17% flucytosine.¹²³ Vaginal use of flucytosine should be kept to a minimum because of the potential for the acquisition of resistance. The drug can also be combined with amphotericin B.¹²⁵ *C krusei* vaginitis is resistant to fluconazole and flucytosine but usually responds to boric acid or other azoles.¹⁹

Over-the-counter antifungal treatment

In most developed countries, topical imidazoles are available over-the-counter—ie, the patient does not need a prescription from a physician.¹²⁶ With rare exceptions, oral azoles are not available over-the-counter.

Of concern is the use of these readily available topical antifungal agents for self-diagnosed vulvovaginal candidosis. Many studies have shown the inability of many women to correctly self-diagnose vulvovaginal candidosis in the presence of vulvovaginal symptoms.¹²⁷ Ferris and colleagues¹²⁷ found that only 34% of women who bought over-the-counter antifungals for presumed vulvovaginal candidosis actually had the infection. Ready access to these products is associated with wasted financial expenditures, unfulfilled expectations, and a delay in correct diagnosis. This problem could be resolved if a simple, inexpensive candida detection diagnostic test was available.

Vulvovaginal candidosis in HIV-positive women

The prevalence and clinical significance of oral and oesophageal candidosis were recognised from the beginning of the AIDS epidemic.¹²⁸ As the numbers of women with HIV grew in the 1980s, vaginal candidosis was increasingly reported.^{129,130} Without supporting data, recurrent vulvovaginal candidosis was deemed to be an AIDS-defining illness. Indeed, in the 1980s, investigators in the USA concluded that women with “chronic refractory” vulvovaginal candidosis should be tested for HIV,^{129,130} without appreciating that recurrent vulvovaginal candidosis

is found in 5–8% of healthy HIV-negative women. Most women with a single episode of vulvovaginal candidosis are obviously not infected with HIV and do not require testing. In women with recurrent vulvovaginal candidosis, the issue is anything but clear, since most women with recurrent vulvovaginal candidosis are HIV negative. Only women with recurrent vulvovaginal candidosis who have risk factors for HIV infection should be tested.

Oral candidosis in HIV-positive women occurs as a result of the loss of oral mucosal cell-mediated immunity; this deficiency was thought initially to apply equally to the vagina.¹³¹ Furthermore, given the enormous quantities of antibiotics administered for prophylactic and therapeutic purposes to women with HIV, together with progressive debilitation, one might anticipate the frequent occurrence of symptomatic candida vaginitis, even in the absence of immunodeficiency. However, the attack rate of symptomatic candida vaginitis in HIV-positive women remains undetermined. Several studies have shown that vaginal colonisation with candida is increased in HIV-positive women compared with those who are HIV negative.^{132,133} Nevertheless, no studies indicate that vulvovaginal candidosis in HIV-infected women is more severe or less likely to respond to therapy than in HIV-negative women.^{133,134} Cross-sectional and cohort studies have shown only a moderate increase in vulvovaginal candidosis in HIV-positive women not receiving antiretroviral therapy compared with HIV-negative women,^{132,135} and the increased incidence of vulvovaginal candidosis in HIV-positive women compared with HIV-negative women was modest compared with the increase in the occurrence of oropharyngeal candidosis.¹³⁵ In one study, higher HIV loads were significantly associated with increased odds of incident or persistent vaginal colonisation and candidosis, whereas CD4 cell counts—indicative of cell-mediated immunity—were not associated with vaginal colonisation or candidosis, despite being significantly associated with increased odds of oral colonisation and candidosis.¹³⁵ By contrast, Duerr and colleagues¹³⁶ noted an association between lower CD4 cell count and vulvovaginal candidosis, although they used a different definition for vulvovaginal candidosis than did my colleagues and I.¹³⁵

The microbiology of vulvovaginal candidosis in HIV-positive women seems to be identical to that of matched high-risk HIV-negative women, although with time and possible unmeasured azole exposure there is a tendency to isolate non-albicans *Candida* spp, notably *C glabrata*¹³⁶ and candida isolates with reduced sensitivity to fluconazole. As with other forms of lower genital tract ulceration and inflammation, vulvovaginal candidosis has been associated with enhanced vaginal HIV shedding and increased concentrations of HIV RNA in the genital tract.^{95,137} Hence, vulvovaginal candidosis might facilitate HIV transmission, although its contributory role is unknown.

An argument can be made for treating asymptomatic and recurrent vulvovaginal candidosis in HIV-positive women in whom candida has been confirmed by microscopy, because of the associated enhanced HIV vaginal shedding. Such treatment should theoretically reduce the risk of transmission of HIV.¹³⁸ Treatment of symptomatic vulvovaginal candidosis, including recurrent infections, in HIV-positive women is identical to that of HIV-negative individuals.

Prevention of vulvovaginal candidosis

Vulvovaginal candidosis after antibiotic treatment is a common problem, and women often resort to probiotic *Lactobacillus* spp to prevent such an occurrence. However, Pirota and colleagues⁹³ recently reported that neither oral nor vaginal lactobacillus administration prevented vulvovaginal candidosis after antibiotic treatment. Many practitioners recommend one dose of prophylactic oral fluconazole 150 mg with onset and another dose on completion of antibiotics. Aimed at susceptible women only, maintenance fluconazole prophylaxis is effective in idiopathic recurrent vulvovaginal candidosis and other categories of secondary recurrent vulvovaginal candidosis—eg, lichen sclerosus and topical oestrogen application.

Future prevention strategies

Although no specific strategies are imminent, possible future treatments include topical vaginal use of recombinant mannose-binding lectin to enhance innate defence mechanisms in the vagina¹³⁹ and the identification and use of vaginal *Lactobacillus* spp that are capable of adhering to vaginal epithelial cells, persisting in the vagina, and that are capable of expressing anti-candida protective factors. Long-acting advanced generation triazoles (eg, albaconazole) might allow suppressive prophylaxis to be administered less often.¹⁴⁰ Anti-candida vaccines and systemically administered antibodies have been effective in preventing vaginal candidosis in rodents, but no data are available in human beings.^{141,142} Further progress is dependent upon delineation of host genetic susceptibility, anti-candida defence mechanisms in the vagina, and yeast genetic factors that induce host inflammation and facilitate vaginal persistence.

Conflict of interest statement

I declare that I have no conflict of interest.

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