Chapter 143: Superficial Fungal Infections

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 40, Fungal Infections, Superficial.

KEY CONCEPTS

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1. Vulvovaginal candidiasis (VVC) is a fungal infection of the vagina that can be classified as uncomplicated or complicated. This classification is useful in determining appropriate pharmacotherapy.
2. *Candida albicans* is the major pathogen responsible for VVC. The number of cases of non–*C. albicans* species appears to be increasing.
3. Signs and symptoms of VVC are not pathognomonic, and reliable diagnosis must be made with laboratory tests including vaginal pH, saline microscopy, and 10% potassium hydroxide (KOH) microscopy.
4. *C. albicans* is the predominant species causing all forms of mucosal candidiasis. Important host and exogenous risk factors have been identified that predispose an individual to the development of mucosal candidiasis. In oropharyngeal and esophageal candidiasis, the key risk factor is impaired host immune system.
5. A topical antimycotic agent is the first choice for treating oropharyngeal candidiasis. Systemic therapy can be used in patients who are not responding to an adequate trial of topical treatment or are unable to tolerate topical agents and in those at high risk for systemic candidiasis. Fluconazole and itraconazole are the most effective azole antimycotic agents.
6. For esophageal candidiasis, topical agents are not of proven benefit; oral fluconazole or itraconazole solution is the first choice.
7. Optimal antiretroviral therapy is important for the prevention of recurrent and refractory candidiasis in patients with human immunodeficiency virus (HIV) infection.
8. Primary or secondary prophylaxis of fungal infection is not recommended routinely for HIV-infected patients; use of secondary prophylaxis should be individualized for each patient.
9. Topical antimycotic agents are first-line treatment for fungal skin infections. Oral therapy is preferred for the treatment of extensive or severe infection and those with tinea capitis or onychomycosis.
10. Oral antimycotic agents such as terbinafine and itraconazole are first-line treatment for toenail and fingernail onychomycosis.

BEYOND THE BOOK

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Watch the YouTube video entitled "Watch and Learn KOH preparation" by Richard Usatine, MD. This 4-minute video demonstrates the quickest and most accurate way to diagnose fungal skin infections. The video is useful in visualizing fungal elements such as hyphae and pseudohyphae.

INTRODUCTION

Superficial mycoses are among the most common infections in the world and the second most common vaginal infections in North America. Mucocutaneous candidiasis can occur in three forms—oropharyngeal, esophageal, and vulvovaginal disease—with oropharyngeal and vulvovaginal disease being the most common. Over the past 15 to 20 years, the occurrence rates of some fungal infections have increased dramatically. The prevalence of fungal skin infections varies throughout different parts of the world, from the most common causes of skin infections in the tropics to relatively rare disorders in the United States.

VULVOVAGINAL CANDIDIASIS

1 *Vulvovaginal candidiasis* (VVC) refers to infections in individuals with or without symptoms who have positive vaginal cultures for *Candida* species. Depending on episodic frequency, VVC can be classified as either sporadic or recurrent.[1] This classification is essential to understanding the pathophysiology, as well as the pharmacotherapy, of VVC. Furthermore, VVC may be defined as uncomplicated, which refers to sporadic infections that are susceptible to all forms of antifungal therapy regardless of the duration of treatment, or complicated, in which consideration of factors affecting the host, microorganism, and pharmacotherapy all have an essential role in successful treatment.[1] Complicated VVC includes recurrent VVC, severe disease, non–*C. albicans* candidiasis, and host factors, including diabetes mellitus, immunosuppression, and pregnancy.[1]

Epidemiology

There is minimal information on the incidence and prevalence of VVC. Healthcare workers are not required to report cases of VVC; therefore, estimates are derived from self-reported histories. Epidemiologic data are limited because VVC usually is diagnosed without microscopy and/or cultures, and antifungal nonprescription preparations are available for self-treatment.[1] Fifty to 72% of females will have had at least one episode of VVC.[1] It is rare before menarche and increases dramatically at about 20 years of age, with the peak incidence between age 30 and 40 years. It is associated with the initial act of sexual intercourse. Between 40% and 50% of females who experience one episode of VVC experience a second episode, and 5% experience recurrent VVC.[2] The incidence after menopause remains unknown. However, healthy postmenopausal females with vulvar conditions taking hormone replacement therapy (HRT) were more prone to developing VVC than those who were not taking HRT (culture-positive, clinical VVC in 49% on HRT vs 1% on those not on HRT).[3]

Costs from VVC can be direct (medical visits and self-treatment) and indirect (nonmedical expenses, eg, time losses from work, costs of travel, and time required in obtaining treatment). There are 6 million visits to healthcare providers each year, resulting in more than $1 billion spent annually on these medical visits and self-treatment.[4] Nonprescription sales for feminine itch and yeast treatments were $302 million in the United States in 2017.[5]

Pathophysiology

2 *C. albicans* is the major pathogen responsible for VVC, accounting for 80% to 92% of symptomatic episodes. The remainder are caused by non–*C. albicans* species, with *Candida glabrata* dominating.[6] The number of cases of non–*C. albicans* candidiasis appears to be increasing, possibly related to the use of nonprescription vaginal antifungal preparations and short-course therapy and/or the increased use of long-term maintenance therapy in preventing recurrent infections.[1]

Candida species can act as commensal members of the vaginal flora. Asymptomatic colonization with *Candida* species occurs in 10% to 20% of females of reproductive age.[6,7] *Candida* organisms are dimorphic; blastospores are responsible for colonization (transmission and spread), whereas germinated *Candida* forms are associated with tissue invasion and symptomatic infections.[8] To colonize the vagina, *Candida* species must be able to

attach to the mucosa. The attachment process is complex. Not only are candidal surface structures important for attachment, but appropriate receptors for attachment must be present in the epithelial tissue. Not all females have the same range of receptors, which may explain variation in colonization.[7] Changes in the host's vaginal environment or response are necessary to induce a symptomatic infection. Unfortunately, in most cases of symptomatic VVC, no precipitating factor can be identified.[8]

Risk Factors

Several factors predispose a woman to VVC. VVC is not considered to be a sexually transmitted disease, although sexual factors can be important. There is a dramatic increase in the frequency of VVC when females become sexually active. In addition, oral-genital contact can increase the risk.[1] However, the treatment of asymptomatic partners is not recommended.[6] Contraceptive agents, including the diaphragm with spermicide, the contraceptive sponge, and the intrauterine device, increase the risk of VVC.[9] *Candida* species are capable of adhering to the contraceptive vaginal ring.[9] Oral contraceptive users demonstrated increased risk of candidiasis; however, these reports were with the higher-dose oral contraceptive pills, and the risk may not be as great with the lower-estrogen-dose oral contraceptives.[8]

Antibiotic use can increase the risk of VVC, but it is significant in only a small number of females. The mechanism by which antibiotics can increase the risk of VVC is unknown; colonization, however, is a prerequisite.[1] Three days of antibiotics increased the prevalence of asymptomatic vaginal colonization of *Candida* and the incidence of symptomatic VVC.[10] Diet (excess refined carbohydrates), douching, and tight-fitting clothing often are listed as important risk factors; however, no association has been established between these factors and increased risk of VVC.[1]

Clinical Presentation

The clinical presentation of VVC is given in Table 143-1.[1,6] These signs and symptoms are not pathognomonic, and a reliable diagnosis cannot be made without laboratory tests. The value of self-diagnosis and the success of self-treatment is limited. Self-diagnosis has a sensitivity of 35%, a specificity of 89%, and a positive predictive value of 62%. Only 30% to 40% of females that complained of vaginal itching had VVC.[8] The American College of Obstetricians and Gynecologists (ACOG) recommends that whenever possible females requesting treatment for VVC should be examined and evaluated. They only recommend self-diagnosis in compliant females with multiple confirmed prior cases of VVC who report the same symptoms. They further recommend that if these individuals fail to improve on a short course of therapy, they be evaluated for a further diagnosis.[11] Therefore, in most instances the diagnosis should be based on both clinical presentation and investigations, including vaginal pH, saline microscopy, and 10% potassium hydroxide (KOH) microscopy of vaginal discharge. The vaginal pH remains normal in VVC, and microscopic investigations should detect blastospores or pseudohyphae. *Candida* cultures usually are not required in the diagnosis of uncomplicated VVC. However, they are recommended when an individual presents with classic signs and symptoms of VVC, has a normal vaginal pH, but microscopy is inconclusive or recurrence is suspected.[6]

TABLE 143-1

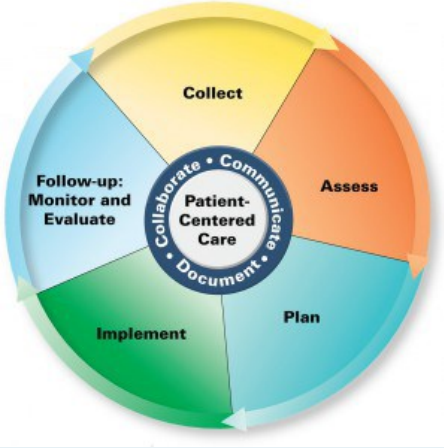
Clinical Presentation of Vulvovaginal Candidiasis

General	Often involves both the vulva and the vagina
Symptoms	Intense vulvar itching, soreness, irritation, burning on urination, and dyspareunia
Signs	Erythema, fissuring, curdy “cheese”-like discharge, satellite lesions, edema
Laboratory tests	Vaginal pH—normal, saline, and 10% KOH microscopy—blastospores or pseudohyphae
Other diagnostic tests	*Candida* cultures not recommended unless classic signs and symptoms with normal vaginal pH and microscopy are inconclusive or recurrence is suspected

KOH, potassium hydroxide.

PATIENT CARE PROCESS

Patient Care Process for Vulcovaginal Candidiasis



Collect

- Patient characteristics (age, pregnancy status)
- Patient medical history (previous vaginal infections, diabetes mellitus)
- Social history (sexual activity)
- Current meds (oral contraceptives, antibiotics)

Assess

- Symptoms consistent with VVC (itching, clumpy white vaginal discharge)
- Absence of fever, pelvic pain, colored or foul smelling vaginal discharge
- Possibility of sexually transmitted disease

- Recurrence of symptoms from previous vaginal infection

Plan*

- Remove predisposing risk factors if possible
- Select a drug therapy regimen including specific antifungal(s) dose, route, frequency, and duration (Table 143-2)
- Education of the patient regarding causes of VVC and the selected treatment
- Refer to other healthcare providers if complicated or recurrent VVC or risk factors for sexually transmitted disease

Implement

- Provide patient counselling (avoid harsh soaps, perfumes, hot tub use, contraceptive use)
- Keep vaginal area clean and dry, avoid constrictive clothing
- Self-assessment of symptom relief is appropriate

Follow-up: Monitor and Evaluate

- Monitor for complete resolution of symptoms within 24-48 hours of initiation of therapy (itching, clumpy white discharge)
- Determine the presence of adverse effects (nausea, abdominal discomfort, vaginal irritation)
- Refer to other healthcare providers if symptoms do not resolve despite adherence

****Collaborate with patient, caregivers, and other healthcare professionals.***

Treatment

Goals of Therapy

The goal of therapy is complete resolution of symptoms in patients who have symptomatic VVC. A test of the cure is not necessary if symptoms resolve.[6] Antimycotic agents used in the treatment of VVC do not meet the definition of being fungicidal agents because of their slower killing rate. At the end of therapy, the number of viable organisms drops below the detectable range. However, by 6 weeks after a course of therapy, 25% to 40% of females will have positive yeast cultures and remain asymptomatic.[1] Asymptomatic colonization with *Candida* species does not require therapy.

