Chapter 39: Fungal Infections, Superficial

VULVOVAGINAL CANDIDIASIS

- Vulvovaginal candidiasis (VVC) refers to infections in individuals with or without symptoms who have positive vaginal cultures for *Candida* species. It may be sporadic or recurrent.
- By 25 years of age, approximately 50% of college-age women will have had at least one episode of VVC.

Pathophysiology

- *C. albicans* is the major pathogen responsible for VVC, accounting for 80%–92% of symptomatic episodes. The remainder are caused by non–*C. albicans* species, with *Candida glabrata* dominating.
- Changes in the host's vaginal environment or response are necessary to induce a symptomatic infection. In most cases of symptomatic VVC, no precipitating factor can be identified.

Clinical Presentation

- There is a dramatic increase in the frequency of VVC when women become sexually active.
- Antibiotic use can increase the risk of VVC, but it is significant in only a small number of women.
- Symptoms include intense vulvar itching, soreness irritation, burning on urination, and dyspareunia.
- Signs include erythema, fissuring, curdy "cheese"-like discharge, satellite lesions, and edema.
- Laboratory tests: Vaginal pH—normal saline, and 10% potassium hydroxide (KOH) microscopy for blastospores or pseudohyphae.
- *Candida* cultures are not recommended unless classic signs and symptoms with normal vaginal pH and microscopy are inconclusive or recurrence is suspected.
- The diagnosis should be based on both clinical presentation and investigations, including vaginal pH, saline microscopy, and 10% KOH microscopy of vaginal discharge.

Treatment

- Goals of Treatment: Complete resolution of symptoms in patients who have symptomatic VVC.

General Approach

- Remove or improve any predisposing factors if they can be identified.
- Avoid harsh soaps and perfumes that can cause or worsen vulvar irritation. The genital area must be kept clean and dry by avoiding constrictive clothing and frequent or prolonged exposure to hot tub use. Douching is not recommended for either prevention or treatment.

Nonpharmacologic Therapy

- The value of oral use of lactobacillus remains unclear. Daily ingestion of 240 mL yogurt containing *Lactobacillus acidophilus* decreased

colonization and symptomatic infections of VVC in women with recurrent infections.

- A trial of an oral mixture of bee-honey and yogurt showed some efficacy with mycotic cure rates of 76.9% compared to cure rates with antifungal agents of 91.5%.

Pharmacologic Therapy

- Effective antimycotic agents should have limited local and systemic side effects, a high cure rate, and easy administration.
- **Table 39-1** lists treatments for uncomplicated VVC. There are no significant differences in in-vitro activity or clinical efficacy among the topical azole agents. Oral azoles (such as **fluconazole** or **itraconazole**) are therapeutically equivalent to topical therapies.
- Patients with complicated VVC (immunocompromised or uncontrolled diabetes mellitus) should be treated for 10–14 days.
- Pregnant patients with VVC should be treated with topical agents.
- Patients with recurrent VVC should receive a 10-day initial treatment (such as with oral **fluconazole** 150 mg) followed by 6 months of prolonged treatment (with oral fluconazole once weekly 150 mg).
- Treatment of VVC is considered to have positive outcomes if the symptoms are resolved within 24–48 hours and no adverse medication events are experienced. Self-assessment of symptom relief is appropriate for most cases of VVC. If symptoms remain unresolved or recur, then further testing and treatment can be required.

