Guidelines for Treatment of Candidiasis

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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). Throughout this document, treatment recommendations are rated according to the standard scoring scheme used in other IDSA guidelines to illustrate the strength of the supporting evidence and quality of the underlying data (table 1). 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 (table 2). 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 HIV infection), but in other patients, the cause is cryptic (e.g., relapsing vaginitis in a healthy woman). Rational strat-

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Table 1. Infectious Diseases Society of America–United States Public Health Service grading system for rating recommendations in clinical guidelines.

Category, grade	Definition
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
Quality of evidence	
1	Evidence from ⩾1 properly randomized, controlled trial
2	Evidence from ⩾1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
3	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

egies 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.

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 associated with invasive candidiasis [1–5]. This shift is particularly problematic in patients with acute 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 3) [1, 4, 6, 11–17, 20–24], 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 species is now well described among HIV-infected individuals with recurrent oropharyngeal candidiasis and is also reported sporadically in critically ill adults with invasive candidiasis [25] or in healthy adults [26]. For this reason, susceptibility testing for azole resistance is increasingly used to guide the management of candidiasis in patients, especially in situations where there is failure to respond to the initial empirical therapy. 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 next section).

Susceptibility testing and drug dosing. Intensive efforts to develop standardized, reproducible, and clinically relevant susceptibility testing methods for fungi have resulted in the development of the NCCLS M27-A methodology (now updated with the essentially identical M27-A2 methodology) for susceptibility testing of yeasts [27, 28]. Data-driven interpretive breakpoints using this method are available for testing the susceptibility of *Candida* species to fluconazole, itraconazole, and flucytosine [28–31]. Several features of these breakpoints are important. First, these interpretive breakpoints should not be applied to other methods without extensive testing. Although the M27-A2 methodology is not the only possible way to determine an MIC, use of the M27-A2 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 "susceptibility–dose/delivery dependent" (S-DD) indicates that maximization of dosage and bioavailability are critical to successful therapy (table 4). In the case of fluconazole, data for both human beings and animals suggest that S-DD isolates may be treated successfully with a dosage of 12 mg/kg per day [30, 32]. 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 more rapidly achieve higher steady-state blood concentrations. In the case of itraconazole, oral absorption is somewhat unpredictable, and achieving blood levels of ⩾0.5 μg/mL (as determined by high-performance liquid chromatography) appears to be important to successful

Table 2. Summary of treatment guidelines for candidiasis.

Condition	Therapy		Duration	Comments
	Primary	Alternative		
Candidemia				
Nonneutropenic adults	AmB 0.6–1.0 mg/kg per day iv; or Flu 400–800 mg/day iv or po; or Casp[a]	AmB 0.7 mg/kg per day plus Flu 800 mg/day for 4–7 day, then Flu 800 mg/day	14 days after last positive blood culture and resolution of signs and symptoms	Remove all intravascular catheters, if possible
Children	AmB 0.6–1.0 mg/kg per day iv; or Flu 6 mg/kg q12 h iv or po	Casp	14–21 days after resolution of signs and symptoms and negative repeat blood cultures	PK data in children for Casp are not available
Neonates	AmB 0.6–1.0 mg/kg per day iv; or Flu 5–12 mg/kg per day iv	Casp	14–21 days after resolution of signs and symptoms and negative repeat blood cultures	PK data in neonates for Casp are not available
Neutropenia	AmB 0.7–1.0 mg/kg per day iv; or LFAmB 3.0–6.0 mg/kg per day; or Casp	Flu 6–12 mg/kg per day iv or po	14 days after last positive blood cultures and resolution of signs and symptoms and resolved neutropenia	Removal of all intravascular catheters is controversial in neutropenic patients; gastrointestinal source is common
Chronic disseminated candidiasis	AmB 0.6–0.7 mg/kg per day or LFAmB 3–5 mg/kg per day	Flu 6 mg/kg per day or Casp	3–6 months and resolution or calcification of radiologic lesions	Flu may be given after 1–2 weeks of AmB therapy if clinically stable or improved
Disseminated cutaneous neonatal candidiasis	AmB 0.5–1.0 mg/kg per day	Flu 6–12 mg/kg per day	14–21 days after clinical improvement	Treat as for neonatal candidemia
Urinary candidiasis	See relevant discussion in text	…	…	…
Osteomyelitis and arthritis	See relevant discussion in text	…	…	…
Intra-abdominal candidiasis	See relevant discussion in text	…	…	…
Endocarditis	AmB 0.6–1.0 mg/kg per day iv; or LFAmB 3.0–6.0 mg/kg per day plus 5-FC 25–37.5 mg/kg po q.i.d.	Flu 6–12 mg/kg per day po or iv; Casp	At least 6 weeks after valve replacement	Valve replacement is almost always necessary; long-term suppression with Flu has been successful for patients who cannot undergo valve replacement
Suppurative phlebitis	See relevant discussion in text	…	…	…
Meningitis	See relevant discussion in text	…	…	…
Endophthalmitis	AmB 0.7–1.0 mg/kg per day iv; or Flu 6–12 mg/kg per day po or iv	…	6–12 weeks after surgery	Vitrectomy is usually performed when vitreitis is present.
Mucocutaneous candidiasis		…	…	…
Oropharyngeal	Clo 10 mg 5 times/day; or Nys 200,000–400,000 U 5 times/day; or Flu 100–200 mg/day po	Itr 200 mg/day po; or AmB 1 mL q.i.d. po;[b] or AmB >0.3 mg/kg per day iv;[b] or Casp 50 mg/day iv[b]	7–14 days after clinical improvement	Long-term suppression with Flu (200 mg/day) in patients with AIDS and a history of OPC is acceptable and does not appear to lead to Flu resistance
Esophageal	Flu 100–200 mg/day po or iv; or Itr 200 mg/day	Vor 4 mg/kg b.i.d. iv or po;[c] or AmB 0.3–.7 mg/kg per day iv;[c] or Casp[c]	14–21 days after clinical improvement	IV therapy is necessary for patients with severe and/or refractory esophagitis
Genital candidiasis	See relevant discussion in text	…	…	…

NOTE. AmB, conventional deoxycholate amphotericin B; Casp, caspofungin; Clo, clotrimazole; Flu, fluconazole; Itr, itraconazole; LF, lipid formulation; Nys, nystatin; PK, pharmacological; Vor, voriconazole; 5-FC, 5-flucytosine.

[a] Casp dosing in adults consists of 70-mg loading dose followed by 50 mg iv.

[b] AmB iv and po and Casp iv are indicated for refractory or pharyngeal candidiasis.

[c] Vor, AmB, and Casp are indicated for severe and/or refractory esophageal candidiasis.

therapy. Finally, these breakpoints were developed on the basis of data from 2 groups of infected adult patients: patients with oropharyngeal and esophageal candidiasis (for fluconazole and itraconazole) and patients with invasive candidiasis (mostly nonneutropenic patients with candidemia; for fluconazole only) [30] and are supported by subsequent reports [27, 31, 33, 34]. Although these limitations are similar to those of interpretive breakpoints for antibacterial agents [27], and ex-

Table 3. General patterns of susceptibility of *Candida* species.

