Practice Guidelines for the Treatment of Candidiasis

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Executive Summary

Infections due to *Candida* species are the most common of the fungal infections. *Candida* species produce a broad range of infections, ranging from non–life-threatening mucocutaneous illnesses to invasive process that may involve virtually any organ. Such a broad range of infections requires an equally broad range of diagnostic and therapeutic strategies. This document summarizes current knowledge about treatment of multiple forms of candidiasis and is the guideline of the Infectious Diseases Society of America (IDSA) for the treatment of candidiasis. Throughout this document, treatment recommendations are scored according to the standard scoring scheme used in other IDSA guidelines to illustrate the strength of the underlying data. The document covers 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. 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 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. Extensive data from randomized trials are really 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, both amphotericin B and the azoles have a role to play in treatment. Choice of therapy is guided by weighing the greater activity of amphotericin B for some non-*albicans* species (e.g., *Candida krusei*) against the lesser toxicity and ease of administration of the azole antifungal agents. Flucytosine has activity against many isolates of *Candida* but is not often 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 have been proven safe and efficacious. A significant problem with mucosal disease is the propensity for a small proportion of patients to suffer repeated relapses. In some situations, the explanation for such a relapse is obvious (e.g., relapsing oropharyngeal candidiasis in an individual with advanced and uncontrolled 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 over time.

Prevention of invasive candidiasis. Prophylactic strategies are useful if the risk of a target disease is sharply elevated in a readily identified group of patients. 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.

Introduction

Relationship between epidemiology of candidal infections and therapy. Although *Candida albicans* remains the most common pathogen in oropharyngeal and cutaneous candidiasis, non-*albicans* species of *Candida* are increasingly frequent problems in both invasive candidiasis [1] and vaginal candidiasis [2]. This is particularly problematic in patients with acutely life-threatening invasive candidal infections. Although the susceptibility of *Candida* to the currently available antifungal agents can be predicted if the species of the infecting isolate is known (table 1) [1, 3–13], individual isolates do not necessarily follow the general pattern. For example, *C. albicans* is usually susceptible to all major agents. However, azole resistance for this

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Table 1. General patterns of susceptibility of *Candida* species.

Candida species	Fluconazole	Itraconazole	Flucytosine	Amphotericin B
C. albicans	S	S	S	S
C. tropicalis	S	S	S	S
C. parapsilosis	S	S	S	S
C. glabrata	S-DD to R[a]	S-DD to R[b]	S	S-I[c]
C. krusei	R	S-DD to R[b]	I-R	S-I[c]
C. lusitaniae	S	S	S	S to R[d]

NOTE. Except for amphotericin B, interpretations are based on use of a reference broth susceptibility testing method [3], and the underlying data were drawn from a variety of sources [1, 4–7]. Data for amphotericin B also include results of studies in which modifications of the reference method have been used in enhanced detection of amphotericin B–resistant isolates [4, 8, 9]. See table 2 for the specific interpretive breakpoints used to construct this table. I, intermediate; R, resistant; S, susceptible; S-DD, susceptible-dose dependent (the category S-DD is discussed in the section Susceptibility Testing and Drug Dosing, in the Introduction).

[a] On the basis of a survey of recent bloodstream isolates [1], 15% of *C. glabrata* isolates are resistant to fluconazole.

[b] In addition, 46% of *C. glabrata* isolates and 31% of *C. krusei* isolates are resistant to itraconazole.

[c] On the basis of a combination of in vitro data [8, 10] and in vivo data [11, 12], it appears that a significant proportion of the isolates of *C. glabrata* and *C. krusei* have reduced susceptibility to amphotericin B.

[d] Although frank amphotericin B resistance is not seen in all isolates, it is well described for isolates of this species [13, 14].

species is now well described among HIV-infected individuals with relapsing oropharyngeal candidiasis and is also reported sporadically in critically ill adults with invasive candidiasis [14]. For this reason, susceptibility testing for azole resistance is increasingly important in the management of candidiasis in patients. On the other hand, most *Candida* isolates appear to remain susceptible to amphotericin B, although recent data suggest that isolates of *Candida glabrata* and *C. krusei* may require maximal doses of amphotericin B (see below).

Susceptibility testing and drug dosing. Intensive efforts to develop standardized, reproducible, and clinically relevant susceptibility testing methods for the fungi have resulted in the development of the NCCLS M27-A methodology for susceptibility testing of yeasts [15]. Data-driven interpretive breakpoints using this method are available for testing the susceptibility of *Candida* species to fluconazole, itraconazole, and flucytosine [15–17]. Several features of these breakpoints are important. First, these interpretive breakpoints should not be used with other methods without extensive testing. Although the M27-A methodology is not the only possible way to determine a minimum inhibitory concentration (MIC), use of the M27-A interpretive breakpoints with other methods should be approached with caution—even small methodological variations may produce results that are not correctly interpreted by means of these breakpoints. Second, these interpretive breakpoints place a strong emphasis on interpretation in the context of the delivered dose of the azole antifungal agent. The novel category S-DD (susceptible-dose/delivery dependent) indicates that maximization of dosage and bioavailability are critical to successful therapy. In the case of fluconazole, both human and animal data suggest that S-DD isolates may be treated successfully with 12 mg/kg/d [16, 18]. Although trials to date have not used this method, administration of twice the usual daily dose of fluconazole as a loading dose is a pharmacologically rational way to achieve more rapidly the higher blood levels of steady state. In the case of itraconazole, oral absorption is somewhat unpredictable, and achievement of blood levels of $\geqslant 0.5$ μg/mL (as determined by high-performance liquid chromatography) appears important to successful therapy. Finally, these breakpoints have been developed on the basis of data from 2 groups of infected patients: patients with oropharyngeal and esophageal candidiasis (fluconazole and itraconazole [16]) and patients with invasive candidiasis (mostly nonneutropenic patients with candidemia; fluconazole only [16, 17]). Although these limitations are similar to those of interpretive breakpoints for antibacterial agents, and although extrapolation of these results to other settings appears rational on the basis of data from in vivo therapy models, it is still prudent to consider the limitations of the data when making use of the breakpoints. Pharmacology, safety, published reports, and drug interactions must be considered along with susceptibility during selection of a therapy. For example, most isolates of *Candida* are susceptible to itraconazole, but this agent until recently lacked a parenteral preparation and has been studied only as a treatment for mucosal infections.

