Candida vulvovaginitis

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INTRODUCTION — Vulvovaginal candidiasis refers to a disorder characterized by signs and symptoms of vulvovaginal inflammation in the presence of *Candida* species. It is the second most common cause of vaginitis symptoms (after bacterial vaginosis) and accounts for approximately one-third of vaginitis cases [1]. In contrast to oropharyngeal candidiasis, it is generally not considered an opportunistic infection, and, unlike trichomonas vaginitis, it is not considered a sexually transmitted disease.

PREVALENCE — *Candida* species can be identified in the lower genital tract in 10 to 20 percent of healthy women in the reproductive age group, 6 to 7 percent of menopausal women, and 3 to 6 percent of prepubertal girls [2,3]. However, identification of vulvovaginal *Candida* is not necessarily indicative of candidal disease, as the diagnosis of vulvovaginitis requires the presence of vulvovaginal inflammation.

The prevalence of vulvovaginal candidiasis is difficult to determine because the clinical diagnosis is often based on symptoms and not confirmed by microscopic examination or culture (as many as one-half of clinically diagnosed women may have another condition [4]). In addition, the widespread use of over-the-counter antimycotic drugs makes epidemiologic studies difficult to perform and culture without clinical correlation is likely to overestimate the prevalence of disease.

In surveys, the prevalence of vulvovaginal candidiasis is highest among women in their reproductive years: 55 percent of female university students report having had at least one healthcare provider-diagnosed episode by age 25 years, 29 to 49 percent of premenopausal women report having had at least one lifetime episode, and 9 percent of women report having had four or more infections in a 12-month period (ie, recurrent vulvovaginal candidiasis [RVVC]) [5,6]. In women with an initial infection, the probability of RVVC was 10 percent by age 25 years, and 25 percent by age 50 years [6].

The prevalence increases with age up to menopause and is higher in African-American women than in other ethnic groups. The disorder is uncommon in postmenopausal women, unless they are taking estrogen therapy. It is also uncommon in prepubertal girls, in whom it is frequently overdiagnosed.

MICROBIOLOGY — *Candida albicans* is responsible for 80 to 92 percent of episodes of vulvovaginal candidiasis [7] and *C. glabrata* accounts for almost all of the remainder [8]. Some, but not all, investigators have reported an increasing frequency of non-albicans species, particularly *C. glabrata* [9,10], possibly due to widespread use of over-the-counter drugs, long-term use of suppressive azoles, and the use of short courses of antifungal drugs.

All *Candida* species produce similar vulvovaginal symptoms, although the severity of symptoms is milder with *C. glabrata* and *C. parapsilosis*.

In contrast to bacterial vaginosis, vulvovaginal candidiasis is not associated with a reduction in vaginal lactobacilli [11-14].

PATHOGENESIS — *Candida* organisms probably access the vagina via migration from the rectum across the perianal area [15]; cultures of the gastrointestinal tract and vagina often show identical *Candida* species. Less commonly, the source of infection is sexual or relapse from a vaginal reservoir.

Symptomatic disease is associated with an overgrowth of the organism and penetration of superficial epithelial cells [16-18]. The mechanism by which *Candida* species transform from asymptomatic colonization to an invasive form causing symptomatic vulvovaginal disease is complex, involving host inflammatory responses and yeast virulence factors. (See "Biology of Candida infections".)

Recurrent vulvovaginal candidiasis — Recurrent vulvovaginal candidiasis is defined as four or more episodes of symptomatic infection within one year [16]. Longitudinal DNA-typing studies suggest that, in most women, recurrent disease is due to relapse from a persistent vaginal reservoir of organisms or endogenous reinfection with the identical strain of susceptible *C. albicans* [19,20]. Rarely, infection is due to a different *Candida* species.

Recurrent vulvovaginal candidiasis has been associated with decreased in vivo concentration of mannose binding lectin (MBL) and increased concentration of interleukin-4. Two specific gene polymorphisms, variants in the MBL and interleukin-4 alleles, can account for this finding in some women. The prevalence of a variant MLB gene is higher in women with recurrent vulvovaginal candidiasis than in controls without candidiasis [21,22]. Since the direct interaction of MBL with *C. albicans* is an

important component of the host's ability to resist candidiasis, impairment of this interaction in MBL-deficient individuals, such as those with certain MBL polymorphisms, appears to predispose these women to recurrent vulvovaginal candidal infection [21,23-26]. These women mount a strong inflammatory response when exposed to small amounts of *Candida*, whereas normal women may not mount any inflammatory response and remain asymptomatic. Interleukin-4 blocks the anti-*Candida* response mediated by macrophages, thus elevated IL-4 levels result in inhibition of local defense mechanisms.

RISK FACTORS — Sporadic attacks of vulvovaginal candidiasis usually occur without an identifiable precipitating factor. Nevertheless, a number of factors predispose to symptomatic infection [27,28]:

- **Diabetes mellitus** — Women with diabetes mellitus who have poor glycemic control are more prone to vulvovaginal candidiasis than euglycemic women [29,30]. In particular, women with Type 2 diabetes appear prone to non-albicans *Candida* species [31].

- **Antibiotic use** — Use of broad spectrum antibiotics significantly increases the risk of developing vulvovaginal candidiasis [32]. As many as one-quarter to one-third of women develop the disorder during or after taking these antibiotics because inhibition of normal bacterial flora favors growth of potential fungal pathogens, such as *Candida*. Administration of lactobacillus (oral or vaginal) during and for four days after antibiotic therapy does not prevent postantibiotic vulvovaginitis [33].

- **Increased estrogen levels** — Vulvovaginal candidiasis appears to occur more often in the setting of increased estrogen levels, such as oral contraceptive use (especially when estrogen dose is high), pregnancy, and estrogen therapy.

- **Immunosuppression** — Candidal infections are more common in immunosuppressed patients, such as those taking glucocorticoids or other immunosuppressive drugs, or with human immunodeficiency virus (HIV) infection [34].

- **Contraceptive devices** — Vaginal sponges, diaphragms, and intrauterine devices have been associated with vulvovaginal candidiasis, but not consistently. Spermicides are not associated with *Candida* infection.

- **Behavioral factors** — Vulvovaginal candidiasis is not traditionally considered a sexually transmitted disease (STD) since it occurs in celibate women and since *Candida* species are considered part of the normal vaginal flora. This does not mean that sexual transmission of *Candida* does not occur or that vulvovaginal candidiasis is not associated with sexual activity. For example, an increased frequency of vulvovaginal candidiasis has been reported at the time most women begin regular sexual activity [5,27,35]. In addition, partners of infected women are four times more likely to be colonized than partners of uninfected women, and colonization is often the same strain in both partners. However, the number of episodes of vulvovaginal candidiasis a woman has does not appear to be related to her lifetime number of sexual partners or the frequency of coitus [27,36,37].

  The type of sex may be a factor. Infection may be linked to orogenital and, less commonly, anogenital sex. Evidence of a link between vulvovaginal candidiasis and hygienic habits (eg, douching, use of tampons/menstrual pads) or wearing tight or synthetic clothing is weak and conflicting [27,38-45].

