

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

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It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

Keywords. candidemia; invasive candidiasis; fungal diagnostics; azoles; echinocandins.

EXECUTIVE SUMMARY

Background

Invasive infection due to *Candida* species is largely a condition associated with medical progress, and is widely recognized as a major cause of morbidity and mortality in the healthcare environment. There are at least 15 distinct *Candida* species that cause human disease, but >90% of invasive disease is caused by the 5 most common pathogens, *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*. Each of these organisms has unique virulence potential, antifungal susceptibility, and epidemiology, but taken as a whole, significant infections due to these organisms are generally referred to as invasive candidiasis. Mucosal *Candida* infections—especially those involving the oropharynx, esophagus, and vagina—are not considered to be classically invasive disease, but they are included in these guidelines. Since the last iteration of these guidelines in 2009 [1], there have been new data pertaining to diagnosis, prevention, and treatment for proven or suspected invasive candidiasis, leading to significant modifications in our treatment recommendations.

Summarized below are the 2016 revised recommendations for the management of candidiasis. Due to the guideline's relevance to pediatrics, the guideline has been reviewed and endorsed by the American Academy of Pediatrics (AAP) and

the Pediatric Infectious Diseases Society (PIDS). The Mycoses Study Group (MSG) has also endorsed these guidelines. The panel followed a guideline development process that has been adopted by the Infectious Diseases Society of America (IDSA), which includes a systematic method of grading both the quality of evidence (very low, low, moderate, and high) and the strength of the recommendation (weak or strong) [2] (Figure 1). [3] The guidelines are not intended to replace clinical judgment in the management of individual patients. A detailed description of the methods, background, and evidence summaries that support each recommendation can be found in the full text of the guideline.

I. What Is the Treatment for Candidemia in Nonneutropenic Patients?

Recommendations

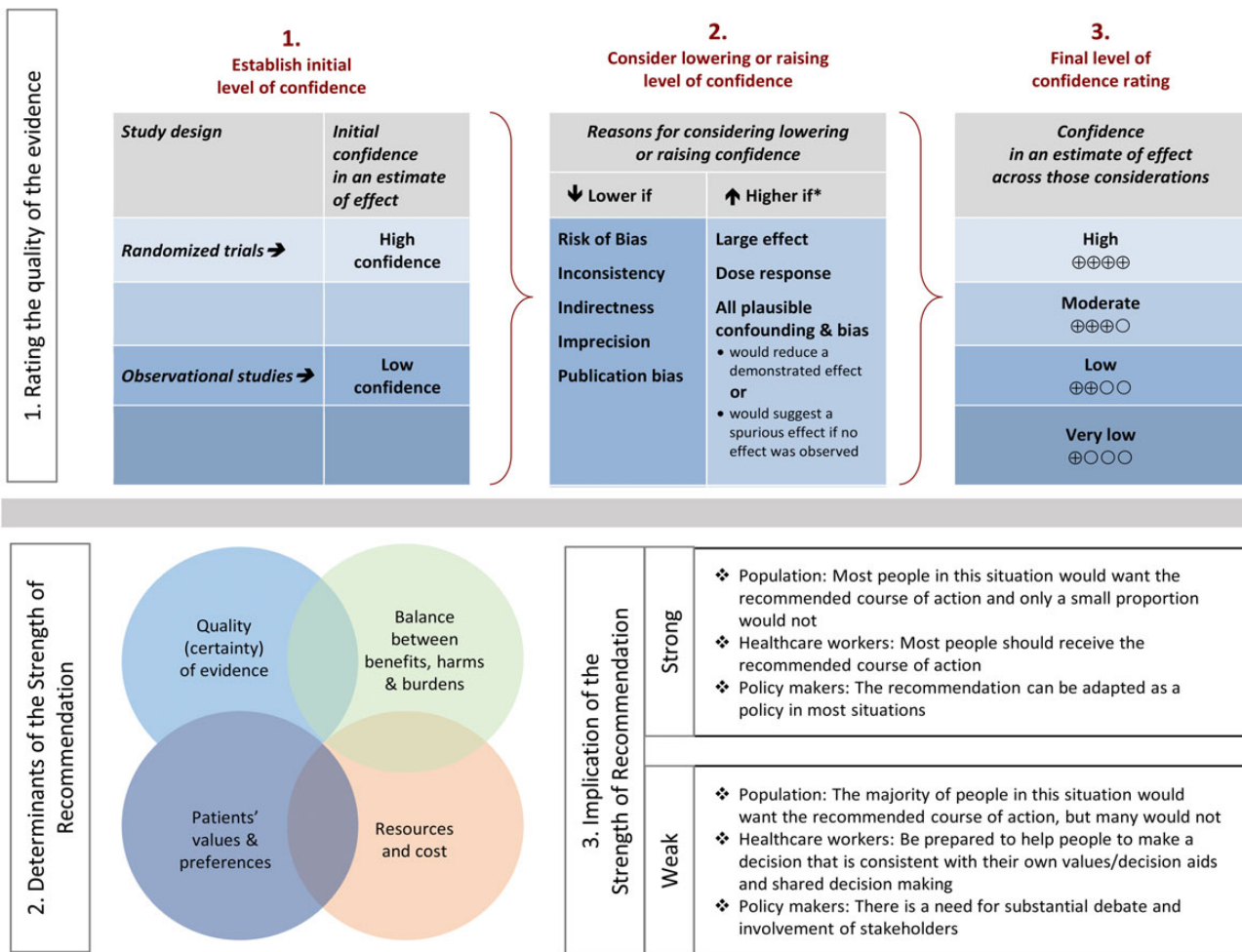
1. An echinocandin (caspofungin: loading dose 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose 200 mg, then 100 mg daily) is recommended as initial therapy (*strong recommendation; high-quality evidence*).
2. Fluconazole, intravenous or oral, 800-mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily is an acceptable alternative to an echinocandin as initial therapy in selected patients, including those who are not critically ill and who are considered unlikely to have a fluconazole-resistant *Candida* species (*strong recommendation; high-quality evidence*).
3. Testing for azole susceptibility is recommended for all blood-stream and other clinically relevant *Candida* isolates. Testing for echinocandin susceptibility should be considered in patients who have had prior treatment with an echinocandin and among those who have infection with *C. glabrata* or *C. parapsilosis* (*strong recommendation; low-quality evidence*).

