



Complete Summary

GUIDELINE TITLE

Guidelines for treatment of candidiasis.

BIBLIOGRAPHIC SOURCE(S)

Pappas PG, Rex JH, Sobel JD, Filler SG, Dismukes WE, Walsh TJ, Edwards JE.
Guidelines for treatment of candidiasis. Clin Infect Dis 2004 Jan 15; 38(2):161-89.
[344 references] [PubMed](#)

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT
CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY

SCOPE

DISEASE/CONDITION(S)

Candidiasis, including invasive and mucocutaneous candidiasis

GUIDELINE CATEGORY

Diagnosis
Management
Treatment

CLINICAL SPECIALTY

Infectious Diseases
Internal Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To summarize current knowledge and provide recommendations for the treatment of multiple forms of candidiasis, including invasive and mucocutaneous candidiasis
- To present prophylactic strategies for the prevention of invasive candidiasis in at-risk patients

TARGET POPULATION

Patients with candidiasis (infections due to *Candida*)

INTERVENTIONS AND PRACTICES CONSIDERED

Microbiology Laboratory Studies

Susceptibility testing, such as the NCCLS M27-A method for testing the susceptibility of *Candida* species to fluconazole, itraconazole, and flucytosine.

Other Studies

1. Ultrasonography or computed tomography for persistent candiduria
2. Ophthalmological examination

Pharmacotherapy

1. Amphotericin B deoxycholate

Note: Lipid-based amphotericin B preparations are considered but not recommended as first-line therapy. They are considered second-line therapy for patients who are intolerant of or refractory to therapy with conventional amphotericin B.

2. Azoles, such as caspofungin, fluconazole, itraconazole, ketoconazole, voriconazole
3. Flucytosine
4. Topical agents, including topical azoles such as clotrimazole, butoconazole, miconazole, tioconazole, terconazole
5. Nystatin, oral or topical

Nonpharmacologic Treatment Options

1. Removal of stents, catheters, and prosthetic devices when possible
2. Surgery including open or arthroscopic debridement or drainage
3. Vitrectomy
4. Intravitreal antifungal therapy (discussed but not recommended)
5. Parenteral therapy (for patients with esophageal candidiasis who are unable to swallow)

MAJOR OUTCOMES CONSIDERED

- Reduction, prevention, or relief from signs and symptoms (e.g., fever)

- Prevention of development or progression of infection and associated complications
- Eradication of infection (e.g., clearance of bloodstream, urine, and/or sites of infection)
- Infection recurrence
- Resolution of radiographic findings
- Return of joint function in cases of candidal osteomyelitis and arthritis
- Preservation of cardiac function in cases of candidal endocarditis, pericarditis, or suppurative phlebitis
- Normalization of cerebrospinal fluid analysis, radiological findings, and stabilization of neurological function in cases of candidal meningitis
- Preservation of sight in cases of candidal endophthalmitis

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Quality of Evidence

1. Evidence from at least one properly randomized, controlled trial
2. Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies or dramatic results from uncontrolled experiments
3. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of Recommendation

- A. Good evidence to support a recommendation for use
- B. Moderate evidence to support a recommendation for use
- C. Poor evidence to support a recommendation
- D. Moderate evidence to support a recommendation against use
- E. Good evidence to support a recommendation against use

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Each recommendation includes a ranking for the strength and the quality of evidence supporting it. Definitions of the levels of evidence (I-III) and grades of recommendation (A-E) are repeated at the end of the Major Recommendations field.

Executive Summary

Candida species are the most common cause of fungal infections. Candida species produce infections that range from non-life-threatening mucocutaneous illnesses to invasive processes that may involve virtually any organ. Such a broad range of infections requires an equally broad range of diagnostic and therapeutic strategies. These guidelines summarize current knowledge about treatment of multiple forms of candidiasis for the Infectious Diseases Society of America (IDSA). This document covers the following 4 major topical areas.

The role of the microbiology laboratory: To a greater extent than for other fungi, treatment of candidiasis can now be guided by in vitro susceptibility testing.

However, susceptibility testing of fungi is not considered a routine testing procedure in many laboratories, is not always promptly available, and is not universally considered as the standard of care. Knowledge of the infecting species, however, is highly predictive of likely susceptibility and can be used as a guide to therapy. The guidelines review the available information supporting current testing procedures and interpretive breakpoints and place these data into clinical context. Susceptibility testing is most helpful in dealing with deep infection due to non–albicans species of *Candida*. In this setting, especially if the patient has been treated previously with an azole antifungal agent, the possibility of microbiological resistance must be considered.