Candida species	Fluconazole	Itraconazole	Voriconazole[d]	Flucytosine	Amphotericin B	Candins[a]
C. albicans	S	S	S	S	S	S
C. tropicalis	S	S	S	S	S	S
C. parapsilosis	S	S	S	S	S	S (to I?)
C. glabrata	S-DD to R[b]	S-DD to R[c]	S to I[d]	S	S to I[e]	S
C. krusei	R	S-DD to R[c]	S to I[d]	I to R	S to I[e]	S
C. lusitaniae	S	S	S	S	S to R[f]	S

NOTE. Except for amphotericin B, interpretations are based on use of the NCCLS M27-A methodology, and the underlying data were drawn from a variety of sources [1, 6–9, 10]. The data for amphotericin B also include results of studies in which modifications of the M27-A methodology have been used to enhance detection of amphotericin B–resistant isolates [6, 11, 12]. See table 4 for the specific interpretive breakpoints used to construct this table. I, intermediately resistant; R, resistant; S, susceptible; S-DD, susceptible-dose/delivery dependent.

[a] Susceptibility methods for the echinocandin antifungal agents (caspofungin, micafungin, and anidulafungin) are not standardized, and interpretive criteria are not available. The 3 drugs show generally similar susceptibility patterns and therefore are shown as a class. On the basis of this overall pattern of relative MICs [13–16], isolates of *C. parapsilosis* and *C. guilliermondii* tend to have numerically higher MICs than do the other species. However, the significance of this is entirely unknown at present, and clinical responses to invasive disease have been observed with all *Candida* species for caspofungin [17].

[b] On the basis of recent surveys of recent bloodstream isolates [1, 4], 10%–15% of *C. glabrata* isolates are resistant to fluconazole.

[c] In addition, 46%–53% of *C. glabrata* isolates and 31% of *C. krusei* isolates are resistant to itraconazole.

[d] The significance of voriconazole MICs has yet to be established. On the basis of recent surveys [18], *C. glabrata* and *C. krusei* have MICs that are consistently higher than those of the other major species. However, these MICs are generally $\leqslant 1$ μg/mL, these isolates are therefore potentially treatable (on the basis of this compound's achievable blood levels), and successful therapy with isolates of these species has been described [19]. The entry in the table is meant to describe this current lack of information.

[e] On the basis of a combination of in vitro data [4, 11, 20] and in vivo data [21, 22], it appears that a significant proportion of the isolates of *C. glabrata* and *C. krusei* have reduced susceptibility to amphotericin B.

[f] Although not seen in all isolates, amphotericin B resistance is well described for isolates of this species [23, 24].

trapolation of these results to other diagnostic settings appears to be 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, drug interactions, and isolate susceptibility [27] must be considered when selecting a therapy. For example, most isolates of *Candida* are susceptible to itraconazole, but this agent only recently became available as a parenteral preparation and has not been studied intensively for candidiasis, except for treatment of mucosal disease.

Reliable and convincing interpretive breakpoints are not yet available for amphotericin B. The NCCLS M27-A2 methodology does not reliably identify amphotericin B–resistant isolates [6]. Variations of the M27-A2 methodology using different media [6], agar-based MIC methods [12, 35, 36], and measurements of minimum fungicidal concentrations [11] 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 *Candida albicans, Candida tropicalis,* and *C. parapsilosis*. Second, isolates of *Candida lusitaniae* most often demonstrate readily detectable and clinically apparent amphotericin B resistance. Not all isolates are resistant [11, 23, 37], but therapeutic failure of amphotericin B is well documented [38]. 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 [4, 11, 20–22]. Of importance, delivery of additional amphotericin B by use of a lipid-based preparation of amphotericin B may be inadequate to overcome this resistance [22]. Also, because of in vitro effects of the lipid, tests for susceptibility to amphotericin B should always use the deoxycholate rather than the lipid formulation [39]. Unfortunately, the clinical relevance of these observations is uncertain. Most rational current therapy of infections due to these species (*C. lusitaniae, C. glabrata,* and *C. krusei*) thus involves (1) awareness of the possibility of true microbiological resistance among the species and (2) judicious and cautious use of susceptibility testing. When amphotericin B deoxycholate is used to treat infections due to *C. glabrata* or *C. krusei*, doses of at least 1 mg/kg per day may be needed, especially in profoundly immunocompromised hosts.

Meaningful data do not yet exist for other compounds. This includes specifically the newer expanded-spectrum triazoles (voriconazole, posaconazole, and ravuconazole) and the echinocandins (caspofungin, micafungin, and anidulafungin). Although MIC data for these compounds are available for all major *Candida* species (table 3), the interpretation of those MICs in relation to achievable blood levels is uncertain [29]. This is particularly true for the echinocandin antifungal agents.

Practical clinical use of antifungal susceptibility testing. Antifungal susceptibility testing has not achieved the status of

Table 4. Interpretive breakpoints for isolates of *Candida* species.

Drug	MIC range, μg/mL		
	Susceptible	Intermediately susceptible	Resistant
Fluconazole	≤8	16–32 (S-DD[a])	>32
Itraconazole	≤0.125	0.25–0.5 (S-DD[a])	>0.5
Flucytosine	≤4	8–16	>16

NOTE. Shown are the breakpoints proposed for use with the NCCLS M27-A broth susceptibility testing method for *Candida* species [30]. Isolates of *Candida krusei* are assumed to be intrinsically resistant to fluconazole and these breakpoints do not apply.

[a] Susceptible-dose/delivery dependent; see Introduction.

a standard of care and is not widely available, and results of testing may not be available for days. The strongest data to date are for fluconazole, an agent for which the issues of resistance are most compelling. The greatest concern for fluconazole resistance relates to *C. glabrata,* for which rates of resistance as high as 15% have been reported [40]. Testing is most often used in 1 of 2 ways [27]. First, susceptibility is useful in the evaluation of the possible causes of lack of clinical response. Second, the data may be used to support a change in therapy from a parenteral agent of any class to oral fluconazole. This consideration is most relevant when considering outpatient therapy and for treating infections that require protracted therapy (e.g., meningitis, endocarditis, and osteomyelitis).

AVAILABLE DRUGS AND DRUG USE

The rapid pace of antifungal drug development has resulted in the recent licensure of 2 new antifungal drugs (voriconazole and caspofungin), along with the active development of 4 others (ravuconazole, posaconazole, micafungin, and anidulafungin). In addition, new data continue to accumulate for itraconazole and the lipid-associated preparations of amphotericin B. Although all these compounds appear to have significant activity against *Candida* species, the size of the published clinical database for these compounds for treatment of candidiasis is limited. In an effort to integrate these agents into the guidelines, the available data on the newly licensed agents will be summarized here.

Itraconazole. An intravenous preparation of itraconazole in hydroxy-propyl-β-cyclodextrin has been licensed. This formulation is administered at a dosage of 200 mg q12h for a total of 4 doses (i.e., 2 days) followed by 200 mg/day 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 do oral preparations of the drug [41–44]. Itraconazole is well known to be active against mucosal forms of candidiasis (see Nongenital Mucocutaneous Candidiasis, below), but the availability of an intravenous form of itraconazole allows for treatment of invasive disease. Although itraconazole would be expected to have activity broadly similar to that of fluconazole, the 2 compounds have quite different pharmacological properties and clinical activities for other mycoses [45]. Moreover, formal studies of intravenous itraconazole for invasive candidiasis are not available. Therefore, the discussion of therapy for invasive candidiasis will generally not address intravenous itraconazole.

