MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

GUIDELINES FOR TREATMENT OF CANDIDEMIA IN ADULTS

General Statements:

- Yeast in a blood culture should **NOT** be considered a contaminant
- If there is a high suspicion that yeast growing in a blood culture is *Histoplasma* or *Cryptococcus*, do not use micafungin and consult Infectious Diseases
- **Infectious Diseases consultation is strongly recommended in all cases of candidemia**
- Blood cultures should be repeated every 24-48 hours until clearance has been documented
- Remove all intravascular catheters whenever possible. In neutropenic patients, as sources of candidiasis other than CVCs predominate, catheter removal should be considered on an individual basis
- Patients should have a dilated fundoscopic exam performed to rule out endophthalmitis within the first week after initiation of therapy
  In neutropenic patients, repeat ophthalmological exam should be considered once neutropenia has resolved
- Additional evaluation for metastatic foci (e.g. echocardiogram) should be considered in patients with persistently positive blood cultures
- Duration of therapy:
  - Patients with no evidence of metastatic complications should be treated for 14 days following the first negative blood culture
  - Patients with metastatic complications (e.g,. endophthalmitis, endocarditis) should have an ID Consult to determine length of therapy
  - Neutropenic patients with no evidence of metastatic complications should be treated for 14 days following the first negative blood culture, provided neutropenia has resolved

INITIAL THERAPY IN PATIENTS WITH POSITIVE BLOOD CULTURES		
Clinical Setting (Does Not Apply to Meningitis, Endocarditis, and Endophthalmitis)[3,4]	**Primary Therapy**	**Alternative Therapy**
Initial therapy for patients with yeast identified in blood culture (prior to species identification and susceptibilities)	**Micafungin** 100 mg IV daily	**Fluconazole** 800 mg IV/PO daily[7] OR **Liposomal Amphotericin B** 3 mg/kg IV daily See comments 1 and 2 regarding use of fluconazole and Liposomal Amphotericin B
DEFINITIVE THERAPY IN PATIENTS WITH POSITIVE BLOOD CULTURES		
Clinical Setting (Does Not Apply to Meningitis, Endocarditis, and Endophthalmitis)[3,4]	**Primary Therapy**	**Subsequent Therapy (once susceptibilities are available)**
Candida albicans *Candida dubliniensis* *Candida parapsilosis* *Candida tropicalis* *Candida lusitaniae*	**Micafungin** 100 mg IV Daily *See comments 1 and 5 regarding primary use of fluconazole and voriconazole*	*Transition to fluconazole once patients are clinically stable, are no longer candidemic, and who have susceptible isolates* Preferred: **Fluconazole** 800 mg x1 day, then 400 mg IV/PO daily[7] Alternatives: **Voriconazole** 6 mg/kg PO/IV q12h x2 doses, then 4 mg/kg PO/IV q12h[8] OR **Liposomal Amphotericin B** 3 mg/kg IV daily (*C. lusitaniae* is considered resistant to Amphotericin B)
Candida glabrata	**Micafungin** 100 mg IV daily *See comments 1,2, and 5 regarding primary use of fluconazole, voriconazole, and Liposomal Amphotericin B.* *Liposomal Amphotericin B is the preferred alternative primary therapy for infections due to C. glabrata*	*Transition to fluconazole or voriconazole in patients in whom an oral option is needed once they are clinically stable, are no longer candidemic, and have isolates in the following MIC ranges:* Preferred (if fluconazole MIC *≤8)*: **Fluconazole** 800 mg IV/PO daily[7] Alternative (if fluconazole MIC >8 and voriconazole MIC *≤0.5)*: **Voriconazole** 6 mg/kg PO/IV q12h x2 doses, then 4 mg/kg PO/IV q12h[8] Alternative: **Liposomal Amphotericin B** 3 mg/kg IV daily
Candida krusei (intrinsically resistant to fluconazole)	**Micafungin** 100 mg IV Daily *See comment 5 regarding primary use of voriconazole*	*Transition to voriconazole within 5-7 days is appropriate in patients who are clinically stable, are no longer candidemic, and who have susceptible isolates* Preferred: **Voriconazole** 6 mg/kg PO/IV q12h x2 doses, then 4 mg/kg PO/IV q12h[8] Alternative: **Liposomal Amphotericin B** 3 mg/kg IV daily
"Other yeast"	Consult ID	Consult ID

