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September 2022 ~ Resource #380904

Managing *Candida* Infections

(modified February 2024)

Candida infections can range from superficial mucosal infections to invasive disease.[1] There is increasing drug resistance with *Candida* strains. Non-*albicans* species are becoming more prevalent, now accounting for about 50% of serious infections.[1] The FAQ below answers common questions about **adult** treatment options for the more common types of *Candida* infections (oropharyngeal and vulvovaginal candidiasis, non-neutropenic invasive candidemia) as well as information on the emerging multidrug-resistant strain, *C. auris*. Candidiasis in pediatric and neutropenic patients are beyond the scope of this document.

Question	Answer/Pertinent Information
Oropharyngeal Candidiasis (thrush, *Candida* stomatitis) causes raised white plaques on the tongue and inside the mouth. **--information in this section is from reference 1, unless otherwise denoted--**	
How do you treat **mild** thrush?	• Clotrimazole oral troche 10 mg (US only; *Mycelex*) five times per day for 7 to 14 days **OR** miconazole mucoadhesive buccal 50 mg tablet (US only; *Oravig*) once daily for 7 to 14 days. • **Alternative** in US, choice in Canada: nystatin oral suspension 100,000 units/mL 4 to 6 mL QID for 7 to 14 days.
How is **moderate to severe** thrush treated?	• Fluconazole oral 100 to 200 mg once daily for 7 to 14 days.
How do you treat **recurrent** thrush?	• Fluconazole oral 100 mg three times weekly. • Long-term suppressive therapy with fluconazole is usually **unnecessary**. It may reduce relapse; however, does result in resistance.
How do you treat **fluconazole-refractory** thrush?	• **Fluconazole-refractory disease** is typically seen in patients who are persistently immunosuppressed (e.g., patients with AIDS and low CD4 cell counts [<50 cells/mcL]). It can be caused by *C. glabrata.* • Usually treat with itraconazole oral solution 200 mg once daily for up to 28 days **OR** posaconazole oral suspension 400 mg BID for 3 days, then 400 mg daily for up to 28 days. • **Alternatives** include (choice based on clinical considerations): ○ voriconazole oral 200 mg BID ○ amphotericin B oral suspension 100 mg/mL QID (compounded product) ○ caspofungin IV 70 mg loading dose, then 50 mg once daily ○ micafungin IV 100 mg daily ○ anidulafungin IV 200 mg loading dose, then 100 mg once daily ○ amphotericin B deoxycholate IV 0.3 mg/kg once daily ○ occasionally tried: immunomodulation with GM-CSF or interferon–alpha
What are important considerations when treating **pregnant patients** with thrush?	• Pregnant patients should start with treatment options for mild thrush (above section). • If needed, amphotericin B IV 0.3 mg/kg once daily can be used. • Systemic azoles (including single 150 mg doses of oral fluconazole [based on limited data]) should be avoided during **pregnancy** due to a potential for increased risk of miscarriage and possible birth defects.[1-4] • There are little data with use of echinocandins during pregnancy. Animal data suggest low to moderate risk.[5]