TABLE 39-1

Treatment for Uncomplicated Vulvovaginal Candidiasis

Active Ingredient	Preparation	Regimen
Nonprescription/Topical vaginal products		
Butoconazole	2% cream	One applicator × 3 days
Clotrimazole	1% cream	One applicator × 1 day
	100 mg tablet	One 100 mg tablet × 7 days
	2% cream	One applicator × 1 day
	200 mg tablet	One 200 mg tablet × 3 days
	10% cream	One applicator × 1 day
	500 mg tablet	One 500 mg tablet × 1 day
Miconazole[a]	2% cream	One applicator × 1 day
	100 mg suppository	One 100 mg suppository × 7 days
	200 mg suppository	One 200 mg suppository × 3 days
	1200 mg ovule	One ovule × 1 day
Ticonazole	2% cream	One applicator × 3 days
	6.5% cream	One applicator × 1 day
Prescription/Topical		
Nystatin	100,000 unit tablet	One tablet × 14 days
Terconazole	0.4% cream	One applicator × 7 days
	0.8% cream	One applicator × 3 days
Oral products		
Fluconazole	150 mg	One tablet × 1 day

[a]The FDA warns of the possible increase in the anticoagulant effects of warfarin with concomitant use.

OROPHYRYNGEAL AND ESOPHAGEAL CANDIDIASIS

- Oropharyngeal candidiasis (OPC), often referred to as thrush, is caused by the yeast *Candida,* most often *C. albicans.*

Pathophysiology

- A variety of host and exogenous factors can lead to the transformation of asymptomatic colonization to symptomatic disease, such as oropharyngeal and esophageal candidiasis.
- Endocrine disorders besides diabetes mellitus, such as hypothyroidism, hypoparathyroidism, and hypoadrenalism, also can predispose patients to *Candida* species overgrowth.
- Patients with primary immune deficiencies such as lymphocytic abnormalities, phagocytic dysfunction, immunoglobulin A (IgA) deficiency, viral-induced immune paralysis, and severe congenital immunodeficiencies are also at risk for OPC as well as disseminated candidiasis.
- OPC remains the most common opportunistic infection in patients with HIV disease. The CD4 T-cell count is the hallmark predictor for development of OPC; however, HIV viral load may have a stronger association with OPC than CD4 cell number.

Clinical Presentation

- Various classifications of OPC are given in **Table 39-2**. The clinical presentation of OPC and esophageal candidiasis is presented in **Table 39-3**.
- A presumptive diagnosis of OPC usually is made by the characteristic appearance on the oral mucosa, with resolution of signs and symptoms after antifungal therapy.

TABLE 39-2

Clinical Classification of Oropharyngeal Candidiasis

Types	Population at Risk	Clinical Signs and Appearance
Pseudomembranous (thrush)	Neonates, patients with HIV or cancer, the debilitated elderly, patients on broad-spectrum antibiotics or steroid inhalers, patients with dry mouth from various causes, and smokers	Classic “cottage cheese” appearance, yellowish white, soft plaques (or milk curds) overlying areas of erythema on the buccal mucosa, tongue, gums, and throat; plaques are easily removed by vigorous rubbing but can leave red or bleeding sites when removed; lesions on the tongue dorsum give it a bald, depapillated appearance
Erythematous (atrophic)	Patients with HIV, patients on broad-spectrum antibiotics or steroid inhalers	Sensitive and painful erythematous mucosa with few, if any, white plaques; lesions are generally on the dorsal surface of the tongue or the hard palate, occasionally on the soft palate, but any part of the mucosa can be involved; appear as flat red patches on the palate or atrophic patches on the tongue dorsum with loss of papillae. Can be acute or chronic
Hyperplastic (candidal leukoplakia)	Smokers; uncommon in patients with HIV	Thick white and adherent keratotic plaques commonly seen on the buccal mucosa and lateral border of the tongue; can also be seen on the lips and the bottom of the mouth; plaques cannot be easily scraped off or only partially removed; this condition is distinct from oral hairy leukoplakia, and it can progress to severe dysplasia or malignancy
Angular cheilitis	Patients with HIV, denture wearers	Painful red, ulcerative, cracking, or fissuring lesion at one or both comers of the mouth because of an inflammatory reaction; usually lesions are small and rather punctate, but occasionally they can extend in a linear fashion from the angles onto the facial skin
Denture stomatitis (chronic atrophic)	Denture wearers who tend to be elderly and have poor oral hygiene	Red, flat lesions on the mucosa beneath the denture and extend right up to the denture border; more commonly located beneath a maxillary denture, although they can be encountered beneath a mandibular denture
Central papillary atrophy (median rhomboid glossitis)	Uncommon (<1% prevalence), men more commonly infected than women (3:1)	Rhomboid-shaped hypertrophic or atrophic plaque in the mid-DORSAL tongue. Lesions may not resolve completely

HIV, human immunodeficiency virus.