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candidemia has been cleared (*strong recommendation; low-quality evidence*).

12. Recommended duration of therapy for candidemia without obvious metastatic complications is for 2 weeks after documented clearance of *Candida* species from the bloodstream and resolution of symptoms attributable to candidemia (*strong recommendation; moderate-quality evidence*).

II. Should Central Venous Catheters Be Removed in Nonneutropenic Patients With Candidemia?

Recommendation

13. Central venous catheters (CVCs) should be removed as early as possible in the course of candidemia when the source is presumed to be the CVC and the catheter can be removed safely; this decision should be individualized for each patient (*strong recommendation; moderate-quality evidence*).

III. What Is the Treatment for Candidemia in Neutropenic Patients?

Recommendations

14. An echinocandin (caspofungin: loading dose 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose 200 mg, then 100 mg daily) is recommended as initial therapy (*strong recommendation; moderate-quality evidence*).
15. Lipid formulation AmB, 3–5 mg/kg daily, is an effective but less attractive alternative because of the potential for toxicity (*strong recommendation; moderate-quality evidence*).
16. Fluconazole, 800-mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily, is an alternative for patients who are not critically ill and have had no prior azole exposure (*weak recommendation; low-quality evidence*).
17. Fluconazole, 400 mg (6 mg/kg) daily, can be used for step-down therapy during persistent neutropenia in clinically stable patients who have susceptible isolates and documented bloodstream clearance (*weak recommendation; low-quality evidence*).
18. Voriconazole, 400 mg (6 mg/kg) twice daily for 2 doses, then 200–300 mg (3–4 mg/kg) twice daily, can be used in situations in which additional mold coverage is desired (*weak recommendation; low-quality evidence*). Voriconazole can also be used as step-down therapy during neutropenia in clinically stable patients who have had documented bloodstream clearance and isolates that are susceptible to voriconazole (*weak recommendation; low-quality evidence*).
19. For infections due to *C. krusei*, an echinocandin, lipid formulation AmB, or voriconazole is recommended (*strong recommendation; low-quality evidence*).
20. Recommended minimum duration of therapy for candidemia without metastatic complications is 2 weeks after documented clearance of *Candida* from the bloodstream, provided neutropenia and symptoms attributable to candidemia have resolved (*strong recommendation; low-quality evidence*).

21. Ophthalmological findings of choroidal and vitreal infection are minimal until recovery from neutropenia; therefore, dilated funduscopic examinations should be performed within the first week after recovery from neutropenia (*strong recommendation; low-quality evidence*).