Treatment of invasive candidiasis: In addition to acute hematogenous candidiasis, the guidelines review strategies for treatment of 15 other forms of invasive candidiasis (See Table 2 in the original guideline). Extensive data from randomized trials are available only for therapy of acute hematogenous candidiasis in the nonneutropenic adult. Choice of therapy for other forms of candidiasis is based on case series and anecdotal reports. In general, amphotericin B–based preparations, the azole antifungal agents, and the echinocandin antifungal agents play a role in treatment. Choice of therapy is guided by weighing the greater activity of amphotericin B–based preparations and the echinocandin antifungal agents for some non–albicans species (e.g., *Candida krusei*) against the ready availability of oral and parenteral formulations for the azole antifungal agents. Flucytosine has activity against many isolates of *Candida* but is infrequently used.

Treatment of mucocutaneous candidiasis: Therapy for mucosal infections is dominated by the azole antifungal agents. These drugs may be used topically or systemically and are safe and efficacious. A significant problem with mucosal disease is the propensity for a small proportion of patients to have repeated relapses. In some situations, the explanation for such a relapse is obvious (e.g., recurrent oropharyngeal candidiasis in an individual with advanced and uncontrolled human immunodeficiency virus [HIV] infection), but in other patients, the cause is cryptic (e.g., relapsing vaginitis in a healthy woman). Rational strategies for these situations are discussed in the guidelines and must consider the possibility of induction of resistance with prolonged or repeated exposure.

Prevention of invasive candidiasis: Prophylactic strategies are useful if the risk of a target disease is sharply elevated in a readily identified patient group. Selected patient groups undergoing therapy that produces prolonged neutropenia (e.g., some bone marrow transplant recipients) or who receive a solid-organ transplant (e.g., some liver transplant recipients) have a sufficient risk of invasive candidiasis to warrant prophylaxis.

Key Recommendations by Diagnosis

Candidemia and Acute Hematogenously Disseminated Candidiasis

If feasible, initial nonmedical management should include removal of all existing central venous catheters (B-II). The evidence for this recommendation is strongest for the nonneutropenic patient population and includes data in which catheter removal was associated with reduced mortality in adults and neonates.

In neutropenic patients, the role of the gut as a source for disseminated candidiasis is evident from autopsy studies, but, in an individual patient, it is difficult to determine the relative contributions of the gut and a catheter as primary sources of fungemia. An exception is made for fungemia due to *C. parapsilosis*, which is very frequently associated with use of catheters (A-II) (Anaissie et al, 1998). There are, however, no randomized studies of this topic, and a recent exhaustive review clearly demonstrates the limitations of the available data. However, the consensus opinion is that existing central venous catheters should be removed, when feasible. Anecdotal reports of successful in situ treatment of infected catheters by instillation of antibiotic lock solutions containing as much as 2.5 mg/mL of amphotericin B deoxycholate suggest this as an option in selected cases, but the required duration of therapy and the frequency of relapse are not known.

Initial medical therapy should involve caspofungin, fluconazole, an amphotericin B preparation, or combination therapy with fluconazole plus amphotericin B. The choice between these treatments depends on the clinical status of the patient, the physician's knowledge of the species and/or antifungal susceptibility of the infecting isolate, the relative drug toxicity, the presence of organ dysfunction that would affect drug clearance, available knowledge of use of the drug in the given patient population, and the patient's prior exposure to antifungal agents. Experience with caspofungin (a 70-mg loading dose followed by 50 mg daily) is, as yet, limited, but its excellent clinical activity, its broad-spectrum activity against *Candida* species, and a low rate of treatment-related adverse events make it a suitable choice for initial therapy in adults (A-I). For clinically stable patients who have not recently received azole therapy, fluconazole (≥ 6 mg/kg per day; i.e., ≥ 400 mg/day for a 70-kg patient) is another appropriate choice (A-I) (Edwards et al, 1997; Buchner et al, 2002). For clinically unstable patients infected with an unspciated isolate, fluconazole has been used successfully, but many authorities prefer amphotericin B deoxycholate (≥ 0.7 mg/kg per day) because of its broader spectrum. If a lipid associated formulation of amphotericin B is selected, a dosage of at least 3 mg/kg/d appears suitable (C-III). A combination of fluconazole (800 mg/day) plus amphotericin B deoxycholate (0.7 mg/kg per day for the first 5 to 6 days) is also suitable (A-I).

Neonates with disseminated candidiasis are usually treated with amphotericin B deoxycholate because of its low toxicity and because of the relative lack of experience with other agents in this population. Fluconazole (6–12 mg/kg per day) has been used successfully in small numbers of neonates. There are currently no data on the pharmacokinetics of caspofungin in neonates.