Recurrent vulvovaginal candidiasis — The risk factors described above are apparent in only a minority of women with recurrent disease (see 'Risk factors' above). In the remainder, factors that predispose to recurrent infection likely involve abnormalities in local vaginal mucosal immunity [46] and genetic susceptibility (see 'Recurrent vulvovaginal candidiasis' above).

The role of sexual transmission in recurrent infection remains unresolved, but does not appear to be a major factor as the bulk of evidence from randomized trials does **not** support treatment of sexual partners [47-50].

CLINICAL FEATURES — Vulvar pruritus is the dominant feature of vulvovaginal candidiasis [8,17,51-53]. Vulvar burning, soreness, and irritation are also common, and can be accompanied by dysuria (typically perceived to be external or vulvar rather than urethral) or dyspareunia. Symptoms are often worse during the week prior to menses [53]. The intensity of signs and symptoms varies from mild to severe, except among women with *C. glabrata* or *C. parapsilosis* infection, who tend to have mild or minimal clinical findings [54].

Physical examination of the external genitalia, vagina, and cervix often reveals erythema of the vulva and vaginal mucosa and vulvar edema. Vulvar excoriation and fissures are present in about one-quarter of patients. There can be little or no discharge; when present, it is classically white, thick, adherent, and clumpy (curd-like or cottage cheese-like) with no or minimal odor. However, the discharge may be thin and loose, watery, homogeneous, and indistinguishable from that in other types of vaginitis. The cervix usually appears normal.

DIAGNOSIS — The general diagnostic approach to women with vaginal complaints is reviewed separately. (See "Approach to women with symptoms of vaginitis".)

The diagnosis of vulvovaginal candidiasis is based on the presence of *Candida* on wet mount, Gram's stain, or culture of vaginal discharge in a woman with characteristic clinical findings (eg, vulvovaginal pruritus, burning, erythema, edema, and/or curd like discharge attached to the vaginal sidewall) and no other pathogens to account for her symptoms. (See 'Clinical features' above.) Because none of the clinical manifestations of vulvovaginal candidiasis is pathognomonic, suspected clinical

diagnosis should always be confirmed by laboratory methods. Importantly, although vulvar pruritus is a cardinal symptom of the disorder, less than 50 percent of women with genital pruritus have vulvovaginitis candidiasis [55].

Office diagnosis — The vaginal pH in women with *Candida* infection is typically normal (4 to 4.5), which distinguishes candidiasis from trichomoniasis or bacterial vaginosis (table 1). *Candida* species can be seen on a wet mount of the discharge; adding 10 percent potassium hydroxide destroys the cellular elements and facilitates recognition of budding yeast, pseudohyphae, and hyphae (picture 1 and picture 2 and picture 3 and picture 4 and picture 5 and picture 6) [56]. Use of Swartz-Lamkins fungal stain (potassium hydroxide, a surfactant, and blue dye) may facilitate diagnosis by staining the *Candida* organisms blue so they are easier to identify [57]. However, microscopy is negative in up to 50 percent of patients with culture confirmed vulvovaginal candidiasis [16].

Microscopy is also important for looking for clue cells or motile trichomonads, which indicate bacterial vaginosis and trichomoniasis, respectively, as alternative diagnoses, co-infection, or mixed vaginitis [58].

Role of culture — We recommend not culturing all patients because culture is not necessary for diagnosis if microscopy shows yeast, and it is costly, delays the time to diagnosis by several days, and may be positive due to colonization rather than infection.

We obtain a culture in:

- Women with clinical features of vulvovaginal candidiasis, normal vaginal pH, and no pathogens (yeast, clue cells, trichomonads) visible on microscopy. A positive culture in these patients confirms the diagnosis and reveals the species of *Candida*, thus avoiding empiric, un-indicated or incorrect therapy.
- Women with persistent or recurrent symptoms because many of these women have non-albicans infection resistant to azoles (see 'Diagnosis of recurrent vulvovaginal candidiasis' below).

To perform a culture, a vaginal sample is obtained from the lateral wall using a cotton tipped swab and inoculated onto Sabouraud agar, Nickerson's medium, or Microstix-candida medium; these media perform equally well [8]. Culture for *Candida* does not require quantification of in vitro colony count. Speciation of *Candida* is not essential for primary diagnostic testing as most isolates are *Candida albicans*; however, species identification is essential in refractory and recurrent disease. Laboratory techniques for identification of multiple *Candida* species are reviewed separately. (See "Biology of Candida infections", section on 'Detection in the microbiology laboratory'.)

Other tests — There are no reliable point of care tests for *Candida* available in the United States [59-64]. A DNA probe test performed in a centralized laboratory offers results comparable to culture with results available in several hours, but no speciation (Affirm VPIII).

Polymerase chain reaction (PCR) methods have high sensitivity and specificity and a shorter turn-around time than culture [65-68], but are costly and offer no proven benefit over culture in symptomatic women [65].

Pap smear is positive in 25 percent of patients with culture positive, symptomatic vulvovaginal candidiasis [8]. It is insensitive because the cells are derived from the cervix, which is not affected by *Candida* vaginitis. Treatment of *Candida* on a Pap smear of an asymptomatic woman is not indicated (see 'Treatment' below).

Self diagnosis — Self-diagnosis of vulvovaginal candidiasis is frequently inaccurate and should be discouraged [69,70]. In a study that administered a questionnaire to 600 women to assess their knowledge of the symptoms and signs of vulvovaginal candidiasis (and other infections) after reading classic case scenarios, only 11 percent of women without a previous diagnosis of vulvovaginal candidiasis correctly diagnosed this infection [69]. Women who had had a prior episode were more often correct (35 percent), but were likely to use over-the-counter drugs inappropriately to treat other, potentially more serious, gynecologic disorders.

In another report, the actual diagnoses in 95 women who self-diagnosed vulvovaginal candidiasis were: vulvovaginal candidiasis (34 percent), bacterial vaginosis (19 percent), mixed vaginitis (21 percent), normal flora (14 percent), trichomonas vaginitis (2 percent), and other (11 percent) [70]. Women with a previous episode of vulvovaginal candidiasis and those who read the package insert for their over-the-counter medication were not more accurate in making a diagnosis than other women.

Some consequences of misdiagnosis and inappropriate therapy include a delay in correct diagnosis and treatment, wasted monetary expenditure, and precipitation of vulvar dermatitis.

Diagnosis of recurrent vulvovaginal candidiasis — Recurrent vulvovaginal candidiasis is defined as four or more episodes of symptomatic infection within one year [16]. Vaginal cultures should always be obtained to confirm the diagnosis and identify less common *Candida* species, if present. As discussed above, recurrent disease is usually due to relapse from a persistent vaginal reservoir of organisms or endogenous reinfection with identical strains of susceptible *C. albicans* [19]; however, rarely, a new strain of *Candida* is responsible for the infection.