Voriconazole and the newer azole antifungal agents. Voriconazole is available in both oral and parenteral preparations. It is as active as fluconazole against esophageal candidiasis, although it was associated with more adverse events in a recent study [46]. Among 4 pediatric patients who received voriconazole as salvage therapy, candidemia cleared in 2 of 2 patients and disseminated candidiasis resolved in 1 of 2 patients [47]. It is notable that voriconazole appears to have the potential to be active against some fluconazole-resistant isolates. Of 12 HIV-infected subjects with fluconazole-refractory esophageal candidiasis due to *C. albicans,* 7 were cured and the conditions of 3 improved because of treatment with voriconazole [48]. Consistent with its activity against *C. krusei* in a guinea pig model [49], recent experience from open-label protocols reported response in 7 (70%) of 10 patients with invasive disease due to this species [19]. On the basis of these data, voriconazole received an indication in the European Union for "treatment of fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*)." Voriconazole is not currently licensed for this indication in the United States, awaiting an analysis of a recently completed worldwide study of its activity in candidemia.

The in vitro anti-*Candida* activity of the other azoles under active development (posaconazole and ravuconazole) also appears to be good [50]. The available clinical data for posaconazole include reports of successful salvage therapy for invasive candidiasis [51], successful salvage therapy of azole-refractory oropharyngeal candidiasis in HIV-infected individuals [52], and 2 randomized comparisons showing efficacy comparable with that of fluconazole for non–azole-refractory esophageal candidiasis [53, 54]. The available data for ravuconazole include a randomized phase II dose-ranging study showing efficacy comparable with that of fluconazole for non–azole-refractory esophageal candidiasis [55].

Caspofungin and the echinocandin antifungal agents. Caspofungin is the first of the echinocandin antifungal agents to be licensed. As with all of the agents of this class, this agent is only available as a parenteral preparation, and its spectrum is largely limited to *Candida* and *Aspergillus* species. Of particular relevance for use as empirical treatment, the agents of this class do not appear to have significant activity against *Cryptococcus neoformans* or against filamentous fungi other than *Aspergillus* [56].

Caspofungin has been shown to be as effective as both amphotericin B deoxycholate and fluconazole when used as therapy for oropharyngeal and esophageal candidiasis [57–60]. Likewise, Mora-Duarte et al. [17] found that caspofungin (70-mg loading dose followed by 50 mg/day in adults) was equivalent to but better tolerated than was amphotericin B deoxycholate (0.6–1.0 mg/kg per day) for cases of invasive candidiasis (83% of which were candidemia, 10% of which were peritonitis, and 7% of which were miscellaneous cases). Finally, caspofungin was effective in 72% of patients with fluconazole-resistant esophageal candidiasis [61]. This agent appears to be active against all *Candida* species; however, the MICs for some isolates of *C. parapsilosis* and *Candida guilliermondii* are relatively higher. The meaning of these higher MICs is still being investigated, but the data from the aforementioned study by Mora-Duarte et al. [17] hint at their possible clinical relevance [62]. Although *C. parapsilosis* caused only 19% of cases of fungemia in the caspofungin-treated group in that study, it was associated with 42% cases of persistent fungemia. Conversely, the species distribution of cases of persistent fungemia for amphotericin B–treated patients more closely paralleled the distribution of infecting species. It must be emphasized, however, that the total number of cases is very small and that the overall success rates for treatment of infections due to *C. parapsilosis* were similar between the study arms. Thus, these data suggest that echinocandins may be used successfully for treatment of *C. parapsilosis* fungemia but that the physician should be aware of the possibility that this species might respond less readily to this class of agents.

The in vitro activity of the other 2 agents in this category (anidulafungin and micafungin) against *Candida* species appears quite similar to that of caspofungin, and clinical data are expected to support similar patterns of utility. However, available clinical data for these agents are as yet limited to open-label dose-ranging studies of micafungin for treatment of esophageal candidiasis [63–65], open-label studies of anidulafungin for esophageal candidiasis [66], open-label data on micafungin administered to patients with candidemia [67, 68], and a randomized, double-blind comparison of micafungin with fluconazole as prophylaxis during the period of risk for neutropenia following bone marrow transplantation [69].

Amphotericin B deoxycholate and the lipid-associated formulations of amphotericin B. The majority of the experience with amphotericin B is with its classic deoxycholate preparation. However, 3 lipid-associated formulations of amphotericin B have been developed and approved for use in humans: amphotericin B lipid complex (ABLC) (Abelcet; Enzon), amphotericin B colloidal dispersion (ABCD) (Amphotec [in the United States] and Amphocil [elsewhere]; InterMune), and liposomal amphotericin B (AmBisome; Vestar). The names of these compounds, along with the requirement for use of the lipid-associated formulations at much higher doses than the deoxycholate preparation, have led to much confusion. The reader should note carefully that (1) "liposomal amphotericin B" is the name of a specific lipid-associated product, (2) a useful general term for the class is "lipid-associated formulations of amphotericin B," (3) the 3 lipid-associated formulations of amphotericin B have different pharmacological properties and rates of treatment-related adverse events and thus should not be interchanged without careful consideration, (4) the typical intravenous dose for amphotericin B deoxycholate is 0.6–1.0 mg/kg per day, and (e) the typical dosage for the lipid-associated formulations when used for candidiasis is 3–5 mg/kg per day.

In this document, a reference to "intravenous amphotericin B" without a specific dose or other discussion of form should be taken to be a reference to the general use of any of the preparations of amphotericin B, with the understanding that the clinical experience is greatest with amphotericin B deoxycholate for essentially all forms of candidiasis and classes of patients. On the other hand, references to a specific formulation and dosage indicate more-specific data. We are not aware of any forms of candidiasis for which a lipid-associated formulation of amphotericin B is superior to amphotericin B deoxycholate [70], but we are also not aware of any situations in which a lipid-associated formulation would be contraindicated. The only possible exception is urinary candidiasis in which the protection of the kidney afforded by the altered pharmacological properties of the lipid-associated preparations of amphotericin B [71] has the theoretical potential to reduce delivery of amphotericin B and thus slow the pace of response [72]. The relative paucity of organized clinical data does, however, produce uncertainty regarding the optimal dose and duration of therapy with these agents.

Only ABLC and liposomal amphotericin B have been approved for use in proven cases of candidiasis. These approvals are for second-line therapy for patients who are intolerant of or have an infection refractory to therapy with conventional amphotericin B deoxycholate; these circumstances were defined in one study in which ABLC was administered as failure of therapy with amphotericin B deoxycholate ($\geqslant$500 mg), initial renal insufficiency (creatinine level of $\geqslant$2.5 mg/dL or creatinine clearance of $<$25 mL/min), a significant increase in creatinine level (up to 2.5 mg/dL in adults or 1.5 mg/dL in children [73]), or severe, acute, administration-related toxicity. Patients with invasive candidiasis also have been treated successfully with ABCD [74, 75]. Both in vivo and clinical studies indicate that these compounds are less toxic but as effective as amphotericin B deoxycholate when used in appropriate dosages [76, 77]. Nevertheless, their higher cost and the paucity of randomized trials of their efficacy against proven invasive candidiasis limit their front-line use for treatment of these infections. These

agents dramatically alter the pharmacology of amphotericin B, and the full implications of these changes are not yet known [78, 79].