General Approaches to Treatment

The approach to therapy is to remove or improve any predisposing factors if they can be identified. An effective antimycotic agent should have limited local and systemic side effects, a high cure rate, and easy administration. Additionally, it would be advantageous to use a treatment that resolves symptoms within 24 hours, has broad antimycotic activity (to cover increasing rates on non–*C. albicans* species), prevents recurrence, and can be used over a shortened period of time, such as 1 to 3 days. Many topical azoles antifungals (such as clotrimazole and miconazole) are available without a prescription, and although this may increase public access to these medications, there is concern that having them available without a prescription may lead to inappropriate use. A study conducted using 10 actors as simulated patients who visited 60 pharmacies found that vaginal antimycotics were more likely to be appropriately provided to individuals as more information was exchanged, if interactions involved a pharmacist, and if questions regarding specific symptoms were used.[12]

Patients should be advised to 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.[13] Douching is not recommended for either prevention or treatment.[8] Cool baths can soothe the skin.[13] The value of oral use of lactobacillus remains unclear, and according to a systematic review the use of

lactobacilli containing vaginal products does not hold much promise. There was no evidence of vaginal colonization after probiotic use.[14]

Treatment of VVC will be considered to have positive outcomes if the symptoms of VVC are resolved within 24 to 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.

Pharmacologic Treatments

Uncomplicated Vulvovaginal Candidiasis

Uncomplicated VVC is an infection in females who are not immunocompromised, do not have diabetes, and are not pregnant. There are many different products, routes, and durations of treatment. No product route or duration of treatment is superior to any other. Cure rates for uncomplicated VVC are between 80% and 95% with topical or oral azoles and between 70% and 90% with nystatin preparations. Table 143-2 lists many available topical and oral preparations for the treatment of uncomplicated VVC. There are no significant differences in in vitro activity or clinical efficacy among the topical azole agents.[1,6,11,13] Some topical products can cause vaginal burning, stinging, or irritation; conversely, the vehicle used in topical creams or gels can provide initial symptomatic relief.[1] Of note, most topical preparations can decrease the efficacy of latex condoms and diaphragms.

TABLE 143-2

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
	1,200 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.

Oral azoles (such as fluconazole or itraconazole) have been used in the treatment of VVC and are therapeutically equivalent to topical therapies.[1] Patients may prefer oral therapy because of its convenience.[15] There were no differences between the routes in short-term mycologic cure rates. There was a significant difference between long-term cure rates in favor of long-term follow-up; however, the clinical significance of this finding is

uncertain.[16]

In the treatment of uncomplicated VVC, the duration of therapy is not critical. Cure rates with different lengths of treatment have not demonstrated that one duration of therapy is significantly better.[15-17]Shorter-duration therapies (eg, clotrimazole 1-day therapy) consist of higher concentrations of azoles that maintain the local therapeutic effect for up to 72 hours and allow for resolution of signs and symptoms.[18] There was less than 7% difference in short-term cure rates or improvement between any two treatments in any two studies and no significant differences in short- or long-term clinical cure rates among 1-day regimens.[17] There are many options for the treatment of uncomplicated VVC, and selection of an azole antimycotic agent should be based primarily on an individual patient's preference and past experience.[17]

Complicated Vulvovaginal Candidiasis

Complicated VVC occurs in patients who are immunocompromised or have uncontrolled diabetes mellitus or are pregnant.[1] Unlike with uncomplicated VVC, product selection is important in these individuals. The duration of therapy and/or route of administration is important. Immunocompromised females or those with uncontrolled diabetes mellitus need a more aggressive treatment plan and treatment should be lengthened to 10 to 14 days regardless of the route of administration.[11] Therapeutic options include those listed in Table 143-2; however, regimens should be continued for 10 to 14 days. Cure rates increased from 67% with single-dose oral fluconazole therapy in females with complicated VVC therapy to 80% when the 150 mg dose of fluconazole was repeated 72 hours after the initial dose.[19]

VVC during pregnancy can be considered complicated because consideration of host factors such as hormonal changes that can affect normal flora are essential in selecting therapeutic regimens. Topical agents are considered to be safe throughout pregnancy. Imidazole topical agents (such as fluconazole) were more effective than nystatin for VVC during pregnancy and treatment for 7 days was more effective than treatments of 4 days or less.[20] Oral therapy is not recommended as larger doses of fluconazole have been linked to birth defects.[8] Instead, the ACOG recommends a topical imidazole therapy for 7 days.[11]

Recurrent Vulvovaginal Candidiasis

Recurrent vulvovaginal candidiasis (RVVC) is defined as having more than four episodes of VVC within a 12-month period. Fewer than 5% of females develop RVVC, and its pathogenesis is poorly understood. A proper diagnosis should be obtained to rule out other infections or nonmycotic contact dermatitis. RVVC is best treated in two stages: an initial intensive stage followed by prolonged antifungal therapy to achieve mycologic remission (with 150 mg oral fluconazole daily for 10 days followed by 6 months of fluconazole 150 mg weekly). Ninety percent of females receiving 10-day initial and 6-month prolonged treatments were symptom free for the 6 months following initial treatment, and there were 50% fewer symptomatic episodes in the 6 months (compared with placebo treatment after the initial 10 days).[21] The Infectious Diseases Society of America recommends 10 to 14 days of induction therapy with a topical or oral azole, followed by 150 mg of fluconazole once weekly for 6 months for recurring *Candida* VVC.[22,23]

Antifungal-Resistant Vulvovaginal Candidiasis

Resistance to azole antimycotics should be considered in individuals who have persistently positive yeast cultures and fail to respond to therapy despite adherence to prescribed regimens.[1] These infections can be treated with boric acid or 5-flucytosine.[24] Boric acid is administered as a 600 mg intravaginal capsule daily for 14 days of induction therapy, followed by a maintenance regimen of one capsule intravaginally twice weekly. Boric acid should not be administered orally, as it is toxic. Flucytosine cream is administered vaginally, 1,000 mg inserted nightly for 7 days. The prevalence of *C. glabrata* is higher in those with diabetes. In a study of patients with diabetes and VVC, 68% had isolates for *C. glabrata* compared with 28.8% for *C. albicans.* Those with *C. glabrata* had significantly higher mycological cure rates with 600 mg of boric acid suppositories for 14 days compared with a single dose of fluconazole 150 mg.[25]

OROPHARYNGEAL AND ESOPHAGEAL CANDIDIASIS

Oropharyngeal and esophageal candidiasis are common and localized infections that occur in patients with human immunodeficiency virus (HIV) infection, diabetes, leukemia, and other malignancies. These infections are also associated with antimicrobial therapy, steroid use, radiation therapy, and denture use.

Oropharyngeal candidiasis (OPC), often referred to as *thrush,* is caused by the yeast *Candida. C. albicans,* a common oral commensal organism, is the most frequent infecting species. OPC is also referred to as *candidiasis* (or the more correct but less commonly used term *candidosis*). The infection may extend into the esophagus, causing esophageal candidiasis.

Epidemiology and Etiology

Candida is a commensal fungus found in the oral cavity in up to 65% of healthy individuals with higher prevalence in healthy children and young adults.[26,27] *Candida* carriage increases in immunocompromised and hospitalized patients.[27] Even in the era of highly active antiretroviral therapy (AART) up to 80% of HIV-infected persons may demonstrate oral yeast colonization.[28] The organism is capable of transition to a pathogen causing symptomatic mucosal infections in association with predisposing host factors.[27] *C. albicans* is the predominant colonizing *Candida* species (70%-80%), but any of the non–*C. albicans* species such as *C. glabrata* and *C. tropicalis,* which may account for 5% to 8%, respectively, can be colonizers. Colonization rates are influenced by the severity and nature of the underlying medical illness and the duration of hospitalization, as well as age (highest in infants younger than 18 months of age and in adults older than 60 years of age). A variety of host and exogenous factors (Table 143-3) can lead to the transformation of asymptomatic colonization to symptomatic disease, such as oropharyngeal and esophageal candidiasis. *C. albicans* is the most common species causing all forms of mucosal candidiasis in humans. Less frequently, non–*C. albicans* species can be pathogenic and cause disease. These include *C. glabrata, C. tropicalis, C. krusei,* and *C. parapsilosis.*[28,29] *C. krusei,* although relatively uncommon, generally is recovered from mucosal surfaces of neutropenic patients with hematologic malignancies.[29] *Candida dubliniensis* has been identified in both HIV-infected and noninfected patients, and may cause ~15% of infections previously ascribed to *C. albicans.*[29] In patients with cancer, non–*C. albicans* species account for almost half of all *Candida* infections.

TABLE 143-3

Risk Factors for the Development of Oropharyngeal and/or Esophageal Candidiasis

Local Factors	Potential Mechanisms
Use of steroids and antibiotics	Suppression of cellular immunity and inhibition of phagocytosis by steroids, including chronic use of inhaled and topical steroids
	Alteration of endogenous oral flora by broad-spectrum antibiotics, especially when used with steroids, creates a milieu for proliferation of *Candida* species because of reduced environmental and nutritional competition
Dentures	Enhanced adherence of *Candida* species to the acrylic material of dentures, reduced saliva flow under surfaces of denture fittings, improperly fitted dentures, and poor oral hygiene provide a milieu conducive to the survival of microorganisms
Xerostomia caused by drugs (eg, tricyclic antidepressants and phenothiazine), chemotherapy, radiotherapy to the head/neck, and various diseases (eg, Sjögren's syndrome, HIV, and cancer of the head/neck), as well as bone marrow transplant recipients	Reduced dilutional and cleansing effect caused by low secretion rate and low pH in saliva: Saliva and mucosa secretions have defense factors, such as lactoferrin, sialoperoxidase, isozyme, histidine-rich polypeptide, secretory IgA antibodies, and specific anti-*Candida* antibodies, that help prevent adhesion and overgrowth of *Candida* species
Smoking	
Disruption of oral mucosa caused by chemotherapy and radiotherapy, ulcers, endotracheal intubation trauma, and burns	Oral mucositis induced by radiation and breaks in the physical barrier of the oral epithelium, which is protective against invasion by microorganisms; altered rate of mucosa regeneration by cancer chemotherapy, which increases vulnerability to infection