Testing for HIV infection — Vulvovaginal candidiasis occurs more frequently and has greater persistence, but not greater severity, in human immunodeficiency virus (HIV)-infected women with very low CD4 counts and high viral load; however, this population is likely to manifest other acquired immune deficiency syndrome (AIDS)-related sentinel conditions [34]. HIV testing of women only for the indication of recurrent vulvovaginal candidiasis is not justified, given that recurrent *Candida* vaginitis is a common condition in women without HIV infection and the majority of cases occur in uninfected women. The microbiology of vulvovaginal candidiasis in HIV-infected women is similar to that in HIV-negative women [8].

Women with risk factors for acquisition of HIV should be counseled and offered screening. These risk factors are described in detail separately. (See "Screening for sexually transmitted infections".)

Differential diagnosis — Other conditions to be considered in the differential diagnosis of vulvovaginitis with normal vaginal pH include hypersensitivity reactions, allergic or chemical reactions, and contact dermatitis. These conditions are discussed in detail elsewhere. Recognizing local adverse reactions to topical agents is important; otherwise, additional topical agents, including high potency corticosteroids, are often prescribed empirically and further aggravate symptoms. (See "Vulvar dermatitis".) Mechanical irritation due to insufficient lubrication during coitus can also result in vaginal discomfort.

If vaginal pH exceeds 4.5 or excess white cells are present, mixed infection with bacterial vaginosis or trichomoniasis may be present. Mixed infection (≥2 pathogens and all are symptomatic) is estimated to occur in <5 percent of patients; coinfection (≥2 pathogens but some are not symptomatic) is more common: 20 to 30 percent of women with bacterial vaginosis are co-infected with *Candida* species [58]. (See "Bacterial vaginosis" and "Trichomoniasis".)

TREATMENT — Treatment is indicated for relief of symptoms. Ten to 20 percent of reproductive age women who harbor *Candida* species are asymptomatic; these women do not require therapy [56].

The treatment regimen is based on whether the woman has an uncomplicated infection (90 percent of patients) or complicated infection (10 percent of patients). Criteria are listed in the table (table 2). Uncomplicated infections usually respond to treatment within a couple of days. Complicated infections require a longer course of therapy and may take two weeks to fully resolve.

Treatment of sexual partners is unnecessary. There is no medical contraindication to sexual intercourse during treatment, but it may be uncomfortable until inflammation improves.

Uncomplicated infection — Criteria for uncomplicated infection include all of the following [17]:

- Sporadic, infrequent episodes (≤3 episodes/year)
- Mild to moderate signs/symptoms
- Probable infection with *Candida* albicans
- Healthy, nonpregnant woman

A variety of oral and topical preparations, many available over-the-counter and in single-dose regimens, is available for the treatment of uncomplicated vulvovaginal candidiasis (table 3) [71]. In randomized trials, oral and topical antimycotic drugs achieved comparable clinical cure rates, which are in excess of 90 percent; short-term mycologic cure is slightly lower (70 to 80 percent) [72-75]. Studies that have assessed patient preference consistently reported a preference for the convenience of oral treatment [73]. However, topical treatments have fewer side effects (eg, possible local burning or irritation), while oral medication may cause gastrointestinal intolerance, headache, rash, and transient liver function abnormalities. In addition, oral medications take a day or two longer than topical therapy to relieve symptoms. The absence of superiority of any formulation, agent, or route of administration suggests that cost, patient preference, and contraindications are the major considerations in the decision to prescribe an anti-fungal for oral or topical administration [75].

We suggest use of oral fluconazole, given that most women consider oral drugs more convenient than those applied intravaginally. Fluconazole maintains therapeutic concentrations in vaginal secretions for at least 72 hours after the ingestion of a single 150 mg tablet [76]. Side effects of single-dose fluconazole (150 mg) tend to be mild and infrequent. However, fluconazole interacts with multiple drugs; therefore, the potential for drug interactions should be addressed when prescribing this agent. Since fluconazole is now available in a generic form, a single dose regimen of fluconazole is less expensive than over-the-counter topical antifungals.

Azole resistance has only been reported in one case of vaginitis caused by *C. albicans* [77]. Thus, in vitro susceptibility tests are rarely indicated unless compliant patients with a culture-proven diagnosis have no response to adequate therapy.

Complicated infections — Characteristics of complicated infections include one or more of the following criteria [17]:

- Severe signs/symptoms
- *Candida* species other than *C. albicans*, particularly *C. glabrata*
- Pregnancy, poorly controlled diabetes, immunosuppression, debilitation
- History of recurrent (≥4/year) culture-verified vulvovaginal candidiasis

The treatment of complicated infection is summarized in the table and described in more detail below (table 4).

Severe symptoms or compromised host — Women with severe inflammation or host factors suggestive of complicated infection need longer courses of oral or topical antimycotic drugs. It is unknown whether one route is more effective than the other, as comparative trials of topical versus oral treatment of complicated infection have not been performed.

Given the convenience of oral therapy, we suggest fluconazole (150 mg orally) for two to three sequential doses 72 hours apart for treatment of complicated infections, depending on the severity of the infection (table 4) [75]. The efficacy of this approach was supported by a trial that randomly assigned 556 women with severe or recurrent candidiasis to therapy with a single dose of fluconazole (150 mg) or two sequential doses given three days apart [78]. Severity of disease was based upon a scoring system involving degree of pruritus and physical signs (erythema, edema, excoriation/fissure formation). The two-dose regimen resulted in significantly higher clinical cure/improvement rates at evaluation on day 14 (94 versus 85 percent) and day 35 (80 versus 67 percent) in women with severe, but not recurrent, disease. However, the response to therapy was lower in the 8 percent of women infected with non-albicans *Candida*.

If the patient prefers topical therapy, observational series report that complicated patients require 7 to 14 days of topical azole therapy (eg, clotrimazole, miconazole, terconazole) rather than a one- to three-day course [1,75].

For severe *Candida* vulvar inflammation (vulvitis), low potency topical corticosteroids can be applied to the vulva for 48 hours until the antifungals exert their effect.

C. glabrata — *C. glabrata* has low vaginal virulence and rarely causes symptoms, even when identified by culture. Every effort should be made to exclude other co-existent causes of symptoms and only then treat for *C. glabrata* vaginitis. Treatment failure with azoles is common (around 50 percent) in patients with *C. glabrata* vaginitis [54]. Moderate success (65 to 70 percent) in women infected with this organism can be achieved with intravaginal boric acid (600 mg capsule once daily at night for two weeks) [54,79]. Better results (>90 percent cure) have been achieved with intravaginal flucytosine cream or amphotericin B cream 4 to 10% (5 g nightly for two weeks) [79]. Neither boric acid capsules nor flucytosine or amphotericin B cream is available commercially and must be made by a compounding pharmacy. **Boric acid capsules can be fatal if swallowed**.

There are no good data regarding use of oral voriconazole for *C. glabrata* vaginitis. Anecdotal reports suggest poor response and rare cures, and the potential for toxicity.

