CLINICAL ARTICLES

Management of Invasive Candidal Infections: Results of a Prospective, Randomized, Multicenter Study of Fluconazole Versus Amphotericin B and Review of the Literature

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We conducted a prospective, randomized, multicenter study comparing fluconazole and amphotericin B in the treatment of candidal infections. One hundred and sixty-four patients (60 of whom were neutropenic) with documented or presumed invasive candidiasis were assigned to treatment with either fluconazole (400 mg daily) or amphotericin B (25–50 mg daily; 0.67 mg/kg daily for neutropenic patients). Clinical response and survival rates were assessed at 48 hours, after 5 days, and at the end of therapy. Overall response rates to fluconazole and amphotericin B were similar (66% and 64%, respectively). There were no differences in response as related to site of infection, pathogen, time to defervescence, relapse, or survival rates between the groups. Adverse effects were more frequent with amphotericin B (35%) than with fluconazole (5%; $P < .0001$). The results of this study confirm that fluconazole is as effective as but better tolerated than amphotericin B in the treatment of candidal infections.

Hematogenous candidiasis and other invasive organ candidiasis are life-threatening infections in susceptible patients [1], and candidiasis is the fourth commonest nosocomial bloodstream infection in the United States [2]. This infection is associated with a 38% attributable mortality rate and a 30-day prolongation of hospital stay [3].

An obstacle to the successful management of hematogenous and organ candidiasis is the limited ability to isolate *Candida* organisms from culture specimens, particularly blood [4]. Hence, it has become an accepted practice to administer empirical antifungal therapy to susceptible patients presumed to have invasive candidiasis [5–7].

Amphotericin B has been routinely used to treat invasive candidiasis [5–7]. Therapy with amphotericin B is limited, however, by its toxicity [8, 9]. Fluconazole is a well-tolerated triazole that is effective against experimental candidiasis [10]. Results of open trials in humans have been encouraging [1, 11–15]. Some concerns have arisen regarding the use of fluconazole to treat serious candidal infections because of the drug's fungistatic activity and its limited activity against certain *Candida* species. These concerns have led clinicians to question the role of fluconazole in treating serious candidal infections and especially whether it can be substituted safely for amphotericin B.

To address these concerns, we conducted a prospective, randomized, multicenter study to compare the activities and toxicities of amphotericin B and fluconazole in the treatment of presumed or proven invasive candidiasis. We also conducted a MEDLINE search of all reports in the literature on the use of fluconazole and amphotericin B in this context.

Methods

Patient Population

Patients were recruited between December 1990 and April 1993 from four medical centers in Houston, Texas: The University of Texas M. D. Anderson Cancer Center, The Veterans Affairs Medical Center, The Methodist Hospital, and St. Luke's Episcopal Hospital. The study protocol was approved by the institutional review boards of the participating institutions. Written informed consent was obtained from all patients, in accordance with institutional policies.

Inclusion Criteria

Patients with documented or presumed invasive candidiasis were included in the study [16]. Patients were considered to have candidemia if *Candida* organisms were isolated from at

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least one blood culture specimen and if they had signs and symptoms of systemic infection (fever, hypotension, tachycardia, etc.). Patients with candidemia were considered to have acute disseminated candidiasis if they had evidence of infection in multiple, noncontiguous organs. The diagnosis of presumed candidiasis was made only for neutropenic and postoperative patients. These patients were considered to have presumed candidiasis if they had persistent fever (temperature, >101°F) despite ≥3 days of therapy with broad-spectrum antibacterial agents and if *Candida* organisms were recovered from two or more body sites, provided no other cause for the fever could be found, such as pulmonary infiltrates suggestive of aspergillosis in neutropenic hosts. Other candidal infections were defined as follows.

Abdominal abscess. Abdominal abscess was considered to be present if *Candida* organisms were recovered in pure culture of drainage material from a patient with a clinically and radiologically diagnosed abscess.

Peritonitis. Patients were considered to have peritonitis if *Candida* organisms were recovered in pure culture of their peritoneal fluid and if signs and symptoms of inflammation were present.

