Antifungal Prophylaxis in Patients With Hematologic Malignancies: A Reappraisal

By Omrum Uzun and Elias J. Anaissie

Fungal infections are an important cause of morbidity and mortality in patients with hematologic malignancies. Prolonged neutropenia, impaired cell-mediated immunity, and fungal colonization after the administration of broad-spectrum antibiotics are known predisposing factors. The risk of invasive fungal infection is particularly high in the setting of allogeneic bone marrow transplantation because of the intensity of the conditioning regimen, the more profound immunosuppressive effect of allografting, and graft-versus-host disease, which leads to the administration of additional immunosuppressive agents. Furthermore, the early diagnosis and therapy of disseminated fungal infection are often difficult and associated with a high mortality rate unless the patients recover from neutropenia. Hence, strategies to prevent fungal infections may have an impact on the overall morbidity and mortality of patients with hematologic malignancies. The recent introduction of the antifungal triazoles and the lipid formulations of amphotericin B have provided us with better opportunities to prevent fungal infections. In this review, we will discuss the current status of antifungal prophylaxis, with particular emphasis on new developments.

Strategies for Antifungal Prophylaxis

Strategies to prevent fungal infections include those aimed at decreasing fungal colonization and those aimed at augmenting the host's immune response. The most common fungal infections in cancer patients are candidiasis and aspergillosis. Therefore, measures for preventing infections caused by Candida and Aspergillus species are particularly important.

The pathogenesis of hematogenous candidiasis with multorgan involvement requires colonization of the gastrointestinal tract by Candida species with subsequent dissemination after immunosuppression and mucosal damage resulting from cytotoxic chemotherapy. Although Candida species have no intrinsic motility, they are able to translocate from the intestinal lumen within a few hours of ingestion. In addition, autopsy studies conducted in patients with hematogenous candidiasis have clearly shown extensive involvement of the gastrointestinal tract and submucosal invasion in most patients. In a retrospective series of 424 neutropenic cancer patients, hematogenous candidiasis developed in 0.5% of noncolonized patients but in 32% of patients colonized at multiple sites. The association between colonization with Candida species and subsequent candidiasis was later investigated in 139 patients with hematologic malignancies in a prospective fashion. Invasive candidiasis was documented in 22% of patients colonized at multiple noncontiguous body sites versus 5% of the patients colonized at a single site and in none of the noncolonized patients (P = .0037 and P = .00026, respectively). In a small retrospective study conducted in bone marrow transplant recipients, serial cultures for Candida from various body sites were more often positive in patients who had hematogenous candidiasis compared with controls (32% vs 12%, P < .001), and consistently negative surveillance cultures were never observed in patients with autopsy-proven hematogenous infection. Thus, it seems reasonable to postulate that topically active antifungal agents that can reduce the fungal burden in the gut are likely to reduce the incidence of invasive candidiasis. Alternatively, one could rely on systemic agents to suppress the fungi that have gained access to the bloodstream. Agents such as fluconazole, which can achieve a high concentration in the gut are likely to be particularly effective.

Sinopulmonary colonization is thought to precede invasive infection by moulds. Therefore, the use of an inhalant form of amphotericin B may reduce the incidence of invasive aspergillosis by eliminating the pathogen from the upper respiratory tract. Alternatively, use of systemically active agents such as itraconazole or intravenous amphotericin B may provide adequate protection from tissue infection. Another approach to prophylaxis could be based on augmentation of the host’s immune response against fungal infections. This may include the prophylactic administration of...
of granulocyte transfusions and colony-stimulating factors as well as the effective prevention of graft-versus-host disease in bone marrow transplant recipients.

An ideal prophylactic antifungal agent should be safe to be administered over long periods of time, effective and fungicidal against a wide spectrum of fungal pathogens that cause life-threatening infections, available in both oral and intravenous formulations, inexpensive, and associated with a very low incidence of emergence of resistance. Unfortunately, none of the currently available agents meets these requirements (Table 1).

