Candidiasis (Mucocutaneous) (Last updated May 26, 2020; last reviewed May 26, 2020)

Epidemiology

Oropharyngeal and esophageal candidiasis are common in patients with HIV infection.[1,2] The vast majority of such infections are caused by *Candida albicans*, although infections caused by non-*C. albicans* species have also been reported in recent years worldwide.[3-6] The occurrence of oropharyngeal or esophageal candidiasis is recognized as an indicator of immune suppression and is most often observed in patients with CD4 T lymphocyte (CD4) cell counts <200 cells/mm^3, with esophageal disease typically occurring at lower CD4 counts than oropharyngeal disease.[1,2] In contrast, vulvovaginal candidiasis—whether a single episode or recurrent—is common in healthy, adult women and does not suggest HIV infection. The advent of antiretroviral therapy (ART) has led to a dramatic decline in the prevalence of oropharyngeal and esophageal candidiasis and a marked diminution in cases of refractory disease.

Fluconazole (or azole) resistance is predominantly the consequence of previous exposure to fluconazole (or other azoles), particularly repeated and long-term exposure.[7-9] In this setting, the vast majority of cases relate to acquisition of *C. albican*s resistance; however, prior exposure to azole therapy has also been associated with a gradual emergence of non-*C. albicans* species, particularly *Candida glabrata*, as a cause of refractory mucosal candidiasis in patients with advanced immunosuppression and low CD4 counts.[7,10]

Clinical Manifestations

Oropharyngeal candidiasis is characterized by painless, creamy white, plaque-like lesions that can occur on the buccal surface, hard or soft palate, oropharyngeal mucosa, or tongue surface. Lesions can be easily scraped off with a tongue depressor or other instrument. Less commonly, erythematous patches without white plaques can be seen on the anterior or posterior upper palate or diffusely on the tongue. Angular cheilosis also can be caused by *Candida*. Because a proportion of patients with HIV who have oropharyngeal candidiasis also manifest esophageal involvement, clinicians should ascertain whether there are symptoms suggestive of esophageal disease in patients with oropharyngeal candidiasis. Esophageal candidiasis generally presents with retrosternal burning pain or discomfort along with odynophagia; occasionally esophageal candidiasis can be asymptomatic. Endoscopic examination reveals whitish plaques similar to those observed with oropharyngeal disease. On occasion, the plaques may progress to superficial ulcerations of the esophageal mucosa with central or peripheral whitish exudates.

In women with HIV infection, *Candida* vulvovaginitis usually presents with white adherent vaginal discharge associated with mucosal burning and itching of mild-to-moderate severity and sporadic recurrences. In women with advanced immunosuppression, episodes may be more severe and recur more frequently. In contrast to oropharyngeal candidiasis, vulvovaginal candidiasis is less common and when it occurs, it is uncommonly refractory to azole therapy unless caused by non-*C. albicans* species.

Diagnosis

Oropharyngeal candidiasis is usually diagnosed clinically based on the characteristic appearance of lesions. In contrast to oral hairy leukoplakia, the white plaques of oropharyngeal candidiasis can be scraped off the mucosa. If laboratory confirmation is required, scrapings can be examined microscopically for characteristic yeast or hyphal forms, using a potassium hydroxide preparation. Cultures of clinical exudative material yield the species of *Candida* present.

The diagnosis of esophageal candidiasis is often made empirically based on symptoms plus response to therapy, or visualization of lesions plus fungal smear or brushings without histopathologic examination. The definitive diagnosis of esophageal candidiasis requires direct endoscopic visualization of lesions with histopathologic demonstration of characteristic *Candida* yeast forms in tissue and confirmation by fungal

culture and speciation.

Vulvovaginal candidiasis usually is diagnosed based on the clinical presentation coupled with the demonstration of characteristic blastosphere and hyphal yeast forms in vaginal secretions when examined microscopically after potassium hydroxide preparation. Culture confirmation is rarely required but may provide supportive information. Self-diagnosis of vulvovaginitis is unreliable; microscopic and culture confirmation is required to avoid unnecessary exposure to treatment.

Preventing Exposure

Candida organisms are common commensals on mucosal surfaces in healthy individuals. No measures are available to reduce exposure to these fungi.