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EMPIRIC THERAPY FOR SUSPECTED INVASIVE CANDIDIASIS IN ICU PATIENTS		
Clinical Setting	**Primary Therapy**	**Alternative Therapy**
Empiric therapy for patients with unexplained fever or other signs of infection and who are at high risk for invasive candidiasis. Randomized clinical trials[2-4] have not demonstrated any mortality benefit to the use of empiric antifungals in immunocompetent critically ill patients. These studies have included patients with multiple risk factors for candidiasis. Given this, such therapy is not generally recommended. Some populations where empiric therapy may be considered include the following: Esophageal perforation pending culture results (see Intra-Abdominal Infection Guidelines) Recent abdominal surgery with *recurrent* gastrointestinal perforations/anastomotic leaks (tertiary peritonitis) (see Intra-Abdominal Infection Guidelines) Immunocompromised patients at high risk (as defined per below linked protocols) for invasive candidiasis who are *not* receiving systemic antifungal prophylaxis (see the following: Kidney/Pancreas Transplantation, Liver Transplantation, Hematology Patient Prophylaxis, BMT Recipient Prophylaxis) *In such patients, a Beta-D-Glucan [Fungitell] assay should be performed prior to or with the initiation of empiric antifungal therapy and appropriate cultures should be taken.*	**Micafungin** 100 mg IV daily NOTE: The Beta-D-Glucan [Fungitell] assay is generally unhelpful for identifying patients with invasive candidiasis, given the very poor positive predictive value of the test. In clinical trials, most critically ill patients *without candidiasis* have at least one positive result. False positives are especially prominent in patients undergoing gastrointestinal surgery. BDG also reacts with non-*Candida* fungi. Given the high negative predictive value of the test (>95%), however, discontinuation of empirical antifungal therapy is strongly encouraged with negative (<80 pg/mL) results.[2, 5, 6] .	**Fluconazole** 800 mg x1 day, then 400 mg IV/PO daily[7] OR **Liposomal Amphotericin B** 3 mg/kg IV daily See comments 1 and 2 regarding use of fluconazole and Liposomal Amphotericin B

Table Comments:

1. Fluconazole may be considered for patients who are clinically stable and have no recent history of azole antifungal exposure prior to positive cultures
2. Micafungin-resistant C. glabrata is emerging at UMHS. Prior exposure is highly correlated to the development of resistance. In critically ill and neutropenic patients, empirical treatment with liposomal amphotericin B may be preferred in patients with recent exposure to echinocandins.
3. Micafungin should not be used for the treatment of meningitis, or candiduria
4. Micafungin and systemic amphotericin B are not recommended for the treatment of endophthalmitis due to poor vitreous penetration. Intravitreal antifungal therapy for patients with severe endophthalmitis and vitritis may be necessary. Please see Ocular Infection Guidelines for the treatment of Candida endophthalmitis.
5. Voriconazole should only be used as empiric therapy if additional coverage of molds is indicated as its spectrum of activity for Candida spp. is similar to fluconazole
6. Oral voriconazole should be administered on an empty stomach, doses should be rounded to nearest 50 mg increment (Tablet available as 50 and 200 mg strengths; suspension also available)
7. Fluconazole requires dose adjustment in patients with renal insufficiency. Please refer to Renal Dosing Recommendations
8. Voriconazole should be dosed based on adjusted body weight in morbidly obese patients. Please refer to Weight-Based Dosing in Obese Patients

References:

1. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016 Feb 15;62(4):e1-50.
2. Timsit JF, et al. Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis, Candida Colonization, and Multiple Organ Failure. JAMA. 2016 Oct 18;316(15):1555-1564.
3. Knitsch W, et al. A randomized, placebo-controlled trial of preemptive antifungal therapy for the prevention of invasive candidiasis following gastrointestinal surgery for intra-abdominal infections. Clin Infect Dis. 2015 Dec 1;61(11):1671-8.
4. Schuster MG et al. Empirical fluconazole versus placebo for intensive care unit patients: a randomized trial. Ann Intern Med. 2008 Jul 15;149(2):83-90.
5. Clancy CJ and Nguyen MH. Finding the "Missing 50%" of Invasive Candidiasis: How Nonculture Diagnostics Will Improve Understanding of Disease Spectrum and Transform Patient Care. Clinical Infectious Diseases 2013;56(9):1284–92.
6. Szyszkowitz A et al. Serum 1,3-Beta-D-Glucan Values During and After Laparoscopic and Open Intestinal Surgery. Open Forum Infect Dis. 2018 Nov 8;5(12):ofy296.

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