Systemic Factors	Potential Mechanisms
Drugs (eg, cytotoxic agents, corticosteroids, and immunosuppressants after organ transplant), omeprazole, and environmental chemicals (eg, benzene and pesticides)	Reduced immunity because of drug-induced neutropenia or cell-mediated immunity; potent inhibition of gastric acid by PPIs can facilitate the growth of *Candida* species; PPIs also can inhibit the cytotoxic effect of lymphocytes and reduce salivary secretion
Neonates or the elderly	Immature immune system of neonates who usually acquire infection during birth to a mother with vaginal candidiasis or from exposure to infected bottle nipples or to skin of adult caregiver
	Elderly—unclear if this is the direct effect of age per se or contribution from dentures or underlying comorbidity
HIV infection/AIDS	Depletion of CD4 T lymphocytes especially below 200-300 cells/mm^3 (0.2×10^9 to 0.3×10^9/L); anti-*Candida* protective mechanism of T lymphocytes at a mucosal level is unclear but can be caused by altered cytokines, especially interferon-γ, that inhibit transformation of *Candida* blastoconidia to the more invasive hyphal phase
Diabetes	Higher than normal numbers of *C. albicans* cultured from saliva of diabetic patients; can be related to the elevated glucose levels and reduced chemotactic factor in saliva, altered neutrophil function, and reduced saliva volume and flow
Malignancies (eg, leukemia and head/neck cancer)	Use of intensive radiotherapy and chemotherapy can disrupt oral mucosa and cause xerostomia; prolonged use of broad-spectrum antibiotics in neutropenic patients can alter the normal oral flora; because of the prolonged neutropenia, the principal immune defect, seen especially in leukemic patients, the initial oropharyngeal candidiasis can become systemic or invasive
Nutritional deficiencies (eg, iron, folate, and vitamins B1, B2, B6, B12, and C)	Can be related to dietary restriction or GI absorption problems; deficiencies can serve to enhance the pathogenic potential of the *Candida* inhabitants, alter host defense mechanisms, or change epithelial barrier integrity

AIDS, acquired immunodeficiency syndrome; GI, gastrointestinal; HIV, human immunodeficiency virus; IgA, immunoglobulin A; PPI, proton pump inhibitor.

Oropharyngeal candidiasis remains the most common opportunistic infection in patients with HIV disease, and it may be the first clinical manifestation of the HIV infection in the majority of untreated patients. OPC occurs in 50% to 90% of HIV-infected patients if the disease progresses to acquired immunodeficiency syndrome (AIDS).[26,28,29] The use of effective antiretroviral therapy has led to a significant reduction in the primary incidence and ultimately refractory disease. The absolute CD4 T-cell count is the primary risk factor for development of OPC with the greatest risk at CD4 T-cell levels <200 cells/mm^3 (0.2×10^9/L). Also, the HIV viral load is a predictor of OPC development; OPC increases with HIV viral loads >10,000 copies/mL (10×10^6/L). This finding correlates with the observation that initiation of antiretroviral therapy and subsequent increase in CD4 T-cell counts does not fully account for the decrease in OPC incidence.[28] Regardless of the CD4 T-cell count, or HIV viral load, OPC is predictive for the development of AIDS-related illnesses if left untreated.[26,29]

In non-HIV diseases, such as cancer, the incidence of OPC varies depending on the type of malignant neoplastic disease, level of immune suppression, and type and duration of treatment, but it is less common than in HIV-infected patients. OPC was initially reported in ~25% of patients with solid tumors and up to 60% in those with hematologic malignancies or bone marrow transplant recipients.[30] Rates of OPC have decreased significantly in these patients because of widespread use of antifungal prophylaxis. Incidence in other patient populations predisposed to OPC such as the hospitalized patient administered broad-spectrum antibiotics or denture and other oral appliance users is not well quantified. However, it does represent at-risk

individuals where the clinical pharmacist has an important patient-care role.[27,30]

OPC can predispose patients to develop more invasive disease, including esophageal candidiasis.[30] The esophagus is the second most common site of gastrointestinal (GI) candidiasis. The prevalence of esophageal candidiasis increased mainly due to the emergence of AIDS, as well as the increased numbers of other severely immunocompromised patients, especially those with hematologic malignancies.[29] The mean incidence of esophageal candidiasis among HIV-infected patients is less than OPC and ranges from 15% to 20%.[29] The risk of esophageal candidiasis is increased in HIV-infected patients when the CD4 T-cell count has dropped below 100 to 200 cells/mm^3 (0.1×10^9 to 0.2×10^9/L), as well as in those with OPC.[30,31] However, the absence of OPC does not necessarily exclude the possibility of esophageal disease. Like OPC, the presence of esophageal candidiasis can help predict HIV disease progression and prognosis.[30] The incidence of esophageal candidiasis in non–HIV-infected immunocompromised patients is not well established. *C. albicans* is the most common cause of esophageal candidiasis, accounting for ~80% of cases, with the rest being caused by non–*C. albicans* species.[28] However, the widespread use of the azole agents for treatment and prophylaxis has led to an emergence of refractory infections that are more challenging to treat.

Pathogenesis and Host Defenses

The pathogenesis of OPC is most clearly elucidated in the setting of HIV infection. There appear to be several levels of immune defense against the development of OPC in HIV-infected persons, and they involve both systemic and local immunity. The primary line of host defense against *C. albicans* is cell-mediated immunity (CMI) at the mucosal surfaces, which is mediated by CD4 T cells.[26] The efficacy of the CD4 T cells is reduced when the number of cells drops below a protective threshold, and protection against infection becomes dependent on secondary or local immune mechanisms.[26,28] When the number of CD4 T cells drops too low, recruitment of these cells to the oral cavity is impaired. 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.[28,32] The possibility that HIV plays a strong role in susceptibility to infection is supported by the observation that OPC is more common in HIV-infected persons than in those with similar immunosuppression, such as lymphoma and bone marrow transplant. When the primary line of defense fails, the secondary host defenses become crucial. These include the CD8 T cells, salivary cytokines, and other innate immune cells, such as the neutrophils, macrophages, and epithelial cells (with anti-*Candida* activity). Deficiencies or dysfunction in any of these can result in increased susceptibility to OPC. The problem with the CD8 T cells is caused more by a dysfunction of the microenvironment, specifically reduction in the E-cadherin adhesion molecule that promotes migration of the cells through mucosal tissues.[29] The role of humoral immunity by antibodies as a protective mechanism is unclear and controversial. The changeover of the role of *Candida* species from commensal to pathogenic in the human host usually occurs when breakdown in these host defenses occurs. The pathogenesis of OPC is still not completely understood. It is important to develop a better understanding of the pathogenesis and role of host defenses, including the mechanism of CD8 T-cell activity, reduced adhesion molecules, and whether other cofactors, such as HIV viral load, AART, and injection drug use, play a role. Immunotherapeutic modalities can then be developed to eliminate the susceptibility factors and significantly reduce OPC in the at-risk populations.

Significant differences exist in the virulence among *Candida* species in mucosal candidiasis. One virulence factor is the ability of the organism to adapt and survive in response to changes in the host environment.[28] The genes required for virulence are regulated in response to the environmental signals indigenous to the host environment (eg, temperature, pH, osmotic pressure, iron and calcium ion concentrations, oxygenation, and carbon and nitrogen availability). The ability of *C. albicans* to undergo reversible morphologic transition between the budding pseudohyphal and the more invasive hyphal growth forms is also a determinant of virulence, and genes are recognized to play a role.[26] Other virulence factors are the adhesive ability of *C. albicans* to epithelial cells and proteins and its ability to invade host cells by means of phospholipase and proteinase enzymes. This may be one of the factors leading to OPC in non–HIV-infected individuals. Other components of the pathogenesis in the absence of HIV are the ability of the *Candida* species to adhere to buccal epithelial cells.[33] This may be a key element in the development of OPC in patients with altered microflora, including those receiving broad-spectrum antimicrobial therapy.

Risk Factors

Several host and exogenous factors contribute to the ability of *Candida* species to cause infection (see Table 143-3). Local and systemic factors, as well as characteristics of the organism itself, can increase the susceptibility of an individual to *Candida* infections.[26] 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 oropharyngeal candidiasis as well as disseminated candidiasis. Oral mucosal disease, such as lichen planus, can be preexistent causes of candidiasis. Smoking has been suggested as a predisposing risk factor. In many cases, multiple concurrent predisposing factors to candidiasis can exist, for example, xerostomia with mucositis and a break in the epithelial surface or immunosuppression, such as might occur in a leukemic patient receiving radiation and chemotherapy. The severity and extent of *Candida* infections increase with the number and severity of predisposing risk factors.[27]

Clinical Presentation and Diagnosis

Oropharyngeal candidiasis can manifest in several major forms (Table 143-4).[26,27] The clinical signs and symptoms of OPC and the locations of the lesions can be quite diverse (Table 143-5). 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. Pseudomembranous candidiasis, commonly known as *oral thrush,* is the classic and most common form seen in immunosuppressed and immunocompetent hosts. Erythematous and hyperplastic candidiasis and angular cheilitis occur less commonly in the HIV-infected population. Dysphagia, odynophagia, and retrosternal chest pain are common complaints of esophageal candidiasis, which is usually, but not always, accompanied by the presence of OPC. Clinical symptomatology, along with a therapeutic trial of antifungal, can provide a reliable presumptive diagnosis of esophageal candidiasis. If antifungal therapy does not lead to resolution, more invasive tests such as upper GI endoscopy can be undertaken.

TABLE 143-4

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 corners 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), males more commonly infected than females (3:1)	Rhomboid-shaped hypertrophic or atrophic plaque in the mid-dorsal tongue. Lesions may not resolve completely

HIV, human immunodeficiency virus.

TABLE 143-5

Clinical Presentation of Oropharyngeal and Esophageal Candidiasis

Oropharyngeal Candidiasis	Esophageal Candidiasis
General	**General**
The clinical features can be quite diverse (see Table 143-4)	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**
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	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**
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	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	**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	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

Desired Outcomes

The primary desired outcome in the management of OPC is a clinical cure, that is, elimination of clinical signs and symptoms. Even when the patient is relatively asymptomatic, it is important to treat the initial episode of OPC to avoid progression to more extensive disease. In the most severe cases, the patient's quality of life can be impaired; this can result in decreased fluid and nutritional intake. Lack of appropriate treatment of OPC can lead to more extensive oral disease, especially in patients who are immunocompromised. The most serious complication of untreated OPC is extension of the infection to esophageal candidiasis which is more debilitating with greater impact on the patient's quality of life. Appropriate antifungal therapy should be initiated for both OPC and esophageal candidiasis. Preventing or minimizing the number of future recurrences of both types of candidiasis is an equally important outcome. The approach depends largely on the underlying predisposing conditions. Mycologic cure is not a necessary treatment outcome because it may not be feasible or realistic, given that *Candida* species exist commonly as part of the normal mouth flora.