Lower urinary tract infection. Patients were considered to have lower urinary tract infection if they had (1) appropriate risk factors (immunocompromising conditions such as diabetes mellitus, presence of anatomical defect, and obstruction or history of recent manipulation of the genitourinary tract), (2) pyuria (≥5 WBCs/mL) and funguria ($\geq 10^3$ cfu/mL) that persisted after removal of the indwelling urinary catheter, and (3) signs and symptoms of urinary tract infection.

Pyelonephritis. Patients were considered to have pyelonephritis if they had fever, chills, flank pain, and laboratory evidence of candidal urinary tract infection, as defined above.

Wound infection. Wound infection was considered to be caused by a *Candida* species if the patient was febrile and had local signs and symptoms of wound inflammation and if gram staining or culture of a purulent discharge demonstrated yeasts only.

Exclusion Criteria

Exclusion criteria were as follows: an age of <13 years; diagnosis of AIDS; pregnancy or lactation; life expectancy of <24 hours; receipt of any dose of systemic antifungal agents within the preceding 5 days; elevation of liver enzyme levels to >5 times the normal values; and renal failure, as defined by a serum creatinine value of ≥3 mg/dL.

Treatment Plan

Pretreatment evaluation for all patients included determination of the medical history; physical examination; pregnancy testing for women with child-bearing potential; hematologic and coagulation evaluations; liver and kidney function tests; appropriate roentgenographic examination of infected sites; and histopathologic examination and/or culture of samples from infected sites. Standard microbiological methods of fungal identification were followed [17]. Patients were examined daily, and the above-described blood tests were performed twice weekly during therapy, at the end of therapy, and 1–2 weeks after the end of therapy. In addition, patients were clinically assessed for recurrence of candidal infection within 3 months after the end of therapy. Roentgenographic examination, histopathologic evaluation, and appropriate cultures were repeated at various intervals, as clinically indicated.

After enrollment, patients were randomly assigned by a computer-generated sequence of numbers to receive either fluconazole or amphotericin B in a stratified fashion, according to the peripheral blood neutrophil count at the time of enrollment (<1,000 cells/mm^3 [neutropenic] vs. ≥1,000 cells/mm^3 [nonneutropenic]) and type of invasive candidal infection (candidemia and acute disseminated candidiasis vs. organ candidiasis vs. presumed candidiasis). Each participating institution had its own randomization table. Randomization was done in a blinded fashion. Moreover, treatment assignments remained unknown to the investigators in charge of determining eligibility, diagnosing infections, and evaluating outcome and adverse events throughout the study.

The blinding of patients and clinicians, however, could not be maintained after randomization because of the inherent differences between the physical characteristics of the two study drugs. Patients assigned to group 1 received fluconazole (400 mg daily), iv for the first 5 days and then orally thereafter (unless their condition precluded reliable oral therapy). Patients assigned to group 2 received iv amphotericin B (25–50 mg daily, for a minimum total dose of 250 mg, for nonneutropenic patients; 0.67 mg/[kg · d], for a minimum total dose of 750 mg, for neutropenic patients).

Outcome Evaluation

Evaluation of response. Patients were considered evaluable with regard to response if their conditions met the criteria for documented or presumed invasive candidiasis and if they had received ≥2 doses of therapy. Intent-to-treat analysis was performed to evaluate the outcome for all patients who were enrolled in the study and who had presumed or documented candidal infection, including those who had received one dose of therapy.

Investigators from all four medical centers evaluated outcome on the basis of predefined criteria. Response was defined as the disappearance of all clinical and laboratory indicators of infection. Failure was defined as no change in or worsening of clinical findings of candidiasis; persistence of candidal infection at originally infected sites; development of candidal infection in new body sites; or drug toxicity requiring discontinuation of study medication. Response was assessed at 48 hours, after 5 days of therapy, and at the end of therapy. Relapse was

Table 1. Characteristics of the 142 evaluable patients with documented or presumed invasive candidiasis.

