Antifungal Prophylaxis during Remission Induction Therapy for Acute Leukemia Fluconazole versus Intravenous Amphotericin B

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Background. **Fungal infection is a frequent and often fatal complication in patients undergoing remission induction therapy for acute leukemia. Although candidiasis is the most common infection, mold infections are increasing in frequency. Fluconazole (FLU) is a new antifungal agent that has been used successfully to treat *Candida* infections and has modest activity against aspergillosis in animal models. Subtherapeutic doses of amphotericin B (AMB) have been considered effective as prophylaxis in these patients. This study was designed to compare the efficacy and toxicity of these agents as antifungal prophylaxis.**

Methods. **Adults with acute leukemia undergoing remission induction chemotherapy randomly were assigned to receive antifungal prophylaxis with AMB (0.5 mg/kg three times weekly) or FLU (400 mg daily). Trimethoprim-sulfamethoxazole was administered as an antibacterial prophylaxis. Prophylaxis was continued until the patient achieved complete remission or was treated for 8 weeks without antileukemic response. Prophylaxis was discontinued if the patient experienced a possible or proven fungal infection or a serious toxicity.**

Results. **Overall, 58% of the 36 patients assigned to AMB successfully completed prophylaxis compared with 80% of the 41 patients assigned to FLU (< 0.05). Proven, probable, or possible fungal infections occurred in 31% and 17% of the patients, respectively. The risk of discontinuing prophylaxis due to fungal infection or toxicity increased with time in the study and was significantly greater for AMB ($P = 0.02$).**

Conclusions. **At the dose used in this study, AMB was no more effective and was more toxic than FLU for prophylaxis of fungal infections in patients undergoing remission induction chemotherapy for acute leukemia.**
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Key words: infection prophylaxis, acute leukemia, neutropenia, fungal infection, amphotericin B, fluconazole

Patients undergoing remission induction chemotherapy for acute leukemia are at high risk of experiencing infectious complications. Fungal infections are increasing in frequency in this patient population and have become a common cause of death. Among 245 patients undergoing initial chemotherapy, 102 failed to achieve a remission of their leukemia.[1] Death from fungal infection accounted for 40% of these failures. The frequency of disseminated candidiasis among leukemia patients has been estimated at 10–12 cases/100 admissions at two large cancer centers.[2,3] The frequency of fungal infections at autopsy examination has increased from less than 10% in the 1960s to as high as 40% in the 1980s.[4]

Often, it is difficult to diagnosis disseminated candidiasis clinically. The organism is cultured from blood specimens of only 25% to 40% of infected patients.[5] Antifungal therapy is seldom effective in neutropenic patients with established infection unless their neutrophil count recovers. Hence, effective prophylaxis represents an important supportive measure for patients undergoing antileukemic chemotherapy.

A variety of antifungal agents have been evaluated for prophylaxis, but each has important limitations. Fluconazole (FLU) is a new triazole that has certain advantages over other agents. It is well absorbed from the gastrointestinal tract and is not dependent upon gastric

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acid for its absorption.[6] It is available as an intravenous preparation when patients are unable to tolerate oral medications. It is active against most *Candida* spp. but is inactive against *Candida krusei* and has variable activity against *Torulopsis glabrata.* It is active against *Trichosporon* spp. but has limited activity against molds. Because fungal infections, including candidiasis, trichosporonosis, aspergillosis, and fusariosis are prevalent among leukemic patients at our institution, we initiated a prospective randomized study of fluconazole versus intravenous amphotericin B (AMB) for antifungal prophylaxis. Amphotericin B was chosen for comparison because of its broad spectrum of activity against most fungal pathogens.

