Antifungal Prophylaxis during Neutropenia and Immunodeficiency

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**INTRODUCTION**

*General Comments*

Systemic mycoses are defined as infections that invade beyond the superficial surfaces into tissues that are normally sterile. During the past three decades, dramatic alterations have occurred in our clinical environment (use of broad-spectrum antibacterial agents and vascular access devices) and patient immune defenses (resulting from chemotherapy and radiation, neutropenia, and lymphopenia of human immunodeficiency virus [HIV] infection). These changes have provided opportunities for fungal pathogens to assume major roles in infectious diseases. Such pathogens in immunocompromised hosts may be separated into those that are community acquired (endemic mycoses and *Cryptococcus neoformans* infection) and those that are nosocomially acquired (*Candida* and *Aspergillus* spp.). The rate of candidal bloodstream infection has increased by as much as 487% throughout the 1980s (258). Other fungi are also being observed more frequently (1) and pose major challenges owing to the lack of effective therapies (357).

The incidence of invasive fungal infections is determined by the interaction between epidemiological factors and the degree of immunosuppression. The advent of AIDS has dramatically increased the problems of mucosal candidiasis, cryptococcosis, histoplasmosis, and coccidioidomycosis, as well as, more recently, penicilliosis in southeast Asia and particularly Northern Thailand.

To prevent antifungal colonization and mainly to counter the rise of severe systemic mycoses, for which the response to curative treatments remains suboptimal, antifungal prophylaxis has been expanded. However, it has also been responsible for rising costs and the emergence of (naturally or not) resis-
tant fungal strains. Simultaneously, indirect ways to prevent invasive fungal infections in immunocompromised hosts have been developed to better control the immune deficiency itself, for example the use of hematopoietic growth factors in neutrophenic patients, the effective prevention of graft versus host disease (GVHD) in allogenic bone marrow transplant (BMT).
patients (139, 146, 288), and the use of more efficient antiretroviral agents in double or triple combination, including protease inhibitors, during AIDS.

When prescribing an antifungal agent for prophylaxis, physicians should be aware of which immunosuppressed patients to treat; which types of pathogens they want to cover in the therapeutic spectrum; the best time for the introduction of antifungal prophylaxis; the potential for emergence of resistant strains; concomitant organ dysfunctions; the potential for drug interactions, especially in transplant recipients treated with cyclosporine or tacrolimus; the effects on survival and quality of life; and the total cost of the treatment.

This paper presents a general review based on articles and recent abstracts published from January 1976 to January 1997. It reports our current knowledge of antifungal prophylaxis in neutropenic and other immunocompromised patients with an emphasis on clinical trials that have demonstrated the efficacy and safety of such treatments. Although anecdotal reports have documented the efficacy of topical chlorhexidine (96), this, like prophylaxis against *Pneumocystis carinii*, which has recently been reclassified by taxonomists as a fungus, will not be further detailed here.

Who Is Susceptible to Fungal Infections?

**Neutropenic patients.** Neutropenic patients are at high risk for developing deep mycoses. Autopsy data show that 5% of patients with solid tumors, 12% of patients with lymphoma, and up to 25% of patients with leukemia have histological evidence of invasive fungal infections (27). One-third to one-half of the patients who die during prolonged episodes of neutropenia have deep mycoses at autopsy (158, 212). Disseminated candidiasis is associated with a 30 to 40% mortality rate in patients with solid tumors (378). Neutropenic patients represent the most appropriate group in which to study antifungal prophylaxis. Indeed, many of the data available on this topic have been obtained in this population.

However, all neutropenic patients with solid or hematological malignancies do not have the same risk for developing a fungal infection, which depends on the magnitude and the duration of the neutropenic phase (28, 124, 375). Indeed, because of the short duration of neutropenia (up to 7 days), no antifungal prophylaxis should be given during cycles of adjuvant chemotherapy (78). Patients with acute myeloblastic leukemia or severe myelodysplasia who require intensive chemotherapeutic regimens need particularly close surveillance for invasive fungal infections. Other patients who should be considered for prophylaxis are those in whom a prolonged course of neutropenia may occur (339). This is the population that we have targeted for our discussion of antifungal prophylaxis. Because of the high incidence of invasive fungal infections in cancer patients, difficulties in obtaining an early diagnosis (because of difficulties in isolating fungi in cultures and interpreting the results and because of an inability to perform invasive procedures in patients with coagulation disorders), and their adverse effect on patient outcome, the need for antifungal prophylaxis is strong. The data obtained from these numerous studies are often difficult to interpret and there is still no definitive consensus on preventive modalities in these patients. The type of underlying disease and thus the type of antineoplastic chemotherapy, mucosal damage, and duration of neutropenia have to be clearly defined before the efficacy of any kind of antifungal prophylactic strategy can be evaluated.

**Bone marrow transplant recipients.** During clinical trials, BMT recipients should be separated from patients with other causes of neutropenia. The most important factor predisposing BMT recipients to fungal infections is the duration of neutropenia. The incidence of fungal infections has been estimated to be 21% in BMT recipients whose neutropenia lasted less than 3 weeks compared with 57% in those whose neutropenia persisted for 6 weeks or more (215). Of 60 deaths in BMT patients with systemic candidiasis, fungal infection was directly responsible for 19 (32%) (344). Among 85 autopsies of BMT recipients (216), Milliken and Powles determined that 26% of the patients had fungal infections. Aspergillosis remains a particularly difficult problem in allogeneic BMT recipients; over 90% of infected patients die (11, 124).