Although there are also no good data on the efficacy of nystatin, which is available as a pessary in some parts of the world, anecdotally, many clinicians consider nystatin the drug of choice for *C. glabrata*. One or two pessaries of 100,000 units nystatin are inserted into the vagina nightly for 14 days [80]. Alternatively, a suppository can be prepared by a compounding pharmacy. Potential side effects include burning, redness, and irritation.

C. krusei — *Candida krusei* is usually resistant to fluconazole, but is highly susceptible to topical azole creams and suppositories, such as clotrimazole, miconazole, and terconazole. We treat for 7 to 14 days. It is also likely to respond to oral itraconazole or ketoconazole, but these oral agents have variable toxicity so topical therapy is advised for first-line therapy. Idiosyncratic hepatotoxicity secondary to ketoconazole therapy is a concern, but rare in this setting. In vitro susceptibility testing is indicated in compliant patients with culture-proven diagnosis of *C. krusei* and no response to a conventional course of one of these non-fluconazole therapies.

Pregnancy — For pregnant women with symptomatic *Candida* vulvovaginitis, we suggest application of a topical imidazole (clotrimazole or miconazole) vaginally for seven days rather than treatment with an oral azole because of potential risks with oral azole therapy in pregnancy. Treatment of pregnant women is primarily indicated for relief of symptoms; vaginal candidiasis is not associated with adverse pregnancy outcomes [81]. This approach is consistent with statements from the United States Centers for Disease Control and Prevention and US Food and Drug Administration [1,82,83].

During pregnancy, we avoid oral azole therapy, particularly during the first trimester, because its impact on miscarriage risk is unclear and high doses appear to increase the risk of birth defects. Since topical therapy is an effective alternative to oral dosing, we prefer vaginal treatment until more data are available to support the safety of low-dose oral treatment.

- Miscarriage: A cohort study of over 3300 women who received 150 to 300 mg oral fluconazole between 7 and 22 weeks of pregnancy reported an approximately 50 percent increased risk of miscarriage in exposed women compared with either unexposed women or women treated with vaginal azole therapy [84]. Stillbirth risk did not differ among the groups, although stillbirth was a relatively rare outcome. This study contrasts with two prior cohort studies totaling just over 1500 women that did not report an association between oral fluconazole and miscarriage [85,86]. As the larger study may have had greater power to detect an increase in miscarriage risk, we prefer to avoid oral azole therapy until more data are available.

- Birth defects: Case reports have described a pattern of birth defects (abnormalities of cranium, face, bones, and heart) after first-trimester exposure to high-dose fluconazole therapy (400 to 800 mg/day) [87,88]. The magnitude of the teratogenic risk is unknown. Further, the impact of low-dose fluconazole exposure is unclear. A United States case-control study including over 31,000 mothers of children with birth defects reported an association with first-trimester fluconazole use and cleft lip with cleft palate and d-transposition of the great arteries [89]. Limitations of this study included that

fluconazole use was assessed by self-report and the total number of cases for each abnormality were small (six cleft lip with palate and three d-transposition of the great arteries), which makes the finding less certain. Multiple smaller epidemiologic studies have not reported an increased risk of birth defects after first-trimester use of a single, low dose of fluconazole 150 mg to treat vaginal yeast infection [85,86,90-94]. In the largest study, which included 7352 pregnancies, there was no overall risk of embryopathy associated with exposure to cumulative fluconazole doses of 150, 300, or 350 to 6000 mg during the first trimester nor with exposure to oral itraconazole or ketoconazole [90]. Overall, these data appear reassuring for women who took low-dose fluconazole before realizing that they were pregnant [95], although an increased risk of specific anomalies cannot be definitively excluded.

Although treatment of vaginal *Candida* colonization in healthy pregnant women is unnecessary, in Germany treatment is recommended in the third trimester because the rate of oral thrush and diaper dermatitis in mature healthy newborns is significantly reduced by maternal treatment [55].

There is less information about the pregnancy safety profile of terconazole, a triazole, than for imidazoles. Vaginal nystatin is another option for treatment. As discussed above, a pessary is available in some parts of the world. One or two pessaries of 100,000 units nystatin are inserted into the vagina nightly for 14 days [80]. Alternatively, a suppository can be prepared by a compounding pharmacy. Potential side effects include burning, redness, and irritation.

Recurrent infection — The treatment of women with recurrent infections can be difficult and frustrating [96]. Recurrent vulvovaginal candidiasis is defined as four or more episodes of symptomatic candidal vaginitis in a 12-month period [1,96]. Attempts should be made to eliminate or reduce risk factors for infection if present (eg, improve glycemic control, switch to lower estrogen dose oral contraceptive). Although not based upon data from randomized trials, implementing a change in one or more behavioral factors (eg, avoidance of panty liners, pantyhose, cranberry juice, sexual lubricants) to see if there is improvement may be beneficial in rare women [38]. Management of sexual dysfunction and the marital discord that frequently accompany chronic vaginitis should also be addressed.

Decreasing gastrointestinal *Candida* colonization by oral administration of nystatin does not prevent recurrent symptomatic vaginal infection [16].

Azoles — Randomized trials comparing different therapeutic regimens have not been performed. Based on the data cited below and personal experience, we believe that the optimal therapy for recurrent vulvovaginal candidiasis in nonpregnant women consists of initial induction therapy with fluconazole 150 mg every 72 hours for three doses, followed by maintenance fluconazole therapy once per week for six months [97]. Therapy is then discontinued, at which point some patients achieve a prolonged remission, while others relapse. A short-term relapse, with culture confirmation of the diagnosis, merits reinduction therapy with three doses of fluconazole, followed by repeat weekly maintenance fluconazole therapy, this time for one year. A minority of women persist in relapsing as soon as fluconazole maintenance is withdrawn (fluconazole dependent recurrent vulvovaginal candidiasis). Symptoms in these patients can be controlled by months or years of weekly fluconazole.

Given the safety profile of low dose fluconazole, most experts do not suggest any laboratory monitoring; however, if other oral imidazoles (ketoconazole, itraconazole) are used, particularly if taken daily, then monitoring liver function tests is recommended. Idiosyncratic hepatotoxicity secondary to ketoconazole therapy is a concern, but rare in this setting.

Although drug interactions are reported with fluconazole and several oral agents (eg, warfarin, rifampin), such interactions are extremely unlikely with maintenance fluconazole due to the low plasma concentrations accompanying the once weekly 150 mg dosing regimen. Accordingly, no additional testing needed.

Alternative approaches that have been suggested include:

- Treat each recurrent episode as an episode of uncomplicated infection (table 3) [1]
- Treat each recurrent episode with longer duration of therapy (eg, topical azole for 7 to 14 days or fluconazole 150 mg orally on day 1, day 4, and day 7) [1]
- The Infectious Diseases Society of America (IDSA) recommends 10 to 14 days of induction therapy with a topical or oral azole, followed by fluconazole 150 mg once per week for six months (clotrimazole 200 mg vaginal cream twice weekly is a nonoral alternative) [75].

