# 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] | | | $MIC_{50}$ ($\mu$g/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.

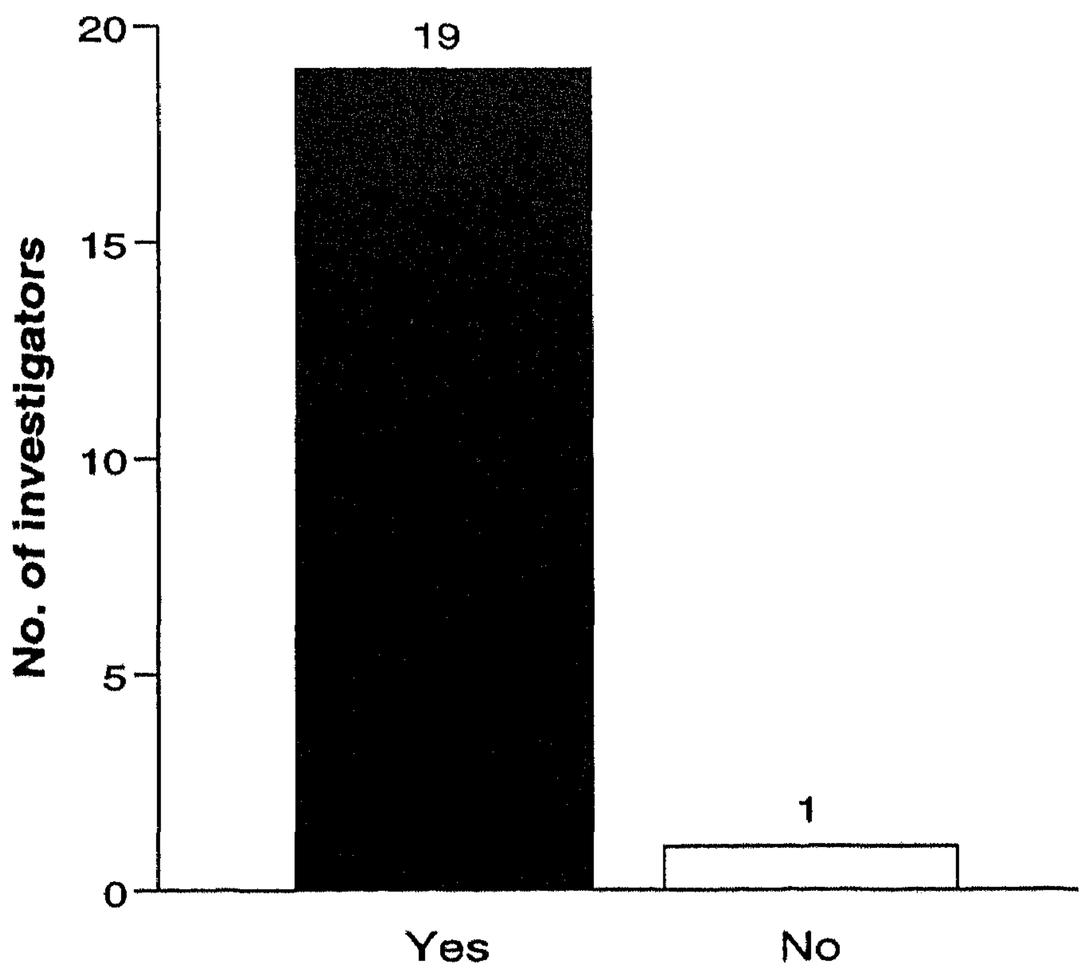


**Figure 1.** Responses to the question "Should all candidemic patients (nonneutropenic and neutropenic) be treated with an antifungal agent?" A total of 20 investigators attending the consensus conference on candidal infections voted.