22. In the neutropenic patient, sources of candidiasis other than a CVC (eg, gastrointestinal tract) predominate. Catheter removal should be considered on an individual basis (*strong recommendation; low-quality evidence*).

23. Granulocyte colony-stimulating factor (G-CSF)–mobilized granulocyte transfusions can be considered in cases of persistent candidemia with anticipated protracted neutropenia (*weak recommendation; low-quality evidence*).

IV. What Is the Treatment for Chronic Disseminated (Hepatosplenic) Candidiasis?

Recommendations

24. Initial therapy with lipid formulation AmB, 3–5 mg/kg daily OR an echinocandin (micafungin: 100 mg daily; caspofungin: 70-mg loading dose, then 50 mg daily; or anidulafungin: 200-mg loading dose, then 100 mg daily), for several weeks is recommended, followed by oral fluconazole, 400 mg (6 mg/kg) daily, for patients who are unlikely to have a fluconazole-resistant isolate (*strong recommendation; low-quality evidence*).
25. Therapy should continue until lesions resolve on repeat imaging, which is usually several months. Premature discontinuation of antifungal therapy can lead to relapse (*strong recommendation; low-quality evidence*).
26. If chemotherapy or hematopoietic cell transplantation is required, it should not be delayed because of the presence of chronic disseminated candidiasis, and antifungal therapy should be continued throughout the period of high risk to prevent relapse (*strong recommendation; low-quality evidence*).
27. For patients who have debilitating persistent fevers, short-term (1–2 weeks) treatment with nonsteroidal anti-inflammatory drugs or corticosteroids can be considered (*weak recommendation; low-quality evidence*).

V. What Is the Role of Empiric Treatment for Suspected Invasive Candidiasis in Nonneutropenic Patients in the Intensive Care Unit?

Recommendations

28. Empiric antifungal therapy should be considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever and should be based on clinical assessment of risk factors, surrogate markers for invasive candidiasis, and/or culture data from nonsterile sites (*strong recommendation; moderate-quality evidence*). Empiric antifungal therapy should be started as soon as possible in patients who have the above risk factors and who have clinical signs of septic shock (*strong recommendation; moderate-quality evidence*).
29. Preferred empiric therapy for suspected candidiasis in nonneutropenic patients in the intensive care unit (ICU) is

an echinocandin (caspofungin: loading dose of 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose of 200 mg, then 100 mg daily) (*strong recommendation; moderate-quality evidence*).

30. Fluconazole, 800-mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily, is an acceptable alternative for patients who have had no recent azole exposure and are not colonized with azole-resistant *Candida* species (*strong recommendation; moderate-quality evidence*).
31. Lipid formulation AmB, 3–5 mg/kg daily, is an alternative if there is intolerance to other antifungal agents (*strong recommendation; low-quality evidence*).
32. Recommended duration of empiric therapy for suspected invasive candidiasis in those patients who improve is 2 weeks, the same as for treatment of documented candidemia (*weak recommendation; low-quality evidence*).
33. For patients who have no clinical response to empiric antifungal therapy at 4–5 days and who do not have subsequent evidence of invasive candidiasis after the start of empiric therapy or have a negative non-culture-based diagnostic assay with a high negative predictive value, consideration should be given to stopping antifungal therapy (*strong recommendation; low-quality evidence*).

VII. Should Prophylaxis Be Used to Prevent Invasive Candidiasis in the Intensive Care Unit Setting?

Recommendations

34. Fluconazole, 800-mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily, could be used in high-risk patients in adult ICUs with a high rate (>5%) of invasive candidiasis (*weak recommendation; moderate-quality evidence*).
35. An alternative is to give an echinocandin (caspofungin: 70-mg loading dose, then 50 mg daily; anidulafungin: 200-mg loading dose and then 100 mg daily; or micafungin: 100 mg daily) (*weak recommendation; low-quality evidence*).
36. Daily bathing of ICU patients with chlorhexidine, which has been shown to decrease the incidence of bloodstream infections including candidemia, could be considered (*weak recommendation; moderate-quality evidence*).

VII. What Is the Treatment for Neonatal Candidiasis, Including Central Nervous System Infection?

What Is the Treatment for Invasive Candidiasis and Candidemia?

Recommendations

37. AmB deoxycholate, 1 mg/kg daily, is recommended for neonates with disseminated candidiasis (*strong recommendation; moderate-quality evidence*).
38. Fluconazole, 12 mg/kg intravenous or oral daily, is a reasonable alternative in patients who have not been on fluconazole prophylaxis (*strong recommendation; moderate-quality evidence*).