Antifungal susceptibility can be broadly predicted once the isolate has been identified to the species level (see the subsection Susceptibility testing and drug dosing, in the Introduction). Infections with *C. albicans*, *C. tropicalis*, and *C. parapsilosis* may be treated with amphotericin B deoxycholate (0.6 mg/kg per day), fluconazole (6 mg/kg per day), or caspofungin (70-mg loading dose followed by 50 mg/day) (A-I). Because *C. glabrata* often has reduced susceptibility to both azoles and amphotericin B, opinions on the best therapy are divided. Both *C. krusei* and *C. glabrata* appear susceptible to caspofungin, and this agent appears to be a good alternative (A-I). Although fungemia due to *C. glabrata* has been treated successfully with fluconazole (6 mg/kg per day), many authorities prefer amphotericin B deoxycholate (≥ 0.7 mg/kg per day) (B-III) (Buchner et al,

2002). On the basis of pharmacokinetic predictions, fluconazole (12 mg/kg per day; 800 mg/day for a 70-kg patient) may be a suitable alternative, particularly in less-critically ill patients (C-III). If the infecting isolate is known or likely to be *C. krusei*, available data suggest that amphotericin B deoxycholate (1.0 mg/kg per day) is preferred (C-III). On the basis of data on open-label salvage therapy, voriconazole is licensed in Europe (but not the United States) for "treatment of fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*)" and could be considered as an alternative choice (B-III). Many, but not all, isolates of *C. lusitanae* are resistant to amphotericin B. Therefore, fluconazole (6 mg/kg per day) is the preferred therapy for this species (B-III). Both voriconazole and caspofungin would be expected to be active against this species (C-III). Issues associated with selection and dosage of the lipid amphotericin preparations are discussed in the Introduction. As discussed above and elsewhere, susceptibility testing may be used to identify isolates that are less likely to respond to fluconazole (A-II) or amphotericin B (B-II) (see table 3 in original guideline document) (Rex & Pfaller, 2002; Rex et al, 1997)].

For candidemia, therapy should be continued for 2 weeks after the last positive blood culture result and resolution of signs and symptoms of infection (A-III). Amphotericin B or caspofungin may be switched to fluconazole (intravenous or oral) for completion of therapy (B-III). Patients who are neutropenic at the time of developing candidemia should receive a recombinant cytokine that accelerates recovery from neutropenia (granulocyte colony-stimulating factor or granulocyte-monocyte colony-stimulating factor). Other forms of immunosuppression should be modified, when possible (e.g., by reduction of a corticosteroid dosage).

Breakthrough (or persistence of) candidemia in the face of ongoing antifungal therapy suggests the possibility of an infected intravascular device, significant immunosuppression, or microbiological resistance. Therapy with an agent from a different class should be started, the isolate should be promptly identified to the species level, and susceptibility testing should be considered. Infected intravascular devices should be removed, when feasible, and immunosuppression should be ameliorated.

Finally, all patients with candidemia should undergo at least 1 ophthalmological examination to exclude the possibility of candidal endophthalmitis (A-II). Although some authors have suggested that examinations should be conducted for 2 weeks after negative findings of an initial examination, these recommendations are based on small numbers of patients. The results of large prospective therapy studies that included careful ophthalmological examinations suggest that onset of retinal lesions is rare following an otherwise apparently successful course of systemic therapy (there were no such cases in 441 successfully treated subjects). The guideline developers thus conclude that candidemic individuals should have at least 1 careful ophthalmological examination, preferably at a time when the candidemia appears controlled and new spread to the eye is unlikely (B-III). These data and recommendations are based almost entirely on experience in the treatment of nonneutropenic patients—neutropenic patients may not manifest visible endophthalmitis until recovery from neutropenia, and, therefore, ophthalmological examination should be performed after recovery of the neutrophil count.

Empirical Treatment of Suspected Disseminated Candidiasis in Febrile Nonneutropenic Patients

The utility of antifungal therapy for this syndrome has not been defined. If therapy is given, its use should be limited to patients with (1) *Candida* species colonization (preferably at multiple sites), (2) multiple other risk factors, and (3) absence of any other uncorrected causes of fever (C-III) (Buchner et al, 2002). The absence of colonization by *Candida* species indicates a lower risk for invasive candidiasis and warrants delaying empirical therapy.

