Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America

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Guidelines for the management of patients with invasive candidiasis and mucosal candidiasis were prepared by an Expert Panel of the Infectious Diseases Society of America. These updated guidelines replace the previous guidelines published in the 15 January 2004 issue of *Clinical Infectious Diseases* and are intended for use by health care providers who care for patients who either have or are at risk of these infections. Since 2004, several new antifungal agents have become available, and several new studies have been published relating to the treatment of candidemia, other forms of invasive candidiasis, and mucosal disease, including oropharyngeal and esophageal candidiasis. There are also recent prospective data on the prevention of invasive candidiasis in high-risk neonates and adults and on the empiric treatment of suspected invasive candidiasis in adults. This new information is incorporated into this revised document.

EXECUTIVE SUMMARY

There have been several significant changes in the management of candidiasis since the last publication of these guidelines in January 2004. Most of these changes relate to the appropriate use of echinocandins and expanded spectrum azoles in the management of candidemia, other forms of invasive candidiasis, and mucosal candidiasis. For some of the less common forms of invasive candidiasis (e.g., chronic disseminated candidiasis, osteomyelitis, and CNS disease), there are few new treatment data since 2004, with only anecdotal experience, case reports, or small series providing some evidence to support new approaches to therapy. Each section of the Guideline begins with a specific clinical question and is followed by numbered recommendations and a summary of the most-relevant evidence in support of the recommendations. The most significant changes and/or additions to existing recommendations are described below in the Executive Summary. The remaining topics are discussed in greater detail in the main body of the guidelines.

Candidemia in Nonneutropenic Patients

- Fluconazole (loading dose of 800 mg [12 mg/kg], then 400 mg [6 mg/kg] daily) or an echinocandin (caspofungin: loading dose of 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose of 200 mg, then 100 mg daily) is recommended as initial therapy for most adult patients (A-I). The Expert Panel favors an echinocandin for patients with moderately severe to severe illness or

Received 21 November 2008; accepted 24 November 2008; electronically published 29 January 2009.

These guidelines were developed and issued on behalf of the Infectious Diseases Society of America.

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Clinical Infectious Diseases 2009; 48:503–35

1058-4838/2009/4805-0001$15.00
DOI: 10.1086/596757

for patients who have had recent azole exposure (A-III). Fluconazole is recommended for patients who are less critically ill and who have had no recent azole exposure (A-III). The same therapeutic approach is advised for children, with attention to differences in dosing regimens.

- Transition from an echinocandin to fluconazole is recommended for patients who have isolates that are likely to be susceptible to fluconazole (e.g.,*Candida albicans*) and who are clinically stable (A-II).
- For infection due to *Candida glabrata,* an echinocandin is preferred (B-III). Transition to fluconazole or voriconazole therapy is not recommended without confirmation of isolate susceptibility (B-III). For patients who have initially received fluconazole or voriconazole, are clinically improved, and whose follow-up culture results are negative, continuing use of an azole to completion of therapy is reasonable (B-III).
- For infection due to *Candida parapsilosis,* treatment with fluconazole is recommended (B-III). For patients who have initially received an echinocandin, are clinically improved, and whose follow-up culture results are negative, continuing use of an echinocandin is reasonable (B-III).
- Amphotericin B deoxycholate (AmB-d) administered at a dosage of 0.5–1.0 mg/kg daily or a lipid formulation of AmB (LFAmB) administered at a dosage of 3–5 mg/kg daily are alternatives if there is intolerance to or limited availability of other antifungals (A-I). Transition from AmB-d or LFAmB to fluconazole is recommended for patients who have isolates that are likely to be susceptible to fluconazole (e.g., *C. albicans*) and who are clinically stable (A-I).
- Voriconazole administered at a dosage of 400 mg (6 mg/kg) twice daily for 2 doses and then 200 mg (3mg/kg) twice daily thereafter is effective for candidemia (A-I), but it offers little advantage over fluconazole and is recommended as step-down oral therapy for selected cases of candidiasis due to *Candida krusei* or voriconazole-susceptible *C. glabrata* (B-III).
- The recommended duration of therapy for candidemia without obvious metastatic complications is for 2 weeks after documented clearance of *Candida* from the bloodstream and resolution of symptoms attributable to candidemia (A-III).
- Intravenous catheter removal is strongly recommended for nonneutropenic patients with candidemia (A-II).

Candidemia in Neutropenic Patients

- An echinocandin (caspofungin: loading dose of 70 mg, then 50 mg daily; micafungin: 100 mg daily [A-II]; anidulafungin: loading dose of 200 mg, then 100 mg daily [A-III]) or LFAmB (3–5 mg/kg daily [A-II]) is recommended for most patients.
- For patients who are less critically ill and who have no recent azole exposure, fluconazole (loading dose of 800 mg [12 mg/kg], then 400 mg [6 mg/kg] daily) is a reasonable alternative (B-III). Voriconazole can be used in situations in which additional mold coverage is desired (B-III).
- For infections due to *C. glabrata,* an echinocandin is preferred (B-III). LFAmB is an effective but less attractive alternative (B-III). For patients who were already receiving voriconazole or fluconazole, are clinically improved, and whose follow-up culture results are negative, continuing use of the azole to completion of therapy is reasonable (B-III).
- For infections due to *C. parapsilosis*, fluconazole or LFAmB is preferred as initial therapy (B-III). If the patient is receiving an echinocandin, is clinically stable, and follow-up culture results are negative, continuing the echinocandin until completion of therapy is reasonable. For infections due to *C. krusei*, an echinocandin, LFAmB, or voriconazole is recommended (B-III).
- Recommended duration of therapy for candidemia without persistent fungemia or metastatic complications is for 2 weeks after documented clearance of *Candida* from the bloodstream, resolution of symptoms attributable to candidemia, and resolution of neutropenia (A-III).
- Intravenous catheter removal should be considered (B-III).

Empirical Treatment for Suspected Invasive Candidiasis in Nonneutropenic Patients

- Empirical therapy for suspected candidiasis in nonneutropenic patients is similar to that for proven candidiasis. Fluconazole (loading dose of 800 mg [12mg/kg], then 400 mg [6 mg/kg] daily), caspofungin (loading dose of 70 mg, then 50 mg daily), anidulafungin (loading dose of 200 mg, then 100 mg daily), or micafungin (100 mg daily) is recommended as initial therapy (B-III). An echinocandin is preferred for patients who have had recent azole exposure, whose illness is moderately severe or severe, or who are at high risk of infection due to *C. glabrata* or *C. krusei* (B-III).
- AmB-d (0.5–1.0 mg/kg daily) or LFAmB (3–5 mg/kg daily) are alternatives if there is intolerance to other antifungals or limited availability of other antifungals (B-III).
- Empirical antifungal therapy should be considered for critically ill patients with risk factors for invasive candidiasis and no other known cause of fever, and it should be based on clinical assessment of risk factors, serologic markers for invasive candidiasis, and/or culture data from nonsterile sites (B-III).

Empirical Treatment for Suspected Invasive Candidiasis in Neutropenic Patients

- LFAmB (3–5 mg/kg daily), caspofungin (loading dose of 70 mg, then 50 mg daily) (A-I), or voriconazole (6 mg/kg administered intravenously twice daily for 2 doses, then 3 mg/kg twice daily) are recommended (B-I).
- Fluconazole (loading dose of 800 mg [12 mg/kg], then 400 mg [6 mg/kg] daily) and itraconazole (200 mg [3mg/kg] twice daily) are alternative agents (B-I).
- AmB-d is an effective alternative, but there is a higher risk

of toxicity with this formulation than with LFAmB (A-I).

- Azoles should not be used for empirical therapy in patients who have received an azole for prophylaxis (B-II).

Treatment for Neonatal Candidiasis

- AmB-d (1 mg/kg daily) is recommended for neonates with disseminated candidiasis (A-II). If urinary tract involvement is excluded, LFAmB (3–5 mg/kg daily) can be used (B-II). Fluconazole (12 mg/kg daily) is a reasonable alternative (B-II). The recommended length of therapy is 3 weeks (B-II).
- A lumbar puncture and a dilated retinal examination, preferably by an ophthalmologist, are recommended in neonates with sterile body fluid and/or urine cultures positive for *Candida* species (B-III). Imaging of the genitourinary tract, liver, and spleen should be performed if the results of sterile body fluid cultures are persistently positive (B-III).
- Echinocandins should be used with caution and are generally limited to situations in which resistance or toxicity precludes the use of fluconazole or AmB-d (B-III).
- Intravascular catheter removal is strongly recommended (A-II).
- In nurseries with high rates of invasive candidiasis, fluconazole prophylaxis may be considered in neonates whose birth weight is <1000 g (A-I). Antifungal drug resistance, drug-related toxicity, and neurodevelopmental outcomes should be observed (A-III).

Antifungal Prophylaxis for Solid-Organ Transplant Recipients, Patients Hospitalized in Intensive Care Units (ICUs), Neutropenic Patients receiving Chemotherapy, and Stem Cell Transplant Recipients at Risk of Candidiasis

- For solid-organ transplant recipients, fluconazole (200–400 mg [3–6 mg/kg] daily) or liposomal AmB (L-AmB) (1–2 mg/kg daily for 7–14 days) is recommended as postoperative antifungal prophylaxis for liver (A-I), pancreas (B-II), and small bowel (B-III) transplant recipients at high risk of candidiasis.
- For patients hospitalized in the ICU, fluconazole (400 mg [6 mg/kg] daily) is recommended for high-risk patients in adult units that have a high incidence of invasive candidiasis (B-I).
- For patients with chemotherapy-induced neutropenia, fluconazole (400 mg [6 mg/kg} daily) (A-I), posaconazole (200 mg 3 times daily) (A-I), or caspofungin (50 mg daily) (B-II) is recommended during induction chemotherapy for the duration of neutropenia. Oral itraconazole (200 mg twice daily) is an effective alternative (A-1), but it offers little advantage over other agents and is less well tolerated.
- For stem cell transplant recipients with neutropenia, fluconazole (400 mg [6 mg/kg] daily), posaconazole (200 mg 3 times daily), or micafungin (50 mg daily) is recommended during the period of risk of neutropenia (A-I).

INTRODUCTION

Candida species are the most common cause of invasive fungal infections in humans, producing infections that range from non–life-threatening mucocutaneous disorders to invasive disease that can involve any organ. Invasive candidiasis is largely a disease of medical progress, reflecting the tremendous advances in health care technology over the past several decades [1–5]. The most frequently implicated risk factors include the use of broad-spectrum antibacterial agents, use of central venous catheters, receipt of parenteral nutrition, receipt of renal replacement therapy by patients in ICUs, neutropenia, use of implantable prosthetic devices, and receipt of immunosuppressive agents (including glucocorticosteroids, chemotherapeutic agents, and immunomodulators) [2–7]. Candidemia is the fourth most common cause of nosocomial bloodstream infections in the United States and in much of the developed world [5, 8–10]. Invasive candidiasis has a significant impact on patient outcomes, and it has been estimated that the attributable mortality of invasive candidiasis is as high as 47% [11], although many authorities estimate the attributable mortality to be 15%–25% for adults and 10%–15% for neonates and children [12, 13]. The estimated additional cost of each episode of invasive candidiasis in hospitalized adults is ~$40,000 [1, 13].

The Expert Panel addressed the following clinical questions:

I. What is the treatment of candidemia in nonneutropenic patients?

II. What is the treatment of candidemia in neutropenic patients?

III. What is the empirical treatment for suspected invasive candidiasis in nonneutropenic patients?

IV. What is the empirical treatment for suspected invasive candidiasis in neutropenic patients?

V. What is the treatment for urinary tract infections due to *Candida* species?

VI. What is the treatment for vulvovaginal candidiais?

VII. What is the treatment for chronic disseminated candidiasis?

VIII. What is the treatment for osteoarticular infections due to *Candida* species?

IX. What is the treatment for CNS candidiasis in adults?

X. What is the treatment for *Candida* endophthalmitis?

XI. What is the treatment for infections of the cardiovascular system due to *Candida* species?

XII. What is the treatment for neonatal candidiasis?

XIII. What is the significance of *Candida* species isolated from respiratory secretions?

XIV. What is the treatment for nongenital mucocutaneous candidiasis?

Table 1. Infectious Diseases Society of America–US Public Health Service Grading System for ranking recommendations in clinical guidelines.

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for or against use
B	Moderate evidence to support a recommendation for or against use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from ⩾1 properly randomized, controlled trial
II	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
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

NOTE. Adapted from Canadian Task Force on the Periodic Health Examination [15].

XV. Should antifungal prophylaxis be used for solid-organ transplant recipients, ICU patients, neutropenic patients receiving chemotherapy, and stem cell transplant recipients at risk of candidiasis?

PRACTICE GUIDELINES

Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances [14]. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation [14].

UPDATE METHODOLOGY

Panel Composition

The Infectious Diseases Society of America (IDSA) Standards and Practice Guidelines Committee (SPGC) convened experts in the management of patients with candidiasis. The specialties of the members of the Expert Panel are listed at the end of the text.

Literature Review and Analysis

For the 2009 update, the Expert Panel completed the review and analysis of data published since 2004. Computerized literature searches of the English-language literature using PubMed were performed.

Process Overview

In evaluating the evidence regarding the management of candidiasis, the Expert Panel followed a process used in the development of other IDSA guidelines. The process included a systematic weighting of the quality of the evidence and the grade of recommendation (table 1) [15].

Consensus Development on the Basis of Evidence

The Expert Panel met in person on 1 occasion and via teleconference 11 times to discuss the questions to be addressed, to make writing assignments, and to deliberate on the recommendations. All members of the Expert Panel participated in the preparation and review of the draft guidelines. Feedback from external peer reviews was obtained. The guidelines were reviewed and approved by the IDSA SPGC and the IDSA Board of Directors prior to dissemination. A summary of the recommendations is included in table 2.

Guidelines and Conflict of Interest

All members of the Expert Panel complied with the IDSA policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel were provided with the IDSA's conflict of interest disclosure statement and were asked to identify ties to companies developing products that might be affected by promulgation of the guidelines. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Expert Panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. Potential conflicts of interest are listed in the Acknowledgments section.

Revision Dates

At annual intervals, the Expert Panel Chair, the SPGC liaison advisor, and the Chair of the SPGC will determine the need for revisions to the guidelines on the basis of an examination

of current literature. If necessary, the entire Expert Panel will be reconvened to discuss potential changes. When appropriate, the Expert Panel will recommend revision of the guidelines to the SPGC and the IDSA Board for review and approval.

LITERATURE REVIEW

Pharmacologic Considerations of Therapy for Candidiasis

Systemic antifungal agents shown to be effective for the treatment of candidiasis comprise 4 major categories: the polyenes (AmB-d, L-AmB, AmB lipid complex [ABLC], and AmB colloidal dispersion [ABCD]), the triazoles (fluconazole, itraconazole, voriconazole, and posaconazole), the echinocandins (caspofungin, anidulafungin, and micafungin), and flucytosine. Clinicians should become familiar with strategies to optimize efficacy through an understanding of relevant pharmacokinetic properties.

Amphotericin B (AmB)

Most experience with AmB is with the deoxycholate preparation (AmB-d). Three LFAmBs have been developed and approved for use in humans: ABLC, ABCD, and L-AmB. These agents possess the same spectrum of activity as AmB-d. The 3 LFAmBs have different pharmacological properties and rates of treatment-related adverse events and should not be interchanged without careful consideration. In this document, a reference to AmB, without a specific dose or other discussion of form, should be taken to be a reference to the general use of any of the AmB preparations. For most forms of invasive candidiasis, the typical intravenous dosage for AmB-d is 0.5–0.7 mg/kg daily, but dosages as high as 1 mg/kg daily should be considered for invasive *Candida* infections caused by less susceptible species, such as *C. glabrata* and *C. krusei*. The typical dosage for LFAmB is 3–5 mg/kg daily when used for invasive candidiasis [16, 17]. Nephrotoxicity is the most common serious adverse effect associated with AmB-d therapy, resulting in acute renal failure in up to 50% of recipients [18]. LFAmBs are considerably more expensive than AmB-d, but all have considerably less nephrotoxicity [19–21]. These agents retain the infusion-related toxicities associated with AmB-d. Among these agents, a comparative study suggests that L-AmB may afford the greatest renal protection [21]. The impact of the pharmacokinetics and differences in toxicity of LFAmB has not been formally examined in clinical trials. We are not aware of any forms of candidiasis for which LFAmB is superior to AmB-d, nor are we aware of any situations in which these agents would be contraindicated, with the exception of urinary tract candidiasis, in which the protection of the kidney afforded by the pharmacological properties of these formulations has the theoretical potential to reduce delivery of AmB [22]. Animal model studies suggest a pharmacokinetic and therapeutic advantage for L-AmB in the CNS [23]. Data demonstrating that AmB-d–induced nephrotoxicity is associated with a 6.6-fold increase in mortality have led many clinicians to use LFAmB as initial therapy for individuals who are at high risk of nephrotoxicity [24].

Triazoles

Fluconazole, itraconazole, voriconazole, and posaconazole demonstrate similar activity against most *Candida* species [25, 26]. Each of the azoles has less activity against *C. glabrata* and *C. krusei*. All of the azole antifungals inhibit cytochrome P450 enzymes to some degree. Thus, clinicians must carefully consider the influence on a patient's drug regimen when adding or removing an azole. In large clinical trials, fluconazole demonstrated efficacy comparable to that of AmB-d for the treatment of candidemia [27, 28] and is also considered to be standard therapy for oropharyngeal, esophageal, and vaginal candidiasis [29, 30]. Fluconazole is readily absorbed, with oral bioavailability resulting in concentrations equal to ~90% of those achieved by intravenous administration. Absorption is not affected by food consumption, gastric pH, or disease state. Among the triazoles, fluconazole has the greatest penetration into the CSF and vitreous body, achieving concentrations of at least 50% of those in serum [31]; for this reason, it is used in the treatment of CNS and intraocular *Candida* infections. Fluconazole achieves urine concentrations that are 10–20 times the concentrations in serum. For patients with invasive candidiasis, fluconazole should be administered with a loading dose of 800 mg (12 mg/kg), followed by a daily dose of 400 mg (6 mg/kg); a lower dosage is required in patients with creatinine clearance <50 mL/min.

Itraconazole is generally reserved for patients with mucosal candidiasis, especially those who have experienced treatment failure with fluconazole [32]. There are few data that examine the use of itraconazole in the treatment of invasive candidiasis. Gastrointestinal absorption differs for the capsule and the oral solution formulations. Histamine receptor antagonists and proton pump inhibitors result in decreased absorption of the capsule formulation, whereas acidic beverages, such as carbonated drinks and cranberry juice, enhance absorption [33]. Administration of the capsule formulation with food increases absorption, but the oral solution is better absorbed on an empty stomach [34]. Oral formulations are dosed in adults at 200 mg 3 times daily for 3 days, then 200 mg once or twice daily thereafter.

Voriconazole is effective for both mucosal and invasive candidiasis. Its clinical use has been primarily for step-down oral therapy for patients with infection due to *C. krusei* and fluconazole-resistant, voriconazole-susceptible *C. glabrata*. CSF and vitreous penetration is excellent [35, 36]. Voriconazole is available in both oral and parenteral preparations. The oral bioavailability of voriconazole is >90% and is not affected by

Table 2. Summary of recommendations for the treatment of candidiasis.

Condition or treatment group	Therapy		
	Primary	Alternative	Comments
Candidemia			
Nonneutropenic adults	Fluconazole 800-mg (12-mg/kg) loading dose, then 400 mg (6 mg/kg) daily or an echinocandin[a] (A-I). For species-specific recommendations, see text.	LFAmB 3–5 mg/kg daily; or AmB-d 0.5–1 mg/kg daily; or voriconazole 400 mg (6 mg/kg) bid for 2 doses, then 200 mg (3 mg/kg) bid (A-I)	Choose an echinocandin for moderately severe to severe illness and for patients with recent azole exposure. Transition to fluconazole after initial echinocandin is appropriate in many cases. Remove all intravascular catheters, if possible. Treat 14 days after first negative blood culture result and resolution of signs and symptoms associated with candidemia. Ophthalmological examination recommended for all patients.
Neutropenic patients	An echinocandin[a] or LFAmB 3–5 mg/kg daily (A-II). For species-specific recommendations, see text.	Fluconazole 800-mg (12-mg/kg) loading dose, then 400 mg (6 mg/kg) daily; or voriconazole 400 mg (6 mg/kg) bid for 2 doses then 200 mg (3 mg/kg) bid (B-III)	An echinocandin or LFAmB is preferred for most patients. Fluconazole is recommended for patients without recent azole exposure and who are not critically ill. Voriconazole is recommended when additional coverage for molds is desired. Intravascular catheter removal is advised but is controversial.
Suspected candidiasis treated with empiric antifungal therapy			
Nonneutropenic patients	Treat as above for candidemia. An echinocandin or fluconazole is preferred (B-III).	LFAmB 3–5 mg/kg daily or AmB-d 0.5–1 mg/kg daily (B-III)	For patients with moderately severe to severe illness and/or recent azole exposure, an echinocandin is preferred. The selection of appropriate patients should be based on clinical risk factors, serologic tests, and culture data. Duration of therapy is uncertain, but should be discontinued if cultures and/or serodiagnostic tests have negative results.
Neutropenic patients	LFAmB 3–5 mg/kg daily, caspofungin 70-mg loading dose, then 50 mg daily (A-I), or voriconazole 400 mg (6 mg/kg) bid for 2 doses then 200 mg (3 mg/kg) bid (B-I).	Fluconazole 800-mg (12-mg/kg) loading dose, then 400 mg (6 mg/kg) daily; or itraconazole 200 mg (3 mg/kg) bid (B-I)	In most neutropenic patients, it is appropriate to initiate empiric antifungal therapy after 4 days of persistent fever despite antibiotics. Serodiagnostic tests and CT imaging may be helpful. Do not use an azole in patients with prior azole prophylaxis.
Urinary tract infection			
Asymptomatic cystitis	Therapy not usually indicated, unless patients are at high risk (e.g., neonates and neutropenic adults) or undergoing urologic procedures (A-III)	…	Elimination of predisposing factors recommended. For high-risk patients, treat as for disseminated candidiasis. For patients undergoing urologic procedures, fluconazole, 200–400 mg (3–6 mg/kg) daily or AmB-d 0.3–0.6 mg/kg daily for several days before and after the procedure.
Symptomatic cystitis	Fluconazole 200 mg (3 mg/kg) daily for 2 weeks (A-III)	AmB-d 0.3–0.6 mg/kg for 1–7 days; or flucytosine 25 mg/kg qid for 7–10 days (B-III)	Alternative therapy as listed is recommended for patients with fluconazole-resistant organisms. AmB-d bladder irrigation is recommended only for patients with refractory fluconazole-resistant organisms (e.g., *Candida krusei* and *Candida glabrata*).
Pyelonephritis	Fluconazole 200–400 mg (3–6 mg/kg) daily for 2 weeks (B-III)	AmB-d 0.5–0.7 mg/kg daily with or without 5-FC 25 mg/kg qid; or 5-FC alone for 2 weeks (B-III)	For patients with pyelonephritis and suspected disseminated candidiasis, treat as for candidemia.