Preventing Disease

Data from prospective controlled trials indicate that fluconazole can reduce the risk of mucosal disease (i.e., oropharyngeal, esophageal, and vulvovaginal disease) in patients with advanced HIV.[11-14] However, routine primary prophylaxis **is not recommended** because mucosal disease is associated with very low attributable morbidity and mortality and, moreover, acute therapy is highly effective. Primary antifungal prophylaxis can lead to infections caused by drug-resistant *Candida* strains and introduce significant drug-drug interactions. In addition, long-term oral prophylaxis is expensive. Therefore, routine primary prophylaxis **is not recommended (AIII)**. Administration of ART and immune restoration is an effective means to prevent disease.

Treating Disease

Oropharyngeal Candidiasis

Oral fluconazole is as effective as or superior to topical therapy for oropharyngeal candidiasis. In addition, oral therapy is more convenient than topical therapy and usually better tolerated. Moreover, oral therapy has the additional benefit over topical regimens in being efficacious in treating esophageal candidiasis. Oral fluconazole at 100 mg once a day is considered the drug of choice to treat oropharyngeal candidiasis except during pregnancy **(AI)**. One to 2 weeks of therapy is recommended for oropharyngeal candidiasis; 2 to 3 weeks of therapy is recommended for esophageal disease.[15]

Using topical agents to treat oropharyngeal candidiasis reduces systemic drug exposure, diminishes the risk of drug-drug interactions and systemic adverse events, and may reduce the likelihood that antifungal resistance develops. Unfavorable taste and multiple daily dosing, such as in the cases of clotrimazole and nystatin, may lead to decreased tolerability of topical therapy. As an alternative to oral fluconazole, once-daily miconazole in 50-mg mucoadhesive buccal tablets **(BI)** or five-times-per-day clotrimazole troches can be used to treat oropharyngeal candidiasis **(BI)**; these regimens were shown to be equivalent in a multicenter, randomized study.[16] Nystatin suspension or pastilles four times daily remains an additional alternative **(BII)**.[17] Topical, low-concentration gentian violet (0.00165%) applied twice daily may be an alternative, well-tolerated (i.e., without mucosal staining), and cost-effective regimen to nystatin suspension **(BI)**.[18]

Itraconazole oral solution for 7 to 14 days is as effective as oral fluconazole for oropharyngeal candidiasis but less well tolerated **(BI)**.[17] Posaconazole oral suspension[19] is also as effective as fluconazole and generally better tolerated than itraconazole solution, although both posaconazole and itraconazole have more drug-drug interactions than fluconazole **(BI)**. Both antifungals are alternatives to oral fluconazole, although few situations require that these drugs be used in preference to fluconazole solely to treat mucosal candidiasis. In a multicenter, randomized study, posaconazole was found to be more effective than fluconazole in sustaining clinical success after antifungal therapy was discontinued.[19] A new solid oral delayed-release tablet formulation of posaconazole, which exhibits less variable absorption than the oral suspension, is now available.[20] Whether it offers any advantage for the treatment of oropharyngeal candidiasis is unknown, and it currently is indicated only for prophylaxis of invasive *Aspergillus* and *Candida* infections.[21] Itraconazole

capsules are less effective than fluconazole because of their more variable absorption, and they are associated with more drug-drug interactions than fluconazole.

Esophageal Candidiasis

Systemic antifungals are required for effective treatment of esophageal candidiasis **(AI)**. A 14-day to 21-day course of either fluconazole (oral or intravenous [IV]) or oral itraconazole solution is highly effective **(AI)**. However, patients with severe symptoms initially may have difficulty swallowing oral drugs. As with oropharyngeal candidiasis, itraconazole capsules for esophageal candidiasis are less effective than fluconazole because of variable absorption **(CII)**. A 2-week course of the newer triazole isavuconazole, given orally at an initial loading dose of 200 mg, followed by 50 mg once daily; or a loading dose of 400 mg followed by 100 mg once daily; or 400 mg once weekly, is also as effective as fluconazole for uncomplicated esophageal candidiasis **(BI)**; a higher rate of gastrointestinal adverse effects was seen with the 100-mg, once-daily isavuconazole regimen than with fluconazole and the other isavuconazole regimens.[22] Voriconazole, amphotericin B (either deoxycholate or lipid formulations), and the echinocandins caspofungin, micafungin, and anidulafungin all effectively treat esophageal candidiasis **(BI)**; however, esophageal candidiasis appears to have a higher relapse rate after treatment with the echinocandins.[23,24] Therefore, oral or IV fluconazole remains the preferred therapy for esophageal candidiasis **(AI)**. Although infection with other pathogens (e.g., cytomegalovirus, herpes simplex virus that causes esophagitis) can result in symptoms that mimic those of esophageal candidiasis, a diagnostic and therapeutic trial of antifungal therapy is usually warranted before endoscopy. In those who do not respond to antifungal therapy, endoscopy is recommended to identify different causes of esophagitis or drug-resistant *Candida* **(AII)**.