Marrow allograft recipients run the highest risk of invasive fungal infections, not only during the neutropenic phase but also during the months following transplantation, especially when GVHD occurs (118, 124, 223). Autologous BMT recipients who undergo total-body irradiation in association with chemotherapy appear to have a duration of neutropenia similar to that observed in intensively treated patients with acute myeloblastic leukemia. For patients who receive intensive chemotherapy followed by stem cell transfusion and treatment with cellular growth factors, the overall risk of infections and that of invasive mycoses is dramatically reduced (243), as these patients have a median duration of neutropenia of 12 days (224). In that study, 2.3% of 219 patients developed invasive fungal infections. It is therefore important to separate these two subpopulations of patients undergoing autografts when selecting candidates for antifungal prophylaxis (357).

In the allograft recipients, one study identified age, acute GVHD, and donor mismatch as risk factors for invasive candidal infection (118). Another study (344) demonstrated that neutropenia was an independent factor associated with the occurrence of systemic candidal infections, as well as increasing age, detection of one or more positive surveillance cultures for *Candida* spp., and total-body irradiation. Positive cytomegalovirus (CMV) serologic test results and age of 18 years or older were significant risk factors for non-*Candida* fungal infections in allogeneic BMT recipients (223). Pretransplant conditioning regimens and T-cell depletion are also recognized risk factors, as are underlying disease, remission status, mucosal damage, and GVHD prophylaxis (244, 359).

Rossetti et al. recently analyzed fungal liver infection after marrow transplantation and found the following predictive factors: any deep fungal infection after transplantation; colonization or superficial infection with fungi after transplantation; severe liver dysfunction caused by venoocclusive disease of the liver; and/or GVHD (285). Interestingly, in that paper, imaging studies performed during the last 15 days of life had a sensitivity of only 18% for detecting fungal liver lesions. Other risk factors are the same as those described in nongrafted neutropenic patients.

Sable and Donowitz separated several periods of risk for infections during BMT (293). During the pretransplantation period, the risk of fungal infection is low. The engraftment period, from days 0 to 30, is associated with an increased risk of invasive fungal infections. During the postengraftment period, from days 30 to 100, any mold infection may occur, but hepatosplenic candidiasis may also occur. During the late posttransplantation period (day 100 or later), systemic fungal infections are unusual and oropharyngeal candidiasis is the most frequent fungal infection (293).

**Solid-organ transplant recipients.** (i) **Generalities.** The success rate of solid-organ transplantation has greatly improved as a result of advances in surgical techniques, immunosuppressive therapy, and medical management. However, infections and allograft rejection remain major causes of morbidity and mortality during solid-organ transplantation. Occasionally, the...
transplanted organ itself is the source of transmission of infection (138). Fungal infections are reported in all types of solid-organ transplantation and are associated with high mortality (27 to 77%) (250), with Aspergillus infections being responsible for the highest death rate. The incidence of fungal infections in solid-organ transplant recipients varies according to the immunosuppressive treatment, transplanted organ, and transplantation team: it is lowest in renal transplant recipients and highest in liver and pancreas transplant recipients, in whom underlying disease and complicated abdominal surgery play important roles (138). This incidence has been estimated to be 2 to 14% of kidney, 18 to 38% of pancreas or pancreas-kidney, 2 to 42% of liver, 0 to 32% of heart, and 15 to 35% of lung/heart-lung transplantations (126, 250, 251, 253, 351).

Immunosuppressive therapy and the use of corticosteroids, particularly when administered as an intravenous bolus for the treatment of acute rejection, are important predisposing factors (88, 127), in association with the type of underlying disease and other factors during the posttransplantation period, including the presence of immunomodulating viral infections, such as Epstein-Barr virus, CMV, and HIV (126). There is still a debate concerning the increased incidence of fungal infections in lung transplant recipients receiving tacrolimus (250).

(ii) Kidney. There is a significant relationship between the total dose of steroids given to renal transplant recipients and the subsequent development of invasive aspergillosis (125). In this population, some precise risk factors for fungal infections have been identified: diabetes, cadaveric allograft, increased corticosteroid use (to prevent or control rejection), retransplantation, and recent CMV infection (126). Recipients of kidney transplants are at high risk for the development of candiduria, including asymptomatic colonization of the bladder, and renal parenchymal diseases may shorten graft survival. In a recent series of 50 transplant recipients (197), 228 episodes of infection were documented (4.5 per patient), 11% of which were fungal; 47% of these episodes occurred within the first 2 months after transplantation. Candida spp. were the only etiological agents isolated. In that prospective study, pyelonephritis due to Candida spp. was the only infection associated with a high risk of allograft loss.

(iii) Liver. Liver transplant recipients are at high risk for developing invasive fungal infections (51), especially when orthotopic liver transplantation is performed. The reasons are the longer duration of the procedure, the frequency of colonization with Candida spp. (166), and surgical complications such as bile duct obstruction and vascular anastomotic problems, which are more common than in other transplant operations (359). In one study, the median posttransplantation time to the first episode of fungal infection has been reported to be 60 days (251). The incidence of invasive fungal infections was reported to be as high as 42% (352). Infections of the abdominal cavity are frequently observed, but urinary tract and chest infections also occur (351), with Candida spp. being responsible for 87% of all deep mycoses (62, 127).

