Genital candidiasis

Jack D Sobel

Abstract

Vulvovaginal candidiasis (vaginal thrush) remains an extremely common clinical problem, with both over- and under-diagnosis and unreliable self-diagnosis. Little progress has been made in providing diagnostic tests, and consequently inappropriate antifungal therapy is common. New genetic susceptibility mechanisms are emerging. No new antifungal drug regimens have recently appeared; accordingly, therapeutic recommendations are unchanged. Antifungal drug resistance fortunately remains rare.

Keywords azole antifungals; candidosis; *C. albicans*; *C. glabrata*; genetic susceptibility; vaginal thrush; vulvovaginal candidiasis

What's new?

- Value of long-term maintenance fluconazole regimens confirmed in additional studies
- No new widely available diagnostic tests
- No new antifungal agents
- Probiotic therapy largely ineffective both as prophylaxis and therapy
- Emerging evidence of genetic contribution to genital candidiasis susceptibility

Yeasts are microscopic, single-celled fungi that reproduce by budding.[1] Strains of *Candida albicans* constitute 90% of yeasts isolated from the vagina. Of the remainder, the most common are *C. glabrata* and *C. tropicalis*. Non-albicans *Candida* spp. can induce vaginitis and are often more resistant to conventional therapy. There is no evidence that the prevalence of non-albicans *Candida* spp. causing vaginitis is increasing.

Candida is the second most common vaginal infection after bacterial vaginosis. During the child-bearing years, 75% of women experience at least one episode of vulvovaginal candidiasis, and 40–50% of these women experience a second episode.[2] A small subpopulation of women suffer repeated recurrent episodes of *Candida* vaginitis.

Asymptomatic candidiasis

Asymptomatic candidiasis is common; *Candida* may be isolated from the genital tract of about 20% of asymptomatic healthy women of child-bearing age. *Candida* gains access to the vaginal lumen and secretions predominantly from the adjacent perianal area, and then adheres to vaginal epithelial cells. The numbers of *C. albicans* that adhere to the vaginal epithelial cells are significantly greater than those of *C. tropicalis*, *C. krusei* and *C. glabrata*.

Several factors are associated with increased prevalence of asymptomatic vaginal colonization with *Candida* (Table 1).[3]

The hormonal dependence of the infection is illustrated by the fact that *Candida* is seldom isolated from premenarchal girls, and that the prevalence of *Candida* vaginitis is lower after the menopause, except in women taking hormone replacement therapy (HRT).

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Pathogenesis[3]

Germination of *Candida* enhances colonization and tissue invasion.[1] Factors that facilitate germination (e.g. oestrogen therapy, pregnancy) tend to precipitate symptomatic vaginitis; measures that inhibit germination may prevent acute vaginitis in women who are asymptomatic carriers of yeast. Other virulence factors include proteolytic enzymes, toxins and phospholipase elaboration. It is uncommon to find a precipitating factor that explains the transformation from asymptomatic carriage to symptomatic vaginitis.

Host factors

Oestrogens: during pregnancy, the incidence of clinical attacks reaches a maximum in the third trimester, but symptomatic recurrences are common throughout pregnancy. It is generally thought that the high level of reproductive hormones increases the glycogen content of the vaginal environment and provide a carbon source for *Candida* growth and germination. Oestrogens increases vaginal epithelial cell avidity for *Candida* adherence, and a yeast cytosol receptor or binding system for female reproductive hormones has been documented. In addition, oestrogens increase formation of yeast mycelia. Low-oestrogen oral contraceptives may also increase *Candida* vaginitis. HRT,

Factors associated with increased asymptomatic vaginal colonization with *Candida*, and with *Candida* vaginitis

- Genetic factors
- Pregnancy
- Uncontrolled diabetes mellitus
- High-oestrogen oral contraceptives
- Corticosteroid therapy
- Tight-fitting, synthetic underclothing (possibly)
- Antimicrobial therapy (oral, parenteral or topical)
- Use of IUD
- High frequency of coitus[a]
- Confectionery-eating binges[a]
- HIV infection

[a] Vaginitis only.

Table 1

especially topical therapy, may contribute to vaginitis in postmenopausal women.

Diabetes mellitus: vaginal colonization with *Candida* is more common in diabetes; uncontrolled diabetes predisposes to symptomatic vaginitis. Glucose tolerance tests have been recommended in women with recurrent vulvovaginal candidiasis; however, the yield is low, and testing is not justified in otherwise healthy premenopausal women. Type 2 diabetes selects for *C. glabrata*. Diets high in, or binges of, refined sugar may precipitate symptomatic vaginitis.