Reliable and convincing interpretive breakpoints are not yet available for amphotericin B. The NCCLS M27-A methodology does not reliably identify amphotericin B–resistant isolates [3]. Variations of the M27-A method using different media [3], agar-based MIC methods [8, 19, 20], and measurements of minimum fungicidal concentrations [7] appear to enhance detection of resistant isolates. Although these methods are as yet insufficiently standardized to permit routine use, several generalizations are becoming apparent. First, amphotericin B resistance appears uncommon among isolates of *C. albicans, Candida tropicalis,* and *Candida parapsilosis.* Second, isolates of *Candida lusitaniae* most often demonstrate readily detectable and clinically apparent amphotericin B resistance. However, the exact frequency of this event is uncertain, and not all isolates are resistant [7, 12]. Third, a growing body of data suggests that a nontrivial proportion of the isolates of *C. glabrata* and *C. krusei* may be resistant to amphotericin B [7, 9–11]. Importantly, delivery of additional amphotericin B by use of a lipid-based preparation of amphotericin B may not always be adequate to overcome this resistance [11]. Also, because of in vitro effects of the lipid, tests for susceptibility to amphotericin B should always use amphotericin B itself rather than a lipid-associated form of the drug [21]. Unfortunately, the true frequency and clinical relevance of these observations is uncertain. Most rational current therapy for infections due to these species (*C. lusitaniae, C. glabrata,* and *C. krusei*) thus revolves around (a) awareness of the possibility of true microbiological resistance among the species and (b) judicious and cautious use of susceptibility testing. When amphotericin B deoxycholate is

used to treat infections due to *C. glabrata* or *C. krusei,* doses approaching or exceeding 1 mg/kg/d may be needed, especially in profoundly immunocompromised hosts.

Lipid-based amphotericin B preparations. Three lipid formulations of amphotericin B have been developed and approved for use in humans: amphotericin B lipid complex (ABLC, Abelcet; Liposome, Princeton, NJ), amphotericin B colloidal dispersion (ABCD, Amphotec; Sequus Pharmaceuticals, Menlo Park, CA), and liposomal amphotericin B (AmBisome; Vestar, San Dimas, CA). Only ABLC and liposomal amphotericin B have been approved for use in proven candidiasis. These approvals are for second-line therapy of patients who are intolerant of or refractory to therapy with conventional amphotericin B (defined in one study using ABLC [22] as failure of ⩾500 mg amphotericin B, initial renal insufficiency (creatinine ⩾2.5 mg/dL or creatinine clearance <25 mL/min), a significant rise in creatinine (to 2.5 mg/dL for adults or 1.5 mg/dL for children), or severe acute administration-related toxicity). Patients with invasive candidiasis also have been treated successfully with ABCD [23, 24]. Both in vivo and clinical studies indicate that these compounds are less toxic but as effective as amphotericin B when used in appropriate dosages [25, 26]. Nevertheless, their higher cost and the paucity of randomized trials in proven invasive candidiasis limit their frontline use in these infections. These agents dramatically alter the pharmacology of amphotericin B, and the full implications of these changes are not yet known [27, 28].

Thus, with regard to *Candida* infections, amphotericin B deoxycholate remains the standard agent. As discussed in the overview for these guidelines [29], a lipid-associated amphotericin B would be appropriate in patients who are refractory to this therapy, intolerant of this therapy, or at high risk of being intolerant of this approach (e.g., high risk for nephrotoxicity due to pre-existing renal dysfunction or continued concomitant use of another nephrotoxic agent, such as *cis*-platinum, an aminoglycoside, or cyclosporine). These agents are licensed at 5 mg/kg/d (ABLC), 3–6 mg/kg/d (ABCD), and 3–5 mg/kg/d (liposomal amphotericin B). The optimal dose of these compounds for serious *Candida* infections is unclear, and the agents appear generally equipotent. Doses of 3–5 mg/kg would appear suitable for treatment of most serious candidal infections.

Appropriate dosages for pediatric patients. The topic of antifungal pharmacology in children and infants has been reviewed in detail [30]. Data on dosing of the antifungal agents in pediatric patients are limited. Amphotericin B appears to have similar kinetics in neonates and adults [31]. A phase 1–2 study of ABLC at 2–5 mg/kg/d in the treatment of hepatosplenic candidiasis in children found that the area under the curve and the maximal concentration of drug were similar to those of adults and that steady state appeared to be achieved by ~7 days [32]. A phase 1–2 study of liposomal amphotericin B is currently in progress. Because clearance of flucytosine is directly proportional to glomerular filtration rate, very-low–birth weight infants may accumulate high plasma concentrations because of immature renal function [33]. The pharmacokinetics of fluconazole varies with age [34–37]. Because of its more rapid clearance in children (plasma half-life, ~14 h) [34], fluconazole should be administered at 6 mg/kg q12h for treatment of life-threatening infections. In comparison with the volume of distribution seen in adults (0.7 L/kg), neonates may have a 2–3 fold higher volume of distribution that falls to <1 L/kg by 3 months of age. In comparison with the half-life of fluconazole in adults (30 h), neonates have a prolonged half-life of 55–90 h [38]. Despite this prolonged half-life, once-daily dosing seems prudent in low– and very-low–birth weight infants who are being treated for disseminated candidiasis. A dosage of 5 mg/kg/d has been used safely and successfully in this population [39]. Itraconazole cyclodextrin oral solution given at 5 mg/kg/d to infants and children was found to provide potentially therapeutic concentrations in plasma [40]. The levels were, however, substantially lower than those attained in adult patients with cancer, particularly in children aged 6 months to 2 years. A recent study of 2.5 mg/kg/d and 5 mg/kg/d of cyclodextrin itraconazole in HIV-infected children did document efficacy in the treatment of oropharyngeal candidiasis in pediatric patients [41]. The newly licensed iv formulation of itraconazole has not been studied in the pediatric setting.

These practice guidelines provide recommendations for treatment of various forms of candidiasis. For each form, we specify objectives; treatment options; outcomes of treatment; evidence; values; benefits, harms, and costs; and key recommendations.

Candidemia and Acute Hematogenously Disseminated Candidiasis

Objective. To resolve signs and symptoms of associated sepsis, to sterilize the bloodstream and any clinically evident sites of hematogenous dissemination, and to treat occult sites of hematogenous dissemination.

Treatment options. Intravenous amphotericin B, iv or oral fluconazole. Flucytosine could be considered in combination with one of these agents for more-severe infections (CIII; see article by Sobel [42] for definitions of categories reflecting the strength of each recommendation for or against its use and grades relecting the quality of evidence on which recommendations are based). Removal of existing intravascular catheters is desirable if feasible, especially in nonneutropenic patients (BII).

(Note added in proof: An iv preparation of itraconazole in hydroxy-propyl-β-cyclodextrin has recently been licensed. This formulation is given at 200 mg q12h for 4 doses (2 d) followed by 200 mg/d and was licensed on the basis of evidence that this dosing regimen achieves adequate blood levels more rapidly and with less patient-to-patient variability than the oral preparations of the drug [43–45]. Formal studies of iv itraconazole

as therapy for invasive candidiasis are in progress but as yet are incomplete. The discussion of therapeutic options for this and all other forms of candidiasis will thus generally not address iv itraconazole.)

Outcomes. Clearance of bloodstream and other clinically evident sites of infection, symptomatic improvement, absence of retinal findings of *Candida* endophthalmitis, adequate follow-up to ensure that late-appearing symptoms of focal hematogenous spread are not overlooked.