Minimizing toxicities and drug-drug interactions of systemic antifungal agents and 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 to Treatment

The management of OPC should be individualized for each patient, taking into consideration the underlying immune status, other concurrent mucosal and medical diseases, concomitant medications, and exogenous infectious sources. Generally, topical therapy is used in mild forms of infections that have limited ability to spread. Systemic therapies are reserved for more moderate infection which may lead to dissemination of the infection.[27,28,34]

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. Selection of an appropriate antifungal agent for treatment of candidiasis requires consideration of several factors, including the patient's drug adherence, adequate saliva for dissolution of solid topical medications, risk of caries from sucrose- or dextrose-containing preparations, potential drug interactions, coexisting medical conditions (eg, liver disease), location and severity of the infection, and the need for long-term maintenance therapy.

5 Topical antimycotic therapies should be the first choice for milder forms of infections.[34] The efficacy of antimycotic agents for OPC varies in different patient populations. Until the polyene antimycotic agents became available in the 1950s, gentian violet, an aniline dye, was used to treat OPC. Problems with gentian violet include fungal resistance, skin irritation, and especially the unaesthetic staining of the oral mucosa. In resource limited areas gentian violet remains a therapeutic option. Gentian violet solution of 0.00165% does not stain the oral mucosa and has potent antifungal activity.[35] Topical agents, such as nystatin and clotrimazole, are the standard of treatment for uncomplicated OPC and generally are effective for treatment in otherwise healthy adults and infants with no underlying immunodeficiencies. Topical agents are available in an assortment of formulations, including oral rinses (suspension), troches, powder, vaginal tablets, creams, and most recently as a mucoadhesive tablet[30,34,36] (Table 143-6).

TABLE 143-6

Therapeutic Options for Mucosal Candidiasis With Strength of Recommendation and Quality of Evidence

Initial Episodes of OPC[a]: Treat for 7-14 Days	Common/Significant Side Effects
Clotrimazole 10 mg troche: hold 1 troche in mouth for 15-20 minutes for slow dissolution five times daily (B-2)	Altered taste, mild nausea, vomiting
Nystatin 100,000 units/mL suspension: 5 mL swish and swallow orally four 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[b]: 100-200 mg orally daily (A-1)	GI upset, hepatitis not common

Itraconazole 10 mg/mL solution[c]: 200 mg orally daily (A-2)	GI upset, not common: hepatotoxicity, CHF, pulmonary edema with long-term use[d]
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 kg), taken on empty stomach (A-3)	GI upset, rash, reversible visual disturbance (altered light perception, photopsia, 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[e]: 1-5 mL swish and swallow orally four 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[c]: 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

CHF, congestive heart failure; GI, gastrointestinal; OPC, oropharyngeal candidiasis.

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

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

[e]See discussion under onychomycosis.

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.

Topical agents require frequent applications because of the short contact time with the oral mucosa; the ideal contact time is 20 to 30 minutes. Sufficient saliva is needed to dissolve clotrimazole troches, and this can be problematic for patients with xerostomia. Also, the rough surface of the tablet can become irritating to the oral soft tissue. Troches also contain dextrose, which has cariogenic potential. Nystatin suspension might be a better choice for patients with xerostomia, but it is difficult to maintain adequate contact time with the oral mucosa. Some patients complain of the unpleasant taste of nystatin, which can cause nausea and vomiting; this is especially problematic in cancer patients experiencing chemotherapy-induced nausea. The high sucrose content of nystatin suspension is cariogenic in dentate patients, and it should be used with caution in diabetic patients.[27,30] Miconazole 50 mg mucoadhesive tablets are a buccal adherent miconazole product approved for the local treatment of OPC in adults and adolescents older than age 16 years.[37] This product offers the advantage of a once-daily formulation that is tasteless, odorless, and sugar free.[36] Topical creams, such as clotrimazole, ketoconazole, miconazole, and nystatin (usually mixed with a steroid), are more appropriate for application three times daily to the corners of the mouth in treating angular cheilitis, the inflammation, drying, and cracking of the corners of the mouth.[34]

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. Effective treatment of esophageal candidiasis generally requires the use of systemic antifungal agents. However, these agents have the disadvantage of producing more side effects (see Table 143-6) and drug-drug interactions (see Chapter 144, "Invasive Fungal Infections"). Fluconazole is inexpensive and generally well tolerated, and its absorption is unaffected by food or gastric acidity. Ketoconazole requires gastric acidity for absorption, which can be problematic and this agent is not recommended today with the availability of more effective triazoles. Itraconazole capsules also have the same absorption problem and are no longer recommended. In contrast, itraconazole solution has enhanced absorption and is best taken in a fasting state; in addition, the solution provides the benefit of both topical effects to the oral mucosa and systemic effects and is beneficial to patients with mucositis or swallowing problems. Whenever possible, it is generally beneficial to limit the use of systemic azole agents to prevent unnecessary drug exposure and to minimize the potential for occurrence of drug-resistant candidiasis, particularly from fluconazole resistance.

Oropharyngeal Candidiasis: Human Immuodeficiency Virus–Infected Patients

Treatment for initial or recurrent episodes of OPC should be started with topical agents, provided that clinical symptoms are not severe and that there is minimal risk of esophageal involvement.[29,34] Clinical responses with the resolution of signs and symptoms generally occur within 5 to 7 days of initiating treatment. Clotrimazole appears to be the most effective topical agent and demonstrates comparable clinical response rates with both fluconazole and itraconazole.[29,34] However, topical therapy is associated with more frequent relapses than with fluconazole.[31,34] This may be of limited clinical significance in patients receiving effective AART because of their decreased susceptibility to opportunistic infection. In practice, nystatin suspension is still used frequently in initial episodes of OPC, although it is the least effective agent and is associated with frequent treatment failures and early relapses, especially in patients with advanced HIV disease or neutropenia.[27,30] Miconazole mucoadhesive tablets 50 mg once daily (MMT) were non-inferior to clotrimazole troches 10 mg five times daily for the treatment of OPC in HIV-infected patients. Safety and tolerability was also similar between treatment groups.[37]

Systemic oral azoles should be reserved for use in the more severe episodes of OPC unresponsive to topical agents or in patients with concurrent esophageal involvement.[30,34] In clinical practice, fluconazole usually is the systemic azole agent of choice because of its proven efficacy, favorable absorption, safety, and drug-interaction profiles, and it is relatively inexpensive. Fluconazole is superior to ketoconazole and itraconazole capsules.[30,34] Fluconazole should be given 100 to 200 mg/day for 7 to 14 days.[34] A single dose of fluconazole 750 mg orally was as effective as fluconazole 150 mg orally for 14 days, which warrants further evaluation, given the potential advantages of adherence and cost-effectiveness.[38] Itraconazole oral solution with an improved absorption profile compared with the capsule formulation is as effective as fluconazole, with comparable clinical and mycologic response and relapse rates.[30,34] However, it carries a higher risk of drug interactions because it is a potent inhibitor of the cytochrome P450 enzymes, and it is associated with more nausea than fluconazole. Posaconazole is an extended-spectrum triazole with potent in vitro activity against both *C. albicans* and non–*C. albicans* species. It is equivalent to fluconazole in terms of efficacy, safety, and tolerability.[39] Posaconazole, itraconazole solution, and voriconazole are the azole alternatives to fluconazole in the management of moderate-to-severe OPC.[33] Other agents that are effective are amphotericin B and the echinocandins (caspofungin, micafungin, and anidulafungin). They are reserved for refractory OPC, however, because of their greater toxicity. They are also more expensive and are less convenient to use.

Oropharyngeal Candidiasis: Non-Human Immunodeficiency Virus–Infected Patients

This patient population includes patients with hematologic malignancy (eg, leukemias) or blood and bone marrow transplantation (BMT) with a long duration of neutropenia and chronic graft-versus-host disease, patients with solid tumors, patients with solid-organ transplants who are receiving immunosuppressive therapy, and patients with diabetes mellitus, as well as patients on prolonged courses of antibiotics or corticosteroids and the debilitated elderly.

Specific antifungal therapy can be unnecessary for asymptomatic patients at relatively low risk for disseminated candidiasis, such as those who are not granulocytopenic or who are expected to have a short duration of granulocytopenia.[34] Many of these infections will clear spontaneously after recovery of the granulocytes or discontinuation of antibiotic and/or immunosuppressive therapy. However, antifungal therapy usually is required for patients who have persistent infection or significant symptoms, usually pain, or who are granulocytopenic with a relatively high risk of fungal dissemination. Topical agents first can be given a therapeutic trial depending on the severity of infection and the degree of immunosuppression. Although both nystatin and clotrimazole can be effective in treating OPC, nystatin suspension does not effectively reduce the incidence of either oropharyngeal or systemic *Candida* infections in immunocompromised patients receiving chemotherapy or radiation; its use often is associated with treatment failures

and early relapses.[34] Clotrimazole appears to be more effective in reducing colonization and treating acute episodes in cancer patients who are immunocompromised. MMTs were superior to miconazole oral gel in patients with head and neck cancer in achieving a complete response to therapy.[40] MMT has not been studied against clotrimazole in this patient population specifically but is approved for use in adults with OPC.

Topical therapy with clotrimazole or nystatin for 7 days is usually adequate for treating mucocutaneous candidiasis in most solid-organ transplant patients.[30] Use of topical therapy will reduce the number of systemic drugs that these patients receive and hence minimize the risk of drug-drug interactions. Failure to respond to topical agents warrants the use of fluconazole. Low-dose amphotericin B solution as "swish and swallow" (100 mg/mL, 1 mL four times daily) for 7 to 10 days is reserved for the unusual cases of treatment failure as it is not readily available and requires compounding.

Patients who develop OPC because of prolonged antibiotic use or aerosolized corticosteroids use can be managed successfully by discontinuation of the offending agent, and the infection usually will resolve. If there is a strong desire to treat because of discomfort or need to hasten symptom resolution or an inability to stop the offending agent, therapy with a topical agent, either MMT, clotrimazole, or nystatin, is effective in most cases. The advantage of systemic azoles is the convenience of less frequent dosing. Symptoms usually improve in 3 or 4 days. Infants should be given smaller amounts more frequently (eg, nystatin 100,000 units every 2-3 hours) to ensure better contact time. For denture-related OPC, or candidal stomatitis, effective therapy requires treatment of both the mouth and the dentures to avoid relapse. The dentures must be brushed vigorously and disinfected every night by soaking in antiseptic solution, such as chlorhexidine gluconate 0.25% or a commercial denture disinfectant product.[30,34] Topical antifungal therapy of the oral cavity is required. Consistent proper oral hygiene and care of the dentures can help prevent relapse.