Empirical Antifungal Treatment of Neutropenic Patients with Prolonged Fever Despite Antibacterial Therapy

Antifungal therapy is appropriate in neutropenic patients who have persistent unexplained fever, despite receipt of 4 to 7 days of appropriate antibacterial therapy. Once begun, therapy is continued until resolution of neutropenia. Amphotericin B deoxycholate (0.5–0.7 mg/kg per day) has traditionally been the preferred agent (A-II). When compared with amphotericin B deoxycholate (median dose, 0.6 mg/kg per day), liposomal amphotericin B (median dose, 3 mg/kg per day) showed similar overall clinical efficacy but demonstrated superior safety and a decreased rate of documented breakthrough fungal infections, particularly in recipients of bone marrow transplants (A-I) (Walsh et al, 1999). When compared with amphotericin B deoxycholate (mean daily dose, 0.7 mg/kg), itraconazole (200 mg intravenously [iv] q12h for 2 days, 200 mg iv per day for 12 days, and then 400-mg solution orally [po] per day) showed similar breakthrough fungal infection rates and mortality but significantly less toxicity (A-I) (Boogaerts et al, 2001). Although the data are controversial because some analyses show that voriconazole was, overall, slightly inferior to liposomal amphotericin B, voriconazole has been shown to be superior to liposomal amphotericin B in the prevention of breakthrough fungal infections in high-risk patients (A-I). Thus, use of this compound should be limited to allogeneic bone marrow transplant recipients and individuals with relapsed leukemia. Fluconazole (400 mg/day) has been used successfully for selected patients (A-I) (Malik et al, 1998; Viscoli et al., 1996; Winston et al, 2000) and could be considered as an alternative strategy if (1) the patient is at low risk for invasive aspergillosis, (2) the patient lacks any other signs or symptoms suggesting aspergillosis, (3) local epidemiologic data suggest that the patient is at low risk for infection with azole-resistant isolates of *Candida*, and (4) the patient has not received an azole antifungal agent as prophylaxis.

Chronic Disseminated Candidiasis (Hepatosplenic Candidiasis)

Fluconazole (6 mg/kg per day) is generally preferred for clinically stable patients (B-III). Amphotericin B deoxycholate (0.6–0.7 mg/kg per day) or a lipid-associated formulation of amphotericin B (3–5 mg/kg per day) may be used in acutely ill patients or patients with refractory disease. Some experts recommend an initial 1- to 2-week course of amphotericin B for all patients, followed by a prolonged course of fluconazole. Therapy should be continued until calcification or resolution of lesions, particularly in patients receiving continued chemotherapy or immunosuppression. Premature discontinuation of antifungal therapy may lead to recurrent infection. Patients with chronic disseminated candidiasis may continue to receive chemotherapy, including ablative therapy for recipients of bone marrow

and/or stem cell transplants. Treatment of chronic disseminated candidiasis in such patients continues throughout chemotherapy.

Disseminated Cutaneous Neonatal Candidiasis

Prematurely born neonates, neonates with low birth weight, or infants with prolonged rupture of membranes who demonstrate the clinical findings associated with disseminated neonatal cutaneous candidiasis should be considered for systemic therapy. Amphotericin B deoxycholate (0.5–1 mg/kg per day, for a total dose of 10–25 mg/kg) is generally used (B-III). Fluconazole may be used as a second-line agent (B-III). Dosing issues for neonates are discussed in more detail in the original guideline document.

Urinary Candidiasis

Determination of the clinical relevance of candiduria can be difficult. Asymptomatic candiduria rarely requires therapy (D-III). Candiduria may, however, be the only microbiological documentation of disseminated candidiasis. Candiduria should be treated in symptomatic patients, patients with neutropenia, infants with low birth weight, patients with renal allografts, and patients who will undergo urologic manipulations (B-III). However, short courses of therapy are not recommended; therapy for 7 to 14 days is more likely to be successful. Removal of urinary tract instruments, including stents and Foley catheters, is often helpful. If complete removal is not possible, placement of new devices may be beneficial. Treatment with fluconazole (200 mg/day for 7–14 days) and with amphotericin B deoxycholate at widely ranging doses (0.3–1.0 mg/kg per day for 1–7 days) has been successful (B-II) (Jacobs et al, 1996). In the absence of renal insufficiency, oral flucytosine (25 mg/kg four times a day [q.i.d.]) may be valuable for eradicating candiduria in patients with urologic infection due to non-albicans species of *Candida* (C-III). However, emergence of resistance may occur rapidly when this compound is used as a single agent. Bladder irrigation with amphotericin B deoxycholate (50–200 micrograms/mL) may transiently clear funguria, but is rarely indicated (C-III), except as a diagnostic localizing tool. Even with apparently successful local or systemic antifungal therapy for candiduria, relapse is frequent, and this likelihood is increased by continued use of a urinary catheter. Persistent candiduria in immunocompromised patients warrants ultrasonography or computed tomography (CT) of the kidney (C-III).

Lower Respiratory Tract Candidiasis (Pulmonary and Laryngeal Candidiasis)

Most patients with primary *Candida* pneumonia and laryngeal candidiasis have been treated with amphotericin B (0.7–1.0 mg/kg per day) (B-III). In cases of secondary pneumonia associated with hematogenously disseminated infection, therapy directed at disseminated candidiasis, rather than at *Candida* pneumonia in particular, is indicated (see the section Candidemia and Acute Hematogenously Disseminated Candidiasis, above). For candidal laryngitis, fluconazole is a suitable alternative in milder cases (B-III).