TABLE 39-3

Clinical Presentation of Oropharyngeal and Esophageal Candidiasis

Oropharyngeal Candidiasis	Esophageal Candidiasis
General The clinical features can be quite diverse (see Table 39-2)	**General** This usually occurs as an extension of OPC; however, the esophagus can be the only site involved; the distal two-thirds, rather than the proximal one-third, is the most common site
Symptoms Symptoms are diverse and range from none to a sore, painful mouth, burning tongue, metallic taste, and dysphagia and odynophagia with involvement of the hypopharynx	**Symptoms** Typically, the symptoms are dysphagia, odynophagia, and retrosternal chest pain but can be asymptomatic in some patients; although rare, epigastric pain can be the dominant symptom
Signs Signs are variable and can include diffuse erythema and white patches on the surfaces of the buccal mucosa, throat, tongue, or gums; constitutional signs are absent	**Signs** Constitutional signs, including fever, occasionally occur; physical findings can range from a few to numerous white or beige plaques of variable size Plaques can be hyperemic or edematous, with ulceration in more severe cases Most advanced cases can occur with increased mucosal friability and narrowing of lumen Uncommon complications include perforation and aortic–esophageal fistula formation
Laboratory tests Scraping of an active lesion for microscopic examination can help confirm the diagnosis (presence of pseudohyphae and budding yeast) but is usually not necessary Cultures are not necessary because isolation of *Candida* species does not distinguish between colonization and true infection; cultures can be taken in patients responding poorly to therapy to determine the infecting species and to predict likely drug resistance	**Laboratory tests** The best test is upper GI endoscopy (more useful than barium swallow); helps exclude other causes of esophagitis (eg, viral, aphthous ulcers); diagnosis is confirmed by the histologic presence of *Candida* species in biopsy lesions taken during endoscopy Cultures to look for drug-resistant *Candida* species are warranted in patients who require endoscopy

GI, gastrointestinal; OPC, oropharyngeal candidiasis.

Treatment

- The primary desired outcome in the management of OPC is a clinical cure; that is, elimination of clinical signs and symptoms. Efficacy end points for oropharyngeal and esophageal candidiasis include rapid relief of symptoms and prevention of complications without early relapse after completion of the course of therapy.
- Minimizing toxicities and drug–drug interactions of systemic antifungal agents, as well as maximizing adherence by ensuring that the patient understands the importance of therapy and the directions to take the medication appropriately, are important secondary outcomes of therapy.

General Approach

- Whenever feasible, it is desirable to minimize all predisposing factors, such as administration of corticosteroids, chemotherapeutic agents, and antimicrobials, as well as to institute proper oral hygiene and resolve concurrent conditions, such as denture stomatitis.

Pharmacologic Therapy

- Topical agents, such as **nystatin** and **clotrimazole**, are the standard treatment for uncomplicated OPC and generally are effective for treatment in otherwise healthy adults and infants with no underlying immunodeficiencies (**Table 39-4**).
- Systemic therapy is necessary in patients with OPC that is refractory to topical treatment, those who cannot tolerate topical agents, have moderate-to-severe disease, and those at high risk for disseminated systemic or invasive candidiasis.
- When patients become unresponsive to topical agents or **fluconazole** and **itraconazole**, alternative agents include **amphotericin B** and other triazoles such as **voriconazole** and **posaconazole** and echinocandins (**caspofungin, micafungin**, and **anidulafungin**).
- Long-term suppressive therapy with fluconazole is effective in preventing recurrences or new infections of OPC in HIV disease and in patients with cancer. However, the indications for antifungal prophylaxis and the best long-term management strategy still have not been well established.
- Patients with a history of one or more episodes of documented esophageal candidiasis and a CD4 T-cell count <200 cells/mm^3 (<0.2 × 10^9/L) despite being on highly active antiretroviral therapy (HAART) are candidates for secondary prophylaxis. Oral **fluconazole** 100 mg three times weekly is the regimen recommended for patients deemed in need of chronic suppressive therapy.

