International Conference for the Development of a Consensus on the Management and Prevention of Severe Candidal Infections

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Because of the rapidly increasing incidence of serious candidal infections, a consensus conference of 22 investigators from the United States, Europe, and Japan was held to discuss strategies for the prevention and treatment of deep-organ infections caused by *Candida* species. Commonly asked questions concerning the management of candidal infections were selected for discussion by the participating investigators. Possible answers to the questions were developed by the investigators, who then voted anonymously for their preferences. In certain instances, unanimity or a strong consensus was the result. In all cases, the full spectrum of responses was recorded and is presented in this report. The forms of candidal infection addressed included candidemia, candiduria, hepatosplenic candidiasis (chronic systemic candidiasis), candidal endophthalmitis, and candidal peritonitis. Prevention and treatment strategies were considered for patients who have undergone surgery, for neutropenic and nonneutropenic patients, and for patients who have undergone bone marrow and solid organ transplantation. The therapeutic roles of amphotericin B (standard and lipid formulations) and the azoles were considered.

According to the results of the National Nosocomial Infections Surveillance System surveys conducted through 1992, *Candida* has become the fourth most common isolate recovered from blood cultures in the United States [1], and rates of candidemia have increased substantially in Europe as well [2]. Epidemiological studies have shown that candidal infections occur on both medical and surgical services; approximately half of all candidal infections occur in surgical intensive care units. A noticeable shift in the species of *Candida* causing infection toward non-*albicans* species has occurred (table 1) [3–5]. Numerous instances of nosocomial transmission of *Candida* species, which have led to outbreaks or clusters of cases, have been described [5]. DNA typing has verified that transmission occurs from patient to patient and from health care worker to patient. Numerous risk factors for candidemia have been identified. They vary among institutions but usually include use of antibiotics, indwelling catheters, hyperalimentation, cancer therapy, and immunosuppressive therapy after organ transplantation; hospitalization in intensive care units; candiduria; and colonization with *Candida* species.

See editorial response by Graybill on pages 60–2.

Although the incidence of serious infections due to *Candida* species is rising rapidly, knowledge of the most appropriate strategies for the management of such infections remains severely limited because large controlled studies of treatment strategies have not been performed. Despite the recent introduction of two new antifungal agents (fluconazole and itraconazole) and less toxic lipid-based formulations of amphotericin B, there are few data on either the overall usefulness or the comparative usefulness of these newer agents. Furthermore, there are relatively few randomized, controlled studies on the use of the traditional agent (deoxycholate amphotericin B) for managing candidal infections. An additional serious problem related to the treatment of candidal infections is the emerging resistance of the organisms to available antifungals and the relative resistance of certain emerging non-*albicans* species at a time when there are relatively few new antifungal agents under development.

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Table 1. Percentages of deep candidal infections due to various *Candida* species in neutropenic and nonneutropenic patients and fluconazole $MICs_{50}$: data from four studies.

Species	Study [reference]			MIC_{50} (μg/mL)*
	Wingard [3]	Rex et al. [4]	Pfaller [5]	
C. albicans	54	56	59	0.25
C. tropicalis	25	17	12	1.0
C. glabrata	8	13	11	16
C. parapsilosis	7	10	10	1.0
C. krusei	4	2	3	32
All others	2	2	3	

* Data are from [30].

The problems of studying serious candidal infection are formidable because of the complex disease profiles of the patients. The purpose of this conference of investigators with extensive experience in treating candidal diseases was to develop a consensus, when possible, on the most effective strategies for the prevention and clinical management of severe candidal infections. When a consensus could not be reached, the goal was to report the full diversity of opinion. Because so few dose-ranging studies have been performed in patients with severe candidal infections, in many instances dosing recommendations could not be given. The results of studies now in progress should allow more precise dosing recommendations in the future.

Methods

This conference was held on 21–22 April 1995 at the Harbor/UCLA Research and Education Institute, St. John's Cardiovascular Research Center, Torrance, California. Additional meetings were held in September 1995 and June 1996 to refine and further develop specific points and sections in the report drafted after the first meeting.

The consensus group consisted of 22 investigators from the United States, Europe, and Japan; an organizing committee selected these investigators for their expertise in studying and managing candidal infections and because of their histories of active participation in clinical trials for the management of candidal infections. All of these investigators are affiliated with academic medical centers. Nearly all of the investigators from countries other than the United States who were known to the organizing committee as having participated substantially in clinical trials for the treatment of candidal infections were invited to participate.

Seven of the participants are affiliated with the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG). Three participants are members of the National Committee for Clinical Laboratory Standards (NCCLS). One participant is a member of the Committee on Infectious Diseases for the American Society of Transplant Physicians (ASTP). Seven participants are members of the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC). Two participants are members of the Japanese Clinical Trials Group. These participants have collectively published at least 500 manuscripts relating to the treatment of candidal infections.

To minimize the possible effects of bias, the conference format included features that distinguished it from customary consensus conferences. A list of commonly asked questions regarding treatment strategies for severe candidal infections was given to each investigator before the meeting. During the meeting, the questions were projected onto a screen of sufficient size to allow all investigators to view the document simultaneously. The questions were extensively reviewed and edited, and new questions were discussed and added. Finally, the wording of possible answers to the questions was reviewed, extensively discussed, and revised.

After the final versions of the questions and possible answers had been formulated, the issues were discussed and the answers to the questions were voted on with use of electronic devices at the participants' seats. To eliminate the influence of peers [6], voting was anonymous, and the outcome was not known by the conference participants until the voting was completed. Each time a vote was taken, all investigators present voted (abstention was not permitted). Because some investigators were unable to be present for each vote, the number of votes did not always total 22. Drafts in progress and final copies of the manuscript were distributed to all participants for their approvals before submission for publication.

Terminology

Neutropenia was defined as an absolute neutrophil count of $<500/mm^3$. (The absolute neutrophil count equals the total WBC count multiplied by the percentage of band forms and mature neutrophils).

Susceptible isolate. At the time of the conference, standardized susceptibility testing and interpretive breakpoints for the susceptibility and resistance of *Candida* species had not been established in either the United States or Europe. Therefore, this term was used to refer to isolates that most clinicians would consider clearly susceptible to an antifungal agent on the basis of the most commonly reported MICs. The term did not refer to isolates believed to have borderline susceptibility.

Stable patient. This term referred to a patient who does not have hypotension and whose overall condition is either improving or remaining the same, with the likelihood of a good clinical outcome.

Unstable patient. This term referred to a patient whose general clinical condition is considered by his or her physician to be worsening, who may or may not have had hypotension, who may have had associated clinical problems, or who may have

had undiagnosed problems, making the likelihood of a favorable clinical recovery uncertain. Such a patient is most commonly hospitalized in an intensive care unit. It is assumed that the severity of the underlying illness in such a patient is so great that it outweighs the impact of any specific therapy and that selected therapy must be rapidly effective to have a reasonable opportunity of being beneficial.

Available drugs. These agents were considered those approved for the management of candidal infections by the U.S. Food and Drug Administration and/or by the corresponding governmental bodies of other countries. Although itraconazole has not been approved in the United States for use in patients with deep (nonmucosal) candidal infections, it is licensed for other uses. It has been approved for the treatment of deep candidal infections in other countries and was therefore considered an available drug. The investigational and commercially available lipid preparations of amphotericin B are referred to collectively as amphotericin B lipid formulations.

Background Data and Questions

Management of Candidemia in Nonneutropenic Patients and General Concepts of the Management of Candidemia

Should all candidemic patients (either neutropenic or nonneutropenic) be treated with an antifungal?

Background data. The mortality rates associated with candidemia are high, ranging from ~40% to 60% [1]. Retrospective studies have shown an error rate of ~30% in defining a population of candidemic patients who do not require treatment [7, 8]. As with nearly all infections, there are certain patients who survive candidemia without receiving specific antibiotic treatment. At present, however, there are no accurate diagnostic tests to define a population of patients with candidemia who do not require antifungal treatment. In addition, current methods of risk factor analysis are not accurate enough to assign a probability of deep-organ infection to a population of candidemic patients.

Responses. Nineteen of 20 investigators answered this question in the affirmative (figure 1). This strong consensus is based on three pivotal facts: (1) predicting which patients need treatment is associated with an unacceptable level of inaccuracy; (2) therapeutic options that are less toxic than amphotericin B are now available; and (3) the morbidity or risk of long-term sequelae is significant for patients with candidemia. This aggressive approach of treating all patients with blood cultures positive for *Candida* species is consistent with other therapeutic paradigms applied to infectious diseases, such as that used in the management of staphylococcal bacteremia.

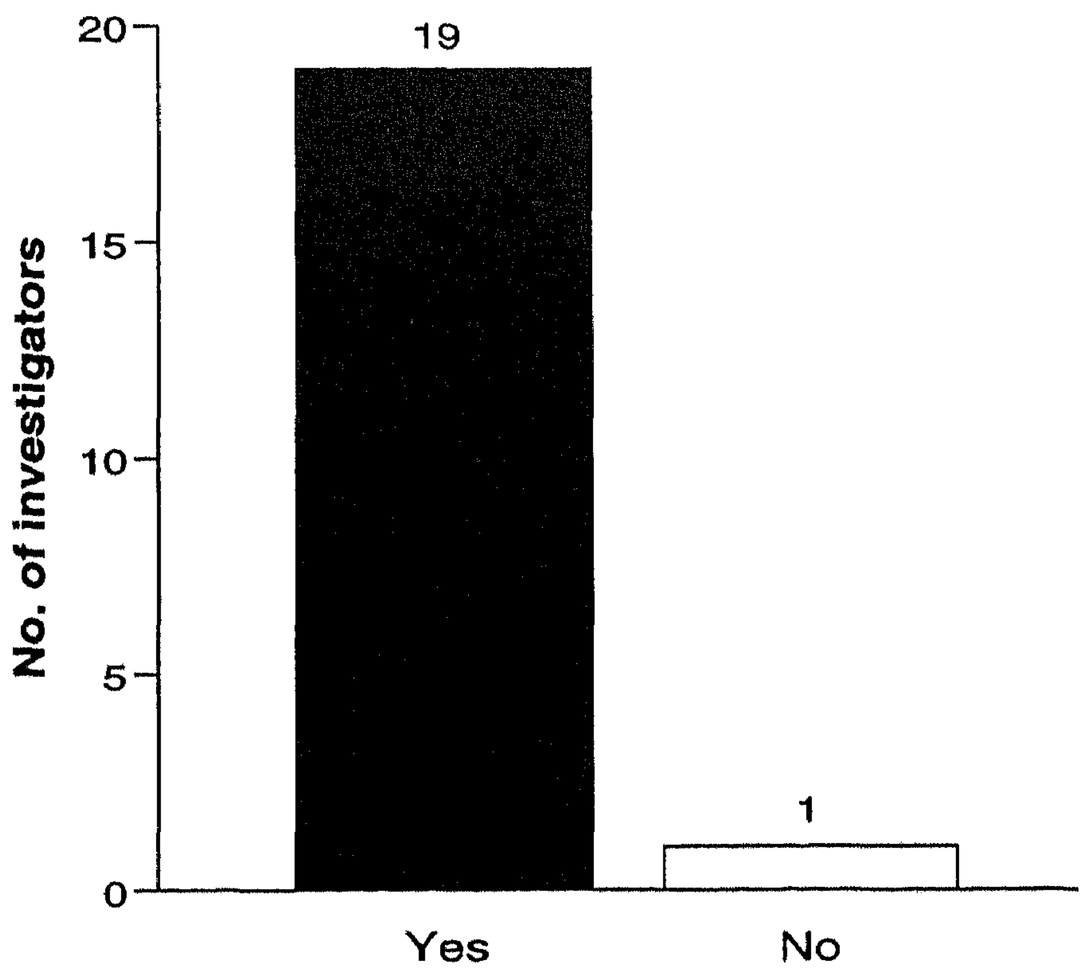

Figure 1. Responses to the question "Should all candidemic patients (nonneutropenic and neutropenic) be treated with an antifungal agent?" A total of 20 investigators attending the consensus conference on candidal infections voted.