Candidal Osteomyelitis (including Mediastinitis) and Arthritis

Osteomyelitis is best treated with combined surgical debridement of the affected area, especially in the case of vertebral osteomyelitis, and antifungal therapy. Courses of amphotericin B deoxycholate (0.5–1 mg/kg per day for 6–10 weeks) have been used successfully.

Fluconazole has been used successfully as initial therapy for susceptible isolates in 3 reports in which doses of 6 mg/kg per day for 6 to 12 months were effective. Addition of amphotericin B deoxycholate to bone cement appears safe and may be of value in complicated cases. Taken together, these data suggest that surgical debridement and an initial course of amphotericin B for 2 to 3 weeks followed by fluconazole, for a total duration of therapy of 6 to 12 months, would be rational (B-III).

Definitive information on treatment of native joint arthritis is limited. Adequate drainage is critical to successful therapy. In particular, management of *Candida* arthritis of the hip requires open drainage. Case reports have documented cures with administration of intravenous amphotericin B and with fluconazole when administered in conjunction with adequate drainage. Fluconazole has occasionally been used alone successfully. As parenteral administration of these agents produces substantial synovial fluid levels, the utility of intra-articular therapy is discouraged. Prolonged courses of therapy similar to those used for treating osteomyelitis appear to be required (C-III).

Although success with medical therapy alone has been described, *Candida* arthritis that involves a prosthetic joint generally requires resection arthroplasty. Subsequent medical therapy mirrors that for native joint disease, and a new prosthesis may be inserted after successful clearance of the local infection (C-III).

On the basis of a small number of cases, *Candida* mediastinitis may be treated successfully with surgical debridement followed by either amphotericin B or fluconazole therapy (C-III) (Malani et al, 2002; Clancy, Nguyen, & Morris, 1997). Irrigation of the mediastinal space with amphotericin B is not recommended, because it may cause chemical mediastinitis. Prolonged courses of therapy, similar to those needed for osteomyelitis at other sites, appear to be appropriate (C-III).

Candidal Infections of the Gallbladder, Pancreas, and Peritoneum

Disease of the biliary tree should be treated by mechanical restoration of functional drainage, combined with therapy with either amphotericin B or fluconazole (C-III). Both agents achieve therapeutic biliary concentrations, and local instillation is not needed. Catheter-associated peritonitis is treated with catheter removal and systemic treatment with amphotericin B or fluconazole (B-III). After removal of the peritoneal dialysis catheter and a delay of at least 2 weeks, a new catheter may be placed (B-III) (Goldie et al, 1996). Intraperitoneal amphotericin B has been associated with painful chemical peritonitis and should, in general, be avoided. *Candida* peritonitis related to intra-abdominal leakage of fecal material is treated with surgical repair, drainage, and therapy with either amphotericin B or fluconazole (C-III). The required duration of therapy for all forms of *Candida* peritonitis is not well defined and should be guided by the patient's response. In general, 2 to 3 weeks of therapy seems to be

required. Surgical patients with recurrent gastrointestinal perforation are at increased risk for *Candida* peritonitis and may benefit from prophylactic antifungal therapy (B-I).

Candidal Endocarditis, Pericarditis, Suppurative Phlebitis, and Myocarditis

Both native valve and prosthetic valve infection should be managed with surgical replacement of the infected valve. Medical therapy with amphotericin B with or without flucytosine at maximal tolerated doses has most often been used (B-III). Total duration of therapy should be at least 6 weeks after surgery, but possibly much longer (C-III). *Candida* endocarditis has a propensity for relapse and requires careful follow-up for at least 1 year. If valve replacement is not possible, long-term (possibly life-long) suppressive therapy with fluconazole may be used (C-III) (Pierrotti & Baddour, 2002; Baddour, 1995; Castiglia, Smego, & Sames, 1994). Successful primary therapy with fluconazole and liposomal amphotericin B has been described for patients with native valve infections.

Candidal pericarditis requires surgical debridement and/or resection, depending on the extent of the disease. Cardiac tamponade is possible and may require an emergency procedure to relieve hemodynamic compromise. Prolonged therapy with amphotericin B or fluconazole should be used (C-III).

Suppurative *Candida* thrombophlebitis of a peripheral vein is best managed with surgical resection of the involved vein segment, followed by antifungal therapy for 2 weeks (B-III).

After vein resection, the general approach to this disease is similar to that for other forms of acute hematogenous dissemination.