Table 2. ***(Continued.)***

Condition or treatment group	Therapy		
	Primary	Alternative	Comments
Urinary fungus balls	Surgical removal strongly recommended (B-III); fluconazole 200–400 mg (3–6 mg/kg) daily; or AmB-d 0.5–0.7 mg/kg daily with or without 5-FC 25 mg/kg qid (B-III)	…	Local irrigation with AmB-d may be a useful adjunct to systemic antifungal therapy.
Vulvovaginal candidiasis	Topical agents or fluconazole 150 mg single dose for uncomplicated vaginitis (A-I)	…	Recurrent vulvovaginal candidiasis is managed with fluconazole 150 mg weekly for 6 months after initial control of the recurrent episode. For complicated vulvovaginal candidiasis, see section VI.
Chronic disseminated candidiasis	Fluconazole 400 mg (6 mg/kg) daily for stable patients (A-III); LFAmB 3–5 mg/kg daily or AmB-d 0.5–0.7 mg/kg daily for severely ill patients (A-III); after patient is stable, change to fluconazole (B-III)	An echinocandin[a] for several weeks followed by fluconazole (B-III)	Transition from LFAmB or AmB-d to fluconazole is favored after several weeks in stable patients. Duration of therapy is until lesions have resolved (usually months) and should continue through periods of immunosuppression (e.g., chemotherapy and transplantation).
Candida osteoarticular infection			
Osteomyelitis	Fluconazole 400 mg (6 mg/kg) daily for 6–12 months or LFAmB 3–5 mg/kg daily for several weeks, then fluconazole for 6–12 months (B-III)	An echinocandin[a] or AmB-d 0.5–1 mg/kg daily for several weeks then fluconazole for 6–12 months (B-III)	Duration of therapy usually is prolonged (6–12 months). Surgical debridement is frequently necessary.
Septic arthritis	Fluconazole 400 mg (6 mg/kg) daily for at least 6 weeks or LFAmB 3–5 mg/kg daily for several weeks, then fluconazole to completion (B-III)	An echinocandin[a] or AmB-d 0.5–1 mg/kg daily for several weeks then fluconazole to completion (B-III)	Duration of therapy usually is for at least 6 weeks, but few data are available. Surgical debridement is recommended for all cases. For infected prosthetic joints, removal is recommended for most cases.
CNS candidiasis	LFAmB 3–5 mg/kg with or without 5-FC 25 mg/kg qid for several weeks, followed by fluconazole 400–800 mg (6–12 mg/kg) daily (B-III)	Fluconazole 400–800 mg (6–12 mg/kg) daily for patients unable to tolerate LFAmB	Treat until all signs and symptoms, CSF abnormalities, and radiologic abnormalities have resolved. Removal of intraventricular devices is recommended.
Candida endophthalmitis	AmB-d 0.7–1 mg/kg with 5-FC 25 mg/kg qid (A-III); or fluconazole 6–12 mg/kg daily (B-III); surgical intervention for patients with severe endophthalmitis or vitreitis (B-III)	LFAmB 3–5 mg/kg daily; voriconazole 6 mg/kg q12h for 2 doses, then 3–4 mg/kg q12h; or an echinocandin[a] (B-III)	Alternative therapy is recommended for patients intolerant of or experiencing failure of AmB and 5-FC therapy. Duration of therapy is at least 4–6 weeks as determined by repeated examinations to verify resolution. Diagnostic vitreal aspiration should be done if etiology unknown.
Candida infection of the cardiovascular system			
Endocarditis	LFAmB 3–5 mg/kg with or without 5-FC 25 mg/kg qid; or AmB-d 0.6–1 mg/kg daily with or without 5-FC 25 mg/kg qid; or an echinocandin[b] (B-III)	Step-down therapy to fluconazole 400–800 mg (6–12 mg/kg) daily for susceptible organism in stable patient with negative blood culture results (B-III)	Valve replacement is strongly recommended. For those who are unable to undergo surgical removal of the valve, chronic suppression with fluconazole 400–800 mg (6–12 mg/kg) daily is recommended. Lifelong suppressive therapy for prosthetic valve endocarditis if valve cannot be replaced is recommended.
Pericarditis or myocarditis	LFAmB 3–5 mg/kg daily; or fluconazole 400–800 mg (6–12 mg/kg) daily; or an echinocandin[b] (B-III)	After stable, step-down therapy to fluconazole 400–800 mg (6–12 mg/kg) daily (B-III)	Therapy is often for several months, but few data are available. A pericardial window or pericardiectomy is recommended.
Suppurative thrombophlebitis	LFAmB 3–5 mg/kg daily; or fluconazole 400–800 mg (6–12 mg/kg) daily; or an echinocandin[b] (B-III)	After stable, step-down therapy to fluconazole 400–800 mg (6–12 mg/kg) daily (B-III)	Surgical incision and drainage or resection of the vein is recommended if feasible. Treat for at least 2 weeks after candidemia has cleared.

Table 2. ***(Continued.)***

Condition or treatment group	Therapy		
	Primary	Alternative	Comments
Infected pacemaker, ICD, or VAD	LFAmB 3–5 mg/kg with or without 5-FC 25 mg/kg qid; or AmB-d 0.6–1 mg/kg daily with or without 5-FC 25 mg/kg qid; or an echinocandin[b] (B-III)	Step-down therapy to fluconazole 400–800 mg (6–12 mg/kg) daily for susceptible organism in stable patient with negative blood culture results (B-III)	Removal of pacemakers and ICDs strongly recommended. Treat for 4–6 weeks after the device removed. For VAD that cannot be removed, chronic suppressive therapy with fluconazole is recommended.
Neonatal candidiasis	AmB-d 1 mg/kg daily (A-II); or fluconazole 12 mg/kg daily (B-II) for 3 weeks	LFAmB 3–5 mg/kg daily (B-III)	A lumbar puncture and dilated retinal examination should be performed on all neonates with suspected invasive candidiasis. Intravascular catheter removal is strongly recommended. Duration of therapy is at least 3 weeks. LFAmB used only if there is no renal involvement. Echinocandins should be used with caution when other agents cannot be used.
Candida isolated from respiratory secretions	Therapy not recommended (A-III)	…	*Candida* lower respiratory tract infection is rare and requires histopathologic evidence to confirm a diagnosis.
Nongenital mucocutaneous candidiasis			
Oropharyngeal	Clotrimazole troches 10 mg 5 times daily; nystatin suspension or pastilles qid (B-II); or fluconazole 100–200 mg daily (A-I)	Itraconazole solution 200 mg daily; or posaconazole 400 mg qd (A-II); or voriconazole 200 mg bid; or AmB oral suspension (B-II); IV echinocandin[a] or AmB-d 0.3 mg/kg daily (B-II)	Fluconazole is recommended for moderate-to-severe disease, and topical therapy with clotrimazole or nystatin is recommended for mild disease. Treat uncomplicated disease for 7–14 days. For refractory disease, itraconazole, voriconazole, posaconazole, or AmB suspension is recommended.
Esophageal	Fluconazole 200–400 mg (3–6 mg/kg) daily (A-I); an echinocandin[a]; or AmB-d 0.3–0.7 mg/kg daily (B-II)	Itraconazole oral solution 200 mg daily; or posaconazole 400 mg bid; or voriconazole 200 mg bid (A-III)	Oral fluconazole is preferred. For patients unable to tolerate an oral agent, IV fluconazole, an echinocandin, or AmB-d is appropriate. Treat for 14–21 days. For patients with refractory disease, the alternative therapy as listed or AmB-d or an echinocandin is recommended,

NOTE. AmB, amphotericin B; AmB-d, amphotericin B deoxycholate; bid, twice daily; ICD, implantable cardiac defibrillator; IV, intravenous; LFAmB, lipid formulation of amphotericin B; qid, 4 times daily; VAD, ventricular assist device; 5-FC, flucytosine.

[a] Echinocandin dosing in adults is as follows: anidulafungin, 200-mg loading dose, then 100 mg/day; caspofungin, 70-mg loading dose, then 50 mg/day; and micafungin, 100 mg/day.

[b] For patients with endocarditis and other cardiovascular infections, higher daily doses of an echinocandin may be appropriate (e.g., caspofungin 50–150 mg/day, micafungin 100–150 mg/day, or anidulafungin 100–200 mg/day).

gastric pH, but it decreases when the drug is administered with food [37]. In adults, the recommended oral dosing regimen includes a loading dose of 400 mg twice daily, followed by 200 mg twice daily. Intravenous voriconazole is complexed to a cyclodextrin molecule; after 2 loading doses of 6 mg/kg every 12 h, a maintenance dosage of 3–4 mg/kg every 12 h is recommended. Because of the potential for cyclodextrin accumulation among patients with significant renal dysfunction, intravenous voriconazole is not recommended for patients with a creatinine clearance <50 mL/min [38]. Oral voriconazole does not require dosage adjustment for renal insufficiency, but it is the only triazole that requires dosage reduction for patients with mild-to-moderate hepatic impairment. Common polymorphisms in the gene encoding the primary metabolic enzyme for voriconazole result in wide variability of serum levels [39, 40]. Drug-drug interactions are common with voriconazole and should be considered when initiating and discontinuing treatment with this compound.

Posaconazole does not have an indication for primary candidiasis therapy. It demonstrates in vitro activity against *Candida* species that is similar to that of voriconazole, but clinical data are inadequate to make an evidence-based recommendation for treatment of candidiasis other than oropharyngeal candidiasis. Posaconazole is currently available only as an oral suspension with high oral bioavailability, especially when given with fatty foods [41], but absorption is saturated at relatively

modest dosage levels. Thus, despite a prolonged elimination half-life (>24 h), the drug must be administered multiple times daily (e.g., 200 mg 4 times daily or 400 mg twice daily). Similar to itraconazole capsules, posaconazole absorption is optimal in an acidic gastric environment.

Echinocandins

Caspofungin, anidulafungin, and micafungin are available only as parenteral preparations [42–44]. The MICs of the echinocandins are low for a broad spectrum of *Candida* species, including *C. glabrata* and *C. krusei. C. parapsilosis* demonstrates less in vitro susceptibility to the echinocandins than do most other *Candida* species, which raises the concern that *C. parapsilosis* may be less responsive to the echinocandins. However, in several clinical trials, this has not been demonstrated [45, 46]. Each of these agents has been studied for the treatment of esophageal candidiasis [47–50] and invasive candidiasis [51–54] in noncomparative and comparative clinical trials, and each has been shown to be effective in these clinical situations. All echinocandins have few adverse effects. The pharmacologic properties in adults are also very similar and are each administered once daily intravenously [42–44]; the major route of elimination is nonenzymatic degradation. None of the echinocandins require dosage adjustment for renal insufficiency or dialysis. Both caspofungin and micafungin undergo minimal hepatic metabolism, but neither drug is a major substrate for cytochrome P450. Caspofungin is the only echinocandin for which dosage reduction is recommended for patients with moderate to severe hepatic dysfunction.

Based on existing data, intravenous dosing regimens for invasive candidiasis with the 3 compounds are as follows: caspofungin, loading dose of 70 mg and 50 mg daily thereafter; anidulafungin, loading dose of 200 mg and 100 mg daily thereafter; and micafungin, 100 mg daily.

Flucytosine

Flucytosine demonstrates broad antifungal activity against most *Candida* species, with the exception of *C. krusei.* The compound is available only as an oral formulation. The drug has a short half-life (2.4–4.8 h) and is ordinarily administered at a dosage of 25 mg/kg 4 times daily for patients with normal renal function. Flucytosine demonstrates excellent absorption after oral administration (80%–90%), and most of the drug (>90%) is excreted unchanged in the urine [55]. Thus, dose adjustment is necessary for patients with renal dysfunction [56].

Flucytosine is rarely administered as a single agent but is usually given in combination with AmB for patients with invasive diseases, such as *Candida* endocarditis or meningitis. Occasionally, it is used for the treatment of urinary tract candidiasis due to susceptible organisms.

Pediatric Dosing

The pharmacokinetics of antifungal agents vary between adult and pediatric patients, but the data on dosing for antifungal agents in pediatric patients are limited. The pharmacological properties of antifungal agents in children and infants have been reviewed in detail [57, 58]. AmB-d kinetics are similar in neonates and adults [59]. There are few data describing the use of LFAmB in neonates and children. A phase I/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 in adults [17]. There are anecdotal data reporting successful use of L-AmB in neonates [60].

Flucytosine clearance is directly proportional to glomerular filtration rate, and infants with a very low birth weight may accumulate high plasma concentrations because of poor renal function due to immaturity [61]. Thus, the use of flucytosine without careful monitoring of serum drug levels is discouraged in this group of patients.

The pharmacokinetics of fluconazole vary significantly with age [62–64]. Fluconazole is rapidly cleared in children (plasma half-life, ~14 h). To achieve comparable drug exposure, the daily fluconazole dose needs to be doubled, from 6 to 12 mg/kg daily, for children of all ages and neonates [62]. In comparison with the volume of distribution (0.7 L/kg) and half-life (30 h) seen in adults, neonates may have a higher volume of distribution and longer half-life [63, 64]; it has been recently reported that the volume of distribution in young infants and neonates is 1 L/kg and that the half-life is 30–50 h [65]. These data indicate that once-daily dosing of 12 mg/kg in premature and term neonates will provide exposure similar to that in adults who receive 400 mg daily. If the young infant's creatinine level is >1.2 mg/dL for >3 consecutive doses, the dosing interval for 12 mg/kg may be increased to once every 48 h until the serum creatinine level is <1.2 mg/dL.

When administered to infants and children, the oral solution of itraconazole (5 mg/kg per day) provides potentially therapeutic concentrations in plasma [66]. Levels in children 6 months to 2 years of age are substantially lower than those attained in adult patients; thus, children usually need twice-daily dosing. A recent study of itraconazole solution in HIV-infected children documented its efficacy for treating oropharyngeal candidiasis in pediatric patients [67].

Voriconazole kinetics vary significantly between children and adults [68], demonstrating linear elimination in children after doses of 3 mg/kg and 4 mg/kg every 12 h. Thus, children up to ~12 years of age require higher doses of voriconazole than do adults to attain similar serum concentrations. A dosage of 7 mg/kg every 12 h is currently recommended to achieve plasma exposures comparable to those in an adult receiving 4 mg/kg given every 12 h.

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

Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Flucytosine	Amphotericin B	Candins
Candida albicans	S	S	S	S	S	S	S
Candida tropicalis	S	S	S	S	S	S	S
Candida parapsilosis	S	S	S	S	S	S	S to R[a]
Candida glabrata	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S	S to I	S
Candida krusei	R	S-DD to R	S	S	I to R	S to I	S
Candida lusitaniae	S	S	S	S	S	S to R	S

NOTE. I, intermediately susceptible; R, resistant; S, susceptible; S-DD: susceptible dose-dependent.

[a] Echinocandin resistance among *C. parapsilosis* isolates is uncommon.

There is growing experience with the echinocandins in children and neonates [45, 69–72]. A recent study of caspofungin in pediatric patients demonstrated the importance of dosing based on body surface area rather than weight. With use of the weight-based approach to pediatric dosing, 1 mg/kg resulted in sub-optimal plasma concentrations for caspofungin, whereas dosing based on 50 mg/m^2 yielded plasma concentrations that were similar to those in adults who were given a standard 50-mg dose of caspofungin. Micafungin has been studied in children and neonates; children should be treated with 2–4 mg/kg daily, but neonates may require as much as 10–12 mg/kg daily to achieve therapeutic concentrations [73]. Anidulafungin has been studied in children 2–17 years of age and should be dosed at 1.5 mg/kg/day [72]. Data for each of the echinocandins suggest safety and efficacy in the pediatric population.

Considerations during Pregnancy

Systemic AmB is the treatment of choice for invasive candidiasis in pregnant women [74]. Most azoles, including fluconazole, itraconazole, and posaconazole, should generally be avoided in pregnant women because of the possibility of birth defects associated with their use (category C). There are fewer data concerning the echinocandins, but these should be used with caution during pregnancy (category C). Flucytosine and voriconazole are contraindicated during pregnancy because of fetal abnormalities observed in animals (category D) [74].

Therapeutic Drug Monitoring

Therapeutic drug monitoring for itraconazole and voriconazole may be useful for patients receiving prolonged courses (e.g., ⩾4 weeks in duration) for deep-seated or refractory candidiasis. Blood concentrations vary widely in patients receiving itraconazole. Serum concentrations are ~30% higher when the solution is used than they are when the capsule is used, but wide intersubject variability exists. Itraconazole concentrations in serum should be determined only after steady state has been reached, which takes ~2 weeks. Serum levels should be obtained to ensure adequate absorption, to monitor changes in the dosage of itraconazole or the addition of interacting medications, and to assess adherence. Because of its long half-life, serum concentrations of itraconazole vary little over a 24-h period, and blood can be collected at any time in relation to drug administration. When measured by high-pressure liquid chromatography, both itraconazole and its bioactive hydroxy-itraconazole metabolite are reported, the sum of which should be considered in assessing drug levels.

Because of nonlinear pharmacokinetics in adults and genetic differences in metabolism, there is both intrapatient and interpatient variability in serum voriconazole concentrations. Therapeutic drug monitoring should be considered for patients receiving voriconazole, because drug toxicity has been observed at higher serum concentrations, and reduced clinical response has been observed at lower concentrations [39, 75].

Antifungal Susceptibility Testing

Intensive efforts to develop standardized, reproducible, and clinically relevant susceptibility testing methods for fungi have resulted in the development of the Clinical and Laboratory Standards Institute M27-A3 methodology for susceptibility testing of yeasts [76]. Data-driven interpretive breakpoints determined with use of this method are available for testing the susceptibility of *Candida* species to fluconazole, itraconazole, voriconazole, flucytosine, and the echinocandins [25, 76]. Although the susceptibility of *Candida* to the currently available antifungal agents is generally predictable if the species of the infecting isolate is known, individual isolates do not necessarily follow this general pattern (table 3) [25, 76]. For this reason, susceptibility testing is increasingly used to guide the management of candidiasis, especially in situations in which there is a failure to respond to initial antifungal therapy. Expert opinion suggests that laboratories perform routine antifungal susceptibility testing against fluconazole for *C. glabrata* isolates from blood and sterile sites and for other *Candida* species that have failed to respond to antifungal therapy or in which azole resistance is strongly suspected. Currently, antifungal resistance in *C. albicans* is uncommon, and routine testing for antifungal susceptibility against this species is not generally recommended.

Non–Culture-Based Diagnostic Techniques

Several new diagnostic techniques offer promise for the early diagnosis of invasive candidiasis. Several of these assays are approved as adjuncts to the diagnosis of invasive candidiasis, but their role in clinical practice is poorly defined. Several other assays are under development but are not yet approved (see below).

RECOMMENDATIONS FOR THE MANAGEMENT OF CANDIDIASES

I. WHAT IS THE TREATMENT OF CANDIDEMIA IN NONNEUTROPENIC PATIENTS?

Recommendations

1. Fluconazole (loading dose of 800 mg [12 mg/kg], then 400 mg [6 mg/kg] daily) or an echinocandin (caspofungin: loading dose of 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose of 200 mg, then 100 mg daily) is recommended as initial therapy for most adult patients (A-I). The Expert Panel favors an echinocandin for patients with moderately severe to severe illness or patients who have had recent azole exposure (A-III). Fluconazole is recommended for patients who are less critically ill and who have no recent azole exposure (A-III). The same therapeutic approach is advised for children, with attention to differences in dosing regimens (B-III).
2. Transition from an echinocandin to fluconazole is recommended for patients who have isolates that are likely to be susceptible to fluconazole (e.g., *C. albicans*) and who are clinically stable (A-II).
3. For infection due to *C. glabrata,* an echinocandin is preferred (B-III). Transition to fluconazole or voriconazole is not recommended without confirmation of isolate susceptibility (B-III). For patients who initially received fluconazole or voriconazole, are clinically improved, and whose follow-up culture results are negative, continuing an azole to completion of therapy is reasonable (B-III).
4. For infection due to *C. parapsilosis,* fluconazole is recommended (B-III). For patients who have initially received an echinocandin, are clinically improved, and whose follow-up culture results are negative, continuing use of an echinocandin is reasonable (B-III).
5. AmB-d (0.5–1.0 mg/kg daily) or LFAmB (3–5 mg/kg daily) are alternatives if there is intolerance to or limited availability of other antifungal agents (A-I). Transition from AmB-d or LFAmB to fluconazole therapy is recommended for patients who have isolates that are likely to be susceptible to fluconazole (e.g., *C. albicans*) and who are clinically stable (A-I).
6. Voriconazole (400 mg [6 mg/kg] twice daily for 2 doses, then 200 mg [3 mg/kg] twice daily) is effective for candidemia (A-I), but it offers little advantage over fluconazole and is recommended as step-down oral therapy for selected cases of candidiasis due to *C. krusei* or voriconazole-susceptible *C. glabrata* (B-III).
7. Recommended duration of therapy for candidemia without obvious metastatic complications is for 2 weeks after documented clearance of *Candida* species from the bloodstream and resolution of symptoms attributable to candidemia (A-III).
8. Intravenous catheter removal is strongly recommended for nonneutropenic patients with candidemia (A-II).