Antibiotics: symptomatic vulvovaginal candidiasis often occurs during or after use of systemic or intravaginal antibiotics possibly as a result of eliminating the normal protective vaginal bacterial flora. Although no antimicrobial agent is free from this complication, it is especially common following the use of broad-spectrum antibiotics[4] (e.g. tetracycline, ampicillin, cephalosporin). *Lactobacillus* spp. in the natural flora are hypothesized to provide a colonization resistance mechanism and prevent germination of *Candida*. However, most women taking antibiotics do not develop *Candida* vaginitis and women deficient in lactobacilli are not at risk of developing *Candida* vaginitis.

Environmental factors that predisposed to *Candida* vaginitis may include tight, poorly ventilated clothing and nylon underclothing, which increase perineal moisture levels and temperature. Chemical contact, local allergy and hypersensitivity reactions may also predispose to symptomatic vaginitis.[5]

Immunosuppression: in patients who are debilitated or immunosuppressed, oral and vaginal thrush correlate well with reduced cell-mediated immunity. This is evident in chronic mucocutaneous candidiasis and AIDS. Lymphocytes might therefore contribute to normal vaginal defence mechanisms, preventing mucosal invasion by *Candida*.

Genetic factors have an important role in determining the risk of both vaginal yeast colonization and symptomatic episodes. Recent studies suggest a role for mannose-binding lectin and dectin-1 receptors polymorphism.[3]

Recurrent and chronic *Candida* vaginitis: various theories have been proposed to explain recurrent vaginitis (Table 2).

Intestinal reservoir — the intestinal reservoir theory is based on recovery of *Candida* on rectal culture in almost 100% of women with vulvovaginal candidiasis. DNA typing of vaginal and rectal cultures obtained simultaneously usually reveals identical strains. However, other studies have shown a lower concordance between rectal and vaginal cultures in patients with recurrent vulvovaginal candidiasis; also, oral nystatin, which reduces intestinal yeast carriage, fails to prevent recurrence of vulvovaginal candidiasis. Repeated re-introduction of yeast into the vagina from the gut is therefore no longer considered a likely cause of recurrent *Candida*.

Sexual transmission — penile colonization with *Candida* is present in about 20% of male partners of women with recurrent vulvovaginal candidiasis; infected partners usually carry identical strains. Oral colonization of partners with an identical strain of *Candida* also occurs and may be a source of orogenital transmission. However, in most studies involving treatment of partners, there was no reduction in the frequency of episodes of vaginitis.

Pathogenesis of recurrent vulvovaginal candidiasis

Source
- More frequent vaginal inoculation
  - Intestinal reservoir theory
  - Sexual transmission
- Vaginal relapse

Mechanism
- Increased *Candida* virulence (seldom the result of antimycotic drug resistance)
- Reduced mucosal immunity (cell-mediated immunity)
- Immediate hypersensitivity reaction (IgE)
- Loss of resistance to bacterial colonization

Table 2

Vaginal relapse — though antimycotic therapy may reduce the number of *Candida* in the lumen and alleviate the signs and symptoms of inflammation, eradication or clearance of *Candida* from the vagina is incomplete because all of the antimycotic agents are fungistatic. The small number of organisms that persist in the vagina result in continued carriage of the organism, so that when host environmental conditions permit, the colonizing organisms increase in number and undergo mycelial transformation, resulting in a new clinical episode.

Drug resistance is seldom responsible for recurrent vulvovaginal candidiasis in women infected with *C. albicans*.

Reduced host resistance — current theories of the pathogenesis of recurrent vulvovaginal candidiasis relate to genetic susceptibility which enhances vaginal colonization, as well as to deficient innate and altered cell-mediated immunity. However, no evidence is available of any deficiency in vaginal lactobacilli, and exogenous recolonization of the vagina with probiotic lactobacilli is therefore not useful. Altered vaginal *Candida*-specific immunity may be responsible for recurrent infection in women with a genetic predisposition.

Clinical features[6]

- Vulvar pruritus is the most common symptom of *Candida* vulvovaginitis and is present in most symptomatic patients.
- Vaginal discharge is often minimal and sometimes absent. Although described as being typically 'cottage cheese-like' in character, this discharge may vary from watery to homogeneously thick.
- Vaginal soreness, irritation, vulvar burning, dyspareunia and external dysuria are common.
- If there is an odour, it is minimal and inoffensive.
- Characteristically, symptoms are exacerbated during the week before the onset of menses. The onset of menstrual flow brings some relief.
- Examination reveals erythema (Figure 1) and swelling of the labia and vulva, often with discrete, pustulopapular, peripheral lesions. The cervix is normal. Vaginal mucosal erythema with adherent whitish discharge is present (Figure 2).