Candidal Meningitis

Amphotericin B deoxycholate (0.7–1 mg/kg per day) plus flucytosine (25 mg/kg q.i.d.) is appropriate as initial therapy (B-III). The flucytosine dose should be adjusted to produce serum levels of 40 to 60 micrograms/mL. Very few data exist on fluconazole for the treatment of candidal meningitis—it has been used as both follow-up therapy and long-term suppressive therapy. Because of the tendency for this disease to relapse, therapy should be administered for a minimum of 4 weeks after resolution of all signs and symptoms associated with the infection. Treatment of *Candida* meningitis associated with neurosurgical procedures should also include removal of prosthetic devices.

Candidal Endophthalmitis

All patients with candidemia should have at least 1 dilated retinal examination, preferably by an ophthalmologist (A-II). The preponderance of clinical experience of treatment is with amphotericin B, often combined with flucytosine (B-III). Recent data also support the use of fluconazole for this indication, particularly as follow-up therapy (B-III). Use of the maximal doses appropriate for other forms of invasive candidiasis would be appropriate to maximize penetration into the eye. Therapy should be continued until complete resolution of visible disease or

convincing stabilization. Courses of 6 to 12 weeks of therapy are typically required.

A diagnostic vitreal aspirate is generally recommended for patients presenting with endophthalmitis of unknown origin. If fungal elements are observed, some ophthalmologists instill intravitreal amphotericin B deoxycholate therapy. The utility of vitrectomy has not been systematically studied. Extrapolation from a study of bacterial endophthalmitis and from anecdotal experiences with *Candida* endophthalmitis suggests that initial vitrectomy and intravitreal amphotericin B therapy may be most appropriate for patients with substantial vision loss.

Nongenital Mucocutaneous Candidiasis

Oropharyngeal and Esophageal Candidiasis

Initial episodes of oropharyngeal candidiasis can be treated with clotrimazole troches (one 10-mg troche 5 times per day) or nystatin (available as a suspension of 100,000 U/mL [dosage, 4–6 mL q.i.d.] or as flavored 200,000 U pastilles [dosage, 1 or 2 pastilles 4–5 times per day for 7–14 days]) (B-II). Oral fluconazole (100 mg/day for 7–14 days) is as effective as—and, in some studies, superior to—topical therapy (A-I). Itraconazole solution (200 mg/day for 7–14 days) is as efficacious as fluconazole (A-I). Ketoconazole and itraconazole capsules are less effective than fluconazole, because of variable absorption (A-I).

Patients tolerate repeated episodes of oropharyngeal candidiasis without difficulty, especially if the episodes occur infrequently (A-I). Suppressing therapy is effective for preventing recurrent infections (A-I). Although it does increase the rate of development of isolates with an increased fluconazole minimal inhibitory concentration (MIC), the use of continuous suppression (rather than episodic or intermittent therapy in response to symptomatic relapse) does not increase the likelihood of developing an infection that fails to respond to fluconazole (A-I).

Fluconazole-refractory oropharyngeal candidiasis will respond to oral itraconazole therapy (≥ 200 mg/day, preferably in solution form) approximately two-thirds of the time (A-II). An oral suspension of amphotericin B (1 mL q.i.d. of the 100 mg/mL suspension) is sometimes effective in patients who do not respond to itraconazole (B-II). There have also been anecdotal reports of responses of refractory disease to use of fluconazole solution (used in a swish-and-swallow fashion) and to use of chewed itraconazole capsules. Intravenous caspofungin (50 mg/day) and intravenous amphotericin B deoxycholate (≥ 0.3 mg/kg per day) are usually effective and may be used in patients with refractory disease (B-II). Denture-related disease may require extensive and aggressive disinfection of the denture for definitive cure.

Systemic therapy is required for effective treatment of esophageal candidiasis (B-II). Although symptoms of esophageal candidiasis may be mimicked by other pathogens, a diagnostic trial of antifungal therapy is often appropriate before performing endoscopy (B-II). A 14- to 21-day course of either oral fluconazole (100 mg/day po) or itraconazole solution (200 mg/day po) is highly effective (A-I). Ketoconazole and itraconazole capsules are less effective than fluconazole, because of variable absorption (A-I). Voriconazole is as effective as fluconazole

but is associated with more adverse events (A-I). Caspofungin (50 mg/day iv) is as efficacious as amphotericin B or fluconazole (A-I). Suppressive therapy may be used for patients with disabling recurrent infections (A-II). Fluconazole-refractory esophageal candidiasis should be treated with itraconazole solution (≥ 200 mg/day po), voriconazole (200 mg b.i.d.), or caspofungin (50 mg/day) (A-II). Intravenous amphotericin B deoxycholate (0.3–0.7 mg/kg per day, as needed to produce a response) may be used for patients with otherwise refractory disease (B-II).

Antifungal susceptibility testing is not generally needed for the management of either oropharyngeal or esophageal candidiasis, but can be useful in patients with refractory infection (B-II). In patients with acquired immune deficiency syndrome (AIDS), treatment of the underlying HIV infection with highly aggressive antiretroviral therapy (HAART) is critical for preventing and managing these infections (B-II).