What antifungal agents should be used for the management of candidemia?

Background data. The data available to guide the choice of antifungal agents for treatment of nonneutropenic patients remain severely limited. A 24-center study in which fluconazole was compared with amphotericin B has been completed in the United States [4]. In this study, nonneutropenic patients who did not have leukemia, lymphoma, or AIDS and had not undergone organ transplantation were treated with either amphotericin B or fluconazole for an additional 2 weeks after the last positive blood-culture results were obtained. There was no statistical difference in clinical response between the two agents. A smaller study showed similar results [9].

Responses. The agents chosen by the investigators for the management of candidemia in stable and unstable nonneutropenic patients are summarized in tables 2 and 3, respectively. For patients whose *Candida* isolates were not resistant to fluconazole and who had no evidence of hematogenous seeding, 20 of 20 investigators chose fluconazole. If the patient had received previous treatment with fluconazole, even if the patient was stable, 17 of 20 investigators chose a regimen that included amphotericin B.

What dose of antifungals should be used for the management of candidemia?

Background data. Because dose-ranging studies are lacking, there are few data to guide the selection of a dose of any antifungal agent. Only one study on the use of two doses of fluconazole for the treatment of candidemia has been published [10]. In addition, there are no clear-cut dose-response data available for amphotericin B.

Table 2. Investigator responses regarding the management of candidemia in stable nonneutropenic patients.

Patient's condition	Agent			
	Fluconazole	Itraconazole capsules	Amphotericin B (standard formulation)	Amphotericin B lipid formulation
Patient stable: *Candida krusei* infection unlikely; no prior fluconazole therapy	20/20	0/20	0/20	0/20
Patient stable, receiving fluconazole for >2 d	3/20	0/20	17/20 (with 5-FC, 7/17; without 5-FC, 10/17)	0/20

NOTE. Data are number of votes/number of investigators voting in the consensus conference on candidal infections. 5-FC = 5-fluorocytosine.

Responses. Figures 2 and 3 summarize the preferences of the investigators. Because of the lack of a substantive body of published data, the responses are based primarily on experience.

What is the appropriate dose of 5-fluorocytosine when it is used in combination with amphotericin B for the treatment of candidemia?

Most investigators thought that the doses of 5-fluorocytosine recommended by the manufacturer may be too high when the drug is used in combination with amphotericin B. Most investigators had witnessed toxicity with the dose recommended in the package insert (150 mg/[kg · d]). Thirteen of 20 investigators favored a dose of 100 mg/(kg · d), while five chose the recommended dose of 150 mg/(kg · d). Two investigators stated that they routinely use a dose of ≤100 mg/(kg · d). Sixteen of 20 investigators indicated that they aim for peak serum levels of 51–100 μg/mL if serum levels are readily obtainable. Only one investigator aims for a level of >100 μg/mL, and three of 20 aim for levels of <50 μg/mL. All investigators agreed that the dose should be adjusted for patients with renal insufficiency. Serum levels of 20–75 μg/mL are well above the MIC of 5-fluorocytosine for most *Candida* isolates.

Should indwelling intravenous catheters be changed in candidemic patients?

Background data. The management of indwelling intravenous catheters in candidemic patients remains highly controversial. The expense of changing lines is considerable. Unfortunately, data regarding the effect of changing catheters on general clinical outcome and on resolution of candidemia are limited. The question of changing catheters is particularly important with respect to surgically implanted catheters, such as Hickman or Broviac lines.

Responses. Fifteen of 20 investigators would change all nonsurgically implanted lines in patients with one or more blood cultures positive for *Candida.* Although five of 21 investigators would also change surgically implanted lines in patients with one or more positive blood cultures, 16 would attempt to sterilize the blood without changing a surgically implanted line. The results of a number of studies suggest that catheter exchanges may be associated with more rapid clearance of the bloodstream and perhaps a better outcome [4, 7, 8, 11, 12]. Although the value of each of these studies is limited by at least some potential bias and none of the studies accounts for the potential role of the gastrointestinal tract in the pathogenesis of candidemia, the collective data

Table 3. Investigator responses regarding the management of candidemia in unstable nonneutropenic patients.

Patient's condition	Agent					
	Fluconazole	Fluconazole + amphotericin B	Amphotericin B	Amphotericin B lipid formulation without 5-FC	Fluconazole with 5-FC	Itraconazole capsules
Patient unstable; *C. krusei* infection unlikely; no prior fluconazole therapy	5/20	5/20	With 5-FC, 4/20; without 5-FC, 4/20	2/20	0/20	0/20

NOTE. Data are number of votes/number of investigators voting in the consensus conference on candidal infections. 5-FC = 5-fluorocytosine.

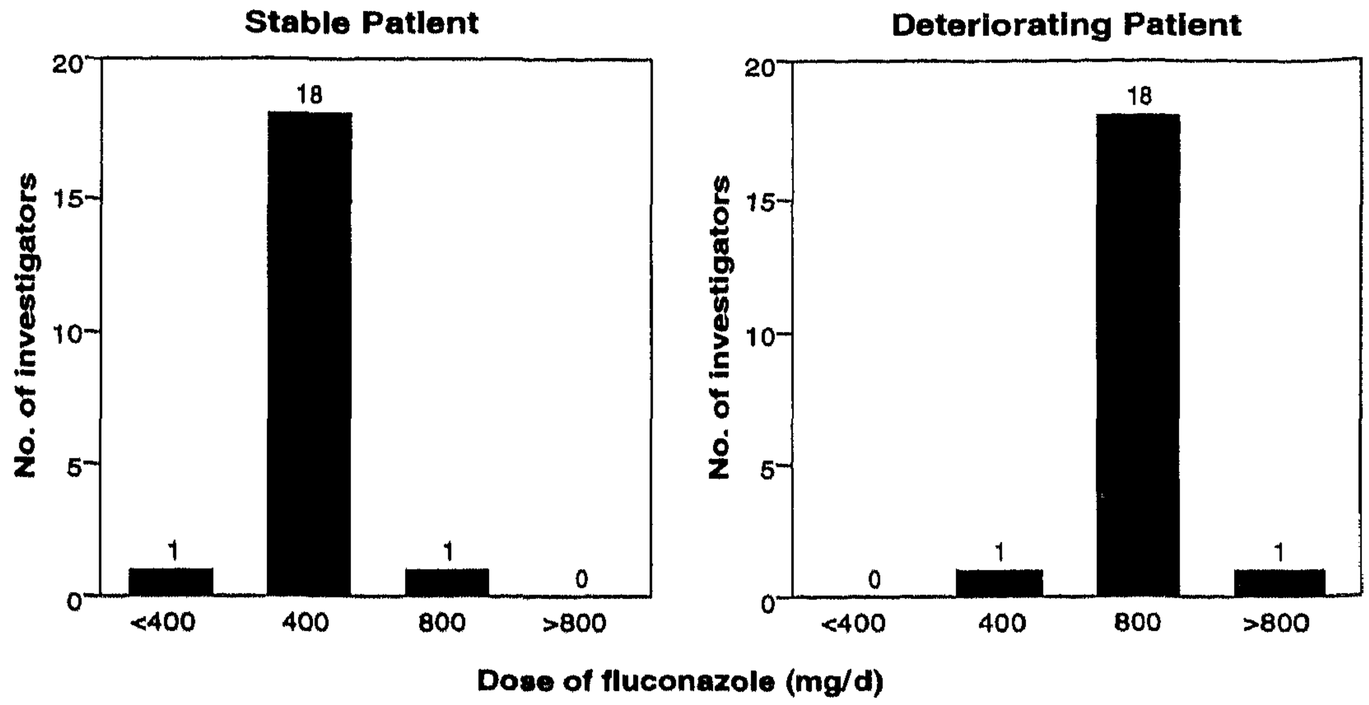

Figure 2. Responses to the question "What dose of fluconazole should be used for the management of candidemia?" A total of 20 investigators attending the consensus conference on candidal infections voted.

strongly suggest that consideration should be given to the removal or changing of all intravascular catheters, especially in patients with persistent candidemia.

What is the role of prophylactic antifungal agents in nonneutropenic patients?

The investigators were unanimous in their belief that antifungal prophylaxis should not be given on a routine basis and that it should be reserved for selected nonneutropenic patients at high risk for candidemia. An example of a situation that might warrant prophylaxis is that in which a patient has received antibacterial therapy for >14 days, has indwelling intravascular lines in place, is receiving hyperalimentation fluids, has had *Candida* isolated from two or more sites, and has undergone complicated intraabdominal surgery. All the investigators chose fluconazole as the most appropriate prophylactic agent for such patients.

When should empirical therapy be given to nonneutropenic patients?

Background data. Controlled, prospective studies that answer this question have not been performed to date. Empirical antifungal therapy should be considered for critically ill, nonneutropenic patients (who have multiple risk factors for disseminated candidiasis) with signs of infection who have not responded to optimal antibacterial therapy and have had thorough evaluations for bacterial infection.

Responses. When *Candida* species are isolated from specimens such as sputum or urine from a nonneutropenic patient with two or more risk factors for invasive candidiasis, 18 of 20 investigators indicated they would administer empirical therapy. When no *Candida* species are isolated, only 10 of 20 investigators would administer empirical therapy. The question of whether routine surveillance cultures should be performed for such patients was not addressed.

When the decision is made to use empirical therapy, what are the most appropriate antifungal agents for nonneutropenic stable patients (i.e., those who are not receiving systemic antifungal prophylaxis)?

Background data. Both antifungal prophylaxis and empirical therapy are costly, and the benefit of an agent must be weighed against its costs. The potential for selecting for strains resistant to azoles is an additional reason to administer prophylactic and empirical therapy conservatively.