Evidence Summary

The selection of any particular agent for the treatment of candidemia should optimally take into account any history of recent azole exposure, a history of intolerance to an antifungal agent, the dominant *Candida* species and current susceptibility data in a particular clinical unit or location, severity of illness, relevant comorbidities, and evidence of involvement of the CNS, cardiac valves, and/or visceral organs. Early initiation of effective antifungal therapy is critical in the successful treatment of candidemia, as demonstrated by recent data suggesting higher mortality rates among patients with candidemia whose therapy was delayed [77, 78].

Fluconazole remains standard therapy for selected patients with candidemia, on the basis of abundant data from well-designed clinical trials [27, 28, 53, 79]. There is little role for itraconazole in this setting, given similar antifungal spectrum, ease of administration, superior pharmacokinetics, and better tolerability of fluconazole. Fluconazole should be considered first-line therapy for patients who have mild to moderate illness (i.e., are hemodynamically stable), who have no previous exposure to azoles, and who do not belong in a group at high risk of *C. glabrata* (infection e.g., elderly patients, patients with cancer, and patients with diabetes). Patients with candidemia and suspected concomitant endocardial or CNS involvement should probably not receive fluconazole as initial therapy; rather, they should receive an agent that is fungicidal, such as AmB (for endocardial or CNS candidiasis) or an echinocandin (for endocardial candidiasis). On the basis of data from recent clinical trials [28, 51, 52, 54, 79], step-down therapy to fluconazole is reasonable for patients who have improved clinically after initial therapy with an echinocandin or AmB and who are infected with an organism that is likely to be susceptible to fluconazole (e.g., *C. albicans, C. parapsilosis,* and *Candida tropicalis*).

The echinocandins demonstrate significant fungicidal activity against all *Candida* species, and each has demonstrated success in ~75% of patients in randomized clinical trials. Because of their efficacy, favorable safety profile, and very few drug interactions, the echinocandins are favored for initial therapy for patients who have a recent history of exposure to an azole,

moderately severe to severe illness (i.e., are hemodynamically unstable), allergy or intolerance to azoles or AmB, or high risk of infection with *C. krusei* or *C. glabrata.* A short course of intravenous echinocandin therapy (3–5 days) followed by transition to oral fluconazole or voriconazole (for *C. krusei* infection) is a reasonable approach to the treatment of candidemia in the stable patient, but there are few clinical data to support this management strategy. The Expert Panel favors fluconazole over the 3 available echinocandins for treatment of candidemia due to *C. parapsilosis* on the basis of the decreased in vitro activity of echinocandins against *C. parapsilosis* [45, 46] and reports of echinocandin resistance among selected isolates [80]. Most experts agree that the echinocandins are sufficiently similar to be considered interchangeable.

Data from a recent randomized study suggest that an echinocandin may be superior to fluconazole as primary therapy for candidemia [53]. Although many experts agree that an echinocandin is favored as initial therapy for patients with moderately severe to severe disease due to invasive candidiasis, few agree that an echinocandin is favored for all episodes, and it is reasonable to consider the history of recent azole exposure, severity of illness, and the likelihood of fluconazole resistance in making a choice for initial antifungal therapy.

Voriconazole was shown to be as effective as AmB induction therapy for 4–7 days, followed by fluconazole for candidemia and invasive candidiasis [79]. Voriconazole possesses activity against most *Candida* species, including *C. krusei* [26, 81], but the need for more-frequent administration, less predictable pharmacokinetics, more drug interactions, and poor tolerance to the drug, compared with other systemic antifungals, make it a less attractive choice for initial therapy. Voriconazole does not provide predictable activity against fluconazole-resistant *C. glabrata* [26, 81]. It does, however, fill an important niche for patients who have fluconazole-resistant isolates of *C. krusei, C. guilliermondii,* or *C. glabrata* that have documented voriconazole susceptibility and who are ready for transition from an echinocandin or AmB to oral therapy.

Posaconazole has excellent in vitro activity against most *Candida* species, but there are few clinical data to support its use among patients with candidemia. On the basis of available data and the lack of an intravenous formulation, it is difficult to envision a significant role for posaconazole in the treatment of candidemia, other than in select patients for whom transition to an expanded-spectrum azole is warranted.

AmB-d is recommended as initial therapy when alternative therapy is unavailable or unaffordable, when there is a history of intolerance to echinocandins or azoles, when the infection is refractory to other therapy, when the organism is resistant to other agents, or when there is a suspicion of infection due to non-*Candida* yeast, such as *Cryptococcus neoformans.* L-AmB at doses of 3 mg/kg daily has been shown to be effective for treatment of candidemia, based on a recent prospective clinical trial [52]. Similarly, ABLC administered at 3 mg/kg/day has been successfully used for the treatment of candidemia (E. J. Anaissie, unpublished data). Infections due to *Candida luistaniae* are uncommon; for this organism, the Expert Panel favors the use of fluconazole or an echinocandin over AmB because of the observation of in vitro polyene resistance.

For all patients with candidemia, a dilated funduscopic examination sometime within the first week after initiation of therapy and routine blood cultures to document clearance of *Candida* from the bloodstream is strongly advised (see Performance Measures). If there are no metastatic complications, the duration of antifungal therapy is 14 days after resolution of signs and symptoms attributable to infection and clearance of *Candida* species from the bloodstream. This recommendation is based on the results of several prospective, randomized trials in which this rule has been successfully applied, and it is generally associated with few complications and relapses [27, 28, 51–54, 79]. The recommended length of therapy pertains to all systemic antifungal therapy and includes sequential therapy with AmB or an echinocandin followed by an azole.

Central venous catheters should be removed when candidemia is documented, if at all possible [82–84]. The data supporting this are strongest among nonneutropenic patients and show that catheter removal is associated with shorter duration of candidemia [82, 83] and reduced mortality in adults [82, 84] and neonates [85]. Recently completed trials in adults suggest better outcomes and shorter duration of candidemia among patients in whom central venous catheters were removed or replaced [28, 54]. Among neutropenic patients, the role of the gastrointestinal tract 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 gastrointestinal tract versus catheter as primary sources of candidemia [82, 86]. An exception is made for candidemia due to *C. parapsilosis,* which is very frequently associated with catheters [87]. There are no randomized studies on this topic, but the Expert Panel strongly favors catheter removal when feasible. The role for antifungal lock solutions is not well defined.

II. WHAT IS THE TREATMENT OF CANDIDEMIA IN NEUTROPENIC PATIENTS?

Recommendations

9. An echinocandin (caspofungin, loading dose of 70 mg, then 50 mg daily; micafungin, 100 mg daily (A-II); anidulafungin, loading dose of 200 mg, then 100 mg daily (A-III)) or LFAmB (3–5 mg/kg daily) (A-II) is recommended for most patients.

10. For patients who are less critically ill and who have no recent azole exposure, fluconazole (800 mg [12 mg/kg] loading

dose, then 400 mg [6 mg/kg] daily) is a reasonable alternative (B-III). Voriconazole (400 mg [6 mg/kg] twice daily for 2 doses, then 200 mg [3 mg/kg] twice daily) can be used in situations in which additional mold coverage is desired (B-III).

11. For infections due to *C. glabrata,* an echinocandin is preferred (B-III); LFAmB is an effective but less attractive alternative because of cost and the potential for toxicity (B-III). For patients who were already receiving voriconazole or fluconazole, are clinically improved, and whose follow-up culture results are negative, continuing use of the azole to completion of therapy is reasonable (B-III).

12. For infections due to *C. parapsilosis*, fluconazole or LFAmB is preferred as initial therapy (B-III). If the patient is receiving an echinocandin and is clinically stable and if follow-up culture results are negative, continuing use of the echinocandin until completion of therapy is reasonable. For infections due to *C. krusei,* an echinocandin, LFAmB, or voriconazole is recommended (B-III).

13. Recommended duration of therapy for candidemia without persistent fungemia or metastatic complications is 2 weeks after documented clearance of *Candida* from the bloodstream and resolution of symptoms attributable to candidemia and resolution of neutropenia (A-III).

14. Intravenous catheter removal should be considered (B-III).

Evidence Summary

Candidemia in neutropenic patients is a life-threatening infection that is associated with acute disseminated candidiasis, a sepsis-like syndrome, multiorgan failure, and death. Candidemia associated with *C. tropicalis* is particularly virulent in neutropenic hosts. Chronic disseminated candidiasis can ensue as a complication of candidemia in neutropenic patients despite antifungal therapy.

There are no adequately powered randomized controlled trials of treatment of candidemia in neutropenic patients. The data are largely derived from single-arm studies or from small subsets of randomized controlled studies that have enrolled mostly nonneutropenic patients. Historically, candidemia in the neutropenic patient has been treated with an AmB formulation. The availability of voriconazole and the echinocandins have led to greater use of these agents in this clinical scenario but without compelling clinical data. The extensive use of fluconazole for prophylaxis to prevent invasive candidiasis in neutropenic patients and the lack of significant prospective data has led to a diminished therapeutic role for this agent among these patients.

The numbers of neutropenic patients included in recent candidemia treatment studies are small, but response rates are encouraging. In these trials, 50% of caspofungin recipients versus 40% of AmB-d recipients [51], 68% of micafungin recipients versus 61% of L-AmB recipients [52], and 69% of micafungin recipients versus 64% of caspofungin recipients [54] with neutropenia at onset of therapy were successfully treated. Data from the recent randomized controlled trial of anidulafungin versus fluconazole enrolled too few neutropenic patients with candidemia to generate meaningful data regarding efficacy [53]. In 2 retrospective studies, successful outcomes for primary treatment of neutropenic patients were reported in 64% of those receiving AmB-d, 64% of those receiving fluconazole, and 68% of those receiving caspofungin [88, 89].

An extremely important factor influencing the outcome of candidemia in neutropenic patients is the recovery of neutrophils during therapy. In a large retrospective cohort of 476 patients with cancer who had candidemia, persistent neutropenia was associated with a greater chance of treatment failure [87].

Additional insights can be gleaned from data derived from studies of empirical antifungal therapy involving febrile patients with neutropenia who had candidemia at baseline. In these studies, baseline candidemia was cleared in 73% of those treated with AmB-d versus 82% of those treated with L-AmB [90] and in 67% of those treated with caspofungin versus 50% of those treated with L-AmB [91]. Data from a large randomized trial also suggest that voriconazole is a reasonable choice for febrile patients with neutropenia and suspected invasive candidiasis for whom additional mold coverage is desired [92].

On the basis of these limited data, the success rates of antifungal therapy for candidemia in patients with neutropenia do not appear to be substantially different from those reported in the large randomized trials of nonneutropenic patients. Moreover, these data do not suggest less favorable outcomes associated with fluconazole and voriconazole, but many physicians prefer LFAmB or an echinocandin, which may be more fungicidal, as first-line agents. Similar to the approach in nonneutropenic patients, the recommended duration of therapy for candidemia in neutropenic patients is for 14 days after resolution of attributable signs and symptoms and clearance of the bloodstream of *Candida* species, provided that there has been recovery from neutropenia. This recommendation is based on the limited data from prospective randomized trials and has been associated with few complications and relapses [51, 52, 54].

The management of intravascular catheters in neutropenic patients with candidemia is less straightforward than in their nonneutropenic counterparts. Distinguishing gut-associated from vascular catheter–associated candidemia can be difficult in these patients [86], the data for catheter removal is less compelling, and the consequences of catheter removal often create significant intravenous access problems. Nonetheless, the Expert Panel suggests consideration of venous catheter removal (including removal of tunneled catheters) for neutropenic patients who have persistent candidemia and in whom it is logistically feasible.

III. WHAT IS THE EMPIRICAL TREATMENT FOR SUSPECTED INVASIVE CANDIDIASIS IN NONNEUTROPENIC PATIENTS?

Recommendations

15. Empirical therapy for suspected candidiasis in nonneutropenic patients is similar to that for proven candidiasis. Fluconazole (800-mg [12-mg/kg] loading dose, then 400 mg [6 mg/kg] daily), caspofungin (70-mg loading dose, then 50 mg daily), anidulafungin (200-mg loading dose, then 100 mg daily), or micafungin (100 mg daily) is recommended as initial therapy (B-III). An echinocandin is preferred for patients with recent azole exposure, patients with moderately severe to severe illness, or patients who are at high risk of infection due to *C. glabrata* or *C. krusei* (B-III).

16. AmB-d (0.5–1.0 mg/kg daily) or LFAmB (3–5 mg/kg daily) are alternatives if there is intolerance to other antifungals or limited availability of other antifungals (B-III).

17. Empirical antifungal therapy should be considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever and should be based on clinical assessment of risk factors, serologic markers for invasive candidiasis, and/or culture data from nonsterile sites (B-III).

Evidence Summary

Candida species are an increasing cause of sepsis among nonneutropenic patients receiving intensive care; one-half to two-thirds of all episodes of candidemia occur in an ICU or surgical ward [5, 8]. Identification of patients at risk of *Candida* infections and prompt initiation of antifungal therapy are critical [77, 78]. *Candida* colonization, severity of illness, number of broad-spectrum antibiotic agents used and duration of use, previous surgery (especially bowel surgery), receipt of dialysis, use of central venous catheters, receipt of parenteral nutrition, and length of ICU stay are important risk factors for invasive candidiasis [93–98]. The level of *Candida* colonization has a low positive predictive value, and routine assessment of colonization is labor intensive and expensive [93, 99]. Signs and symptoms of candidiasis are nonspecific, and microbiology and imaging techniques lack sensitivity and specificity.

Early diagnosis of invasive candidiasis remains a challenge; thus, clinical prediction rules have been developed to identify patients in the ICU who are at high risk of candidiasis [100–102]. Characterized by high specificity but a low sensitivity, these rules allow the identification of only a small proportion of ICU patients who will develop candidiasis. Newer serological diagnostic tests have become available to assist in the assessment of patients with suspected candidiasis. Combined measurement of mannan and anti-mannan antibodies has yielded encouraging results and is worthy of additional evaluation [103]. Detection of β-D-glucan has shown good overall performance characteristics, with a sensitivity of 80%–90% in patients with candidemia [104, 105], confirming previous results obtained in patients with hematological malignancies [106]. Real-time PCR is a nonvalidated but intriguing methodology that holds promise as an early diagnostic aid for candidemia [107]. These encouraging data offer new perspectives for early diagnosis of *Candida* infections, but continued evolution of these assays will be required before they can be used routinely.

Few clinical studies have carefully examined the impact of empirical or preemptive treatment strategies. In one study, preemptive therapy with fluconazole in selected colonized patients in a surgical ICU was associated with reduced incidence of proven candidiasis [108], and in another study, early preemptive fluconazole therapy in patients who had had gastrointestinal surgery for bowel obstruction or perforation had some impact on the resolution of fever, the incidence of candidemia, the length of ICU stay, and mortality [109]. In a more recent study of ICU patients at risk of invasive candidiasis and with unexplained fever, empiric fluconazole (800 mg daily for 14 days) was not associated with better outcomes, compared with placebo [110].

Criteria for starting empirical antifungal therapy in nonneutropenic patients remain poorly defined. Early initiation of antifungal therapy may reduce morbidity, mortality, and length of stay in critically ill patients, but the widespread use of these agents must be balanced against the risk of toxicity, costs, and the emergence of resistance. Empirical antifungal therapy should be considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever. Preference should be given to an echinocandin in hemodynamically unstable patients, in patients previously exposed to an azole, and in those known to be colonized with azole-resistant *Candida* species. LFAmB and AmB-d are alternatives to an echinocandin, but the risk of toxicity is a concern. Empirical therapy with fluconazole may be considered in non–critically ill patients who are known to be colonized with azole-susceptible *Candida* species or who have no prior exposure to azoles.

IV. WHAT IS THE EMPIRICAL TREATMENT FOR SUSPECTED INVASIVE CANDIDIASIS IN NEUTROPENIC PATIENTS?

Refer to the 2002 IDSA guidelines for the use of antimicrobial agents in neutropenic patients with cancer [111].

Recommendations

18. LFAmB (3–5 mg/kg daily), caspofungin (70-mg loading dose, then 50 mg daily) (A-I), or voriconazole (6 mg/kg twice daily for 2 doses, then 3 mg/kg twice daily) are recommended (B-I).

19. Fluconazole (800-mg [12-mg/kg] loading dose, then 400 mg [6 mg/kg] daily) and itraconazole (200 mg [3mg/kg] twice daily) are alternative agents (B-I).

20. AmB-d is an effective alternative, but there is a higher risk of toxicity than there is with LFAmB (A-I).

21. Azoles should not be used for empirical therapy in patients who have received an azole for prophylaxis (B-II).

Evidence Summary

Empirical antifungal therapy in persistently febrile and neutropenic patients with hematological malignancies, allogeneic hematopoietic stem cell transplantation, and other underlying conditions became a standard of care in the late 1980s when it became clear that the lack of sensitivity of microbiological and clinical findings resulted in delayed diagnosis. AmB-d in neutropenic patients with persistent, unexplained fever despite 4–7 days of broad-spectrum antibiotics was shown to reduce the occurrence of invasive fungal infections and related mortality in 2 randomized, prospective clinical trials [112, 113]. Although these studies provided the scientific basis for empirical antifungal therapy, they were statistically underpowered. Since that time, several clinical trials have compared the efficacy and safety of various antifungal agents for this indication. In a majority of studies, the overall response was assessed by a composite end point consisting of a combination of resolution of fever during neutropenia, successful treatment of baseline fungal infections, absence of breakthrough fungal infection, discontinuation of therapy because of drug-related lack of efficacy or toxicity, and survival.

In recent years, imaging techniques, such as chest CT, and serial measurements of fungal antigens have become integral to the evaluation of the neutropenic patient with persistent, unexplained fever despite broad-spectrum antibacterial therapy [114, 115]. Serial measurements of *Aspergillus* galactomannan, mannan and anti-mannan antibodies, or β-D-glucan have been shown to be useful additions to culture methods [105, 116–118]. Combined serum galactomannan screening, chest CT, and bronchoalveolar lavage can enhance the diagnosis of invasive fungal infections and reduce the use of empirical therapy in neutropenic patients [119].

Empirical therapy in persistently febrile and neutropenic patients should cover infections caused by yeasts and molds. Given its toxicity, AmB-d is no longer a treatment of first choice unless other safer agents are unavailable. L-AmB is as efficacious as AmB-d and is associated with fewer breakthrough fungal infections and less infusion-related toxicity and nephrotoxicity [90]. ABCD and ABLC are efficacious but associated with a higher incidence of infusion-related toxicity than L-AmB [120, 121].

Fluconazole is less toxic, but its usefulness is limited by its relatively narrow spectrum [122–124]. Itraconazole has been shown to be as efficacious as AmB-d and less toxic [125]; it is available only as an oral formulation and has variable oral bioavailability and frequent gastrointestinal adverse effects. Voriconazole has been shown to prevent breakthrough fungal infections and is effective for aspergillosis and candidemia [79, 92]. Posaconazole has been shown to be effective prophylaxis against invasive fungal infections in high-risk neutropenic patients and allogeneic hematopoietic stem cell transplant recipients [126, 127], but its role as empirical therapy has not been determined. Azoles are unsuitable for empirical therapy if they have been used for prior prophylaxis.

Among the echinocandins, caspofungin has been shown to be as effective as and better tolerated than L-AmB for empirical therapy [91]. Micafungin has been shown to prevent fungal infections in hematopoietic stem cell transplant recipients [42, 128], but micafungin and anidulafungin have not been studied as empirical therapy for neutropenic patients.

V. WHAT IS THE TREATMENT FOR URINARY TRACT INFECTIONS DUE TO CANDIDA SPECIES?

Recommendations: asymptomatic candiduria

22. Treatment is not recommended unless the patient belongs to a group at high risk of dissemination (A-III). Elimination of predisposing factors often results in resolution of candiduria (A-III).

23. High-risk patients include neutropenic patients, infants with low birth weight, and patients who will undergo urologic manipulations. Neutropenic patients and neonates should be managed as described for invasive candidiasis. For those patients undergoing urologic procedures, fluconazole administered at a dosage of 200- 400 mg (3–6 mg/kg) daily or AmB-d administered at a dosage of 0.3–0.6 mg/kg daily for several days before and after the procedure is recommended (B-III).

24. Imaging of the kidneys and collecting system to exclude abscess, fungus ball, or urologic abnormality is prudent when treating asymptomatic patients with predisposing factors (B-III).

Recommendations: symptomatic candiduria

25. For candiduria with suspected disseminated candidiasis, treatment as described for candidemia is recommended (A-III).

26. For cystitis due to a fluconazole-susceptible *Candida* species, oral fluconazole at a dosage of 200 mg (3 mg/kg) daily for 2 weeks is recommended (A-III). For fluconazole-resistant organisms, AmB-d at a dosage of 0.3–0.6 mg/kg daily for 1–7 days or oral flucytosine at a dosage of 25 mg/kg 4 times daily for 7–10 days are alternatives (B-III). AmB-d bladder irrigation is generally not recommended but may be useful for treatment of patients with fluconazole-resistant *Candida* species, especially *C. glabrata* (B-III).

27. For pyelonephritis due to fluconazole-susceptible organisms, oral fluconazole at a dosage of 200–400 mg (3–6 mg/

kg) daily for 2 weeks is recommended (B-III). For patients with fluconazole-resistant *Candida* strains, especially *C. glabrata*, alternatives include AmB-d at a dosage of 0.5–0.7 mg/kg daily with or without flucytosine at a dosage of 25 mg/kg 4 times daily (B-III), or flucytosine alone at a dosage of 25 mg/kg 4 times daily (B-III) for 2 weeks.