Systemic azole agents are used for treating OPC in patients who have failed or who are unable to take topical therapy.[30,34,39] The preceding discussion on the relative efficacy of fluconazole, itraconazole, and ketoconazole in HIV-infected patients can be extrapolated to the non–HIV-infected population. Oral fluconazole 100 to 200 mg daily is used more commonly because of more extensive experience with its use, and it is more effective and has a more favorable absorption and side-effect profile compared with other available azoles.[34] If the oral route is not feasible for reasons such as severe chemotherapy-induced mucositis, fluconazole can be administered IV. In patients unresponsive to azoles, IV amphotericin B in relatively low doses of 0.1 to 0.3 mg/kg/day can be tried.[34] Because of the higher risk for dissemination in patients who are severely neutropenic (<100 neutrophils/mm^3 [0.1×10^9/L]) or clinically unstable (hypotensive or febrile), some clinicians prefer to initiate therapy with IV amphotericin B at 0.6 mg/kg/day, with therapy continued until the neutropenia has resolved, or an echinocandin.[34] The echinocandins caspofungin, micafungin, and anidulafungin are all effective for the treatment of OPC, thus offering other options, with fewer adverse effects in the patient with refractory disease.[34]

Esophageal Candidiasis: Human Immunodeficiency Virus–Infected Patients

6 Treatment of esophageal candidiasis has not been as well studied as OPC. Because of the significant morbidity of esophageal candidiasis and the absence of evidence supporting the efficacy of topical antifungals, treatment requires systemic antifungal agents.[26,28] Fluconazole is superior to ketoconazole and itraconazole capsules with respect to endoscopic cure and clinical response and usually produces a more rapid onset of action and resolution of symptoms. Fluconazole is as effective as itraconazole solution, with reported response rates of >80% to 90%.[31,34] However, itraconazole solution causes more nausea and drug interactions because of inhibition of the cytochrome P450 enzymes. Amphotericin B, voriconazole, posaconazole, and the echinocandins are also effective in esophageal candidiasis, but they are generally reserved for patients with advanced or inadequately controlled HIV disease where the candidiasis tends to recur or becomes refractory to azole therapy.[41-43]

Esophageal Candidiasis: Non-Human Immunodeficiency Virus–Infected Patients

As in the case of HIV-infected patients, treatment of esophageal candidiasis requires systemic therapy. Patients can be started on oral fluconazole 200 to 400 mg/day for 14 to 21 days.[34] Higher fluconazole doses (up to 400 mg/day) have been suggested for patients with severe symptoms or those who are neutropenic.[44] Other agents recommended if fluconazole is not an option are an echinocandin or IV amphotericin B at 0.3 to 0.7 mg/kg. Itraconazole solution, posaconazole, and voriconazole are effective alternatives that may be considered for those not responding adequately to fluconazole. An echinocandin or IV amphotericin B may be selected over fluconazole for initial therapy in neutropenic patients who present with severe symptoms or who are at high risk for dissemination of *Candida* species, such as those receiving other aggressive immunosuppressive therapy (eg, corticosteroids, total-body irradiation, or antithymocyte globulin) and who have documented evidence of esophageal candidiasis or who have failed

an initial empirical trial of oral nonabsorbable agents or systemic azoles.[34] Therapy should be continued at least until the neutropenia resolves. For patients whose symptoms have resolved and who are afebrile and clinically stable, therapy should be discontinued, and the patients should be monitored closely for infection recurrence. In high-risk patients, particularly those with persistent fever and neutropenia, the potential presence of clinically occult, diffuse GI or disseminated candidiasis should be considered. The echinocandins and newer azole agents (voriconazole and posaconazole) offer less toxic alternatives or oral agents and are preferred in patients who are intolerant of amphotericin B deoxycholate or who have preexisting renal impairment.[30,44,45]

Antifungal-Refractory Oral Mucosal Candidiasis

Treatment failure is generally defined as persistence of signs and symptoms of OPC or esophageal candidiasis after an appropriate trial of antifungal therapy.[29] Treatment of refractory oral mucosal candidiasis is frequently unsatisfactory, and clinical response is usually short-lived, with rapid and periodic recurrences. The key risk factors for occurrence of refractory candidiasis are advanced stage of AIDS with low CD4 cell counts (<50 cells/mm^3 [0.05×10^9/L]) and repeated or prolonged courses of various systemic antifungal agents, in particular systemic azoles.[30,34] Frequent or prolonged use of fluconazole can be associated with fluconazole-refractory candidiasis because of selection of more resistant non–*C. albicans* species. An important initial management strategy is to assess and optimize the antiretroviral therapy of the patient with refractory OPC to help improve the immune function. With the widespread use of AART, fluconazole-refractory OPC is now less commonly encountered. It is also important to identify and rectify potentially correctable causes of clinical failures of mucosal candidiasis, such as poor drug adherence, adequate dosing, reduced drug absorption associated with hypochlorhydria, and drug-drug interactions.

Few controlled studies have assessed the effectiveness of antifungal agents. Doubling of the fluconazole dosage to 400 or 800 mg/day can be effective in some patients with infection caused by *Candida* species of intermediate resistance, although the response may be only transient.[31] Fluconazole oral suspension can be beneficial in some patients because of increased salivary concentrations obtained when the suspension is taken with the swish and swallow technique.[34] Patients with fluconazole-refractory mucosal candidiasis can be treated with itraconazole oral suspension because it can be effective in 64% to 80% of patients; however, the benefit is short-lived if chronic suppressive therapy is not maintained.[29,34] Posaconazole suspension was successful in ~74% of patients with refractory oral or esophageal candidiasis; voriconazole may also be efficacious in these patients. Amphotericin B oral suspension is another alternative for azole-refractory patients.[31,34] It has broad-spectrum activity against many fungal species and low likelihood of *Candida* species resistance. Amphotericin B suspension is no longer available commercially in the United States, but it can be prepared extemporaneously by the pharmacy.[46]

IV amphotericin B deoxycholate has been the alternative for patients with endoscopically proven disease who have failed fluconazole or itraconazole therapy. Patients with severe disease unresponsive to other agents require IV amphotericin B 0.3 to 0.7 mg/kg/day for 7 to 10 days to achieve clinical response; higher dose or longer treatment duration can be needed in more severe disease.[31,34] After response, suppressive therapy with amphotericin B is required to increase disease-free intervals. Patients who fail to respond to amphotericin B and require >1 mg/kg/day might be candidates for liposomal amphotericin B preparations because of renal and/or bone marrow toxicities, although at a markedly higher cost. Flucytosine usually is not used as monotherapy because of rapid development of resistance but can be used in combination with an azole or amphotericin B.[31] Less toxic agents that are also effective are voriconazole and the echinocandins.[44,45] Voriconazole, a triazole antifungal available in both oral and IV preparations, is as effective as fluconazole for esophageal candidiasis, and has shown success in treatment of fluconazole-refractory disease.[43] However, voriconazole has more side effects and multiple pharmacokinetic drug interactions compared to fluconazole.[43] Caspofungin is the first of the echinocandins to be approved for esophageal candidiasis. Micafungin and anidulafungin have been approved for this indication. All three echinocandins have similar efficacy and tolerability profile as fluconazole, although higher relapse has been reported with caspofungin and anidulafungin compared with fluconazole.[34,45] Because the echinocandins require IV administration and are expensive, they are primarily used in patients who are refractory to the triazoles or have serious triazole-related adverse effects. As a class, the echinocandins have a favorable adverse effect profile. They are less toxic than amphotericin B (see Table 143-6) and have less impact on the cytochrome P450 enzymes than either itraconazole or voriconazole. Immunomodulation with adjunctive granulocyte-macrophage colony-stimulating factor and interferon have been used for refractory oral candidiasis in limited numbers of patients.[34]

Antifungal Prophylaxis

7 Ensuring that the HIV-infected patient is receiving appropriate antiretroviral therapy to enhance the immune system is perhaps the most important measure in preventing future episodes of mucosal candidiasis (oropharyngeal, esophageal, and vulvovaginal).[34] Initial success of treatment often is followed by symptomatic recurrences, especially in patients with advanced or poorly controlled HIV disease. Long-term suppressive therapy with fluconazole is effective in preventing recurrences or new infections of OPC in HIV disease and in patients with cancer.[34] However, the indications for antifungal prophylaxis and the best long-term management strategy still have not been well established. Fluconazole does not provide complete protection, and breakthrough infections can occur.[31] The reduced risk of recurrence of OPC does not improve survival. In addition, chronic exposure to azole therapy might lead to the development of refractory disease or emergence of azole resistance.[34] However, in a randomized trial of continuous versus episodic fluconazole therapy, continuous therapy did not result in a higher rate of refractory OPC or esophageal disease.[47] HIV specialists do not recommend primary or secondary prophylaxis for OPC.[31] The rationale includes effectiveness of therapy for acute episodes of OPC, low incidence of serious invasive fungal disease, low mortality associated with mucosal candidiasis, potential for drug interactions, potential for emergence of drug resistance, and the prohibitive long-term cost of prophylaxis.

8 The decision to use secondary prophylaxis should be individualized for each patient. Secondary prophylaxis can be considered in patients with multiple recurrent episodes of symptomatic OPC or when the disease is sufficiently severe and affecting the quality of life.[31] Patients with a history of one or more episodes of documented esophageal candidiasis and a CD4 T-cell count still <200 cells/mm^3 (0.2×10^9/L) despite being on AART are candidates for secondary prophylaxis. Oral fluconazole 100 mg three times weekly is the regimen recommended by the Infectious Diseases Society of America for patients deemed in need of chronic suppressive therapy.[22] Itraconazole solution 200 mg daily orally is an alternative as suppressive therapy for OPC.[34]

Patients with malignant neoplastic diseases who are receiving irradiation, cytotoxic, and/or immunosuppressive therapy are at high risk for fungal infections in addition to bacterial and viral infections. Prophylaxis of *Candida* infection is controversial, and the results of studies have been conflicting and difficult to evaluate. In the hematopoietic stem cell transplant (HSCT) population, fluconazole prophylaxis is recommended prior to engraftment. Cross-resistance to other azoles may occur among *Candida* species; this should be a treatment consideration in a patient who develops a breakthrough fungal infection. Micafungin is an alternative to fluconazole prophylaxis of candidiasis.[48] The value of antifungal prophylaxis in these patients needs to be considered in the broader context of not only reducing colonization and the risk of superficial candidiasis but also, more importantly, reducing the risk for invasive candidiasis and improving survival. Management of these infections in this patient population is discussed further in Chapter 145, “Infections in Immunocompromised Patients.”

Evaluation of Therapeutic Outcomes

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.[31,34] Sterilization of the oral cavity is not a feasible end point because mycologic eradication is rarely achievable, especially in HIV-positive patients. Symptomatic relief of presenting signs and symptoms (see Table 143-5) generally occurs within 48 to 72 hours of starting therapy, with complete resolution by 7 to 10 days. Patients should be advised about the time course and told to return for reassessment when signs and symptoms recur. It is usually unnecessary for the patient to be reassessed soon after finishing the treatment course. However, HIV patients should be questioned and examined for the occurrence of mucosal candidiasis as part of their regular follow-up. The frequency of monitoring can be more often in neutropenic patients because of concern for dissemination of candidiasis. During the period of neutropenia, temperature should be monitored daily, as well as signs of dissemination.

Efficacy of the antifungal agent is partly influenced by patient adherence to the medication regimen. Patients must be counseled on proper administration and dosing, in particular for topical agents (Table 143-7).[44] Safety end points include monitoring for occurrence of the relevant drug side effects and drug interactions (see Table 143-6). Mild GI intolerance can occur with topical therapy, but serious adverse effects are rare. It is prudent to monitor for hypersensitivity reactions, especially rash and pruritus that might occur with any medication. GI intolerance is more associated with the oral azoles. Hepatotoxicity can occur when azole therapy is prolonged beyond 7 to 10 days or high doses are used. Periodic monitoring of liver enzymes (alanine transaminase and aspartate amino-transferase) should be considered, especially if prolonged therapy (longer than 21 days) is anticipated. Patients who are receiving IV amphotericin B require daily monitoring by a pharmacist.