Materials and Methods

Patient Eligibility

The study was confined to adult patients (older than or equal to 16 years old) with acute leukemia or blastic transformation of chronic myelogenous leukemia who were to receive remission induction chemotherapy. All of the eligible patients on the Leukemia Service of this institution were recruited and entered in the study by the investigators. No eligible patients were excluded. Patients admitted for bone marrow transplantation were not eligible. Patient groups were stratified according to whether they were to receive initial induction or reinduction (after relapse) chemotherapy and whether they were treated in a laminar airflow room or a conventional room. Patients were excluded from the study if they had a known or suspected fungal infection at the onset of chemotherapy, were pregnant or lactating women, had human immunodeficiency viral infection, or were receiving barbiturates, coumarin-type anticoagulants, or oral hypoglycemic agents. Also excluded were patients with a history of allergy to imidazoles or an unacceptable toxicity from prior AMB therapy, prolonged nausea or vomiting, moderate liver disease (as measured by serum glutamic oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], or alkaline phosphatase values greater than three times the upper limits of normal range or bilirubin > 3 mg/dl), or renal impairment (as measured by a serum creatinine level of > 1.8 mg/dl). Initially, patients were permitted to receive oral nonabsorbable antifungal agents concomitantly, but after enrollment of 16 patients, this practice was no longer permitted. Patients who had received a systemic antifungal agent for any reason from the date of diagnosis or onset of relapse were ineligible for this study. Informed consent was obtained according to institutional policies.

Treatment Plan

All patients were given trimethoprim-sulfamethoxazole (1 double-strength tablet every 8 hours) as an antibacterial prophylaxis. Trimethoprim (160 mg every 8 hours) was substituted for patients allergic to the combination. Patients were assigned according to a computer-generated sequence of random numbers to receive either fluconazole or AMB prophylaxis, beginning at initial antileukemic chemotherapy. Fluconazole was administered orally at a single daily dose of 400 milligrams. Patients unable to ingest oral medications were given the drug intravenously at a dose of 400 milligrams infused over 1 hour. Amphotericin B was given intravenously for 4–6 hours at a dose of 0.5 mg/kg every Monday, Wednesday, and Friday after the patient tolerated an initial 1-milligram dose given over 1 hour. Informed consent was obtained from every patient according to institutional policies.

Pretreatment and Treatment Evaluation

The following laboratory tests were determined at the onset of prophylaxis and at least weekly thereafter: complete blood count with differential and platelet count; SGOT; SGPT; total bilirubin; creatinine; blood urea nitrogen; alkaline phosphatase; prothrombin time; partial thromboplastin time; and throat culture. Hepatitis Bs antigen and a pregnancy test (on women of childbearing potential) were obtained before entry in the study. Patients were examined at least twice weekly for fungal infection and potential adverse effects. Appropriate radiographic examinations, culture specimens, and, when possible, tissue biopsies of suspected fungal lesions were obtained, as clinically indicated.

Termination of Prophylaxis

Patients were continued in the study until one of the following events occurred: they achieved a complete remission of their leukemia, and their neutrophil count returned to greater than $1000/mm^3$; they experienced a serious drug-related toxicity requiring discontinuation of prophylaxis; they experienced a suspected or proven fungal infection; they died of other causes; or they completed 8 weeks of prophylaxis and had not responded to antileukemic therapy.

Definitions Used for Analysis

Patients were considered to have received an inadequate trial if their antifungal prophylaxis was discontinued for any reason during the first 4 days. Major organ or hematogenous fungal infection was considered to be proven if the patient had signs and symptoms of infection (including fever) and a fungus was observed or cultured from a biopsy specimen or a body fluid that was normally sterile, i.e. blood, cerebrospinal fluid, etc. Mold pneumonia was considered to be probable in the absence of a positive culture if the patient had persistent fever for at least 4 days despite broad-spectrum antibacterial antibiotics, had no positive blood, sputum, or bronchoalveolar lavage cultures suggestive of another diagnosis, and had the characteristic abnormalities suggestive of mold pneumonia on a chest roentgenogram as described by Libschitz.[7] The diagnosis of probable mold pneumonia was made by one of the principle investigators (E.A.) who was masked regarding the antifungal prophylaxis administered to the patient. *Candida* esophagitis was diagnosed in a symptomatic patient by esophagogram plus proven thrush or esophagoscopy with biopsy. Thrush was diagnosed because of a positive oropharyngeal culture and potassium hydroxide preparation of oral scrapings of lesions in a symptomatic patient. The remaining patients were considered to have a possible fungal infection if they had a persistent fever of greater than 101°F (with or without a pulmonary infiltrate) of unknown cause that persisted for at least 4 days despite administration of broad-spectrum antibiotics. For many years, it has been the policy at this institution to treat such patients empirically with an antifungal agent.