Evidence for suppressive therapy — Multiple observational studies of nonpregnant women with recurrent vulvovaginal candidiasis have shown that antifungal maintenance suppressive therapy taken for six months after an initial induction regimen resulted in negative cultures [72,98]. The best available option in nonpregnant women is fluconazole 150 mg orally once per week for six months [75]. However, maintenance therapy is only effective for preventing recurrent infection as long as the medication is being taken. This was illustrated in a trial of 387 women with recurrent vulvovaginal candidiasis treated with open-label fluconazole (150 mg orally at 72-hour intervals for three doses) and then randomly assigned to weekly doses of fluconazole (150 mg) or placebo for six months [97]. The maintenance therapy phase was begun two weeks after initiation of treatment in patients who were clinically cured. Study drugs were discontinued in patients diagnosed with recurrent candidal infection during follow-up visits.

- The proportion of women who remained disease-free was significantly higher in the fluconazole group (91 versus 36 percent at 6 months, 73 versus 28 percent at 9 months, and 43 versus 22 percent at 12 months).
- The mean time to recurrence in the fluconazole and placebo groups was 10.2 and 4.0 months, respectively.
- Resistant isolates of *C. albicans* or superinfection with *C. glabrata* were not observed.

Although this regimen of maintenance fluconazole was convenient, safe, and as effective as other therapies, long-term cure of recurrent vulvovaginal candidiasis was not achieved in one-half of the women studied. Episodes of recurrent candidiasis resumed when maintenance therapy was discontinued.

Fluconazole resistance — In women with recurrent vulvovaginal candidiasis, there is some evidence that frequent and prolonged use of fluconazole can infrequently select for fluconazole resistance in *C. albicans* strains previously susceptible to fluconazole, which limits the options available for treating these women. In a study of 25 women with refractory *Candida* vaginitis and a *C. albicans* isolate with fluconazole minimum inhibitory concentration (MIC) ≥2 micrograms/mL, those with fluconazole MIC values of 2 or 4 micrograms/mL were treated successfully by increasing fluconazole dosage to 200 mg twice weekly [99]. In the authors' experience, a higher dose of fluconazole was not effective for women with MIC ≥8 micrograms/mL. These women should be evaluated for cross-resistance to itraconazole and ketoconazole, as some patients can be treated effectively with long-term maintenance daily imidazole therapy. However, use of itraconazole or ketoconazole requires intermittent hepatic function testing. Idiosyncratic hepatotoxicity secondary to ketoconazole therapy is a concern, but rare in this setting.

Women with severe recurrent vulvovaginal candidiasis infection and high-level pan azole resistance do not have options other than topical boric acid (see 'Boric acid' below) or nystatin suppositories [100].

In women with refractory vulvovaginal candidiasis with persistently positive *C. albicans* cultures, MICs to various antifungals can be tested by using the broth microdilution method conducted in accordance with Clinical and Laboratory Standards Institution (CLSI) criteria and breakpoints [101]. (See "Antifungal susceptibility testing".)

Probiotics — There is no evidence that women with recurrent vulvovaginal candidiasis have vaginal flora deficient in lactobacilli, and therefore we do not recommend use of probiotic lactobacilli [11,12]. Although there is a popular belief that ingestion or vaginal administration of yogurt or other agents containing live lactobacilli decreases the rate of candidal colonization and symptomatic relapse, the few studies in this area have a number of methodologic flaws (eg, no control group, short follow-up) and small numbers of subjects [102-106]. The value of administering live lactobacilli to women with recurrent infection has been refuted in other studies [38,107] and this approach should be considered unproven. The quality of probiotics varies worldwide; in the United States these products are not standardized and often of poor quality. The US Food and Drug Administration has cautioned against using probiotics with bacteria or yeast in immunocompromised patients [108].

Gentian violet — Topical gentian violet was widely used prior to the availability of the topical azole intravaginal antifungal creams and suppositories. Use of this agent has largely been abandoned because azole antimycotics are more effective (potent) and because it is messy and inconvenient (eg, it permanently stains clothes). However, it is useful as a vulvar antipruritic and for occasional refractory cases of vulvovaginal candidiasis, especially those demonstrating azole resistance [109]. The drug is applied to affected areas of the vulva and vagina daily for 10 to 14 days.

Boric acid — We believe boric acid has no role in treatment of recurrent vulvovaginitis due to *C. albicans*, unless azole resistance is demonstrated by in vitro tests [110]. There are no safety data on long-term use of boric acid, which causes significant local irritation and has the potential for toxicity (including death) if ingested by accident. A course of boric acid (600 mg intravaginal boric acid vaginal suppositories daily for two weeks) should be considered only in cases of proven azole-resistant infection; these cases are rare.

Immunotherapy — Local vaginal hypersensitivity to *C. albicans* has been proposed as the cause of recurrent infection in some women [111]. Immunotherapy of candidal vaginitis for both prevention and treatment is a therapeutic approach under investigation [112]. A prophylactic vaccine would need to induce a host immune response against fungal virulence traits without altering the tolerance/inflammation balance of the vaginal environment, whereas a therapeutic vaccine indicated for women with recurrent vulvovaginal candidiasis could enhance or rectify tolerance/inflammation imbalance in the vagina [113]. Two vaccines are in development.

Allergy to fluconazole — The incidence of fluconazole allergy in women with acute *Candida* vaginitis is unknown, but uncommon. The author has seen patients with allergic symptoms, varying from rash to, occasionally, angioedema. It is important to recognize that fluconazole is one member of the azole class of drugs and it is difficult to distinguish between patients with allergy to fluconazole alone versus those with allergy to the entire azole class. Therefore, other oral azoles such as ketoconazole (Nizoral) or itraconazole (Sporanox) should not be prescribed to patients with true fluconazole allergy. However, patients with fluconazole allergy can receive topical azoles, such as miconazole or clotrimazole. For those patients with fluconazole allergy manifested by angioedema or severe rash, the author has resorted to use of topical agents instead of weekly fluconazole 150 mg. Both miconazole and clotrimazole can be prescribed on a once weekly high dose regimen, 500 to 1500 mg, depending on the dose commercially available locally. Other options include nystatin per vagina 100,000 units daily

for 7 days for acute vaginitis or boric acid per vagina for 7 days. Discussion with an allergist is recommended. There are no data on the efficacy of fluconazole desensitization, which is theoretically possible.

Treatment of partners — Although sexual transmission of *Candida* species can occur, most experts do not recommend treatment of sexual partners since sexual activity is not a significant cause of infection or reinfection. Although the bulk of evidence from randomized trials does **not** support treatment of sexual partners [47-50], in woman with recurrent vulvovaginitis, this issue remains controversial.

Treatment of symptomatic men is reviewed separately. (See "Balanitis and balanoposthitis in adults".)

Breastfeeding women — Nystatin does not enter breast milk and is compatible with breastfeeding. Fluconazole is excreted in human milk, but the American Academy of Pediatrics (AAP) considers the use of fluconazole compatible with breastfeeding [114], as no adverse effects have been reported in breastfed infants or infants treated with parenteral fluconazole [115]. There is no information on the effect of miconazole, butoconazole, clotrimazole, tioconazole, or terconazole on nursing infants, but systemic absorption after maternal vaginal administration is minimal, hence topical use in nursing mothers is reasonable.