TABLE 143-7

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. Troches should be slowly dissolved in the mouth, not chewed or swallowed whole, over 15-20 minutes, and the saliva swallowed.
4. Suspension should be swished 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, the patient should rinse or drink water prior to dosing. For xerostomia, suggest nonpharmacologic measures for symptomatic relief (eg, ice chips, sugarless gum or hard candy, citrus beverages).
7. Dentures should be removed and disinfected 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.

Data from Reference 42.

MYCOTIC INFECTIONS OF THE SKIN, HAIR, AND NAILS

Superficial cutaneous mycoses affect up to 20% to 25% of the population globally.[49] The usual pathogens are the dermatophytes classified by genera: *Trichophyton*, *Epidermophyton*, and *Microsporum*.[50] Less frequently infection is caused by nondermatophyte fungi (eg, *Malassezia furfur*) and *Candida* species. Dermatophytes can penetrate keratinous structures of the body and therefore infections are limited to hair, nails, and skin. These infections affect both males and females and all races. Reservoirs of mycotic infections include humans, animals, and soil.[50,51] Individuals can develop an infection if they come in contact with a reservoir in addition to having a conducive environment for mycotic growth (ie, moist conditions). 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, and close living quarters (dormitories, barracks).[51]

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.[52] The central clearing of the lesion may distinguish dermatophytoses from other skin eruptions such as psoriasis or lichen planus that have a more uniform inflammatory presentation.[52] Infections of the nail can appear chalky and dull yellow or white and become brittle and crumbly.

Diagnosis usually is based on patient history, as well as the physical examination.[53,54] 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, whereas cultures are more expensive and take longer to obtain results. Diagnostic tests are recommended when systemic therapy is likely to be prescribed.[53,54]

9 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.[55,56] Table 143-8 lists specific treatments for each mycotic infection. Superficial mycotic infections are categorized by the pattern and site of infection.[50] The most commonly occurring infections in North America are detailed in the following sections.

TABLE 143-8

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	Terbinafine 250 mg/day × 2 weeks
	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	
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	Ketoconazole 200 mg daily × 4 weeks
	Selenium sulfide daily × 2 weeks	Itraconazole 100-200 mg/day × 4-6 weeks
		Griseofulvin 500 mg/day × 4-6 weeks
Pityriasis versicolor	Clotrimazole, twice daily	Ketoconazole
	Econazole, daily	
	Haloprogin, twice daily	Fluconazole
	Ketoconazole, daily	
	Miconazole, twice daily	Itraconazole 200 mg daily × 3-7 days
	Oxiconazole cream only, twice daily	
	Sulconazole, twice daily	
	Tolnaftate, three times daily	
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.

Tinea Pedis

Tinea pedis is the most common dermatophytoses (affecting ~70% of adults). It is better known as “athlete’s foot” and occurs in hot weather, with exposure to surface reservoirs (locker room floors), and with use of occlusive footwear.[51] Tinea pedis has three common presentations. The most common is the interdigital form which is characterized by fissuring, maceration, and scaling of the spaces between the toes (most frequently the fourth and fifth toes). Patients often complain of itching and burning. The “moccasin-like” distribution presentation is usually caused by *Trichophyton*

rubrum. In this form the plantar surface becomes chronically scaly and thickened with accompanying erythema of the soles, heels, and sides of the foot. The third presentation, vesiculobulous tinea pedis, is characterized by the formation of vesicles, pustules, and occasionally bullae typically on the soles of the foot. Contact dermatitis, pustular psoriasis, and eczema would be in the differential diagnosis. Disruption of skin integrity with tinea pedis is a risk factor for streptococcal cellulitis as a complication. Treatment with topical therapy for 2 to 4 weeks often is adequate for mild infections; however, severe infections or involvement of the nails require oral therapy[51] (see Table 143-8). Recurrence of infection occurs in up to 70% of individuals especially if there is concomitant onychomycosis. Prolonged treatment with either topical or systemic therapy may be required.[50,55] Other nonpharmacologic measures such as disinfecting footwear, avoidance of walking barefoot in public places, controlling hyperhidrosis, wearing absorbent socks, and nonocclusive shoes should be advised.

Tinea Manuum

Tinea manuum is a superficial fungal infection of one or infrequently both hands, and can involve the feet (tinea pedis). The infection presents with dry and hyperkeratotic palmar surface of the hand. The fingernails, when involved, may present with vesicles and scaling. Contact dermatitis, eczema, psoriasis, and callus formation should be in the differential diagnosis. Treatment of this infection is similar to tinea pedis (see Table 143-8). Emollients that contain lactic acid also can be useful.[51] Relapse or recurrence is frequent especially if tinea pedis or onychomycosis is present.

Tinea Cruris

Tinea cruris is an infection of the proximal thighs and buttocks.[56] It is referred to as “jock itch” and is more common in males. Tinea cruris and tinea pedis often occur concurrently. High humidity and warm temperatures along with wet or tight-fitting clothes contribute to the development of tinea cruris. The scrotum and penis often are spared from infection. The lesions are red, scaling with raised borders. Pustules or vesicles and maceration are usually found along the active border. Itching and burning are the most common patient complaint. The differential diagnosis would include candida infection, erythrasma, mechanical intertrigo, psoriasis, and seborrheic dermatitis.[52] Treatment with topical therapy is recommended and should continue for 1 to 2 weeks after symptom resolution. Severe infections can require oral therapy (see Table 143-8). Relief of pruritus and burning can be facilitated with short-term (2 or 3 days) topical steroids (2.5% hydrocortisone).[51] The feet of the patient should also be examined as a source of infection. Nonpharmacological measures such as keeping the area dry or avoiding prolonged exposure to moisture are important patient counselling points.

Tinea Corporis

Tinea corporis, also known as ringworm, is an infection of the glabrous skin of the trunk, extremities, or face.[52] Lesions of tinea corporis may be singular or multiple and appear as round, scaly lesions with central clearing and a raised border with sharp margination. The border may exhibit pustules. The degree of pruritis is variable. The differential diagnosis includes nummular eczema, contact dermatitis, psoriasis, pityriasis rosea, tinea versicolor, granuloma annulare, and Lyme disease.[52] Prior use of topical corticosteroid preparations may alter the appearance such that the central clearing and raised borders are no longer apparent impacting diagnosis. Diagnosis should be confirmed with KOH examination of skin scrapings of the edge of the lesion. Therapy is similar to that for tinea pedis, tinea manuum, and tinea cruris (see Table 143-8). If the infection is widespread, systemic antifungal therapy may be necessary.

Tinea Capitis

Tinea capitis is a mycotic infection involving the scalp, hair follicles, and adjacent skin that primarily affects children.[57,58] Treatment should consist of oral therapy, as well as the cleaning of combs and brushes, which can be contaminated (see Table 143-8). Daily shampooing is recommended for removal of scales. Some children and adults can be asymptomatic carriers, thereby facilitating spread of the infection.[58] Terbinafine had the highest cure rates at 75%-78% when compared with griseofluvin, ketoconazole, itraconazole, and fluconazole.[59] Family members who culture positive for *Trichophyton tonsurans* should be treated with an antifungal shampoo (eg, ketoconazole, selenium sulfide, or povidone-iodine).[58]

Tinea Barbae

Tinea barbae affects the hairs and follicles of beards and mustaches.[58] Treatment is similar to that for tinea capitis (see Table 143-8). Removal of the

beard or mustache is recommended.[51]

Pityriasis Versicolor

Hyper- and hypopigmented scaly patches characterize pityriasis versicolor, which is also known as *tinea versicolor*. It is caused by yeasts of the *Malassezia* genus that, with the exception of *Malassezia pachydermatis*, are all lipophilic. The seborrheic areas (scalp, face, back and front of the trunk) of the human body are always colonized by one or more *Malassezia* spp., such as *M. globosa*, *M. sympodialis*, *M. sloffiae*, and *M. restricta* are the most common colonizers; *M. globosa* and *M. furfur* are most frequent clinical infection isolates. The lesions are found on the trunk, face, and extremities.[50] It is more common in adults and in areas with tropical ambient temperatures. Topical treatment usually is adequate unless there is extensive involvement, recurrent infections, or failure of topical therapy.[60] Ketoconazole 2% shampoo was significantly more effective than selenium sulfide 2.5% shampoo (89% vs 35% cure rate).[60] Recurrence of infection after cessation of treatment may be as high as 60% in the first year and 80% the second year. Suppressive maintenance therapy either orally or topically may be used in these cases.[49]

Onychomycosis (Tinea Unguium)

Onychomycosis is a fungal infection of the nail apparatus and is the most common single cause of nail dystrophy, affecting up to 8% of the general population and accounting for up to 50% of all nail problems.[60-63] Onychomycosis more commonly affects the toenails (2%-14% of adults), ~4 to 19 times more frequently than fingernails, with prevalence increasing with age.[62] This can be because of the slower growth of toenails (three times slower than fingernails), making it easier for fungi to establish infection. Onychomycosis has a significant impact on quality of life, both functional and psychosocial. In addition, the affected nails can disrupt the integrity of the surrounding skin, potentially increasing the risk of secondary bacterial infections.[62]

Onychomycosis is due to infection by dermatophytes (tinea unguium), yeasts, and nondermatophyte fungi.[64] Dermatophytes are the most frequent causes of onychomycosis (~90% in toenail and ~50% in fingernail infections).[65] The dermatophytes responsible for causing >90% of cases of onychomycosis are *Trichophyton rubrum* (71%) and *Trichophyton mentagrophytes* (20%).[57,58] Less common fungi causing onychomycosis are the nondermatophytic molds (2.3%-11%) and yeasts (5.6%). *C. albicans* is the most commonly isolated yeast and typically affects fingernails rather than toenails.[60,66] Risk factors for dermatophytic onychomycosis are increasing age (especially older than 40 years), family history and genetic factors, immunodeficiency (eg, HIV, renal transplant, immunosuppressive therapy, and defective polymorphonuclear chemotaxis), diabetes mellitus, psoriasis, peripheral vascular disease, smoking, prevalence of tinea pedis, frequent nail trauma, and sporting activities such as swimming.[66,67] These risk factors also appear to apply to recurrence of onychomycosis. Mold onychomycosis does not seem to be associated with systemic or local predisposing factors, but there is a risk of systemic dissemination in immunosuppressed patients.[66] *Candida* onychomycosis seems to always occur in immunosuppressed patients.[66]