Evidence. *Candida* bloodstream infections are frequently associated with clinical evidence of the sepsis syndrome and high associated attributable mortality [46]. In addition, hematogenous seeding may compromise the function of one or more organs. Two recent large randomized studies [47, 48] and 2 recent large observational studies [49, 50] have demonstrated that fluconazole at 400 mg/d and amphotericin B at 0.5–0.6 mg/kg/d are similarly effective as therapy. The randomized studies are limited to nonneutropenic patients, whereas the observational studies provide data suggesting that fluconazole and amphotericin B are similarly effective in neutropenic patients. ABLC and liposomal amphotericin B are indicated for patients intolerant of or refractory to conventional antifungal therapy (defined in one study using ABLC [22] as failure of ⩾500 mg amphotericin B, initial renal insufficiency [creatinine ⩾2.5 mg/dL or creatinine clearance <25 mL/min], a significant increase in creatinine [to 2.5 mg/dL for adults or 1.5 mg/dL for children], or severe acute administration-related toxicity). Open-label therapy of candidemia with ABCD at 2–6 mg/kg/d has been successful [24]. In a randomized trial, ABLC at 5 mg/kg/d was found to be equivalent to 0.6–1.0 mg/kg/d amphotericin B as therapy for nosocomial candidiasis (mostly candidemia) [51]. Candidemia due to *C. parapsilosis* has increased in frequency among pediatric populations and appears to be associated with a lower mortality rate than other species of *Candida* [52–54]

Values. Without adequate therapy, endophthalmitis, endocarditis, and other severe disseminated forms of candidiasis may complicate candidemia. Given the potential severity of the clinical syndrome, it is important that the initial empirical choice be adequate to address the most likely species and their associated susceptibility to the various agents

Benefits, harms, and costs. Effective therapy is potentially lifesaving. Amphotericin B–induced nephrotoxicity can complicate management of critically ill patients.

Key recommendations. If feasible, initial nonmedical management should include removal of all existing central venous catheters (BII). The evidence for this recommendation is strongest in the nonneutropenic patient population [50, 55]. 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 contribution of gut versus catheter as the primary source of fungemia [49, 50]. An exception is made for fungemia due to *C. parapsilosis,* which is very frequently associated with catheters (AII) [49].

Choice of medical therapy depends on both the clinical status of the patient and the physician's knowledge of the species and/or antifungal susceptibility of the infecting isolate. In stable patients who have not recently received azole therapy, most experts would initiate therapy with fluconazole at ⩾6 mg/kg/d (i.e., 400 mg/d in a 70-kg patient) [56]. In the clinically unstable patient infected with an isolate of unknown species, fluconazole has been used successfully, but amphotericin B at ⩾0.7 mg/kg/d is preferred by some authorities [56] because of its broader spectrum (table 1). Neonates with disseminated candidiasis are usually treated with amphotericin B because of its low toxicity and because of the lack of experience with other agents in this population. Antifungal susceptibility can be broadly predicted once the isolate has been identified to the species level (see the section on Susceptibility and Drug Dosing in the Introduction, above). *C. albicans, C. tropicalis,* and *C. parapsilosis* may be treated with either amphotericin B at 0.6 mg/kg/d or fluconazole at 6 mg/kg/d (AI). Because *C. glabrata* often has reduced susceptibility to both azoles and amphotericin B, opinions on best empirical therapy are divided. Although some patients have been treated successfully with fluconazole at 6 mg/kg/d, most authorities recommend amphotericin B at ⩾0.7 mg/kg/d as initial therapy (BIII). Fluconazole at 12 mg/kg/d (800 mg/d in a 70-kg patient) may also be suitable, particularly in less–critically ill patients (BIII). If the infecting isolate is known or likely to be *C. krusei,* available data suggest that amphotericin B at 1.0 mg/kg/d is preferred (BIII). Many but not all isolates of *C. lusitaniae* are resistant to amphotericin B; thus, fluconazole at 6 mg/kg/d is the preferred therapy for this species (BIII). Issues related to selection and dosage of the lipid amphotericin preparations are discussed in the section Lipid-Based Amphotericin B Preparations in the Introduction, above. As discussed in the section Susceptibility Testing and Drug Dosing (in the Introduction, above), susceptibility testing of the infecting isolate is a useful adjunct to species identification during selection of a therapeutic approach, since it can be used to identify isolates that are unlikely to respond to fluconazole (AII) or amphotericin B (BII) table 2) [16]. For candidemia, therapy should be continued for 2 weeks after the last positive blood culture and resolution of signs and symptoms of infection (AIII). Amphotericin B may be switched to fluconazole (iv or po) for

Table 2. Interpretive breakpoints for isolates of *Candida.*

Drug	Minimum inhibitory concentration, μg/mL		
	S	S-DD or I	R
Fluconazole	⩽8	S-DD, 16–32	>32
Itraconazole	⩽0.125	S-DD, 0.25–0.5	>0.5
Flucytosine	⩽4	I, 8–16	>16

NOTE. Shown are the breakpoints proposed for use with the reference broth susceptibility testing method [3] for *Candida* [16]. Isolates of *Candida krusei* are assumed to be intrinsically resistant to fluconazole, and breakpoints for these isolates do not apply. I, intermediate; R, resistant; S, susceptible; S-DD, susceptible-dose dependent (the category S-DD is discussed in the section Susceptibility Testing and Drug Dosing, in the Introduction).

completion of therapy (BIII). The duration of therapy for patients with evidence of visceral spread is discussed elsewhere. As discussed elsewhere [57], patients who are neutropenic at the time of developing candidemia should receive a recombinant cytokine that accelerates recovery from neutropenia (G-CSF or GM-CSF).

Empirical Therapy for Suspected Disseminated Candidiasis in Febrile Nonneutropenic Patients

Objective. To treat early occult *Candida* infection.

Treatment options. Intravenous amphotericin B or iv or oral fluconazole.

Outcomes. Reduction in fever and prevention of development of overt candidal bloodstream infection and the complications of hematogenously disseminated candidiasis.

Evidence. Although *Candida* is now the fourth most common bloodstream isolate and is the most common invasive fungal infection in critically ill nonneutropenic patients, accurate early diagnostic tools for invasive candidiasis are lacking. Colonization by *Candida* of multiple nonsterile sites, prolonged use of antibacterial antibiotics, central venous catheters, hyperalimentation, surgery (especially surgery that transects the gut wall), and prolonged ICU stay have all been linked to increased risk of invasive candidiasis [58–60]. Although empirical therapy is intuitively attractive, compelling data defining appropriate subsets of patients for such therapy are lacking.

Values. Prevention of clinically evident invasive candidiasis could potentially reduce morbidity and mortality.

Benefits, harms, and costs. Given the ill-defined nature of this syndrome, preference is often given to therapies with lesser toxicity. Widespread use of inappropriate antifungal therapy may have deleterious epidemiological consequences, including selection of resistant organisms.

Key recommendations. Appropriate use of antifungal therapy in this setting has not been defined. If therapy is given, its use should be limited to patients with (a) *Candida* colonization (preferably at multiple sites [58]), (b) multiple other risk factors, and (c) absence of any other uncorrected causes of fever (CIII).

Empirical Antifungal Therapy for Neutropenic Patients with Prolonged Fever Despite Antibacterial Therapy

Objective. To treat early occult fungal infection.

Treatment options. Empirical therapy should address both yeast and mold infections. Until recently, amphotericin B was the only sufficiently broad-spectrum agent available in a reliable parenteral form. Itraconazole has an adequate antifungal spectrum of activity and may represent a suitable alternative therapy [61]. However, extensive data with it in this setting are not yet available, and its proper role for empirical antifungal therapy remains to be determined. If used, initiation of therapy with the iv formulation is appropriate, as the bioavailability of the current oral formulations of itraconazole (including the cyclodextrin solution) is unpredictable [62, 63]. Fluconazole is often inappropriate because of both prior fluconazole therapy and its limited spectrum.