39. Lipid formulation AmB, 3–5 mg/kg daily, is an alternative, but should be used with caution, particularly in the presence of urinary tract involvement (*weak recommendation; low-quality evidence*).

40. Echinocandins should be used with caution and generally limited to salvage therapy or to situations in which resistance or toxicity preclude the use of AmB deoxycholate or fluconazole (*weak recommendation; low-quality evidence*).
41. A lumbar puncture and a dilated retinal examination are recommended in neonates with cultures positive for *Candida* species from blood and/or urine (*strong recommendation; low-quality evidence*).
42. Computed tomographic or ultrasound imaging of the genitourinary tract, liver, and spleen should be performed if blood cultures are persistently positive for *Candida* species (*strong recommendation; low-quality evidence*).
43. CVC removal is strongly recommended (*strong recommendation; moderate-quality evidence*).
44. The recommended duration of therapy for candidemia without obvious metastatic complications is for 2 weeks after documented clearance of *Candida* species from the bloodstream and resolution of signs attributable to candidemia (*strong recommendation; low-quality evidence*).

What Is the Treatment for Central Nervous System Infections in Neonates?

Recommendations

45. For initial treatment, AmB deoxycholate, 1 mg/kg intravenous daily, is recommended (*strong recommendation; low-quality evidence*).
46. An alternative regimen is liposomal AmB, 5 mg/kg daily (*strong recommendation; low-quality evidence*).
47. The addition of flucytosine, 25 mg/kg 4 times daily, may be considered as salvage therapy in patients who have not had a clinical response to initial AmB therapy, but adverse effects are frequent (*weak recommendation; low-quality evidence*).
48. For step-down treatment after the patient has responded to initial treatment, fluconazole, 12 mg/kg daily, is recommended for isolates that are susceptible to fluconazole (*strong recommendation; low-quality evidence*).
49. Therapy should continue until all signs, symptoms, and cerebrospinal fluid (CSF) and radiological abnormalities, if present, have resolved (*strong recommendation; low-quality evidence*).
50. Infected central nervous system (CNS) devices, including ventriculostomy drains and shunts, should be removed if at all possible (*strong recommendation; low-quality evidence*).

What Are the Recommendations for Prophylaxis in the Neonatal Intensive Care Unit Setting?

Recommendations

51. In nurseries with high rates (>10%) of invasive candidiasis, intravenous or oral fluconazole prophylaxis, 3–6 mg/kg twice

weekly for 6 weeks, in neonates with birth weights <1000 g is recommended (*strong recommendation; high-quality evidence*).

52. Oral nystatin, 100 000 units 3 times daily for 6 weeks, is an alternative to fluconazole in neonates with birth weights <1500 g in situations in which availability or resistance preclude the use of fluconazole (*weak recommendation; moderate-quality evidence*).

53. Oral bovine lactoferrin (100 mg/day) may be effective in neonates <1500 g but is not currently available in US hospitals (*weak recommendation; moderate-quality evidence*).

VIII. What Is the Treatment for Intra-abdominal Candidiasis?

Recommendations

54. Empiric antifungal therapy should be considered for patients with clinical evidence of intra-abdominal infection and significant risk factors for candidiasis, including recent abdominal surgery, anastomotic leaks, or necrotizing pancreatitis (*strong recommendation; moderate-quality evidence*).

55. Treatment of intra-abdominal candidiasis should include source control, with appropriate drainage and/or debridement (*strong recommendation; moderate-quality evidence*).

56. The choice of antifungal therapy is the same as for the treatment of candidemia or empiric therapy for nonneutropenic patients in the ICU (See sections I and V) (*strong recommendation; moderate-quality evidence*).

57. The duration of therapy should be determined by adequacy of source control and clinical response (*strong recommendation; low-quality evidence*).

IX. Does the Isolation of *Candida* Species From the Respiratory Tract Require Antifungal Therapy?

Recommendation

58. Growth of *Candida* from respiratory secretions usually indicates colonization and rarely requires treatment with antifungal therapy (*strong recommendation; moderate-quality evidence*).

X. What Is the Treatment for *Candida* Intravascular Infections, Including Endocarditis and Infections of Implantable Cardiac Devices?

What Is the Treatment for *Candida* Endocarditis?

Recommendations

59. For native valve endocarditis, lipid formulation AmB, 3–5 mg/kg daily, with or without flucytosine, 25 mg/kg 4 times daily, OR high-dose echinocandin (caspofungin 150 mg daily, micafungin 150 mg daily, or anidulafungin 200 mg daily) is recommended for initial therapy (*strong recommendation; low-quality evidence*).