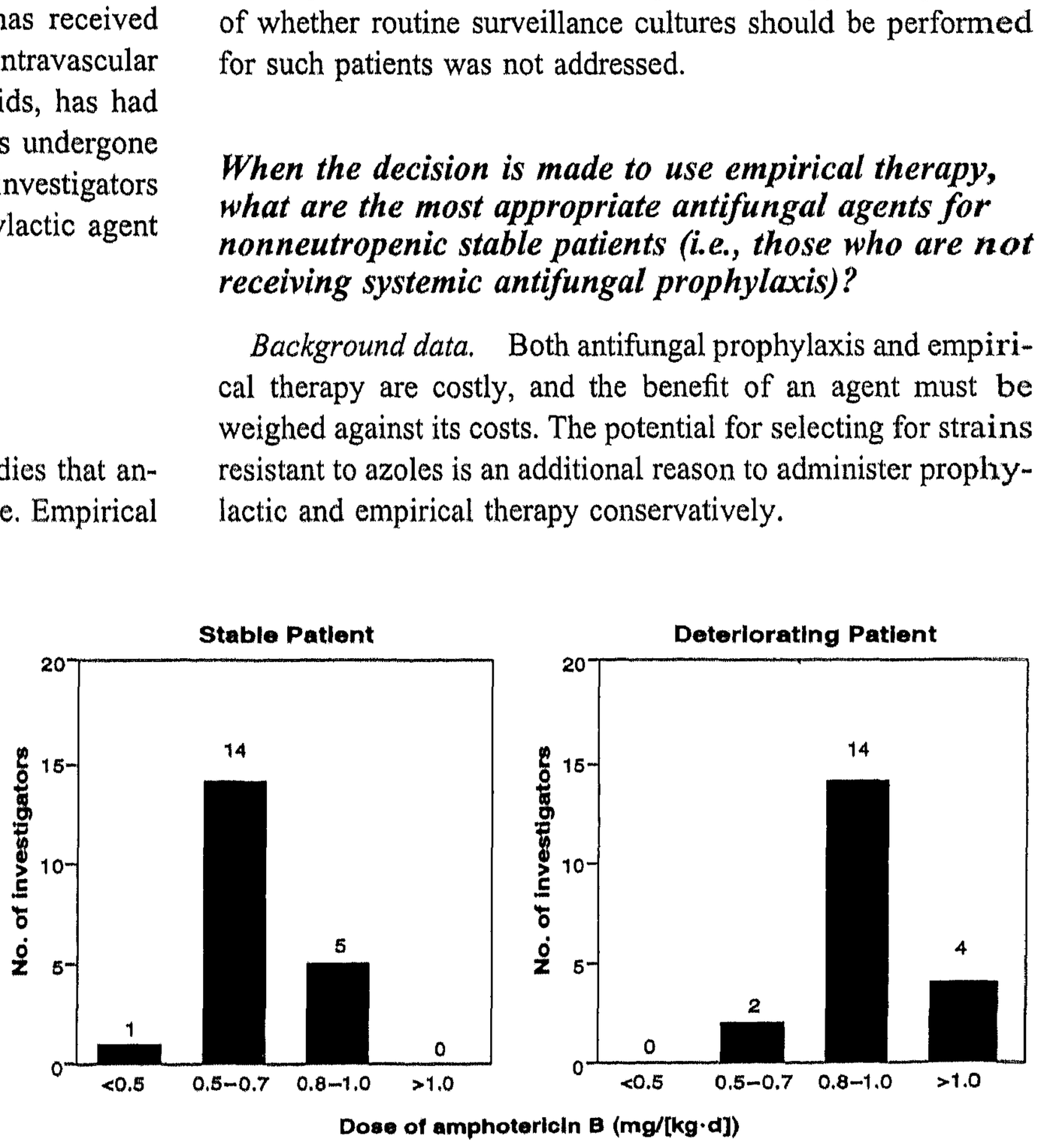

Figure 3. Responses to the question "What dose of amphotericin B should be used for the management of candidemia?" A total of 20 investigators attending the consensus conference on candidal infections voted.

Responses. Fifteen of 20 investigators selected fluconazole, and five of 20 selected the standard formulation of amphotericin B. The lipid formulations of amphotericin B, itraconazole capsules, and the lipid formulations of amphotericin B were not selected.

What are the dosing recommendations for antifungal agents used for treatment of candidal infections in both neutropenic and nonneutropenic children?

Background data. The pharmacokinetic properties of antifungal compounds in children differ from those in adults. Lee and colleagues [13] investigated the safety, tolerability, and pharmacokinetics of fluconazole in neutropenic children with neoplastic diseases and found that the mean terminal plasma half-life of fluconazole (±SD) was substantially shorter than that in adults (i.e., 16.8 ± 1.1 hours vs. 27–37 hours, respectively). The linear dose proportionality to peak plasma concentrations for children was similar to that for adults. These findings were confirmed by Seay et al. [14], who found that the mean plasma half-life of fluconazole (±SD) in children with leukemia or other hematologic diseases was 15.6 ± 3.2 hours, which again is approximately one-half that in adults.

Despite the differences in the pharmacokinetic properties of amphotericin B in infants, the recommended milligram-per-kilogram dose of amphotericin B for children is similar to that for adults; this recommendation has been summarized previously [15]. The renal clearance of 5-fluorocytosine tends to be more rapid in children than in adults; therefore, the dose should be adjusted to achieve near-peak plasma levels of 40–60 μg/mL [16].

Responses. In light of the more rapid clearance of fluconazole in children, the investigators recommended that life-threatening invasive candidiasis in children be treated with fluconazole at a dosage of 6 mg/kg twice daily, assuming that renal function is normal. Twice-daily dosing provides an area under the concentration vs. time curve in children that approximates that in adults treated once daily. This dosing recommendation for children does not apply to infants, whose renal clearance of fluconazole is slower than that of older children. For children with mucosal candidiasis, a fluconazole dose of 2–3 mg/kg may be administered once daily [17]. Amphotericin B should be used to treat life-threatening invasive candidiasis.

How long is follow-up necessary for both neutropenic and nonneutropenic patients who develop candidemia?

The investigators unanimously agreed that because of the late complications of candidemia (such as hematogenous endophthalmitis; hematogenous osteomyelitis; and chronic disseminated candidiasis of the liver, spleen, or kidneys), all neutropenic and nonneutropenic patients with candidemia should be routinely followed up for ≥3 months after the initial episode of candidemia. The investigators observed that most late complications occur during the first 3 months after an episode of candidemia [18–21]. Patients should be made aware of the importance of informing their physicians of symptoms such as visual disturbances, bone pain, abdominal pain, or fever and fatigue suggestive of chronic disseminated candidiasis to the liver, spleen, or kidneys [22–24]. Depending on the results of the clinical assessment, appropriate studies (e.g., roentgenography, CT, or an ophthalmologic consultation) should be performed.

Management of Candidemia in Neutropenic Patients

As discussed above, the investigators unanimously agreed that all candidemic neutropenic patients should be treated with an antifungal agent.

Which antifungal agents should be used for managing candidemia in stable neutropenic patients?

Background data. Underlying disease, use of indwelling catheters, severity and duration of the neutropenia, use of antifungal prophylaxis or cytotoxic chemotherapy regimens, and epidemiology of fungal infections within a given institution were considered by the investigators to be critical factors in determining how to treat neutropenic patients. Because these factors differ among institutions, the neutropenic patient population is highly heterogeneous. The lack of large-scale, comparative studies of neutropenic patients precludes a simple, unified answer to this question.

Responses. In the absence of an optimal database, 17 of 20 investigators chose fluconazole for a stable neutropenic patient with uncomplicated candidemia, assuming that triazoles had not been administered prophylactically before the onset of candidemia and that there were no sites of hematogenously seeded infection or other forms of deep candidal infection. The remaining three investigators chose amphotericin B. Experimental findings in profoundly neutropenic rabbits may provide a scientific foundation for this strategy [25]. The results of a study to compare the efficacy of fluconazole with that of amphotericin B have been published [26] but were not available at the time of the consensus conference.

The investigators' selection of fluconazole over amphotericin B was based primarily on fluconazole's relative lack of toxicity. Itraconazole was discussed as an alternative, but it was considered to have the disadvantages of being unavailable in intravenous form and of having variable absorption when given orally to this population of patients. In addition, data from large, convincing studies on the efficacy of itraconazole for candidal infections are lacking at present, and the drug has not been approved for treatment of deep candidal infections by governmental authorities in various countries. The selection of a first-line therapeutic agent for neutropenic patients under a variety of clinical circumstances is discussed below. While cost issues