Outcomes. Resolution of fever and prevention of development of clinically overt infection

Evidence. Randomized prospective clinical trials have demonstrated that neutropenic patients with persistent fever despite broad-spectrum antimicrobial therapy have an ~20% risk of developing an overt invasive fungal infection [64, 65]. Empirical antifungal therapy reduces the frequency of development of clinically overt invasive fungal infection in this high-risk population [64–66].

Values. Early antifungal therapy is more likely to succeed in neutropenic patients. Advanced infection is associated with high morbidity and mortality.

Benefits, harms, and costs. Early treatment of fungal infections should reduce fungal infection–associated morbidity.

Key recommendations. Therapy is appropriate in neutropenic patients who have persistent unexplained fever despite 4–6 days of appropriate antibacterial therapy. Once begun, therapy is continued until resolution of neutropenia. Amphotericin B at 0.5–0.7 mg/kg/d has traditionally been the preferred agent (AII). When compared with amphotericin B at 0.6 mg/kg/d (median dose), liposomal amphotericin B (AmBisome) at 3 mg/kg/d (median dose) has been shown to have similar overall clinical efficacy in the primary analysis. In secondary analyses, liposomal amphotericin B showed superior safety and tolerance and a decreased rate of documented breakthrough fungal infections, particularly in bone-marrow transplant recipients (AI) [67].

Chronic Disseminated Candidiasis (Hepatosplenic Candidiasis)

Objective. To eradicate foci of chronic disseminated candidiasis.

Treatment options. Intravenous amphotericin B, iv or oral fluconazole. Flucytosine could be considered in combination with 1 of these agents for more-refractory infections.

Outcomes. Resolution of clinical signs and symptoms of infection, resolution of radiographic findings of visceral involvement

Evidence. Open-label and observational studies have evaluated the utility of amphotericin B [68, 69], lipid-associated amphotericin B [32], and fluconazole [70, 71].

Values. This syndrome is not acutely life-threatening but does require prolonged therapy to produce a cure. Thus, importance is placed on use of a convenient and nontoxic long-term regimen.

Benefits, harms, and costs. Amphotericin B, although efficacious, requires iv therapy. Fluconazole can be given orally.

Key recommendations. Fluconazole at 6 mg/kg/d is gen-

erally preferred in stable patients (BIII). Amphotericin B at 0.6–0.7 mg/kg/d may be used in acutely ill patients or patients with refractory disease. Some but not all experts recommend an initial 1- to 2-week course of amphotericin B for all patients, followed by a prolonged course of fluconazole [56]. 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 bone marrow/stem cell transplantation. Treatment of chronic disseminated candidiasis in these cases continues throughout chemotherapy [69].

Disseminated Cutaneous Neonatal Candidiasis

Objective. To treat infants with disseminated cutaneous neonatal candidiasis (also known as congenital candidiasis) who are at high risk for developing acute disseminated candidiasis.

Treatment options. In healthy, normal birth weight, term infants, therapy of the primary cutaneous disease with topical agents is generally appropriate. In patients at risk for acute bloodstream or visceral dissemination, therapies used for acute disseminated candidiasis are appropriate.

Outcomes. The neonatal candidiasis syndrome is a unique syndrome in which widespread dermatitis due to *Candida* is seen in neonates. This syndrome is thought to be secondary to contamination of the amniotic fluid, and, in healthy, term infants, this process is usually limited to the skin and resolves with topical therapy [72]. However, in premature or low–birth weight neonates or infants with prolonged rupture of membranes, the cutaneous process may become invasive and thus produce acute disseminated candidiasis [73].

Evidence. Essentially all data are derived from small case series and individual reports. Most reports have been limited to use of amphotericin B.

Values. If not anticipated and treated, development of acute disseminated candidiasis can be lethal.

Benefits, harms, and costs. Amphotericin B is well tolerated in neonates. Fluconazole has not been as well studied. In particular, the pharmacology of fluconazole varies with neonatal age, making rational dosing somewhat difficult [31, 35, 36].

Key recommendations Premature neonates, low–birth weight neonates, or infants with prolonged rupture of membranes who demonstrate the clinical findings of disseminated neonatal cutaneous candidiasis should be considered for systemic therapy. Amphotericin B at 0.5–1 mg/kg/d for a total dose of 10–25 mg/kg is generally used (BIII). Fluconazole may be used as a second-line agent (BIII; dosing issues for the azole antifungals for children are discussed in the section Appropriate Dosages for Pediatric Patients, in the Introduction, above).

Urinary Candidiasis

Objective. To eradicate signs and symptoms associated with parenchymal infection of the urinary collecting system. In selected patients, such therapy might reduce the risk of ascending or disseminated infection.

Treatment options. Fluconazole (oral or iv), amphotericin B (iv), or flucytosine (oral). Amphotericin B bladder irrigation fails to treat disease above the level of the bladder.

Outcomes. Clearance of the urine.

Evidence. Urinary candidiasis includes an ill-defined group of syndromes [74]. The most common risk factors for candiduria include urinary tract instrumentation, recent antibiotic therapy, and advanced age [75]. *Candida* is now the most frequently isolated organism from the urine of patients in surgical intensive care units. In most patients, isolation of *Candida* represents only colonization and is a benign event. In candiduric individuals, Foley catheter change alone rarely results in elimination of candiduria (<20%); however, discontinuation of the catheter alone may result in eradication of candiduria in almost 40% of patients [76] (BIII). A recently completed placebo-controlled trial found that fluconazole at 200 mg/d for 14 d hastened the time to a negative urine culture, but that 2 weeks after the end of therapy the frequency of a negative urine culture was the same in both treatment groups (~60% for catheterized patients and ~73% for noncatheterized patients) [76]. In other patients, candiduria may be the source of subsequent dissemination (e.g., a patient with obstructive uropathy) [77] or a marker of acute hematogenous dissemination [74]. These concerns are especially applicable to neutropenic patients, patients without current or recent instrumentation of the urinary tract, and low–birth weight infants. Data on the outcome of therapy are limited by the heterogeneity of the underlying diseases and the lack of clear definitions.

Values. Therapy of asymptomatic candiduria in the non-neutropenic catheterized patient has never been shown to be of value. Candiduria in neutropenic patients, critically-ill patients in intensive care units, low–birth weight infants, and transplant recipients may be a clue to disseminated candidiasis.

Benefits, harms, and costs. Therapy of appropriately selected patients may reduce the risk of ascending and/or hematogenously disseminated disease. Therapy of persistently febrile patients who have candiduria but who lack evidence for infections at other sites may treat occult disseminated candidiasis. Inappropriate therapy may select for resistant organisms.