TABLE 39-4

Therapeutic Options for Mucosal Candidiasis

Initial Episodes of OPC[a]: Treat for 7–14 Days (Strength of Recommendation and Level of Evidence)	**Common/Significant Side Effects**
Clotrimazole 10 mg troche: hold 1 troche in mouth for 15–20 minutes for slow dissolution 5 times daily (B-2)[b]	Altered taste, mild nausea, vomiting
Nystatin 100,000 units/mL suspension: 5 mL swish and swallow orally 4 times daily (B-2)	Mild nausea, vomiting, diarrhea
Miconazole 50 mg mucoadhesive buccal tablets 50 mg orally daily (A-1)	Diarrhea, headache, nausea, dysgeusia, upper abdominal pain, and vomiting
Fluconazole 100 mg tablets[c]: 100–200 mg orally daily (A-1)	GI upset, hepatitis not common
Itraconazole 10 mg/mL solution[d]: 200 mg orally daily (A-2)	GI upset, not common: hepatotoxicity, CHF, pulmonary edema with long-term use[e]
Posaconazole 40 mg/mL suspension: 400 mg orally daily with a full meal (A-2)	GI upset, fever, headache, increased hepatic transaminases not common
Fluconazole-refractory OPC: Treat for ≥14 days	
Itraconazole 10 mg/mL solution: 200 mg orally daily (A-3)	See above
Voriconazole 200 mg tablets: 200 mg orally twice daily (>40	GI upset, rash, reversible visual disturbance (altered light perception, photopsia,

kg), taken on empty stomach (A-3)	chromatopsia, photophobia), increased hepatic transaminases, hallucinations, or confusion
Posaconazole 40 mg/mL suspension: 400 mg orally twice daily × 3 days, then 400 mg daily × 28 days (A-2)	See above
Amphotericin B 100 mg/mL suspension[f]: 1–5 mL swish and swallow orally 4 times daily (B-2)	Oral: nausea, vomiting, diarrhea with higher dose
Amphotericin B deoxycholate 50 mg injection: 0.3–0.7 mg/kg/day IV daily (B-2)	IV: fever, chills, sweats, nephrotoxicity, electrolyte disturbances, bone marrow suppression
Caspofungin 50 mg IV daily (B-2)	Fever, headache, infusion-related reactions (<5%) (eg, rash, facial swelling, pruritus, vasodilation), hypokalemia, increased hepatic transaminases, anemia, neutropenia
Micafungin 150 mg IV daily (B-2)	Similar to caspofungin
Anidulafungin 200 mg IV daily (B-2)	Similar to caspofungin
Esophageal candidiasis[a]: Treat for 14–21 days	
Fluconazole 100 mg tablets: 200–400 mg orally (3–6 mg/kg) daily (A-1)	See above
Echinocandin: see above (B-2)	See above
Amphotericin B deoxycholate 50 mg injection: 0.3–0.7 mg/kg/day IV daily (B-2)	See above
Posaconazole 40 mg/mL suspension: 400 mg orally twice daily (A-3)	See above
Itraconazole 10 mg/mL solution[d]: 200 mg orally daily (A-3)	See above
Voriconazole 200 mg tablets: 200 mg orally twice daily (>40 kg) (A-3)	See above
Voriconazole IV and echinocandins (A-1): generally reserved for refractory cases	See above
Fluconazole-refractory EC: Treat for 21–28 days	
Itraconazole 10 mg/mL solution: 200 mg orally daily (A-2)	See above
Posaconazole 40 mg/mL suspension: 400 mg orally twice daily (A-3)	See above
Voriconazole 200 mg tablets: 200 mg orally twice daily (>40 kg), taken on empty stomach (A-3)	See above
Caspofungin 50 mg IV daily (B-2)	See above

