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NEWSLETTER

VULVOVAGINAL CANDIDIASIS

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Vulvovaginal candidiasis (VVC) is usually caused by *C. albicans,* but can occasionally be caused by other *Candida* species. Typical symptoms of VVC include pruritus, vaginal soreness, dyspareunia, dysuria, and abnormal vaginal discharge. An estimated 75% of women will have at least one episode of VVC in their lifetime.

VVC can be classified as either uncomplicated or complicated.

- **Uncomplicated** infection is defined by:
  - Sporadic, infrequent episodes (⩽ 3 episodes/year)
  - Mild to moderate signs/symptoms
  - Probable infection with *Candida albicans*
  - Healthy, non-pregnant woman

- **Complicated** infections are defined by:
  - Severe signs/symptoms
  - *Candida* species other than *C. albicans,* particularly *C. glabrata*
  - Pregnancy, poorly controlled diabetes, immunosuppression, debilitation
  - History of recurrent (⩾ 4 episodes/year) culture-verified vulvovaginal candidiasis

Approximately 10% – 20% of women will have complicated VVC, requiring special diagnostic and therapeutic considerations.

Microbiology

Candida species can be identified in the lower genital tract of 10% – 20% of healthy women in their reproductive years. It is important to remember that the identification of vulvovaginal *Candida* does not equate to candidal disease – the diagnosis of VVC requires the presence of both *Candida* AND vulvovaginal inflammation. *Candida albicans* is responsible for 80% – 92% of episodes of VVC, while *C. glabrata* accounts for almost all of the rest. Some researchers have reported an increasing frequency of non-albicans species, particularly *C. glabrata.* This may be due to widespread use of over-the-counter drugs, long-term use of suppressive azoles, and the use of short courses of antifungal drugs.

Pathogenesis

Candida organisms access the vagina via migration from the rectum across the perianal area, as cultures from both the vagina and gastro-intestinal tract often show identical *Candida* species. Symptomatic disease is associated with an overgrowth of the organism and penetration of superficial epithelial cells. 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.

Risk factors

Sporadic attacks of vulvovaginal candidiasis usually occur without an identifiable precipitating factor. However, a number of factors have been reported to predispose to symptomatic infection:

- **Diabetes mellitus:** Women with diabetes mellitus who have poor glycaemic control are more prone to vulvovaginal candidiasis than euglycaemic women. In particular, women with Type 2 diabetes appear prone to infection with non-albicans *Candida* species.
- **Antibiotic use:** Use of broad spectrum antibiotics significantly increases the risk of developing vulvovaginal candidiasis.
- **Increased oestrogen levels:** Vulvovaginal candidiasis occurs more often in the setting of increased oestrogen levels, such as oral contraceptive use, pregnancy, and oestrogen therapy.
- **Immunosuppression:** Candidal infections are more common in immunosuppressed patients, including those taking glucocorticoids or other immunosuppressive drugs, and HIV infection.
- **Contraceptive devices:** Vaginal sponges, diaphragms, and intrauterine devices have been associated with VVC. Spermicides, however, are not associated with *Candida* infection.
- **Behavioural factors:** While VVC is not traditionally considered a sexually transmitted disease (STD) since *Candida* species are considered part of the normal vaginal flora, sexual transmission does occur.

The risk factors described above are apparent in only a minority of women with recurrent disease. In the majority, factors that predispose to recurrent infection more likely involve abnormalities in the local vaginal mucosal immunity and genetic susceptibility.

Diagnosis

The diagnosis of vulvovaginal candidiasis is primarily based on the presence of yeast on wet mount or Gram stain, and the culture of *Candida* from a relevant clinical sample (e.g. vaginal discharge) in a woman with characteristic clinical findings (e.g. vulvovaginal pruritus, burning, erythema, oedema, and/or curd-like discharge attached to the vaginal sidewall), with no other pathogens to account for her symptoms. Importantly, although vulvar pruritus is a cardinal symptom of the disorder, less than 50% of women with genital pruritus have vulvovaginal candidiasis. Cultures are useful in women with persistent or recurrent symptoms as many of these women may be infected with non-albicans *Candida* species (which are resistant to the azoles).