Although amphotericin B deoxycholate has long been the standard agent for treatment of invasive candidiasis, the toxicity of this preparation is increasingly appreciated. Lipid-associated preparations have previously been considered primarily for patients who are intolerant of or have an infection refractory to the deoxycholate preparation. However, data showing that amphotericin B–induced nephrotoxicity may be associated with an up to 6.6-fold increase in mortality [80] makes consideration of initial use of lipid-associated amphotericin B appropriate for individuals who are at high risk of being intolerant of amphotericin B deoxycholate (e.g., those who require prolonged therapy; have preexisting renal dysfunction; or require continued concomitant use of another nephrotoxic agent, such as *cis*-platinum, an aminoglycoside, or cyclosporine [81, 82]). Some authors have also suggested that residence in an intensive care unit (ICU) or an intermediate care unit at the time of initiation of amphotericin B deoxycholate therapy is an additional risk factor for renal failure [82]. Additional work is required to help identify those individuals who can safely tolerate the deoxycholate preparation. The lipid-associated agents are licensed to be administered at the following dosages: ABLC, 5 mg/kg per day; ABCD, 3–6 mg/kg per day; and liposomal amphotericin B, 3–5 mg/kg per day. The optimal dosages of these compounds for serious *Candida* infections is unclear, and the agents appear generally equipotent. Dosages of 3–5 mg/kg would appear suitable for treatment of most serious candidal infections [83, 84].

Appropriate dosages in pediatric patients. The topic of the pharmacological properties of antifungal agents in children and infants has been reviewed in detail [85]. Data on dosing for the antifungal agents in pediatric patients are limited. Amphotericin B deoxycholate appears to have similar kinetics in neonates and adults [86]. A phase I and II study of ABLC (2–5 mg/kg per day) 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 concentration appeared to be achieved after ~7 days of therapy [83]. Anecdotal data suggest that liposomal amphotericin B can be used in neonates [87]. Because clearance of flucytosine is directly proportional to glomerular filtration rate, infants with very low birth weight may accumulate high plasma concentrations because of immature renal function [88].

The pharmacokinetics of fluconazole vary with age [89–92]. Because of its more rapid clearance in children (plasma half-life, ~14 h) [89], fluconazole at a dosage of 6 mg/kg q12h should be administered 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), the half-life in neonates is 55–90 h [93]. Despite this prolonged half-life, once-daily dosing seems prudent in infants with low or very low birth weight who are being treated for disseminated candidiasis. A dosage of 5 mg/kg per day has been used safely and successfully in this population [94].

Itraconazole cyclodextrin oral solution (5 mg/kg per day) administered to infants and children was found to provide potentially therapeutic concentrations in plasma [95]. The levels were, however, substantially lower than those attained in adult patients with cancer, particularly in children aged between 6 months and 2 years. A recent study of itraconazole cyclodextrin oral solution (2.5 mg/kg per day and 5 mg/kg per day) in HIV-infected children documented its efficacy for treating oropharyngeal candidiasis in pediatric patients [96]. The newly licensed intravenous formulation of itraconazole has not been studied in pediatric patients.

The published data on the use of the echinocandins in pediatric or neonatal patients includes small numbers of patients treated with caspofungin and micafungin [97–99]. The data suggest safety and efficacy in such patients.

TREATMENT GUIDELINES OVERVIEW

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. Please see the discussion above with regard to available therapeutic agents: the amount of data on the newest agents (caspofungin and voriconazole) is quite limited, and they will be mentioned below only in reference to selected presentations of candidiasis.

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, intravenous or oral fluconazole, intravenous caspofungin, or the combination of fluconazole plus amphotericin B (with the amphotericin B administered for the first 5–6 days only). Flucytosine could be considered in combination with amphotericin B for more-severe infections (C-III; see table 1 and Sobel [100] for definitions of categories reflecting the strength of each recommendation for or against its use and grades reflecting the quality of evidence on which recommendations are based). Re-

moval of existing intravascular catheters is desirable, if feasible, especially in nonneutropenic patients (B-II).

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

Evidence. *Candida* bloodstream infections are increasingly frequent [101, 102] and are often associated with clinical evidence of sepsis syndrome and high associated attributable mortality [103, 104]. In addition, hematogenous seeding may compromise the function of ⩾1 organ. Two large randomized studies [105, 106] and 2 large observational studies [107, 108] have demonstrated that fluconazole (400 mg/day) and amphotericin B deoxycholate (0.5–0.6 mg/kg per day) are similarly effective as therapy. A large randomized study has demonstrated that caspofungin (70 mg on the first day followed by 50 mg/day) is equivalent to amphotericin B deoxycholate (0.6–1.0 mg/kg per day) for invasive candidiasis (mostly candidemia) [17]. Caspofungin was better tolerated and had a superior response rate in a predefined secondary analysis of evaluable patients. A comparison of fluconazole (800 mg/day) with the combination of fluconazole (800 mg/day) plus amphotericin B deoxycholate (~0.7 mg/kd per day for the first 5–6 days) as therapy for candidemia was confounded by differences in severity of illness between the study groups, but the study found the regimens to be comparable and noted a trend toward better response (based principally on more-effective bloodstream clearance) in the group receiving combination therapy. The randomized studies are largely 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 with infection refractory to conventional antifungal therapy. Open-label therapy of candidemia with ABCD (2–6 mg/kg per day) has been successful [75]. In a randomized trial, ABLC (5 mg/kg per day) was found to be equivalent to amphotericin B deoxycholate (0.6–1.0 mg/kg per day) as therapy for nosocomial candidiasis [109].

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. Candidemia due to *C. parapsilosis* has increased in frequency in pediatric populations and appears to be associated with a lower mortality rate than is candidemia due to other species of *Candida* [110–113]. Candidemia due to *C. glabrata* may be associated with increased mortality in patients with cancer [113]. In neonates, a duration of candidemia of ⩾5 days has been linked to the likelihood of ophthalmologic, renal, and cardiac involvement [114].

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 (B-II). The evidence for this recommendation is strongest for the nonneutropenic patient population [108, 115, 116] and includes data in which catheter removal was associated with reduced mortality in adults [108, 116] and neonates [117]. 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 [107, 108, 118]. An exception is made for fungemia due to *C. parapsilosis,* which is very frequently associated with use of catheters (A-II) [107]. There are, however, no randomized studies of this topic, and a recent exhaustive review [119] clearly demonstrates the limitations of the available data. However, the consensus opinion is that existing central venous catheters should be removed, when feasible [120]. 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 [121–125] 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 [17], 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) [126, 127]. For clinically unstable patients infected with an unspeciated isolate, fluconazole has been used successfully, but many authorities prefer amphotericin B deoxycholate (⩾0.7 mg/kg per day) [126, 127] 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 deoxychol-

ate (0.7 mg/kg per day for the first 5–6 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 [128–131]. 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 [127]. 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) [105, 132], many authorities prefer amphotericin B deoxycholate (≥0.7 mg/kg per day) (B-III) [127]. On the basis of pharmacokinetic predictions [133], 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*)" [19] and could be considered as an alternative choice (B-III). Many, but not all, isolates of *C. lusitaniae* 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) (table 3) [27, 30].