The risk factors for systemic fungal infections were retrospectively analyzed in 186 orthotopic liver transplant procedures performed in 152 patients (37). The total incidence of invasive fungal infections was 16.5% (25 of 152). The incidence of disseminated candidiasis, aspergillosis, and combined candidiasis plus aspergillosis was 6.5, 7.2, and 2.6%, respectively. The mortality rate associated with invasive fungal infections was 80%. Of 10 patients with disseminated candidiasis, 4 survived; of 11 patients with invasive aspergillosis, only 1 survived. Acute renal failure requiring hemofiltration and the amount of fresh plasma transfused because of poor initial function of the liver allograft were independent significant risk factors for invasive fungal infections. Requirement for intensive care, mechanical ventilation before transplantation, operative time, type of anastomosis, and operative transfusion requirements were also defined as risk factors for fungal infections in liver transplant recipients (51, 251, 352, 384). Enhanced immunosuppression with steroids, OKT3 monoclonal antibody treatment of rejection, and prior CMV infection may facilitate the development of invasive fungal infections. In a multivariate analysis of factors associated with invasive lung aspergillosis after liver transplantation (167), high creatinine levels at the time of Aspergillus isolation and use of OKT3 monoclonal antibody were significant risk factors. In that study, respiratory secretions and wound drainage positive for Aspergillus organisms were associated with invasive disease.

(iv) Pancreas. In pancreas transplant recipients, the most common sites of fungal infections are surgical wounds and the urinary tract. Infectious complications following pancreatic transplantation were recently analyzed in 34 consecutive recipients. In 27 recipients who developed severe infectious episodes, 26% of the infections were caused by fungi (87% by Candida spp.) (192). In a recent retrospective study, intra-abdominal fungal infections occurred after pancreatic transplantation in 41 (9.2%) of 445 patients (20). In that study, the rate of infections was higher for enteric-drained (21%) than for bladder-drained (10%) transplants, for organs donated by living relatives (16%) than for those from cadavers (9%), and for pancreas-after-kidney (12%) and simultaneous pancreas-kidney (11%) than for pancreas-only (5%) recipients. The rate of fungal infections was 6% in patients receiving prophylaxis (fluconazole, 400 mg/day for 7 days) compared with 10% in those without prophylaxis. It should be noted that the 1-year graft survival rate was significantly decreased for recipients with infection.

(v) Heart, lung, and heart-lung. Fungal infections frequently occur during the first month posttransplantation. Most fungal infections in these patients are caused by Candida and Aspergillus spp. (155). Some risk factors are more specifically associated with the surgical procedures used in heart or lung transplants: colonization of the donor trachea by Candida spp. is a notable risk factor for pneumonia, anastomotic dehiscence, and mediastinitis in the recipient (69, 84). In a series of 100 consecutive heart transplant recipients, Waser et al. (360) reported only one lethal case of Candida sepsis (originating from a peritoneal dialysis catheter) and one lethal case of invasive aspergillosis occurring 27 months postoperatively.

Kramer et al. (162) published a retrospective analysis of 200 episodes of serious infections in 73 heart-lung recipients. Fourteen percent were fungal, with Aspergillus spp. (14 episodes) and C. albicans (12 episodes) being the most common pathogens. C. albicans infected mainly the upper tracheobronchial tree and was the second most common pathogen in patients with obliterator bronchiolitis. Aspergillus spp. tended to disseminate and were responsible for the death of three patients. However, in these recipients, it is sometimes difficult to distinguish between Aspergillus infection and colonization (162). Preoperative colonization with Aspergillus spp. in patients with cystic fibrosis, intercurrent infection with CMV, neutropenia, and steroid therapy has been reported to increase the incidence of the disease (155).

HIV-infected individuals. Opportunistic fungal infections are common in patients with HIV infection and represent major causes of morbidity (10, 375). Their incidence increases with the progression of the HIV infection and reduction of the CD4 lymphocyte counts. Specific risk factors for each opportunistic fungus are detailed below. Decisions to administer
primary prophylaxis must consider the prevalence and severity of these infections, the efficacy and safety of antifungal treatment, the risk of emergence of resistant fungal species, the quality of life and the survival time in control groups of patients without prophylaxis, and the cost of antifungal treatment. Indeed, it was estimated in 1994 that antifungal prophylaxis for 100,000 AIDS patients in the United States would cost over half a billion dollars yearly (368). The impact on overall survival is minimal, since the incidence of systemic fungal infections is low.

Other high-risk groups. (i) Qualitative defects of neutrophils. Chronic granulomatous disease is a hereditary abnormality of phagocytic cells and causes microbicidal defects due to a lack of production of reactive oxygen species necessary for microbicidal activity. Aspergillus and Candida spp. were isolated in 20.4% of a large series of 245 patients and were frequently responsible for infection (60). In a French series, 14 of 37 affected children who presented with invasive aspergillosis were characterized by a paucity of symptoms (225). Myeloperoxidase deficiency, a hereditary defect of the lysosomal enzyme myeloperoxidase, may also favor Candida infections (294).

(ii) Connective tissue diseases. Despite the extensive immunosuppressive regimens administered and the use of prolonged steroid therapy during systemic inflammatory diseases, patients with connective tissue diseases are not specifically prone to developing deep fungal infections. Invasive fungal infections in these populations have been reported in the literature but not to a degree that requires general recommendations for their prophylaxis (183). However, monitoring for fungal colonization to ensure rapid diagnosis of such infections should be performed in patients with prolonged neutropenia or profound CD4 lymphocyte depletion, in particularly patients with Wegener’s granulomatosis or systemic lupus erythematosus (183).

