Candidiasis (Mucocutaneous)

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Epidemiology

Oropharyngeal and esophageal candidiasis are common in people with HIV.[1] The vast majority of such infections are caused by *Candida albicans*, although infections caused by non–*C. albicans* species have been increasingly reported worldwide, in part due to increased selection pressure from increased use of azoles.[2-9] The occurrence of oropharyngeal or esophageal candidiasis is recognized as an indicator of immune suppression and is most often observed in people with CD4 T lymphocyte (CD4) cell counts <200 cells/mm^3, with esophageal disease typically occurring at lower CD4 counts than oropharyngeal disease.[10,11] In contrast, vulvovaginal candidiasis—whether a single episode or recurrent—is common in healthy adults and does not suggest HIV.

Clinical Manifestations

Oropharyngeal candidiasis (oral thrush) is characterized by painless, creamy white, plaque-like lesions that can occur on the buccal surface, hard or soft palate, gums, oropharynx, or tongue surface. In many cases, lesions can be 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 people with HIV who have oropharyngeal candidiasis also manifest esophageal involvement, clinicians should ascertain whether there are symptoms suggestive of esophageal disease in people 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 contrast to oropharyngeal candidiasis, vulvovaginal candidiasis is less common in people with HIV and when it occurs, it is uncommonly refractory to azole therapy unless caused by non-*C. albicans* species. In people with HIV, *Candida* vulvovaginitis usually presents with white adherent vaginal discharge associated with mucosal burning and itching of mild-to-moderate severity and sporadic recurrences. In those with advanced immunosuppression, episodes may be more severe and recur more frequently.

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.

Esophageal candidiasis should be suspected in people with low CD4 count with substernal chest pain, dysphagia, and odynophagia, especially if there is oral thrush present (though the absence of oral thrush does not rule out esophageal involvement). The diagnosis of esophageal candidiasis is often made empirically based on symptoms plus response to therapy. 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 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 and to assess for other potential pathogens including those that cause sexually transmitted infections (STIs).

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

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.[12,13] Primary antifungal prophylaxis can lead to infections caused by drug-resistant *Candida* strains and introduce significant drug–drug interactions and QTc (QT corrected for heart rate) prolongation. In addition, long-term oral prophylaxis is expensive. Therefore, routine primary prophylaxis **is not recommended (AIII).** Administration of antiretroviral therapy (ART) and immune restoration is the most effective means to prevent disease.

Treating Disease

Treating Mucosal Candidiasis
Oropharyngeal Candidiasis: Initial Episodes (Duration of Therapy: 7–14 Days) *Preferred Therapy* • Fluconazole 200-mg loading dose, followed by 100–200 mg PO once daily (AI) *Alternative Therapy* • 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 the product label for more detailed application instructions. (BI), *or* • One 10-mg clotrimazole troche PO five times a day (BI), *or* • Nystatin suspension 4–6 mL PO four times daily (BII), *or* • Itraconazole oral solution 200 mg PO daily (BI), *or* • Posaconazole oral suspension 400 mg (10 mL) PO twice daily for 1 day, then 400 mg daily (BI), *or*

- Posaconazole tablet 300 mg PO twice daily for 1 day, then 300 mg daily (BI)

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

Note: Systemic antifungals are required for effective treatment of esophageal candidiasis (AI); topical therapy alone is not recommended (AI).

Preferred Therapy

- Fluconazole 200-mg loading dose, followed by 100–200 mg (up to 400 mg) PO or IV daily (AI); consider oral suspension for people with severe symptoms and difficulty swallowing.