Postcoital hypersensitivity reaction in male partner — In a variant syndrome, male partners of women with vaginal *Candida* colonization develop immediate postcoital itching and burning with redness and a rash of the penis. This postcoital syndrome probably represents an acute hypersensitivity reaction to *Candida* organisms or antigens in the partner's vagina, even in the absence of symptomatic vulvovaginitis.

Males with recurrent postcoital symptoms do not benefit from topical antimycotic therapy since the key to eradicating symptoms lies in eliminating *Candida* organisms from the lower genital tract of the female sexual partner. This often requires the female partner to follow a long-term maintenance antimycotic regimen.

A postcoital shower and application of a topical low potency corticosteroid to the penis may provide symptomatic relief within 12 to 24 hours. Penile cultures may remain positive for *Candida* despite normal physical findings.

PREVENTION — As discussed above, oral nystatin does not prevent vaginal candidiasis and lactobacillus (oral or vaginal) does not prevent postantibiotic vulvovaginitis. In women susceptible to symptomatic yeast infections when taking antibiotic therapy, a dose of fluconazole (150 mg orally) at the start and end of antibiotic therapy may prevent postantibiotic vulvovaginitis [8].

COMPLEMENTARY AND ALTERNATIVE MEDICINE — There is no evidence from randomized trials that garlic, tea tree oil, yogurt (or other products containing live Lactobacillus species), or douching is effective for treatment or prevention of vulvovaginal candidiasis due to *Candida albicans* [116].

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword (s) of interest.)

- Basics topics (see "Patient education: Vulvovaginal yeast infection (The Basics)" and "Patient education: Vulvar itching (The Basics)")
- Beyond the Basics topics (see "Patient education: Vaginal yeast infection (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- *Candida* is considered part of the normal vaginal flora, but overgrowth of the organism and penetration of superficial epithelial cells can result in vulvovaginitis. *Candida albicans* accounts for 80 to 92 percent of episodes of vulvovaginal candidiasis; *Candida glabrata* is the next most common species. (See 'Prevalence' above and 'Microbiology' above and 'Pathogenesis' above.)
- Vulvar pruritus is the dominant symptom. Vulvar burning, soreness, and irritation are common and may result in dysuria and dyspareunia. The vulva and vagina appear erythematous, and vulvar excoriation and fissures may be present. There is often little or no discharge; when present, it is classically white, thick, adherent, and clumpy (curd-like or cottage cheese-like) with no or minimal odor. (See 'Clinical features' above.)
- The diagnosis of vulvovaginal candidiasis is based on the presence of *Candida* on wet mount, Gram’s stain, or culture of vaginal discharge in a woman with characteristic clinical findings. (See 'Office diagnosis' above.)

- Culture is not necessary for diagnosis if microscopy shows yeast, but should be obtained in (see 'Role of culture' above):
  - Women with clinical features of vulvovaginal candidiasis, normal vaginal pH, and negative microscopy.
  - Women with persistent or recurrent symptoms because many of these women have non-albicans infection resistant to azoles.

Treatment

- Treatment is indicated to relieve symptoms. Asymptomatic women and sexual partners do not require treatment. (See 'Treatment' above and 'Treatment of partners' above.)
- The treatment regimen is based on whether the woman has an uncomplicated infection (90 percent of patients) or complicated infection (10 percent of patients). Criteria are listed in the table (table 2). (See 'Treatment' above.)

Uncomplicated infections — Oral and topical antimycotic drugs achieve comparable clinical cure rates, which are in excess of 80 percent in uncomplicated infection (table 3). (See 'Uncomplicated infection' above.)

- We suggest a single dose of oral fluconazole (150 mg) for treatment of uncomplicated infections rather than multidose and topical regimens (**Grade 2C**). (See 'Uncomplicated infection' above.)

Complicated infections — Women with complicated infection require longer courses of therapy than women with uncomplicated infection. (See 'Complicated infections' above.)

- For women with severe symptoms, we suggest fluconazole (150 mg) in two sequential doses given three days apart rather than topical antimycotic agents (**Grade 2C**). (See 'Severe symptoms or compromised host' above.)
- For treatment of *C. glabrata*, we suggest intravaginal boric acid (600 mg capsule once daily at night for two weeks) (**Grade 2C**). Alternative treatments include intravaginal nystatin pessary 1,000,000 units daily, amphotericin B, or flucytosine cream. (See 'C. glabrata' above.)
- For pregnant women, we suggest a topical imidazole (clotrimazole, miconazole) vaginally for seven days rather than a nystatin pessary or an oral azole (**Grade 2C**). Case reports have described a pattern of birth defects (abnormalities of cranium, face, bones, and heart) after first trimester exposure to high dose oral azole therapy (400 to 800 mg/day) and cohort studies have reported conflicting data on risk of miscarriage. (See 'Pregnancy' above.)
- For women with recurrent vulvovaginitis (≥4 episodes/year), we suggest suppressive maintenance therapy rather than treatment of individual episodes (**Grade 2B**). We prescribe initial induction therapy with fluconazole 150 mg every 72 hours for three doses, then maintenance fluconazole 150 mg once per week for six months. Women with recurrent infection should try to eliminate or reduce risk factors for infection. (See 'Recurrent infection' above.)

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Topic 5452 Version 50.0

GRAPHICS

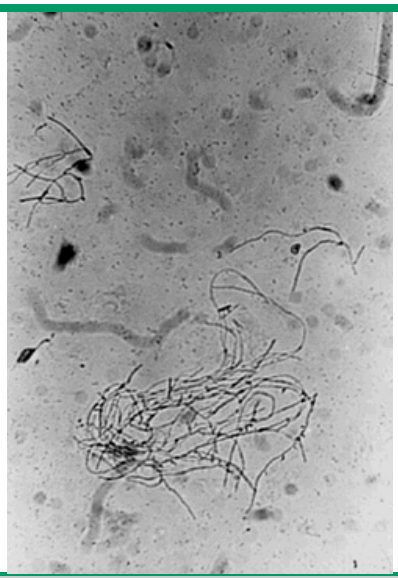
Clinical findings in women with vaginitis