Vulvovaginal Candidiasis

In most women with HIV infection, vulvovaginal candidiasis is uncomplicated and responds readily to short-course oral or topical treatment with any of several therapies, including:

- Oral fluconazole **(AII)**
- Topical azoles (i.e., clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) **(AII)**
- Itraconazole oral solution **(BII)**

Severe or recurrent episodes of vaginitis should be treated with oral fluconazole or topical antifungal therapy for ≥7 days **(AII)**. For more information, see the Vulvovaginal Candidiasis section in the Sexually Transmitted Diseases Treatment Guidelines from the Centers for Disease Control and Prevention.

Special Considerations with Regard to Starting Antiretroviral Therapy

There are no special considerations regarding initiation of ART in patients with mucocutaneous candidiasis. Specifically, there is currently no evidence that treatment with ART needs to be delayed until treatment for candidiasis has been completed.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

For most patients with mucocutaneous candidiasis, response to antifungal therapy is rapid; signs and symptoms improve within 48 to 72 hours. Short courses of topical therapy rarely result in adverse effects, although patients may experience cutaneous hypersensitivity reactions characterized by rash and pruritus. Oral azole therapy can be associated with nausea, vomiting, diarrhea, abdominal pain, or transaminase elevations. Periodic monitoring of liver function studies should be considered if azole therapy is anticipated for >21 days, especially in patients with other hepatic comorbidities **(AII)**. The echinocandins appear to be associated with very few adverse reactions: histamine-related infusion toxicity, transaminase elevations, and rash have been attributed to these drugs. No dose adjustments are required in renal failure.

Immune reconstitution inflammatory syndrome (IRIS) with ART has not yet been reported for

mucocutaneous candidiasis in patients with HIV infection. Indeed, ART is associated with a markedly reduced incidence of candidiasis.

Managing Treatment Failure

Antifungal treatment failure is typically defined as the persistence of signs or symptoms of oropharyngeal or esophageal candidiasis after 7 to 14 days of appropriate antifungal therapy. Refractory disease occurs in approximately 4% to 5% of patients with HIV infection who have oral or esophageal candidiasis, typically those with CD4 counts <50 cells/mm^3 and who have received multiple courses of azole antifungals.[8] Confirmatory culture and, in the case of esophageal candidiasis, endoscopy are necessary to confirm treatment failure due to azole resistance or other causes of esophagitis, especially if these procedures were not initially performed.

Posaconazole immediate-release oral suspension (400 mg twice daily for 28 days) is effective in 75% of patients with azole-refractory oropharyngeal or esophageal candidiasis **(AI)**.[25] Again, although the new solid delayed-release tablet formulation of posaconazole has been recently made available, it is not known whether it offers an advantage over the suspension for treating this particular disease. Alternatively, oral itraconazole solution is effective, at least transiently, in approximately two-thirds of patients with fluconazole-refractory mucosal candidiasis **(BII)**.[17] If necessary, azole-refractory esophageal candidiasis also can be treated with anidulafungin **(BII)**, caspofungin **(BII)**, micafungin **(BII)**, or voriconazole **(BII)**.

IV amphotericin B is usually effective for treating refractory disease **(BII)**. Both amphotericin B deoxycholate and the lipid preparations of amphotericin B have been used successfully **(BII)**. Amphotericin B oral suspension (1 mL of the 100-mg/mL suspension four times daily) is sometimes effective in patients whose oropharyngeal candidiasis does not respond to itraconazole **(BII)**, but this product is not commercially available in the United States.

Preventing Recurrence

When to Start Secondary Prophylaxis

A randomized clinical trial[14] in patients with HIV infection with CD4 counts <150 cells/mm^3 documented significantly fewer episodes of oropharyngeal candidiasis and other invasive fungal infections with continuous fluconazole therapy (three times a week) than with episodic fluconazole treatment for recurrences. This clinical trial also demonstrated no difference in the risk of developing clinically significant fluconazole resistance between the two groups among those receiving ART.