28. For fungus balls, surgical intervention is strongly recommended in nonneonates (B-III). Fluconazole at a dosage of 200–400 mg (3–6 mg/kg) daily is recommended (B-III). AmB-d at a dosage of 0.5–0.7 mg/kg daily with or without flucytosine at a dosage of 25 mg/kg 4 times daily is an alternative (B-III). If access to the renal collecting system is available, an adjunct to systemic therapy is irrigation with AmB-d at a concentration of 50 mg/L of sterile water (B-III). Treatment duration should be until symptoms have resolved and urine cultures no longer yield *Candida* species (B-III).

Evidence Summary

The presence of yeast in the urine, whether microscopically visualized or grown in culture, must be evaluated in the context of the particular clinical setting to determine its relevance and the need for antifungal therapy. If no predisposing condition is uncovered in an asymptomatic patient, only observation is warranted [129, 130]. Among patients with predisposing conditions, management of that condition alone, such as removal of an indwelling catheter, may be sufficient to eliminate candiduria without specific antifungal therapy. Several conditions require an aggressive approach to persistent candiduria, even among asymptomatic patients. These include neonates with low birth weight and severely immunocompromised patients with fever and candiduria, in whom disseminated candidiasis should be considered. For *Candida* cystitis, fluconazole is the drug of first choice. It is highly water-soluble, primarily excreted in urine in its active form, and easily achieves urine levels exceeding the MIC for most *Candida* strains. No other currently available azole is useful, because of minimal excretion of active drug into urine. For patients who have cystitis and who are allergic to fluconazole or who clearly experience treatment failure despite maximum doses and optimal management of urologic abnormalities, treatment with oral flucytosine, systemic AmB-d, and bladder irrigation with AmB-d are alternatives.

Flucytosine demonstrates good activity against most *Candida* isolates and is concentrated in urine. Treatment with flucytosine is limited by toxicity and the development of resistance when flucytosine is used alone; it is not recommended as primary therapy for patients with uncomplicated *Candida* cystitis.

Irrigation of the bladder with a suspension of AmB-d resolves candiduria in >90% of patients [131], but there is a high relapse rate. This approach is generally discouraged except as a measure to treat refractory cystitis due to azole-resistant organisms, such as *C. glabrata* and *C. krusei*.

For most patients with *Candida* pyelonephritis, fluconazole is the drug of choice. However, *C. glabrata* accounts for ~20% of urine isolates obtained from adults [132, 133], and such infections frequently require treatment with AmB-d. LFAmB should not be considered as a first choice because of presumed low concentrations of the drug in renal tissue. Failure of LFAmB therapy has been described in the treatment of *Candida* pyelonephritis in experimental animals and patients [22, 134].

There are several animal studies and a report describing a small number of patients in which echinocandins were used successfully for the treatment of renal parenchymal infections [135, 136]. Although there are clinical circumstances, such as renal insufficiency and/or the isolation of fluconazole-resistant organisms, in which an echinocandin or voriconazole may be considered for the treatment of *Candida* pyelonephritis, the Expert Panel does not currently recommend these agents because of very limited clinical data and poor urinary concentrations.

Candida prostatitis and epididymo-orchitis are rare [137–139]. Most patients will require surgical drainage of abscesses or other surgical debridement, as well as antifungal therapy. Fluconazole is the agent of choice, but treatment recommendations are based on anecdotal data.

Fungus balls can occur anywhere in the urinary collecting system. Aggressive surgical debridement is central to successful treatment in most nonneonatal cases. Systemic treatment with AmB-d (with or without flucytosine) or fluconazole has been used most often [140, 141]. If a percutaneous device provides direct access to the renal pelvis, ureters, or bladder, local irrigation with AmB-d at a dosage of 50 mg/L of sterile water should be considered as an adjunct to systemic antifungal therapy, but the optimal dose and duration of AmB-d irrigation have not been defined [141]. Other methods to facilitate the breakdown and passage of fungus balls include intermittent saline irrigation, debulking of the fungal mass through a percutaneous device, and irrigation with streptokinase [142–144].

VI. WHAT IS THE TREATMENT FOR VULVOVAGINAL CANDIDIASIS (VVC)?

Recommendations

29. Several topical antifungal agents are effective therapy for VVC, and no agent is clearly superior (table 4) (A-I).

30. A single 150-mg dose of fluconazole is recommended for the treatment of uncomplicated *Candida* VVC (A-I).

31. For recurring *Candida* VVC, 10–14 days of induction therapy with a topical or oral azole, followed by fluconazole at a dosage of 150 mg once per week for 6 months, is recommended (A-I).

Evidence Summary

VVC is usually caused by *C. albicans* but can be caused by other *Candida* species. A diagnosis of *Candida* VVC can usually

Table 4. Intravaginal agents.

Butoconazole 2% cream 5 g intravaginally for 3 days OR
Butoconazole 2% cream 5 g (butoconazole1-sustained release), single intravaginal application OR
Clotrimazole 1% cream 5 g intravaginally for 7–14 days OR
Clotrimazole 100-mg vaginal tablet for 7 days OR
Clotrimazole 100-mg vaginal tablet, 2 tablets for 3 days OR
Miconazole 2% cream 5 g intravaginally for 7 days OR
Miconazole 100-mg vaginal suppository, 1 suppository for 7 days OR
Miconazole 200-mg vaginal suppository, 1 suppository for 3 days OR
Miconazole 1200-mg vaginal suppository, 1 suppository for 1 day OR
Nystatin 100,000-unit vaginal tablet, 1 tablet for 14 days OR
Tioconazole 6.5% ointment 5 g intravaginally in a single application OR
Terconazole 0.4% cream 5 g intravaginally for 7 days OR
Terconazole 0.4% cream 5 g intravaginally for 3 days OR
Terconazole 80-mg vaginal suppository, 1 suppository for 3 days

be made clinically when a woman complains of pruritus, irritation, vaginal soreness, external dysuria, and dyspareunia often accompanied by a change in vaginal discharge. Signs include vulvar edema, erythema, excoriation, fissures, and a white, thick, curd-like vaginal discharge. Unfortunately, these symptoms and signs are nonspecific and can be the result of a variety of infectious and noninfectious etiologies. Before proceeding with empirical antifungal therapy, diagnosis should be confirmed by a wet mount preparation with use of saline and 10% potassium hydroxide to demonstrate the presence of yeast or hyphae. In addition, VVC is associated with normal pH (<4.5). For those with negative wet mount findings, vaginal cultures for *Candida* should be obtained.

VVC can be classified as either uncomplicated (as in ~90% of cases) or complicated (~10% of cases) on the basis of clinical presentation, microbiological findings, host factors, and response to therapy [145]. Complicated VVC is defined as severe or recurrent disease, infection due to *Candida* species other than *C. albicans*, and/or VVC in an abnormal host [145]. A variety of topical and systemic or oral agents are available. No evidence exists to show the superiority of any topical agent formulation or regimen [146, 147]. Similarly, oral and topical antimycotics achieve entirely equivalent results [148]. Uncomplicated VVC can be effectively treated with either single-dose or short-course therapy, both of which achieve >90% response. Complicated VVC requires topical therapy administered intravaginally daily for ~7 days or multiple doses of fluconazole (150 mg every 72 h for 3 doses) [147]. Therapy with an azole, including voriconazole, is frequently unsuccessful for *C. glabrata* VVC. Topical boric acid, administered in a gelatin capsule at a dosage of 600 mg daily for 14 days, may be successful [149]. Other alternatives include topical 17% flucytosine cream alone or in combination with 3% AmB cream administered daily for 14 days; these agents must be compounded by a pharmacy. Azole-resistant *C. albicans* infections are extremely rare [150].

Recurrent VVC is defined as ⩾4 episodes of symptomatic VVC within 1 year and is usually caused by azole-susceptible *C. albicans* [151]. After control of contributing factors, such as diabetes, induction therapy with 10–14 days of a topical or oral azole should be followed by a suppressive regimen for at least 6 months. The most convenient and well-tolerated regimen is once weekly oral fluconazole at a dose of 150 mg, which achieves control of symptoms in >90% of patients [151]. After cessation of maintenance therapy, a 40%–50% recurrence rate can be anticipated. If fluconazole therapy is not feasible, topical clotrimazole (200 mg twice weekly) or clotrimazole (500-mg vaginal suppository once weekly) or other intermittent topical azole treatments are advised. Treatment of VVC should not differ on the basis of HIV infection status; identical response rates are anticipated for HIV-positive and HIV-negative women.

VII. WHAT IS THE TREATMENT FOR CHRONIC DISSEMINATED CANDIDIASIS?

Recommendations

32. Fluconazole at a dosage of 400 mg (6 mg/kg) daily is recommended for clinically stable patients (A-III). LFAmB at a dosage of 3–5 mg/kg daily or AmB-d at a dosage of 0.5–0.7 mg/kg daily can be used to treat acutely ill patients or patients with refractory disease (A-III). Induction therapy with AmB for 1–2 weeks, followed by oral fluconazole at a dosage of 400 mg (6 mg/kg) daily, is also recommended (B-III).

33. Anidulafungin (loading dose of 200 mg, then 100 mg daily), micafungin (100 mg daily), or caspofungin (loading dose of 70 mg, then 50 mg daily for 1–2 weeks) are alternatives for initial therapy, followed by oral fluconazole when clinically appropriate (B-III).

34. Therapy should be continued for weeks to months, until calcification occurs or lesions resolve (A-III). Premature discontinuation of antifungal therapy can lead to recurrent infection.

35. Patients with chronic disseminated candidiasis who require ongoing chemotherapy or undergo stem cell transplantation should continue to receive antifungal therapy throughout the period of high risk to prevent relapse (A-III).

Evidence Summary

Approaches to this syndrome, also termed hepatosplenic candidiasis, are based on anecdotal case reports and open-label series. The bulk of the data and clinical experience are with AmB-d [152, 153], LFAmB [154], and fluconazole [155, 156].

Some experts feel it helpful to begin treatment with AmB for 1–2 weeks, followed by fluconazole therapy for as long as several months. Caspofungin [157], micafungin [54], and voriconazole [158] have also been used successfully in small numbers of cases. Receipt of therapy for several months and until lesions have either calcified or cleared radiographically is essential to prevent relapse. Additional chemotherapy and stem cell transplantation can proceed when clinically appropriate, provided that antifungal therapy is continued. A novel approach recently put forward is to consider this syndrome, which almost always appears during recovery from neutropenia, to be a form of immune reconstitution inflammatory syndrome and to use corticosteroids in conjunction with antifungal agents for treatment [159]. Additional studies will be required in order to establish the benefit of this approach.

VIII. WHAT IS THE TREATMENT FOR OSTEOARTICULAR CANDIDA INFECTIONS?

Recommendations

36. For osteomyelitis, the Expert Panel recommends fluconazole at a dosage of 400 mg (6 mg/kg) daily for 6–12 months or LFAmB at a dosage of 3–5 mg/kg daily for at least 2 weeks, followed by fluconazole at a dosage of 400 mg daily for 6–12 months (B-III). Alternatives include an echinocandin or AmB-d at a dosage of 0.5–1 mg/kg daily for at least 2 weeks, followed by fluconazole at a dosage of 400 mg daily for 6–12 months (B-III). Surgical debridement in selected cases is advised (B-III).

37. For septic arthritis, the Expert Panel recommends treatment for at least 6 weeks with fluconazole at a dosage of 400 mg (6 mg/kg) daily or LFAmB at a dosage of 3–5 mg/kg daily for at least 2 weeks, followed by fluconazole at a dosage of 400 mg daily (B-III). Alternatives include an echinocandin or AmB-d at a dosage of 0.5–1 mg/kg daily for at least 2 weeks, followed by fluconazole at a dosage of 400 mg daily for the remainder of therapy (B-III). Surgical debridement is indicated in all cases (A-III).

38. For infection involving a prosthetic device, device removal is recommended for most cases (A-III). Therapy for at least 6 weeks with the above dosages of fluconazole, LFAmB, an echinocandin, or AmB-d is recommended (B-III). If the device cannot be removed, chronic suppression with fluconazole is recommended (B-III).

Evidence Summary

Approaches to osteoarticular infections are based on anecdotal case reports and open-label series. The published experience is heavily dominated by reports of use of AmB-d, fluconazole, and more recently, caspofungin. Use of LFAmB, other azoles, and other echinocandins would appear to be reasonable, but experience is limited.

Candida osteomyelitis appears to be best treated with surgical debridement of the affected area in conjunction with antifungal therapy. Some authors have shown that surgical therapy is important for vertebral osteomyelitis [160, 161], but this is not a commonly held view. AmB-d at a dosage of 0.5–1 mg/kg daily for 6–10 weeks has been used successfully [161]. Fluconazole has been used successfully as initial therapy for patients who have susceptible isolates, although treatment failures have also been reported [162–165]. There are reports of the use of itraconazole [166] and caspofungin [167]. The addition of AmB-d to bone cement appears to be safe and may be of value in complicated cases [168]. The data suggest that surgical debridement and an initial course of AmB for 2–3 weeks, followed by treatment with fluconazole for a total duration of therapy of 6–12 months, would also be rational.

On the basis of a small number of cases, *Candida* mediastinitis and sternal osteomyelitis in patients who have undergone sternotomy can be treated successfully with surgical debridement followed by either AmB or fluconazole [163, 169]. Irrigation of the mediastinal space with AmB-d is not recommended, because it can cause irritation. Antifungal therapy of several months' duration, similar to that needed for osteomyelitis at other sites, appears to be appropriate.

Adequate drainage is critical to successful therapy of *Candida* arthritis. In particular, management of *Candida* arthritis of the hip requires open drainage. Case reports have documented cures with AmB, fluconazole, and caspofungin therapy in combination with adequate drainage [170–172]. Administration of either AmB or fluconazole produces substantial synovial fluid levels, so that intra-articular therapy is not necessary. Therapy for at least 6 weeks is required in most cases.

Candida prosthetic joint infection generally requires resection arthroplasty, although success with medical therapy alone has been described [173, 174]. Antifungal therapy mirrors that for native joint infection. A new prosthesis may be inserted after documentation of clearance of the infection, typically weeks or months after prosthetic joint removal. If the prosthetic device cannot be removed, then chronic suppression with an antifungal, usually fluconazole, is necessary.

IX. WHAT IS THE TREATMENT FOR CNS CANDIDIASIS IN ADULTS?

Recommendations

39. LFAmB at a dosage of 3–5 mg/kg daily, with or without flucytosine at a dosage of 25 mg/kg 4 times daily, is recommended for the initial several weeks of treatment (B-III).

40. Fluconazole at a dosage of 400–800 mg (6–12 mg/kg) daily is recommended as step-down therapy after the patient responds to initial treatment with LFAmB and flucytosine. Therapy should continue until all signs and symptoms, CSF

abnormalities, and radiologic abnormalities have resolved (B-III).

41. Removal of infected ventricular devices is recommended (A-III).

Evidence Summary

CNS *Candida* infections in adults can occur as a manifestation of disseminated candidiasis, as a complication of a neurosurgical procedure (especially after CSF shunt placement), or as an isolated chronic infection [175–181]. Meningitis is the most common presentation, but multiple small abscesses throughout the brain parenchyma, large solitary brain abscesses, and epidural abscesses have been reported [182–184]. Most cases are due to *C. albicans*, with very few reports of *C. glabrata* and other species causing infection [176, 178, 179, 181, 183].

No randomized controlled trials have been performed to evaluate the most appropriate treatment. Single cases and small series are reported, and most experience has accrued with the use of AmB-d, with or without flucytosine [175, 176, 178–181]. The Expert Panel favors LFAmB because of the decreased risk of nephrotoxicity. L-AmB attained higher levels in the brain than did ABLC and AmB-d in a rabbit model of *Candida* meningoencephalitis [23], and there is some clinical experience with use of this formulation for *Candida* meningitis in neonates [185]. The combination of AmB and flucytosine is appealing because of the in vitro synergism noted with the combination and the excellent CSF concentrations achieved by flucytosine [181]. The length of therapy with AmB alone or in combination with flucytosine has not been defined, but the Expert Panel favors several weeks of therapy before transition to treatment with an azole (after the patient has shown clinical and CSF improvement).

Fluconazole achieves excellent levels in CSF and brain tissue and has proved useful for treatment of *Candida* CNS infections as step-down therapy after AmB and flucytosine [175–177]. Fluconazole has been used successfully as sole therapy [175, 176, 179, 186], but treatment failures also have been noted, and it is not favored by the Expert Panel as primary therapy [175, 176, 179, 187]. On the basis of these limited data, the Expert Panel recommends that fluconazole as initial therapy be reserved for those patients for whom LFAmB is contraindicated. Fluconazole combined with flucytosine has been reported to cure *Candida* meningitis in a few patients [178, 188].

There are no reports of the use of voriconazole or posaconazole for CNS candidiasis. Voriconazole achieves excellent levels in CSF [36], but posaconazole CSF levels are low [189]. For the rare case of *C. glabrata* or *C. krusei* meningitis, voriconazole seems to be appropriate therapy after initial treatment with AmB and flucytosine.

Echinocandins have been used infrequently for CNS candidiasis. There are case reports of both treatment failure and success [184, 190], and there are reports of CNS breakthrough infections after therapy for candidemia. These agents cannot be recommended for CNS candidiasis.

Removal of an infected ventricular device without the administration of an antifungal agent has proved curative in some patients [176, 177, 179]. However, most physicians combine device removal with systemic antifungal therapy or use both systemic and intraventricular AmB-d injected into the device before its removal [175, 179].

X. WHAT IS THE TREATMENT FOR CANDIDA ENDOPHTHALMITIS?

Recommendations

42. AmB-d at a dosage of 0.7–1 mg/kg daily, combined with flucytosine at a dosage of 25 mg/kg administered 4 times daily, is recommended for advancing lesions or lesions threatening the macula (A-III). Fluconazole at a dosage of 400–800 mg daily (loading dose of 12 mg/kg then 6–12 mg/kg daily) is an acceptable alternative for less severe endophthalmitis (B-III). LFAmB at a dosage of 3–5 mg/kg daily, voriconazole at a dosage of 6 mg/kg twice daily for 2 doses and 3–4 mg/kg twice daily thereafter, or an echinocandin can be used to treat patients who are intolerant of or experiencing treatment failure with AmB-d in combination with flucytosine or fluconazole (B-III).

43. The recommended duration of therapy is at least 4–6 weeks and is determined by the stabilization or resolution of lesions as documented by repeated ophthalmological examinations (A-III).

44. All patients with candidemia should have at least 1 dilated retinal examination early in the course of therapy, preferably performed by an ophthalmologist (A-II). It is especially important to examine patients who cannot communicate regarding visual disturbances.

45. A diagnostic vitreal aspirate is recommended for patients with endophthalmitis of unknown origin (A-III). The Expert Panel strongly recommends ophthalmologic consultation for consideration of partial vitrectomy and intravitreal antifungal therapy with AmB-d for all patients with severe endophthalmitis and vitreitis (B-III).

Evidence Summary

There are no prospective studies for the treatment of *Candida* endophthalmitis. The majority of published cases report the use of intravenous and/or intravitreal AmB-d with or without oral flucytosine as initial therapy [191–195]. Oral or intravenous fluconazole has also been used successfully as initial, salvage, and transition therapy [195, 196]. Although the data are very limited, LFAmB, the echinocandins, and voriconazole are reasonable options for treatment of patients who are not responding to conventional therapy with AmB-d or fluconazole [197–200]. However, caution is advised with use of the echinocandins because of their poor ocular penetration. Voriconazole

at a dosage of 3–4 mg/kg twice daily appears to be safe and achieves excellent intravitreal levels [35]; it can also be given topically [201]. Among the newer antifungal agents, the published experience is greatest with voriconazole [35, 197, 200, 201].

Early surgical intervention with a partial vitrectomy is an important adjunct to antifungal therapy in more-advanced cases and can be a sight-saving procedure [195]. The value of intraocular instillation of antifungals at the time of vitrectomy, in addition to standard systemic and topical therapy, has not been well studied, but it is commonly practiced. The optimal duration of antifungal therapy has not been determined, but most experts advise at least 4–6 weeks of systemic treatment and continuation of treatment until all clinical evidence of intraocular infection has resolved.

The definitive diagnosis of *Candida* endophthalmitis still rests on the isolation of the organism from the vitreous body by culture methods or histopathological identification of the organism. There are few data on the value of non–culture-based methodology, such as PCR, in this condition [202].

XI. WHAT IS THE TREATMENT FOR CANDIDA INFECTIONS OF THE CARDIOVASCULAR SYSTEM?

Recommendations

46. For native valve endocarditis, LFAmB at a dosage of 3–5 mg/kg daily with or without flucytosine at a dosage of 25 mg/kg 4 times daily is recommended (B-III). Alternatives include AmB-d at a dosage of 0.6–1 mg/kg daily with or without flucytosine at a dosage of 25 mg/kg 4 times daily or an echinocandin (higher dosages may be necessary than for treatment of candidemia; e.g., caspofungin at a dosage of 50–150 mg daily, micafungin at a dosage of 100–150 mg daily, or anidulafungin at a dosage of 100–200 mg daily) (B-III). Step-down therapy to fluconazole at a dosage of 400–800 mg (6–12 mg/kg) daily should be considered among patients with susceptible *Candida* isolates who have demonstrated clinical stability and clearance of *Candida* from the bloodstream (B-III). Valve replacement is recommended, and treatment should continue for at least 6 weeks after valve replacement and should continue for a longer duration in patients with perivalvular abscesses and other complications (B-III).

47. For patients who cannot undergo valve replacement, long-term suppression with fluconazole at a dosage of 400–800 mg (6–12 mg/kg) daily is recommended (B-III).

48. For prosthetic valve endocarditis (PVE), the recommendations above apply, and suppressive therapy should be lifelong if valve replacement is not possible (B-III).

49. For pericarditis, LFAmB at a dosage of 3–5 mg/kg daily, AmB-d at a dosage of 0.6–1 mg/kg daily, an echinocandin administered at the dosages noted in recommendation 46, or fluconazole at a dosage of 400–800 mg (6–12 mg/kg) daily for as long as several months, in combination with either a pericardial window or pericardiectomy, is recommended (B-III). Step-down therapy to fluconazole at a dosage of 400–800 mg (6–12 mg/kg) daily should be considered for patients who have initially responded to AmB or an echinocandin and who are clinically stable (B-III).