**IMPORTANT CONSIDERATIONS IN DESIGNING STUDIES FOR ANTIFungal PROPHYLAXIS**

Several issues need to be addressed in designing studies of antifungal prophylaxis. First, we need to decide which patients should receive prophylaxis. This decision is usually based on the incidence and severity of fungal infection in a particular patient population. However, what constitutes an acceptable risk for one investigator (thus, not warranting prophylaxis) may be totally unacceptable for another (thus, warranting prophylaxis for all patients). Because the cutoff above which antifungal prophylaxis should be administered remains controversial, every effort should be made to define the subgroups of cancer patients at high risk for morbidity and mortality from fungal infections and to identify the time period during which this risk is highest.

Second, the safety and efficacy of the antifungal agent used in these trials should be carefully evaluated. A prophylactic agent should be safe enough to warrant its use for several weeks in immunocompromised patients who receive intensive chemotherapy and may suffer from the side effects of multiple agents being administered simultaneously. Important drug interactions may occur, resulting in either subtherapeutic or toxic serum or tissue concentrations.

Third, the efficacy of a particular prophylactic regimen should be assessed in prospective randomized, placebo-controlled (when applicable) trials, with an adequate sample size of the patient population being studied. The application of proper statistical methodology is necessary in designing a clinical prophylactic trial. In this context, the objective(s) should be clearly defined beforehand and not be subject to change during the study. A clinical trial on antifungal prophylaxis should have sufficient statistical power to detect differences between the treatment groups. This is particularly true if the incidence of fungal infections is low in the study population. An insufficient sample size may result in an insignificant finding that may be caused by a type II error. In addition, the patient population should be described clearly so that the results of a particular study can be generalized properly and compared with those of other trials. The results of such studies should be interpreted with particular emphasis on the similarity of the groups studied for key baseline characteristics, especially baseline colonization status, and the degree and duration of immunosuppression and graft-versus-host disease. An imbalance of prognostic factors in treatment groups may affect the outcome independent of the prophylactic modality that is tested. To prevent the potential for such a distortion, stratified randomization (ie, the randomization of the patients within certain categories of risk factors) may be performed. In the final stage of analyzing and reporting, all patients randomized in the trial should be evaluated (intent-to-treat analysis) to prevent bias and the reasons for dropouts should be clearly stated. A high rate of withdrawal (>10%) from the study may adversely affect the randomization, even if these dropouts are included in a subsequent intent-to-treat analysis.

Fourth, the potential for fungi to develop resistance during prophylaxis should be carefully assessed by obtaining fungal surveillance cultures regularly and testing all fungi isolated from study patients for susceptibility to the prophylactic agent used as well as to other classes of antifungal agents.

## Table 1. Antifungal Agents Currently Used as Prophylaxis in Patients With Hematologic Malignancies

<table>
<thead>
<tr>
<th>Antifungal Agent</th>
<th>Route</th>
<th>Dosage</th>
<th>Daily Cost</th>
<th>Most Common Adverse Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>PO or IV</td>
<td>400 mg/d</td>
<td>PO: $18, IV: $99</td>
<td>Rash, nausea, vomiting, transaminases</td>
<td>Reduces morbidity and mortality from fungal infection; plasma levels of cyclosporine, FK506.</td>
</tr>
<tr>
<td>Aerosol amphotericin B</td>
<td>Nasal or inhaled</td>
<td>25 mg/kg/d*</td>
<td>$25-$55</td>
<td>Cough, bad taste, epistaxis</td>
<td>Efficacy not established in controlled trials.</td>
</tr>
<tr>
<td>Low-dose amphotericin B</td>
<td>IV</td>
<td>0.5 mg/kg, every other day*</td>
<td>$13 (1 dose)</td>
<td>Nausea, chills, fever, hypokalemia, nephrotoxicity</td>
<td>Nephrotoxicity synergistic with cyclosporine, foscartern, FK506, and vancomycin; cost does not include premedication, monitoring, and management of toxicity; efficacy not established in controlled trials.</td>
</tr>
<tr>
<td>Lipid formulations of amphotericin B</td>
<td>IV</td>
<td>1.0 mg/kg/d*</td>
<td>Same as amphotericin B, except for significantly less nephrotoxicity</td>
<td>Not commercially available; likely to be expensive.</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>PO</td>
<td>200 mg twice daily</td>
<td>$16</td>
<td>Same as fluconazole</td>
<td>Erratic absorption with antacids, H2-blocker, sucralfate; more drug interactions than with fluconazole; prophylactic role not demonstrated.</td>
</tr>
</tbody>
</table>

**Abbreviations:** IV, intravenous; PO, peroral.

* Optimal dose unknown (recommended dose based on limited clinical experience).
The cost of prophylaxis can be enormous. Hence, prophylactic studies should also include a cost-benefit analysis. Finally, it is necessary to analyze the impact of prophylaxis on the overall outcome of the patient, including its effect on the patient’s quality of life, duration of hospitalization, and survival.