Characteristic	No. (%) of patients or other data, per treatment group		Pearson χ^2 or other value	*P* value
	Amphotericin B (n = 67)	Fluconazole (n = 75)		
Median age, in years (range)	58 (18–82)	62 (22–79)	−1.53*	.12
Sex				
Male	42 (63)	46 (61)	0.03	.87
Female	25 (37)	29 (39)		
Underlying condition				
Leukemia and bone marrow transplantation	10 (15)	16 (21)	0.97	.32
Other cancer	32 (48)	27 (36)	2.02	.16
Other disease	25 (37)	32 (43)	0.42	.52
Median simplified acute physiology score (range)	9 (1–21)	8 (1–13)	−1.28*	.20
Central venous catheter	57 (85)	60 (80)	0.63	.43
Neutropenia				
<1,000 cells/mm^3	21 (31)	22 (29)	0.07	.80
100–499 cells/mm^3	5 (7)	4 (5)	...†	.74
<100 cells/mm^3	15 (22)	12 (16)	0.94	.33
Corticosteroid use	5 (7)	10 (13)	1.29	.26
Use of broad-spectrum antibiotic(s)	57 (85)	65 (87)	0.07	.78
Concomitant infection(s)	6 (9)	8 (11)	0.12	.73
Shock	5 (7)	4 (5)	...†	.74
Pneumonia (of any etiology)	12 (18)	14 (19)	0.01	.91
Median duration of treatment, in days (range)	11 (2–39)	11 (2–33)	−0.25*	.80
Causative *Candida* species				
albicans	19 (46)	26‡ (58)	1.12	.29
Non-*albicans*§	16 (39)	15 (33)	0.30	.58
Not determined	6 (15)	4 (9)	...†	.51
Infection diagnosed				
Candidemia‖	24 (36)	29# (39)	0.12	.73
Organ infection**	17 (25)	16 (21)	0.32	.57
Presumed fungal infection	26 (39)	30 (40)	0.02	.88

* Mann-Whitney test value.

† Per Fisher's exact test.

‡ Includes 4 cases of polymicrobial infection, due to *Candida albicans* + *Candida parapsilosis* (2) and *C. albicans* + *Torulopsis glabrata* (2).

§ Includes *Candida* tropicalis (7 patients in each treatment group), *C. parapsilosis* (7 patients received amphotericin B and 4 fluconazole), and *T. glabrata* (2 patients received amphotericin B and 4 fluconazole).

‖ Includes acute disseminated candidiasis in 10 patients (3 received amphotericin B and 7 fluconazole).

Includes one patient with septic thrombophlebitis.

** Includes urinary tract infection (19 patients), intraabdominal infection (9), postoperative wound infection (3) cholangitis (1), and pericarditis (1).

defined as recurrence of infection with the same organism at any body site or recurrence of presumed infection within 1 month of discontinuation of therapy.

Evaluation of toxicity. All patients were considered evaluable with regard to drug toxicity. To avoid any potential bias, drug toxicity was assessed in a blinded fashion after the evaluation of clinical response. The severity of an adverse event and its relationship to the study drug were agreed upon by all investigators.

Statistical Analysis

The primary analysis was a comparison of the response rates to amphotericin B and fluconazole among all evaluable patients. Sample-size calculations were based on the primary objective. A power of 80% and an alpha level of 0.05 were used. Other analyses decided upon in advance included a comparison of the survival rates and adverse event rates of patients receiving the two drugs and an intent-to-treat analysis for all patients who were enrolled in the study and who had presumed or documented candidal infection. A number of post-hoc analyses were also performed. All statistical tests were two-tailed. Data were analyzed with the χ^2 test, Fisher's exact test, and Cochran-Mantel-Haenzel test to examine differences in proportions. The Mann-Whitney test was used to evaluate differences between medians. Time-to-event variables were estimated according to the method of Kaplan and Meier [18] and compared by means of the log-rank test. Computations of 95% confidence intervals were performed for differences in outcomes between the two treatment groups. No interim analyses were performed.

Table 2. Outcome of primary therapy for documented or presumed invasive candidiasis, among the 142 patients deemed evaluable.