Key recommendations. Asymptomatic candiduria rarely requires therapy (DIII). Candiduria may, however, be the only microbiological documentation of disseminated candidiasis. Candiduria should be treated in symptomatic patients, neutropenic patients, low–birth weight infants, patients with renal allografts, and patients who will undergo urologic manipulations (BIII). However, as with any other complicated urinary tract infection, short courses of therapy are not recommended and therapy for 7–14 days is more likely to be successful. Re-

moval of urinary tract instruments, including stents and Foley catheters, is often helpful. If complete removal is not possible, placement of new materials may be beneficial. Therapy with fluconazole at 200 mg/d for 7–14 days has been used, as have courses of amphotericin B at widely ranging doses (0.3–1.0 mg/kg/d for 1–7 days) [78] (BII). In the absence of renal insufficiency, oral flucytosine at 25 mg/kg/q.i.d. may be valuable in eradicating candiduria, especially in patients with urologic infection due to non-*albicans Candida* species (CIII). However, emergence of resistance to flucytosine may occur rapidly when this compound is used as a single agent [79]. Bladder irrigation or wash with amphotericin B (50-200 μg/mL) may transiently clear funguria [80] but is rarely indicated (CIII) except as a diagnostic localizing tool [81]. Even with apparently successful local or systemic antifungal therapy, relapse is frequent and the likelihood of relapse is increased by continued use of a urinary catheter. Persistent candiduria in immunocompromised patients warrants ultrasound or CT scan of the kidney (CIII).

Candidal Pneumonia

Objective. To eradicate infection and prevent loss of pulmonary reserve.

Treatment options. Intravenous amphotericin B or fluconazole.

Outcomes. Clearance of local sites of infection along with any associated sites of systemic infection.

Evidence. Observational reports and case series have shown that proven *Candida* pneumonia is associated with high mortality in patients with malignancies [82]. No convincing data for any particular form of therapy exist.

Values. *Candida* pneumonia appears to exist in 2 forms. First, after aspiration of *Candida*-laden oropharyngeal material, primary pneumonia due to *Candida* will rarely develop [82–84]. Second, and more common, hematogenously disseminated candidiasis produces pulmonary lesions along with involvement of multiple other organs. Although often entertained as a diagnostic possibility in immunocompromised patients, firm diagnosis of these entities is elusive and requires histopathological confirmation. Finally, benign colonization of the airway with *Candida* and/or contamination of the respiratory secretions with oropharyngeal material is much more common than either of the 2 forms of true *Candida* pneumonia. Thus, diagnoses of *Candida* pneumonia that are based solely on microbiological data will often be incorrect [85] (BIII). The diagnostic difficulty is further confounded by the frequent presence of *Candida* infection at other sites in these patients.

Benefits, harms, and costs. Injudicious use of antifungal therapy in patients with tracheobronchial colonization or oropharyngeal contamination of respiratory secretions may lead to selection of resistant organisms. Definitive diagnosis of *Candida* pneumonia requires histopathological confirmation.

Key recommendations. Reported therapy of patients with primary *Candida* pneumonia has generally used amphotericin B (BIII). In cases of secondary pneumonia related to hematogenously disseminated infection, therapy directed at disseminated candidiasis rather than *Candida* pneumonia in particular is indicated (see the section Candidemia and Acute Hematogenously Disseminated Candidiasis, above).

Laryngeal Candidiasis

Objective. To treat symptoms and signs of laryngeal infection and to prevent airway obstruction.

Treatment options. Intravenous amphotericin B, oral or iv fluconazole.

Outcomes. Early clinical detection and documentation, preferably by otolaryngologist-directed fiberoptic laryngoscopy or indirect laryngoscopy, demonstrates localization of lesions, allows assessment of airway patency, permits acquisition of cultures, and enables rapid initiation of antifungal therapy. Impending airway obstruction is managed by endotracheal intubation. Successful medical therapy resolves laryngeal stridor, prevents airway obstruction, and reduces the risk of aspiration of inflammatory debris–infected *Candida.*

Evidence. The available data are based on small series and individual case reports [86–88]. Most data on therapy have been limited to amphotericin B.

Values. If not diagnosed and treated promptly, airway obstruction and potentially respiratory arrest may ensue.

Benefits, harms, and costs. Given the severe morbidity and potential mortality, rapid clinical and otolaryngologic diagnosis and prompt initiation of therapy are important and outweigh any adverse effects of antifungal therapy.

Key recommendations. The majority of the experience has been with amphotericin B at 0.7–1.0 mg/kg/day (BIII). Fluconazole may be appropriate for treatment of infection due to susceptible isolates once symptoms and signs are improving. There is a paucity of experience with fluconazole as primary therapy.

Candidal Osteomyelitis (Including Mediastinitis) and Arthritis

Objective. To relieve symptoms and eradicate infection.

Treatment options. Following open or arthroscopic debridement or drainage, both iv amphotericin B and oral or iv fluconazole have been used.

Outcomes. Eradication of infection and symptoms, return of joint function

Evidence. Multiple observational studies have been reported, most of which have employed iv amphotericin B as the primary therapy, sometimes followed by a course of an azole antifungal agent. Only a small number of reports have described initial therapy with an azole.

Values. Untreated disease leads to crippling disability.

Benefits, harms, and costs. The high morbidity of untreated disease makes aggressive surgical and medical therapy appropriate. Surgical debridement, biopsy, and drainage also serve to provide more-definitive histopathological and microbiological documentation before initiation of the prolonged therapy required for this class of infection.

Key recommendations. Osteomyelitis is best treated initially with surgical debridement of the affected area. Courses of amphotericin B (0.5–1 mg/kg/d for 6–10 weeks) have been successfully employed [89, 90]. Fluconazole has been used successfully as initial therapy of susceptible isolates in 3 reports in which doses of 6 mg/kg/d for 6–12 months were effective [91–93]. Taken together, these data suggest that an initial course of amphotericin B for 2–3 weeks followed by fluconazole for a total duration of therapy of 6–12 months would be rational. (BIII)

Definitive information on therapy of native joint arthritis is limited. Adequate and/or repeated drainage is often critical to successful therapy [94]. In particular, management of *Candida* arthritis of the hip requires open drainage. Case reports have documented cures with iv amphotericin B and fluconazole when used in conjunction with adequate drainage. As parenteral administration of these agents produces substantial synovial fluid levels, the utility of intra-articular therapy is unclear and its use is discouraged. Prolonged courses of therapy similar to those used for osteomyelitis appear to be required (CIII).

Involvement of a prosthetic joint with *Candida* arthritis requires resection arthroplasty [95]. Subsequent medical therapy mirrors that for native joint disease, and a new prosthesis may be inserted after successful clearance of the local infection as defined by lack of return of symptoms after cessation of therapy (CIII).

On the basis of a small number of cases, *Candida* mediastinitis may be treated with surgical debridement followed by either amphotericin B or fluconazole [96] (CIII). 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, appear appropriate (CIII).

Candidal Infections of the Gallbladder, Pancreas, and Peritoneum

Objective. To eradicate *Candida* infection and prevent recurrence of infection.

Treatment options. Intravenous amphotericin B, oral or iv fluconazole.

Outcomes. Clearance of infection as judged by resolution of local signs and symptoms along with sterilization of cultures.

Evidence. Therapy of *Candida* infection of the pancreas and biliary tree has been described in case reports and small series. Successful therapy with either amphotericin B or fluconazole has been described.