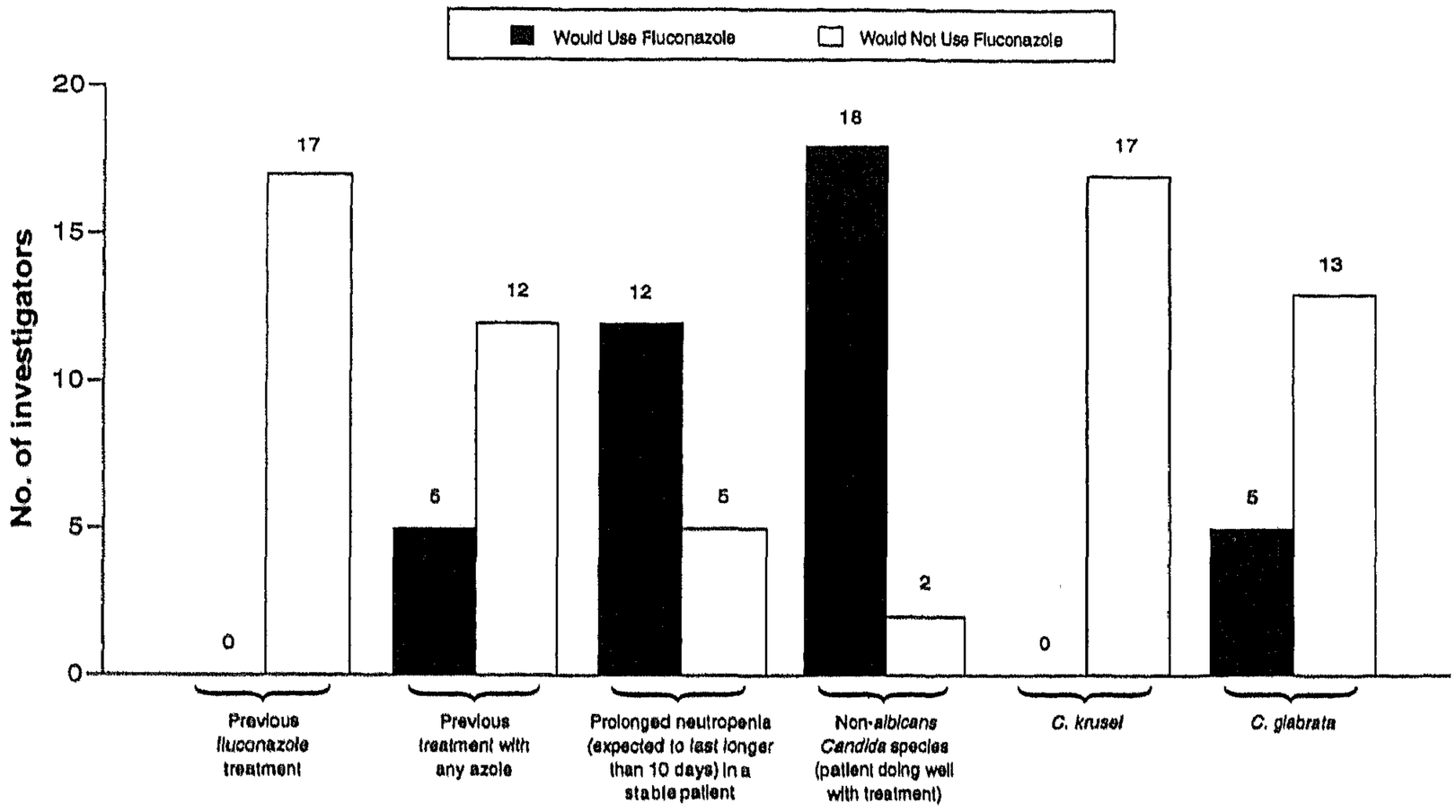

Figure 4. Investigator responses regarding the use of fluconazole in various clinical situations. The total number of investigators voting on the uses varied from 17 to 20 (the investigators attended the consensus conference on candidal infections).

were considered, they were thought to be less important in the choice of the first-line agents than were clinical advantages such as gastrointestinal absorption, lack of toxicity, ease of administration, and known efficacy.

How does recovery of a non-albicans species affect the choice of a therapeutic agent in neutropenic patients with candidemia?

Background data. Data correlating clinical outcome of therapy in patients infected with *C. albicans* or the various non-*albicans* species of *Candida* with the in vitro susceptibility of the organisms are limited. Furthermore, the methodology for susceptibility testing has not been standardized. Efforts are under way to standardize susceptibility testing for fungi by the NCCLS [27] and the European mycological societies. Once this standardization has been completed, a more meaningful correlation of in vitro susceptibilities and the in vivo efficacy of antifungal agents will be possible. Efforts are also in progress to develop a correlation between in vitro data and clinical outcome [28]. The conference participants recommended that until fungal susceptibility testing is fully standardized, fungal isolates should not be routinely tested for susceptibility to antifungal agents in the clinical laboratory.

C. albicans clinical isolates, particularly those from patients who have not received prior treatment with azoles, are usually susceptible in vitro to the azoles [29]. However, susceptibility may vary in patients who have received repeated courses of azoles. Non-*albicans* species vary in susceptibility to the azoles. For example, *Candida krusei* is intrinsically resistant to fluconazole, and *Candida glabrata* may be relatively resistant to fluconazole [30].

It is of interest that one study showed that statistically significantly higher mortality rates are associated with infections due to *C. glabrata* and *Candida tropicalis* than with infections due to *C. albicans* and *Candida parapsilosis* [2].

Responses. Figure 4 summarizes the responses of the investigators with regard to the use of fluconazole in various clinical situations, according to the duration of neutropenia and the recovery of specific candidal species from blood. Most of the investigators (18 of 20) would continue fluconazole treatment if a patient's clinical condition was improving, regardless of the species of *Candida* isolated. In the case in which a patient was receiving fluconazole at the time of a positive blood culture, other antifungal agents were selected. In addition, most of the investigators (12 of 17) chose an alternative to fluconazole if the patient had been receiving prophylaxis with any azole.

Fluconazole therapy is frequently initiated before the *Candida* species is identified. In such a circumstance, five of 18 investigators would continue fluconazole therapy even after *C. glabrata* had been identified if a patient was responding to treatment. However, 13 of 18 investigators would change the treatment to amphotericin B once the species was identified as *C. glabrata,* regardless of the clinical response. If the isolate was identified as *C. krusei,* all of the investigators indicated they would not use fluconazole. The preferred alternative to fluconazole in each of these clinical situations was a treatment regimen that included amphotericin B.

A method used in most institutions to rapidly separate isolates into *C. albicans* and non-*albicans* species is the germ tube test [31]. Isolates that are germ tube negative are nearly always non-*albicans* species. As discussed above, non-*albicans* species vary in their susceptibility to fluconazole [30]. Two days are usually required to definitively identify germ tube–negative organisms. If germ tube–negative organisms are recovered from blood before the species is identified, five of 20 investigators would continue treatment with fluconazole in all patients who were responding to the drug, 13 of 20 would continue treatment with the drug only in patients considered

Table 4. Investigator responses regarding management of candidemia in neutropenic patients who are either clinically unstable or have evidence of deep-organ candidal infection.

Amphotericin B and 5-FC	Fluconazole and amphotericin B	Fluconazole	Amphotericin B lipid formulation	Fluconazole and 5-FC	Amphotericin B (standard formulation)	Fluconazole, amphotericin B, and 5-FC
10/20	4/20	2/20	2/20	1/20	1/20	0/20

NOTE. Data are number of votes/number of investigators voting in the consensus conference on candidal infections. 5-FC = 5-fluorocytosine.

stable when the candidemia was discovered, and two of 20 would change therapy regardless of a patient's response.

Species that are germ tube negative and have varying susceptibilities to fluconazole are *Candida guilliermondii* and *Candida lusitaniae,* but these species are infrequently recovered in blood cultures. *C. lusitaniae* has been relatively resistant to amphotericin B [32–35]. Efforts to develop tests that allow for rapid species determination are ongoing, but no such test is currently commercially available. A differential culture medium, CHROMagar Candida (CHROMagar Co., Paris), is available, and published studies indicate that it is reliable for the presumptive identification of *C. albicans, C. tropicalis,* and *C. krusei* [36].

How should neutropenic patients with candidemia who are either clinically unstable or have evidence of deep-organ candidal infection be treated?

Background data. Patients whose general clinical conditions do not improve were defined by the investigators as unstable (see the Terminology section). These patients may have periods of hypotension and/or evidence of hematogenously seeded deep-organ infection. They are not patients who are only candidemic, are in stable or improving clinical conditions, or do not evidence complications of their candidemia.

Responses. Eighteen of 20 investigators were reluctant to use fluconazole as a single agent for first-line therapy in this patient population. Strong agreement over a specific strategy for these patients was not reached. Ten of 20 investigators chose combined treatment with amphotericin B and 5-fluorocytosine. Table 4 shows the responses of the investigators. Three chose regimens that did not include amphotericin B because they believed that there are no substantive data demonstrating a high level of efficacy of amphotericin B in this clinical situation. These investigators reemphasized that comparative studies are needed to validate the superiority of any one regimen over another.

Should the dose of antifungals be increased in neutropenic patients with candidemia?

In part because of a paucity of clinical-trials data, the investigators disagreed on the need for an increased dose of antifungals in neutropenic patients with candidemia. Twelve of 20 favored an increase above routine doses. All agreed that intravenous fluconazole, rather than oral fluconazole, be administered initially to unstable patients and/or patients with questionable gastrointestinal absorption. Nineteen of 20 investigators recommended giving amphotericin B daily rather than administering twice the daily dose every other day.

The investigators agreed that when 5-fluorocytosine is used, especially in combination with amphotericin B, severe bone marrow depression may occur. This depression is especially common in neutropenic patients who have received antineoplastic chemotherapy [37] and patients who have undergone bone marrow transplantation. Although the specific dose of 5-fluorocytosine was not discussed, there was general agreement that doses lower than those recommended in the package insert should be used when this drug is used in combination with amphotericin B. Furthermore, no intravenous preparation of 5-fluorocytosine is commercially available in the United States. Monitoring serum levels of 5-fluorocytosine is helpful in minimizing or avoiding toxicity [38].

The role of combinations of amphotericin B with an azole for *Candida* infections has not been determined. While there are reports of antagonism in vitro and in vivo when moulds are exposed to the combination of amphotericin B with either of the lipophilic azoles (ketoconazole and itraconazole) [39, 40], the results of studies examining the effect of combining fluconazole with amphotericin B are less clear [41–43]. Fluconazole and amphotericin B have been shown to be antagonistic for *Candida* under carefully selected in vitro conditions that involve the use of sub-MIC concentrations of both drugs [33, 41]. However, an in vivo study did not demonstrate this antagonism [44]. This topic has been well reviewed [43], and a trial of amphotericin B plus fluconazole for the treatment of candidemia in nonneutropenic patients is currently under way under the supervision of investigators at the MSG.

To treat patients with neutropenia who initially receive amphotericin B and whose conditions become clinically stable or improve (even though neutropenia persists), eight of 20 investigators would change the therapeutic regimen to fluconazole alone, assuming there are no contraindications to the use of fluconazole, such as recovery of a resistant isolate. There was no consensus regarding a specific dose or the duration of therapy with amphotericin B before therapy was changed to

fluconazole. However, the investigators agreed that a patient should be clinically stable before therapy is changed. If the neutropenia resolved and the patient remained stable, 17 of 20 investigators would change treatment to that with fluconazole. Itraconazole was discussed as an alternative, but, as mentioned above, it has not been approved by governmental agencies in various countries for treatment of deep candidal infections, and there are few data to support its use.

Although dose-ranging studies for either azoles or amphotericin B have not been performed in patients with candidemia or deep candidal infections, there was general agreement on a dose of 800 mg/d of fluconazole and ≥0.7 mg/(kg·d) of amphotericin B for adults. Some of the investigators would use ≤1.5 mg/(kg·d) of amphotericin B in unstable patients. The dose of 800 mg/d of fluconazole is consistent with that used in the candidemia trial that is being conducted by the MSG and has been supported by the results of a recent study in which 400 mg/d were compared with 800 mg/d in a sequential fashion [10].

Furthermore, the 800-mg dose was selected because a 15% failure rate was observed in a previous study [4] and because of the lack of toxicity of the 400-mg dose. There was also unanimity on continuing treatment for ≥2 weeks after the last positive blood-culture results are obtained and all clinical manifestations of candidal infection have resolved. Antifungal therapy should be continued throughout the duration of neutropenia to prevent relapse of infection.

What is the role of treatment with cytokines in neutropenic patients with candidal infections?

Background data. Members of the American Society of Clinical Oncology recently recommended that granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) be administered to adults and children with febrile neutropenia, for whom the expected incidence of infection is ≥40% [45, 46]. These cytokines are also recommended for future chemotherapy cycles after a documented febrile episode occurs in association with neutropenia during a prior chemotherapy cycle. Similar recommendations have been made by the European School of Oncology Consensus Conference [47]. These recommendations are designed to prevent future infectious complications and to maintain dose intensity during subsequent treatment cycles. They also apply to high-dose chemotherapy given to patients undergoing autologous progenitor cell transplantation.