Outcome variable	No. (%) of patients or other data, per treatment group: Amphotericin B (n = 67)	Fluconazole (n = 75)	Pearson χ^2 or other value	P value
Response				
At 48 hours*	23 (34)	19 (26)	1.26	.26
In 5 days†	29 (51)	33 (50)	0.00	.92
At end of therapy	44 (66)	48 (64)	0.04	.84
Median no. of days to defervescence (range)	5 (1–33)	5 (1–29)	0.02‡	.89
Survival				
At 48 hours	67 (100)	74 (99)	...§	1.00
In 5 days‖	60 (91)	67 (93)	0.22	.64
At end of therapy	58 (87)	66 (88)	0.07	.80
Cause of death				
Candidiasis	4 (6)	2 (3)	...§	.42
Other	5 (7)	7 (9)	0.16	.69

NOTE. Percentages are based on the total number of patients who qualified for evaluation of each specific outcome.

* One patient receiving fluconazole died of an unrelated cause within 48 hours.

† Ten patients in the amphotericin B group (of whom 2 died) and 9 patients in the fluconazole group (of whom 3 died) received the study drug for <5 days and hence were not evaluated for response at 5 days of therapy.

‡ Log-rank test value.

§ Per Fisher's exact test.

‖ One patient who was assigned to receive amphotericin B and 3 patients who were randomized to receive fluconazole were also treated with another systemic antifungal agent and hence were not included in the survival analysis at 5 days.

MEDLINE Search

A MEDLINE search was conducted for all study reports published from 1980 to 1996 on the use of fluconazole and amphotericin B for the treatment of hematogenous candidiasis.

Results

Patients' Characteristics

One hundred sixty-four patients were enrolled in the study. Fourteen patients (evenly distributed among the two groups) were removed from the study because bacterial, viral, or mold infection was documented only after their enrollment (11 patients with presumed fungal infection) or because they had no fever or documented infection (three patients).

Eight additional patients were considered inevaluable for response because they had received only one dose of therapy before death (4 patients, of whom 3 received amphotericin B) or before they were given treatment with another antifungal agent (4 patients, of whom 3 received amphotericin B). These patients were included in the intent-to-treat analysis, however.

One hundred and forty-two patients were evaluable for outcome. These 142 patients in the two treatment groups were similar with regard to characteristics (age, sex, underlying disease, presence of central venous catheter, neutropenia, simplified acute physiology score, use of steroids and broad-spectrum antibiotics, presence of concomitant infections, infecting species, shock and pneumonia, median duration of treatment, and type of infection) (table 1). The median dose of amphotericin B given was 311 mg (range, 75–1,092 mg).

Response

The overall response rates at 48 hours, after 5 days, and at the end of therapy were not significantly different between the two study groups. The median time to defervescence was 5 days in both groups (table 2). Two patients, one in each group, relapsed. Both patients had presumed fungal infection and relapsed, with the same diagnosis. In addition to these two patients, eight patients with documented candidal infection received empirical antifungal treatment for fever within 3 months from the end of primary therapy. Seven of these patients had received fluconazole as primary therapy. The median duration of therapy for the 53 patients with candidemia was 9 days, in both the fluconazole and amphotericin B groups (Z statistic = −0.26; P = 0.80).

There were no differences in survival rates at the above-mentioned endpoints, and causes of deaths (candidiasis or other causes) were similar in the two groups of patients. No significant differences could be detected in the survival rates of pa-

Table 3. Response at the end of therapy for candidiasis, as related to site of infection and infecting species.

Variable	No. of patients (% responders), per treatment group		Pearson χ^2 or other value	*P* value
	Amphotericin B	Fluconazole		
Site or type of infection	(*n* = 67)	(*n* = 75)		
Bloodstream only	21 (71)	22 (59)	0.72	.40
Organ	20 (50)	23 (70)	1.71	.19
Disseminated	3 (0)	7 (71)	...*	.17
Abscess†	7 (14)	1 (100)	...*	.25
Pyelonephritis	3 (100)	6 (83)	...*	1.00
Other‡	5 (80)	3 (33)	...*	.46
Lower urinary tract only	2 (100)	6 (67)	...*	1.00
Presumed	26 (73)	30 (63)	0.61	.44
Causative *Candida* species	(*n* = 41)	(*n* = 45)		
albicans	19 (58)	26 (65)	0.26	.61
Non-*albicans*	16 (69)	15 (60)	0.26	.61
Not determined	6 (67)	4 (75)	...*	1.00