(iii) Other immune deficits. Other defects can be classified as chronic quantitative neutrophil deficiencies, in which systemic candidiasis and invasive aspergillosis are most common, or as cellular immune deficits, such as idiopathic low-C4 syndrome, in which Cryptococcus neoformans, candidal mucosal infection, and dimorphic fungal infections are more likely to develop. Infants with severe combined immunodeficiency may also develop fungal infections, particularly candidiasis (320, 361). Thus, these patients should be managed with antifungal prophylaxis according to the nature of their immunodeficiency, which indicates the probable type of fungal infections to prevent.

No specific study has addressed the use of antifungal prophylaxis in these last two populations. Thus, they will not be further discussed here.

Which Pathogens To Consider?

Aspergillus and Candida spp. are the most common fungal pathogens isolated from neutropenic patients and represent 90% of all fungal infections (343). They are thus the most common fungal targets of prophylaxis in all types of immunodeficiencies.

Candida spp. (i) Mucosal infection. In neutropenic patients, predisposition to mucosal Candida infections is facilitated by antineoplastic chemotherapeutic regimens and radiation, which cause mucosal ulcerations. The use of broad-spectrum antibiotics with anaerobic activity (295) or glycopeptides (280) also promotes the growth of Candida spp. Thus, trials of prophylaxis against Candida spp. should include groups of patients with similar exposure to antibiotics (386). Mucosal infections are also more common in patients with T-cell deficiencies, like those observed during lymphomas. Interestingly, recovery of Candida spp. from the mouths of neutropenic patients is predictive of the subsequent occurrence of oropharyngeal candidiasis (389).

Mucosal candidiasis contributes markedly to the morbidity of HIV-infected patients in both developed and developing nations, as it is the most common fungal infection in this population (373). The increasing resistance of C. albicans, which occurs in 7 to 15% (89, 234) (but up to 41% in a recent report [195]) of HIV-infected patients undergoing long-term fluconazole therapy to control mucosal candidiasis, has become a major problem (16, 47, 99, 260, 278, 290, 298, 299). In this population, fluconazole MICs correlated with the clinical outcome (105, 278). In three recent studies, prior use of azole therapy was identified as a risk factor associated with the emergence of resistant candidiasis (194, 195, 337). The recent extension of Candida resistance to other antifungal drugs is worrisome (159, 174). Chronic administration of low doses of fluconazole may also facilitate the emergence of C. glabrata and C. krusei, but the precise impact of azoles on these species remains controversial (259). These species have been isolated from the oral cavity of AIDS patients (55, 75, 290), but their pathogenicity in HIV-infected individuals remains to be elucidated. Indeed, in a recent study, none of 10 patients from whom only non-albicans species of Candida were isolated had active thrush (195). For patients harboring resistant or less-susceptible strains of C. albicans, C. krusei, and C. glabrata, strict hygienic procedures must be used to avoid transmission within the hospital (347). Such transmission has also been clearly documented between sexual partners and may explain the discovery of azole-resistant Candida spp. isolated from previously untreated patients (85).

(ii) Systemic infection. Systemic infections are of both endogenous (61) and exogenous (259) origins. The insertion of central venous catheters predisposes neutropenic patients to fungemia, especially those receiving parenteral nutrition (100). Hematogenous candidiasis also follows colonization of the mouth or gastrointestinal tract (42, 72, 297), as reported for patients hospitalized in surgical intensive care units (263). Colonization of multiple noncontiguous sites in contrast to colonization of a single site, is highly predictive of invasive candidiasis in neutropenic patients (198). Because the duration of prophylactic treatment is short, the appearance of fluconazole-resistant C. albicans is less likely to be problematic for patients with cancer (379). Whether these patients need more protection when they are housed next to HIV units requires further investigation. The major problem in this neutropenic population is the emergence of fluconazole-resistant C. krusei (204, 208, 256, 380) and C. glabrata (92, 236, 381). C. parapsilosis (187, 362) may also emerge as a significant pathogen, particularly in patients receiving parenteral nutrition.

Systemic candidal infections have been reported in 11.4 to 12.5% of BMT recipients (118, 344) within a median time of 15 days after transplantation (118). In one study, the incidence of candidal infections was similar in allogeneic and autologous marrow recipients (344). The mortality is 39% for candidemia alone and 90% when tissues are involved with or without fungemia (118). Candida infection of multiple organs was diagnosed postmortem in 26 of 132 patients (344). In BMT patients, C. albicans remains by far the most frequent pathogen responsible for fungal infections (313), but C. tropicalis has emerged as another frequent pathogen (359). In liver transplant recipients, more than 85% of invasive fungal infections are candidal (138) and occur early after transplantation (62). The incidence of candidal infection in pancreas transplant recipients approaches 100% (137).
The occurrence of candidemia in HIV-infected children (356) and adults (173) cannot be ignored, especially in AIDS patients with central venous catheters for prolonged periods (115). Fungalemia due to fluconazole-resistant *Candida* and non-*Candida* *Candida* species are now being reported in this population (168, 173, 336).