Renal toxicity was defined as a serum creatinine level greater than 2.0 mg/dl for more than 72 hours or a repeated serum potassium level of less than 3.5 mEq/l. Severe renal toxicity requiring discontinuation of prophylaxis was defined as a greater than 100% increase in serum creatinine levels (also exceeding 2.0 mg/dl) developing in less than 1 week. Attempts to reduce nephrotoxicity of AMB, such as through saline loading, were not used in this study. No patient received an aminoglycoside as antibacterial therapy. Hepatic toxicity was defined as any value of SGPT, SGOT, alkaline phosphatase, or bilirubin that exceeded three times the upper limits of normal. If these abnormalities persisted for more than 3 days or deteriorated further, prophylaxis was discontinued. Other reasons for discontinuation of prophylaxis were acute anaphylactoid reaction, generalized skin rash, or intractable nausea and vomiting.

Patients failed prophylaxis if they experienced any of the severe toxicities as defined above, or if they experienced a proven, probable, or possible fungal infection during prophylaxis. These latter patients were treated with therapeutic doses of AMB (0.6–1.0 mg/kg/day). Patients who experienced fever or infection were followed until a diagnosis was established, all signs and symptoms of infection resolved, or the patient died, to ensure that no patient's febrile episode was diagnosed incorrectly. Uninfected patients were followed for 2 weeks after terminating prophylaxis.

Statistical Considerations

This study was designed to detect a 30% difference between the more effective and less effective antifungal agent with a P value of 0.05 and a beta error of 0.8. Ideally, an effective agent would result in no more than a 10% frequency of fungal infection. A total of 70 patients were needed to satisfy these requirements.

Continuous variables were described as means, and the corresponding 95% confidence limits were computed using the Student t-test distribution. Differences between categorical variables were examined using the two-tailed chi square test (or Fisher's exact test when appropriate), and those between continuous variables were examined using the Mann–Whitney test. The impact of the duration of profound neutropenia and the prophylactic regimen on the duration and outcome of prophylaxis were analyzed using the Kaplan–Meier product-limit method, and differences were compared using the Mantel–Cox log-rank test. Statistical analyses were computed using BMDP PC-90 (BMDP Statistical Software, Inc., Berkley, CA).

Results

A total of 90 patients were entered in this study between May 1989 and December 1990. Seven patients were ineligible (four assigned to AMB and 3 assigned to FLU); six because they had a preexistent proven or probable fungal infection and one because of an elevated serum creatinine level. There were four patients assigned to AMB who could not be evaluated because they received only one to three doses because of renal failure secondary to tumor lysis syndrome,[2] cardiac instability,[1] and early death from heart failure.[1] There were two patients assigned to FLU who could not be evaluated; one died of cerebral hemorrhage after receiving only three doses, and one patient was discharged from the hospital and discontinued prophylaxis after 4 days.

Of the 77 patients who could be evaluated, 36 were assigned to AMB, and 41 were assigned to FLU. The characteristics of these patients are shown in Table 1.

Table 1. Patient Characteristics

	AMB	FLU
Entered	44	46
Eligible	40	43
Evaluable	36	41
Male/female	19/17	21/20
Median (range) age (yr)	47 (17–80)	46 (17–75)
Acute myelogenous leukemia	27	36
Acute lymphocytic leukemia	1	4
Acute promyelocytic leukemia	4	1
Blastic transformation of chronic myelogenous leukemia	4	0
Initial induction	25	27
Reinduction	11	14
Laminar airflow unit	13	9
Nonabsorbable antifungal	9	7

AMB: amphotericin B; FLU: fluconazole.