Alternative Therapy

- Itraconazole oral solution 200 mg PO daily (AI), *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*
- Voriconazole 200 mg PO or IV twice daily (BI), *or*
- Posaconazole oral suspension 400 mg (10 mL) PO twice daily for 1 day, then 400 mg daily (BI), *or*
- Posaconazole tablet 300 mg PO twice daily for 1 day, then 300 mg daily (BI), *or*
- Lipid formulation of amphotericin B 3–4 mg/kg IV daily (BI)
- Caspofungin 70-mg loading dose IV, followed by 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)

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

Uncomplicated Vulvovaginal Candidiasis

- Fluconazole 150 mg PO for one dose (AII), *or*
- Topical azoles (i.e., clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for 3–7 days (AII), *or*
- Ibrexafungerp 300 mg PO twice daily for 1 day (BI), *or*
- For azole-refractory *Candida glabrata* vaginitis, boric acid 600 mg vaginal suppository once daily for 14 days (BII)

Severe or Recurrent Vulvovaginal Candidiasis

- Oral fluconazole (100–200 mg) PO daily or topical antifungals for ≥7 days (AII)
- *For recurrent only (the following regimens include treatment for the acute episode plus treatment to reduce incidence of recurrent episodes):*
  - Oteseconazole 600 mg PO at Day 1, 450 mg at Day 2, followed by once weekly 150 mg dosing starting at Day 14 for 11 weeks (AI) (for those who are not of reproductive potential); *or*
  - Fluconazole 150 mg PO at Days 1, 4, and 7, followed by oteseconazole 150 mg PO daily at Days 14 through 20, followed by oteseconazole 150 mg once weekly starting at Day 28 for 11 weeks (Weeks 4–14) (AI) (for those who are not of reproductive potential); or
  - Fluconazole 150 mg PO every 72 hours x 3 doses, followed by ibrexafungerp 300 mg PO twice daily 1 day per month for 6 months (BI) (use an effective form of contraception during treatment and for 4 days after the last dose)

Other Considerations
• Systemic azoles may have significant drug–drug interactions with ARV drugs (refer to Drug–Drug Interactions section of the Adult and Adolescent Antiretroviral Guidelines) and other drugs used for the treatment of opportunistic infections (refer to Table 4: Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections). Consider TDM if prolonged use is indicated. • Fluconazole, itraconazole, posaconazole, and voriconazole can increase the risk for QTc prolongation, especially when co-administered with other QTc prolonging drugs that are cleared by CYP3A4. • Chronic or prolonged use of azoles might promote development of resistance.
Considerations During Pregnancy and Lactation
• Topical therapy is preferable for treatment of oral candidiasis and vulvovaginal candidiasis in pregnancy. Oral fluconazole should be avoided when treating vulvovaginal candidiasis in the first trimester (AIII). • During pregnancy, substitution of amphotericin B for fluconazole in the first trimester is recommended for invasive or refractory esophageal *Candida* infections (AIII). • Human data are not available for micafungin, anidulafungin, caspofungin, thus their use in human pregnancy is not recommended (AIII). Human data on the use of voriconazole are also not available, so its use is not recommended. • Oteseconazole is contraindicated during pregnancy and when lactating as animal studies have shown fetal malformations including ocular toxicity. Due to its long half-life, it is also contraindicated in females of reproductive potential despite the use of oral or other contraception. • Ibrexafungerp is teratogenic in animal studies. Use during pregnancy and when lactating is contraindicated.

Key: ARV = antiretroviral; CYP = cytochrome P450; IV = intravenous; PO = orally; QTc = QT corrected for heart rate; TDM = therapeutic drug monitoring

Oropharyngeal Candidiasis

Oral fluconazole is as effective as or superior to topical therapy for oropharyngeal candidiasis.[14] In addition, oral therapy is more convenient than topical therapy and usually better tolerated. Oral therapy has the additional benefit over topical regimens of being efficacious in treating esophageal candidiasis. Oral fluconazole at 100 to 200 mg once a day is considered the drug of choice to treat oropharyngeal candidiasis except during pregnancy **(AI).**[14] One to 2 weeks of therapy until resolution of infection is recommended for oropharyngeal candidiasis.[14]

Using topical agents to treat oropharyngeal candidiasis includes several advantages: it reduces systemic drug exposure, diminishes the risk of drug–drug interactions and systemic adverse events, and may reduce the likelihood that antifungal resistance develops. 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. Nystatin suspension four times daily remains an additional alternative **(BII).**[15] Unfavorable taste and multiple daily dosing, such as in the cases of clotrimazole and nystatin, may lead to decreased tolerability of and adherence to these topical therapies. If esophageal involvement is suspected, topical therapy alone is not recommended **(AI).**