PREVENTION OF CANDIDIASIS

Reduction of Environmental Exposure

Although most cases of hematogenous candidiasis result from colonization of the gastrointestinal tract and subsequent dissemination, nosocomial transmission of Candida species has been described and associated with hand carriage by health care workers.27-28 Therefore, careful handwashing should be stressed as an important component of any strategy aimed at preventing candidiasis.

Chemoprophylaxis

Prophylaxis of oropharyngeal candidiasis in neutropenic patients can be effectively achieved by a variety of agents, including topical chlorhexidine, oral polyanes (nystatin and amphotericin B), topical azoles (clotrimazole and miconazole), and systemic azoles (ketoconazole, fluconazole, and itraconazole). Among these, fluconazole is the most effective and best tolerated agent and has also been shown to prevent hematogenous candidiasis in certain settings.29-32

Topically Effective Antifungal Agents

Oral polyanes. Oral nystatin27,33-41 and amphotericin B42-45 have been used either alone or in combination with antibacterial agents for prophylaxis. In an autopsy study, oral amphotericin B was shown to prevent hematogenous candidiasis.44 However, randomized trials have failed to show a beneficial effect of oral polyanes in preventing hematogenous candidiasis.27,33,35,36 Several factors account for the failure of oral polyanes to prevent candidiasis. Oral polyanes have (1) a limited effect on eradicating Candida species from the gastrointestinal tract,27,35,39 (2) poor bioavailability (nystatin is almost completely insoluble, and oral amphotericin B is inactivated in fecal material), and (3) a poor taste, resulting in a low compliance.

Imidazoles. Clotrimazole troches46-48 and oral miconazole49,50 were shown to reduce oropharyngeal candidiasis; however, there are no data supporting their effectiveness in preventing disseminated infection.

Systemic Antifungal Agents

Intravenous miconazole. Only one study evaluated the role of intravenous miconazole therapy started concomitantly with empiric antibiotic therapy in patients with fever and neutropenia.24 Morbidity and mortality from fungal sepsis was significantly reduced in miconazole-treated patients compared with patients who received placebo. However, the substantial side effects of miconazole preclude its widespread use either for prophylaxis or therapy. Among these side effects, local phlebitis (30% to 35%), pruritus (20% to 35%), nausea (20% to 45%), vomiting (<10%), and fever and chills (10%) are the most frequent.25 In addition, changes in hematologic (thrombocytopenia, thrombocytopenia, and anemia) and biochemical (hyponatremia and hyperlipidemia) profiles may occur. Fatal cardiac toxic effects have also been reported.

Ketoconazole. The systemically absorbed ketoconazole has been shown to prevent oropharyngeal candidiasis as well as esophagitis and hematogenous candidiasis when administered at a dose of 400 mg/d.27 However, the erratic bioavailability of ketoconazole limits its usefulness, particularly in patients undergoing allogeneic bone marrow transplantation and in those receiving antacids or H2-blockers.23 Furthermore, colonization and infection by Torulopsis glabrata may occur.55,59,60 A recent placebo-controlled study in patients with acute leukemia suggested a reduction in fungal colonization in patients receiving ketoconazole but no significant effect on the incidence of documented fungal infections or mortality.61

Fluconazole. The introduction of fluconazole has had a dramatic effect on the prevention and treatment of opportunistic mycoses in cancer patients. Fluconazole effectively prevented oropharyngeal candidiasis in patients with solid organ tumors.62 However, the most impressive effects of fluconazole have been shown in bone marrow transplant recipients. In two prospective, randomized, placebo-controlled trials, 400 mg/d of fluconazole was shown to reduce fungal colonization, superficial and hematogenous candidiasis, and mortality significantly.40,31 The efficacy of fluconazole in preventing mucosal candidiasis was shown in patients with acute leukemia in a large, randomized, placebo-controlled trial.29 Although fluconazole prophylaxis resulted in a reduction of hematogenous candidiasis (from 8% in the control group to 4% in the fluconazole group), the difference was not statistically significant because of the low incidence of hematogenous infection in the control group.