* Per Fisher's exact test.
† Pancreatic, pelvic, or retroperitoneal.
‡ Includes pericarditis, peritonitis, cholangitis, and extensive gastrointestinal tract candidiasis (one patient each), as well as wound infection (four patients).

tients infected with *Candida albicans* or non-*albicans Candida* species. The log-rank test evaluating the difference in time to death of patients who died while receiving amphotericin B or fluconazole did not yield statistically significant results (log rank test = 0.01; $P = .91$). Data regarding response to and survival with both antifungal agents were also similar when they were analyzed by intent-to-treat criteria (χ^2 test values = 0.07 and 0.35; $P = .80$ and .56; 95% CIs for the differences, −14% to 18% and −8% to 15%, respectively).

Response was similar in the two groups of patients, irrespective of the type of infection and the infecting species (table 3). A microbiological diagnosis was obtained for 86 patients. Infections caused by *C. albicans* accounted for 45 episodes and responded equally well to fluconazole and amphotericin B. The response rate for infections caused by species other than *C. albicans* (a total of 31 episodes) was 69% to amphotericin B vs. 60% to fluconazole (χ^2 test = 0.26; $P = .61$; 95% CI for the difference, −25% to 42%). No infections, however, were caused by *Candida krusei* or *Candida lusitaniae.*

We also examined the response to therapy in relation to patients' neutrophil counts (table 4). Response rates to amphotericin B and fluconazole were not significantly different (74% and 58%, respectively; χ^2 test = 2.60; $P = .11$; 95% CI for the difference, −3% to 34%) for patients in both groups whose

Table 4. Response rates at the end of therapy, as related to neutrophil count.

Neutrophil count (cells/mm^3)	No. of patients (percentage responders), per treatment group*		Pearson χ^2 or other value	*P* value
	Amphotericin B	Fluconazole		
≥1,000 At enrollment	46 (74)	53 (58)	2.60	.11
<1,000 At enrollment	21 (48)	22 (77)	4.04	.04
<1,000 With subsequent recovery	14 (50)	15 (93)	...†	.01
<1,000 With no recovery‡	6 (33)	5 (40)	...†	1.00

* Based on no. of patients for whom data were available, per neutrophil count category.
† Per Fisher's exact test.
‡ Responding patients had presumed fungal infection.

peripheral neutrophil count was adequate at enrollment ($\geq$1,000 cells/mm^3). However, the findings from these and other post-hoc analyses need to be interpreted in light of the limited power permitted by the number of patients available in each subgroup. Fluconazole was superior to amphotericin B (77% vs. 48% responding, respectively; χ^2 test = 4.04; P = .04; 95% CI for the difference, 2% to 57%) for patients who were neutropenic when they embarked on therapy.

Because of the concerns about the inclusion of patients with presumed candidiasis, wound infection, and lower urinary tract infection, we reanalyzed our data after excluding such patients. The result of this reanalysis indicated that 22 of 37 patients (60%) responded to amphotericin B and 24 of 37 (65%) responded to fluconazole (Pearson χ^2 = 0.23; P = .63). Survival rates at the end of therapy were 92% and 84% for amphotericin B and fluconazole, respectively (P = .48, Fisher's exact test). Candidiasis was the cause of death for 3 and 2 patients, respectively (P = 1.00, Fisher's exact test). Hence, the exclusion of these patients did not significantly alter the response rates.

Failure

A total of 50 patients' treatment failed (27 of these patients received fluconazole and 23 received amphotericin B; χ^2 test = 0.04; P = .84; 95% CI for the difference, −17% to 14%). Failure was caused by persistent proven or presumed infection in 46 patients. Twenty-six of these 46 patients (including 2 who died) had received fluconazole as primary therapy, whereas the remaining 20 (including 4 who died) were given amphotericin B. Treatment failure was secondary to toxicity in one patient receiving fluconazole and in 3 patients receiving amphotericin B.