Question	Answer/Pertinent Information
Vulvovaginal Candidiasis (VVC) symptoms include: pruritus, vaginal soreness, dyspareunia, abnormal vaginal discharge.[4,6]	
What are the **first line treatments** for **uncomplicated** VVC?	• Short-course (single dose or once daily for three days) vaginal azole (any)[4,6,b,c] o Note that OTC formulations should be used as labeled, which may be for 7 to 14 days duration.[4] **OR** • Oral fluconazole 150 mg x 1 dose (<$10 [US])[4,6,d]
What are the **first line treatments** for **complicated** VVC?	• **Pregnancy**: vaginal azole[b,c] for 7 days.[4,6] Up to 14 days and/or repeat treatments may be required.[6] Avoid oral fluconazole and intravaginal boric acid.[4,6] • **Severe infection** (e.g., extensive vulvar erythema, edema, excoriation, fissures). US guidelines recommend one of the following:[4] o vaginal azole[b,c] for 7 to 14 days o oral fluconazole 150 mg every 3 days for two doses • **Recurrent infection (**≥3 episodes/year [Canada: ≥4 episodes/year]):[4,6] o Induction:[4,6] ▪ vaginal azole[b,c] for a longer course (i.e., 7 to 14 days). ▪ oral fluconazole (100, 150, or 200 mg) every 3 days for three doses (Canadian guidelines specify 150 mg dose). ▪ Canadian guidelines also include choices of:[6] • boric acid capsule (compounded) vaginally 300 to 600 mg daily x 14 days. • clotrimazole vaginal insert 500 mg once monthly for six months. o Maintenance should start immediately after induction and typically continue for six months:[4,6] ▪ once weekly oral fluconazole (100, 150, or 200 mg) for at least six months (US preferred) (Canadian guidelines specify the 150 mg dose).[4,6] ▪ intermittent vaginal azole[b,c] (US, not preferred)[4] ▪ Canadian guidelines also include choices of:[6] • boric acid capsule (compounded) vaginally 300mg for five days at the beginning of each menstrual cycle. • ketoconazole oral 100 mg once daily (Canada). Must be monitored for hepatoxicity and drug interactions.
What are **other treatments options** for VVC?	• For **non-albicans infections** (usually *C. glabrata*) consider: o 7 to 14 days with a **non-fluconazole** azole regimen (oral or vaginal) (US preferred).[4,6] o boric acid capsule (compounded) vaginally 300 to 600 mg once daily (600 mg dose in US) for three weeks (14 days per Canadian guidelines).[4,6] o Canadian guidelines also include choices of:[6] ▪ flucytosine vaginal cream 5 g once daily for 14 days. ▪ amphotericin B vaginal suppository 50 mg once daily for 14 days. ▪ nystatin vaginal suppository 100,000 units once daily for three to six months.

Question	Answer/Pertinent Information
Vulvovaginal Candidiasis (VVC), continued	
What is the role of **ibrexafungerp** for VVC?	• Ibrexafungerp (*Brexafemme*, US only [$475]) is an oral triterpenoid antifungal for vulvovaginal candidiasis.[7] o 300 mg orally every 12 hours x two doses.[7,d] o Ibrexafungerp is **contraindicated** during **pregnancy**; no data are available with breastfeeding.[7] o Under review for FDA-approval for prophylaxis of recurrent candidiasis; however, data are limited.[15]
What is the role of **oteseconazole** for VVC?	• Oteseconazole (*Vivjoa*, US only [$2,700]) is an oral azole antifungal for **recurrent** vulvovaginal candidiasis.[7,d] o Two regimens are approved:[7] ▪ Oteseconazole 600 mg on day one, then 450 mg on day two, then (starting on day 14) 150 mg once weekly for 11 weeks. ▪ Fluconazole every 3 days for 3 doses, followed by oteseconazole (150 mg once daily for 7 days, then once weekly for 11 weeks). o Generally saved as the last resort for **recurrent** (three or more infections per year) vulvovaginal candidiasis. o **ONLY use for patients who are permanently infertile or who are postmenopausal** (NOT to be used in childbearing-aged females, even if they are on contraceptives). Oteseconazole is teratogenic in animals and can be detected in human tissues for two years following treatment.[7]
Non-neutropenic Candidemia	
What are **risk factors** for invasive candidiasis?	• Risk factors for the development of invasive candidiasis include comorbid conditions (e.g., colonization with *Candida*, immunosuppression, diabetes, sepsis) and the following recent medical interventions:[8,9] o surgery, especially abdominal surgery (the gut is colonized with *Candida*). o use of broad-spectrum antibiotics for longer than 72 hours. o receiving a central line, blood transfusion, parenteral nutrition, dialysis, or mechanical ventilation.
When should **empiric antifungal therapy be considered**?	• Guidance is NOT clear on who is most likely to benefit from, or when to start, empiric antifungal therapy. • Use clinical judgment of invasive candidiasis risk factors.[10] Consider starting empiric therapy in patients: o with an intra-abdominal infection with a compromised GI tract (e.g., recent abdominal surgery, anastomotic leaks, necrotizing pancreatitis, perforation).[11] o in the ICU with persistent fever despite broad-spectrum antibiotics and ≥1 risk factors (see row above).