We compared the prophylactic administration of 400 mg/d of fluconazole with 0.5 mg/kg of amphotericin B administered three times a week in 90 patients with acute leukemia.63 No significant difference in outcome could be detected between the two groups, except for a higher frequency of serious toxicity in the amphotericin B–treated patients (11% vs 2.5%). In a similar study with a larger sample size (233 patients) and including bone marrow transplant recipients, no significant difference in the incidence of disseminated fungal infection was observed between the fluconazole- and amphotericin B–treated patient groups.64

Lower doses (50 to 200 mg/d) of fluconazole have been shown to have similar or better efficacy when compared with oral polyanes in the prevention of oropharyngeal candidiasis.65,67 In a recent comparative trial of oral fluconazole and clotrimazole in patients with hematologic malignancies and bone marrow transplant recipients, the frequency of candidal infections was higher in patients receiving clotrimazole troches when compared with those receiving 200 mg/d of fluconazole (0 vs 9; P < .01).68 Death directly attributable to fungal infection occurred in 2 of 42 (4.8%) patients on fluconazole and in 9 of 48 patients (18.8%) on clotrimazole (P < .06).

In addition to observations of increased colonization by T glabrata in patients receiving fluconazole prophylaxis,
there have been concerns of emergence of *Candida krusei*, an organism known to be resistant to fluconazole, as an important pathogen.\textsuperscript{76,77} However, it is not clear whether the increased incidence of *C krusei* reflects nosocomial transmission\textsuperscript{78} or is an expected complication of fluconazole prophylaxis.

**Itraconazole.** An important limitation of itraconazole is its erratic bioavailability in certain settings.\textsuperscript{79} No preventive effect could be observed when plasma levels of itraconazole were less than 250 ng/mL.\textsuperscript{79} In a prospective randomized trial in patients with hematologic malignancies, the incidence of fungal infections, duration of fever, or use of intravenous amphotericin B was essentially similar in itraconazole-treated patients and those receiving placebo in addition to oral amphotericin B.\textsuperscript{80} In nonrandomized trials, itraconazole was shown to reduce the frequency of fungal infections when compared with historical controls who received no prophylaxis,\textsuperscript{81-83} and it had similar efficacy as ketoconazole.\textsuperscript{84,85} The question as to whether azole prophylaxis prolongs the duration of neutropenia has been a concern raised by some investigators. The mean number of days spent with a neutrophil count less than 100/μL was slightly longer in patients receiving ketoconazole prophylaxis (11.3 ± 1.6 days) compared with those receiving nystatin plus oral amphotericin B (8.6 ± 1.6 days); however, this difference was not statistically significant.\textsuperscript{82} In another study of ketoconazole prophylaxis, a higher incidence of bacteremias in leukemia patients receiving ketoconazole was observed (74% v 37% in control group; *P* = .004).\textsuperscript{81} This finding could not be explained by the prolongation of neutropenia in the ketoconazole-treated patients. In a clinical trial by Schaffner et al,\textsuperscript{85} a higher, although not statistically significant incidence of gram-negative bacteremias was observed in patients receiving fluconazole prophylaxis (16% v 5% in the control group; *P* = .07), and the duration of neutropenia was significantly longer in the fluconazole-treated patients (16 ± 9 days) when compared with controls (12 ± 6 days; *P* = .005). However, three prospective randomized multicenter trials failed to show such an effect.\textsuperscript{29,30} Given the large sample size of these three trials and the lack of any effect of fluconazole on prolonging neutropenia in bone marrow transplant recipients who are highly susceptible to myelotoxic agents,\textsuperscript{29,30} we believe that fluconazole prophylaxis is unlikely to have any significant adverse effect on recovery from immunosuppression.