50. For myocarditis, treatment as for endocarditis (as outlined in recommendation 46) is recommended (B-III).

51. For suppurative thrombophlebitis, catheter removal and incision and drainage or resection of the vein, if feasible, is recommended (B-III). LFAmB at a dosage of 3–5 mg/kg daily, AmB-d at a dosage of 0.6–1 mg/kg daily, fluconazole at a dosage of 400–800 mg (6–12 mg/kg) daily, or an echinocandin at the dosages noted in recommendation 46 for at least 2 weeks after candidemia has cleared is recommended (B-III). Step-down therapy to fluconazole at a dosage of 400–800 mg (6–12 mg/kg) daily should be considered for patients who have initially responded to AmB or an echinocandin and who are clinically stable (B-III). Resolution of the thrombus can be used as evidence to discontinue antifungal therapy if clinical and culture data are supportive (B-III).

52. For pacemaker and implantable cardiac defibrillator wire infections, removal of the entire device and systemic antifungal therapy with LFAmB at a dosage of 3–5 mg/kg daily with or without flucytosine at a dosage of 25 mg/kg 4 times daily, AmB-d at a dosage of 0.6–1 mg/kg daily with or without flucytosine at a dosage of 25 mg/kg 4 times daily, or an echinocandin at the dosages noted in recommendation 46 is recommended (B-III). Step-down therapy to fluconazole at a dosage of 400–800 mg (6–12 mg/kg) daily should be considered for patients with susceptible *Candida* isolates who have demonstrated clinical stability and clearance of *Candida* from the bloodstream (B-III). For infections limited to generators and/or pockets, 4 weeks of antifungal therapy after removal of the device is recommended (B-III). For pacemaker and implantable cardiac defibrillator wire infections, at least 6 weeks of antifungal therapy after wire removal is recommended (B-III).

53. For ventricular assist devices that cannot be removed, treatment with LFAmB, AmB-d, or an echinocandin at the dosages noted in recommendation 46 is recommended (B-III). After candidemia has cleared and the patient has responded clinically, fluconazole at a dosage of 400–800 mg (6–12 mg/kg) daily is recommended as step-down therapy (B-III). Chronic suppressive therapy with fluconazole is warranted until the device is removed (B-III).

Evidence Summary

Medical therapy of endocarditis has occasionally been curative [203–211], but the optimum therapy for both native and prosthetic valve endocarditis in adults is a combination of valve

replacement and a long course of antifungal therapy [212, 213]. This recommendation is based on anecdotal case reports, case series, and clinical experience. Valve repair and vegetectomy are alternatives to valve replacement. Most of the cases reported in the literature have been treated with AmB-d with or without flucytosine [205, 212–217]. Azoles, usually fluconazole, have been used for completion of therapy. Because of less toxicity and the ability to administer higher dosages, LFAmB are currently favored over AmB-d. A prospective, open-label clinical trial and several case reports show a role for the echinocandins in the treatment of endocarditis [209, 211, 218–224]. Caspofungin at a dosage of 50–150 mg daily has been used successfully; data are limited for the other echinocandins. Higher-than-usual dosages of the echinocandins may be necessary to treat *Candida* endocarditis. Other cases have been reported of successful treatment using caspofungin in combination with LFAmB, fluconazole, or voriconazole [209, 221, 222].

In neonates, medical therapy alone, usually with AmB-d, has been most frequently used [216, 217]. Success rates for the treatment of neonatal *Candida* endocarditis are comparable for those treated medically and those treated with combined medical and surgical therapy [216]. Mural endocarditis, an entity associated with a high failure rate, has been successfully treated with caspofungin combined with voriconazole [222].

Lifelong suppressive therapy with fluconazole at a dosage of 400–800 mg daily has been successfully used after a course of primary therapy in patients for whom cardiac surgery is judged to be unacceptably risky and also has been advocated to prevent late recurrence of *Candida* PVE [221, 225]. Because *Candida* endocarditis has a propensity to relapse months to years later, follow-up should be maintained for several years [214, 215].

Most experience in the treatment of pericarditis is with AmB-d or fluconazole, as noted in case reports and small series [226, 227]. A few patients have been cured with only pericardiocentesis and antifungal therapy [226], but the preferred procedures are creation of a pericardial window or pericardiectomy. There are few other data to guide therapy. Antifungal treatment should continue for several months until resolution of signs and symptoms of pericardial inflammation.

AmB-d or LFAmB, with or without flucytosine, and voriconazole have all been used successfully to treat myocarditis. Treatment duration may need to be for as long as several months if myocardial abscesses are present [228].

Although most experience treating suppurative thrombophlebitis has been with AmB-d, the Expert Panel supports the use of LFAmB because of decreased nephrotoxicity and the need to treat for prolonged periods. Fluconazole therapy has also been successful in some cases [229, 230]. Any of the agents used for primary treatment of candidemia, including echinocandins and voriconazole, should be effective [231]. Surgical excision of the vein plays an important role in the treatment of peripheral *Candida* thrombophlebitis. When a central vein is involved, surgery is not usually an option. In some cases, systemic anticoagulation or thrombolytic therapy has been used as adjunctive therapy, but there are insufficient data to routinely recommend their use.

There are a few case reports of *Candida* infections of transvenous pacemakers [232, 233] and implantable cardiac defibrillators [234, 235]. Combined surgical and medical therapy is advocated [232, 234, 235]. Medical therapy alone has failed [233]. There is a paucity of data on *Candida* infections of ventricular assist devices, but the Expert Panel feels that suppressive azole therapy after initial AmB or echinocandin therapy is warranted until the device is removed.

XII. WHAT IS THE TREATMENT FOR NEONATAL CANDIDIASIS?

Recommendations

54. AmB-d at a dosage of 1 mg/kg daily is recommended for neonates with disseminated candidiasis (A-II). If urinary tract involvement is excluded, LFAmB at a dosage of 3–5 mg/kg daily can be used (B-II). Fluconazole at a dosage of 12 mg/kg daily is a reasonable alternative (B-II). The recommended length of therapy is 3 weeks (B-II).

55. A lumbar puncture and a dilated retinal examination are recommended in neonates with sterile body fluid and/or urine cultures positive for *Candida* species (B-III). Imaging of the genitourinary tract, liver, and spleen should be performed if sterile body fluid cultures have persistently positive results (B-III).

56. Echinocandins should be used with caution and generally limited to situations in which resistance or toxicity preclude the use of fluconazole or AmB-d (B-III).

57. Intravascular catheter removal is strongly recommended (A-II).

58. In nurseries with high rates of invasive candidiasis, fluconazole prophylaxis may be considered in neonates with birth weights <1000 g (A-I). Antifungal drug resistance, drug-related toxicity, and neurodevelopmental outcomes should be observed (A-III).

Evidence Summary

Neonatal candidiasis differs from invasive disease in older patients. Neonates present with subtle symptoms. The primary risk factors are prematurity and day of life; younger and premature infants are more often infected. Dosing of antifungal agents is substantially different for neonates than it is for older children. Outcomes for neonates differ markedly from those for older patients. Although mortality is lower (~20%) in neonates, these infants frequently have CNS disease [236]. CNS involvement in the neonate usually manifests as meningoencephalitis and should be assumed to be present in the neonate

with candidemia because of the high incidence of this complication. Neurologic impairment is common in survivors; therefore, careful follow-up of neurodevelopmental parameters is important.

Failure to promptly remove or replace central venous catheters for infants with candidemia places the infant at increased risk of prolonged infection, mortality, and long-term irreversible neurodevelopmental impairment [85, 236]. Removal or replacement of the catheter at an anatomically distinct site should be performed unless contraindicated.

Treatment of neonatal candidiasis with fluconazole and AmB-d has been evaluated in small, single-center trials [237–239] and in a multi-center cohort study [236]. Fluconazole and AmB-d both appear to be acceptable choices for therapy. The role of flucytosine in neonates with *Candida* meningitis is questionable and is not routinely recommended [181, 236].

Fluconazole prophylaxis at a dosage of 3 mg/kg or 6 mg/kg twice weekly significantly reduces rates of invasive candidiasis in premature neonates in nurseries that have a very high incidence of *Candida* infections. In 2 recent studies, the incidence of candidiasis in the placebo arms were 20% in neonates weighing <1000 g and 13% in neonates weighing 1000–1500 g [240, 241]. In contrast, most neonatal intensive care units have an incidence of <5% in neonates who weigh <1000 g and ~1% in neonates who weigh 1000–1500 g. Almost 40% of neonatal nurseries have an incidence that is 10-fold less (<2% in neonates who weigh <1000 g) than that reported in the randomized trials [236, 242, 243]. Pharmacokinetic and prospective safety data are very limited for fluconazole in premature infants, and systematic long-term neurologic follow-up data after routine prophylaxis have not been reported. Because there are unknown risks for neurologic and cognitive disorders after fluconazole exposure in neonates, neurodevelopmental parameters should be followed in neonates who receive this agent. The Expert Panel recommends routine fluconazole prophylaxis for premature infants and infants with extremely low birth weights in nurseries that have a high incidence of invasive candidiasis.

XIII. WHAT IS THE SIGNIFICANCE OF CANDIDA ISOLATED FROM RESPIRATORY SECRETIONS?

Recommendation

59. Growth of *Candida* from respiratory secretions rarely indicates invasive candidiasis and should not be treated with antifungal therapy (A-III)

Evidence Summary

Candida pneumonia and lung abscess are very uncommon [244, 245]. *Candida* colonization of the bronchial tree in critically ill patents who receive mechanical ventilation is common, but the lungs have innate defense mechanisms that render them relatively resistant to tissue invasion by *Candida* species. Only rarely after aspiration of oropharyngeal material does a primary *Candida* pneumonia or abscess develop. More commonly, hematogenously disseminated candidiasis produces lesions in the lung, as well as in other organs. Diagnosis of bona fide *Candida* pneumonia requires histopathological confirmation.

In contrast to pneumonia, colonization of the airway with *Candida* species and/or contamination of the respiratory secretions with oropharyngeal material are extremely common. Unfortunately, a positive culture from respiratory secretions is frequently used as an indication to initiate antifungal therapy in febrile patients who have no other evidence of invasive disease. Multiple prospective and retrospective studies, including autopsy studies, consistently demonstrate the poor predictive value of the growth of *Candida* from respiratory secretions, including bronchoalveolar lavage fluid. Because of the rarity of *Candida* pneumonia, the extremely common finding of *Candida* in respiratory secretions, and the lack of specificity of this finding [246–248], a decision to initiate antifungal therapy should not be made on the basis of respiratory tract culture results alone.

XIV. WHAT IS THE TREATMENT FOR NONGENITAL MUCOCUTANEOUS CANDIDIASIS?

Recommendations: oropharyngeal candidiasis

60. For mild disease, clotrimazole troches at a dosage of 10 mg 5 times daily, nystatin suspension at a concentration of 100,000 U/mL and a dosage of 4–6 mL 4 times daily, or 1–2 nystatin pastilles (200,000 U each) administered 4 times daily for 7–14 days is recommended (B-II).

61. For moderate to severe disease, oral fluconazole at a dosage of 100–200 mg (3 mg/kg) daily for 7–14 days is recommended (A-I).

62. For fluconazole-refractory disease, either itraconazole solution at a dosage of 200 mg daily or posaconazole suspension at a dosage of 400 mg twice daily for 3 days, then 400 mg daily for up to 28 days, are recommended (A-II). Voriconazole at a dosage of 200 mg twice daily or a 1-mL oral suspension of AmB-d, administered at a dosage of 100 mg/mL 4 times daily, are recommended when treatment with other agents has failed (B-II). Intravenous echinocandin or AmB-d at a dosage of 0.3 mg/kg daily can be used in treating patients with refractory disease (B-II).

63. Chronic suppressive therapy is usually unnecessary for patients with HIV infection (A-I). If suppressive therapy is required, fluconazole at a dosage of 100 mg 3 times weekly is recommended (A-I). Treatment with HAART is recommended to reduce recurrent infections (A-I).

64. For denture-related candidiasis, disinfection of the denture, in addition to antifungal therapy, is recommended (B-II).

Recommendations: esophageal candidiasis

65. Systemic antifungal therapy is always required (A-II). Oral fluconazole at a dosage of 200–400 mg (3–6 mg/kg) daily for 14–21 days is recommended (A-I). Intravenous fluconazole at a dosage of 400 mg (6 mg/kg) daily, AmB-d at a dosage of 0.3–0.7 mg/kg daily, or an echinocandin should be used for patients who cannot tolerate oral therapy (B-II). A diagnostic trial of antifungal therapy is appropriate before performing an endoscopic examination (B-II).

66. For fluconazole-refractory disease, itraconazole solution at a dosage of 200 mg daily, posaconazole suspension at a dosage of 400 mg twice daily, or voriconazole at a dosage of 200 mg twice daily administered intravenously or orally for 14–21 days is recommended (A-III). Micafungin at a dosage of 150 mg daily, caspofungin at a dosage of 50 mg daily, anidulafungin at a dosage of 200 mg daily, or AmB-d at a dosage of 0.3–0.7 mg/kg daily are acceptable alternatives (B-II).

67. Suppressive therapy with fluconazole at a dosage of 100–200 mg 3 times weekly is recommended for recurrent infections (A-I).

68. In patients with AIDS, treatment with HAART is recommended to reduce recurrent infections (A-I).

Evidence Summary

Most cases of oropharyngeal and esophageal candidiasis are caused by *C. albicans*, either alone or in mixed infection [249, 250]. Symptomatic infections caused by *C. glabrata* and *C. krusei* alone have been described [251]. Multiple randomized prospective studies of oropharyngeal candidiasis have been performed involving patients with AIDS and patients with cancer. Most patients respond initially to topical therapy [249, 252, 253]. In HIV-infected patients, symptomatic relapses may occur sooner with topical therapy than with fluconazole [252], and resistance may develop with either regimen. Fluconazole and itraconazole solution are superior to ketoconazole and itraconazole capsules [254–256]. A dosage of itraconazole solution of 2.5 mg/kg twice daily has been recommended for pediatric patients ⩾5 years of age [67]. Local effects of oral solutions may be as important as systemic effects. Posaconazole suspension is also as efficacious as fluconazole in patients with AIDS [257].

Recurrent infections typically occur in patients with ongoing immunosuppression, especially those who have AIDS. Long-term suppressive therapy with fluconazole is effective in the prevention of oropharyngeal candidiasis [30, 258, 259]. Long-term suppressive therapy with fluconazole was compared with the episodic use of fluconazole in response to symptomatic disease. Continuous suppressive therapy reduced the relapse rate more effectively than did intermittent therapy, but it was associated with increased microbiological resistance. The frequency of refractory disease was the same for the 2 groups [30]. Oral AmB-d, nystatin, and itraconazole capsules are less effective than fluconazole in preventing oropharyngeal candidiasis [260, 261].

Fluconazole-refractory infections should be treated initially with itraconazole solution. Between 64% and 80% of patients will respond to this therapy [251, 262]. Posaconazole suspension is efficacious in ~74% of patients with refractory oropharyngeal or esophageal candidiasis [263], and voriconazole may be efficacious for fluconazole-refractory infections [264]. Intravenous caspofungin, micafungin, or anidulafungin are reasonable alternatives to the triazoles [47–50]. Oral or intravenous AmB-d is also effective in some patients [265]. Immunomodulation with adjunctive granulocyte-macrophage colony-stimulating factor [266] and IFN-γ [267] have been used for refractory oral candidiasis.

The presence of oropharyngeal candidiasis and dysphagia or odynophagia is predictive of esophageal candidiasis. A therapeutic trial with fluconazole for patients with presumed esophageal candidiasis is a cost-effective alternative to endoscopic examination; most patients with esophageal candidiasis will have resolution of their symptoms within 7 days after the start of therapy [268]. Fluconazole is superior to ketoconazole, itraconazole capsules, and flucytosine; itraconazole solution is comparable to fluconazole for the treatment of esophageal candidiasis [269, 270]. Up to 80% of patients with fluconazole-refractory infections will respond to itraconazole solution [262]. Voriconazole is as efficacious as fluconazole and has shown success in the treatment of cases of fluconazole-refractory disease, but it is associated with a higher rate of adverse events [264, 271].

The echinocandins are associated with relapse rates that are higher than those noted with fluconazole [47–50]. Fluconazole-refractory disease responds to caspofungin, and it is likely that micafungin and anidulafungin are similarly effective. In patients with advanced AIDS, recurrent infections are common, and long-term suppressive therapy with fluconazole is effective in preventing recurrences [30].

In HIV-infected patients, the use of HAART has been associated with decreasing rates of oral carriage of *C. albicans* and reduced frequency of symptomatic oropharyngeal candidiasis [272]. Thus, HAART should be used as adjunctive therapy whenever possible for all HIV-infected patients with oropharyngeal or esophageal candidiasis.

Chronic mucocutaneous candidiasis is a rare condition that is characterized by chronic, persistent onychomycosis and mucocutaneous lesions due to *Candida* species. Some patients have a thymoma or autoimmune polyendocrinopathy syndrome type 1 [273]. Fluconazole should be used as initial therapy for candidiasis in these patients. Response to antifungal therapy

may be delayed when there is extensive skin or nail involvement, and relapses almost invariably occur. Thus, most patients require chronic suppressive antifungal therapy. Development of fluconazole-refractory infections is common [274]. Patients with fluconazole-refractory *Candida* infections should be treated similar to patients with AIDS who have fluconazole-refractory infections.

XV. SHOULD ANTIFUNGAL PROPHYLAXIS BE USED FOR SOLID-ORGAN TRANSPLANT RECIPIENTS, ICU PATIENTS, NEUTROPENIC PATIENTS RECEIVING CHEMOTHERAPY, AND STEM CELL TRANSPLANT RECIPIENTS AT RISK OF CANDIDIASIS?

Recommendations

69. For solid-organ transplant recipients, fluconazole at a dosage of 200–400 mg (3–6 mg/kg) daily or LAmB at a dosage of 1–2 mg/kg daily, each for at least 7–14 days, is recommended as postoperative prophylaxis for high-risk liver (A-I), pancreas (B-II), and small bowel (B-III) transplant recipients.

70. For ICU patients, fluconazole at a dosage of 400 mg (6 mg/kg) daily is recommended for high-risk patients in adult units with a high incidence of invasive candidiasis (B-I).

71. For patients with chemotherapy-induced neutropenia, fluconazole at a dosage of 400 mg (6 mg/kg) daily (A-I), posaconazole at a dosage of 200 mg 3 times per day (A-I), or caspofungin at a dosage of 50 mg daily (B-II) is recommended during induction chemotherapy for the duration of neutropenia. Oral itraconazole at a dosage of 200 mg daily is an effective alternative (**A-I**) but offers little advantage and is less well tolerated than these agents.

72. For stem cell transplant recipients with neutropenia, fluconazole at a dosage of 400 mg (6 mg/kg) daily, posaconazole at a dosage of 200 mg 3 times daily, or micafungin at a dosage of 50 mg daily is recommended during the period of risk of neutropenia (A-I).

Evidence Summary

Patients who undergo liver transplantation who have at least 2 key risk factors, including retransplantation, creatinine level >2.0 mg/dL, choledochojejunostomy, intraoperative use of >40 U of blood products, prolonged intraoperative time (>1 h), and fungal colonization detected at least 2 days before and 3 days after transplantation have been identified as being at high risk of invasive candidiasis [275, 276]. One retrospective trial using fluconazole [277] and several prospective trials using L-AmB [278] or fluconazole [279, 280] showed reduced rates of invasive fungal infection. The largest study compared fluconazole with placebo, both given for 70 days after surgery, and showed fungal infections in 6% of fluconazole recipients, compared with 23% of placebo recipients [280]. The most recent study of antifungal prophylaxis in high-risk liver transplant recipients compared L-AmB administered at a dosage of 2 mg/kg/day with placebo for 14 days after transplantation and demonstrated a numerical benefit for L-AmB [281].

The risk of candidiasis among pancreas transplant recipients is probably less than that among liver transplant recipients. However, a retrospective review of 445 consecutive pancreas transplant recipients revealed a 6% frequency of intra-abdominal fungal infection in those who received fluconazole prophylaxis at a dosage of 400 mg/day for 7 days after transplantation, compared with a 10% frequency (P = not significant) for those who did not receive prophylaxis [282]. There also were significant improvements in 1-year graft survival rate and overall survival among patients without infection. Small bowel transplant recipients are a group at great risk of invasive fungal infection [283]. There are no randomized trials of antifungal prophylaxis among this small group of patients, but most experts agree that fluconazole at a dosage of 400 mg daily (6 mg/kg daily in children) for at least 2 weeks after transplantation is reasonable. The risk of invasive candidiasis after transplantation of other solid organs, such as kidneys and hearts, appears to be too low to warrant routine prophylaxis [284].

For ICUs that show very high rates of invasive candidiasis, compared with the normal rates of 1%–2%, antifungal prophylaxis may be warranted [285], and selected ICU patients who are at highest risk (>10%) of invasive candidiasis may benefit from antifungal prophylaxis [102]. There are 3 randomized, placebo-controlled trials that have shown a reduction in the incidence of invasive candidiasis in single units or single hospitals selecting patients at high risk of infection [286–288]. Recent meta-analyses have confirmed this finding; however, it is important to stress that the primary studies and subsequent analysis have all failed to show a survival benefit associated with this strategy [289, 290]. None of the above studies of antifungal prophylaxis in the ICU have demonstrated increased resistance to fluconazole or major ecological shifts in *Candida* species.

In neutropenic chemotherapy recipients, a meta-analysis of randomized, placebo-controlled trials has shown that systemically active antifungal agents can reduce the number of superficial and invasive *Candida* infections [291]. A randomized controlled trial showed that receipt of posaconazole decreased invasive fungal infections, compared with receipt of fluconazole or itraconazole in patients with chemotherapy-induced neutropenia who had acute leukemia and myelodysplastic syndrome [127], and an open-label study of prophylaxis with caspofungin versus itraconazole in patients with hematologic malignancies undergoing induction chemotherapy found the 2 drugs to be equivalent [292]. A meta-analysis of 13 randomized controlled trials demonstrated the efficacy of itraconazole (administered orally and intravenously) as antifungal prophylaxis in neutropenic patients with hematologic malignacies, but itra-

conazole offers little advantage over many other antifungal agents and is less well tolerated [293].