Parameter	Normal findings	Vulovaginal candidiasis	Bacterial vaginosis	Trichomoniasis
Symptoms	None or mild, transient	Pruritus, soreness, dyspareunia	Malodorous discharge, no dyspareunia	Malodorous discharge, burning, postcoital bleeding, dyspareunia, dysuria
Signs	Normal vaginal discharge consists of 1 to 4 mL fluid (per 24 hours), which is white or transparent, thin or thick, and mostly odorless	Vulvar erythema and/or edema. Discharge may be white and clumpy and may or may not adhere to vagina.	Off-white/gray thin discharge that coats the vagina	Thin green-yellow discharge, vulvovaginal erythema
Vaginal pH	4.0 to 4.5	4.0 to 4.5	>4.5	5.0 to 6.0
Amine test	Negative	Negative	Positive (in 70-80 percent of patients)	Often positive
Saline microscopy	PMN:EC ratio <1; rods dominate; squames +++	PMN:EC ratio <1; rods dominate; squames +++; pseudohyphae (present in about 40 percent of patients); budding yeast for nonalbicans Candida	PMN:EC <1; loss of rods; increased coccobacilli; clue cells comprise at least 20 percent of epithelial cells (present in >90 percent of patients)	PMN ++++; mixed flora; motile trichomonads (present in about 60 percent of patients)
10 percent potassium hydroxide microscopy	Negative	Pseudohyphae (in about 70 percent of patients)	Negative	Negative
Other tests	–	If microscopy nondiagnostic: Culture DNA hybridization probe (eg, Affirm VP III)	Quantitative Gram stain (eg, Nugent criteria, Hay/Ison criteria) DNA Hybridization probe (eg, Affirm VP III) Culture of **no** value	If microscopy nondiagnostic: Culture (eg, InPouch TV culture system) Rapid antigen test (eg, OSOM Trichomonas Rapid Test) Nucleic acid amplification test (eg, APTIMA Trichomonas vaginalis test) DNA Hybridization probe (eg, Affirm VP III)
Differential diagnosis	Physiologic leukorrhea	Contact irritant or allergic vulvar dermatitis, chemical irritation, focal vulvitis (vulvodynia)	Elevated pH in trichomoniasis, atrophic vaginitis, and desquamative inflammatory vaginitis	Purulent vaginitis, desquamative inflammatory vaginitis, atrophic vaginitis, erosive lichen planus

PMN: polymorphonuclear leukocytes; EC: vaginal epithelial cells.

Graphic 68759 Version 10.0

Candida albicans vaginitis

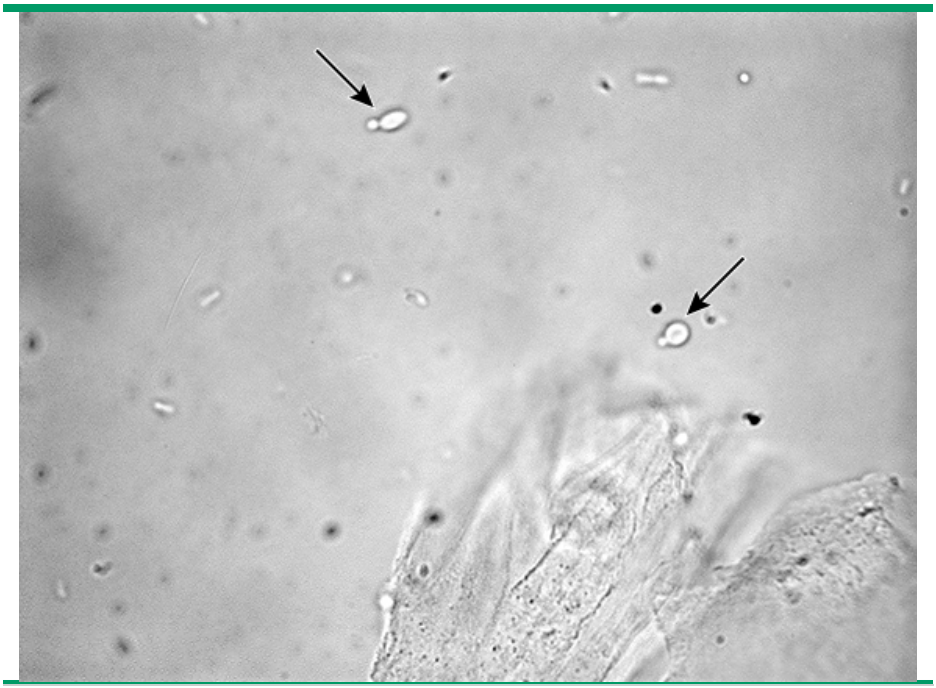


Low-power micrograph of hyphal elements seen on 10% potassium hydroxide examination of a patient with *C. albicans* vaginitis.

Courtesy of Jack D Sobel, MD.

Graphic 59030 Version 4.0

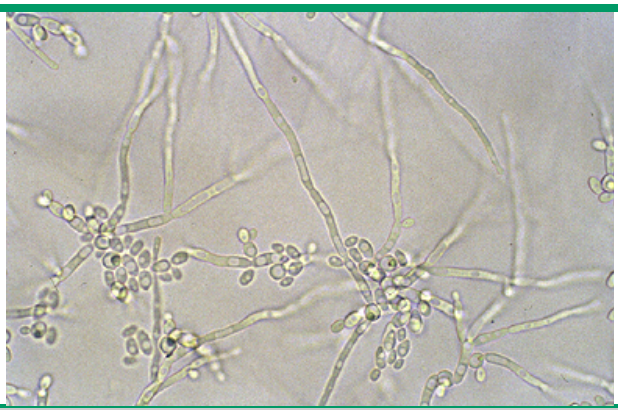
Budding yeast



Budding yeast representing C. glabrata.

Graphic 61326 Version 2.0

Budding cells of Candida species

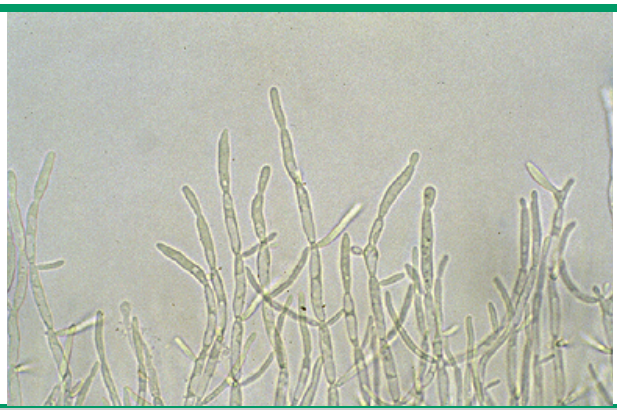


Candida albicans, *C. krusei*, *C. parapsilosis* and *C. tropicalis* all form elliptical budding cells that typically are larger in size than those of *C. glabrata*. Elaborate multicellular filaments, particularly when in contact with a solid substrate such as mucosal membranes or agar culture media.

Courtesy of Wiley Schell, MS.

Graphic 53369 Version 3.0

Candida pseudohyphae

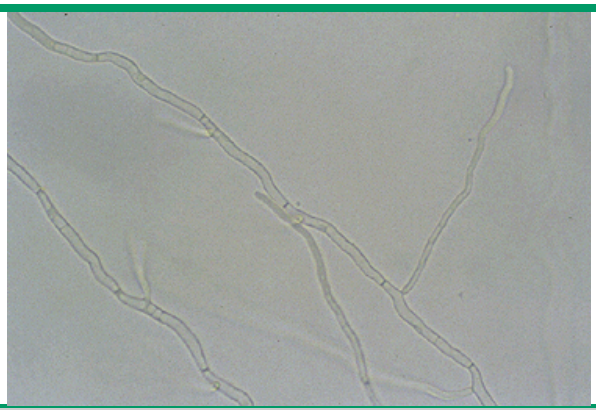


Pseudohyphae (as opposed to true hyphae) are formed when buds elongate with differential rates of wall synthesis at various points along the cell wall. Elongation then stops, and the cell produces a new apical bud which elongates. This repeated process of budding and elongation can result in extensive filamentation. Side branches initiate as buds and develop in the same manner. In most cases, a constriction remains and can be seen at the origin of each bud.