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) [134]. 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 [135], significant immunosuppression [136], 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 [137], 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 [17, 105, 132]. We 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

Objective. To treat early occult *Candida* infection.

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

Outcomes. Reduction in fever and prevention of development of overt candidal bloodstream infection and the complications associated with 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. One study found that candidemia increased the length of hospitalization by 22 days and increased costs by $34,000–$44,000 [138]. Colonization by *Candida* of multiple nonsterile sites,

prolonged use of antibacterial antibiotics, presence of 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 [139–141]. Although empirical therapy is intuitively attractive, colonization does not always imply infection [142], and compelling data that define 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. 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 [139, 143]), (2) multiple other risk factors, and (3) absence of any other uncorrected causes of fever (C-III) [127]. 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

Objective. To treat early occult fungal infection and prevent fungal infection in high-risk patients.

Treatment options. Empirical therapy should address both yeast and mould 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 has been shown to have activity equivalent to that of amphotericin B [144]. If itraconazole is used, initiation of therapy with the intravenous formulation is appropriate, because the bioavailability of the current oral formulations of itraconazole (including the cyclodextrin solution) is unpredictable [145, 146]. Fluconazole may be inappropriate because of prior exposure and its limited spectrum. Voriconazole has been shown to be active in high-risk patients (e.g., allogeneic bone marrow transplant recipients and individuals with relapsed leukemia) for prevention of breakthrough fungal infections [147]. The role of caspofungin and the other echinocandin antifungal agents in the treatment of such patients is uncertain.

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

Evidence. This clinical condition has recently been reviewed, and there is a related guideline from the IDSA [134]. Randomized, prospective clinical trials have demonstrated that neutropenic patients with persistent fever despite receipt of broad-spectrum antimicrobial therapy have an ~20% risk of developing an overt invasive fungal infection [148, 149]. Empirical antifungal therapy reduces the frequency of development of clinically overt invasive fungal infection in this high-risk population [148–150].

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. Antifungal therapy is appropriate in neutropenic patients who have persistent unexplained fever, despite receipt of 4–7 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) [151]. When compared with amphotericin B deoxycholate (mean daily dose, 0.7 mg/kg), itraconazole (200 mg iv q12h for 2 days, 200 mg iv per day for 12 days, and then 400-mg solution po per day) showed similar breakthrough fungal infection rates and mortality but significantly less toxicity (A-I) [144]. Although the data are controversial because some analyses show that voriconazole was, overall, slightly inferior to liposomal amphotericin B [147, 152–155], 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) [156–158] and could be considered as an alternative strategy [127] 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)

Objective. To eradicate foci of chronic disseminated candidiasis.

Treatment options. Intravenous amphotericin B or intra-

venous or oral fluconazole. Flucytosine in combination with one of these agents could be considered for more-refractory infections.

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

Evidence. Open-label and observational studies have evaluated the utility of amphotericin B deoxycholate [159, 160], lipid-associated amphotericin B [83], and fluconazole [161, 162]. A recent case report suggests that caspofungin might have activity against this form of candidiasis [163].

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, must be administered intravenously. Fluconazole can be given orally.

Key recommendations. 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 1–2-week course of amphotericin B for all patients, followed by a prolonged course of fluconazole [126]. 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 [160].

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 infants with normal birth weight, treatment of primary cutaneous candidiasis 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* infection 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 [164]. However, neonates born prematurely or infants with low birth weight and prolonged rupture of cutaneous membranes, the cutaneous process may become invasive and produce acute disseminated candidiasis [165].

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 treated, acute disseminated candidiasis may develop, which can be lethal.

Benefits, harms, and costs. Amphotericin B deoxycholate therapy is generally well tolerated in neonates. Fluconazole has not been as well studied. In particular, the pharmacological properties of fluconazole vary with neonatal age, making the choice of dosage somewhat difficult [86, 90, 91].

Key recommendations. 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 the subsection Appropriate dosages for pediatric patients, in the section Available Drugs and Drug Use (above).

URINARY CANDIDIASIS

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

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

Outcome. Clearance of infection in urine.

Evidence. Urinary candidiasis includes an ill-defined group of syndromes [166]. The most common risk factors for candiduria include urinary tract instrumentation, recent receipt of antibiotic therapy, and advanced age [167]. *Candida* species are now the organisms most frequently isolated from the urine of patients in surgical ICUs. In most patients, isolation of *Candida* species represents only colonization as a benign event. In individuals with candidemia, Foley catheter change alone rarely results in clearance of candiduria (<20%). However, discontinuation of catheter use alone may result in eradication of candiduria in almost 40% of patients [168] (B-III). A recently completed placebo-controlled trial found that fluconazole (200 mg/day for 14 days) hastened the time to negative results of urine culture but that the frequency of negative urine culture

results was the same in both treatment groups 2 weeks after the end of therapy (~60% for catheterized patients and ~73% for noncatheterized patients) [168]. The minimal utility of antifungal therapy against urinary candidiasis is also supported by a recent large observational study [169]. On the other hand, candidal urinary tract infections that were accompanied by radiographic evidence of a bezoar have responded to fluconazole alone [131]. In other patients (e.g., those with obstructive uropathy), candiduria may rarely be the source of subsequent dissemination [170] or a marker of acute hematogenous dissemination [166]. These concerns are especially applicable to neutropenic patients, patients without current or recent placement of medical instruments in the urinary tract, and infants with low birth weight. Data on the outcome of therapy are limited by the heterogeneity of the underlying diseases and by the lack of clear definitions.

Values. Treatment of asymptomatic candiduria in nonneutropenic catheterized patients has never been shown to be of value. Treatment with fluconazole will briefly clear funguria in approximately one-half of treated patients, but recurrence is prompt, selection of resistant *Candida* species is possible, and therapy does not appear to alter clinical outcome [168]. Candiduria in neutropenic patients, critically ill patients in ICUs, infants with low birth weight, and recipients of a transplant may be an indicator of disseminated candidiasis.

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

Key recommendations. Determination of the clinical relevance of candiduria can be difficult [171]. 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 7–14 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 [172] (B-II). In the absence of renal insufficiency, oral flucytosine (25 mg/kg 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 [173]. Bladder irrigation with amphotericin B deoxycholate (50–200 μg/mL) may transiently clear funguria [174] but is rarely indicated (C-III), except as a diagnostic localizing tool [175]. 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 CT of the kidney (C-III).

LOWER RESPIRATORY TRACT CANDIDIASIS (PULMONARY AND LARYNGEAL CANDIDIASIS)

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

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

Outcomes. For pneumonia, treatment clears local sites of infection along with any associated sites of systemic infection. For laryngitis, early clinical detection and documentation by fiberoptic or indirect laryngoscopy demonstrates localization of lesions and assessment of airway patency, permits acquisition of samples for culture, 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.

Evidence. Observational reports and case series have shown that proven *Candida* pneumonia is associated with high mortality among patients with malignancies [176]. No convincing data for any particular form of therapy exist. Data for laryngitis are based on small series and individual case reports [177, 178]. Most cases have been managed with amphotericin B therapy, but milder cases been successfully managed with fluconazole therapy [179, 180].