Micafungin 150 mg IV daily (B-2)	Similar to caspofungin
Anidulafungin 100 mg IV on day 1, then 50 mg IV daily (B-2)	Similar to caspofungin
Amphotericin B deoxycholate: 0.3–0.7 mg/kg/day IV, or lipid-based amphotericin 3–5 mg/kg/day IV (B-2)	See above

[a]Initial episodes of OPC can be adequately treated first with topical agents before resorting to systemic therapy (B-2), but systemic therapy is required for effective treatment of esophageal candidiasis. (A-2) Suppressive therapy is recommended for patients with frequent or severe recurrences (A-1).

[b]Fluconazole is more effective than ketoconazole (A-1).

[c]Strength of Recommendation and Level of Evidence

[d]Solution is more effective than capsule (A-1); solution is better taken on an empty stomach.

[e]Suspension is not marketed; can be prepared extemporaneously by pharmacy.

[f]See discussion under onychomycosis.

CHF, congestive heart failure; EC, esophageal candidiasis; GI, gastrointestinal; IV, intravenous; OPC, oropharyngeal candidiasis.

Recommendation grades: Strength of recommendation: **A**—Both strong evidence for efficacy and substantial clinical benefit to support recommendation for use. *Should always be offered.* **B**—Moderate evidence for efficacy but only limited clinical benefit, to support recommendation for use. *Should generally be* offered. **C**—Evidence for efficacy is insufficient to support recommendation for or against use; or evidence for efficacy might not outweigh adverse consequences or cost of the treatment under consideration. *Optional.* **D**—Moderate evidence for lack of efficacy or adverse outcome supports a recommendation against use. *Should generally not be offered.* Quality of evidence: 1—Evidence from at least one properly designed randomized, controlled trial. 2—Evidence from at least one well-designed trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies, or dramatic results from uncontrolled experiments. 3—Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees. (UR) Evidence currently unrated.

Evaluation of Therapeutic Outcomes

- Patient counseling tips for managing OPC are given in **Table 39-5**.

TABLE 39-5

Patient Counseling Tips for Managing Oropharyngeal Candidiasis

1. Clean the oral cavity prior to administering the topical antifungal agent. Daily fluoride rinses can help reduce the risk of caries when using an agent containing sucrose or dextrose.
2. Use the topical antifungal agent after meals, as saliva flow and mouth movements can reduce the contact time.
3. Dissolve troches slowly in the mouth and swallow the saliva; do not chew or swallow them whole.
4. Swish the suspension, around the mouth in the oral cavity to cover all areas for as long as possible, ideally at least 1 minute, then gargled and swallowed.
5. Remove dentures while medication is being applied to the oral tissues.
6. Use a suspension or buccal mucoadhesive tablet instead of a troche if xerostomia is present; if a troche is preferred, rinse or drink water prior to dosing. For xerostomia, you may use nonpharmacologic measures for symptomatic relief (eg, ice chips, sugarless gum or hard candy, citrus beverages).
7. Remove dentures and disinfect overnight using an antiseptic solution (eg, chlorhexidine 0.12%–0.2%). Disinfect oral tissues in addition to dental prosthesis.
8. Complete treatment course even though symptomatic improvement can occur in 48–72 hours.
9. Maintain good oral hygiene. Brush teeth daily (twice daily) and floss, rinse mouth, or brush teeth after eating sweets.
10. Stop smoking; avoid alcohol.