In summary, the results from well-designed trials show that fluconazole is the drug of choice for the prevention of candidiasis.\textsuperscript{29,31} Topical agents are not effective in preventing hematogenous infection. Ketoconazole and itraconazole may have erratic absorption and are thus not reliable in high-risk patients. A significant decrease in fungal-associated\textsuperscript{85,86} and overall mortality\textsuperscript{77} is observed only in patients receiving fluconazole prophylaxis. In addition to its proven efficacy, fluconazole is safe in patients with hematologic malignancies. However, along with its widespread use, the potential for resistance and the increasing cost of patient care should also be kept in mind.

In view of the currently available data, we believe that the use of fluconazole prophylaxis is warranted in high-risk patients (Fig 1). This population consists of patients with expected protracted (>3 weeks) and profound (<100/μL) neutropenia and severe mucositis. Therefore, allogeneic bone marrow transplant recipients and patients with acute myelogenous leukemia or myelodysplastic syndrome undergoing intensive induction or salvage therapy are candidates for antifungal prophylaxis with fluconazole. Patients with other types of underlying diseases (acute lymphoblastic leukemia, chronic leukemias, multiple myeloma, and lymphomas) or those undergoing autologous bone marrow transplantation or peripheral blood stem cell collection should be considered for prophylaxis if a severe and prolonged course of neutropenia with mucositis is anticipated. Based on previous findings, it appears that fungal surveillance cultures can be used to determine the subset of the patients who are most likely to develop hematogenous candidiasis.\textsuperscript{20,22} In addition, because of the cost of fluconazole prophylaxis (daily cost: for oral treatment $18, for intravenous treatment $99) and the potential for the development of resistance, we recommend weekly surveillance throat and stool cultures ($29 each, $57 including identification) in high-risk patients (allogeneic bone marrow transplant recipients, patients with acute myelogenous leukemia or myelodysplastic syndrome, etc) and initiating fluconazole prophylaxis only in those patients colonized with *Candida* species known to be susceptible to fluconazole, ie, *Candida albicans, C tropicalis*, and *C parapsilosis*. The patients at high risk for hematogenous infection and who are colonized by fluconazole-resistant *Candida* species, ie, *C krusei* and *T glabrata*, should be monitored closely and early empiric therapy with amphotericin B should be initiated immediately as the signs and symptoms of systemic infection develop.

**PREVENTION OF ASPERGILLOSIS**

**Reduction of Environmental Exposure**

*Aspergillus* species are ubiquitous in nature, particularly in organic debris and construction material. Outbreaks of aspergillosis have been described during periods of construction work.\textsuperscript{87-89} The use of high-efficacy particulate air (HEPA) filters in recipients of allogeneic bone marrow transplants and patients with acute leukemia has been shown to reduce the incidence of invasive aspergillosis.\textsuperscript{76,80} Simple measures such as removal of the plants from the patient's room, sealing of construction areas to prevent air exchange, and avoiding foodstuffs contaminated with *Aspergillus* spores may be effective in the prevention of aspergillosis in patients at risk.\textsuperscript{91}

**Chemoprophylaxis**

The only effective agents against *Aspergillus* species currently available are itraconazole and amphotericin B; therefore, prophylactic studies against aspergillosis should include either of these agents.

**Locally Administered Antifungal Agents**

**Aerosol amphotericin B.** The incidence of aspergillosis was shown to be lower in patients who received intranasal amphotericin B prophylaxis compared with historical controls\textsuperscript{82,92}; however, various uncontrolled environmental and
host factors make it difficult to reach firm conclusions. In another study, no difference in the incidence of aspergillosis was found between patients receiving amphotericin B spray and the controls. In a placebo-controlled trial, colonization but not invasive aspergillosis was markedly decreased by intranasal amphotericin B.

Delivery of aerosol amphotericin B to the lower respiratory tract has been thought to be a more effective approach than intranasal administration and is currently being investigated. However, a preliminary report showed no reduction in the incidence of invasive pulmonary aspergillosis with aerosol amphotericin B prophylaxis. Until a beneficial effect is demonstrated in carefully planned randomized trials, it is difficult to recommend the routine use of aerosol amphotericin B to prevent aspergillosis.