In stem cell transplant recipients, micafungin administered at a dosage of 50 mg daily before engraftment significantly reduced episodes of candidiasis, compared with fluconazole administered at a dosage of 400 mg daily, and was associated with a trend toward lower rates of aspergillosis [128]. After transplantation, posaconazole was shown to be more effective than fluconazole in preventing invasive fungal infections in stem cell transplant recipients who had severe graft-versus-host disease [126]. A recently completed randomized, double-blind study that compared fluconazole (400 mg daily) with voriconazole (200 mg twice daily) for 100 days after transplantation as primary antifungal prophylaxis in allogeneic stem cell transplant recipients demonstrated no significant differences in the incidence of invasive fungal infection or fungus-free survival [294]. The usefulness of other potentially active agents, such as itraconazole and AmB, in stem cell transplant recipients is limited by toxicity, drug-drug interactions, logistical issues, or bioavailability [295]. The optimal duration of prophylaxis is not known but should, at a minimum, include the period of risk of neutropenia.

PERFORMANCE MEASURES

1. All patients with candidemia should undergo a dilated ophthalmological evaluation to exclude *Candida* endophthalmitis. This procedure has direct therapeutic implications, because patients with endophthalmitis may require surgery and local therapy, and patients with disseminated disease require longer courses of systemic therapy. We suggest that this be performed at a time when the candidemia appears to be controlled and when new spread to the eye is unlikely. Neutropenic patients may not manifest visible endophthalmitis until recovery from neutropenia; therefore, ophthalmological examination in neutropenic patients should be performed after recovery of the neutrophil count.
2. Antifungal therapy should be started on all candidemic patients within 24 h after a blood culture positive for yeast. Recent studies stress the importance of addressing a positive blood culture result with prompt initiation of systemic antifungal therapy, because delays are associated with increased mortality.

Follow-up blood cultures should be obtained for all patients with candidemia to ensure clearance of *Candida* from the bloodstream. The Expert Panel recommends that blood cultures be performed daily or every other day until they no longer yield yeast.

EXPERT PANEL SPECIALTIES

The following members of the Expert Panel specialized in infectious diseases: P.G.P. (Chair), C.A.K., D.A., T.F.C., J.E.E., S.G.F., J.F.F., B.-J.K., L.O.-Z., A.C.R., J.H.R., and J.D.S. The following members of the Expert Panel specialized in pediatric infectious diseases: D.K.B. and T.J.W.

Acknowledgments

The Expert Panel thanks Drs. William Dismukes, Preeti N. Malani, Marcio Nucci, and Coleman Rotstein for their thoughtful review of earlier drafts of the guidelines.

Financial support. The Infectious Diseases Society of America.

Potential conflicts of interest. P.G.P. has received honoraria and research grants and has served as a consultant to Schering-Plough, Astellas Pharma, Merck, Novartis, Basilea, and Pfizer Pharmaceuticals. D.A. has served as an advisor and received honoraria from Pfizer Pharmaceuticals, Merck, and Astellas Pharma and has received research grants from Astellas Pharma, Pfizer Pharmaceuticals, and the National Institutes of Health. D.K.B. has received research funding from Astellas Pharma, Biosynexus, Associates of Cape Cod, Pfizer, Rockeby, National Institute of Child Health and Human Development, and Thrasher Research Fund and has received organizational grants from AstraZeneca International, Johnson and Johnson, Medicines Company, MedImmune, and Pfizer. T.C. has served as a consultant to Pfizer Pharmaceuticals, Merck, and Novartis and has received honoraria from Pfizer Pharmaceuticals, Merck, Novartis, Schering Plough, and Roche Diagnostics. S.G.F. has received research grants from Pfizer, Amgen, and Merck; has received research funding from the National Institutes of Health and Columbia University; has served as a consultant for Theravance, Forest Pharmaceuticals, and Semorex; and holds stock in NovaDigm Therapeutics. J.F.F. has received honoraria from Pfizer Pharmaceuticals, Merck, and Wyeth. C.A.K. receives royalties from UpToDate and Springer Publisher and has received funding from Merck, the Centers for Disease Control and Prevention, Astellas Pharma, and Romark Laboratories. B.-J.K. has served as a consultant or advisor to Basilea Pharmaceutica, Novartis, Pfizer Pharmaceuticals, and Schering-Plough and has received honoraria from MSD, Pfizer Pharmaceuticals, and Schering-Plough. L.O.-Z. has served as a consultant for Astellas Pharma, Merck, Pfizer Pharmaceuticals, and Viracor; has received honoraria from Gilead, Merck, Pfizer, and Astellas Pharma; and has received research grants from Merck, Pfizer Pharmaceuticals, Astellas Pharma, Basilea Pharmaceutica, Associates of Cape Cod, and Viracor. A.C.R. has served as a consultant or advisor for Pfizer Pharmaceuticals, Astellas Pharma, and Merck; has received honoraria from Pfizer Pharmaceuticals; and has received research grants from Pfizer Pharmaceuticals and Merck. J.E.E. has received research funding from Schering-Plough, Schering, Enzon, Merck, Basilea Pharmaceutica, Pfizer Pharmaceuticals, Astellas Pharma, and Cubist Pharmaceuticals; has been on the scientific advisory boards of Merck, Pfizer, Gilead, Enzon, Cerexa, and Calixia; and is a founder of NovaDigm Therapeutics. J.D.S. has received honoraria from Pfizer Pharmaceuticals, Merck, and KV Pharmaceuticals; has received research funding from Pfizer Pharmaceuticals, Merck, and Astellas Pharma; and has served as a consultant for Merck, Pfizer, and Embil. T.J.W. has received research funding from Astellas Pharma and Vicuron through the Cooperative Research and Development Agreement. J.F.R. is an employee of Astra Zeneca.

References

1. Fridkin SK. The changing face of fungal infections in health care settings. Clin Infect Dis **2005**; 41:1455–60.
2. Pappas PG, Rex JH, Lee J, et al. A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. Clin Infect Dis **2003**; 37: 634–43.
3. Tortorano AM, Peman J, Bernhardt H, et al. Epidemiology of candidaemia in Europe: results of 28-month European Confederation of Medical Mycology (ECMM) hospital-based surveillance study. Eur J Clin Microbiol Infect Dis **2004**; 23:317–22.
4. Trick WE, Fridkin SK, Edwards JR, Hajjeh RA, Gaynes RP. Secular

trend of hospital-acquired candidemia among intensive care unit patients in the United States during 1989–1999. Clin Infect Dis **2002**; 35:627–30.
5. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis **2004**; 39:309–17.
6. Marr KA, Seidel K, White TC, Bowden RA. Candidemia in allogeneic blood and marrow transplant recipients: evolution of risk factors after the adoption of prophylactic fluconazole. J Infect Dis **2000**; 181: 309–16.
7. Viscoli C, Girmenia C, Marinus A, et al. Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). Clin Infect Dis **1999**; 28:1071–9.
8. Marchetti O, Bille J, Fluckiger U, et al. Epidemiology of candidemia in Swiss tertiary care hospitals: secular trends, 1991–2000. Clin Infect Dis **2004**; 38:311–20.
9. Arendrup MC, Fuursted K, Gahrn-Hansen B, et al. Seminational surveillance of fungemia in Denmark: notably high rates of fungemia and numbers of isolates with reduced azole susceptibility. J Clin Microbiol **2005**; 43:4434–40.
10. Richet H, Roux P, Des Champs C, Esnault Y, Andremont A. Candidemia in French hospitals: incidence rates and characteristics. Clin Microbiol Infect **2002**; 8:405–12.
11. Gudlaugsson O. Attributable mortality of nosocomial candidemia, revisited. Clin Infect Dis **2003**; 37:1172–7.
12. Zaoutis TE, Argon J, Chu J, Berlin JA, Walsh TJ, Feudtner C. The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the United States: a propensity analysis. Clin Infect Dis **2005**; 41:1232–9.
13. Morgan J, Meltzer MI, Plikaytis BD, et al. Excess mortality, hospital stay, and cost due to candidemia: a case-control study using data from population-based candidemia surveillance. Infect Control Hosp Epidemiol **2005**; 26:540–7.
14. Field MJ. Institute of Medicine Committee to Advise the Public Health Service on Clinical Practice Guidelines, Clinical Practice Guidelines: Directions for a New Program. Washington, DC: National Academy Press, **1990**.
15. Canadian Task Force on the Periodic Health Examination. The periodic health examination. Can Med Assoc J **1979**; 121:1193–254.
16. Linden P, Lee L, Walsh TJ. Retrospective analysis of the dosage of amphotericin B lipid complex for the treatment of invasive fungal infections. Pharmacotherapy **1999**; 19:1261–8.
17. Walsh TJ, Whitcomb P, Piscitelli S, et al. Safety, tolerance, and pharmacokinetics of amphotericin B lipid complex in children with hepatosplenic candidiasis. Antimicrob Agents Chemother **1997**; 41: 1944–8.
18. Deray G. Amphotericin B nephrotoxicity. J Antimicrob Chemother **2002**; 49(Suppl 1):37–41.
19. Bowden RA, Cays M, Gooley T, Mamelok RD, van Burik JA. Phase I study of amphotericin B colloidal dispersion for the treatment of invasive fungal infections after marrow transplant. J Infect Dis **1996**; 173:1208–15.
20. Walsh TJ, Hiemenz JW, Seibel NL, et al. Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. Clin Infect Dis **1998**; 26:1383–96.
21. Wingard JR. Lipid formulations of amphotericins: are you a lumper or a splitter? Clin Infect Dis **2002**; 35:891–5.
22. Agustin J, Lacson S, Raffalli J, Aguero-Rosenfeld ME, Wormser GP. Failure of a lipid amphotericin B preparation to eradicate candiduria: preliminary findings based on three cases. Clin Infect Dis **1999**; 29: 686–7.
23. Groll AH, Giri N, Petraitis V, et al. Comparative efficacy and distribution of lipid formulations of amphotericin B in experimental *Candida albicans* infection of the central nervous system. J Infect Dis **2000**; 182:274–82.
24. Bates DW, Su L, Yu DT, et al. Mortality and costs of acute renal failure associated with amphotericin B therapy. Clin Infect Dis **2001**; 32: 686–93.
25. Pfaller MA, Diekema DJ, Sheehan DJ. Interpretive breakpoints for fluconazole and *Candida* revisited: a blueprint for the future of antifungal susceptibility testing. Clin Microbiol Rev **2006**; 19:435–47.
26. Espinel-Ingroff A, Barchiesi F, Cuenca-Estrella M, et al. International and multicenter comparison of EUCAST and CLSI M27-A2 broth microdilution methods for testing susceptibilities of *Candida* spp. to fluconazole, itraconazole, posaconazole, and voriconazole. J Clin Microbiol **2005**; 43:3884–9.
27. Rex JH, Bennett JE, Sugar AM, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. Candidemia Study Group and the National Institute. N Engl J Med **1994**; 331:1325–30.
28. Rex JH, Pappas PG, Karchmer AW, et al. A randomized and blinded multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia and its consequences in nonneutropenic subjects. Clin Infect Dis **2003**; 36: 1221–8.
29. Sobel JD, Kapernick PS, Zervos M, et al. Treatment of complicated *Candida vaginitis:* comparison of single and sequential doses of fluconazole. Am J Obstet Gynecol **2001**;185:363–9.
30. Goldman M, Cloud GA, Wade KD, et al. A randomized study of the use of fluconazole in continuous versus episodic therapy in patients with advanced HIV infection and a history of oropharyngeal candidiasis: AIDS Clinical Trials Group Study 323/Mycoses Study Group Study 40. Clin Infect Dis **2005**; 41:1473–80.
31. Arndt CA, Walsh TJ, McCully CL, Balis FM, Pizzo PA, Poplack DG. Fluconazole penetration into cerebrospinal fluid: implications for treating fungal infections of the central nervous system. J Infect Dis **1988**; 157:178–80.
32. Eichel M, Just-Nubling G, Helm EB, Stille W. Itraconazole suspension in the treatment of HIV-infected patients with fluconazole-resistant oropharyngeal candidiasis and esophagitis. Mycoses **1996**; 39(Suppl 1):102–6.
33. Lange D, Pavao JH, Wu J, Klausner M. Effect of a cola beverage on the bioavailability of itraconazole in the presence of H2 blockers. J Clin Pharmacol **1997**; 37:535–40.
34. Van Peer A, Woestenborghs R, Heykants J, Gasparini R, Gauwenbergh G. The effects of food and dose on the oral systemic availability of itraconazole in healthy subjects. Eur J Clin Pharmacol **1989**; 36:423–6.
35. Hariprasad SM, Mieler WF, Holz ER, et al. Determination of vitreous, aqueous, and plasma concentration of orally administered voriconazole in humans. Arch Ophthalmol **2004**; 122:42–7.
36. Lutsar I, Roffey S, Troke P. Voriconazole concentrations in the cerebrospinal fluid and brain tissue of guinea pigs and immunocompromised patients. Clin Infect Dis **2003**; 37:728–32.
37. Leveque D, Nivoix Y, Jehl F, Herbrecht R. Clinical pharmacokinetics of voriconazole. Int J Antimicrob Agents **2006**; 27:274–84.
38. von Mach MA, Burhenne J, Weilemann LS. Accumulation of the solvent vehicle sulphobutylether beta cyclodextrin sodium in critically ill patients treated with intravenous voriconazole under renal replacement therapy. BMC Clin Pharmacol **2006**; 6:6.
39. Smith J, Safdar N, Knasinski V, et al. Voriconazole therapeutic drug monitoring. Antimicrob Agents Chemother **2006**; 50:1570–2.
40. Ikeda Y, Umemura K, Kondo K, Sekiguchi K, Miyoshi S, Nakashima M. Pharmacokinetics of voriconazole and cytochrome P450 2C19 genetic status. Clin Pharmacol Ther **2004**; 75:587–8.
41. Courtney R, Pai S, Laughlin M, Lim J, Batra V. Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. Antimicrob Agents Chemother **2003**; 47:2788–95.
42. Chandrasekar PH, Sobel JD. Micafungin: a new echinocandin. Clin Infect Dis **2006**; 42:1171–8.

43. Vazquez JA, Sobel JD. Anidulafungin: a novel echinocandin. Clin Infect Dis **2006**; 43:215–22.
44. Deresinski SC, Stevens DA. Caspofungin. Clin Infect Dis **2003**; 36: 1445–57.
45. Walsh TJ. Echinocandins—an advance in the primary treatment of invasive candidiasis. N Engl J Med **2002**; 347:2070–2.
46. Bennett JE. Echinocandins for candidemia in adults without neutropenia. N Engl J Med **2006**; 355:1154–9.
47. Villanueva A, Arathoon EG, Gotuzzo E, Berman RS, DiNubile MJ, Sable CA. A randomized double-blind study of caspofungin versus amphotericin for the treatment of candidal esophagitis. Clin Infect Dis **2001**; 33:1529–35.
48. Villanueva A, Gotuzzo E, Arathoon EG, et al. A randomized double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis. Am J Med **2002**; 113:294–9.
49. de Wet N, Llanos-Cuentas A, Suleiman J, et al. A randomized, double-blind, parallel-group, dose-response study of micafungin compared with fluconazole for the treatment of esophageal candidiasis in HIV-positive patients. Clin Infect Dis **2004**; 39:842–9.
50. Krause DS, Simjee AE, van Rensburg C, et al. A randomized, double-blind trial of anidulafungin versus fluconazole for the treatment of esophageal candidiasis. Clin Infect Dis **2004**; 39:770–5.
51. Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med **2002**; 347: 2020–9.
52. Kuse ER, Chetchotisakd P, da Cunha CA, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. Lancet **2007**; 369:1519–27.
53. Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med **2007**; 356:2472–82.
54. Pappas PG, Rotstein CM, Betts RF, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. Clin Infect Dis **2007**; 45:883–93.
55. Schonebeck J, Polak A, Fernex M, Scholer HJ. Pharmacokinetic studies on the oral antimycotic agent 5-fluorocytosine in individuals with normal and impaired kidney function. Chemotherapy **1973**; 18: 321–36.
56. Stamm AM, Diasio RB, Dismukes WE, et al. Toxicity of amphotericin B plus flucytosine in 194 patients with cryptococcal meningitis. Am J Med **1987**; 83:236–42.
57. Groll AH, Piscitelli SC, Walsh TJ. Clinical pharmacology of systemic antifungal agents: a comprehensive review of agents in clinical use, current investigational compounds, and putative targets for antifungal drug development. Adv Pharmacol **1998**; 44:343–500.
58. Steinbach WJ. Antifungal agents in children. Pediatr Clin North Am **2005**; 52:895–915.
59. van den Anker JN, van Popele NM, Sauer PJ. Antifungal agents in neonatal systemic candidiasis. Antimicrob Agents Chemother **1995**; 39:1391–7.
60. Juster-Reicher A, Leibovitz E, Linder N, et al. Liposomal amphotericin B (AmBisome) in the treatment of neonatal candidiasis in very low birth weight infants. Infection **2000**; 28:223–6.
61. Baley JE, Meyers C, Kliegman RM, Jacobs MR, Blumer JL. Pharmacokinetics, outcome of treatment, and toxic effects of amphotericin B and 5-fluorocytosine in neonates. J Pediatr **1990**; 116:791–7.
62. Lee JW, Seibel NL, Amantea M, Whitcomb P, Pizzo PA, Walsh TJ. Safety and pharmacokinetics of fluconazole in children with neoplastic diseases. J Pediatr **1992**; 120:987–93.
63. Saxen H, Hoppu K, Pohjavuori M. Pharmacokinetics of fluconazole in very low birth weight infants during the first two weeks of life. Clin Pharmacol Ther **1993**; 54:269–77.
64. Seay RE, Larson TA, Toscano JP, Bostrom BC, O'Leary MC, Uden DL. Pharmacokinetics of fluconazole in immune-compromised children with leukemia or other hematologic diseases. Pharmacotherapy **1995**; 15:52–8.
65. Wade KC, Wu D, Kaufman DA, et al. Population pharmacokinetics of fluconazole in young infants. Antimicrob Agents Chemother **2008**; 52:4043–9.
66. de Repentigny L, Ratelle J, Leclerc JM, et al. Repeated-dose pharmacokinetics of an oral solution of itraconazole in infants and children. Antimicrob Agents Chemother **1998**; 42:404–8.
67. Groll AH, Wood L, Roden M, et al. Safety, pharmacokinetics, and pharmacodynamics of cyclodextrin itraconazole in pediatric patients with oropharyngeal candidiasis. Antimicrob Agents Chemother **2002**; 46:2554–63.
68. Walsh TJ, Karlsson MO, Driscoll T, et al. Pharmacokinetics and safety of intravenous voriconazole in children after single- or multiple-dose administration. Antimicrob Agents Chemother **2004**; 48:2166–72.
69. Steinbach WJ, Benjamin DK. New antifungal agents under development in children and neonates. Curr Opin Infect Dis **2005**; 18: 484–9.
70. Seibel NL, Schwartz C, Arrieta A, et al. Safety, tolerability, and pharmacokinetics of Micafungin (FK463) in febrile neutropenic pediatric patients. Antimicrob Agents Chemother **2005**; 49:3317–24.
71. Heresi GP, Gerstmann DR, Reed MD, et al. The pharmacokinetics and safety of micafungin, a novel echinocandin, in premature infants. Pediatr Infect Dis J **2006**; 25:1110–5.
72. Benjamin DK Jr, Driscoll T, Seibel NL, et al. Safety and pharmacokinetics of intravenous anidulafungin in children with neutropenia at high risk for invasive fungal infections. Antimicrob Agents Chemother **2006**; 50:632–8.
73. Smith PB. Pharmacokinetics of an elevated dosage of micafungin in premature neonates. Ped Infect Dis J (in press).
74. Moudgal VV, Sobel JD. Antifungal drugs in pregnancy: a review. Expert Opin Drug Saf **2003**; 2:475–83.
75. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin Infect Dis **2008**; 46:201–11.
76. Clinical and Laboratory Standards Institute (CLSI). Reference method for broth dilution antifungal susceptibility testing of yeasts: Approved standard, 3rd. ed. CLSI document M27-A3. Wayne, PA: CLSI, **2008**.
77. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of *Candida* bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. Antimicrob Agents Chemother **2005**; 49:3640–5.
78. Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. Clin Infect Dis **2006**; 43:25–31.
79. Kullberg BJ, Sobel JD, Ruhnke M, et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. Lancet **2005**; 366:1435–42.
80. Wiederhold NP, Lewis RE. The echinocandin antifungals: an overview of the pharmacology, spectrum and clinical efficacy. Expert Opin Investig Drugs **2003**; 12:1313–33.
81. Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: a persistent public health problem. Clin Microbiol Rev **2007**; 20:133–63.
82. Nguyen MH, Peacock JE Jr, Tanner DC, et al. Therapeutic approaches in patients with candidemia: evaluation in a multicenter, prospective, observational study. Arch Intern Med **1995**; 155:2429–35.
83. Rex JH, Bennett JE, Sugar AM, et al. Intravascular catheter exchange and duration of candidemia. NIAID Mycoses Study Group and the Candidemia Study Group. Clin Infect Dis **1995**; 21:994–6.
84. Luzzati R, Amalfitano G, Lazzarini L, et al. Nosocomial candidemia in non-neutropenic patients at an Italian tertiary care hospital. Eur J Clin Microbiol Infect Dis **2000**; 19:602–7.
85. Karlowicz MG, Hashimoto LN, Kelly RE Jr, Buescher ES. Should central venous catheters be removed as soon as candidemia is detected in neonates? Pediatrics **2000**; 106:E63.
86. Nucci M, Anaissie E. Revisiting the source of candidemia: skin or gut? Clin Infect Dis **2001**; 33:1959–67.
87. Anaissie EJ, Rex JH, Uzun O, Vartivarian S. Predictors of adverse