Itraconazole is formulated as an oral solution or capsules, which differ in dosing and efficacy. Oral itraconazole for 7 to 14 days is as effective as oral fluconazole for oropharyngeal candidiasis but less well tolerated.[16] Posaconazole oral suspension[17] is also as effective as fluconazole and generally better tolerated than itraconazole solution, but it is more expensive. Although both posaconazole and

itraconazole have more drug–drug interactions than fluconazole, there are a few situations, such as *in vitro* resistance or poor clinical response, that would suggest these drugs be used in preference to fluconazole solely to treat mucosal candidiasis **(BI).** In a multicenter, randomized study, posaconazole was found to be more effective than fluconazole in sustaining clinical success after antifungal therapy was discontinued.[17] A oral delayed-release tablet formulation of posaconazole, which exhibits less variable absorption than the oral suspension, has been available.[18] Whether it offers any advantage for the treatment of oropharyngeal candidiasis has not been formally tested; however, it has been shown that switching from the oral suspension to the tablet formulation of posaconazole results in greater serum concentrations.[19] 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 and therefore recommended **(AI).** As with oropharyngeal candidiasis, however, itraconazole capsules for esophageal candidiasis may be less effective than fluconazole because of variable absorption Therefore, oral or IV fluconazole remains the preferred therapy for esophageal candidiasis **(AI).** People with severe symptoms initially may have difficulty swallowing oral drugs; oral fluconazole suspension is available and should be considered in such patients. A 2-week course of isavuconazole, given orally at an initial loading dose of 400 mg followed by 100 mg once daily **(BI)** or 400 mg once weekly, is as effective as fluconazole for uncomplicated esophageal candidiasis and is recommended as an alternative regimen **(BI);** however, 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.[20] Posaconazole, voriconazole, amphotericin B (lipid formulations), and the echinocandins caspofungin, micafungin, and anidulafungin all effectively treat esophageal candidiasis and also can be administered as alternatives **(BI);** however, esophageal candidiasis appears to have a higher relapse rate after treatment with the echinocandins.[21,22] Cost and insurance coverage also might be issues for the newer therapies.

Although infection with other pathogens that can cause esophagitis (e.g., cytomegalovirus, herpes simplex virus) 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 within 7 days, endoscopy is recommended to identify other potential causes of esophagitis or drug-resistant *Candida* **(AII).**

Vulvovaginal Candidiasis

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

- Oral fluconazole **(AII)**
- Topical azoles (i.e., clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) **(AII)**
- Oral ibrexafungerp **(BI)**

Severe or recurrent episodes of vaginitis should be treated with oral fluconazole or topical antifungal therapy for ≥7 days **(AII).**

There are now additional options for recurrent vulvovaginal candidiasis that include treatment for the acute episode plus treatment to reduce incidence of recurrent episodes. One option for people who are not of reproductive potential is oteseconazole, a new tetrazole antifungal that was U.S. Food and Drug Administration (FDA)–approved in 2022. It exhibited efficacy when administered as 600 mg on Day 1 and 450 mg on Day 2, followed by once-weekly 150 mg dosing starting at Day 14 for 11 weeks or when it was administered after three fluconazole 150-mg doses administered at Days 1, 4, and 7, followed by oteseconazole 150 mg daily dosing at Days 14 through 20, followed by oteseconazole 150 mg once weekly starting at Day 28 for 11 weeks (Weeks 4 through 14) **(AI).**[23,24]