However, secondary prophylaxis (chronic suppressive therapy) for recurrent oropharyngeal or vulvovaginal candidiasis **is not recommended** by most HIV specialists unless patients have frequent or severe recurrences **(BIII)** because therapy for acute disease is effective, mortality associated with mucocutaneous disease is low, potential exists for drug interactions and for the development of antifungal-resistant *Candida*, and prophylaxis is costly.

If recurrences are frequent or severe, oral fluconazole can be used as suppressive therapy for either oropharyngeal **(BI)**, esophageal **(BI)**, or vulvovaginal **(BII)** candidiasis.[11-13] Oral posaconazole twice daily is also effective for esophageal candidiasis **(BII)**.[26] The potential for development of secondary azole resistance should be considered when contemplating chronic maintenance therapy using azoles in patients with HIV infection who are severely immunocompromised. Several important factors should be considered when making the decision to use secondary prophylaxis. These factors include the effect of recurrences on the patient's well-being and quality of life, the need for prophylaxis against other fungal infections, cost, adverse events, and, most importantly, drug-drug interactions.[27]

Rates of relapse are high in patients with azole-refractory oropharyngeal or esophageal candidiasis who have initially responded to echinocandins, voriconazole, or posaconazole therapy. In such patients, secondary prophylaxis should be instituted until ART produces immune reconstitution **(AIII)**.

When to Stop Secondary Prophylaxis

In situations where secondary prophylaxis has been instituted, no data exist to guide recommendations regarding its discontinuation. Based on experience with other opportunistic infections, it would be reasonable to discontinue secondary prophylaxis when the CD4 count has increased to >200 cells/mm^3 following initiation of ART **(AIII)**.

Special Considerations During Pregnancy

Pregnancy increases the risk of vaginal colonization with *Candida* species. Diagnosis of oropharyngeal, esophageal, and vulvovaginal candidiasis is the same in pregnant women as in those who are not pregnant.

Topical therapy is preferable for treatment of oral candidiasis in pregnancy, but is essential for vulvovaginal candidiasis, especially during the first trimester. Data derived from women with vulvovaginal candidiasis suggest that fluconazole should not be used at any dose (including a single 150-mg dose) in the first trimester due to the risk of spontaneous abortion, while higher exposures (>150 mg dosing) during the first trimester are associated with cardiac septal closure defects.[28-32] A recent analysis of registry data from Sweden and Denmark did not find any increase in stillbirth or neonatal death associated with exposure to fluconazole at any dose during pregnancy.[33] Five cases of a syndrome consisting of craniosynostosis, characteristic facies, digital synostosis, and limb contractures (fluconazole embryopathy) have been reported in women chronically prescribed fluconazole at doses of 400 mg daily or higher in pregnancy.[30] A report from a national cohort register in Denmark found an increased hazard ratio (HR) of 1.48 (95% CI, 1.23-1.77) for spontaneous pregnancy loss with any exposure to oral fluconazole from 7 to 22 weeks of pregnancy compared to unexposed, matched controls.[31] An increased HR of 1.47 (95% CI, 1.22–1.77) was also noted with low-dose (150–300 mg cumulative dose) exposure. No increase in stillbirth was seen with fluconazole exposure broadly, but an increase in risk of stillbirth (HR, 4.10; CI 95%, 1.89–8.90) was noted with fluconazole doses >300 mg. Based on these data, substitution of amphotericin B for fluconazole in the first trimester is recommended for invasive or refractory esophageal candidal infections **(AIII)**. Neonates born to women receiving chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

Itraconazole at high doses has been shown to be teratogenic in animals, but the metabolic mechanism accounting for these defects is not present in humans, so the data supporting this finding may not be applicable to human pregnancy. Case series in humans do not suggest an increased risk of birth defects with itraconazole,[34] but experience is limited. Human data are not available for posaconazole; however, the drug was associated with skeletal abnormalities in rats and was embryotoxic in rabbits when given at doses that produced plasma levels equivalent to those seen humans. Evidence is inconclusive or inadequate for determining fetal risk associated with voriconazole use during pregnancy. An association with cleft palate and renal defects has been seen in rats, as well as embryotoxicity seen in rabbits. Human data on the use of voriconazole are not available, so its use **is not recommended**. In animals, multiple anomalies have been seen with exposure to micafungin, and ossification defects have been seen with the use of anidulafungin and caspofungin.[35] Human data are not available for these drugs, thus their use in human pregnancy **is not recommended (AIII)**.