MYCOTIC INFECTIONS OF THE SKIN, HAIR, AND NAILS

Pathophysiology

- Superficial cutaneous mycoses affect up to 20%–25% of the population globally. The usual pathogens are the dermatophytes classified by genera: *Trichophyton, Epidermophyton*, and *Microsporum*.
- Dermatophytes have the ability to penetrate keratinous structures of the body and therefore infections are limited to hair, nails, and skin. These infections affect both male and female genders and all races. Reservoirs of mycotic infections include humans, animals, and soil.
- Risk factors for the development of an infection include prolonged exposure to sweat or soaking in water, maceration, intertriginous folds, sharing personal belongings such as combs, close living quarters (dormitories, barracks).

Clinical Presentation

- Mycotic infections of the skin have a classic appearance that consists of a central clearing surrounded by an advancing red, scaly, elevated border, also referred to as an “active” border.
- Diagnosis usually is based on patient history, as well as the physical examination. Diagnostic tests include direct microscopic examination of a specimen after the addition of KOH or fungal cultures. The KOH test is quick, inexpensive, and easy to perform.

Treatment

General Approach

- A general approach to treatment of superficial mycotic infections includes keeping the infected area dry and clean and limiting exposure to the infected reservoir. Topical agents generally are considered to be first-line therapy for infections of the skin. Oral therapy is preferred when the infection is extensive or severe or when treating *tinea capitis* or onychomycosis.
- Treatment of mycoses of the skin, hair, and nails is given in **Table 39-6**.

TABLE 39-6

Treatment of Mycoses of the Skin, Hair, and Nails

	Topical[a,b]	Oral Regimen[c]
Tinea pedis	Butenafine, daily Sertaconazole, twice daily Luliconazole, daily Naftifine cream daily, gel daily	Fluconazole 150 mg 1 per week × 1–4 weeks
Tinea manuum	Ciclopirox, twice daily	Ketoconazole 200 mg daily × 4 weeks
Tinea cruris	Clotrimazole, twice daily Luliconazole, daily Naftifine cream, daily	Itraconazole 200–400 mg/day × 1 week
Tinea corporis	Econazole, daily Haloprogin, twice daily Ketoconazole cream, daily Luliconazole, daily Miconazole, twice daily Naftifine cream, daily Oxiconazole, twice daily Sulconazole, twice daily Terbinafine, twice daily Tolnaftate, twice daily Triacetin cream, solution, three times daily Undecylenic acid, various preparations: apply as directed	Terbinafine 250 mg/day × 2 weeks
Tinea capitis	Shampoo only in conjunction with oral therapy **or** for treatment of asymptomatic carriers	Terbinafine 250 mg/day × 4–8 weeks
Tinea barbae	Ketoconazole twice weekly × 4 weeks Selenium sulfide daily × 2 weeks	Ketoconazole 200 mg daily × 4 weeks Itraconazole 100–200 mg/day × 4–6 weeks Griseofulvin 500 mg/day × 4–6 weeks
Pityriasis versicolor	Clotrimazole, twice daily Econazole, daily Haloprogin, twice daily Ketoconazole, daily Miconazole, twice daily Oxiconazole cream only, twice daily Sulconazole, twice daily Tolnaftate, three times daily	Fluconazole 300 mg once weekly × 2 weeks. Itraconazole 200 mg daily × 3–7 days
Onychomycosis	Ciclopirox 8% nail lacquer: apply solution at night for up to 48 weeks (fingernails and toenails) Efinaconazole 10% topical solution daily for 48 weeks (toenails) Tavaborole 5% topical solution daily for 48 weeks (toenails)	Terbinafine 250 mg/day × 6 weeks (fingernail), 12 weeks (toenail) Itraconazole 200 mg twice daily × 1 week/month for 2 months (fingernail); 200 mg daily × 12 weeks (toenail) Fluconazole 50 mg daily or 300 mg once weekly for ≥6 months (fingernail) or 12 months (toenail)

[a]Other products are available, including combination products.

[b]Length of therapy depends on mycotic sensitivity and severity of infection.

[c]Only capsule formulation studied; give with food for increased absorption.

See Chapter 138, Superficial Fungal Infections, authored by Thomas E.R. Brown and Linda Dresser, for a more detailed discussion of this topic.