outcome in cancer patients with candidemia. Am J Med **1998**; 104: 238–45.
88. Anaissie EJ, Vartivarian SE, Abi-Said D, et al. Fluconazole versus amphotericin B in the treatment of hematogenous candidiasis: a matched cohort study. Am J Med **1996**; 101:170–6.
89. Betts R, Glasmacher A, Maertens J, et al. Efficacy of caspofungin against invasive *Candida* or invasive *Aspergillus* infections in neutropenic patients. Cancer **2006**; 106:466–73.
90. Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. N Engl J Med **1999**; 340:764–71.
91. Walsh TJ, Teppler H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med **2004**; 351: 1391–402.
92. Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med **2002**; 346:225–34.
93. Pittet D, Monod M, Suter PM, Frenk E, Auckenthaler R. *Candida* colonization and subsequent infections in critically ill surgical patients. Ann Surg **1994**; 220:751–8.
94. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Risk factors for hospital-acquired candidemia: a matched case-control study. Arch Intern Med **1989**; 149:2349–53.
95. Calandra T, Bille J, Schneider R, Mosimann F, Francioli P. Clinical significance of *Candida* isolated from peritoneum in surgical patients. Lancet **1989**; 2:1437–40.
96. Blumberg HM, Jarvis WR, Soucie JM, et al. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. The National Epidemiology of Mycosis Survey. Clin Infect Dis **2001**; 33:177–86.
97. Puzniak L, Teutsch S, Powderly W, Polish L. Has the epidemiology of nosocomial candidemia changed? Infect Control Hosp Epidemiol **2004**; 25:628–33.
98. Leleu G, Aegerter P, Guidet B. Systemic candidiasis in intensive care units: a multicenter, matched-cohort study. J Crit Care **2002**; 17: 168–75.
99. Sandven P, Giercksky KE. Yeast colonization in surgical patients with intra-abdominal perforations. Eur J Clin Microbiol Infect Dis **2001**; 20:475–81.
100. Leon C, Ruiz-Santana S, Saavedra P, et al. A bedside scoring system ("*Candida* score") for early antifungal treatment in nonneutropenic critically ill patients with *Candida* colonization. Crit Care Med **2006**; 34:730–7.
101. Paphitou NI, Ostrosky-Zeichner L, Rex JH. Rules for identifying patients at increased risk for candidal infections in the surgical intensive care unit: approach to developing practical criteria for systematic use in antifungal prophylaxis trials. Med Mycol **2005**; 43:235–43.
102. Ostrosky-Zeichner L, Sable C, Sobel J, et al. Multicenter retrospective development and validation of a clinical prediction rule for nosocomial invasive candidiasis in the intensive care setting. Eur J Clin Microbiol Infect Dis **2007**; 26:271–6.
103. Sendid B, Jouault T, Coudriau R, et al. Increased sensitivity of mannanemia detection tests by joint detection of α- and β-linked oligomannosides during experimental and human systemic candidiasis. J Clin Microbiol **2004**; 42:164–71.
104. Ostrosky-Zeichner L, Alexander BD, Kett DH, et al. Multicenter clinical evaluation of the (1→3) β-D-glucan assay as an aid to diagnosis of fungal infections in humans. Clin Infect Dis **2005**; 41:654–9.
105. Obayashi T. Reappraisal of the serum (1→3)-β-D-glucan assay for the diagnosis of invasive fungal infections: a study basd on autopsy cases from 6 years. Clin Infect Dis **2008**; 46:1864–70.
106. Odabasi Z, Mattiuzzi G, Estey E, et al. Beta-D-glucan as a diagnostic adjunct for invasive fungal infections: validation, cutoff development, and performance in patients with acute myelogenous leukemia and myelodysplastic syndrome. Clin Infect Dis **2004**; 39:199–205.
107. McMullen R, Metwally L, Coyle, PV, et al. A prospective clinical trial of a real-time PCR assay for the diagnosis of candidemia in nonneutropenic, critically ill adults. Clin Infect Dis **2008**; 46:890–6.
108. Piarroux R, Grenouillet F, Balvay P, et al. Assessment of preemptive treatment to prevent severe candidiasis in critically ill surgical patients. Crit Care Med **2004**; 32:2443–9.
109. Shan YS, Sy ED, Wang ST, Lee JC, Lin PW. Early presumptive therapy with fluconazole for occult *Candida* infection after gastrointestinal surgery. World J Surg **2006**; 30:119–26.
110. Schuster MG, Edwards JE Jr, Sobel JD, et al. Empirical fluconazole versus placebo for intensive care unit patients: a randomized trial. Ann Intern Med **2008**; 149:83–90.
111. Hughes WT, Armstrong D, Bodey GP, et al. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis **2002**; 34:730–51.
112. Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. Am J Med **1982**; 72:101–11.
113. Empiric antifungal therapy in febrile granulocytopenic patients. EORTC International Antimicrobial Therapy Cooperative Group. Am J Med **1989**; 86:668–72.
114. Caillot D, Casasnovas O, Bernard A, et al. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. J Clin Oncol **1997**; 15:139–47.
115. Caillot D, Couaillier JF, Bernard A, et al. Increasing volume and changing characteristics of invasive pulmonary aspergillosis on sequential thoracic computed tomography scans in patients with neutropenia. J Clin Oncol **2001**; 19:253–9.
116. Maertens J, Verhaegen J, Lagrou K, Van Eldere J, Boogaerts M. Screening for circulating galactomannan as a noninvasive diagnostic tool for invasive aspergillosis in prolonged neutropenic patients and stem cell transplantation recipients: a prospective validation. Blood **2001**; 97:1604–10.
117. Prella M, Bille J, Pugnale M, et al. Early diagnosis of invasive candidiasis with mannan antigenemia and antimannan antibodies. Diagn Microbiol Infect Dis **2005**; 51:95–101.
118. Senn L, Robinson JO, Schmidt S, et al. 1,3-β-D-glucan antigenemia for early diagnosis of invasive fungal infections in neutropenic patients with acute leukemia. Clin Infect Dis **2008**; 46:878–85.
119. Maertens J, Theunissen K, Verhoef G, et al. Galactomannan and computed tomography–based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. Clin Infect Dis **2005**; 41:1242–50.
120. White MH, Bowden RA, Sandler ES, et al. Randomized, double-blind clinical trial of amphotericin B colloidal dispersion vs. amphotericin B in the empirical treatment of fever and neutropenia. Clin Infect Dis **1998**; 27:296–302.
121. Wingard JR, White MH, Anaissie E, Raffalli J, Goodman J, Arrieta A. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. L Amph/ABLC Collaborative Study Group. Clin Infect Dis **2000**; 31:1155–63.
122. Winston DJ, Hathorn JW, Schuster MG, Schiller GJ, Territo MC. A multicenter, randomized trial of fluconazole versus amphotericin B for empiric antifungal therapy of febrile neutropenic patients with cancer. Am J Med **2000**; 108:282–9.
123. Malik IA, Moid I, Aziz Z, Khan S, Suleman M. A randomized comparison of fluconazole with amphotericin B as empiric anti-fungal agents in cancer patients with prolonged fever and neutropenia. Am J Med **1998**; 105:478–83.
124. Viscoli C, Castagnola E, Van Lint MT, et al. Fluconazole versus amphotericin B as empirical antifungal therapy of unexplained fever in granulocytopenic cancer patients: a pragmatic, multicentre, prospective and randomised clinical trial. Eur J Cancer **1996**; 32A:814–20.
125. Boogaerts M, Winston DJ, Bow EJ, et al. Intravenous and oral itraconazole versus intravenous amphotericin B deoxycholate as empirical

antifungal therapy for persistent fever in neutropenic patients with cancer who are receiving broad-spectrum antibacterial therapy: a randomized, controlled trial. Ann Intern Med **2001**; 135:412–22.
126. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med **2007**; 356:335–47.
127. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med **2007**; 356:348–59.
128. Van Burik JA. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis **2004**; 39: 1407–16.
129. Tambyah PA, Maki DG. Catheter-associated urinary tract infection is rarely symptomatic: a prospective study of 1,497 catheterized patients. Arch Intern Med **2000**; 160:678–82.
130. Kauffman CA, Vazquez JA, Sobel JD, et al. Prospective multicenter surveillance study of funguria in hospitalized patients. The National Institute for Allergy and Infectious Diseases (NIAID) Mycoses Study Group. Clin Infect Dis **2000**; 30:14–8.
131. Jacobs LG, Skidmore EA, Cardoso LA, Ziv F. Bladder irrigation with amphotericin B for treatment of fungal urinary tract infections. Clin Infect Dis **1994**; 18:313–8.
132. Kobayashi CC, de Fernandes OF, Miranda KC, de Sousa ED, Silva Mdo R. Candiduria in hospital patients: a study prospective. Mycopathologia **2004**; 158:49–52.
133. Alvarez-Lerma F, Nolla-Salas J, Leon C, et al. Candiduria in critically ill patients admitted to intensive care medical units. Intensive Care Med **2003**; 29:1069–76.
134. van Etten EW, van den Heuvel-de Groot C, Bakker-Woudenberg IA. Efficacies of amphotericin B-desoxycholate (fungizone), liposomal amphotericin B (ambisome), and fluconazole in the treatment of systemic candidosis in immunocompetent and leucopenic mice. J Antimicrob Chemother **1993**; 32:723–39.
135. Abruzzo GK, Gill CJ, Flattery AM, et al. Efficacy of the echinocandin caspofungin against disseminated aspergillosis and candidiasis in cyclophosphamide-induced immunosuppressed mice. Antimicrob Agents Chemother **2000**; 44:2310–8.
136. Sobel JD, Bradshaw SK, Lipka CJ, Kartsonis NA. Caspofungin in the treatment of symptomatic candiduria. Clin Infect Dis **2007**; 44:e46–9.
137. Wise GJ, Shteynshlyuger A. How to diagnose and treat fungal infections in chronic prostatitis. Curr Urol Rep **2006**; 7:320–8.
138. Bartkowski DP, Lanesky JR. Emphysematous prostatitis and cystitis secondary to *Candida albicans*. J Urol **1988**; 139:1063–5.
139. Jenkin GA, Choo M, Hosking P, Johnson PD. Candidal epididymo-orchitis: case report and review. Clin Infect Dis **1998**; 26:942–5.
140. Chung BH, Chang SY, Kim SI, Choi HS. Successfully treated renal fungal ball with continuous irrigation of fluconazole. J Urol **2001**; 166:1835–6.
141. Bartone FF, Hurwitz RS, Rojas EL, Steinberg E, Franceschini R. The role of percutaneous nephrostomy in the management of obstructing candidiasis of the urinary tract in infants. J Urol **1988**; 140:338–41.
142. Shih MC, Leung DA, Roth JA, Hagspiel KD. Percutaneous extraction of bilateral renal mycetomas in premature infant using mechanical thrombectomy device. Urology **2005**; 65:1226.
143. Babu R, Hutton KA. Renal fungal balls and pelvi-ureteric junction obstruction in a very low birth weight infant: treatment with streptokinase. Pediatr Surg Int **2004**; 20:804–5.
144. Chitale SV, Shaida N, Burtt G, Burgess N. Endoscopic management of renal candidiasis. J Endourol **2004**; 18:865–6.
145. Sobel JD, Faro S, Force RW, et al. Vulvovaginal candidiasis: epidemiologic, diagnostic, and therapeutic considerations. Am J Obstet Gynecol **1998**; 178:203–11.
146. Reef SE, Levine WC, McNeil MM, et al. Treatment options for vulvovaginal candidiasis, 1993. Clin Infect Dis **1995**; 20(Suppl 1):S80–90.
147. Sobel JD. Vaginitis. N Engl J Med **1997**; 337:1896–903.
148. Watson MC, Grimshaw JM, Bond CM, Mollison J, Ludbrook A. Oral versus intra-vaginal imidazole and triazole anti-fungal agents for the treatment of uncomplicated vulvovaginal candidiasis (thrush): a systematic review. Bjog **2002**; 109:85–95.
149. Sobel JD, Chaim W, Nagappan V, Leaman D. Treatment of vaginitis caused by *Candida glabrata*: use of topical boric acid and flucytosine. Am J Obstet Gynecol **2003**; 189:1297–300.
150. Sobel JD, Vazquez JA. Symptomatic vulvovaginitis due to fluconazole-resistant *Candida albicans* in a female who was not infected with human immunodeficiency virus. Clin Infect Dis **1996**; 22:726–7.
151. Sobel JD, Wiesenfeld HC, Martens M, et al. Maintenance fluconazole therapy for recurrent vulvovaginal candidiasis. N Engl J Med **2004**; 351:876–83.
152. Thaler M, Pastakia B, Shawker TH, O'Leary T, Pizzo PA. Hepatic candidiasis in cancer patients: the evolving picture of the syndrome. Ann Intern Med **1988**; 108:88–100.
153. Walsh TJ, Whitcomb PO, Revankar SG, Pizzo PA. Successful treatment of hepatosplenic candidiasis through repeated cycles of chemotherapy and neutropenia. Cancer **1995**; 76:2357–62.
154. Gokhale PC, Barapatre RJ, Advani SH, Kshirsagar NA, Pandya SK. Successful treatment of disseminated candidiasis resistant to amphotericin B by liposomal amphotericin B: a case report. J Cancer Res Clin Oncol **1993**; 119:569–71.
155. Anaissie E, Bodey GP, Kantarjian H, et al. Fluconazole therapy for chronic disseminated candidiasis in patients with leukemia and prior amphotericin B therapy. Am J Med **1991**; 91:142–50.
156. Kauffman CA, Bradley SF, Ross SC, Weber DR. Hepatosplenic candidiasis: successful treatment with fluconazole. Am J Med **1991**; 91: 137–41.
157. Sora F, Chiusolo P, Piccirillo N, et al. Successful treatment with caspofungin of hepatosplenic candidiasis resistant to liposomal amphotericin B. Clin Infect Dis **2002**; 35:1135–6.
158. Ostrosky-Zeichner L, Oude Lashof AM, Kullberg BJ, Rex JH. Voriconazole salvage treatment of invasive candidiasis. Eur J Clin Microbiol Infect Dis **2003**; 22:651–5.
159. Legrand F, Lecuit M, Dupont B, et al. Adjuvant corticosteroid therapy for chronic disseminated candidiasis. Clin Infect Dis **2008**; 46: 696–702.
160. Hendrickx L, Van Wijngaerden E, Samson I, Peetermans WE. Candidal vertebral osteomyelitis: report of 6 patients, and a review. Clin Infect Dis **2001**; 32:527–33.
161. Miller DJ, Mejicano GC. Vertebral osteomyelitis due to *Candida* species: case report and literature review. Clin Infect Dis **2001**; 33:523–30.
162. Hennequin C, Bouree P, Hiesse C, Dupont B, Charpentier B. Spondylodiskitis due to *Candida albicans*: report of two patients who were successfully treated with fluconazole and review of the literature. Clin Infect Dis **1996**; 23:176–8.
163. Malani PN, McNeil SA, Bradley SF, Kauffman CA. *Candida albicans* sternal wound infections: a chronic and recurrent complication of median sternotomy. Clin Infect Dis **2002**; 35:1316–20.
164. Sugar AM, Saunders C, Diamond RD. Successful treatment of *Candida osteomyelitis* with fluconazole: a noncomparative study of two patients. Diagn Microbiol Infect Dis **1990**; 13:517–20.
165. Dan M, Priel I. Failure of fluconazole therapy for sternal osteomyelitis due to *Candida albicans*. Clin Infect Dis **1994**; 18:126–7.
166. Petrikkos G, Skiada A, Sabatakou H, Antoniadou A, Dosios T, Giamarellou H. Case report: successful treatment of two cases of post-surgical sternal osteomyelitis, due to *Candida krusei* and *Candida albicans*, respectively, with high doses of triazoles (fluconazole, itraconazole). Mycoses **2001**; 44:422–5.
167. Legout L, Assal M, Rohner P, Lew D, Bernard L, Hoffmeyer P. Successful treatment of *Candida parapsilosis* (fluconazole-resistant) osteomyelitis with caspofungin in a HIV patient. Scand J Infect Dis **2006**; 38:728–30.
168. Marra F, Robbins GM, Masri BA, et al. Amphotericin B–loaded bone cement to treat osteomyelitis caused by *Candida albicans*. Can J Surg **2001**; 44:383–6.

169. Clancy CJ, Nguyen MH, Morris AJ. Candidal mediastinitis: an emerging clinical entity. Clin Infect Dis **1997**; 25:608–13.
170. Harris MC, Pereira GR, Myers MD, et al. Candidal arthritis in infants previously treated for systemic candidiasis during the newborn period: report of three cases. Pediatr Emerg Care **2000**; 16:249–51.
171. Weigl JA. Candida arthritis in a premature infant treated successfully with oral fluconazole for six months. Ann Acad Med Singapore **2000**; 29:253–5.
172. Sim JP, Kho BC, Liu HS, Yung R, Chan JC. *Candida tropicalis* arthritis of the knee in a patient with acute lymphoblastic leukaemia: successful treatment with caspofungin. Hong Kong Med J **2005**; 11:120–3.
173. Merrer J, Dupont B, Nieszkowska A, De Jonghe B, Outin H. *Candida albicans* prosthetic arthritis treated with fluconazole alone. J Infect **2001**; 42:208–9.
174. Tunkel AR, Thomas CY, Wispelwey B. *Candida* prosthetic arthritis: report of a case treated with fluconazole and review of the literature. Am J Med **1993**; 94:100–3.
175. Sanchez-Portocarrero J, Perez-Cecilia E, Corral O, Romero-Vivas J, Picazo JJ. The central nervous system and infection by *Candida* species. Diagn Microbiol Infect Dis **2000**; 37:169–79.
176. Nguyen MH, Yu VL. Meningitis caused by *Candida* species: an emerging problem in neurosurgical patients. Clin Infect Dis **1995**; 21:323–7.
177. Sanchez-Portocarrero J, Martin-Rabadan P, Saldana CJ, Perez-Cecilia E. *Candida* cerebrospinal fluid shunt infection: report of two new cases and review of the literature. Diagn Microbiol Infect Dis **1994**; 20:33–40.
178. Voice RA, Bradley SF, Sangeorzan JA, Kauffman CA. Chronic candidal meningitis: an uncommon manifestation of candidiasis. Clin Infect Dis **1994**; 19:60–6.
179. Geers TA, Gordon SM. Clinical significance of *Candida* species isolated from cerebrospinal fluid following neurosurgery. Clin Infect Dis **1999**; 28:1139–47.
180. Casado JL, Quereda C, Oliva J, et al. Candidal meningitis in HIV-infected patients: analysis of 14 cases. Clin Infect Dis **1997**; 25:673–6.
181. Smego RA Jr, Perfect JR, Durack DT. Combined therapy with amphotericin B and 5-fluorocytosine for *Candida* meningitis. Rev Infect Dis **1984**; 6:791–801.
182. Burgert SJ, Classen DC, Burke JP, Blatter DD. Candidal brain abscess associated with vascular invasion: a devastating complication of vascular catheter-related candidemia. Clin Infect Dis **1995**; 21:202–5.
183. Bonomo RA, Strauss M, Blinkhorn R, Salata RA. *Torulopsis (Candida) glabrata*: a new pathogen found in spinal epidural abscess. Clin Infect Dis **1996**; 22:588–9.
184. Prabhu RM, Orenstein R. Failure of caspofungin to treat brain abscesses secondary to *Candida albicans* prosthetic valve endocarditis. Clin Infect Dis **2004**; 39:1253–4.
185. Scarcella A, Pasquariello MB, Giugliano B, Vendemmia M, de Lucia A. Liposomal amphotericin B treatment for neonatal fungal infections. Pediatr Infect Dis J **1998**; 17:146–8.
186. Gurses N, Kalayci AG. Fluconazole monotherapy for candidal meningitis in a premature infant. Clin Infect Dis **1996**; 23:645–6.
187. Epelbaum S, Laurent C, Morin G, Berquin P, Piussan C. Failure of fluconazole treatment in *Candida* meningitis. J Pediatr **1993**; 123: 168–9.
188. Marr B, Gross S, Cunningham C, Weiner L. Candidal sepsis and meningitis in a very-low-birth-weight infant successfully treated with fluconazole and flucytosine. Clin Infect Dis **1994**; 19:795–6.
189. Torres HA, Hachem RY, Chemaly RF, Kontoyiannis DP, Raad, II. Posaconazole: a broad-spectrum triazole antifungal. Lancet Infect Dis **2005**; 5:775–85.
190. Liu KH, Wu CJ, Chou CH, et al. Refractory candidal meningitis in an immunocompromised patient cured by caspofungin. J Clin Microbiol **2004**; 42:5950–3.
191. Axelrod AJ, Peyman GA. Intravitreal amphotericin B treatment of experimental fungal endophthalmitis. Am J Ophthalmol **1973**; 76: 584–8.
192. Edwards JE Jr, Foos RY, Montgomerie JZ, Guze LB. Ocular manifestations of *Candida* septicemia: review of seventy-six cases of hematogenous *Candida* endophthalmitis. Medicine Baltimore **1974**; 53: 47–75.
193. Parke DW 2nd, Jones DB, Gentry LO. Endogenous endophthalmitis among patients with candidemia. Ophthalmology **1982**; 89:789–96.
194. McQuillen DP, Zingman BS, Meunier F, Levitz SM. Invasive infections due to *Candida krusei:* report of ten cases of fungemia that include three cases of endophthalmitis. Clin Infect Dis **1992**; 14:472–8.
195. Essman TF, Flynn HW Jr, Smiddy WE, et al. Treatment outcomes in a 10-year study of endogenous fungal endophthalmitis. Ophthalmic Surg Lasers **1997**; 28:185–94.
196. Akler ME, Vellend H, McNeely DM, Walmsley SL, Gold WL. Use of fluconazole in the treatment of candidal endophthalmitis. Clin Infect Dis **1995**; 20:657–64.
197. Breit SM, Hariprasad SM, Mieler WF, Shah GK, Mills MD, Grand MG. Management of endogenous fungal endophthalmitis with voriconazole and caspofungin. Am J Ophthalmol **2005**; 139:135–40.
198. Goldblum D, Rohrer K, Frueh BE, Theurillat R, Thormann W, Zimmerli S. Ocular distribution of intravenously administered lipid formulations of amphotericin B in a rabbit model. Antimicrob Agents Chemother **2002**; 46:3719–23.
199. Darling K, Singh J, Wilks D. Successful treatment of *Candida glabrata* endophthalmitis with amphotericin B lipid complex (ABLC). J Infect **2000**; 40:92–4.
200. Varma D, Thaker HR, Moss PJ, Wedgwood K, Innes JR. Use of voriconazole in *Candida* retinitis. Eye **2005**; 19:485–7.
201. Thiel MA, Zinkernagel AS, Burhenne J, Kaufmann C, Haefeli WE. Voriconazole concentration in human aqueous humor and plasma during topical or combined topical and systemic administration for fungal keratitis. Antimicrob Agents Chemother **2007**; 51:239–44.
202. Hidalgo JA, Alangaden GJ, Eliott D, et al. Fungal endophthalmitis diagnosis by detection of *Candida albicans* DNA in intraocular fluid by use of a species-specific polymerase chain reaction assay. J Infect Dis **2000**; 181:1198–201.
203. Venditti M, De Bernardis F, Micozzi A, et al. Fluconazole treatment of catheter-related right-sided endocarditis caused by *Candida albicans* and associated with endophthalmitis and folliculitis. Clin Infect Dis **1992**; 14:422–6.
204. Czwerwiec FS, Bilsker MS, Kamerman ML, Bisno AL. Long-term survival after fluconazole therapy of candidal prosthetic valve endocarditis. Am J Med **1993**; 94:545–6.
205. Nguyen MH, Nguyen ML, Yu VL, McMahon D, Keys TF, Amidi M. *Candida* prosthetic valve endocarditis: prospective study of six cases and review of the literature. Clin Infect Dis **1996**; 22:262–7.
206. Lejko-Zupanc T, Kozelj M. A case of recurrent *Candida parapsilosis* prosthetic valve endocarditis: cure by medical treatment alone. J Infect **1997**; 35:81–2.
207. Melamed R, Leibovitz E, Abramson O, Levitas A, Zucker N, Gorodisher R. Successful non-surgical treatment of *Candida tropicalis* endocarditis with liposomal amphotericin-B (AmBisome). Scand J Infect Dis **2000**; 32:86–9.
208. Aaron L, Therby A, Viard JP, Lahoulou R, Dupont B. Successful medical treatment of *Candida albicans* in mechanical prosthetic valve endocarditis. Scand J Infect Dis **2003**; 35:351–2.
209. Jimenez-Exposito MJ, Torres G, Baraldes A, et al. Native valve endocarditis due to *Candida glabrata* treated without valvular replacement: a potential role for caspofungin in the induction and maintenance treatment. Clin Infect Dis **2004**; 39:e70–3.
210. Westling K, Thalme A, Julander I. *Candida albicans* tricuspid valve endocarditis in an intravenous drug addict: successful treatment with fluconazole. Scand J Infect Dis **2005**; 37:310–1.
211. Rajendram R, Alp NJ, Mitchell AR, Bowler IC, Forfar JC. *Candida* prosthetic valve endocarditis cured by caspofungin therapy without valve replacement. Clin Infect Dis **2005**; 40:e72–4.
212. Steinbach WJ, Perfect JR, Cabell CH, et al. A meta-analysis of medical