Values. There are 2 major syndromes of peritoneal candidiasis. In disease related to peritoneal dialysis catheters, catheter removal is often required for successful therapy [97–100]. Both amphotericin B and fluconazole have been used successfully [98–100].

Candida peritonitis may also develop in association with surgical or traumatic injury to the gut wall. In this setting, *Candida* is usually part of a polymicrobial infection, and case series suggest that therapy directed toward *Candida* is indicated, particularly when *Candida* is isolated as part of a complex infection or in an immunocompromised patient (as opposed to isolation in association with promptly repaired acute traumatic injury) [101–103]. A recent small but placebo-controlled trial demonstrated that fluconazole at 400 mg/d reduced the likelihood of developing symptomatic *Candida* peritonitis in surgical patients with recurrent gastrointestinal perforations or anastomotic leakage [104].

Benefits, harms, and costs. Routine treatment of *Candida* isolated after prompt and definitive repair of an acutely perforated viscus in otherwise healthy patients without signs of sepsis is probably not needed and could lead to selection of resistant organisms.

Key recommendations. Disease of the biliary tree should be treated by mechanical restoration of functional drainage combined with therapy with either amphotericin B or fluconazole (CIII). Both agents achieve therapeutic biliary concentrations, and local instillation is not needed [105]. Catheter-associated peritonitis is treated with catheter removal and systemic therapy with amphotericin B or fluconazole (BIII). 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 (CIII). 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, 2–3 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 (BI).

Candidal Endocarditis, Pericarditis, and Suppurative Phlebitis

Objective. To eradicate *Candida* infection and prevent recurrence of infection.

Treatment options. Intravenous amphotericin B, oral or iv fluconazole. Oral flucytosine may be added to amphotericin B.

Outcomes. Clearance of infection as judged by sterilization of the bloodstream and preservation of cardiac function.

Evidence. All data are derived from individual case reports and case series.

Values. Combined medical and surgical therapy is key for

all of these syndromes. Removal of infected valves, resection of infected peripheral veins, and debridement of infected pericardial tissue are almost always required for successful therapy [106, 107]. Suppurative phlebitis of the central veins has responded to prolonged medical therapy with amphotericin B [108–110]. Suppurative peripheral thrombophlebitis responds to surgical resection of the infected vein and antifungal therapy with amphotericin B or fluconazole [111]. The utility of anticoagulation as part of such purely medical therapy is uncertain.

Benefits, harms, and costs. These infections are associated with high morbidity and mortality [112], thus justifying aggressive medical and surgical therapy.

Key recommendations. 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 (BIII). Primary therapy with fluconazole has been successfully used on occasion, but fluconazole is more often employed as part of a long-term suppressive regimen. Total duration of therapy should be ⩾6 weeks after surgery, but possibly much longer (CIII). *Candida* endocarditis has a propensity for relapse and requires careful follow-up for ⩾1 year [113]. If valve replacement is not possible, life-long suppressive therapy with fluconazole may be used (CIII) [114, 115].

Candida. Pericarditis requires surgical debridement and/or resection, depending on the extent of the disease [116]. Cardiac tamponade is possible and may require an emergency procedure to relieve hemodynamic compromise. Prolonged therapy with amphotericin B [107] or fluconazole should then be used (CIII).

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 (BIII). Following vein resection, the general approach to this disease is similar to that for other forms of acute hematogenous dissemination and the possibility of other sites of disease spread should always be entertained.

Candidal Meningitis

Objective. To achieve rapid clearance of the infection and return of normal neurological function.

Treatment options. Intravenous amphotericin B or fluconazole. Flucytosine may be added to amphotericin B.

Outcomes. Sterilization of the cerebrospinal fluid often precedes eradication of parenchymal infection. Thus, therapy should be continued until normalization of all cerebrospinal fluid analyses, normalization of radiological findings, and stabilization of neurological function.

Evidence. Most data are based on observational reports of use of amphotericin B. Liposomal amphotericin B was used successfully in 5 of 6 cases of *Candida* meningitis in newborn infants [117]. Because of its ability to penetrate the blood-brain barrier, flucytosine has often been added [118]. Fluconazole with flucytosine was used successfully in 1 case [119].

Values. *Candida* meningitis often follows candidemia in newborn infants and has a high propensity for relapse. Untreated disease is lethal.

Benefits, harms, and costs. Because of the high morbidity and mortality of this infection, very aggressive therapy is warranted.

Key recommendations. Amphotericin B (0.7–1 mg/kg/d) plus flucytosine 25 mg/kg qid is appropriate as initial therapy (BIII). The flucytosine dose should be adjusted to produce serum levels of 40–60 μg/mL [79]. Very few data exist on fluconazole—it has been used as both followup therapy and suppressive therapy. Because of the tendency for this disease to relapse, therapy should be given for a minimum of 4 weeks after resolution of all signs and symptoms related to the infection.

Therapy of *Candida* meningitis associated with neurosurgical procedures should include removal of prosthetic material and treatment of *Candida* meningitis as noted above [120].

Candidal Endophthalmitis

Objective. To resolve sight-threatening lesions.

Treatment options. Intravenous amphotericin B has most often been used [121, 122]. Recent reports have also examined oral or iv fluconazole [123]. Flucytosine has been used in combination with amphotericin B. Vitrectomy may at times be sight-saving. The role of intravitreal antifungal therapy is unclear.

Outcomes. Preservation of sight.

Evidence. Individual case reports and small case series have demonstrated that amphotericin B, amphotericin B plus flucytosine, and fluconazole may be effective. The role of vitrectomy remains uncertain, but a recent study of *C. albicans* endophthalmitis in injection drug abusers suggested that the combination of early vitrectomy plus antifungal therapy was most likely to lead to a good outcome with preservation of vision [124]. Of additional interest is a recent National Eye Institute–sponsored randomized study of therapy of bacterial endophthalmitis in which initial pars plana vitrectomy with intravitreal antibiotics followed by retap and reinjection of eyes that did poorly after 36–60 h was compared with a strategy of initial anterior chamber and vitreous tap and/or biopsy [125]. For patients who presented with visual acuity of light perception only, initial vitrectomy tripled the chance of achieving 20/40 or better acuity.

Values. Early aggressive therapy is critically important. Delays in diagnosis may lead to loss of vision.

Benefits, harms, and costs. Given the devastating consequences of loss of sight, aggressive therapy is warranted.

Key recommendations. All patients with candidemia should have a dilated retinal examination, preferably by an ophthal-

mologist (AII). The preponderance of clinical experience is with amphotericin B, often combined with flucytosine (BIII). Recent data also support the use of fluconazole for this indication, particularly as followup therapy (BIII). The maximal doses appropriate for other forms of invasive candidiasis would be appropriate and should maximize penetration into the eye. Therapy should be continued until complete resolution of visible disease or convincing stabilization. Courses of 6–12 weeks of therapy are typically required.

A diagnostic vitreal aspirate is generally recommended in patients presenting with endophthalmitis of unknown origin. If fungal elements are observed, some ophthalmologists instill intravitreal amphotericin B. The utility of vitrectomy has not been systematically studied. Extrapolation from a study of bacterial endophthalmitis [125] and from anecdotal experiences with *Candida* endophthalmitis [124], initial vitrectomy and intravitreal amphotericin B may be most appropriate for patients with substantial visual loss.