Candidal Onychomycosis

Whereas onychomycosis is usually caused by a dermatophyte, infections due to *Candida* species also occur. Topical agents are usually ineffective. For onychomycosis, oral griseofulvin has largely been replaced by more-effective agents, including oral terbinafine or itraconazole. With respect to *Candida* onychomycosis, terbinafine has only limited and unpredictable in vitro activity and has not demonstrated consistently good activity in clinical trials. Although the number of reported cases is small, therapy with itraconazole does appear to be effective. Itraconazole (200 mg b.i.d. for 1 week, repeated monthly for 3–4 months) appears to be the most appropriate treatment (A-II).

Candidal Skin Infections and Paronychia

Nonhematogenous primary skin infections typically occur as intertrigo in skin folds, especially in obese and diabetic patients. Topical azoles and polyenes, including clotrimazole, miconazole, and nystatin, are effective. Keeping the infected area dry is important. For paronychia, the most important intervention is drainage.

Mammary Candidiasis

Although a clear association remains to be determined, because of the lack of application of consistent clinical and microbiological criteria, nipple or breast pain in nursing mothers has been linked to the presence of *C. albicans*. Nursing worsens or precipitates the pain. Classical findings of mastitis are absent, as is fever, and the findings of a local physical examination are often unimpressive. The infant may or may not have signs of mucosal or cutaneous candidiasis. Microbiological studies have found both bacteria and *C. albicans*, with bacteria appearing to predominate. The true cause of the pain associated with this syndrome is unclear, but treatment of the mother and the infant with an antifungal agent has produced relief, according to some reports. Optimal diagnostic criteria and management strategies are not certain, but both topical nystatin and oral fluconazole are safe for infants and could be considered as therapy for mother and child if the presentation is strongly suggestive of candidiasis.

Chronic Mucocutaneous Candidiasis

The persistent immunological defect associated with chronic mucocutaneous candidiasis requires a long-term approach that is analogous to that used in patients with AIDS and rapidly relapsing oropharyngeal candidiasis. Systemic therapy is needed, and all of the azole antifungal agents (ketoconazole, fluconazole, and itraconazole) have been used successfully. The required dosages are similar to those used for other forms of mucocutaneous candidiasis. As with HIV-infected patients, development of resistance to these agents has also been described.

Genital Candidiasis

Vaginal candidiasis may be classified into complicated and uncomplicated forms (see table 5 in the original guideline document). Uncomplicated vaginitis is seen in 90% of patients and responds readily to short-course oral or topical therapy with any of the therapies listed above, including the single-dose regimens (A-I). In contrast, the complicated vaginitis seen in approximately 10% of patients requires antimycotic therapy for ≥ 7 days, either daily as topical therapy or as two 150-mg doses of fluconazole administered 72 h apart (A-I) (Sobel et al, 2001). Azole therapy is unreliable for non-albicans species of *Candida* (B-III). Infections with *C. glabrata*, *C. krusei*, and the other non-albicans species frequently respond to topical boric acid 600 mg/day for 14 days (B-II) or topical flucytosine (B-II). Azole-resistant *C. albicans* infections are extremely rare.

Recurrent vaginitis is usually due to azole-susceptible *C. albicans*. After control of causal factors (e.g., uncontrolled diabetes), induction therapy with 2 weeks of a topical or oral azole should be followed by a maintenance regimen for 6 months. Suitable maintenance regimens include fluconazole (150 mg po every week), ketoconazole (100 mg per day), itraconazole (100 mg q.o.d.) or daily therapy with any topical azole (A-I). Chronic use of fluconazole in HIV-infected women has been associated with increased vaginal carriage of non-albicans species of *Candida*, but the significance of this observation is uncertain.

Prophylaxis

HIV-Infected Patients

See the section on Oropharyngeal and Esophageal Candidiasis, above.

Neutropenic Patients

Fluconazole (400 mg/day) or itraconazole solution (2.5 mg/kg q12h po during the period of risk for neutropenia) are appropriate therapies for patients who are at significant risk for invasive candidiasis (A-I). Although not licensed at the time of this writing, micafungin demonstrated favorable activity, on the basis of results in the recently reported comparative trial, and may become an option for antifungal prophylaxis in neutropenic patients. Such patient groups might include patients receiving standard chemotherapy for acute myelogenous leukemia, allogeneic bone marrow transplants, or high-risk autologous bone marrow transplants. However, in this context, it is important to understand that, among these

populations, chemotherapy or bone marrow transplantation protocols do not all produce equivalent risk and that local experience with particular chemotherapy and cytokine regimens should be used to determine the relevance of prophylaxis. The optimal duration of prophylaxis is not known but should include the period of risk for neutropenia at a minimum.