versus surgical therapy for *Candida* endocarditis. J Infect **2005**; 51: 230–47.
213. Ellis ME, Al-Abdely H, Sandridge A, Greer W, Ventura W. Fungal endocarditis: evidence in the world literature, 1965–**1995**. Clin Infect Dis **2001**; 32:50–62.
214. Muehrcke DD, Lytle BW, Cosgrove DM 3rd. Surgical and long-term antifungal therapy for fungal prosthetic valve endocarditis. Ann Thorac Surg **1995**; 60:538–43.
215. Mayayo E, Moralejo J, Camps J, Guarro J. Fungal endocarditis in premature infants: case report and review. Clin Infect Dis **1996**; 22: 366–8.
216. Levy I, Shalit I, Birk E, et al. *Candida* endocarditis in neonates: report of five cases and review of the literature. Mycoses **2006**; 49:43–8.
217. Noyola DE, Fernandez M, Moylett EH, Baker CJ. Ophthalmologic, visceral, and cardiac involvement in neonates with candidemia. Clin Infect Dis **2001**; 32:1018–23.
218. Mrowczynski W, Wojtalik M. Caspofungin for *Candida* endocarditis. Pediatr Infect Dis J **2004**; 23:376.
219. Moudgal V, Little T, Boikov D, Vazquez JA. Multiechinocandin- and multiazole-resistant *Candida parapsilosis* isolates serially obtained during therapy for prosthetic valve endocarditis. Antimicrob Agents Chemother **2005**; 49:767–9.
220. Bacak V, Biocina B, Starcevic B, Gertler S, Begovac J. *Candida albicans* endocarditis treatment with caspofungin in an HIV-infected patient--case report and review of literature. J Infect **2006**; 53:e11–4.
221. Lye DC, Hughes A, O'Brien D, Athan E. *Candida glabrata* prosthetic valve endocarditis treated successfully with fluconazole plus caspofungin without surgery: a case report and literature review. Eur J Clin Microbiol Infect Dis **2005**; 24:753–5.
222. Lopez-Ciudad V, Castro-Orjales MJ, Leon C, et al. Successful treatment of *Candida parapsilosis* mural endocarditis with combined caspofungin and voriconazole. BMC Infect Dis **2006**; 6:73.
223. Cornely OA, Lasso M, Betts R, et al. Caspofungin for the treatment of less common forms of invasive candidiasis. J Antimicrob Chemother **2007**; 60:363–9.
224. Baddley JW, Benjamin DK Jr, Patel M, et al. *Candida* infective endocarditis. Eur J Clin Microbiol Infect Dis **2008**; 27:519–29.
225. Penk A, Pittrow L. Role of fluconazole in the long-term suppressive therapy of fungal infections in patients with artificial implants. Mycoses **1999**; 42(Suppl 2):91–6.
226. Schrank JH Jr, Dooley DP. Purulent pericarditis caused by *Candida* species: case report and review. Clin Infect Dis **1995**; 21:182–7.
227. Neughebauer B, Alvarez V, Harb T, Keefer M. Constrictive pericarditis caused by *Candida glabrata* in an immunocompetent patient: case report and review of literature. Scand J Infect Dis **2002**; 34:615–9.
228. Azizov VA, Kuliev OA, Isaev IM, Aikhanova ZE. Fungal myocarditis in deep visceral candidiasis [in Russian]. Kardiologiia **2002**; 42:56–59.
229. Friedland IR. Peripheral thrombophlebitis caused by *Candida*. Pediatr Infect Dis J **1996**; 15:375–7.
230. Benoit D, Decruyenaere J, Vandewoude K, et al. Management of candidal thrombophlebitis of the central veins: case report and review. Clin Infect Dis **1998**; 26:393–7.
231. Pan SC, Hsieh SM, Chang SC, Lee HT, Chen YC. Septic *Candida krusei* thrombophlebitis of inferior vena cava with persistent fungemia successfully treated by new antifungal agents. Med Mycol **2005**; 43: 731–4.
232. Joly V, Belmatoug N, Leperre A, et al. Pacemaker endocarditis due to *Candida albicans*: case report and review. Clin Infect Dis **1997**; 25: 1359–62.
233. Roger PM, Boissy C, Gari-Toussaint M, et al. Medical treatment of a pacemaker endocarditis due to *Candida albicans* and to *Candida glabrata*. J Infect **2000**; 41:176–8.
234. Brown LA, Baddley JW, Sanchez JE, Bachmann LH. Implantable cardioverter-defibrillator endocarditis secondary to *Candida albicans*. Am J Med Sci **2001**; 322:160–2.
235. Hindupur S, Muslin AJ. Septic shock induced from an implantable cardioverter-defibrillator lead-associated *Candida albicans* vegetation. J Interv Card Electrophysiol **2005**; 14:55–9.
236. Benjamin DK Jr, Stoll BJ, Fanaroff AA, et al. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. Pediatrics **2006**; 117:84–92.
237. Driessen M, Ellis JB, Cooper PA, et al. Fluconazole vs. amphotericin B for the treatment of neonatal fungal septicemia: a prospective randomized trial. Pediatr Infect Dis J **1996**; 15:1107–12.
238. Linder N, Klinger G, Shalit I, et al. Treatment of candidaemia in premature infants: comparison of three amphotericin B preparations. J Antimicrob Chemother **2003**; 52:663–7.
239. Wurthwein G, Groll AH, Hempel G, Adler-Shohet FC, Lieberman JM, Walsh TJ. Population pharmacokinetics of amphotericin B lipid complex in neonates. Antimicrob Agents Chemother **2005**; 49:5092–8.
240. Kaufman D, Boyle R, Hazen KC, Patrie JT, Robinson M, Donowitz LG. Fluconazole prophylaxis against fungal colonization and infection in preterm infants. N Engl J Med **2001**; 345:1660–6.
241. Manzoni P, Stolfi I, Pugni L, et al. A multicenter, randomized trial of prophylactic fluconazole in preterm neonates. N Engl J Med **2007**; 356:2483–95.
242. Benjamin DK Jr, Stoll BJ. Infection in late preterm infants. Clin Perinatol **2006**; 33:871–82.
243. Smith PB, Steinbach WJ, Benjamin DK Jr. Neonatal candidiasis. Infect Dis Clin North Am **2005**; 19:603–15.
244. Masur H, Rosen PP, Armstrong D. Pulmonary disease caused by *Candida* species. Am J Med **1977**; 63:914–25.
245. Kontoyiannis DP, Reddy BT, Torres HA, et al. Pulmonary candidiasis in patients with cancer: an autopsy study. Clin Infect Dis **2002**; 34: 400–3.
246. Rello J, Esandi ME, Diaz E, Mariscal D, Gallego M, Valles J. The role of *Candida* sp. isolated from bronchoscopic samples in nonneutropenic patients. Chest **1998**; 114:146–9.
247. el-Ebiary M, Torres A, Fabregas N, et al. Significance of the isolation of *Candida* species from respiratory samples in critically ill, nonneutropenic patients: an immediate postmortem histologic study. Am J Respir Crit Care Med **1997**; 156:583–90.
248. Wood GC, Mueller EW, Croce MA, Boucher BA, Fabian TC. *Candida* sp. isolated from bronchoalveolar lavage: clinical significance in critically ill trauma patients. Intensive Care Med **2006**; 32:599–603.
249. Sangeorzan JA, Bradley SF, He X, et al. Epidemiology of oral candidiasis in HIV-infected patients: colonization, infection, treatment, and emergence of fluconazole resistance. Am J Med **1994**; 97:339–46.
250. Bonacini M, Young T, Laine L. The causes of esophageal symptoms in human immunodeficiency virus infection: a prospective study of 110 patients. Arch Intern Med **1991**; 151:1567–72.
251. Phillips P, Zemcov J, Mahmood W, Montaner JS, Craib K, Clarke AM. Itraconazole cyclodextrin solution for fluconazole-refractory oropharyngeal candidiasis in AIDS: correlation of clinical response with in vitro susceptibility. AIDS **1996**; 10:1369–76.
252. Pons V, Greenspan D, Debruin M. Therapy for oropharyngeal candidiasis in HIV-infected patients: a randomized, prospective multicenter study of oral fluconazole versus clotrimazole troches. The Multicenter Study Group. J Acquir Immune Defic Syndr **1993**; 6:1311–6.
253. Finlay PM, Richardson MD, Robertson AG. A comparative study of the efficacy of fluconazole and amphotericin B in the treatment of oropharyngeal candidosis in patients undergoing radiotherapy for head and neck tumours. Br J Oral Maxillofac Surg **1996**; 34:23–5.
254. Cartledge JD, Midgely J, Gazzard BG. Itraconazole solution: higher serum drug concentrations and better clinical response rates than the capsule formulation in acquired immunodeficiency syndrome patients with candidosis. J Clin Pathol **1997**; 50:477–80.
255. Queiroz-Telles F, Silva N, Carvalho MM, et al. Evaluation of efficacy and safety of itraconazole oral solution for the treatment of oropharyngeal candidiasis in aids patients. Braz J Infect Dis **2001**; 5:60–6.
256. Phillips P, De Beule K, Frechette G, et al. A double-blind comparison

of itraconazole oral solution and fluconazole capsules for the treatment of oropharyngeal candidiasis in patients with AIDS. Clin Infect Dis **1998**; 26:1368–73.
257. Vazquez JA, Skiest DJ, Nieto L, et al. A multicenter randomized trial evaluating posaconazole versus fluconazole for the treatment of oropharyngeal candidiasis in subjects with HIV/AIDS. Clin Infect Dis **2006**; 42:1179–86.
258. Havlir DV, Dube MP, McCutchan JA, et al. Prophylaxis with weekly versus daily fluconazole for fungal infections in patients with AIDS. Clin Infect Dis **1998**; 27:1369–75.
259. Meunier F, Paesmans M, Autier P. Value of antifungal prophylaxis with antifungal drugs against oropharyngeal candidiasis in cancer patients. Eur J Cancer B Oral Oncol **1994**; 30B:196–9.
260. Philpott-Howard JN, Wade JJ, Mufti GJ, Brammer KW, Ehninger G. Randomized comparison of oral fluconazole versus oral polyenes for the prevention of fungal infection in patients at risk of neutropenia. Multicentre Study Group. J Antimicrob Chemother **1993**; 31:973–84.
261. Smith D, Midgley J, Gazzard B. A randomised, double-blind study of itraconazole versus placebo in the treatment and prevention of oral or oesophageal candidosis in patients with HIV infection. Int J Clin Pract **1999**; 53:349–52.
262. Saag MS, Fessel WJ, Kaufman CA, et al. Treatment of fluconazole-refractory oropharyngeal candidiasis with itraconazole oral solution in HIV-positive patients. AIDS Res Hum Retroviruses **1999**; 15: 1413–7.
263. Skiest DJ, Vazquez JA, Anstead GM, et al. Posaconazole for the treatment of azole-refractory oropharyngeal and esophageal candidiasis in subjects with HIV infection. Clin Infect Dis **2007**; 44:607–14.
264. Hegener P, Troke PF, Fatkenheuer G, Diehl V, Ruhnke M. Treatment of fluconazole-resistant candidiasis with voriconazole in patients with AIDS. AIDS **1998**; 12:2227–8.
265. Dewsnup DH, Stevens DA. Efficacy of oral amphotericin B in AIDS patients with thrush clinically resistant to fluconazole. J Med Vet Mycol **1994**; 32:389–93.
266. Vazquez JA, Hidalgo JA, De Bono S. Use of sargramostim (rh-GM-CSF) as adjunctive treatment of fluconazole-refractory oropharyngeal candidiasis in patients with AIDS: a pilot study. HIV Clin Trials **2000**; 1:23–9.
267. Bodasing N, Seaton RA, Shankland GS, Pithie A. Gamma-interferon treatment for resistant oropharyngeal candidiasis in an HIV-positive patient. J Antimicrob Chemother **2002**; 50:765–6.
268. Wilcox CM, Alexander LN, Clark WS, Thompson SE 3rd. Fluconazole compared with endoscopy for human immunodeficiency virus–infected patients with esophageal symptoms. Gastroenterology **1996**; 110:1803–9.
269. Barbaro G, Barbarini G, Calderon W, Grisorio B, Alcini P, Di Lorenzo G. Fluconazole versus itraconazole for *Candida esophagitis* in acquired immunodeficiency syndrome. Gastroenterology **1996**; 111:1169–77.
270. Wilcox CM, Darouiche RO, Laine L, Moskovitz BL, Mallegol I, Wu J. A randomized, double-blind comparison of itraconazole oral solution and fluconazole tablets in the treatment of esophageal candidiasis. J Infect Dis **1997**; 176:227–32.
271. Ally R, Schurmann D, Kreisel W, et al. A randomized, double-blind, double-dummy, multicenter trial of voriconazole and fluconazole in the treatment of esophageal candidiasis in immunocompromised patients. Clin Infect Dis **2001**; 33:1447–54.
272. Martins MD, Lozano-Chiu M, Rex JH. Declining rates of oropharyngeal candidiasis and carriage of *Candida albicans* associated with trends toward reduced rates of carriage of fluconazole-resistant *C. albicans* in human immunodeficiency virus-infected patients. Clin Infect Dis **1998**; 27:1291–4.
273. Kirkpatrick CH, Windhorst DB. Mucocutaneous candidiasis and thymoma. Am J Med **1979**; 66:939–45.
274. Kamai Y, Maebashi K, Kudoh M, et al. Characterization of mechanisms of fluconazole resistance in a *Candida albicans* isolate from a Japanese patient with chronic mucocutaneous candidiasis. Microbiol Immunol **2004**; 48:937–43.
275. Hadley S, Samore MH, Lewis WD, Jenkins RL, Karchmer AW, Hammer SM. Major infectious complications after orthotopic liver transplantation and comparison of outcomes in patients receiving cyclosporine or FK506 as primary immunosuppression. Transplantation **1995**; 59:851–9.
276. Karchmer AW, Samore MH, Hadley S, Collins LA, Jenkins RL, Lewis WD. Fungal infections complicating orthotopic liver transplantation. Trans Am Clin Climatol Assoc **1995**; 106:38–47; discussion, 47–8.
277. Kung N, Fisher N, Gunson B, Hastings M, Mutimer D. Fluconazole prophylaxis for high-risk liver transplant recipients. Lancet **1995**; 345: 1234–5.
278. Tollemar J, Hockerstedt K, Ericzon BG, Jalanko H, Ringden O. Liposomal amphotericin B prevents invasive fungal infections in liver transplant recipients: a randomized, placebo-controlled study. Transplantation **1995**; 59:45–50.
279. Lumbreras C, Cuervas-Mons V, Jara P, et al. Randomized trial of fluconazole versus nystatin for the prophylaxis of *Candida* infection following liver transplantation. J Infect Dis **1996**; 174:583–8.
280. Winston DJ, Pakrasi A, Busuttil RW. Prophylactic fluconazole in liver transplant recipients: a randomized, double-blind, placebo-controlled trial. Ann Intern Med **1999**; 131:729–37.
281. Hadley S, Huckabee C, Pappas PG. Outcomes of anifungal prophylaxisin high-risk liver transplant recients. Transpl Infect Dis **2009**; 11: 40–8.
282. Benedetti E, Gruessner AC, Troppmann C, et al. Intra-abdominal fungal infections after pancreatic transplantation: incidence, treatment, and outcome. J Am Coll Surg **1996**; 183:307–16.
283. Guaraldi G, Cocchi S, Codeluppi M, et al. Outcome, incidence, and timing of infectious complications in small bowel and multivisceral organ transplantation patients. Transplantation **2005**; 80:1742–8.
284. Grossi P, Farina C, Fiocchi R, Dalla Gasperina D. Prevalence and outcome of invasive fungal infections in 1,963 thoracic organ transplant recipients: a multicenter retrospective study. Italian Study Group of Fungal Infections in Thoracic Organ Transplant Recipients. Transplantation **2000**; 70:112–6.
285. Ostrosky-Zeichner L. Prophylaxis and treatment of invasive candidiasis in the intensive care setting. Eur J Clin Microbiol Infect Dis **2004**; 23:739–44.
286. Garbino J, Lew DP, Romand JA, Hugonnet S, Auckenthaler R, Pittet D. Prevention of severe *Candida* infections in nonneutropenic, high-risk, critically ill patients: a randomized, double-blind, placebo-controlled trial in patients treated by selective digestive decontamination. Intensive Care Med **2002**; 28:1708–17.
287. Pelz RK, Hendrix CW, Swoboda SM, et al. Double-blind placebo-controlled trial of fluconazole to prevent candidal infections in critically ill surgical patients. Ann Surg **2001**; 233:542–8.
288. Eggimann P, Francioli P, Bille J, et al. Fluconazole prophylaxis prevents intra-abdominal candidiasis in high-risk surgical patients. Crit Care Med **1999**; 27:1066–72.
289. Playford EG, Webster AC, Sorrell TC, Craig JC. Antifungal agents for preventing fungal infections in non-neutropenic critically ill and surgical patients: systematic review and meta-analysis of randomized clinical trials. J Antimicrob Chemother **2006**; 57:628–38.
290. Shorr AF, Chung K, Jackson WL, Waterman PE, Kollef MH. Fluconazole prophylaxis in critically ill surgical patients: a meta-analysis. Crit Care Med **2005**; 33:1928–35; quiz 36.
291. Bow EJ, Laverdiere M, Lussier N, Rotstein C, Cheang MS, Ioannou S. Antifungal prophylaxis for severely neutropenic chemotherapy recipients: a meta analysis of randomized-controlled clinical trials. Cancer **2002**; 94:3230–46.
292. Mattiuzzi GN, Alvarado G, Giles FJ, et al. Open-label, randomized comparison of itraconazole versus caspofungin for prophylaxis in patients with hematologic malignancies. Antimicrob Agents Chemother **2006**; 50:143–7.

293. Glasmacher A, Prentice A, Gorschluter M, et al. Itraconazole prevents invasive fungal infections in neutropenic patients treated for hematologic malignancies: evidence from a meta-analysis of 3,597 patients. J Clin Oncol **2003**; 21:4615–26.
294. Wingard JR. Results of a randomized, double-blind trial of fluconazole versus voriconazole for the prevention of invasive fungal infections in 600 allogeneic blood and marrow transplant patients. In: 49th American Society of Hematology Annual Meeting and Exposition. Atlanta, GA: American Society of Hematology, **2007**.
295. Segal BH, Almyroudis NG, Battiwalla M, et al. Prevention and early treatment of invasive fungal infection in patients with cancer and neutropenia and in stem cell transplant recipients in the era of newer broad-spectrum antifungal agents and diagnostic adjuncts. Clin Infect Dis **2007**; 44:402–9.