Values. *Candida* pneumonia seems to exist in 2 forms. Rarely, after aspiration of oropharyngeal material, primary pneumonia due to *Candida* may develop [176, 181,182]. More commonly, hematogenously disseminated candidiasis produces pulmonary lesions, along with involvement of multiple additional organs. Firm diagnosis of these disease entities is elusive and requires histopathological confirmation. Benign colonization of the airway with *Candida* species and/or contamination of the respiratory secretions with oropharyngeal material is much more common than either form of true *Candida* pneumonia. Thus, diagnoses of *Candida* pneumonia that are based solely on microbiological data are often incorrect [183, 184] (B-III).

If not diagnosed and treated promptly, laryngitis may lead to airway obstruction and respiratory arrest.

Benefits, harms, and costs. Injudicious use of antifungal

therapy for 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. In contrast, because of the severe morbidity and potential mortality associated with laryngeal candidiasis, rapid clinical diagnosis and prompt initiation of therapy are important and outweigh any adverse effects of antifungal therapy.

Key recommendations. 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

Objective. To relieve symptoms and eradicate infection.

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

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

Evidence. Multiple observational studies have been reported, most of which have used intravenous amphotericin B as the primary therapy, sometimes followed by a course of treatment with an azole antifungal agent. A few reports have described initial therapy with an azole.

Values. Untreated disease leads to crippling disability.

Benefits, harms, and costs. The high morbidity associated with untreated disease makes aggressive surgical and medical therapy appropriate. The presentation of candidal mediastinitis may be indolent and delayed [185]. 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 with combined surgical debridement of the affected area, especially in the case of vertebral osteomyelitis, and antifungal therapy [186]. Courses of amphotericin B deoxycholate (0.5–1 mg/kg per day for 6–10 weeks) have been used successfully [187–189]. Fluconazole has been used successfully as initial therapy for susceptible isolates in 3 reports in which doses of 6 mg/kg per day for 6–12 months were effective [190–192]. Addition of amphotericin B deoxycholate to bone cement appears safe and may be of value in complicated cases [193]. Taken together, these data suggest that surgical debridement and 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 (B-III).

Definitive information on treatment of native joint arthritis is limited. Adequate drainage is critical to successful therapy [194]. In particular, management of *Candida* arthritis of the hip requires open drainage. Case reports have documented cures with administration of intravenous amphotericin B [195] and with fluconazole when administered in conjunction with adequate drainage. Fluconazole has occasionally been used alone successfully [196]. 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 [197], *Candida* arthritis that involves a prosthetic joint generally requires resection arthroplasty [198]. 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 [185, 199] (III-C). 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

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

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

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

Evidence. Treatment 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 associated with use of catheters for peritoneal dialysis, catheter removal is often required for successful therapy [200–203]. Both systemic amphotericin B and fluconazole therapies have been used successfully [201–203].

Candida peritonitis may also develop in association with

surgical or traumatic injury to the gut wall. Others at risk include patients who recently received chemotherapy for neoplasm or immunosuppressive therapy for transplantation or to those with inflammatory diseases [204]. *Candida* is usually part of a polymicrobial infection, and case series suggest that therapy directed toward *Candida* species is indicated, particularly when *Candida* organisms are isolated as part of a complex infection or in an immunocompromised patient [205–209]. Uncontrolled *Candida* superinfection has been associated with significant mortality in patients with acute necrotizing pancreatitis [210–213]. A recent small but placebo-controlled trial demonstrated that fluconazole (400 mg/day) reduced the likelihood of developing symptomatic *Candida* peritonitis in surgical patients with recurrent gastrointestinal perforations or anastomotic leakage [214].

Benefits, harms, and costs. Routine treatment of *Candida* isolated following 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 (C-III). Both agents achieve therapeutic biliary concentrations, and local instillation is not needed [215]. 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) [200]. 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, 2–3 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

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

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

Outcome. 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. Although the available data are limited [216], combined medical and surgical therapy generally appears to be the key for treatment of candidal endocarditis, pericarditis, and suppurative phlebitis. As emphasized by a report of a native valve that was not sterilized after 160 days of amphotericin B deoxycholate therapy [217], removal of infected valves, resection of infected peripheral veins, and debridement of infected pericardial tissue are almost always required for successful therapy [218, 219]. Suppurative phlebitis of the central veins has responded to prolonged medical therapy with amphotericin B [220–222]. Suppurative peripheral thrombophlebitis responds to surgical resection of the infected vein and antifungal therapy with amphotericin B or fluconazole [223]. The utility of anticoagulation as part of such purely medical therapy is uncertain. Candidal myocarditis is usually part of the syndrome of disseminated candidiasis, is clinically silent, and is treated as part of the therapy of disseminated disease [224]. However, candidal myocarditis may cause complete atrioventricular block, necessitating placement of a pacemaker [225].

Benefits, harms, and costs. These infections are associated with high morbidity and mortality, 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 (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 [227]. If valve replacement is not possible, long-term (possibly life-long) suppressive therapy with fluconazole may be used (C-III) [216, 228, 229]. Successful primary therapy with fluconazole [105] and liposomal amphotericin B [230] has been described for patients with native valve infections.

Candidal pericarditis requires surgical debridement and/or resection, depending on the extent of the disease [231, 232]. Cardiac tamponade is possible and may require an emergency procedure to relieve hemodynamic compromise. Prolonged therapy with amphotericin B [219] 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

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

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

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

Evidence. Most data are based on observational reports of use of amphotericin B deoxycholate [233, 234]. Liposomal amphotericin B was used successfully in 5 of 6 cases of *Candida* meningitis in newborn infants [235]. Because of its ability to penetrate the blood-brain barrier, flucytosine is often added to the course of therapy [236]. Fluconazole with flucytosine was used successfully in 1 case [237].

Values. *Candida* meningitis often follows candidemia in newborn infants [234] and has a high propensity for relapse. Untreated disease is lethal.

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

Key recommendations. 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 40–60 μg/mL [173]. 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 [238, 239].

CANDIDAL ENDOPHTHALMITIS

Objective. To resolve sight-threatening lesions.

Treatment options. Intravenous amphotericin B has been used most often [240, 241]. Recent reports have also examined the efficacy of oral or intravenous fluconazole [242]. Flucytosine has been used in combination with amphotericin B. ABLC (4.5 mg/kg per day for 6 weeks) combined with vitrectomy produced a successful outcome in 1 case [243]. Vitrectomy may sometimes preserve sight. The role of intravitreal antifungal therapy is unclear.

Outcome. 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. PCR-based testing may assist in confirming the diagnosis [244, 245]. The role of vitrectomy in therapy remains uncertain, but a recent study of *C. albicans* endophthalmitis in injection drug users suggested that the combination of early vitrectomy plus antifungal therapy was most likely to lead to a favorable outcome and preservation of vision. [246]. Of additional interest is a recent randomized study of therapy for bacterial endophthalmitis sponsored by the National Eye Institute, in which initial pars plana vitrectomy with use of intravitreal antibiotics followed by a second vitreous tap and reinjection of eyes that had a poor response to therapy after 36–60 h was compared with a strategy of initial anterior chamber and vitreous tap and/or biopsy [247]. For patients in this study who presented with visual acuity of light perception only, initial vitrectomy tripled the chance of achieving acuity of 20/40 or better. These results are supported by anecdotal reports [248].