Eighteen patients, equally distributed between the two groups, died during therapy. Death was caused by candidal infection in four patients (6%) treated with amphotericin B and two patients (3%) treated with fluconazole, but the difference was not statistically significant (P = .42, Fisher's exact test) (table 2). All six of these patients had fever and other signs and symptoms of infection at the time of death.

Adverse Events

The incidence of drug-related adverse events was significantly higher among patients who received amphotericin B (35%) than among those who received fluconazole (5%; χ^2 test = 23.9; P < .0001) (table 5). Nephrotoxicity occurred in 22 patients (28%) treated with amphotericin B but was attributed to fluconazole in only one case (1%). Amphotericin B administration was discontinued for three of eight patients with moderate to severe nephrotoxicity (serum creatinine level, 2.5–6 times baseline level). Of the 22 patients who had nephrotoxicity while receiving amphotericin B, the kidney function of 16 (73%) had returned to baseline level by the last examination. One patient's level of serum alkaline phosphatase became elevated (229 IU/mL) during treatment with fluconazole, which prompted withdrawal of the study drug. This abnormal laboratory value subsequently returned to baseline.

Table 5. Incidence of drug-related adverse events* among all enrolled patients.

Adverse-event variable	Data per treatment group		P value
	Amphotericin B	Fluconazole	
No. (%) of patients who had an adverse event	28 (35)	4 (5)	<.0001†
No. of adverse-event episodes (range)	38 (0–3)	4 (0–1)	<.0001‡
Nephrotoxicity§	22	1	
Hypokalemia	5	0	
Fever or chills	3	0	
Hepatic toxicity‖	3	2	
Skin rash	2	0	
Nausea, vomiting, or diarrhea	2	0	
Neutropenia	1	0	
Hypophosphatemia	0	1	

* Events that were possibly, probably, or definitely related to study drug.
† Pearson χ^2 = 23.9.
‡ Mann-Whitney test value = −4.87.
§ Eight patients' serum creatinine values were 2.5–6 times baseline level. Amphotericin B was withdrawn from 3 patients because of nephrotoxicity. Serum creatinine level returned to baseline in 16 of 22 patients treated with amphotericin B and in the single patient who was thought to have fluconazole-related nephrotoxicity.
‖ Fluconazole was withdrawn from one patient with hepatic toxicity.

Discussion

Hematogenous candidiasis is a serious infection associated with a high degree of morbidity and mortality. For many years, amphotericin B was the only agent available for the treatment of this condition, and it yielded a response rate of ~70% [19]. The acute and chronic toxicities associated with this drug [20], however, created a need for effective yet less toxic alternatives. Fluconazole is a well-tolerated antifungal triazole that has been effective in experimental use against hematogenous candidiasis [10]. The published experience derived from the compassionate use of fluconazole as an investigational agent suggested a response rate of 60% to 65% for serious infections, including hematogenous candidiasis. A number of small series and retrospective studies [11–15, 21], one large prospective observational study [22], and two prospective randomized clinical trials [23, 24] compared the efficacy of fluconazole with that of amphotericin B in the treatment of serious candidal infections.

The first study was conducted by Van't Wout et al. [11]. This study showed an 85% response rate among 13 nonneutropenic patients with deep-seated candidiasis who received fluconazole at a dosage of 50–100 mg/d. Ikemoto [15] reported a response rate of ~78% among 18 patients treated for candidemia. Kujath

and Lerch [12] reported an 88% response rate among 25 surgical patients who received fluconazole at a dosage of 200–400 mg/d for the treatment of invasive candidiasis. A 100% response rate was observed in a study of six critically ill surgical patients with candidemia who were treated with fluconazole (100–200 mg/d) [13].

A retrospective matched-cohort study conducted at The University of Texas M. D. Anderson Cancer Center compared the outcome for 45 patients with hematogenous candidiasis who were treated with fluconazole (200–600 mg/d) in an open-label trial between February 1990 and June 1992 with the outcome for 45 contemporary matched controls who were treated with amphotericin B (0.3–1.2 mg/[kg · d]) for the same illness ([21] and authors' unpublished data). Criteria for matching included the following prognostic variables at initiation of therapy: pneumonia, neutropenia (<1,000 cells/mm^3), number of positive blood cultures before therapy, the *Candida* species causing infection, underlying disease, and the simplified acute physiology score.