60. Step-down therapy to fluconazole, 400–800 mg (6–12 mg/kg) daily, is recommended for patients who have susceptible *Candida* isolates, have demonstrated clinical stability, and have cleared *Candida* from the bloodstream (*strong recommendation; low-quality evidence*).

61. Oral voriconazole, 200–300 mg (3–4 mg/kg) twice daily, or posaconazole tablets, 300 mg daily, can be used as step-down therapy for isolates that are susceptible to those agents but not susceptible to fluconazole (*weak recommendation; very low-quality evidence*).

62. Valve replacement is recommended; treatment should continue for at least 6 weeks after surgery and for a longer duration in patients with perivalvular abscesses and other complications (*strong recommendation; low-quality evidence*).

63. For patients who cannot undergo valve replacement, long-term suppression with fluconazole, 400–800 mg (6–12 mg/kg) daily, if the isolate is susceptible, is recommended (*strong recommendation; low-quality evidence*).

64. For prosthetic valve endocarditis, the same antifungal regimens suggested for native valve endocarditis are recommended (*strong recommendation; low-quality evidence*). Chronic suppressive antifungal therapy with fluconazole, 400–800 mg (6–12 mg/kg) daily, is recommended to prevent recurrence (*strong recommendation; low-quality evidence*).

What Is the Treatment for *Candida* Infection of Implantable Cardiac Devices?

Recommendations

65. For pacemaker and implantable cardiac defibrillator infections, the entire device should be removed (*strong recommendation; moderate-quality evidence*).

66. Antifungal therapy is the same as that recommended for native valve endocarditis (*strong recommendation; low-quality evidence*).

67. For infections limited to generator pockets, 4 weeks of antifungal therapy after removal of the device is recommended (*strong recommendation; low-quality evidence*).

68. For infections involving the wires, at least 6 weeks of antifungal therapy after wire removal is recommended (*strong recommendation; low-quality evidence*).

69. For ventricular assist devices that cannot be removed, the antifungal regimen is the same as that recommended for native valve endocarditis (*strong recommendation; low-quality evidence*). Chronic suppressive therapy with fluconazole if the isolate is susceptible, for as long as the device remains in place is recommended (*strong recommendation; low-quality evidence*).

What Is the Treatment for *Candida* Suppurative Thrombophlebitis?

Recommendations

70. Catheter removal and incision and drainage or resection of the vein, if feasible, is recommended (*strong recommendation; low-quality evidence*).

71. Lipid formulation AmB, 3–5 mg/kg daily, OR fluconazole, 400–800 mg (6–12 mg/kg) daily, OR an echinocandin (caspofungin 150 mg daily, micafungin 150 mg daily, or anidulafungin 200 mg daily) for at least 2 weeks after candidemia

(if present) has cleared is recommended (*strong recommendation; low-quality evidence*).

72. Step-down therapy to fluconazole, 400–800 mg (6–12 mg/kg) daily, should be considered for patients who have initially responded to AmB or an echinocandin, are clinically stable, and have a fluconazole-susceptible isolate (*strong recommendation; low-quality evidence*).

73. Resolution of the thrombus can be used as evidence to discontinue antifungal therapy if clinical and culture data are supportive (*strong recommendation; low-quality evidence*).

XI. What Is the Treatment for *Candida* Osteoarticular Infections?

What Is the Treatment for *Candida* Osteomyelitis?

Recommendations

74. Fluconazole, 400 mg (6 mg/kg) daily, for 6–12 months OR an echinocandin (caspofungin 50–70 mg daily, micafungin 100 mg daily, or anidulafungin 100 mg daily) for at least 2 weeks followed by fluconazole, 400 mg (6 mg/kg) daily, for 6–12 months is recommended (*strong recommendation; low-quality evidence*).

75. Lipid formulation AmB, 3–5 mg/kg daily, for at least 2 weeks followed by fluconazole, 400 mg (6 mg/kg) daily, for 6–12 months is a less attractive alternative (*weak recommendation; low-quality evidence*).

76. Surgical debridement is recommended in selected cases (*strong recommendation; low-quality evidence*).

What Is the Treatment for *Candida* Septic Arthritis?