Chemoprophylaxis, either chronic maintenance therapy or secondary prophylaxis, against oropharyngeal, esophageal, or vaginal candidiasis using systemically absorbed azoles **should not be initiated** during pregnancy **(AIII)**. Furthermore, prophylaxis with systemic azoles **should be discontinued** in women with HIV who become pregnant **(AIII)**.

Recommendations for Treating Mucosal Candidiasis (page 1 of 2)

Oropharyngeal Candidiasis: Initial Episodes (Duration of Therapy: 7–14 Days)

Preferred Therapy:

- Fluconazole 100 mg PO once daily **(AI)**

Alternative Therapy:

- One 10-mg clotrimazole troche PO five times a day **(BI)**, *or*
- One 50-mg miconazole mucoadhesive buccal tablet once daily: Apply to mucosal surface over the canine fossa (do not swallow, chew, or crush tablet). Refer to product label for more detailed application instructions **(BI)**, *or*
- Itraconazole oral solution 200 mg PO daily **(BI)**, *or*
- Posaconazole oral suspension 400 mg PO twice daily for 1 day, then 400 mg daily **(BI)**, *or*
- Nystatin suspension 4–6 mL four times daily or 1–2 flavored pastilles four to five times daily **(BII)**, *or*
- Gentian violet (0.00165%) topical application twice daily **(BI)**

Esophageal Candidiasis (Duration of Therapy: 14–21 Days)

Note: Systemic antifungals are required for effective treatment of esophageal candidiasis **(AI)**.

Preferred Therapy:

- Fluconazole 100 mg (up to 400 mg) PO or IV daily **(AI)**, *or*
- Itraconazole oral solution 200 mg PO daily **(AI)**

Alternative Therapy:

- Voriconazole 200 mg PO or IV twice daily **(BI)**, *or*
- Isavuconazole 200 mg PO as a loading dose, followed by isavuconazole 50 mg PO daily **(BI)**, *or*
- Isavuconazole 400 mg PO as a loading dose, followed by isavuconazole 100 mg PO daily **(BI)**, *or*
- Isavuconazole 400 mg PO once weekly **(BI)**, *or*
- Caspofungin 50 mg IV daily **(BI)**, *or*
- Micafungin 150 mg IV daily **(BI)**, *or*
- Anidulafungin 100 mg IV for one dose, then anidulafungin 50 mg IV daily **(BI)**, *or*
- Amphotericin B deoxycholate 0.6 mg/kg IV daily **(BI)**, *or*
- Lipid formulation of amphotericin B 3-4 mg/kg IV daily **(BIII)**

Note: A higher rate of esophageal candidiasis relapse has been reported with echinocandins than with fluconazole.

Uncomplicated Vulvovaginal Candidiasis

Preferred Therapy:

- Oral fluconazole 150 mg for one dose **(AII)**, *or*
- Topical azoles (i.e., clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for 3–7 days **(AII)**

Alternative Therapy:

- Itraconazole oral solution 200 mg PO daily for 3-7 days **(BII)**
- For azole-refractory *Candida glabrata* vaginitis, boric acid 600 mg vaginal suppository once daily for 14 days **(BII)**

Note: Severe or recurrent vaginitis should be treated with oral fluconazole (100–200 mg) or topical antifungals for ≥7 days **(AII)**.

Chronic Suppressive Therapy

- Chronic suppressive therapy is usually not recommended unless patients have frequent or severe recurrences **(BIII)**.
- If used, it is reasonable to discontinue therapy if CD4 count >200 cells/mm^3 **(AIII)**.

If Decision Is to Use Suppressive Therapy

Oropharyngeal Candidiasis:

- Fluconazole 100 mg PO once daily or three times weekly **(BI)**

Esophageal Candidiasis:

- Fluconazole 100–200 mg PO daily **(BI)**
- Posaconazole oral suspension 400 mg PO twice daily **(BII)**

Vulvovaginal Candidiasis:

- Fluconazole 150 mg PO once weekly **(BII)**

Recommendations for Treating Mucosal Candidiasis (page 2 of 2)

Other Considerations

- Chronic or prolonged use of azoles might promote development of resistance.
- Systemic azoles may have **significant** drug-drug interactions with ARV drugs and other drugs for treatment of OIs; refer to Table 5 for dosing recommendations. Consider TDM if prolonged use is indicated.

Key: ARV = antiretroviral; CD4 = CD4 T lymphocyte; IV = intravenous; OI = opportunistic infection; PO = orally; TDM = therapeutic drug monitoring

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