Recombinant G-CSF or GM-CSF are also recommended for persistently neutropenic patients who have proven invasive candidiasis and are not already receiving a recombinant colony-stimulating factor. These recommendations have been made in the absence of any data from clinical trials, and it is not clear that the use of cytokines prolongs survival. The issue is discussed further in two reviews [48, 49].

Responses. Despite these qualifications, the group unanimously agreed with the recommendations of these two societies. This consensus was based on evidence that in addition to accelerating recovery from neutropenia, certain colony-stimulating factors may enhance the activity of neutrophils against *Candida* species [50, 51].

What is the role of prophylactic antifungals in neutropenic patients at high risk for candidal infections?

Background data. Before administering antifungal agents prophylactically, it is important to implement general measures to reduce the possibility that a patient will acquire a disseminated mycosis. Optimal hygiene, including hand washing by visitors, nurses, doctors, and other personnel, is paramount. Neglect of this principle undermines the efficacy of all other sophisticated or expensive interventions.

For many clinicians concerned about the possibility of life-threatening infections during aggressive treatment of a malignant disease, the temptation to use one of the available antifungal drugs prophylactically is irresistible. Unfortunately, the efficacy of such a strategy is controversial for most patients. The findings of previous studies on the prophylactic use of polyenes and older azoles are generally outdated since the chemotherapy regimens for hematologic malignancies and solid tumors have changed substantially. Earlier studies of the oral polyenes (nystatin and amphotericin B) and the older imidazoles (miconazole, ketoconazole, and clotrimazole), show that these drugs are active against superficial infections caused by *C. albicans* but are largely ineffective in the prevention of disseminated mycoses [29, 52, 53].

Two studies have shown a reduction in the incidence of hematogenously disseminated deep-organ fungal infection among bone marrow transplant recipients given fluconazole prophylaxis [54, 55]. Another study, performed in leukemic patients with neutropenia, showed a reduction in the incidence of mucocutaneous candidiasis but not in that of hematogenously disseminated fungal infections [56]. Additional problems with the use of fluconazole as prophylaxis in leukemic patients and bone marrow transplant recipients include the variable susceptibilities of non-*albicans* species and the risk of infection with molds that are resistant to fluconazole. In institutions where there is a high rate of infection with *Aspergillus* species, investigators have used "low-dose" amphotericin B in neutropenic bone marrow transplant recipients [57]. However, this strategy remains controversial and numerous prospective controlled studies have not been performed. The use of low-dose amphotericin B in leukemic neutropenic patients also remains controversial.

There are only a few studies of prophylaxis with itraconazole. In retrospective uncontrolled studies, Boogaerts et al. [58] and Thunnissen et al. [59] found that the prophylactic use of itraconazole in patients with neutropenia decreased the inci-

dence of fungal infection. A gradual shift in the species of pathogenic fungi was seen, leading to a reduction in *C. albicans* and *Aspergillus* infections and an increase in *C. glabrata, Fusarium,* and *Mucorales* infections. Vreugdenhil and colleagues [60] observed a lower incidence of *C. albicans* infections when itraconazole, rather than placebo, was administered; however, there was no significant improvement in the prevention of fungal infections, nor was there a decrease in mortality with itraconazole.

Todeschini and colleagues [61] also reported promising results in a prospective uncontrolled evaluation of itraconazole administered as capsules (200 mg/d) in combination with intranasal amphotericin B. Potential antagonism between itraconazole and amphotericin B against *Aspergillus* species has been reported [40], but more extensive clinical experience and controlled trials are needed. Large controlled clinical trials for evaluating itraconazole as chemoprophylaxis are ongoing. Administration of ketoconazole has also been found to diminish colonization with *Candida* species in susceptible populations, but this drug is not considered effective in preventing disseminated candidiasis [62].

Responses regarding prophylaxis in neutropenic leukemic patients. There was no strong agreement among the investigators regarding the use of prophylactic fluconazole, itraconazole, or amphotericin B in neutropenic leukemic patients. Until further studies are conducted, clinicians at each center will have to determine their own strategies on the basis of the unique fungal epidemiology at the center.

Responses regarding prophylaxis in bone marrow transplant patients. In a prospective, double-blind, placebo-controlled, multicenter study of patients undergoing bone marrow transplantation, prophylaxis with fluconazole at a dose of 400 mg once daily was shown to be effective in preventing superficial and disseminated candidiasis and was associated with a lower overall mortality [55]. These results were confirmed in a retrospective study in which a lower dose of 100–200 mg/d was given [63]. The data from a study by Goodman and associates [54], who used a dose of 400 mg/d, are the most convincing. The results from another study suggested that a lower dose of fluconazole (e.g., 150 mg/d or 200 mg/d) may suffice in cases of neutropenia [64]. Fluconazole was well tolerated at all dosages. Selection of resistant species, such as *C. glabrata* and *C. krusei,* may be a problem [3], but such selection did not occur in several prospective, randomized studies involving neutropenic patients [56, 65, 66].

There was strong agreement among the investigators that prophylaxis with fluconazole is effective in patients undergoing allogeneic and high-risk autologous bone marrow transplantation. Until studies that may show otherwise have been completed, 400 mg/d administered either orally or intravenously is the recommended dose.

Responses regarding surveillance cultures. There was consensus among the investigators that surveillance cultures that are positive for *C. albicans* and *C. tropicalis* are predictive of the development of candidemia. Such findings allow the identification of subsets of patients who would benefit from prophylaxis (some investigators would use positive results of surveillance cultures to define a subset of patients at high risk who are candidates for empirical rather than prophylactic strategies). However, the cost of surveillance cultures has limited their routine use in all the centers represented by the investigators at this meeting. This topic has been well reviewed [67].

What is the role of empirical antifungal therapy in neutropenic patients?

Background data. The rationale for empirical antifungal therapy is to treat invasive fungal infections at the earliest stage in patients at high risk for such infections. Empirical therapy was considered appropriate for neutropenic patients who were at high risk for developing fungal infections, had had persistent fever for 5–7 days despite appropriate antibacterial therapy (some investigators considered 3 days as the criterion), and had no identifiable source of fever after a thorough evaluation for a nonfungal (i.e., bacterial or viral) infection. Benefit from the use of amphotericin B therapy in neutropenic patients has been reported [68]. In a randomized pilot study, investigators found that fluconazole was equivalent to amphotericin B as empirical therapy in persistently febrile and neutropenic cancer patients at low risk for aspergillosis, as measured by response of fever and survival [69].

Responses. The investigators' responses regarding the use of empirical therapy in neutropenic patients when a mould infection appeared either unlikely or likely are summarized in figure 5. When a mould infection was likely, amphotericin B was chosen by nearly all the investigators.

Management of Candiduria

Candiduria is one of the most difficult problems related to candidal infections [70]. It is frequently not clear whether the yeast is merely colonizing the bladder or causing infection, whether the bladder or the kidney is involved if infection is deemed to be present, or whether the yeast in urine is present as a result of hematogenous dissemination or reflects ascending infection. Despite the many questions that invariably arise in the care of patients with candiduria, there was surprising agreement among the investigators with regard to treatment.

Should patients who do not have diabetes mellitus or genitourinary abnormalities or have not undergone renal transplantation and who have one or more cultures showing the presence of asymptomatic (without pyuria) candiduria be treated?

Nineteen of 20 investigators thought that patients in this clinical situation should not be treated with an antifungal agent.

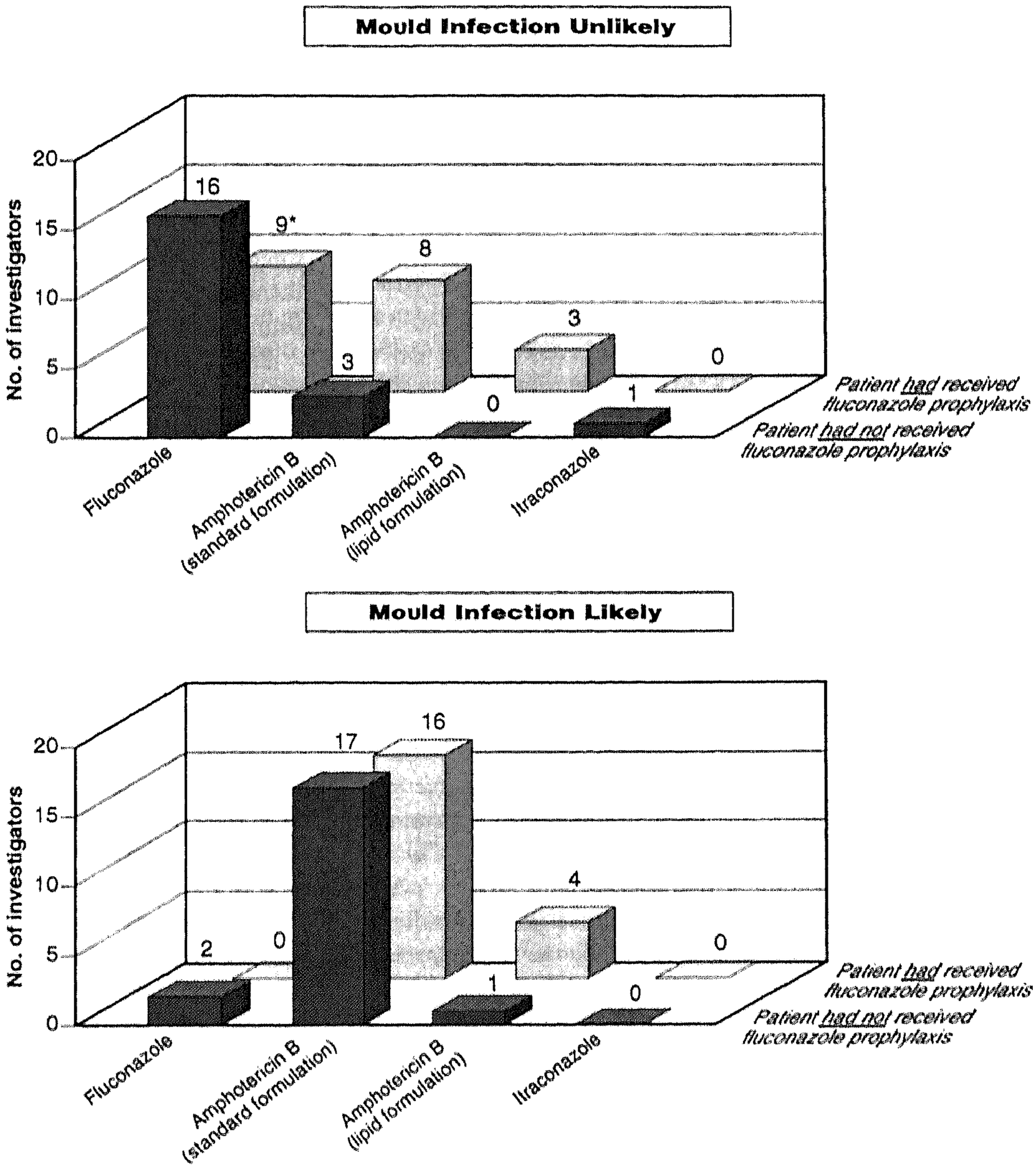

Figure 5. Investigator responses regarding the use of empirical therapy in febrile neutropenic patients. A total of 20 investigators, who attended the consensus conference on candidal infections, voted. Considerable discussion was generated by this response. Most of the investigators concluded that mould infection and infection by fluconazole-resistant *Candida* species are unlikely and that a bacterial or viral infection is the most likely cause of fever in neutropenic patients. Therefore, the investigators would elect to continue fluconazole therapy. The results of a surveillance culture, however, might lead to a different treatment decision.