More patients with acute myelogenous leukemia were assigned to FLU (P = NS). Other characteristics were similar in both groups.

Overall, 58% of 36 evaluable patients successfully completed prophylaxis with AMB compared with 80% of the 41 evaluable patients with FLU ($P < 0.05$, Table 2). Considering all eligible patients with intent to treat, 53% of the 40 patients assigned to AMB successfully completed prophylaxis compared with 77% of the 43 patients assigned to FLU ($P = 0.07$). Four patients failed AMB because of toxicity, and 11 experienced proven, probable, or possible fungal infections; one patient failed FLU because of toxicity, and seven experienced

Table 2. Overall Results of Antifungal Prophylaxis

	AMB	FLU	P
Evaluable patients	36	41	
Successes (%)	21 (58)*	33 (80)*	< 0.05†
Toxicity	4	1	
Fungal infection (%)	11 (31)‡	7 (17)‡	0.19†
Proven	3	2	0.66†
Probable	7	3	
Possible	1	2	
Time on study: median days (range)	19 (6–43)	24 (9–61)	0.01§
PMN/mm^3 < 1000: median days (range)	16 (6–38)	20 (3–61)	0.08§
PMN/mm^3 < 100: median days (range)	12 (2–27)	14 (0–55)	0.8§

PMN: polymorphonuclear leukocytes.

* 95% confidence intervals: FLU is 22% superior (1%–43%).

† Fisher exact test.

‡ 95% confidence intervals: FLU is 14% superior (−6%–34%).

§ Mann–Whitney test.

Table 3. Fungal Infections Related to Prophylaxis

	AMB	FLU
Proven (total)	3	2
Hematogenous candidiasis	2	0
Hematogenous torulopsosis	0	1
Pulmonary aspergillosis	0	1
Multiple infections*	1	0
Probable or possible (total)	8	5
Mold pneumonia	7	3
Persistent FUO	1	2

* Hematogenous candidiasis and pulmonary aspergillosis.

proven, probable, or possible fungal infections. Because fewer patients failed FLU prophylaxis, they spent a longer time in the study and a longer time with neutropenia than those receiving AMB prophylaxis (Table 2). Considering only those patients who did not have prophylaxis terminated because of toxicity, 11 of 32 (34%) assigned to AMB and 7 of 40 (18%) assigned to FLU experienced a fungal infection ($P = 0.19$). The types of fungal infection diagnosed in each group are listed in Table 3. None of the patients in either group experienced thrush or *Candida* esophagitis. The administration of oral nonabsorbable antifungal agents did not affect the frequency of fungal infections in either group. Only patients who failed antifungal prophylaxis because of proven, probable, or possible fungal infection received any antifungal therapy.

Thirty-two of the 36 patients (89%) assigned to AMB achieved a complete remission of their leukemia compared with 33 of the 41 patients (80%) assigned to FLU. The remission rates during initial induction therapy were 92% and 81%, respectively, and for subsequent reinduction therapies were 82% and 79%, respectively. Four patients (9%) assigned to AMB prophylaxis and six (15%) assigned to FLU died; however only two and three patients, respectively, died while in the study. One patient assigned to AMB prophylaxis died of a fungal infection (*Aspergillus* pneumonia and disseminated candidiasis) and one patient assigned to FLU died of pneumonia, possibly because of fungal infection, but no autopsy examination was obtained.

Throat cultures were collected at the onset and after 1 week of prophylaxis from 54 patients (Table 4). The majority of patients were not colonized with fungi initially and remained free from colonization during prophylaxis. Five of the eight patients colonized initially were no longer colonized during prophylaxis. Persistent colonization was observed only during FLU prophylaxis (three patients), but the number was too small to draw any conclusions. Acquisition of fungi during

Table 4. Fungal Throat Cultures During Prophylaxis

Culture results		No. of patients	
Initial	*Subsequent*	*AMB (19 total)*	*FLU (35 total)*
Positive	Total	2	6
	Negative	2	3
	Positive	0	3
Negative	Total	17	29
	Negative	14	26
	Positive	3	3

prophylaxis occurred in three patients in each group. Unfortunately, because only small numbers of yeasts were isolated from these cultures, the laboratory did not identify them further.