**Systemic Antifungal Agents**

**Intravenous amphotericin B.** Important questions such as the degree of prevention provided by intravenous amphotericin B, its optimal dosage schedule, and the patient population most likely to benefit from such a regimen have not been answered yet. Low-dose amphotericin B prophylaxis, alone or in combination with nasal amphotericin B, has been shown to decrease the incidence of aspergillosis in bone marrow transplant recipients compared with historical controls. In a recent retrospective study, the incidence of all fungal infections was shown to decrease from 30% to 9% with the initiation of low-dose amphotericin B prophylaxis. The incidence of aspergillosis in the first 100 days after transplantation decreased from 16% to 6%. Of note, cyclosporine levels were lower in patients who received amphotericin B, leading to an increased rate of graft-versus-host disease. However, a prospective randomized trial conducted in patients undergoing autologous bone marrow transplantation showed no significant reduction in the incidence of invasive fungal infections, but the control arm included very few cases of invasive mycoses. In another prospective study, no systemic fungal infection developed in 17 bone marrow transplant recipients randomized to receive amphotericin B at 0.1 mg/kg/d compared with 28% in those receiving placebo (P = .045); however, the only documented case of invasive aspergillosis was in the amphotericin B group.

The recent availability of the lipid formulations of amphotericin B has permitted the use of escalating doses of this agent. Tollemar et al. could not detect a significant reduction in invasive fungal infection in autologous bone marrow transplant recipients treated with liposomal amphotericin B (AmBisome; Nexstar Pharmaceutical, San Dimas, CA) when compared with those receiving placebo. Unfortunately, the sample size of this study was small (76 patients) and the risk of invasive mycoses was low (7.5%) in the control group.
Given the toxicity of intravenous amphotericin B, particularly in the setting of allogeneic bone marrow transplantation, and the lack of conclusive data supporting its prophylactic use, low-dose amphotericin B prophylaxis should be considered investigational at this point in time.

Itraconazole. Experience with itraconazole in the prevention of invasive aspergillosis is mostly limited to retrospective studies based on historical controls. A recent prospective, placebo-controlled, randomized trial of itraconazole prophylaxis in patients with acute leukemia failed to show a significant reduction in the incidence of invasive aspergillosis. Unfortunately, the bioavailability of itraconazole was not monitored. In conclusion, the use of HEPA filter is the only strategy with proven efficacy against aspergillosis. Other modalities such as aerosolized or low-dose intravenous amphotericin B, lipid formulations of amphotericin B, and itraconazole should be considered investigational until further data regarding their efficacy and safety are available (Fig 1). We recommend secondary prophylaxis with intravenous amphotericin B for patients who have had a previous episode of proven or probable invasive aspergillosis and who are undergoing bone marrow transplantation or intensive cytotoxic chemotherapy. Simple measures directed at decreasing the fungal burden in the air, such as preventing air flow from construction areas and removing plants from the room of a profoundly neutropenic patient, are cost-effective and may prove beneficial.

STRATEGIES FOR BOOSTING THE IMMUNE RESPONSE
A number of new approaches aimed at immune reconstitution include the effective prevention and treatment of graft-versus-host disease, the prophylactic use of granulocyte transfusions, and the use of colony-stimulating factors.

Prophylactic Granulocyte Transfusions
The strong association between the risk of infection and the neutrophil count suggests that reducing the depth and duration of neutropenia may result in a low risk for invasive fungal infection. In this sense, prophylactic granulocyte transfusions were tried without much success. Granulocyte transfusions obtained by stimulating the donors with granulocyte colony-stimulating factor (G-CSF) have been shown to result in greater increments in the number of neutrophils to be transfused and may potentially be useful in preventing invasive mycoses.

The Prophylactic Use of Growth Factors
Administration of recombinant human growth factors such as G-CSF and granulocyte-macrophage colony-stimulating factor has been shown to shorten the duration of chemotherapy-induced neutropenia, which possibly leads to a reduction of infectious episodes. However, protection against fungal infections was not investigated in particular. On the other hand, macrophage colony-stimulating factor, which has given promising results in the treatment of fungal infections, is no longer available.

Interferon-γ, which was shown to reduce the incidence of serious infections in a placebo-controlled trial in patients with chronic granulomatous disease, enhances the activity of neutrophils against Aspergillus fumigatus in vitro. The role of this cytokine as a prophylaxis has yet to be studied.

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