**Aspergillus spp.** Aspergillus *fumigatus* and *A. flavus* are the most common pathogenic species, but other species are also responsible for human infections. *Aspergillus* spp. are observed mainly in patients with prolonged neutropenia, those with qualitative disturbances of their neutrophil function, or those receiving steroids (100). Invasive aspergillosis has recently been described in patients with lymphoid hematological malignancies who are receiving purine analogs (56). The risk was calculated by Gerson et al., who estimated it to be from 1% per day after the first 3 weeks of neutropenia to 4.5% per day after 5 weeks (104). The risk of developing invasive aspergillosis is also dependent on the environment; therefore, historical controls cannot be used for studies on *Aspergillus* chemoprophylaxis (386).

Invasive aspergillosis was most often reported in patients with acute leukemia or in allogeneic BMT recipients, especially those with GVHD (205); it is a leading cause of death in the latter group (79). The incidence of invasive aspergillosis may be as high as 25% in some allogeneic BMT populations (287). More recent data were summarized by Denning (77) and showed that the incidence varied between 3.8 and 8.7% in allogeneic BMT recipients and between 0.6 and 4.5% in autologous BMT recipients. *Aspergillus* spp. were the most prevalent fungi responsible for brain abscesses following marrow transplantation in one recent report (128).

The incidence of invasive aspergillosis among renal transplant recipients was estimated to be around 3% in the early 1980s (125, 363); it was 5.5% and 14 to 19% in liver and heart transplant recipients, respectively (77, 155). A recent study reported an incidence of 16.5% in orthotopic liver transplant recipients (145), and the eyes were the second most common site of infection. The outcome of infection in the solid-organ transplant recipient population depends on the extent of the fungal disease (79, 359).

In HIV-infected patients, aspergillosis is becoming more prevalent as a consequence of longer survival and complications of other therapies (160, 188). A higher risk for invasive aspergillosis is observed when patients have a CD4+ cell count below 50/mm³ and when they have recently taken corticosteroids. *C. neoformans* infection rarely occurs during the first 4 to 6 months after organ transplantation (138). A recent paper reported 10 cryptococcal infections occurring after liver transplantation within a median of 3.5 months after transplantation (148). In that study, the incidence of cryptococcal infection was 0.25%. In France, 14% of cryptococcal diseases occur in non-HIV-infected immunodeficient individuals (80).

**Cryptococcus neoformans.** Cryptococcosis is observed mainly in patients with impaired T-lymphocyte–monocyte/macrophage interactions, such as HIV-infected individuals (58), those with Hodgkin’s disease, and those receiving high-dose corticosteroids. *C. neoformans* infection rarely occurs during the first 4 to 6 months after organ transplantation (138). A recent paper reported 10 cryptococcal infections occurring after liver transplantation within a median of 3.5 months after transplantation (148). In that study, the incidence of cryptococcal infection was 0.25%. In France, 14% of cryptococcal diseases occur in non-HIV-infected immunodeficient individuals (80).

In most areas of the world, this fungal infection occurs in 5 to 10% of HIV-infected patients (86, 262), but in Africa it affects up to 30% (217), and it may become an even larger problem in Thailand (147). By contrast, recent results of a multicenter population-based surveillance showed a decrease in the incidence of cryptococcal infection in North America (129). The risk of cryptococcosis among HIV-infected individuals is highest at CD4+ lymphocyte counts below 100/mm³.

**Endemic mycoses.** Endemic systemic mycoses are geographically restricted and include histoplasmosis, blastomycosis, paracoccidioidomycosis, coccidioidomycosis, and penicilliosis. However, the transformation of endemic mycoses into opportunistic diseases is now being noted. In immunocompromised patients, they may be observed as primary infections, reinfections, or reactivation which may occur much later, sometimes several years after the person has left the area of endemic infection (138). Such mycoses are particularly problematic in patients with AIDS because of their high incidence in areas of endemic infection and their major comorbidity.

Histoplasmosis due to the *H. capsulatum* has been reported in 2 to 5% of patients with AIDS in areas of endemic infection in the United States and up to 25% in selected cities (367). In a recent survey in France, we found 56 AIDS patients who developed the disease sometimes up to 21 years after they had left the area of endemic infection (182). Most cases have been observed during the last 5 years, which should serve as an alert to physicians. By contrast, *Histoplasma capsulatum* histoplasmosis is rare in the immunocompromised host. Indeed, in a recent national survey in France involving 25 patients, we found this organism in only 2 HIV-infected individuals (90).

During the early 1990s, the incidence of *Coccidioides immitis* infection increased dramatically (161). Disseminated coccidioidomycosis has been reported in 602 AIDS patients in the United States (151).

Penicilliosis is increasing sharply in Thailand (325), South China (76), and Hong Kong (57) and has become the third most common infection associated with AIDS after extrapulmonary tuberculosis and cryptococcal meningitis in Northern Thailand (325). Paracoccidioidomycosis is still rare in this population, with 27 cases reported in the literature (111), as is blastomycosis (249). Antifungal prophylaxis might have the greatest impact on HIV-infected patients with less than 100 CD4+ T cells living in areas where these pathogens are hyperendemic.

In transplant recipients, histoplasmosis is the most frequent endemic fungal infection, causing primarily disseminated but also chronic forms of disease (138). Coccidioidomycosis has been reported mostly in renal, heart, and heart-lung transplant recipients (138, 162), but blastomycosis is rarely reported (307).

**Emerging fungal pathogens.** The members of the *Mucorales* are ubiquitous molds that cause invasive fungal infections in neutropenic patients whether or not the patients have undergone BMT (100). The most frequent organisms responsible for zygomycosis are *Rhizopus arrhizus*, *Absidia corymbifera*, and *Rhizomucor pusillus* (359). Zygomyces also arise in profoundly immunocompromised HIV-infected individuals (341). They may also be observed in transplant recipients treated with steroids (250), usually several months after transplantation. However, a case occurring 5 days after heart transplantation has also been reported (227).