Courtesy of Wiley Schell, MS.

Graphic 80723 Version 2.0

True hyphae of Candida albicans

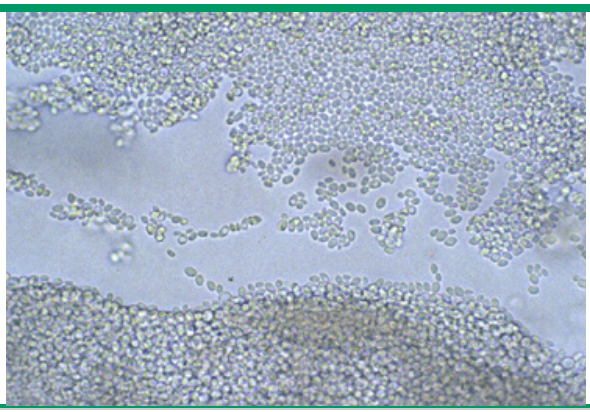


True hyphae (as opposed to pseudohyphae) elongate through a process of apical synthesis that does not involve budding. Since buds are not present at the hyphal tips, the hyphae do not exibit periodic constrictions associated with the budding process.

Courtesy of Wiley Schell, MS.

Graphic 76924 Version 1.0

Candida glabrata



Candida glabrata grows as a small, elliptical, budding, unicellular yeast. Buds rarely adhere to one another in rudimentary chains, but filamentous growth does not occur.

Courtesy of Wiley Schell, MS.

Graphic 61641 Version 3.0

Classification of candidal vaginitis

Variable	Uncomplicated disease*	Complicated disease¶
Symptom severity	Mild or moderate	Severe
Frequency	Sporadic	Recurrent
Organism	Candida albicans	Nonalbicans species
Host	Normal	Abnormal (eg, uncontrolled diabetes mellitus, recurrent infections, immunosuppression)

* Patients must have ALL of these features.

¶ Patients may have ANY of these features.

Graphic 62038 Version 3.0

Treatment of uncomplicated vaginal candidiasis

Drug and trade name (s)	Requires a prescription in US	Preparation	Intravaginal* dose for adult
Clotrimazole			
Gyne-Lotrimin¶	No	1 percent cream	1 applicatorful (~5 g) daily for 7 days
Gyne-Lotrimin 3¶	No	2 percent cream	1 applicatorful (~5 g) daily for 3 days
Gyne-LotriminΔ	Not applicable (not available in US)	100 mg vaginal tabletΔ	Insert 1 vaginal tablet daily for 7 days or 2 tablets daily for 3 days
Miconazole			
Monistat 7¶	No	2 percent cream (combination kit may include 2 percent miconazole cream for external use)	1 applicatorful (~5 g) daily for 7 days
Monistat 3¶	No	4 percent cream	1 applicatorful (~5 g) daily for 3 days
Monistat 7¶	No	100 mg vaginal suppository	1 suppository daily for 7 days
Monistat 3¶, Vagistat-3	No (combination kit) Yes (generic suppository)	200 mg vaginal suppository (combination kit may include 2 percent miconazole cream for external use)	1 suppository daily for 3 days
Monistat 1	No	1200 mg vaginal suppository (combination kit may include 2 percent miconazole cream for external use)	1 suppository for 1 day
Nystatin◇			
Nystatin vaginalΔ (former US trade name Mycostatin)	Not applicable (not available in US)	100,000 unit vaginal tablet	Insert 1 vaginal tablet daily for 14 days
Terconazole¥			
Terazole 7, Zazole¶	Yes	0.4 percent cream	1 applicatorful (~5 g) daily at bedtime for 7 days
Terazole 3, Zazole¶	Yes	0.8 percent cream	1 applicatorful (~5 g) daily at bedtime for 3 days
Terazole 3, Zazole¶	Yes	80 mg vaginal suppository	1 suppository daily at bedtime for 3 days
Tioconazole			
Vagistat-1, 1-Day (from Monistat)¶	No	6.5 percent ointment	1 applicatorful (~5 g) at bedtime as a single dose
Butoconazole			
Gynazole-1	Yes	2 percent cream	1 applicatorful (~5 g) as a single dose
Fluconazole ORAL ADMINISTRATION§			
Diflucan¶	Yes	150 mg oral tablet	Single dose by mouth

There are no significant differences in efficacy among topical and systemic azoles (cure rates >80 percent for uncomplicated vulvovaginal candidiasis).

g: grams.
* Except fluconazole (oral administration).
¶ Generic equivalent preparation(s) are available in US.
Δ Not available in US.
◇ Cure rate with nystatin is 70 to 80 percent.
§ Itraconazole is another oral antifungal that appears to be effective. Pitsouni E, et al. Am J Obstet Gynecol 2008; 198:153.
¥ Rare cases of anaphylaxis and toxic epidermal necrolysis have been reported during terconazole therapy.

Graphic 71686 Version 15.0

Treatment of complicated vaginal candidiasis

Severe vaginitis symptoms
Oral fluconazole 150 mg every 72 hours for 2 or 3 doses (depending on severity)
OR
Topical azole antifungal therapy daily for 7 to 14 days. A low potency topical corticosteroid can be applied to the vulva for 48 hours to relieve symptoms until the antifungal drug exerts its effect.
Recurrent vulvovaginal candidiasis
Induction with fluconazole 150 mg every 72 hours for 3 doses, followed by maintenance fluconazole 150 mg once per week for 6 months. If fluconazole is not feasible, options include 10 to 14 days of a topical azole or alternate oral azole (eg, itraconazole) followed by topical maintenance therapy for 6 months (eg, clotrimazole 200 mg [eg, 10 grams of 2 percent] vaginal cream twice weekly or 500 mg vaginal suppository once weekly).
Non-albicans Candida vaginitis
Therapy depends upon species identified:
C. glabrata: Intravaginal boric acid* 600 mg daily for 14 days
If failure occurs: 17 percent topical flucytosine cream, 5 grams nightly for 14 days
C. krusei: Intravaginal clotrimazole, miconazole, or terconazole for 7 to 14 days
All other species: Conventional dose fluconazole
Compromised host (eg, poorly controlled diabetes, immunosuppression, debilitation) and Candida isolate susceptible to azoles
Oral or topical therapy for 7 to 14 days
Pregnancy
Topical clotrimazole or miconazole for 7 days

Boric acid capsules and flucytosine cream are not commercially available, but can be made by a compounding pharmacy.

* Boric acid capsules can be fatal if swallowed.

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1. *Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Socity of America. Clin Infect Dis 2009; 48:503.*

Graphic 50932 Version 8.0

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