Drug-related toxicities occurred more frequently during AMB prophylaxis (Table 5). As expected, nephrotoxicity occurred only during AMB prophylaxis. Eight patients had moderate to severe nephrotoxicity, requiring discontinuation of treatment in four. All four of these patients had a normal serum creatinine level initially (0.8–1.3 mg/dl) that more than doubled in less than 1 week (2.3–3.6 mg/dl). One patient required hemodialysis, whereas renal function recovered in the remaining patients after AMB was discontinued. Fluconazole was discontinued in a patient who experienced an extensive skin rash and an increase in SGPT from 36 units/ml to 314 units/ml in less than 1 week. This patient was receiving other agents capable of causing these toxicities, including trimethoprim-sulfamethoxazole. Differences in the frequencies of other toxicities were small between the two regimens.

In order to further evaluate toxicities, the greatest change in serum concentrations of creatinine, potassium, SGPT, and bilirubin were determined for each patient, and the mean, ranges, and percent changes were calculated (Table 6). No effort was made in these calculations to ascertain cause-and-effect relationships. The differences in mean percent changes in serum creatinine levels and potassium were significantly greater among those patients receiving AMB.

Table 5. Drug-Related Toxicities

	AMB	FLU
Evaluable patients	36	41
Toxicity requiring cessation	4	1
Nephrotoxicity	8*	0*
Moderate†	4	0
Severe‡	4	0
Rash	2	3
Nausea, vomiting	4	2
Diarrhea	4	4

* $P = 0.01$, Fisher exact test.

† Moderate: serum creatinine > 2.0 mg/dl for > 72 hours or repeated serum potassium < 3.5 mEq/l.

‡ Severe: greater than 100% increase in serum creatinine (also > 2.0 mg/dl) developing in less than 1 week.

Because the risks of experiencing fungal infection and toxicity were related to the time in the study and time with severe neutropenia (<100 neutrophils/mm^3), these variables were examined. Figure 1 shows a Kaplan–Meier plot of the proportion of patients removed from study because of failure (development of fungal infection or toxicity) with the duration of time in the study study. This figure shows differences between AMB and FLU that became apparent after 2 weeks. The difference between the two curves was statistically significant ($P = 0.02$). Figure 2 considers the failure rate related to duration of time with severe neutropenia. Differences became apparent after 8 days, and the difference between these two curves was of borderline significance ($P = 0.07$).

Discussion

Antifungal agents have been incorporated into many prophylactic antimicrobial regimens, but only a few studies have been designed to evaluate their efficacy. Many studies have been of limited value because they have not included a control group or have entered too few patients to derive any meaningful conclusions. Oral nystatin has been used most extensively, but its efficacy is uncertain.[8] Comparative studies indicate that the orally absorbable drug, ketoconazole, is more effective than nonabsorbable agents.[9] In one prospective, randomized study, ketoconazole reduced the frequency of superficial and systemic fungal infections when compared with controls.[10] Fluconazole has been effective as prophylaxis against thrush in patients undergoing chemotherapy for solid tumors.[11] Two large multiinstitutional studies in leukemia patients and bone marrow transplant recipients demonstrated that fluconazole was effective for preventing superficial and systemic candidiasis when compared with a placebo, although, in the former group, the difference in systemic inflections was not statistically significant.[12,13]

Intravenous AMB has been evaluated as a prophylactic agent. In a prospective randomized study of 182 bone marrow transplant recipients, there were no significant differences in the frequency of oral yeast infections or in the use of therapeutic AMB for persistent fever between patients assigned to AMB (0.1 mg/kg/day) compared with those assigned to no prophylaxis.[14]