Onychomycosis can present in four or five different major clinical forms, of which lateral distal subungual onychomycosis is the most common type.[60,66,68] In distal subungual onychomycosis, the nail plate, the nail bed, and, in advanced cases, the matrix are all affected, and *T. rubrum* is the most common etiologic cause. The worst case of onychomycosis is progression of the infection to total dystrophic onychomycosis, characterized by almost complete destruction of the nail plate. White superficial onychomycosis is usually caused by *T. mentagrophytes*, where the infection is localized to the surface of the nail plate. In proximal subungual onychomycosis, the fungi (usually *T. rubrum*) invade the nail through the proximal nail fold and spread to the nail plate and matrix. Although proximal subungual onychomycosis is relatively uncommon in the general population, it occurs most frequently in severely immunocompromised patients and is often considered a marker for AIDS.[66,68] Because of the multifactorial etiology of onychomycosis, it is important to differentiate onychomycosis from other causes of nail dystrophies so that the patient receives appropriate therapy and is not subjected to prolonged treatment with unnecessary drugs. Besides clinical history and physical examination, proper diagnosis of onychomycosis can include the combination of direct microscopy of scrapings from the appropriate nail area to look for fungal hyphae and fungal cultures, and, if necessary, histologic examination.[62,69,70] Table 143-9 provides a differential diagnosis for fungal nail diseases.[71]

TABLE 143-9

Differential Diagnosis of Fungal Nail Infections

Diagnosis	Features Consistent with Diagnosis
Psoriasis	Nail pitting, rash elsewhere on body, family history of psoriasis
Lichen planus	Nail atrophy, scarring at proximal aspect of the nail
Periungual squamous cell carcinoma	Single nail affected, pain, warty nail fold change, or ooze from the edge of nail
Yellow nail syndrome	Multiple nails turn yellow, grow slowly, increased longitudinal and transverse curvature, intermittent pain and shedding, associated with chronic sinusitis, bronchiectasis, lymphedema
Trauma	Single nail affected, homogeneous alteration of nail color and altered shape of nail

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Treatment

General Approach

In general, onychomycosis of the toenail is more difficult to treat than fingernails, requires longer treatment duration, and is associated with a higher recurrence. The treatment options for onychomycosis include oral and topical therapies, mechanical or chemical nail avulsion, or a combination of these. Onychomycosis merits proper assessment and treatment consideration because it is a debilitating disease and can exert a negative impact on quality of life (eg, cosmetic and psychosocial effects, pain, discomfort, and decreased ambulation).[62,64,66,72] It is reasonable to not treat persons with minimal toenail involvement and no associated symptoms.[71] Although definitive data are lacking regarding the risk of progression of untreated disease, it can lead to complications such as cellulitis or reduced mobility, which can further compromise peripheral circulation in those with diabetes or peripheral vascular disease; additionally, infected nails can serve as a source of transmission of fungi to other areas of the body, as well as to other people, such as close household contacts, or in communal bathing places.[63,64,66,72,73] Treatment decisions should be made on an individual basis. The primary end point of treatment is eradication of the organism, with secondary end points being clinical cure and improvement.[63] Assessment of clinical success (cure or improvement) requires follow-up for several months after the end of treatment because of the slow growth rate of nails, especially toenails (1 mm/month).[62,66] Successful eradication of the fungus does not always result in normalization of the nails because they can have been dystrophic prior to infection. This can cause patient dissatisfaction, especially if this is not explained before starting treatment.[68] There are several factors that must be taken into account on a patient-by-patient basis to ensure appropriate treatment decisions (Table 143-10). The impact of patient adherence on the success of treatment cannot be overemphasized. Patients need to be educated about their disease, expectations of treatment, and prevention of recurrence, and various strategies have been suggested to improve treatment success.[70]

TABLE 143-10

Factors That May Impact Treatment Decisions and Outcomes

- Type and severity of onychomycosis
- Causative organism—dermatophyte vs molds or yeast
- Infection of the finger vs toenail
- Extent of disease—involvement of matrix, one or two lateral edges, number of nails
- Thickness of nail plate
- Other sites of mycotic infection (palms, soles, toe webs)
- Other nail alterations affecting outcome (onycholysis, paronychia, dermatophytoma, etc.)
- Other nail diseases and symptoms
- Age and underlying medical conditions (diabetes, poor perfusion, immunocompromised)
- Drug interactions and adverse effects
- Cost of therapy

Data from References 67, 69, and 70.

Topical Therapy

10 Conventional topical antifungal products are available as creams, ointments, powders, and solutions.[64,66,73] Mycological cure rates in open labeled trials are between 45% and 65%; however, cure rates in high quality studies are low (2%-10%). Despite this, most experts consider topical therapy a feasible option when the infection is superficial involving the nail plate without matrix involvement, such as white superficial onychomycosis, involves a partial area of the nail plate not exceeding 50% (owing to difficulty of applying treatment to the margin of the nail), is limited to a few (three or four) nails, is in the early stages of distal subungual onychomycosis when infection is still confined to the distal edge of the nail, or when systemic therapy is contraindicated.[62,66,72] Four products demonstrated cure rates between 2% and 10% after 48 weeks of treatment.[74] The highest quality of evidence was with efinconazole, an azole antifungal agent. Moderate quality evidence was with tavaborole, an oxaborole antifungal, and ciclopirox hydrolacquer. The poorest quality was with ciclopirox 8% lacquer. Amoroline 5% nail lacquer was not included in the review. In separate studies amorolfine produced higher mycologic and treatment cure rates than ciclopirox 8% lacquer.[64,72] Nail lacquers contain a volatile vehicle, used to deliver the drug, evaporates and leaves an occlusive film with a high-drug concentration on the nail surface.[66,73] These insolble therapies require nail filing before application. The ciclopirox hyprolacquer is a water soluble product that does not require nail filing for absorption into the nail.[62,66,72] Combining topical therapy with debridement of the affected nail (thus diminishing the amount of nail requiring treatment) may increase the likelihood of successful treatment, although there is no strong supporting evidence.[71] Topical therapy is not associated with systemic adverse effects or drug interactions. Any adverse effect will be localized to the application site, such as mild erythema in the adjacent skin area.

Systemic Therapy

Oral antifungal therapy is considered to be more effective than topical for treating onychomycosis. Terbinafine and itraconazole (capsule), the first-line agents for treatment, have yielded higher efficacy rates using shorter treatment periods (generally 3 months or shorter) for toenail and fingernail onychomycosis compared with the traditional agents, such as griseofulvin and ketoconazole, which are rarely used nowadays. Terbinafine, an allylamine, exerts fungicidal activity and demonstrates the greatest in vitro activity against dermatophytes compared with the other oral antifungals; it has good activity against nondermatophyte molds and only marginal activity against *Candida* species.[62,73] Like other azoles, itraconazole is fungistatic, has a broad antifungal spectrum, and is active against dermatophytes, nondermatophytes, and *Candida* species.[62,73] Both agents have lipophilic and keratinophilic properties, which explains their excellent penetration (appearing in the nail plate within days of treatment initiation) and accumulation in the nails, achieving concentrations far exceeding the minimal inhibitory concentration (MIC) of most dermatophytes. Nail terbinafine concentrations are detected within 1 week of starting therapy, whereas itraconazole can be detected 1 (fingernails) to 2 weeks (toenails) after starting therapy.[66] Both drugs are slowly eliminated from the nail, with effective drug concentrations persisting in nails for 30 to 36 weeks after completion of treatment with

terbinafine and for 27 weeks with itraconazole.[68] The persistence of drug in the nails explains in part the long-term protection against relapses after the end of treatment and also permits use of intermittent (pulse) dosing.

The treatment of toenail onychomycosis requires a 12-week course, whereas a 6-week course is adequate for fingernail onychomycosis with either drug (see Table 143-8).[63,68,75] Terbinafine is the first-line agent for onychomycosis; itraconazole is the alternative. Terbinafine is more effective than itraconazole either by continuous or pulse dosing.[62,72,73] Mycologic cure rates for terbinafine range from 77% to 100% depending on the study.[66,76,77] Continuous terbinafine was the most effective therapy for toenail onychomycosis.[78-81] In addition, terbinafine was reported to achieve high cure rates in high-risk immunosuppressed patients, such as diabetics and organ transplant recipients, comparable to the immunocompetent population, with no significant adverse effects or drug interactions. It also appears to be effective in HIV patients and nondermatophyte infections.[75,81,82] Itraconazole pulse therapy is the preferred method over continuous dosing for fingernail infections, and it is licensed as twice-daily dosing for a 1-week cycle per month for two consecutive months (ie, two pulses), or as daily therapy for 6 weeks (see Table 143-8).[68,75] Although itraconazole pulse therapy is not approved by the US Food and Drug Administration (FDA), three or four pulses are effective for toenail infections; otherwise, half the dose is taken daily for 3 months (see Table 143-8).[68,75] In addition to lower drug cost, the potential advantages of itraconazole pulse therapy compared with continuous therapy are a lower risk of adverse drug effects and improved patient adherence.

Terbinafine was the most cost-effective therapy in terms of highest success rate, lowest relapse rate, and highest number of disease-free days for both fingernail and toenail infections.[83] The cost per cure with the use of oral terbinafine (based on cure rates from clinical trials) ranged from $2,439 to $7,944, depending on disease severity.[84] Compared with the amount of money a patient would consider reasonable to spend on treatment, the expense for a course of systemic therapy is considerably higher.[84,85]

Both terbinafine and itraconazole generally are well tolerated. The more common adverse effects reported with terbinafine are GI (eg, diarrhea, dyspepsia, nausea, and abdominal pain), dermatologic (eg, rash, urticaria, and pruritus), and headache; less common adverse effects are taste disturbances, fatigue, inability to concentrate, and asymptomatic liver enzyme abnormalities.[68,72,75] Terbinafine can cause transient decrease in absolute lymphocyte counts; hence, monitoring of complete blood counts can be useful, especially in immunocompromised patients.[75] Although uncommon, severe adverse effects have been reported with terbinafine, including erythema multiforme, Stevens-Johnson's syndrome, toxic epidermal necrolysis, pancytopenia, lupus erythematosus, psoriasis, hair loss, and hepatotoxicity. Severe hepatotoxicity is rare.[86] Terbinafine thus is not recommended for patients with chronic or active liver disease, although hepatotoxicity can occur in patients with no preexisting liver disease or serious underlying medical condition. Prior to initiating terbinafine treatment, it is recommended to obtain appropriate nail specimens for laboratory testing to confirm the diagnosis of onychomycosis. Liver function parameters (serum transaminases) should be assessed at baseline and periodically during treatment with terbinafine.[75,86]

The common adverse effects of itraconazole are similar to those of terbinafine, such as GI disturbance, dermatologic disorders, and headache; less common adverse effects include dizziness, fatigue, fever, decreased libido, and asymptomatic liver enzyme abnormalities (1%-5% with continuous dosing and ~2% with pulse dosing).[68,72,87] Although still considered rare, 24 serious cases of liver failure, including transplantation and death, have been reported with the use of itraconazole.[86] Some of these patients did not have preexisting liver disease or serious underlying medical conditions, and some developed within the first week of treatment. Itraconazole should be avoided in patients with elevated liver enzymes or active liver disease or in those who have experienced other drug-induced liver toxicity. Liver function parameters (serum transaminases) should be assessed prior to and periodically during treatment. However, some experts have suggested that frequent monitoring is not as necessary if pulse therapy is used because symptomatic hepatotoxicity has not been reported with pulse therapy.[87] In addition, there is risk of developing congestive heart failure (CHF) associated with the use of itraconazole, possibly related to its potential negative inotropic effect.[63,76] Therefore, itraconazole should not be used in patients with evidence of ventricular dysfunction, such as CHF. Symptomatic assessment for the development of CHF also should be included as part of therapy monitoring. Before a patient is subjected to several months of itraconazole treatment, it is important to confirm the diagnosis of onychomycosis.

