

are recommended (*strong recommendation; moderate-quality evidence*).

126. Alternatives for fluconazole-refractory disease include voriconazole, 200 mg twice daily, OR AmB deoxycholate oral suspension, 100 mg/mL 4 times daily (*strong recommendation; moderate-quality evidence*).
127. Intravenous echinocandin (caspofungin: 70-mg loading dose, then 50 mg daily; micafungin: 100 mg daily; or anidulafungin: 200-mg loading dose, then 100 mg daily) OR intravenous AmB deoxycholate, 0.3 mg/kg daily, are other alternatives for refractory disease (*weak recommendation; moderate-quality evidence*).
128. Chronic suppressive therapy is usually unnecessary. If required for patients who have recurrent infection, fluconazole, 100 mg 3 times weekly, is recommended (*strong recommendation; high-quality evidence*).
129. For HIV-infected patients, antiretroviral therapy is strongly recommended to reduce the incidence of recurrent infections (*strong recommendation; high-quality evidence*).
130. For denture-related candidiasis, disinfection of the denture, in addition to antifungal therapy, is recommended (*strong recommendation; moderate-quality evidence*).

Evidence Summary

Oropharyngeal and esophageal candidiasis occur in association with HIV infection, diabetes, leukemia and other malignancies, steroid use, radiation therapy, antimicrobial therapy, and denture use [528, 529], and their occurrence is recognized as an indicator of immune dysfunction. In HIV-infected patients, oropharyngeal candidiasis is most often observed in patients with CD4 counts <200 cells/ μ L [528–530]. The advent of effective antiretroviral therapy has led to a dramatic decline in the prevalence of oropharyngeal candidiasis and a marked diminution in cases of refractory disease [531].

Fluconazole or multiazole resistance is predominantly the consequence of previous repeated and long-term exposure to fluconazole or other azoles [530–533]. Especially in patients with advanced immunosuppression and low CD4 counts, *C. albicans* resistance has been described, as has gradual emergence of non-*albicans* *Candida* species, particularly *C. glabrata*, as a cause of refractory mucosal candidiasis [532, 533].

Most cases of oropharyngeal candidiasis are caused by *C. albicans*, either alone or in mixed infections. Symptomatic infections caused by *C. glabrata*, *C. dubliniensis*, and *C. krusei* alone have been described [532–534]. Multiple randomized prospective studies of oropharyngeal candidiasis have been performed involving patients with AIDS and patients with cancer. Most patients will respond initially to topical therapy [532, 535, 536]. In HIV-infected patients, symptomatic relapses occur sooner and more frequently with topical therapy than with fluconazole [535]. In a multicenter randomized study among HIV-infected individuals, 50-mg mucoadhesive buccal tablets of

miconazole applied once daily to the mucosal surface over the canine fossa were as effective as 10-mg clotrimazole troches used 5 times daily [537].

Fluconazole tablets and itraconazole solution are superior to ketoconazole and itraconazole capsules [538–540]. Local effects of oral solutions may be as important as the systemic effects. Posaconazole suspension is also as efficacious as fluconazole in patients with AIDS [541]. Posaconazole, 100-mg delayed release tablets, given as 300 mg daily as a single dose, are FDA approved for the prophylaxis of fungal infections in high-risk patients. The tablets provide a stable bioavailability (approximately 55%), once-daily dosing, and the convenience of less stringent food requirements for absorption. This formulation has not been fully evaluated for mucosal candidiasis, but, with further study, could replace the oral suspension for this purpose.

Recurrent infections typically occur in patients who have persistent immunosuppression, especially those who have AIDS and low CD4 cell counts (<50 cells/ μ L) [530–533]. Long-term suppressive therapy with fluconazole has been shown to be effective in the prevention of oropharyngeal candidiasis [53, 542, 543]. In a large multicenter study of HIV-infected patients, long-term suppressive therapy with fluconazole was compared with the episodic use of fluconazole in response to symptomatic disease. Continuous suppressive therapy reduced the relapse rate more effectively than did intermittent therapy, but was associated with increased in vitro resistance. The frequency of refractory disease was the same for both groups [53]. Oral AmB deoxycholate, nystatin solution, and itraconazole capsules are less effective than fluconazole in preventing oropharyngeal candidiasis [544, 545].

Fluconazole-refractory infections should be treated initially with itraconazole solution; between 64% and 80% of patients will respond to this therapy [546, 547]. Posaconazole suspension is efficacious in approximately 75% of patients with refractory oropharyngeal or esophageal candidiasis [548], and voriconazole also is efficacious for fluconazole-refractory infections [549]. Intravenous caspofungin, micafungin, and anidulafungin have been shown to be effective alternatives to azole agents for refractory candidiasis [24, 87, 88, 550]. Oral or intravenous AmB deoxycholate is also effective in some patients; however, a pharmacist must compound the oral formulation [551]. Immunomodulation with adjunctive granulocyte-macrophage colony-stimulating factor or interferon- γ have been occasionally used in the management of refractory oral and esophageal candidiasis [552, 553].

Decreasing rates of oral carriage of *Candida* species and a reduced frequency of symptomatic oropharyngeal candidiasis are seen among HIV-infected patients on effective antiretroviral therapy [554]. Thus, antiretroviral therapy should be used whenever possible for HIV-infected patients with oropharyngeal or esophageal candidiasis.

Chronic mucocutaneous candidiasis is a rare condition that is characterized by chronic, persistent onychomycosis and/or