Table 6. Changes in Laboratory Tests

	AMB		FLU		
	Median	*Range*	*Median*	*Range*	*P**
Creatinine					
Initial (mg/dl)	0.9	0.5–2.0	0.8	0.5–2.0	
Highest (mg/dl)	1.4	0.7–3.6	1.0	0.6–2.8	0.02
Percent change†	51	0–350	22	0–200	0.006
Potassium					
Initial (mEq/l)	4.1	3.7–5.8	4.0	2.7–5.1	
Lowest (mEq/l)	3.2	2.5–4.2	3.5	2.7–4.0	0.03
Percent change†	22	5–43	11	0–40	0.0001
Bilirubin					
Initial (mg/dl)	0.6	0.3–1.9	0.5	0.1–4.3	
Highest (mg/dl)	1.5	0.4–8.1	1.2	0.4–18.5	0.12
Percent change†	92	0–1057	166	0–1666	0.34
Serum glutamic pyruvic transaminase					
Initial (U/ml)	31	4–176	34	8–173	
Highest (U/ml)	69	23–459	81	22–461	0.29
Percent change†	72	0–2833	110	0–1913	0.79

* Mann–Whitney test.

† Percent change: the median of the percentage changes per patient.

Even this low dose of AMB resulted in a significant difference in infusion related side effects. Another study evaluated bone marrow transplant recipients who were kept in a laminar airflow unit.[15] The cumulative incidence of aspergillosis was 3% among 110 patients given AMB prophylaxis (20 mg/day) compared with 23% among 48 previous patients given no prophylaxis ($P = 0.003$). However, the use of empiric AMB for persistent fever was similar in both groups.

Our study was designed to compare fluconazole with AMB as an antifungal prophylaxis. A control group was not included because of the high frequency of fungal infections among leukemic patients at this institution, and because a previous study showed that antifungal prophylaxis was effective in reducing superficial and systemic infections.[10] Intravenous AMB was selected in hopes that it could prevent the mold infections prevalent at our institution. The dose of 0.5 mg/kg three times weekly was chosen arbitrarily as one that could be tolerated for prolonged administration. It is possible that higher doses might be tolerated if attempts to reduce nephrotoxicity, such as through sodium load-

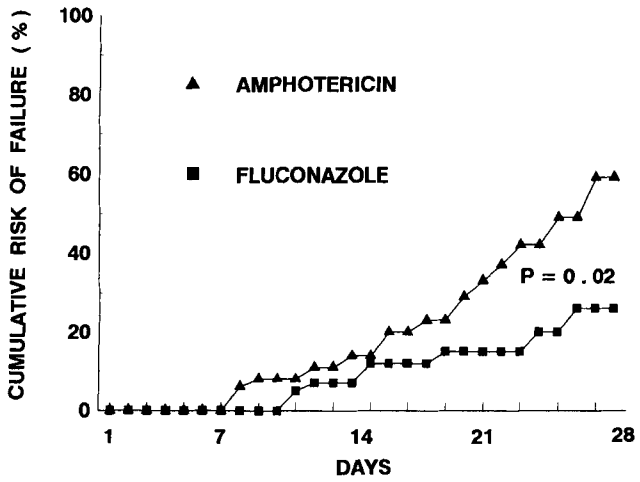

Figure 1. Cumulative risk of failure (severe toxicity or fungal infection as defined in the text) related to duration of prophylaxis for all evaluable patients.

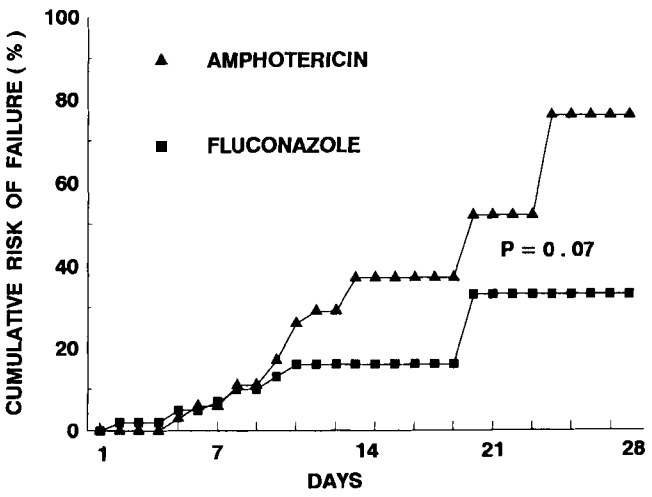

Figure 2. Cumulative risk of failure during prophylaxis related to duration of severe neutropenia (<100 neutrophils/mm^3).