Their reasons were that colonization is exceedingly common, that it is often caused by antibiotic and catheter use, and that removing these factors usually leads to clearing of the candiduria [70, 71].

Should patients with candiduria be treated before undergoing a genitourinary tract procedure?

Eighteen of the 20 participants agreed that treatment of candiduria is warranted in this situation. Their position was based on data showing that candidemia can be linked to a urinary tract source and often occurs after genitourinary tract manipulation [72].

Should prosthetic materials in the urinary tracts of patients with candiduria be removed?

It is not surprising that since catheters are a major risk factor for the development of candiduria, all the investigators believed that all catheters and prosthetic materials should be removed, if possible.

What is the most appropriate therapy for candidal (non-krusei) cystitis?

Although several treatment options exist [73], 19 of 20 investigators chose oral fluconazole for the treatment of candidal cystitis. One of 20 chose bladder irrigation with amphotericin B as the treatment of choice. These two treatments have been compared in only a few studies, but they seem to be equally efficacious [71, 74].

What is the most appropriate therapy for presumed upper urinary tract infection due to non-krusei Candida species?

Sixteen of 18 investigators preferred initial treatment with fluconazole. One investigator selected itraconazole capsules, and one chose intravenous amphotericin B.

Management of Selected Candidal Infections of Specific Organs

How should patients with possible or probable candidal peritonitis be managed?

Background data. Since *Candida* inhabits the healthy gastrointestinal tract, there is always a risk that *Candida* peritonitis will develop following any perforation of the intestines. In addition, *Candida* may be present in the stomach, especially in situations of relative alkalinity. The management of perforation of the gastrointestinal tract remains controversial with respect to antifungal therapy for suspected candidal peritonitis.

Responses. Eleven of 18 investigators would begin treatment of patients who have peritoneal candidiasis with fluconazole alone. Four of 18 would start therapy with amphotericin B, followed by fluconazole. Of the other possible choices (fluconazole plus 5-fluorocytosine, amphotericin B lipid formulation, amphotericin B plus 5-fluorocytosine, and standard amphotericin B formulation alone), two investigators chose fluconazole plus 5-fluorocytosine, and one selected amphotericin B lipid formulation.

Eighteen of 20 investigators would not initiate anticandidal therapy in patients with perforated stomachs or duodenums before cultures had been processed because colonization by *Candida* is infrequent in the upper gastrointestinal tract. For patients with community-acquired perforations of the stomach or duodenum (such as a gunshot wound) who had *Candida* species recovered in combination with bacteria from the peritoneal culture, 10 of 20 investigators would initiate antifungal therapy only if there had been no response to antibacterial therapy. Four of 20 would withhold therapy and continue to observe the patient. Six of 20 investigators would initiate antifungal therapy as a response to the isolation of *Candida* species, whether the fungus was recovered alone or in combination with bacteria.

Patients at high risk for complications of candidal peritoneal infection after perforation of the stomach or duodenum include patients with cancer, patients with neglected perforation (those who don't receive treatment for >24 hours after the perforation occurred), patients with generally unstable conditions, patients requiring a second unplanned abdominal operation, immunosuppressed patients, patients with hospital-acquired perforation, and patients with hepatic cirrhosis or pancreatitis. Patients for whom intraoperative findings are consistent with peritonitis and whose cultures are positive for *Candida* should receive antifungal therapy (20 of 20 investigators agreed on this point).

Most of the investigators would give antifungal therapy to a patient whose peritoneal culture yields *Candida* species, even if bacteria were isolated in association with *Candida*. In general, positive cultures of peritoneal drains were considered by the investigators to be of less significance than positive cultures of specimens obtained directly from the cavity.

All investigators agreed that prosthetic materials such as drains should be removed whenever possible from patients with suspected candidal peritonitis.

How should chronic disseminated candidiasis (formerly called hepatosplenic candidiasis) be managed in patients who are no longer neutropenic?

Background data. Two studies have shown a successful response to fluconazole in patients with chronic disseminated candidiasis who have been treated initially with amphotericin B [75, 76]. Furthermore, the progress of treatment can be monitored with CT scans. If a patient is not responding to azole therapy, alternative agents such as amphotericin B or lipid formulations of amphotericin B can be used.

Responses. Most (11 of 18) of the investigators chose fluconazole as initial therapy. A minority (four of 18) chose amphotericin B as initial therapy, followed by fluconazole. Two investigators preferred fluconazole plus 5-fluorocytosine as the initial treatment, and one preferred a lipid formulation of amphotericin B for the entire therapeutic course.

What is the most appropriate treatment for uncomplicated candidal endophthalmitis (lesions that are not advancing rapidly, are relatively small, and are not localized in the area of the macula)?

Background data. Until the introduction of azoles, amphotericin B, with or without 5-fluorocytosine, was the treatment of choice. There are very few data on the efficacy of azole therapy for hematogenous candidal endophthalmitis. The findings in limited case series and noncomparative studies suggest that fluconazole is effective for hematogenous candidal endophthalmitis [77, 78]. One clinical study [79] and experimental studies in animal models [80, 81] have shown less satisfactory results. The eye can be accurately assessed for efficacy of therapy, and therapy can be changed if there is no therapeutic response. Management of complicated hematogenous candidal endophthalmitis requires an ophthalmologic consultation to assess the need for partial vitrectomy, which can be a sight-saving procedure.

Responses. Eleven of 18 investigators chose fluconazole alone for treatment of uncomplicated hematogenous candidal endophthalmitis. Although the data are extremely limited, six of 18 investigators chose fluconazole plus 5-fluorocytosine. One chose amphotericin B plus 5-fluorocytosine. None of the investigators selected amphotericin B as the initial therapy.

For patients with enlarging lesions or lesions that threaten the macula, treatment with amphotericin B in combination with 5-fluorocytosine was chosen by all of the investigators. After consultation with an ophthalmologist, the intravitreal administration of an antifungal can be considered, but this practice is controversial. Partial vitrectomy should also be considered.

Antifungal Therapy in Solid Organ Transplant Recipients

The prevention and treatment of candidal infection in solid organ transplant recipients is complicated by the potential for interactions between antifungal drugs and cyclosporine and

FK-506 (tacrolimus), the mainstays of modern antirejection therapy, as well as with other components of the therapeutic regimen. The azoles, through their effects on hepatic microsomal (cytochrome P-450 linked) function, inhibit the metabolism of cyclosporine (and, it is assumed, that of FK-506). Ketoconazole and itraconazole are the azoles with the most striking effect on cyclosporine metabolism [82–84]. When fluconazole is administered, there is a measurable but less dramatic effect, often requiring a 50–100-mg decrease in the daily dose of cyclosporine to maintain the desired therapeutic blood level of cyclosporine. Virtually all the clinical experience with fluconazole in solid organ transplant recipients has been with doses of 200–400 mg/d.

There is currently no information on drug interactions or on the potential toxicity associated with higher doses of fluconazole in this patient population. There is, however, significant experience demonstrating the safety and efficacy of the 200–400 mg/d dose in liver transplant recipients, including those with severe allograft dysfunction [84–86].

Amphotericin B can contribute to an accelerated form of drug-induced nephrotoxicity in some patients receiving cyclosporine [87]. Thus as little as 10 mg of amphotericin B may produce oliguric renal failure in transplant recipients whose renal function had been normal. There is too little information on the interaction of liposomal amphotericin B with cyclosporine and FK-506 to make any statement about the potential for nephrotoxicity. Another drug interaction of potential importance is that between antacids, H_2 blockers, and omeprazole, which can render the absorption of ketoconazole and itraconazole unreliable [88].

Because of these pharmacologic considerations, the mainstays of anticandidal therapy in the organ transplant recipient are fluconazole and amphotericin B. At present, liposomal amphotericin B is reserved for patients with renal toxicity who still require amphotericin B therapy.

How should candidemia be managed in the stable patient after solid organ transplantation?

The rate for visceral seeding following candidemia in solid organ transplant recipients is significantly higher than that for the general population, exceeding 50% at some centers [86]. Therefore, there was agreement among the investigators that all candidemic organ transplant recipients should be treated with antifungals and that they should receive systemic therapy for a minimum of 2 weeks after the last positive blood culture is performed and clinical response has occurred. In addition, all nonessential vascular access lines, including temporary subclavian catheters, should be removed (arteriovenous fistulas created for dialysis access are the exception). Initial therapy should be similar to that discussed for stable neutropenic patients. If such a patient has not received fluconazole, then 18 of 18 investigators would recommend initial therapy with fluconazole. If fluconazole has been administered, candidemia should be initially treated with amphotericin B.

How should candidemia be managed in the unstable patient after solid organ transplantation?

The investigators unanimously agreed that immediate initiation of systemic antifungal therapy is obligatory, but there was disagreement on what this therapy should be. The selections of the investigators are shown in table 5.

Once a patient has been stabilized, consideration should be given to switching to longer-term oral fluconazole therapy, with a treatment duration of ≥3 weeks beyond the time of clinical response and the last positive blood culture. The longer duration of therapy was suggested because of the continued immunosuppression experienced by these patients.

Should prophylactic antifungals be given to solid organ transplant recipients?

The investigators unanimously agreed that for liver transplant recipients at high risk for fungal infections, systemic prophylaxis with fluconazole should be considered. No precise definition of high risk was formulated by the group. Examples of liver transplant recipients at high risk for fungal infections are discussed in the study by Collins et al. [89]. For liver transplant recipients who are not receiving fluconazole prophylaxis, clinicians should consider selective gastrointestinal decontamination with nonabsorbable antifungal agents that are administered before and after the operation.

All lung and heart-lung transplant recipients should receive fluconazole prophylaxis for a minimum of 10–14 days after transplantation to protect the bronchial tissue and tracheobronchial tree, but this recommendation is not based on solid data. In institutions in which aspergillus infections are frequent after lung transplantation, use of antifungals with antiaspergillus activity should be considered during the first 10–14 days of the postoperative period.