Ibrexafungerp is an oral b-glucan synthase inhibitor that belongs in the class of triterpenoids. It was effective in Phase 2 and Phase 3 clinical trials of uncomplicated vulvovaginal candidiasis and was approved by the FDA in 2021.[25,26] In December 2022, ibrexafungerp was approved by the FDA for women with recurrent vulvovaginal candidiasis. Specifically, administration of fluconazole 150 mg every 72 hours for three doses, followed by ibrexafungerp 300 mg twice daily 1 day per month for 6 months was associated with absence of recurrent infection through week 24 in 65.4% of women compared to 53.1% of women who received placebo. These findings have been reported only in a press release,[27] with results available at ClinicalTrials.gov and on the FDA label,[28] and are thereby less compelling than peer-reviewed publication. Therefore, ibrexafungerp can be administered for recurrent vulvovaginal candidiasis **(BI).** Given the potential teratogenic effects of ibrexafungerp, treatment of women with recurrent vulvovaginal candidiasis who may become pregnant requires institution and documentation of effective contraception during treatment and for 4 days after the last dose.[29] For additional advice on managing Vulvovaginal Candidiasis, see the section in the STI Treatment Guidelines from the Centers for Disease Control and Prevention.

Special Considerations with Regard to Starting ART

There are no special considerations regarding initiation of ART in people with mucocutaneous candidiasis. Specifically, there is currently no evidence that treatment with ART needs to be delayed until treatment for candidiasis has been completed. For information about drug–drug interactions between azoles and ARV agents, see the Drug–Drug Interactions section in the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. For information about drug–drug interactions between azoles and other drugs used for the treatment of opportunistic infections, see Table 4: Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections.

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

For most people 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 people 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. Liver function and the QTc interval should be monitored if azole therapy is anticipated for >21 days, especially in people with other hepatic comorbidities or on concomitant hepatotoxic drugs **(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.[30]

Immune reconstitution inflammatory syndrome (IRIS) with ART has rarely been reported for mucocutaneous candidiasis in people with HIV. Indeed, ART is associated with a markedly reduced incidence of candidiasis.[31,32]

Managing Treatment Failure

Antifungal treatment failure is typically defined as the persistence of signs or symptoms of oropharyngeal or esophageal candidiasis within 7 days of appropriate antifungal therapy. Refractory disease occurs in approximately 4% to 5% of people with HIV who have oral or esophageal candidiasis, typically those with CD4 counts <50 cells/mm^3 who have received multiple courses of azole antifungals.[4] Confirmatory culture with drug susceptibilities and, in the case of esophageal candidiasis, endoscopy, are necessary to assess for 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 people with azole-refractory oropharyngeal or esophageal candidiasis and is therefore recommended **(AI).**[33] Again, although the delayed-release tablet formulation of posaconazole is now 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 people with fluconazole-refractory mucosal candidiasis and can be used as alternative therapy **(BII).**[16] If necessary, azole-refractory esophageal candidiasis also can be treated with anidulafungin **(BII),** caspofungin **(BII),** micafungin **(BII),** or voriconazole **(BII).**[21,22,34,35]

IV amphotericin B **(BII),** amphotericin B deoxycholate **(BII),** and the lipid preparations of amphotericin B **(BII)** are usually effective for treating azole-refractory disease and are therefore recommended. Amphotericin B oral suspension (1 mL of the 100-mg/mL suspension four times daily) can be administered to people with refractory oropharyngeal candidiasis who cannot take other oral options **(BII),** but this product is not commercially available in the United States and requires compounding by pharmacies.[36]

Patients with refractory vaginal candidiasis may benefit from intravaginal boric acid suppositories, which are commercially available at 600 mg.[37,38]

Preventing Recurrence

Preventing Recurrence
• Chronic suppressive therapy for recurrent oropharyngeal or vulvovaginal candidiasis is usually not recommended unless people have frequent or severe recurrences (CIII). • If used, it is reasonable to discontinue therapy if CD4 count increased to >200 cells/mm^3 following initiation of ART (AIII).
If the Decision Is to Use Suppressive Therapy Because of Frequent or Severe Recurrences
Oropharyngeal Candidiasis
• Fluconazole 100 mg PO once daily or three times weekly (BI)
Esophageal Candidiasis
• Fluconazole 100–200 mg PO daily (BI), *or*