77. Fluconazole, 400 mg (6 mg/kg) daily, for 6 weeks OR an echinocandin (caspofungin 50–70 mg daily, micafungin 100 mg daily, or anidulafungin 100 mg daily) for 2 weeks followed by fluconazole, 400 mg (6 mg/kg) daily, for at least 4 weeks is recommended (*strong recommendation; low-quality evidence*).

78. Lipid formulation AmB, 3–5 mg/kg daily, for 2 weeks, followed by fluconazole, 400 mg (6 mg/kg) daily, for at least 4 weeks is a less attractive alternative (*weak recommendation; low-quality evidence*).

79. Surgical drainage is indicated in all cases of septic arthritis (*strong recommendation; moderate-quality evidence*).

80. For septic arthritis involving a prosthetic device, device removal is recommended (*strong recommendation; moderate-quality evidence*).

81. If the prosthetic device cannot be removed, chronic suppression with fluconazole, 400 mg (6 mg/kg) daily, if the isolate is susceptible, is recommended (*strong recommendation; low-quality evidence*).

XII. What Is the Treatment for *Candida* Endophthalmitis?

What Is the General Approach to *Candida* Endophthalmitis?

Recommendations

82. All patients with candidemia should have a dilated retinal examination, preferably performed by an ophthalmologist,

within the first week of therapy in nonneutropenic patients to establish if endophthalmitis is present (*strong recommendation; low-quality evidence*). For neutropenic patients, it is recommended to delay the examination until neutrophil recovery (*strong recommendation; low-quality evidence*).

83. The extent of ocular infection (chorioretinitis with or without macular involvement and with or without vitritis) should be determined by an ophthalmologist (*strong recommendation; low-quality evidence*).

84. Decisions regarding antifungal treatment and surgical intervention should be made jointly by an ophthalmologist and an infectious diseases physician (*strong recommendation; low-quality evidence*).

What Is the Treatment for *Candida* Chorioretinitis Without Vitritis?

Recommendations

85. For fluconazole-/voriconazole-susceptible isolates, fluconazole, loading dose, 800 mg (12 mg/kg), then 400–800 mg (6–12 mg/kg) daily OR voriconazole, loading dose 400 mg (6 mg/kg) intravenous twice daily for 2 doses, then 300 mg (4 mg/kg) intravenous or oral twice daily is recommended (*strong recommendation; low-quality evidence*).

86. For fluconazole-/voriconazole-resistant isolates, liposomal AmB, 3–5 mg/kg intravenous daily, with or without oral flucytosine, 25 mg/kg 4 times daily is recommended (*strong recommendation; low-quality evidence*).

87. With macular involvement, antifungal agents as noted above PLUS intravitreal injection of either AmB deoxycholate, 5–10 µg/0.1 mL sterile water, or voriconazole, 100 µg/0.1 mL sterile water or normal saline, to ensure a prompt high level of antifungal activity is recommended (*strong recommendation; low-quality evidence*).

88. The duration of treatment should be at least 4–6 weeks, with the final duration depending on resolution of the lesions as determined by repeated ophthalmological examinations (*strong recommendation; low-quality evidence*).

What Is the Treatment for *Candida* Chorioretinitis With Vitritis?

Recommendations

89. Antifungal therapy as detailed above for chorioretinitis without vitritis, PLUS intravitreal injection of either amphotericin B deoxycholate, 5–10 µg/0.1 mL sterile water, or voriconazole, 100 µg/0.1 mL sterile water or normal saline is recommended (*strong recommendation; low-quality evidence*).

90. Vitrectomy should be considered to decrease the burden of organisms and to allow the removal of fungal abscesses that are inaccessible to systemic antifungal agents (*strong recommendation; low-quality evidence*).

91. The duration of treatment should be at least 4–6 weeks, with the final duration dependent on resolution of the lesions

as determined by repeated ophthalmological examinations (*strong recommendation; low-quality evidence*).

XIII. What Is the Treatment for Central Nervous System Candidiasis?

Recommendations

92. For initial treatment, liposomal AmB, 5 mg/kg daily, with or without oral flucytosine, 25 mg/kg 4 times daily is recommended (*strong recommendation; low-quality evidence*).
93. For step-down therapy after the patient has responded to initial treatment, fluconazole, 400–800 mg (6–12 mg/kg) daily, is recommended (*strong recommendation; low-quality evidence*).
94. Therapy should continue until all signs and symptoms and CSF and radiological abnormalities have resolved (*strong recommendation; low-quality evidence*).
95. Infected CNS devices, including ventriculostomy drains, shunts, stimulators, prosthetic reconstructive devices, and bio-polymer wafers that deliver chemotherapy should be removed if possible (*strong recommendation; low-quality evidence*).
96. For patients in whom a ventricular device cannot be removed, AmB deoxycholate could be administered through the device into the ventricle at a dosage ranging from 0.01 mg to 0.5 mg in 2 mL 5% dextrose in water (*weak recommendation; low-quality evidence*).