#### *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.

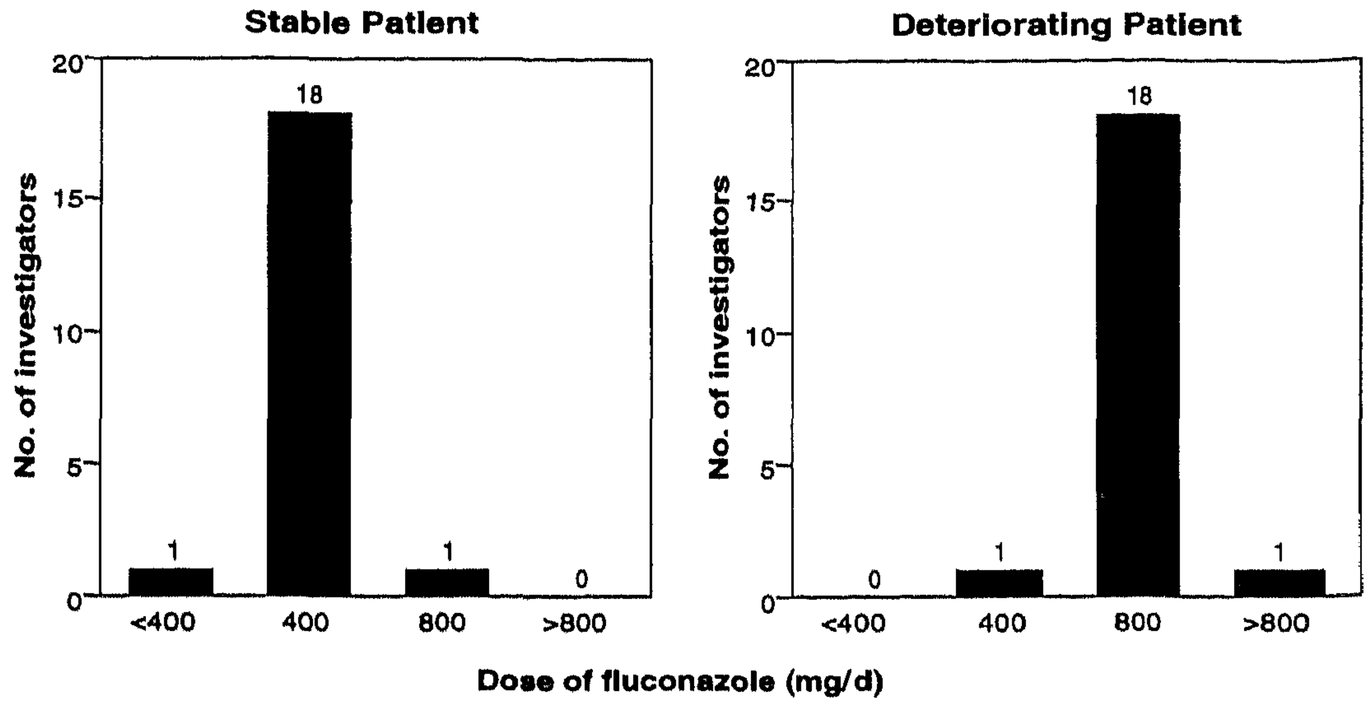


**Figure 2.** Responses to the question "What dose of fluconazole should be used for the management of candidemia?" A total of 20 investigators attending the consensus conference on candidal infections voted.

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.

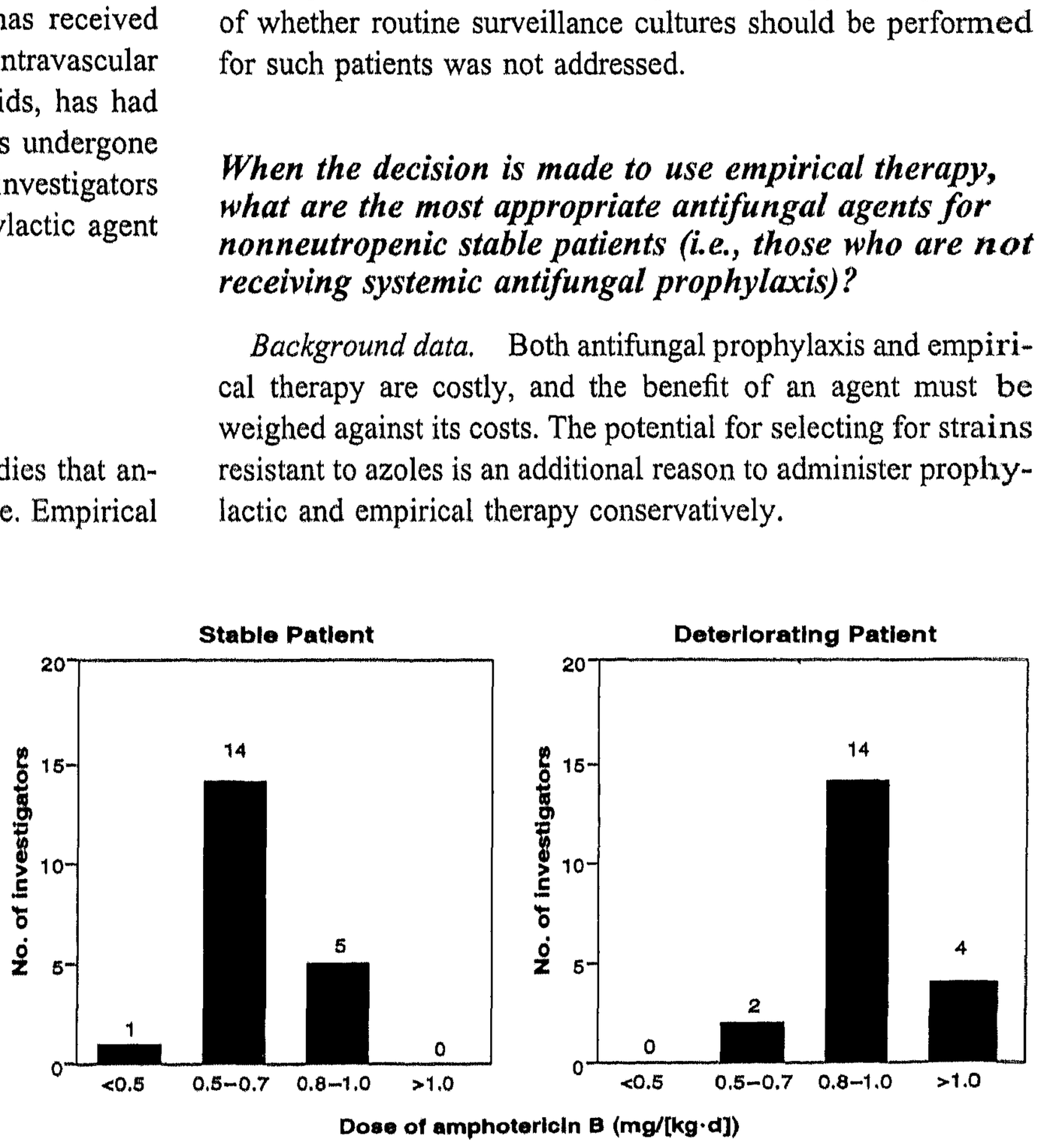


**Figure 3.** Responses to the question "What dose of amphotericin B should be used for the management of candidemia?" A total of 20 investigators attending the consensus conference on candidal infections voted.

*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