In contrast to the azoles, terbinafine does not inhibit the cytochrome P450 (CYP)3A4 isoenzymes, but it is a potent inhibitor of the CYP2D6 isoenzymes, which are responsible for metabolism of tricyclic antidepressants and other psychotropic drugs.[63,68,75] The most significant drug interactions with terbinafine are decreased clearance of 33% by cimetidine and increased clearance of 100% by rifampin. Other drug interactions of variable clinical significance are tricyclic antidepressants, cyclosporine, caffeine, theophylline, and terfenadine. Itraconazole and its major metabolite can inhibit the

CYP3A4 isoenzymes and result in numerous clinically significant drug interactions where coadministration with several drugs are contraindicated (eg, alprazolam, midazolam, triazolam, pimozide, lovastatin, simvastatin, cisapride, and terfenadine).[62,68,75]

Fluconazole is also active against dermatophytes, *Candida* species, and some nondermatophytes[68,72]; however, it does not have FDA approval for treatment of onychomycosis. The overall mycologic cure rate of fluconazole is 48%, which is lowest compared with all other oral agents.[78] The most effective dose and treatment duration have not been clearly established, with a variety of dosing regimens used, ranging from 50 mg daily to 300 mg once weekly for 6 to 12 months (see Table 143-8).[68,75] The advantages of fluconazole include a relatively good safety profile and fewer drug interactions compared with itraconazole.[68,75]

These three oral antifungal agents have superseded the use of griseofulvin and ketoconazole as treatments of choice for onychomycosis.[62,72,73] Griseofulvin has a narrow antifungal spectrum, low clinical efficacy, especially for toenail infections, high relapse rates, and the need for prolonged treatment duration (up to 12-18 months for toenails). Use of ketoconazole is also associated with high relapse rates, and the prolonged treatment duration carries an increased risk of hepatotoxicity.

Treatment Response and Recurrence

Treatment failures and recurrence rates of infection following initial cure are high, ranging from 20% to 50%.[63,71] Recurrence could be either a relapse (original infection not completely cured) or reinfection (new infection after achieving a cure of the original). Factors associated with poor response to systemic therapy include a compromised immune system (AIDS), reduced blood flow (diabetes, peripheral vascular disease, vasculitis, connective tissue disease, and CHF), coexisting nail disease (psoriasis), nail factors (slow growth, thick nails, and severe disease), drug-resistant organisms because of extensive prior drug exposure, and reduced bioavailability (absorption problems, poor compliance, and drug interactions).[68,71] To improve treatment outcomes and reduce recurrence, patients should be counseled on the importance of proper foot hygiene, for example, wearing breathable footwear and 100% cotton socks with frequent changes, keeping the nails short and clean, keeping the feet dry, protecting the feet in shared bathing areas, treating tinea pedis, and controlling other predisposing medical conditions.[71]

The use of combination therapy (topical–oral or oral–oral agents) can improve cure rates and shorten treatment duration, as this approach provides complementary mechanisms of attack.[71,72] Favorable results were achieved with itraconazole or terbinafine combined with amorolfine.[71,72] To date, no specific combination has been approved or endorsed for use. Other novel approaches include giving supplemental therapy and use of boosted therapy.[71,72] The efficacy and role of either approach remain to be defined.

ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
AIDS	acquired immune deficiency syndrome
BMT	bone marrow transplantation
CHF	congestive heart failure
CMI	cell-mediated immunity
CYP	cytochrome P450
FDA	Food and Drug Administration
GI	gastrointestinal
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HSCT	hematopoietic stem cell transplant
IgA	immunoglobulin A
KOH	potassium hydroxide
MIC	minimum inhibitory concentration
MMT	miconazole mucoadhesive tablet
OPC	oropharyngeal candidiasis
RVVC	recurrent vulvovaginal candidiasis
VVC	vulvovaginal candidiasis

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SELF-ASSESSMENT QUESTIONS

1. The goal of therapy in patients with VVC is:
   A. Resolution of symptoms
   B. Eradication of viable *Candida*
   C. A test of cure
   D. No recurrence within 6 weeks of therapy
2. The following should be recommended as a general approach to treatment of VVC:
   A. Keep vagina clean by douching
   B. Soothe skin with warm baths
   C. Avoid harsh soaps
   D. All the above
3. A young otherwise healthy female is determined to have VVC. She had the same symptoms 2 years ago. Which of the following would be the best treatment for her?
   A. Fluconazole 150 mg tablet, 1 orally × 3 day
   B. Miconazole 200 mg suppository, 1 per vagina × 3 days

C. Clotrimazole 100 mg tablet, 1 per vagina × 3 days

D. Nystatin 100,000 unit tablet, 1 orally × 14 days

4. A 33-year-old pregnant female has the classic symptoms of VVC. Which of the following would be the best treatment option for her?

A. Tiaconazole 6.5% cream, 1 applicator per vagina × 4 days

B. Fluconazole 150 mg, 1 orally × 7 days

C. Nystatin 100,000 unit tablet, 1 tablet orally × 14 days

D. Clotrimazole 100mg tablet, 1 per vagina × 7 days

5. A young patient with diabetes who has had four episodes of VVC in the last 8 months has tested positive for *C. glabrata*. Which of the following treatments should be used for induction therapy?

A. Boric acid suppositories 600 mg × 14 days

B. Fluconazole 150 mg tablet × 10 days

C. 5 Flucytosine cream 1000 mg × 14 days

D. Itraconazole 100 mg tablet × 10 days plus oral lactobacillus

6. OPC is an opportunistic infection that is common in which of the following clinical settings?

A. HIV patients on effective ART

B. Patients receiving short course antimicrobial therapy

C. Patients with hematological and other malignancies

D. Adults with poor dental hygiene

7. Which of the following products would be best for patients who have a mild form of OPC but also complain of xerostomia and diabetes mellitus?

A. Nystatin suspension

B. Clotrimazole troche

C. Amphotericin B suspension

D. Miconazole mucoadhesive tablets

8. The best option for the treatment of a HIV-infected patient with esophageal candidiasis would be which of the following options?

A. Clotrimazole troches

B. Fluconazole oral tablets

C. Itraconazole oral suspension

D. Nystatin oral suspension

9. A patient with profound neutropenia due to chemotherapy for acute leukemia has developed severe esophageal candidiasis. Which of the following is the best recommendation to treat this infection?

A. Amphotericin b IV

B. Fluconazole IV

C. Itraconazole IV

D. Micafungin IV

10. Which of the following is the best strategy to prevent future episodes of mucosal candidiasis in HIV-infected patients?

A. Primary prophylaxis

B. Secondary prophylaxis

C. Long-term suppressive therapy

D. Appropriate antiretroviral therapy

11. Risk factors for refractory oral mucosal candidiasis include which of the following:

A. Prolonged antibiotic exposure, uncontrolled HIV-infection, prior use of an azole antifungal

B. Uncontrolled HIV-infection, repeated courses of antifungal therapy, poor adherence to antifungal therapy

C. Prolonged antibiotic exposure, colonization with non–*C. albicans* species, prior azole therapy

D. Colonization with non–*C. albicans* species, poor adherence to antifungal therapy

12. A young female was recently diagnosed with HIV infection through routine pregnancy screening. She is currently asymptomatic and has started on antiretroviral therapy.

A. She should be started on primary antifungal prophylaxis with fluconazole.

B. Antifungal prophylaxis should be offered but is not required unless symptomatic.

C. Antifungal prophylaxis should be reserved until after her first episode of oral mucosal candidiasis.

D. Neither primary nor secondary antifungal prophylaxis should be considered in this patient.

13. When is oral therapy recommended in patients with tinea pedis?

A. Mild infections

B. Moccasin-type

C. Involvement of the nail

D. Presentation with vesicles and pustules

14. A 76-year-old male patient with CHF and diabetes has just been diagnosed with onychomycosis in his fingers. Which of the following would be considered the most effective therapy?

A. Terbinafine × 6 weeks

B. Terbinafine × 12 weeks

C. Itraconazole pulse × 3 months

D. Ciclopriox × 48 weeks

15. Which of the following is not a strategy to prevent the recurrence of onychomycosis?

A. Protect feet in shared bathing areas

B. Keep feet dry

C. Manicure with nail polish

D. Wear cotton socks

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** Asymptomatic colonization does not need to be treated.
2. **C.** Warm baths and douching can cause further irritation.
3. **B.** Nystatin is inferior to the azoles, and doses for the azoles other than clotrimazole are incorrect.
4. **D.** Oral therapy should not be used due to the risk of fetal abnormalities. Nystatin and courses of therapy less than 7 days are inferior.
5. **A.** The dose of 5 flucytosine is incorrect and azoles are inferior.
6. **A.** Such patient populations are those with impaired immune systems due to diseases, such as malignancy or diabetes, infection with HIV, and extremes of age (neonates, very elderly). Other significant risk factor is prolonged exposure to broad-spectrum antibiotics.
7. **D.** In patients with diabetes miconazole tablets have the advantage of less sucrose content.
8. **A.** Nystatin and clotrimazole are not suitable for esophageal candidiasis. Fluconazole is superior to ketoconazole and itraconazole tablets and comparable to itraconazole suspension with fewer drug interactions.
9. **C.** Echinocandin or amphotericin B preferred in severe disease or patients at high risk of dissemination of infection. Echinocandins generally preferred over amphotericin B in patients at high risk of nephrotoxicity due to other drugs.
10. **D.** Antifungal therapy for OPC in patients with inadequately controlled HIV infection will only give a transient clinical response and high risk of relapse. Treatment with effective antiretroviral therapy is critical for these patients.
11. **B.** Refer to the Section "Antifungal-Refractory Oral Mucosal Candidiasis" for risk factors for refractory and recurrent oral mucosal candidasis.
12. **D.** Currently neither primary nor secondary antifungal prophylaxis is recommended for OPC due to availability of effective therapy, low risk of serious invasive disease, and high incidence of adverse effects or drug interactions with antifungal therapy.
13. **C.** Refer to the Section "Tinea Pedis." Most forms of Tinea Pedis can be treated with topical agents; however, infection of the nail requires oral therapy.
14. **A.** Refer to Table 98-8 and to the Section "Systemic Therapy." Oral therapy is still considered more effective than topical for treatment of onychomycosis. Treatment of finger infections are shorter duration compared to regimens for toenail onychomycosis.
15. **C.** To improve treatment outcomes and prevent recurrence appropriate foot hygiene should be emphasized.