How should mucocutaneous candidiasis that develops after organ transplantation be managed?

For the majority of organ transplant recipients with mucocutaneous candidiasis, topical therapy with oral nystatin or clotrimazole for 7 days is usually adequate for eradicating the infection. Topical therapy is recommended to minimize the number of systemic drugs such patients receive. For patients who fail to respond to such therapy, fluconazole at a dose of 200–400 mg/d is the treatment of choice. Low-dose amphotericin B (5–10 mg/d administered intravenously for 7–10 days) is reserved for the rare patient who fails to respond.

Table 5. Investigator responses regarding the management of candidemia in unstable patients after solid organ transplantation.

Fluconazole	Amphotericin B (standard formulation)	Amphotericin B and 5-FC	Amphotericin B lipid formulation	Amphotericin B and fluconazole	Itraconazole capsules
7/18	4/18	4/18	2/18	1/18	0/18

NOTE. Data are number of votes/number of investigators voting in the consensus conference on candidal infections. 5-FC = 5-fluorocytosine.

How should asymptomatic candidal colonization of the urinary tract and biliary tree after solid organ transplantation be managed?

Background data. Asymptomatic candiduria that persists even after removal of the urinary catheter is a common problem among renal transplant recipients. Asymptomatic candiduria occurs frequently in diabetic patients with poor bladder function and also in renal transplant recipients who are being treated with high-dose steroids and have incomplete bladder emptying. There is a significant risk of ureterovesical obstruction from a fungal ball, of ascending infection, and of candidal pyelonephritis with candidemia. Because of these potential complications, preemptive therapy for asymptomatic candiduria is advocated.

Responses. Fluconazole was agreed upon as the treatment of choice for these infections (unless they were due to *C. krusei* or *C. glabrata*). If candiduria is due to these more-resistant species, therapy with low-dose amphotericin B, either alone or in combination with 5-fluorocytosine, is recommended.

Candidal colonization of the biliary tree occurs less commonly in the first few months after liver transplantation (at a time when the T-tube is still in place and biliary specimens for culture can be obtained with ease). Since such colonization of the biliary tree can also result in obstruction that causes ascending cholangitis, treatment of asymptomatic colonization of this site was also advocated by the investigators. Treatment approaches are the same as those discussed above for the urinary tract.

Summary

The incidence of candidal infections has increased to the point that *Candida* is the fourth most common organism isolated from the blood of hospitalized patients. The trends associated with this increase include a shift in the incidence of species to more non-*albicans* isolates and the appearance of candidal isolates resistant to both amphotericin B and the newer azoles. There has not been widespread acceptance of a serodiagnostic test to determine which patients with candidemia have infection in deep organs. The increase in clinical infections with *Candida* has occurred at a rate that far exceeds the rate of completion of studies addressing the complex issues of treatment.

In general, the investigators participating in this consensus conference agreed on the need for a much more aggressive approach to the management of candidal infections with antifungal agents than was the practice in the past, when many candidemic patients were not treated with chemotherapeutic agents. This consensus is based on an appreciation for the potentially high morbidity and mortality associated with candidal infections and the availability of the newer anticandidal agents, which are less toxic than amphotericin B. There was a strong consensus that all candidemic patients should be treated and that intravenous lines should be withdrawn from candidemic patients whenever feasible. Although there are few studies in which the azoles have been compared with amphotericin B for nearly all forms of candidal infections, most of the investigators would use fluconazole as first-line therapy for stable patients with candidal infections (the other azoles are not approved for treatment of deep candidal infections in the United States at this time). For patients with life-threatening infections, amphotericin B was generally considered the first-line agent of choice. Amphotericin B was also chosen for treatment of infections due to isolates of *Candida* that are highly resistant to azoles (e.g., *C. krusei*).

The advisability of prophylactic and empirical antifungal therapy is a complex issue, and practices vary considerably from institution to institution. There was strong agreement regarding the benefit of fluconazole prophylaxis in bone marrow transplant recipients. Because of the development of resistance to the azoles and the lack of solid data indicating their prophylactic efficacy, there was concern regarding the widespread use of prophylaxis in other patient populations such as neutropenic leukemic patients and patients hospitalized in surgical intensive care units. Some investigators favored the empirical use of fluconazole in patient populations or hospitals in which the likelihood of mould infections is low. Where mould infection rates are high, the inclusion of amphotericin B–containing regimens was favored.

The introduction of the azoles has provided efficacious, less toxic agents for treating candidal infections. Additional studies are now needed to determine the best treatment strategies for the various types of candidal infection, to develop a clearer definition of risk factors, to improve our knowledge of candidal epidemiology, and to develop improved methods of diagnosis. The development of strategies for managing the inevitable

emergence of resistance to the antifungal agents is critical and is linked to the need for a broader antifungal armamentarium.

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References

1. Jarvis WR. Epidemiology of nosocomial fungal infections, with emphasis on *Candida* species. Clin Infect Dis **1995**;20:1526–30.
2. Viscoli C, Girmenia C, Marinus A, Martino P. Meunier F. A surveillance study of fungemia in cancer patients in Europe. Invasive Fungal Infections Cooperative Group (IFIG of EORTC) [abstract 2]. Trends in Invasive Fungal Infections 3 (Brussels). **1995**.
3. Wingard JR. Importance of *Candida* species other than *C. albicans* as pathogens in oncology patients. Clin Infect Dis **1995**;20:115–25.
4. 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. N Engl J Med **1994**;331:1325–30.
5. Pfaller MA. Nosocomial candidiasis: emerging species, reservoirs, and modes of transmission. Clin Infect Dis **1996**;22:S89–94.
6. Asch SE. Studies of independence and conformity. I. A minority of one against a unanimous majority. Psychological Monographs **1956**;70.
7. Lecciones JA, Lee JW, Navarro EE, et al. Vascular catheter–associated fungemia in patients with cancer: analysis of 155 episodes. Clin Infect Dis **1992**;14:875–83.
8. Fraser VJ, Jones M, Dunkel J, Storfer S, Medoff G, Dunagan WC. Candidemia in a tertiary care hospital: epidemiology, risk factors, and predictors of mortality. Clin Infect Dis **1992**;15:414–21.
9. Phillips P, Shafran S, Garber G, et al. Fluconazole (FLU) versus amphotericin B (AMB) for candidemia in non-neutropenic patients: a multicenter randomized trial [abstract no LM 20]. In: Program and abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco). Washington, DC: American Society for Microbiology, **1995**.
10. Graninger W, Presteril E, Schneeweiss B, Teleky B, Georgopoulos A. Treatment of *Candida albicans* fungaemia with fluconazole. J Infect **1993**;26:133–46.
11. Karabinis A, Hill C, Leclercq B, Tancrede C, Baume D, Andremont A. Risk factors for candidemia in cancer patients: a case-control study. J Clin Microbiol **1988**;26:429–32.
12. 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.
13. 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.
14. 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 disease. Pharmacotherapy **1995**;15:52–8.
15. Walsh TJ, Gonzalez C, Lyman CA, Chanock SJ, Pizzo PA. Invasive fungal infections in children: recent advances in diagnosis and treatment. Adv Pediatr Infect Dis **1996**;11:187–290.
16. Francis P, Walsh TJ. Evolving role of flucytosine in immunocompromised patients: new insights into safety, pharmacokinetics, and antifungal therapy. Clin Infect Dis **1992**;15:1003–18.
17. Viscoli C, Castagnola E, Fioredda F, Ciravegna B, Barigione G, Terragna A. Fluconazole in the treatment of candidiasis in immunocompromised children. Antimicrob Agents Chemother **1991**;35:365–7.
18. 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.
19. Donahue SP, Greven CM, Zuravleff JJ, et al. Intraocular candidiasis in patients with candidemia: clinical implications derived from a prospective multicenter study. Ophthalmology **1994**;101:1302–9.
20. von Eiff M, Fahrenkamp A, Roos N, Fegeler W, van de Loo J. Hepatosplenic candidosis—a late manifestation of Candida septicemia. Mycoses **1990**;33:283–90.
21. Almekinders LC, Greene WB. Vertebral *Candida* infections: a case report and review of the literature. Clin Orthop **1991**;267:174–8.
22. Blade J, Lopez-Guillermo A, Rozman C, et al. Chronic systemic candidiasis in acute leukemia. Ann Hematol **1992**;64:240–4.
23. Meunier F, Gérard M, Richard V, Debusscher L, Bleiberg H, Malengrau A. Hepatic candidosis in a patient with acute leukemia. Mycoses **1989**;32:421–6.