Several other species are becoming increasingly recognized as the source of deep fungal infections in cancer patients (13, 254); they include *Fusarium* spp. (102, 207), *Trichosporon asahii* (beigeli), *Blastoschizomyces capitatus* (254, 358), and *Scedosporium* spp. (11). Disseminated fusariosis frequently manifests itself as cutaneous lesions, and the fungus has frequently been isolated from blood cultures (207). Potentially severe infections caused by *Acremonium* spp., *Malassezia furfur*, and dematiaceous fungi have also been reported (254). They are often resistant to one or several antifungal agents (357), and effective antifungal prophylaxis remains to be found. Interest-
ingly, twelve different unusual fungal pathogens were isolated from cancer patients at M. D. Anderson Hospital between 1974 and 1986 (13).

In HIV-infected patients, invasive fungal infections due to unusual pathogens have also been found (65, 185).

**When To Administer Drugs?**

When antifungal prophylaxis is used in neutropenic patients, it should be started at the time chemotherapy is initiated so as to be active when the neutrophil count drops. Once the neutrophil count recovers, the prophylaxis should be discontinued (339).

In BMT recipients, prophylaxis must be continued, regardless of the neutrophil count, because of the risk of systemic fungal infections should the patient develop GVHD. Particular attention must be paid to patients who need high-dose steroids to counter transplant rejection and those with active CMV infection. Although no optimal duration of antifungal prophylaxis has been defined for this population, a recent recommendation proposed a duration of 3 months posttransplantation (386).

For solid-organ transplant recipients, this question remains unanswered, but antifungal prophylaxis might be indicated for at least the first month posttransplantation.

In HIV-infected patients, the risk of systemic fungal infections dramatically increases below a level of 100 CD4+ lymphocytes/mm³. Thus, studies on primary prophylaxis should target these patients. Lifelong suppressive therapy should be given to patients who previously experienced a systemic fungal infection.

**COMMON PROPHYLACTIC MEASURES FOR ALL IMMUNOCOMPROMISED INDIVIDUALS**

Careful barrier nursing is essential for all immunosuppressed patients (269). In addition, specific measures are taken for certain fungal agents.

**Candida spp.**

The most important prophylaxis against candidiasis is to minimize the factors predisposing to Candida infections. Individual major risk factors for systemic candidiasis in the immunocompromised host were defined in at least four case-control studies (40, 156, 280, 365). Risk factors for candidemia mainly include the use of invasive procedures, neutropenia, and administration of at least two broad-spectrum antibiotics (364). Several clusters or outbreaks of candidiasis have been reported (100, 259, 283). Therefore, it is absolutely essential that physicians, nurses, and people visiting the patients be made aware of the potential transmission of Candida species by their hands (323) and be taught strict hygienic (handwashing) practices. These steps will permit prophylactic drugs to play their role.

**Aspergillus spp.**

Aspergillus spp. are ubiquitous in nature. The incidence of invasive aspergillosis is increased during hospital renovation and/or construction and when air filtration is inadequate (100, 286, 359). However, a recent study failed to demonstrate any temporal association between periods of high Aspergillus spore counts and cases of aspergillosis (116). Exposure to plants is strongly contraindicated (78), as is the consumption of raw vegetables and pepper (70), and food must be properly cooked. Regular cleaning and maintenance of a dust-free environment, especially wall surfaces, are important. Modern equipment such as high-efficiency particulate air filters, laminar air flow, positive room air pressure to the corridor, well-sealed rooms, and high rates of room air changes can reduce the incidence of aspergillosis (100, 279, 310, 363), but these precautions are not available everywhere.

Simplification of the procedures used for the care of neutropenic patients, including outpatient management, should specifically address the risk of fungal infection. It has been proposed that all high-risk neutropenic patients should be examined for possible colonization by Aspergillus spp. in the nasal cavity and the upper respiratory tract before high-dose chemotherapy is given or prior to BMT (364). This practice is not standard and is costly but may provide data with which to initiate preemptive therapy. Particularly rigorous precautions should be taken when renovation, repair, and/or construction work is under way in medical units for care of HIV-infected individuals.

Although inhaled spores have been thought to be the major source of invasive aspergillosis, reactivation of endogenous Aspergillus spp. can also be responsible for the disease (283). Recent studies that investigated the epidemiology of aspergillosis by molecular techniques provided limited evidence for a readily identifiable environmental source of Aspergillus strains that can be shown to be responsible for either sporadic cases or outbreaks of aspergillosis (106, 189). Ideally, prevention of invasive aspergillosis involves action at two different levels: environmental control to avoid acquisition, and chemoprophylaxis of already colonized patients (283).

**Zygomycosis (Mucormycosis)**

There is no recognized method to prevent systemic infections with members of the Mucorales. Housing patients with severe neutropenia in rooms supplied with laminar-flow-purified air has been shown to reduce the risks of aspergillosis and mucormycosis (324). Replacing deferoxamine by hydroxypropyridinone chelators may be one approach to decreasing the risk of developing mucormycosis in patients requiring such therapy (31). Deferoxamine allows a significant uptake of iron by Rhizopus spp. and promotes the in vitro growth of these pathogens.