Nongenital Mucocutaneous Candidiasis

Oropharyngeal and Esophageal Candidiasis

Objective. To eliminate signs and symptoms of the disease and to prevent recurrences.

Treatment options. Oropharyngeal candidiasis: topical azoles (clotrimazole troches), oral azoles (fluconazole, ketoconazole, or itraconazole), or oral polyenes (such as nystatin or amphotericin B suspension) are usually effective. For refractory or recurrent infections, orally administered and absorbed azoles (ketoconazole, fluconazole, or itraconazole solution), amphotericin B suspension, or iv amphotericin B (only in azole-refractory infections) may be used.

Esophageal candidiasis: topical therapy is ineffective. Azoles (fluconazole or itraconazole solution) or iv amphotericin B (necessary only in azole-refractory infections) are effective. In patients who are unable to swallow, parenteral therapy should be used.

Outcomes. Resolution of disease without recurrence.

Evidence. Oropharyngeal candidiasis: multiple randomized prospective studies have been performed in both AIDS patients and patients with cancer. Most patients will respond initially to topical therapy [126–128]. In HIV-infected patients, symptomatic relapses may occur sooner with topical therapy than with fluconazole [126], and resistance may develop with either regimen [129]. Fluconazole is superior to ketoconazole [130]. Itraconazole capsules are equivalent in efficacy to ketoconazole [131]. Itraconazole solution is better absorbed than the capsules [132], and it is comparable in efficacy to fluconazole [133, 134]. Topical effects of oral solutions may be as important as effects due to absorption [135, 136]. Recurrent infections typically occur in patients with immune suppression, especially AIDS. Chronic suppressive therapy with fluconazole is effective in the prevention of oropharyngeal candidiasis in both AIDS [18, 137] and cancer patients [138]. In one study, chronic suppressive therapy in HIV-infected patients reduced the relapse rate relative to intermittent therapy and was associated with similar rates of development of microbiological resistance [18]. Oral polyenes, such as amphotericin B or nystatin, are less effective at preventing this infection [139]. Approximately 64% of patients with fluconazole-refractory infections will respond to itraconazole solution [140]. Oral or iv amphotericin B is also effective in some patients [141].

Esophageal candidiasis: much of the information of the microbiology of esophageal candidiasis is extrapolated from studies of oropharyngeal candidiasis. However, it is known that, in patients with either AIDS or esophageal cancer, *C. albicans* remains the most common species isolated when candidal esophagitis is present [142, 143]. The presence of oropharyngeal candidiasis plus symptoms of esophagitis (dysphagia or odynophagia) is predictive of esophageal candidiasis [144]. A therapeutic trial with fluconazole for patients with presumed esophageal candidiasis is a cost-effective alternative to endoscopy; most patients with esophageal candidiasis will have resolution of their symptoms within 7 days after the start of therapy [145]. Fluconazole is superior to ketoconazole, itraconazole capsules, and flucytosine for the treatment of esophageal candidiasis [146–148]. Itraconazole capsules plus flucytosine is as effective as fluconazole [149]. Itraconazole solution has efficacy comparable with that of fluconazole [150]. Up to 80% of patients with fluconazole-refractory infections will respond to itraconazole solution [151]. Intravenous amphotericin B is also effective [152]. In patients with advanced AIDS, recurrent infections are common [153] and chronic suppressive therapy with fluconazole (100 mg/d) is effective in preventing recurrence [154].

Both: the vast majority of infections are caused by *C. albicans*, either alone or in mixed culture [127]. However, symptomatic infections caused by *C. glabrata* and *C. krusei* alone have been described [140]. Azole-refractory infections are associated with prior use of azoles, especially oral fluconazole, and CD4 count $<50/mm^3$ [155]. Antifungal susceptibility testing has been shown to be predictive of clinical response to fluconazole and itraconazole [16]. In HIV-infected patients, use of increasingly active antiretroviral therapy has been associated with both declining rates of carriage of *C. albicans* and reduced frequency of symptomatic episodes of oropharyngeal candidiasis [156].

Values. The symptoms of oropharyngeal and esophageal candidiasis may reduce oral intake of food and liquids and significantly reduce the quality of life.

Benefits, harms, and costs. Maintenance of adequate nutrition and hydration is essential in immunocompromised hosts. Many individuals have asymptomatic oropharyngeal colonization with *Candida* species, and treatment frequently does not result in microbiological cure. Therefore, oropharyngeal fungal cultures are of little benefit. Repeated courses of therapy or the use of suppressive therapy for recurrent infections are major

risk factors for the development of an azole-refractory infection.

Key recommendations. Oropharyngeal candidiasis: initial episodes can be treated with clotrimazole troches (one 10-mg troche 5 times daily) or nystatin (available as a suspension of 100,000 U/mL [4–6 mL q.i.d.] or as flavored 200,000 U pastilles [one or two 4–5 times daily] for 7–14 days) (BII). Oral fluconazole (100 mg/d for 7–14 days orally) is as effective as and in some studies superior to topical therapy (AI). Itraconazole solution (200 mg/d for 7–14 days orally) is as efficacious as fluconazole (AI). Ketoconazole and itraconazole capsules are less effective than fluconazole because of variable absorption (AI). Suppressive therapy is effective for the prevention of recurrent infections (AI), but to reduce the likelihood of development of antifungal resistance, it should be used only if the recurrences are frequent or disabling (IIB). Fluconazole-refractory oropharyngeal candidiasis will respond to itraconazole (≥200 mg/d orally, preferably as the solution) approximately two-thirds of the time (AII). Amphotericin B oral suspension (1 mL q.i.d. of the 100 mg/mL suspension) is sometimes effective in patients who do not respond to itraconazole (BII). Anecdotal responses of refractory disease to fluconazole solution (used in a swish-and-swallow fashion) [136] and chewed itraconazole capsules have also been noted. Intravenous amphotericin B (0.3 mg/kg/d) is usually effective and may be used as a last resort in patients with refractory disease (BII). Denture-related disease may require thorough disinfection of the denture for definitive cure [157, 158].

Esophageal candidiasis: systemic therapy is required for effective treatment of esophageal candidiasis (BII). Although symptoms of esophageal candidiasis may be mimicked by other pathogens, a diagnostic trial of antifungal therapy is often appropriate before endoscopy to search for other causes of esophagitis (BII). A 14–21 day course of either fluconazole (100 mg/d orally) or itraconazole solution (200 mg/d orally) is highly effective (AI). Ketoconazole and itraconazole capsules are less effective than fluconazole because of variable absorption (AI). Suppressive therapy should be used occasionally in patients with disabling recurrent infections (AII). Fluconazole-refractory esophageal candidiasis should be treated with itraconazole solution (≥200 mg/d orally) (AII). Intravenous amphotericin B (0.3–0.7 mg/kg/d as needed to produce a response) may be used in patients with otherwise refractory disease (BII).

Both: antifungal susceptibility testing is not generally needed but can be useful in patients with refractory infection (BII). In patients with AIDS, treatment of the underlying HIV infection with highly active antiretroviral therapy (HAART) is critical for prevention and management of these infections (BII).