24. Bodey GP, Anaissie EJ. Chronic systemic candidiasis. Eur J Clin Microbiol Infect Dis **1989**;8:855–7.
25. Walsh TJ, Lee JW, Roilides E, et al. Experimental antifungal chemotherapy in granulocytopenic animal models of disseminated candidiasis: approaches to understanding investigational antifungal compounds for patients with neoplastic diseases. Clin Infect Dis **1992**;14(suppl 1): S139–47.
26. Anaissie EJ, Darouiche RO, Abi-Said D, et al. Management of invasive candidal infections: results of a prospective, randomized, multicenter study of fluconazole versus amphotericin B and review of the literature. Clin Infect Dis **1996**;23:964–72.
27. Galgiani JN, Bartlett MS, Ghannoum MA, et al. Reference method for broth dilution antifungal susceptibility testing of yeasts: tentative standard. Wayne, Pennsylvania: National Committee for Clinical Laboratory Standards, **1995**.
28. Ghannoum MA, Rex JH, Galgiani JN. Susceptibility testing of fungi: current status of correlation of in vitro data with clinical outcome. J Clin Microbiol **1996**;34:489–95.
29. 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.
30. Rex JH, Pfaller MA, Barry AL, et al. Antifungal susceptibility testing of isolates from a randomized, multicenter trial of fluconazole versus amphotericin B as treatment of nonneutropenic patients with candidemia. Antimicrob Agents Chemother **1995**;39:40–4.
31. Kwon-Chung KJ, Bennett JE. Medical mycology. Philadelphia: Lea & Febiger, **1992**:44–71.
32. Pappagianis D, Collins MS, Hector R, Remington J. Development of resistance to amphotericin B in *Candida lusitaniae* infecting a human. Antimicrob Agents Chemother **1979**;16:123–6.
33. Dick JD, Merz WG, Saral R. Incidence of polyene-resistant yeasts recovered from clinical specimens. Antimicrob Agents Chemother **1980**;18: 158–63.
34. Guinet R, Chanas J, Goullier A, Bonnefoy G, Ambroise-Thomas P. Fatal septicemia due to amphotericin B–resistant *Candida lusitaniae*. J Clin Microbiol **1983**;18:443–4.
35. Merz WG. *Candida lusitaniae:* frequency of recovery, colonization, infection, and amphotericin B resistance. J Clin Microbiol **1984**;20: 1194–5.
36. Pfaller MA, Houston A, Coffmann S. Application of CHROMagar Candida for rapid screening of clinical specimens for *Candida albicans, Candida tropicalis, Candida krusei,* and *Candida (Torulopsis) glabrata*. J Clin Microbiol **1996**;34:58–61.
37. Hiddemann W, Essink ME, Fegeler W, Zuhlsdorf M, Sauerland C, Buchner T. Antifungal treatment by amphotericin B and 5-fluorocytosine delays the recovery of normal hematopoietic cells after intensive cytostatic therapy for acute myeloid leukemia. Cancer **1991**;68:9–14.
38. Dellamonica P, Fournier JP, Garraffo R, et al. Contribution à la surveillance des traitements comportant de la 5-fluorocytosine. Pathol Biol (Paris) **1985**;33:642–5.
39. Schaffner A, Frick PG. The effect of ketoconazole on amphotericin B in a model of disseminated aspergillosis. J Infect Dis **1985**;151:902–10.
40. Schaffner A, Böhler A. Amphotericin B refractory aspergillosis after itraconazole: evidence for significant antagonism. Mycoses **1993**;36: 421–4.
41. Scheven M, Senf L. Quantitative determination of fluconazole-amphotericin B antagonism to *Candida albicans* by agar diffusion. Mycoses **1994**; 37:205–7.
42. Ghannoum MA, Fu Y, Ibrahim AS, et al. In vitro determination of optimal antifungal combinations against *Cryptococcus neoformans* and *Candida albicans*. Antimicrob Agents Chemother **1995**;39:2459–65.
43. Sugar AM. Use of amphotericin B with azole antifungal drugs: what are we doing? Antimicrob Agents Chemother **1995**;39:1907–12.
44. Sugar AM, Hitchcock CA, Troke PF, Picard M. Combination therapy of murine invasive candidiasis with fluconazole and amphotericin B. Antimicrob Agents Chemother **1995**;39:598–601.
45. American Society of Clinical Oncology. American Society of Clinical Oncology recommendations for the use of hematopoietic colony–stimulating factors: evidence-based, clinical practice guidelines. J Clin Oncol **1994**;12:2471–508.
46. Bodey GP, Anaissie E, Gutterman J, Vadhan-Raj S. Role of granulocyte-macrophage colony-stimulating factor as adjuvant therapy for fungal infection in patients with cancer. Clin Infect Dis **1993**;17:705–7.
47. Boogaerts M, Cavalli F, Cortés-Funes H, et al. Granulocyte growth factors: achieving a consensus. Ann Oncol **1995**;6:237–44.
48. Freifeld A, Pizzo P. Colony-stimulating factors and neutropenia: intersection of data and clinical relevance. J Natl Cancer Inst **1995**;87:781–2.
49. Mayordomo JI, Rivera F, Diaz-Puente MT, et al. Improving treatment of chemotherapy-induced neutropenic fever by administration of colony-stimulating factors. J Natl Cancer Inst **1995**;87:803–8.
50. Vecchiarelli A, Monari C, Baldelli F, et al. Beneficial effect of recombinant human granulocyte colony-stimulating factor on fungicidal activity of polymorphonuclear leukocytes from patients with AIDS. J Infect Dis **1995**;171:1448–54.
51. Bober LA, Grace MJ, Pugliese-Sivo C, et al. The effect of GM-CSF and G-CSF on human neutrophil function. Immunopharmacology **1995**;29: 111–9.
52. Ninane J, Multicenter Study Group. A multicentre study of fluconazole versus oral polyenes in the prevention of fungal infection in children with hematological or oncological malignancies. Eur J Clin Microbiol Infect Dis **1994**;13:330–7.
53. Working Party of the British Society for Antimicrobial Chemotherapy: chemoprophylaxis for candidosis and aspergillosis in neutropenia and transplantation: a review and recommendations. J Antimicrob Chemother **1993**;32:5–21.
54. Goodman JL, Winston DJ, Greenfield RA, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. N Engl J Med **1992**;326:845–51.
55. Slavin MA, Osborne B, Adams R, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation—a prospective, randomized, double-blind study. J Infect Dis **1995**;171: 1545–52.
56. Winston DJ, Chandrasekar PH, Lazarus HM, et al. Fluconazole prophylaxis of fungal infections in patients with acute leukemia: results of a randomized placebo-controlled, double-blind, multicenter trial. Ann Intern Med **1993**;118:495–503.
57. Perfect JR, Klotman ME, Gilbert CC, et al. Prophylactic intravenous amphotericin B in neutropenic autologous bone marrow transplant recipients. J Infect Dis **1992**;165:891–7.
58. Boogaerts MA, Verhoef GE, Zachee P, Demuynck H, Verbist L, De Beule K. Antifungal prophylaxis with itraconazole in prolonged neutropenia: correlation with plasma levels. Mycoses **1989**;32(suppl 1):103–8.
59. Thunnissen PL, Sizoo W, Hendriks WD. Safety and efficacy of itraconazole in prevention of fungal infections in neutropenic patients. Neth J Med **1991**;39:84–91.
60. Vreugdenhil G, Van Dijke BJ, Donnelly JP, et al. Efficacy of itraconazole in the prevention of fungal infections among neutropenic patients with hematologic malignancies and intensive chemotherapy. A double blind, placebo controlled study. Leuk Lymphoma **1993**;11:353–8.
61. Todeschini G, Murari C, Bonesi R, et al. Oral itraconazole plus nasal amphotericin B for prophylaxis of invasive aspergillosis in patients with hematological malignancies. Eur J Clin Microbiol Infect Dis **1993**;12: 614–8.
62. Palmblad J, Lönnqvist B, Carlsson B, et al. Oral ketoconazole prophylaxis for *Candida* infections during induction therapy for acute leukaemia in adults: more bacteraemias. J Intern Med **1992**;231:363–70.
63. Alangaden G, Chandrasekar PH, Bailey E, Khaliq Y, The Bone Marrow Transplantation Team. Antifungal prophylaxis with low-dose fluconazole during bone marrow transplantation. Bone Marrow Transplant **1994**;14:919–24.

64. Menichetti F, Del Favero A, Martino P, et al. Preventing fungal infection in neutropenic patients with acute leukemia: fluconazole compared with oral amphotericin B. Ann Intern Med **1994**;120:913–8.
65. Ellis ME, Clink H, Ernst P, et al. Controlled study of fluconazole in the prevention of fungal infections in neutropenic patients with haematological malignancies and bone marrow transplant recipients. Eur J Clin Microbiol Infect Dis **1994**;13:3–11.
66. Philpott-Howard JN, Wade JJ, Mufti GJ, Brammer KW, Ehninger G, Multicentre Study Group. Randomized comparison of oral fluconazole versus oral polyenes for the prevention of fungal infection in patients at risk of neutropenia. J Antimicrob Chemother **1993**;31:973–84.
67. Walsh TJ. Role of surveillance cultures in prevention and treatment of fungal infections. NCI Monogr **1990**;9:43–5.
68. EORTC International Antimicrobial Therapy Cooperative Group. Empiric antifungal therapy in febrile granulocytopenic patients. Am J Med **1989**; 86:668–72.
69. 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, multicenter, prospective and randomised clinical trial. Eur J Cancer **1996**;32A:814–20.
70. Fisher JF, Newman CL, Sobel JD. Yeast in the urine: solutions for a budding problem. Clin Infect Dis **1995**;20:183–9.
71. Leu H-S, Huang C-T. Clearance of funguria with short-course antifungal regimens: a prospective, randomized, controlled study. Clin Infect Dis **1995**;20:1152–7.
72. Ang BSP, Telenti A, King B, Steckelberg JM, Wilson WR. Candidemia from a urinary tract source: microbiological aspects and clinical significance. Clin Infect Dis **1993**;17:662–6.
73. Jacobs LG. Fungal urinary tract infections in the elderly: treatment guidelines. Drugs Aging **1996**;8:89–96.
74. Jacobs LG, Skidmore EA, Freeman K, Lipschultz D, Fox N. Oral fluconazole compared with bladder irrigation with amphotericin B for treatment of fungal urinary tract infections in elderly patients. Clin Infect Dis **1996**;22:30–5.
75. Kauffman CA, Bradley SF, Ross SC, Weber DR. Hepatosplenic candidiasis: successful treatment with fluconazole. Am J Med **1991**;91:137–41.
76. 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.
77. del Palacio A, Cuétara MS, Ferro M, et al. Fluconazole in the management of endophthalmitis in disseminated candidosis of heroin addicts. Mycoses **1993**;36:193–9.
78. 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.
79. Nomura J, Ruskin J. Failure of therapy with fluconazole for candidal endophthalmitis. Clin Infect Dis **1993**;17:888–9.
80. Filler SG, Crislip MA, Mayer CL, Edwards JE Jr. Comparison of fluconazole and amphotericin B for treatment of disseminated candidiasis and endophthalmitis in rabbits. Antimicrob Agents Chemother **1991**;35: 288–92.
81. Savani DV, Perfect JR, Cobo LM, Durack DT. Penetration of new azole compounds into the eye and efficacy in experimental *Candida* endophthalmitis. Antimicrob Agents Chemother **1987**;31:6–10.
82. Ferguson RM, Sutherland DER, Simmons RL, Najarian JS. Ketoconazole, cyclosporin metabolism, and renal transplantation [letter]. Lancet **1982**; 2:882–3.
83. Kwan JTC, Foxall PJD, Davidson DGC, Bending MR, Eisinger AJ. Interaction of cyclosporin and itraconazole [letter]. Lancet **1987**;2:282.
84. Hibberd PL, Rubin RH. Clinical aspects of fungal infection in organ transplant recipients. Clin Infect Dis **1994**;19(suppl 1):S33–40.
85. Hadley S, Karchmer AW. Fungal infections in solid organ transplant recipients. Infect Dis Clin N Am **1995**;9:1045–74.
86. Rubin RH. Infection in organ transplant recipients. In: Rubin RH, Young LS, eds. Clinical approach to infection in the immunocompromised host. 3rd ed. New York: Plenum Medical Book Company, **1994**:629–705.
87. Ringdén O, Andström E, Remberger M, Svahn BM, Tollemar J. Safety of liposomal amphotericin B (Ambisome) in 187 transplant recipients treated with cyclosporin. Bone Marrow Transplant **1994**;14(suppl 5): S10–4.
88. Conti DJ, Tolkoff-Rubin NE, Baker GP Jr, et al. Successful treatment of invasive fungal infections with fluconazole in organ transplant recipients. Transplantation **1989**;48:692–5.
89. Collins LA, Samore MH, Roberts MS, et al. Risk factors for invasive fungal infections complicating orthotopic liver transplantation. J Infect Dis **1994**;170:644–52.