Molecular methods (e.g. PCR) have high sensitivity and specificity, but are costly and offer no proven benefit over culture in symptomatic women.

Yeast-like bodies consistent with *Candida* species can be detected in only 25% of cytology (Pap smear) samples from patients with culture positive, symptomatic vulvovaginal candidiasis. It is insensitive for the diagnosis of vulvovaginal candidiasis because the cells are derived from the cervix, which is not affected by *Candida* vaginitis. Treatment of *Candida* detected on a Pap smear of an asymptomatic woman is not currently indicated.

Conditions to be considered in the differential diagnosis of vulvovaginitis with normal vaginal pH include hypersensitivity reactions, allergic or chemical reactions, and contact dermatitis.

Treatment

Treatment is indicated for relief of symptoms, and the treatment regimen is based on whether the woman has an uncomplicated infection (90% of patients) or complicated infection (10% of patients).

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.** The absence of superiority of any formulation, agent, or route of administration suggests that cost, patient preference, and contra-indications are the major considerations in the decision to prescribe an anti-fungal for oral or topical administration. Fluconazole (150 mg as a single oral dose) is generally recommended, as therapeutic concentrations are maintained for at least 72 hours after ingestion and side-effects tend to be mild and infrequent. Clinical cure rates are in excess of 80%, and treatment of sexual partners is unnecessary. There is no medical contra-indication to sexual intercourse during treatment, but it may be uncomfortable until inflammation improves.

Women with **complicated vulvovaginal candidiasis** require longer courses of therapy than women with uncomplicated infection. Therapeutic options include:

- Fluconazole (150 mg) for two or three sequential doses given three days apart. If the patient prefers topical therapy, observational series report that complicated patients require 7 to 14 days of topical azole therapy (e.g. clotrimazole, miconazole, econazole) rather than a one- to three-day course.
- For treatment of *C. glabrata* vulvovaginitis that is unresponsive to oral azoles, intravaginal boric acid (600 mg capsule once daily at night for two weeks) or 17% flucytosine cream (5g nightly for 14 days) may be an option. Neither boric acid capsules nor flucytosine cream is available commercially and must be made by a compounding pharmacy. There is insufficient evidence for the use of oral voriconazole for the treatment of *C. glabrata* vaginitis.
- In pregnant women, a topical imidazole (clotrimazole or miconazole) vaginally for 7 days, rather than a nystatin pessary or an oral azole, may be used. Case reports have described a pattern of birth defects after first trimester exposure to high dose oral fluconazole therapy (400 to 800 mg/day) and cohort studies have reported conflicting data on the risk of miscarriage. Vaginal candidiasis is not associated with any adverse pregnancy outcomes.
- For women with recurrent vulvovaginitis ($\geqslant$ 4 episodes/year), suppressive maintenance therapy rather than treatment of individual episodes may be considered. 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.
- Alternative approaches to recurrent infection that have been suggested include:
  - Treat each recurrent episode as an episode of uncomplicated infection
  - Treat each recurrent episode with longer duration of therapy (e.g. topical azole for 7 to 14 days or fluconazole 150 mg orally on day 1, day 4, and day 7)
  - 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 non-oral alternative)

In women with refractory vulvovaginal candidiasis with persistently positive *C. albicans* cultures, MICs to various antifungals can be tested. True azole resistance is very rare in patients who are fully compliant with their treatment regimen. The use of probiotic lactobacilli as well as gentian violet is not recommended.

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, as no adverse effects have been reported in breastfed infants or infants treated with parenteral fluconazole. The use of topical agents in nursing mothers is reasonable.

References

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