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

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

Key recommendations. 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 6–12 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 [247] and from anecdotal experiences with *Candida* endophthalmitis [246] 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

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

Treatment options. Topical azoles (clotrimazole troches),

oral azoles (fluconazole, ketoconazole, or itraconazole), or oral polyenes (such as nystatin or oral amphotericin B) are usually effective treatments for oropharyngeal candidiasis. For refractory or recurrent infections, orally administered and absorbed azoles (ketoconazole, fluconazole, or itraconazole solution), amphotericin B suspension, intravenous caspofungin, or intravenous amphotericin B (only for otherwise unresponsive infections) may be used.

For treatment of esophageal candidiasis, topical therapy is ineffective. Azoles (fluconazole, itraconazole solution, or voriconazole), intravenous caspofungin, and intravenous amphotericin B (necessary only for otherwise unresponsive infections) are effective. for patients who are unable to swallow, parenteral therapy should be used.

Outcome. Resolution of disease without recurrence.

Evidence. Multiple randomized prospective studies of oropharyngeal candidiasis have been performed in patients with AIDS and patients with cancer. Most patients respond initially to topical therapy [249–251]. In HIV-infected patients, symptomatic relapses may occur sooner with topical therapy than with fluconazole [249], and resistance may develop with either regimen [252]. Fluconazole is superior to ketoconazole [253]. Itraconazole capsules are equivalent in efficacy to ketoconazole [254]. Itraconazole solution is better absorbed than the capsules [255] and is comparable in efficacy to fluconazole [256–258]. A dosage of itraconazole solution of 2.5 mg/kg twice daily has been recommended as suitable for treating oropharyngeal candidiasis in pediatric patients $\geq$5 years of age [96]. Topical effects of oral solutions may be as important as effects due to absorption [259, 260].

Recurrent infections typically occur in patients with immunosuppression, especially AIDS. Long-term suppressive therapy with fluconazole is effective in the prevention of oropharyngeal candidiasis in patients with AIDS [32, 261–263] and patients with cancer [264]. One study found that a fluconazole dosage of 200 mg/day was superior to that of 400 mg/week for prevention of symptomatic oropharyngeal disease in HIV-infected patients [262]. Long-term suppressive therapy with fluconazole in HIV-infected patients has been shown to reduce the incidence of invasive fungal infections but has no effect on overall survival [32, 261–263]. In a recent large study, long-term suppressive therapy with fluconazole was compared with episodic use of fluconazole in response to symptomatic mucosal disease. Continuous suppressive therapy reduced the relapse rate relative to intermittent therapy and was associated with an increased rate of development of in vitro microbiological resistance, but the frequency of clinically refractory disease was the same for the 2 study groups [263].

Oral polyenes, such as amphotericin B or nystatin, are less effective than fluconazole in preventing this infection [265]. In a placebo-controlled study of HIV-infected patients [266], itraconazole (200 mg/day) was no more effective than placebo for preventing development of mucosal candidiasis. However, a second study found that itraconazole (200 mg/day) was effective as suppressive therapy for up to 6 months after a course of oral or esophageal candidiasis [267]. Between 64% and 80% of patients with fluconazole-refractory infections will respond to treatment with itraconazole solution [268–270]. Intravenous caspofungin is a reasonable alternative [58]. Oral or intravenous amphotericin B is also effective in some patients [271]. Intravenous antifungal therapy can sometimes be avoided by using either IFN-γ or GM-CSF in combination with oral antifungal therapy [272, 273]. However, a second study found that itraconazole (200 mg/day) was effective as suppressive therapy for up to 6 months after an episode of oral or esophageal candidiasis [267]. Itraconazole oral solution has also proven to be effective in cases of fluconazole-refractory oral candidiasis [268–270]. Oral solution of amphotericin B has also been successfully used to treat fluconazole-resistant thrush [271]. Finally, immunomodulation with adjunctive sargramostim (rGM-CSF) [272] and INF-γ [273] have been used for refractory oral candidiasis.

Much of the information on 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 etiological agent [274, 275]. The presence of oropharyngeal candidiasis and symptoms of esophagitis (i.e., dysphagia or odynophagia) is predictive of esophageal candidiasis [276]. 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 [277]. Fluconazole is superior to ketoconazole, itraconazole capsules, and flucytosine for the treatment of esophageal candidiasis [278–280]. Itraconazole capsules plus flucytosine are as effective as fluconazole [281]. The efficacy of itraconazole solution has been shown to comparable to that of fluconazole [282]. Up to 80% of patients with fluconazole-refractory infections will respond to itraconazole solution [269, 270]. Voriconazole (200 mg b.i.d. for a median duration of 14 days) is as efficacious as fluconazole (400 mg loading dose followed by 200 mg/day for a median duration of 15 days) but is associated with a higher rate of treatment-related adverse events [46]. Voriconazole has shown success in treatment of cases of fluconazole-refractory disease [48]. Intravenous amphotericin B is also effective [283]. Caspofungin acetate has shown activity and safety equivalent to fluconazole [58–60], including good responses in individuals with fluconazole-refractory disease [61]. In patients with advanced AIDS, recurrent infections are common [284], and long-term suppressive therapy with flu-

conazole (100 mg/day) is effective in preventing recurrence [285].

In cases of both oropharyngeal and esophageal candidiasis, the vast majority of infections are caused by *C. albicans,* either alone or in mixed infection [250]. However, symptomatic infections caused by *C. glabrata* and *C. krusei* alone have been described [268]. Before the HAART era, azole-refractory infections were associated with prior use of azoles, especially oral fluconazole, and CD4 cell counts of <50 cells/mm^3 [286]. A large randomized trial performed during the HAART era found that the rate of development of clinical fluconazole resistance was the same for individuals receiving long-term suppressive therapy as for those receiving episodic (intermittent) therapy [263], even though the *Candida* isolates recovered from the patients receiving continuous therapy showed reduced susceptibility to fluconazole. Antifungal susceptibility testing has been shown to be predictive of clinical response to fluconazole and itraconazole [30]. In HIV-infected patients, use of HAART has been associated with both declining rates of carriage of *C. albicans* and reduced frequency of symptomatic episodes of oropharyngeal candidiasis [287].

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

Benefits, harms, and costs. Maintenance of adequate nutrition and hydration is essential for 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. Multiple courses of therapy or the use of suppressive therapy for recurrent infection are major risk factors for the development of an azole-refractory infection.

Key recommendations. 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). Suppressive therapy is effective for preventing recurrent infections (A-I). Although it does the increase the rate of development of isolates with an increased fluconazole 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) [260] 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 [288–290].

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 14–21-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 AIDS, treatment of the underlying HIV infection with 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 [291]. Topical agents are usually ineffective [292]. For onychomycosis, oral griseofulvin has largely been replaced by more-effective agents, including oral terbinafine or itraconazole [293]. With respect to *Candida* onychomycosis, terbinafine has only limited and unpredictable in vitro activity [294, 295] and has not demonstrated consistently good activity in clinical trials [296]. Al-

though the number of reported cases is small, therapy with itraconazole does appear to be effective [297, 298]. 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* [299]. 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 [300]. The infant may or may not have signs of mucosal or cutaneous candidiasis. Microbiological studies have found both bacteria [300, 301] and *C. albicans* [300], 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 [302, 303]. Optimal diagnostic criteria and management strategies are not certain, but both topical nystatin and oral fluconazole are safe for infants [304–306] 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 [307]. Systemic therapy is needed, and all of the azole antifungal agents (ketoconazole, fluconazole, and itraconazole) have been used successfully [307, 308]. 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 [309, 310].