Question	Answer/Pertinent Information
Non-neutropenic Candidemia, continued	
Which **empiric antifungal** should be used?	• Use **echinocandins** (e.g., caspofungin, micafungin, anidulafungin) first line, especially in patients with hemodynamic instability, recent azole exposure, or known colonization with fluconazole-resistant *Candida*.[11,12] o Broader spectrum of coverage compared to fluconazole, are fungicidal, are well tolerated, do NOT require dosage adjustments based on kidney function, and have minimal drug interactions.[11] o Poor penetration to aqueous sites (e.g., CSF, synovial fluid, brain tissue, urine).[11] • **Azoles**: use **fluconazole** in non-critically ill patients if your hospital's main pathogen is fluconazole-susceptible *Candida albicans* and the patient has NOT recently received an azole.[1,13] Note: **voriconazole** is primarily used as oral step-down therapy for specific *Candida* species.[1] • Use **amphotericin B lipid formulation** last-line, due its significant adverse effects (e.g., kidney toxicity).[9] o primarily used if there is intolerance, limited availability, or resistance to other antifungals.[1]
What are **pregnancy considerations** for antifungal therapy?	• **Amphotericin B is the preferred antifungal during pregnancy**.[1] • There are little data with use of echinocandins during pregnancy. Animal data suggest low to moderate risk.[15] • Avoid **fluconazole** use, especially in the first trimester, due to potential for increased risk of miscarriage.[1,3,7] • Avoid **voriconazole** use, especially in the first trimester, due to fetal abnormalities seen in animal studies.[1,5]
What **antifungal doses** should be used?	• **Echinocandins** (Generally considered interchangeable; use formulary echinocandin.):[1] o caspofungin: 70 mg IV, followed by 50 mg IV once daily. o micafungin: 100 mg IV once daily. o anidulafungin: 200 mg IV, followed by 100 mg IV once daily (may be preferred with severe liver impairment).[7,11] o rezafungin: 400 mg IV, followed by 200 mg IV once weekly (generally considered last resort).[16] • **Fluconazole**:[1] 12 mg/kg IV or 800 mg, followed by 6 mg/kg or 400 mg IV once daily. Adjust for kidney impairment.[7] • **Voriconazole**:[1] 6 mg/kg or 400 mg PO x 2 doses 12 hours apart, followed by 3 to 4 mg/kg or 200 mg PO every 12 hrs. • **Amphotericin B** (lipid formulation):[1] 3 to 5 mg/kg IV once daily.
What **susceptibility testing** is recommended?	• Test all patients with candidemia or other cases of invasive candidiasis for **azole susceptibility**.[1] • Consider **echinocandin susceptibility** testing:[1,17] o when *C. glabrata*, *C. parapsilosis*, or *C. auris* are identified. o in patients previously treated with an echinocandin. o if rezafungin is being considered for treatment.
How should echinocandin or amphotericin B antifungal therapy be **stepped down**?	• Step down to oral fluconazole 6 mg/kg or 400 mg once daily (usually within three to seven days) **when isolates show susceptibility to fluconazole**.[1,14] • For infections due to ***C. glabrata***, transition to:[1] o high-dose oral fluconazole (12 mg/kg or 800 mg once daily) if susceptible to fluconazole. o oral voriconazole (3 to 4 mg/kg or 200 to 300 mg once daily) if susceptible to voriconazole.