XIV. What Is the Treatment for Urinary Tract Infections Due to *Candida* Species?

What Is the Treatment for Asymptomatic Candiduria?

Recommendations

97. Elimination of predisposing factors, such as indwelling bladder catheters, is recommended whenever feasible (*strong recommendation; low-quality evidence*).
98. Treatment with antifungal agents is NOT recommended unless the patient belongs to a group at high risk for dissemination; high-risk patients include neutropenic patients, very low-birth-weight infants (<1500 g), and patients who will undergo urologic manipulation (*strong recommendation; low-quality evidence*).
99. Neutropenic patients and very low-birth-weight infants should be treated as recommended for candidemia (see sections III and VII) (*strong recommendation; low-quality evidence*).
100. Patients undergoing urologic procedures should be treated with oral fluconazole, 400 mg (6 mg/kg) daily, OR AmB deoxycholate, 0.3–0.6 mg/kg daily, for several days before and after the procedure (*strong recommendation; low-quality evidence*).

What Is the Treatment for Symptomatic *Candida* Cystitis?

Recommendations

101. For fluconazole-susceptible organisms, oral fluconazole, 200 mg (3 mg/kg) daily for 2 weeks is recommended (*strong recommendation; moderate-quality evidence*).
102. For fluconazole-resistant *C. glabrata*, AmB deoxycholate, 0.3–0.6 mg/kg daily for 1–7 days OR oral flucytosine, 25 mg/

kg 4 times daily for 7–10 days is recommended (*strong recommendation; low-quality evidence*).

103. For *C. krusei*, AmB deoxycholate, 0.3–0.6 mg/kg daily, for 1–7 days is recommended (*strong recommendation; low-quality evidence*).

104. Removal of an indwelling bladder catheter, if feasible, is strongly recommended (*strong recommendation; low-quality evidence*).

105. AmB deoxycholate bladder irrigation, 50 mg/L sterile water daily for 5 days, may be useful for treatment of cystitis due to fluconazole-resistant species, such as *C. glabrata* and *C. krusei* (*weak recommendation; low-quality evidence*).

What Is the Treatment for Symptomatic Ascending *Candida* Pyelonephritis?

Recommendations

106. For fluconazole-susceptible organisms, oral fluconazole, 200–400 mg (3–6 mg/kg) daily for 2 weeks is recommended (*strong recommendation; low-quality evidence*).
107. For fluconazole-resistant *C. glabrata*, AmB deoxycholate, 0.3–0.6 mg/kg daily for 1–7 days with or without oral flucytosine, 25 mg/kg 4 times daily, is recommended (*strong recommendation; low-quality evidence*).
108. For fluconazole-resistant *C. glabrata*, monotherapy with oral flucytosine, 25 mg/kg 4 times daily for 2 weeks, could be considered (*weak recommendation; low-quality evidence*).
109. For *C. krusei*, AmB deoxycholate, 0.3–0.6 mg/kg daily, for 1–7 days is recommended (*strong recommendation; low-quality evidence*).
110. Elimination of urinary tract obstruction is strongly recommended (*strong recommendation; low-quality evidence*).
111. For patients who have nephrostomy tubes or stents in place, consider removal or replacement, if feasible (*weak recommendation; low-quality evidence*).

What Is the Treatment for *Candida* Urinary Tract Infection Associated With Fungus Balls?

Recommendations

112. Surgical intervention is strongly recommended in adults (*strong recommendation; low-quality evidence*).
113. Antifungal treatment as noted above for cystitis or pyelonephritis is recommended (*strong recommendation; low-quality evidence*).
114. Irrigation through nephrostomy tubes, if present, with AmB deoxycholate, 25–50 mg in 200–500 mL sterile water, is recommended (*strong recommendation; low-quality evidence*).

XV. What Is the Treatment for Vulvovaginal Candidiasis?

Recommendations

115. For the treatment of uncomplicated *Candida* vulvovaginitis, topical antifungal agents, with no one agent superior to

another, are recommended (*strong recommendation; high-quality evidence*).