The response rates of the two groups at 48 hours and 5 days were similar. Overall response rates were 73% for patients treated with fluconazole and 71% for patients treated with amphotericin B ($P = .78$). There were no differences in survival rates or causes of death. Toxicity was observed in 9% of patients treated with fluconazole and in 67% of patients treated with amphotericin B ($P < .0001$).

Adverse events associated with amphotericin B included renal insufficiency, hypokalemia, and fever and chills. Graninger et al. [14] studied 65 patients with *C. albicans* fungemia who were admitted to intensive care units and treated intravenously with fluconazole. Among 60 evaluable patients, clinical response to fluconazole was 60% in the group given 5 mg/(kg · d) and 83% in the group given 10 mg/(kg · d). Fluconazole was well tolerated. The authors concluded that fluconazole at a dosage of 10 mg/(kg · d) was an effective and safe treatment for *C. albicans* fungemia.

Kujath et al. [23] conducted the first prospective randomized study comparing fluconazole with amphotericin B. Forty surgical patients with systemic candidiasis were randomly assigned to receive fluconazole or amphotericin B plus flucytosine. Among the 35 evaluable patients, no significant difference in response could be found between the two study groups ($P = .44$), but this finding could be attributed to the inadequate power of the trial.

Another multicenter study, by Rex et al. [24], randomized 237 nonneutropenic patients with candidemia to treatment with either amphotericin B or fluconazole. Among the 206 patients who met all enrollment criteria, no statistically significant difference in response was found between the group treated with fluconazole (70%) and the group treated with amphotericin B (79%; $P = .22$). The bloodstream infection failed to clear in 12 patients in the amphotericin B group and in 15 in the fluconazole group. There were 41 deaths in the amphotericin B group and 34 in the fluconazole group ($P = .20$). The safety profile observed for fluconazole was superior to that observed for amphotericin B.

The results of our prospective randomized multicenter study confirm the observations of previous reports indicating that fluconazole is effective and safe for the treatment of severe candidal infections. Since our patients were enrolled from four different institutions—two private general hospitals, a referral cancer center, and a Veterans Affairs hospital—the results of this study apply to a vast array of patient populations with various underlying diseases. In addition, our study differs from those of others in several aspects.

Unlike the study by Rex et al. [24], our study excluded patients who had received any antifungal therapy immediately prior to study enrollment. Therapy given before initiation of treatment with the study drug may affect the evaluation of final outcome. Our study also included neutropenic patients with hematogenous candidiasis. Persistent neutropenia is a poor prognostic factor for outcome of hematogenous candidiasis [4].

Controlled data comparing the outcome of treatment with either fluconazole or amphotericin B for hematogenous candidiasis in neutropenic hosts have not been previously published. A favorable response rate with fluconazole therapy was obtained in the neutropenic population. Combining data from this trial and from our matched cohort study [21] (for a total of 40 neutropenic patients with candidemia) in a meta-analysis, we noted that fluconazole (63% response) was as effective as amphotericin B (52% response) in the neutropenic host ($P > .1$).

Furthermore, our trial evaluated the role of fluconazole in the empirical treatment of candidiasis. The practice of administering antifungal therapy to patients with presumed fungal infection has gained popularity in the past 2 decades, particularly in centers treating patients with hematologic malignancies, those with organ transplants, and patients undergoing therapy in an intensive care setting. Empirical antifungal therapy for presumed candidiasis has been evaluated in clinical trials, and an apparent, although indefinite, benefit has been observed in those treated [25, 26].

Amphotericin B has been the drug of choice for empirical antifungal therapy and has been associated with a high frequency of side effects. Fluconazole has been used, but formal data evaluating the comparative efficacy of the two drugs and the appropriate duration of empirical antifungal therapy for patients with presumed fungal infection are limited. The study by LaPierre et al. showed similar efficacy of fluconazole and amphotericin B as empirical therapy for invasive candidiasis [27].