- Posaconazole oral suspension 400 mg PO twice daily (BII), *or*
- Posaconazole tablet 300 mg PO daily (BII)

Vulvovaginal Candidiasis

- Fluconazole 150 mg PO once weekly (BII) *or*
- Oteseconazole 600 mg at Day 1, 450 mg at Day 2 for treatment of the acute episode, followed by once-weekly 150-mg doses starting at Day 14 for 11 weeks (AI) (for those who are not of reproductive potential); *or*
- Fluconazole 150 mg at Days 1, 4, and 7 for treatment of the acute episode, followed by oteseconazole 150 mg daily at Days 14–20, followed by oteseconazole 150 mg once weekly starting at Day 28 for 11 weeks (Weeks 4–14) (AI) (for those who are not of reproductive potential); *or*
- Ibrexafungerp 300 mg twice daily 1 day per month for 6 months (BI) (use an effective form of contraception during treatment and for 4 days after the last dose.)

Considerations During Pregnancy and Lactation

- 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 during pregnancy (AIII).
- Oteseconazole is contraindicated during pregnancy and when lactating as animal studies have shown fetal malformations including ocular toxicity. Due to its long half-life, it is also contraindicated in females of reproductive potential despite the use of oral or other contraception.
- Ibrexafungerp is teratogenic in animal studies. Use during pregnancy or when lactation is contraindicated.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; PO = orally

When to Start Suppressive Therapy

A randomized clinical trial[39] of people with HIV who had 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 fluconazole-treated groups among patients who were receiving ART.

However, secondary prophylaxis (chronic suppressive therapy) for recurrent oropharyngeal or vulvovaginal candidiasis **is not recommended** by most HIV specialists unless people have frequent or severe recurrences **(CIII)** 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 oropharyngeal **(BI),** esophageal **(BI),** or vulvovaginal **(AII)** candidiasis.[40-42] Oral posaconazole twice daily is also effective for esophageal candidiasis **(BII).**[43] The potential for development of secondary azole resistance should be considered when contemplating chronic maintenance therapy using azoles in people with HIV who are severely immunocompromised.[44] Several important factors should be considered when making the decision to use secondary prophylaxis. These factors include the effect of recurrences on the person's well-being and quality of life, the need for prophylaxis against other fungal infections, cost, adverse events, and, most importantly, drug–drug interactions.[45]

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

For information regarding oteseconazole and ibrexafungerp, see the Vulvovaginal Candidiasis Treatment Section above.

When to Stop Suppressive Therapy

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. During pregnancy, diagnosis and management of oropharyngeal, esophageal, and vulvovaginal candidiasis are the same as for other people with HIV, with several considerations.

Topical therapy is preferable for treatment of oral candidiasis and vulvovaginal candidiasis in pregnancy. Oral fluconazole should be avoided when treating vulvovaginal candidiasis in the first trimester **(AIII).** 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.[46-50] 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.[51] 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.[48] A report from a national cohort register in Denmark found an increased hazard ratio (HR) of 1.48 for spontaneous pregnancy loss with any exposure to oral fluconazole from 7 to 22 weeks of pregnancy compared to unexposed, matched controls.[49] An increased HR of 1.47 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) 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 *Candida* infections **(AIII).** Neonates born to those receiving chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

Other azoles are similarly not recommended in pregnancy. Itraconazole at high doses has been shown to be teratogenic in animals,[52] but the metabolic mechanism accounting for these defects is not present in humans, so the data supporting this finding are of uncertain significance to human pregnancy. Case series in humans do not suggest an increased risk of birth defects with itraconazole,[53] 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 in humans.[54] 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.[55] 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.[56] Human data are not available for these drugs, thus their use in human pregnancy **is not recommended (AIII).**

The recently FDA-approved drugs for the treatment of vulvovaginal candidiasis, ibrexafungerp and oteseconazole, are **contraindicated** in pregnancy as animal studies have shown fetal malformations including ocular toxicity from oteseconazole.[29,57]

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** during pregnancy **(AIII).**

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