Candida Onychomycosis

Although onychomycosis is usually caused by a dermatophyte, infections due to *Candida* species also occur [159]. Topical agents are usually ineffective. For onychomycosis in general, oral therapy with griseofulvin has largely been supplanted by more-effective therapy with oral terbinafine or itraconazole [160]. With respect to *Candida* onychomycosis, terbinafine has only limited and unpredictable in vitro activity [161, 162] and has not demonstrated consistently good activity in clinical trials [163]. Although the number of reported cases is small, therapy with itraconazole does appear to be effective [164, 165]. Therapy with itraconazole (200 mg b.i.d. for a week, repeated monthly for 3–4 months) appears most appropriate (AII).

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 area dry is also important. For paronychia, the most important aspect is drainage.

Chronic Mucocutaneous Candidiasis

The persistent immunological defect of chronic mucocutaneous candidiasis requires a long-term approach that is analogous to that used in AIDS patients with rapidly relapsing oropharyngeal candidiasis. Systemic therapy is needed, and all of the azole antifungal agents (ketoconazole, fluconazole, and itraconazole) have been used successfully [166, 167]. 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 [168, 169].

Genital Candidiasis

Objective. To achieve rapid and complete relief of signs and symptoms of vulvovaginal inflammation and to prevent recurrences.

Treatment options. Topical agents including azoles (all are used for 1–7 days depending on risk classification: clotrimazole [over the counter {OTC}], butoconazole [OTC], miconazole [OTC], tioconazole [OTC], terconazole), nystatin 100,000 U daily × 7–14 d, oral azoles (ketoconazole 500 mg b.i.d. × 5 d (not approved in the United States); itraconazole 200 mg b.i.d. × 1 d or 200 mg q.d. × 3 d (not approved in the United States); fluconazole 150 mg × 1 dose [170]. Boric acid (600 mg in a gelatin capsule, 1 daily per vagina × 14 d) is also effective [171].

Outcomes. Resolution of signs and symptoms of vaginitis in 48–72 h; mycological cure in 4–7 days.

Evidence. Multiple double-blind randomized studies [2, 170].

Values. Highly effective relief of symptoms that are asso-

ciated with substantial morbidity can be achieved promptly with current therapies.

Benefits, harms, and costs. Self-diagnosis of yeast vaginitis is unreliable. Incorrect diagnosis results in overuse of topical antifungal agents with subsequent risk of contact and irritant vulvar dermatitis.

Key recommendations. Vaginal candidiasis may be classified into complicated and uncomplicated forms (table 3) [172]. Uncomplicated vaginitis is seen in 90% of patients and responds readily to short-course oral or topical treatment with any of the therapies listed above, including the single-dose regimens (AI). In contrast, the complicated vaginitis seen in ~10% of patients requires antimycotic therapy for ⩾7 days (BIII). Azole therapy is unreliable for non-*albicans* species of *Candida* (BIII). *C. glabrata* and the other non-*albicans* infections frequently respond to topical boric acid 600 mg/d × 14 days (BII) or topical flucytosine (BII). Azole-resistant *C. albicans* infections are extremely rare [173].

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 orally every week), ketoconazole (100 mg q.d.) [174], itraconazole (100 mg q.o.d.) or daily therapy with any topical azole (AII).

Table 3. Classification of candidal vaginitis.

Feature	Uncomplicated[a]	Complicated[b]
Severity	Mild or moderate	Severe
Frequency	Sporadic	Recurrent
Organism	*Candida albicans*	Non-*albicans* species of *Candida*
Host	Normal	Abnormal (uncontrolled diabetes mellitus)

NOTE. Patients with vaginitis can be classified as having uncomplicated disease (90% of patients) or complicated disease (~10% of patients).

[a] Patients with all of these features are defined as having uncomplicated vaginitis.

[b] Patients with any of these features are defined as having complicated vaginitis [173].

Prophylaxis

HIV-Infected Patients

See the subsection Oropharyngeal and Esophageal Candidiasis in the Nongenital Mucocutaneous Candidiasis section.

Neutropenic Patients

Objective. To prevent development of invasive fungal infections during periods of risk.

Treatment options. Intravenous amphotericin B, iv or oral fluconazole. (Note added in proof: Pending results of ongoing trials, the recently licensed iv form of itraconazole may provide an additional therapeutic option).

Outcomes. Prevention of onset of signs and symptoms of invasive candidiasis.

Evidence. Randomized, prospective, placebo-controlled trials have shown that systemically active antifungal agents can reduce the rate of development of invasive *Candida* infections in high-risk patients. The best data have compared fluconazole at 400 mg/d with placebo in bone-marrow transplant recipients [175, 176]. The utility of other potentially active agents (amphotericin B, itraconazole) may be limited by toxicity or bioavailability.

Values. Prevention of invasive fungal infection would presumably lower morbidity [177]. Observed effects on overall mortality have either been none [176] or beneficial [175], but both studies did demonstrate a reduction in the rate of fungal-associated deaths.

Benefits, harms, and costs. Inappropriate use of prophylaxis in low-risk patient populations could apply epidemiological pressure that could select for resistant organisms.

Key recommendations. Fluconazole at 400 mg/d during the period of neutropenia is warranted in patients who are at significant risk of invasive candidiasis (AI). Such patient groups include selected 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 transplant 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 [178].

Solid-Organ Transplantation

Objective. To prevent development of invasive fungal infections during periods of risk.

Treatment options. Intravenous amphotericin B, iv or oral fluconazole.

Outcomes. Prevention of onset of signs and symptoms of invasive candidiasis.

Evidence. Patients undergoing liver transplantation who have ⩾2 of a group of key risk factors (retransplantation, creatinine of >2.0 mg/dL, choledochojejunostomy, intraoperative use of ⩾40 units of blood products, fungal colonization detected within the first 3 days after transplantation) have been identified as being at high risk for invasive fungal infections, especially invasive candidiasis [179–181]. In prospective randomized studies, amphotericin B deoxycholate (10–20 mg/d), liposomal amphotericin B (AmBisome, 1 mg/kg/d), and fluconazole (400 mg/d) may have reduced both fungal colonization and the risk of serious *Candida* infections [182–184].

The risk for candidiasis following pancreatic transplantation may be comparable to that following liver transplantation. A recent retrospective review of 445 consecutive pancreatic trans-

plant recipients revealed a 6% frequency of intra-abdominal fungal infections in those who received fluconazole prophylaxis (400 mg/d) for 7 days after transplantation, compared with 10% for those without prophylaxis [185]. There also was significant improvement of 1-year graft survival rate and overall survival in patients who had no infection. Prospective and case-controlled studies will further help to delineate the population of patients at high risk for invasive candidiasis and the potential benefits of fluconazole prophylaxis.

The risk of invasive candidiasis following transplantation of other solid organs appears to be too low to warrant systemic prophylaxis.

Values. Prevention of the significant morbidity associated with invasive candidiasis is warranted.

Benefits, harms, and costs. Injudicious use of prophylaxis in low-risk settings might lead to selection of resistant organisms.

Key recommendations. High-risk liver transplant recipients should receive prophylactic antifungal therapy during the early postoperative period (AI).

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