Solid-Organ Transplant Recipients

High-risk recipients of liver transplants should receive prophylactic antifungal therapy during the early postoperative period (A-I).

Patients in Intensive Care Units (ICUs) and Other Care Settings

Knowledge about this class of infections is evolving. The primary data showing utility of prophylaxis are from studies at single centers with high baseline rates of infections. The broader applicability of these rules in other ICUs remains a subject of significant debate. Institutions where high rates of invasive candidiasis in the adult or neonatal ICU persist despite standard infection-control procedures could consider fluconazole prophylaxis for carefully selected patients in these care areas (A-I).

Definitions:

Quality of Evidence

1. Evidence from at least one properly randomized, controlled trial
2. Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies or dramatic results from uncontrolled experiments
3. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

Strength of Recommendation

- A. Good evidence to support a recommendation for use
- B. Moderate evidence to support a recommendation for use
- C. Poor evidence to support a recommendation
- D. Moderate evidence to support a recommendation against use
- E. Good evidence to support a recommendation against use

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

[References open in a new window](#)

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for select recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Early treatment of fungal infections should reduce fungal infection–associated morbidity.

Subgroups Most Likely to Benefit

The following patients are likely to benefit from aggressive therapy because of the associated high morbidity and mortality of their diagnosis:

- Neutropenic patients with prolonged fever despite antibacterial therapy
- Patients with otolaryngologic candidiasis
- Patients with candidal osteomyelitis (including mediastinitis) and arthritis
- Patients with candidal endocarditis, pericarditis, and suppurative phlebitis
- Patients with candidal meningitis
- Patients with candidal endophthalmitis

POTENTIAL HARMS

Antifungal Therapy

- Conventional amphotericin B is associated with significant toxicity, including infusion-related events, such as chills, fever, headache, nausea and vomiting, and dose-limiting nephrotoxicity.
- Lipid formulations of amphotericin B, although offering several therapeutic advantages over conventional amphotericin B, are considerably more expensive, ranging from 10- to 20-fold higher in cost.
- One potential limitation of the azole antifungal drugs is the frequency of their interactions with coadministered drugs, which results in adverse clinical consequences. One type of azole-drug interaction may lead to decreased plasma concentration of the azole, related to either decreased absorption or increased metabolism of the azole. A second type of azole-drug interaction may lead to an unexpected toxicity of the coadministered drug, relating to the ability of the azoles to increase plasma concentrations of other drugs by altering hepatic metabolism via the cytochrome P-450 system.
- A second potential limitation of the azoles is the emergence of resistance of fungal organisms, especially *Candida* species, to fluconazole.
- Widespread use of inappropriate antifungal therapy may have deleterious epidemiological consequences, including selection of resistant organisms.

Subgroups Most Likely to Be Harmed

Critically ill patients

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Pappas PG, Rex JH, Sobel JD, Filler SG, Dismukes WE, Walsh TJ, Edwards JE. Guidelines for treatment of candidiasis. Clin Infect Dis 2004 Jan 15; 38(2): 161-89. [344 references] [PubMed](#)

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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GUIDELINE DEVELOPER(S)

Infectious Diseases Society of America - Medical Specialty Society

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Infectious Diseases Society of America (IDSA)

GUIDELINE COMMITTEE

Infectious Diseases Society of America (IDSA) Practice Guidelines Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Peter G. Pappas has received grant support from Merck, Fujisawa, Pfizer, Shering-Plough, Enzon, and Vicuron. He has been a speaker for Merck, Fujisawa, Enzon, and Pfizer and has served as a consultant for Merck and Schering-Plough.

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GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Rex JH, Walsh TJ, Sobel JD, Filler SG, Pappas PG, Dismukes WE, Edwards JE. Practice guidelines for the treatment of candidiasis. *Infectious Diseases Society of America. Clin Infect Dis* 2000 Apr; 30(4):662-78.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Infectious Diseases Society of America (IDSA) via the *Clinical Infectious Diseases* journal Web site:

- [HTML Format](#)
- [Portable Document Format \(PDF\)](#)

Print copies: Available from Infectious Diseases Society of America, 66 Canal Center Plaza, Suite 600, Alexandria, VA 22314.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Kish MA. Guide to development of practice guidelines. Clin Infect Dis 2001 Mar 15; 32(6):851-4.

Electronic copies: Available from the [Infectious Diseases Society of America \(IDSA\) Web site](#).

Print copies: Available from Infectious Diseases Society of America, 66 Canal Center Plaza, Suite 600, Alexandria, VA 22314.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on May 1, 2001. The information was verified by the guideline developer on June 29, 2001. This summary was updated by ECRI on April 20, 2004.

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