GENITAL CANDIDIASIS

Objective. To achieve rapid and complete relief of signs and symptoms of vulvovaginal inflammation, along with prevention of future recurrences.

Treatment options. Topical agents including azoles (all are used for 1–7 days depending on risk classification: over-the-counter [OTC] clotrimazole, OTC butoconazole, OTC miconazole, OTC tioconazole, terconazole), nystatin [100,000 U per day for 7–14 days], oral azoles (ketoconazole [400 mg b.i.d. for 5 days], which is not approved in the United States); itraconazole [200 mg b.i.d. for 1 day, or 200 mg per day for 3 days], which is not approved in the United States; and fluconazole [150 mg]) [311]. Boric acid administered vaginally (600-mg gelatin capsule, once per day for 14 days) is also effective [312].

Outcomes. Resolution of signs and symptoms of vaginitis 48–72 h after initiation of therapy, and mycological cure 4–7 days after initiation of therapy.

Evidence. Multiple double-blind randomized studies [311, 313, 314].

Values. Highly effective relief of symptoms that are associated 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 5) [315]. 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 ~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 [314] (A-I). Azole therapy is unreliable for non-*albicans* species of *Candida* (B-III). Infections with *C. glabrata*, *C. krusei* [316], 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 [317].

Recurrent vaginitis is usually due to azole-susceptible *C. al-*

Table 5. Classification of vaginitis.

Feature	Uncomplicated[a]	Complicated[b]
Severity	Mild or moderate **and**	Severe **or**
Frequency	Sporadic **and**	Recurrent **or**
Organism	*C. albicans* **and**	Non-*albicans* species of *Candida* **or**
Host	Normal	Abnormal (e.g., 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 considered to have uncomplicated vaginitis.

[b] Patients with any of these features are considered to have complicated vaginitis [315].

bicans. 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) [318], ketoconazole (100 mg per day) [319], 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* [320], but the significance of this observation is uncertain.

PROPHYLAXIS

HIV-Infected Patients

See the subsection Oropharyngeal and Esophageal Candidiasis, above.

Neutropenic Patients

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

Treatment options. Intravenous amphotericin B, intravenous or oral fluconazole, intravenous or oral itraconazole, or intravenous micafungin (under investigation; see the subsection Key recommendations, below)

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 superficial and invasive *Candida* infections in high-risk patients [321]. The best data have compared the efficacy of fluconazole (400 mg/day) with that of placebo in bone-marrow transplant recipients [322, 323] and/or patients receiving intensive cytotoxic therapy for acute leukemia [324]. Itraconazole (2.5 mg/kg q12h po) was at least as effective overall as fluconazole (100 mg/day po) and better for prevention of aspergillosis when used as prophylaxis in patients undergoing chemotherapy or bone marrow transplantation for hematological malignancy [325]. Micafungin (50 mg/day iv during the period of neutropenia) reduced the use of empirical amphotericin B, relative to that of fluconazole (400 mg/day), as prophylaxis during the neutropenic phase in bone marrow transplant recipients and was associated with a trend toward lower rates of aspergillosis in micafungin-treated patients [69]. Although continuing prophylaxis for the minimum duration in which the patient is at risk for neutropenia seems appropriate, prophylaxis in bone marrow transplant recipients beyond the period of engraftment was, in one large randomized placebo-controlled study, associated with a significant mortality benefit [322, 326]. The utility of other potentially active agents (e.g., amphotericin B) may be limited by toxicity or bioavailability.

Values. Prevention of invasive fungal infection lowers morbidity and infection-related mortality [321]. Observed effects on overall mortality have either been none [323] or beneficial [322], but these 2 studies did demonstrate a reduction in the rate of fungus-associated deaths.

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

Key recommendations. 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 [69], 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 [327–329]. The optimal duration of prophylaxis is not known but should include the period of risk for neutropenia at a minimum.

Solid-Organ Transplant Recipients

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

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

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

Evidence. Patients undergoing liver transplantation who have $\geq$2 key risk factors (i.e., retransplantation, creatinine level of >2.0 mg/dL, choledochojejunostomy, intraoperative use of $\geq$40 units of blood products, and fungal colonization detected $\leq$2 days previous to and 3 days after transplantation) have been identified as being at high risk for invasive fungal infections, especially invasive candidiasis [330–332]. Conversely, patients without these risk factors are at low risk of invasive candidiasis [333]. Amphotericin B deoxycholate (10–20 mg/day in a retrospective observational study [334]), liposomal amphotericin B (1 mg/kg per day in a prospective randomized study vs. placebo [335]), and fluconazole (100 mg/day in a retrospective observational study [336], 100 mg/day in a prospective randomized study vs. nystatin [337], and 400 mg/day in a prospective randomized study vs. placebo [338]) reduced or trended towards reducing rates of invasive fungal infections.

The largest and most convincing study was by Winston et al. [338], in which fluconazole (400 mg/day) reduced rates of fungal infections (including superficial infections) in a series of unselected patients from 23% to 6% ($P < .001$).

The risk for candidiasis among patients who received a pancreas transplant is probably less than that for those who received a liver transplant. A recent retrospective review of 445 consecutive pancreas transplant recipients revealed a 6% frequency of intra-abdominal fungal infection in those who received fluconazole prophylaxis (400 mg/day) for 7 days after transplantation, compared with 10% for those who did not received prophylaxis [339]. There also was significant improvement in 1-year graft survival rate and overall survival among 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.

Data from a small series of patients undergoing small-bowel transplantation documented 20 invasive fungal infections (16 of which were due to *Candida* species) among 29 transplant recipients [340], which suggests a potential role for prophylaxis. The risk of invasive candidiasis after transplantation of other solid organs appears to be too low to warrant systemic prophylaxis [341].

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

Benefits, harms, and costs. Injudicious use of prophylaxis for patients at low risk might lead to selection of resistant organisms.

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

Patients in ICUs and Other Care Settings

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

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

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

Evidence. This topic has been extensively reviewed, and prophylaxis may be warranted in hospital units that show very high rates of disease despite use of aggressive infection-control procedures [342]. Oral fluconazole (400 mg/day) produced a trend toward decreased rates of invasive candidiasis in selected adult patients in the surgical ICU with an expected ICU stay of at least 3 days [343]. In preterm infants with birth weights of <1000 g, 6 weeks of fluconazole therapy (3 mg/kg iv every third day during the first 2 weeks of life, every other day during the third and fourth weeks of life, and every day during the fifth and sixth weeks of life) reduced the rate of invasive candidiasis from 20% to 0% ($P = .008$) [344]. Fluconazole prophylaxis (400 mg/day) reduced the rate of candidal peritonitis in patients with refractory gastrointestinal perforation [214].

Values. Prevention of the significant morbidity associated with invasive candidiasis is warranted. Candidemia is associated with significant costs [138].

Benefits, harms, and costs. Injudicious use of prophylaxis in low-risk hospital units where the risk of candidiasis is low might lead to selection of resistant organisms.

Key recommendations. 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).

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