Unfortunately, most of the studies conducted (including ours) have enrolled a small number of patients; hence, the possibility of a type II error must be kept in mind. In addition, even if the conclusion held true for all patients, it may not hold in subgroups of patients, e.g., those infected with different *Candida* species and those with poor prognostic factors. Because of the serious morbidity and mortality among high-risk patients and the variable susceptibility of non-*albicans Candida*

species to the two drugs (e.g., the low susceptibility of *C. krusei* [28, 29] and *Torulopsis glabrata* [29] to fluconazole and the low susceptibility of *C. lusitaniae* to amphotericin B [30]), it would seem important to adjust antifungal therapy according to the risk group and infecting species. The most definitive study to evaluate the efficacy of an antifungal agent against hematogenous candidiasis will have to take into consideration the multiple variables that affect outcome. Such a study, however, would require the enrollment of >1,000 patients and hence is unlikely to be conducted, at least in the near future.

The optimal duration of effective therapy for candidemia is not well defined and ranges from 15 to 33 days [11–13, 24]. The current practice is to continue therapy at least until the resolution of granulocytopenia and fever. In this study, the median duration of therapy was 9 days. It was 11 days in the matched-cohort study conducted at one of the institutions involved in this trial [21]. However, the outcome for patients with candidemia in both our studies was similar to that reported by others (with regard to both response and relapse). This suggests that while extended therapy is required for patients with extensive visceral involvement, a short duration of therapy for candidemia may be adequate, at least for the low-risk group of patients.

Another controversial issue is the dosage of the antifungal drugs. Data from this study and others support the use of either fluconazole (400 mg/d) or amphotericin B (0.5–0.7 mg/[kg · d]) to treat low-risk patients with hematogenous infection caused by *C. albicans*. These findings may not necessarily apply, however, to infections resulting from non-*albicans Candida* species (which may be resistant to fluconazole or amphotericin B) and to overwhelming infections in high-risk patients [29, 31]. Higher doses of antifungal agents should be investigated in this setting, given the recent findings by Graninger et al. that a higher dosage of fluconazole (10 mg/[kg · d]) was associated with a better response rate in candidemic patients than was the standard dosage (5 mg/[kg · d]) [14].

On the basis of the above-mentioned findings and the variable susceptibilities of *Candida* species to fluconazole, an iv fluconazole dosage of 800 mg/d may be considered as primary therapy for hematogenous candidiasis. This dosage could be decreased to 400 mg/d and given orally, depending on the rapidity of the response. In the case of amphotericin B, a daily iv dose of 0.5–1.0 mg/kg is recommended. A combination of antifungals should be used for patients with high-grade persistent fungemia or when organisms exhibit some resistance to a single antifungal agent, because additive activities of certain drug pairs have been observed.

In conclusion, our data and those of others suggest that therapy with fluconazole is effective and better tolerated than therapy with amphotericin B for invasive candidiasis, including hematogenous infection. The good activity and safety profile of this drug, together with the convenience and lower cost of administering oral fluconazole, perhaps in an outpatient setting, suggest that fluconazole is the drug of choice for candidal infections caused by fluconazole-susceptible pathogens in hemodynamically stable patients.

Several important issues remain to be answered, such as the drug of choice for infections caused by the various non-*albicans Candida* species, the dosage schedule and duration of antifungal therapy for low- and high-risk patients, and the role of vascular catheters in the management of hematogenous candidiasis. In view of the high mortality rate associated with hematogenous candidiasis, the high prevalence of this infection at autopsy, and the lack of sensitive and specific laboratory tests necessary for the premortem diagnosis of this infection, empirical antifungal therapy is recommended for high-risk patients.

Given the high incidence of adverse events associated with antifungal therapy, limiting the administration of empirical antifungal therapy to high-risk patients aims at balancing the risks and benefits to the patients. High-risk patients include those with known risk factors for the disease, such as neutropenia of at least 1 week's duration or other immunosuppression; those who remain febrile despite broad-spectrum antibiotic therapy; those who have no obvious focus of infection; and those who are colonized by *Candida* species.

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