116. Alternatively, for the treatment of uncomplicated *Candida* vulvovaginitis, a single 150-mg oral dose of fluconazole is recommended (*strong recommendation; high-quality evidence*).
117. For severe acute *Candida* vulvovaginitis, fluconazole, 150 mg, given every 72 hours for a total of 2 or 3 doses, is recommended (*strong recommendation; high-quality evidence*).
118. For *C. glabrata* vulvovaginitis that is unresponsive to oral azoles, topical intravaginal boric acid, administered in a gelatin capsule, 600 mg daily, for 14 days is an alternative (*strong recommendation; low-quality evidence*).
119. Another alternative agent for *C. glabrata* infection is nystatin intravaginal suppositories, 100 000 units daily for 14 days (*strong recommendation; low-quality evidence*).
120. A third option for *C. glabrata* infection is topical 17% fluocytosine cream alone or in combination with 3% AmB cream administered daily for 14 days (*weak recommendation; low-quality evidence*).
121. For recurring vulvovaginal candidiasis, 10–14 days of induction therapy with a topical agent or oral fluconazole, followed by fluconazole, 150 mg weekly for 6 months, is recommended (*strong recommendation; high-quality evidence*).

XVI. What Is the Treatment for Oropharyngeal Candidiasis?

Recommendations

122. For mild disease, clotrimazole troches, 10 mg 5 times daily, OR miconazole mucoadhesive buccal 50-mg tablet applied to the mucosal surface over the canine fossa once daily for 7–14 days are recommended (*strong recommendation; high-quality evidence*).
123. Alternatives for mild disease include nystatin suspension (100 000 U/mL) 4–6 mL 4 times daily, OR 1–2 nystatin pastilles (200 000 U each) 4 times daily, for 7–14 days (*strong recommendation; moderate-quality evidence*).
124. For moderate to severe disease, oral fluconazole, 100–200 mg daily, for 7–14 days is recommended (*strong recommendation; high-quality evidence*).
125. For fluconazole-refractory disease, itraconazole solution, 200 mg once daily OR posaconazole suspension, 400 mg twice daily for 3 days then 400 mg daily, for up to 28 days 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*).

XVII. What Is the Treatment for Esophageal Candidiasis?

Recommendations

131. Systemic antifungal therapy is always required. A diagnostic trial of antifungal therapy is appropriate before performing an endoscopic examination (*strong recommendation; high-quality evidence*).
132. Oral fluconazole, 200–400 mg (3–6 mg/kg) daily, for 14–21 days is recommended (*strong recommendation; high-quality evidence*).
133. For patients who cannot tolerate oral therapy, intravenous fluconazole, 400 mg (6 mg/kg) daily, OR an echinocandin (micafungin, 150 mg daily, caspofungin, 70-mg loading dose, then 50 mg daily, or anidulafungin, 200 mg daily) is recommended (*strong recommendation; high-quality evidence*).
134. A less preferred alternative for those who cannot tolerate oral therapy is AmB deoxycholate, 0.3–0.7 mg/kg daily (*strong recommendation; moderate-quality evidence*).
135. Consider de-escalating to oral therapy with fluconazole 200–400 mg (3–6 mg/kg) daily once the patient is able to tolerate oral intake (*strong recommendation; moderate-quality evidence*).
136. For fluconazole-refractory disease, itraconazole solution, 200 mg daily, OR voriconazole, 200 mg (3 mg/kg) twice daily either intravenous or oral, for 14–21 days is recommended (*strong recommendation; high-quality evidence*).
137. Alternatives for fluconazole-refractory disease include an echinocandin (micafungin: 150 mg daily; caspofungin: 70-mg loading dose, then 50 mg daily; or anidulafungin: 200 mg daily) for 14–21 days, OR AmB deoxycholate, 0.3–0.7 mg/kg daily, for 21 days (*strong recommendation; high-quality evidence*).
138. Posaconazole suspension, 400 mg twice daily, or extended-release tablets, 300 mg once daily, could be considered for fluconazole-refractory disease (*weak recommendation; low-quality evidence*).
139. For patients who have recurrent esophagitis, chronic suppressive therapy with fluconazole, 100–200 mg 3 times

weekly, is recommended (*strong recommendation; high-quality evidence*).

140. For HIV-infected patients, antiretroviral therapy is strongly recommended to reduce the incidence of recurrent infections (*strong recommendation; high-quality evidence*).

Notes

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References

1. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 48:503–35.
2. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336:924–6.
3. US GRADE Network. Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE methodology. Available at: <http://www.gradeworkinggroup.org/>. Accessed 10 November 2015.