**Cryptococcus neoformans**

The lungs are the major portal of entry of Cryptococcus neoformans through inhalation of yeasts or basidiospores of the fungus. The fungus is ubiquitous in the soil; therefore, there is no way to avoid inhalation. Bird (pigeon and canary) droppings are a source of contamination of dust and soil, although there is no proof that droppings are the primary environmental source of cryptococcosis (262). In any case, patients with cellular immunodeficiency, AIDS, or on high-dose corticosteroids should probably avoid close contact with birds (262). There is no documented interhuman transmission of cryptococcosis, and no special recommendation can be given for hospital practice.

**Endemic Mycoses**

Educational efforts should be made to better acquaint the public with histoplasmosis in areas of endemic infection and the types of leisure or work activities that can increase the risk of contracting infections. For severely immunocompromised patients not living in regions of highly endemic infection, travel in these areas should be discouraged. For European travelers, the French Antilles and French Guiana should be considered high-risk areas. Visiting caves should also be proscribed for...
these patients because of possible contamination by animal droppings (130). Immunosuppressed patients should remain indoors during dust storms in areas where of Coccidiodes immitis is endemic (203).

It is important to look for serological evidence of previous exposure to Histoplasma capsulatum or C. immitis when immunodeficiency is diagnosed or before transplantation in people who have lived or traveled in areas of endemic infection. No general recommendation can be made for the prevention of blastomycosis in immunocompromised individuals, and serological tests to determine possible exposure to Blastomyces dermatitidis are not reliable. Immunocompromised individuals, especially those infected with HIV, should be aware of Penicillium marneffei and Hong Kong. Finally, immunocompromised individuals should not work in mycology laboratories.

Other Fungal Pathogens

The remaining pathogens may be assigned to two categories: endogenous fungal flora, including yeasts such as Trichosporon, Malassezia, Rhodotorula, and Saccharomyces spp.; and exogenous, mainly filamentous fungi, such as Fusarium, Scedosporium, Penicillium, Curvularia, Bipolaris, and Alternaria spp. (254). The portal of entry of endogenous fungi is the digestive mucosa or skin; exogenous fungi are generally contracted by inhalation of spores. As a rule, to prevent these yeast infections, the integrity of the skin and mucosal barriers must be preserved and the use of antibiotics and intravenous lines must be limited. For the filamentous fungi, the main prophylactic measure is efficient air filtration and laminar air flow.

NEUTROPENIC PATIENTS OTHER THAN TRANSPLANT RECIPIENTS

Nonabsorbed Oral Therapy

Nonabsorbed oral treatments have been designed to reduce fungal colonization and infection of the digestive tract and are not used for primary prophylaxis of invasive aspergillosis.

Topical azoles. (i) Clotrimazole. Clotrimazole troches (10 mg three times a day [t.i.d.]) were studied versus placebo in 84 patients (this study also included 47 patients who had undergone renal transplantation). Clotrimazole was superior to placebo in preventing oral candidiasis in patients with acute leukemia showed fewer oral candidal infections in the clotrimazole group (67). A third study evaluated clotrimazole (10 mg t.i.d.) versus no treatment and showed the superiority of clotrimazole in preventing oral can-

didiasis (1% became infected versus 27% in the untreated group) (389).

These three studies suggest that topical clotrimazole is an effective alternative for the prevention of oral candidiasis in cancer patients, but there are no data to support its use for the prevention of systemic infections (211).

(ii) Oral miconazole. Oral miconazole as capsules or buccal gel is marketed in some countries. As capsules, the drug is poorly absorbed, and gastrointestinal intolerance and side effects are frequent. Very few data concerning its use in the prophylaxis of fungal diseases are available (38). The buccal gel, a formulation available in France, represents an effective topical treatment against oropharyngeal candidiasis in our clinical practice; however, no comparative randomized study has been undertaken to assess its use as a prophylactic agent.

Oral polynes. (i) Oral amphoteracin B versus placebo or no treatment. Amphotericin B is inactivated in feces (142), so that high doses are necessary to obtain antifungal activity (81). One old study demonstrated that oral amphoteracin B (200 mg/d) was significantly superior to placebo in preventing disseminated candidiasis (this formulation is not available in the United States (95). Amphoteracin B (tablets or in suspension) has sometimes been shown to be effective in preventing candidiasis, but these formulations are poorly tolerated by patients (206), which may greatly affect the outcome. Yamada et al. reported that oral amphoteracin B in combination with norfloxacin was able to lower the rate of fungal infections compared with amphoteracin B alone (388). Resistant fungal strains have been found in patients receiving topical polynes (267). Because of the lack of convincing data showing that oral amphoteracin B is effective as antifungal prophylaxis, the Working Party of the British Society for Antimicrobial Therapy did not recommend its use alone (386), as had been previously suggested (73, 314).

(ii) Nystatin suspension versus no treatment. It has been demonstrated in healthy volunteers that there is no inhibitory concentration of nystatin against C. albicans in the feces, despite treatment with as much as 12 × 10⁶ U/day (141). In an uncontrolled study, nystatin could not eradicate existing Candida colonization or prevent colonization in patients with initially negative cultures (17). The results of studies on nystatin suspension vs no treatment are summarized in Table 1.

An old study reported that nystatin used in association with antibiotics had a poor efficacy against disseminated candidiasis, which was not attenuated, regardless of the dose (350). In another study reported by the same group, filamentous fungi were acquired significantly more frequently by patients receiving a combination of trimethoprim-sulfamethoxazole plus nystatin than those receiving nalidixic acid plus nystatin (349).