Question	Answer/Pertinent Information
Non-neutropenic Candidemia, continued	
What is the **duration of therapy for empiric antifungals**?	• Generally, continue empiric therapy for two weeks in patients who respond.[1,12,14] • Consider stopping empiric therapy after four or five days in patients who are NOT improving and don't have other signs of a fungal infection.[1,12,14]
What is the **duration of therapy** of invasive candidiasis?	• Generally, recommend two weeks of therapy AFTER negative cultures and resolution of symptoms.[1] • Longer therapy may be required for patients with complications of invasive candidiasis (e.g., metastatic organ involvement such as *Candida* endocarditis or endophthalmitis).[1]
What is the role for **non-culture-based testing** (NCBTs) and antifungal therapy?	• Some institutions may use NCBTs (e.g., PCR) along WITH blood cultures and other clinical data to assist with decisions about antifungal therapy, due to blood culture limitations (e.g., sensitivity, timeliness, contamination versus infection).[11] • NCBTs do NOT provide definitive results, they assess the likelihood of infection.[11]
Candida auris	
What is *C. auris*?	• *C. auris* is an emerging multidrug-resistant yeast, associated with a high mortality rate (~30% to 50%).[18] • It is easily spread within healthcare settings (unlike other *Candida* infections).[19] • In the US, resistance to fluconazole is ~90% and to amphotericin B is ~30% (range of 5% to 85%, depending on the region).[20,23] • Associated with various infections (bloodstream, CNS, intra-abdominal, osteomyelitis, pericarditis). • Appears to colonize respiratory and urine specimens; however, risk of infections in these sites is unclear.
What are the risk factors for *C. auris* infections?	• Risk factors for *C. auris* include: o hospitalizations, especially in an ICU, long admissions, in non-US countries (e.g., India, Pakistan, South Africa). o nursing home care, especially homes that use ventilators. o use of invasive devices (central venous catheter, breathing tube, feeding tube). o history of broad-spectrum antibiotic or antifungal use. o immunosuppression. o recent surgery.
How should *C. auris* infections be treated?	• Consult the infectious disease team if a *C. auris* infection is suspected.[19] • Treat only if there is evidence of infection (e.g., fever, increased white blood cell count). • Consider treatment with anidulafungin, caspofungin, micafungin, or rezafungin.[16,19] o Consider switching to (or adding)[22] liposomal amphotericin B for patients who do not respond to initial therapy.[19] o For CNS infections, the ID team may choose flucytosine plus liposomal amphotericin B.[1]

Question	Answer/Pertinent Information
Candida auris, continued	
How can *C. auris* infections be prevented and spread controlled?	• Patients (with or without prior infection) may be colonized with *C. auris* for long periods of time (maybe indefinitely).[19] Decolonization is not recommended due to lack of data.[19] • Use standard and contact precautions (including proper hand hygiene) when caring for patients with *C. auris* infections or colonization for the duration of their stay in all healthcare facilities.[19] o In nursing homes, Enhanced Barrier Precautions may be recommended. See CDC's guidance on the prevention of spread of multidrug-resistant organisms at https://www.cdc.gov/hai/containment/PPE-Nursing-Homes.html. • *C. auris* can persist on surfaces outside of the human body for weeks.[19] • Rooms should be cleaned daily with an agent from EPA's "List P." If unavailable, use disinfectants active against *C. diff* spores (i.e., EPA List K).[21]

Abbreviations: BID = twice daily; BV = bacterial vaginosis; CrCl = creatinine clearance; CNS = central nervous system; CSF = cerebrospinal fluid; EPA = US Environmental Protection Agency; GI = gastrointestinal; GM-CSF = granulocyte-macrophage colony-stimulating factor; HIV = human immunodeficiency virus; ICU = intensive care unit; IV = intravenous; PCR = polymerase chain reaction; PO = orally; QHS = at bedtime; QID = four times daily; STIs = sexually transmitted infections; VVC = vulvovaginal candidiasis.

a. The potential for a disulfiram reaction between alcohol and metronidazole is controversial. Some guidance still recommends instructing patients not to drink alcohol during and for 24 hours after completing oral metronidazole therapy due to possible disulfiram reaction (e.g., severe nausea and vomiting), while other guidance indicates this is not necessary.[4,6,7] Product labeling recommends avoidance of alcohol during treatment and for two days (secnidazole) or three days (tinidazole) after treatment is over.[7]
b. Creams and ovules (vaginal suppositories) may reduce efficacy of latex condoms and diaphragms during use and for five days after use.[4,6]
c. Vaginal azoles may be available as creams, ointments, vaginal tablets, or vaginal suppositories.[4,7] Available vaginal azoles include: butoconazole; clotrimazole; miconazole; terconazole; and tioconazole (US only). Some require a prescription; but many are available over the counter (OTC).
d. **Oral therapy** pricing (for generic when available) based on wholesale acquisition cost (WAC). US medication pricing by Elsevier, accessed August 2022.

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Cite this document as follows: **Clinical Resource,** ***Managing Candida Infections. Pharmacist's Letter/Prescriber's Letter.*** **September 2022. [380904]**