ing, were made. The dose selected actually was associated with more frequent toxicity than was anticipated. Lipid preparations of AMB that diminish acute and chronic toxicities and permit administration of higher doses are potentially attractive formulations for prophylaxis.[19] A dose of 400 mg/day of fluconazole was chosen (which at initiation of this study was considered to be a high dose), hoping that it also might prevent mold infections. Animal studies indicated that fluconazole had some activity against aspergillosis.[16]

Significantly more patients successfully completed fluconazole prophylaxis than AMB (80% versus 58%). There were 10 proven or probable fungal infections among the 36 patients assigned to AMB compared with 5 among the 41 patients assigned to fluconazole (P = 0.23). Interestingly, three patients given AMB experienced hematogenous candidiasis compared with none among those given fluconazole. One case of hematogenous Torulopsis infection occurred in a patient receiving fluconazole prophylaxis.

Several studies have shown that fluconazole is effective in preventing superficial and disseminated candidiasis.[11-13] The failure of AMB to prevent *Candida* infections was unexpected, although different dosage schedules might be more effective. Low-dose (0.1 mg/kg/day) AMB failed to prevent even oral infections.[14] It is not surprising that fluconazole failed to prevent Torulopsis infection because some of these strains are resistant. Colonization and infection due to *T. glabrata* and *C. krusei* have been reported among patients receiving fluconazole prophylaxis.[17] However, in the multiinstitutional studies, this occurred with equal frequency among patients receiving fluconazole and a placebo.[12] It is likely that *C. krusei* is acquired from a contaminated source within the hospital because it is not usually a component of the normal human flora. In this setting, fluconazole prophylaxis may facilitate colonization resulting in subsequent infection.

Proven or probable mold infections occurred in patients receiving either prophylactic regimen. Fluconazole has activity in an animal model of aspergillosis, but it appears to be ineffective as therapy for established infection.[18] Amphotericin B was also ineffective in this study. In a previous study using 20 mg/day, AMB appeared to prevent aspergillosis.[15] That study used historical controls and is difficult to interpret because of the usual sporadic occurrences of aspergillosis. Both groups of patients occupied laminar air flow rooms, and the 23% frequency of aspergillosis in the control group is exceptionally high. The air filtration system in these units should eliminate Aspergillus spores, and we have experienced a less than 5% frequency of aspergillosis in over 1000 leukemia and transplant patients treated in a laminar airflow unit (Bodey, unpublished data).

Fluconazole was better tolerated than AMB. Prophylaxis had to be discontinued because of toxicity in 2.5% and 11% of patients, respectively. Eight patients assigned to AMB experienced moderate to severe nephrotoxicity, and the entire group of patients given AMB had a significantly greater mean change in serum creatinine and potassium levels. These are known side effects of AMB, and the frequency of their occurrence suggests that higher doses of AMB would probably not be acceptable for prophylaxis.

Fluconazole is effective prophylaxis against *Candida* infection and is well tolerated for this purpose. Even at 400 milligrams daily, it does not reliably prevent mold infections, but neither does AMB at the dose selected in this study. Itraconazole may be effective for this purpose, but this has not been demonstrated by a prospective comparative trial. Lower doses of fluconazole may be just as effective, because 50 milligrams daily prevented superficial infections in a less immunocompromised population.[11] Because colonization and infection with *T. glabrata* or *C. krusei* has occurred at some institutions, it might be advisable to combine fluconazole with oral AMB in settings where these organisms are prevalent.

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