(ii) Nystatin suspension versus topical clotrimazole. Clotrimazole (25 mg t.i.d.) was more effective and better tolerated than oral nystatin for the prevention of oropharyngeal candi-

<table>
<thead>
<tr>
<th>Population</th>
<th>No. of patients</th>
<th>Method</th>
<th>Main results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute leukemia in children</td>
<td>67</td>
<td>Randomized*</td>
<td>No reduction of FUO; reduction in hospitalization</td>
<td>172</td>
</tr>
<tr>
<td>Cancer</td>
<td>164</td>
<td>Comparative</td>
<td>Reduction of multiple-site colonization; no change in IFI rate</td>
<td>42</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>70</td>
<td>Retrospective</td>
<td>No reduction of OPC; no reduction of disseminated candidiasis</td>
<td>72</td>
</tr>
<tr>
<td>Leukemia in children</td>
<td>94</td>
<td>Historical comparative</td>
<td>Reduction of clinical candidiasis</td>
<td>49</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>56</td>
<td>Randomized</td>
<td>No difference</td>
<td>376</td>
</tr>
</tbody>
</table>

* In association with trimethoprim-sulfamethoxazole.

a FUO, fever of unknown origin; IFI, invasive fungal infection; OPC, oropharyngeal candidiasis.

TABLE 1. Studies on nystatin prophylaxis versus no treatment in neutropenic patients

- 1000 U/day (141). In a
Hematological or solid-organ malignancies

Acute leukemia and BMT

Hematological or solid-organ malignancies

Systemic Therapy

Intravenous amphotericin B. Amphotericin B has been proposed as a prophylactic antifungal agent because it has a broad spectrum of antifungal activities, but its potential for immediate toxicity (nausea, fever, and chills) and renal damage, which is further enhanced in combination with other nephrotoxic drugs, may limit its use in clinical practice. A recent study demonstrated that patients without myocardial or renal dysfunction receiving hydrocortisone and diphenhydramine can tolerate central line infusions of prophylactic amphotericin B for 2 h (237). At present, its parenteral use is not associated with the emergence of resistant strains.

Systemic azoles versus placebo or no treatment. Most of the regimens described here were used for anti-Candida prophylaxis.

(i) Intravenous miconazole. Only one double-blind study has evaluated intravenous miconazole (5 mg/kg t.i.d.) versus placebo (180 patients were studied); the overall incidence of fungal sepsis was significantly lower in the miconazole group, but deaths resulting from fungal sepsis were not statistically different between the groups (382). Miconazole was well tolerated in this study, but severe side effects, mainly nausea and vomiting, pruritus, phlebitis, and cardiac arrhythmias, have been reported by others. Wiley et al. (375) demonstrated in a multivariate analysis that administration of intravenous miconazole (5 mg/kg t.i.d.) to children with acute leukemia, beginning at the onset of the first fever during neutropenia, was a negative risk factor for the development of invasive fungal infections.

(ii) Ketoconazole. Ketoconazole was the first systemic imidazole investigated for antifungal prophylaxis (39, 94, 209). Ketoconazole (400 mg/day) versus placebo was investigated in a prospective, randomized, double-blind study: no fungal infection occurred in the ketoconazole group, but there was no difference between the groups in terms of the number of febrile days, the number of days during which antibiotics were administered, or the need for amphotericin B (132). A placebo-controlled study suggested a reduction in fungal colonization in patients receiving ketoconazole, but no significant effect on the incidence of documented fungal infections or mortality was found (247). One study of patients with solid tumors reported that 400 mg was more effective than 200 mg/day in preventing colonization (306).

Different published trials with ketoconazole demonstrate that it may be useful in preventing oropharyngeal disease and reducing yeast colonization. Ketoconazole has no activity against Aspergillus spp. and members of the Mucorales; it may select for some resistant fungal strains; its absorption may be impaired in cases of achlorhydria, whether induced by drugs or not; it may interact with other drugs such as cyclosporine in transplant recipients (222); and its potential liver toxicity is a matter of concern. Thus, it can no longer be recommended as a first-line prophylactic regimen for patients with neutropenia.

(iii) Fluconazole. Fluconazole is water soluble and has favorable pharmacokinetic properties, including a large volume of distribution and high-level penetration into most tissues. It has a long half-life and few interactions with other drugs during its absorption phase and metabolism (36, 109). Fluconazole bioavailability is not affected by changes of gastric acidity. Fluconazole is also available in an intravenous form and can therefore be administered to patients who have difficulty in swallowing. Its safety has been demonstrated.

Fluconazole is effective in the treatment of oropharyngeal candidiasis (109), chronic disseminated candidiasis in leukemic patients (12, 98, 158), and candidemia (277). A recent paper suggested that it could minimize or prevent acute mucositis in association with sulfafrate in patients undergoing radiation therapy above the diaphragm (8). However, the respective role of each drug remains unknown, and no mycological data were reported in the paper. Walsh et al. demonstrated that fluconazole was most effective against disseminated candidiasis in persistently granulocytopenic rabbits when used for prevention or early treatment of infection (354).

Therefore, the availability of fluconazole led to large multicenter protocols to evaluate the drug for prophylaxis in neutropenic patients. The main studies of fluconazole versus placebo or no treatment in neutropenic patients are summarized in Table 2.

Fluconazole is presently the most effective agent to prevent
oropharyngeal candidiasis in neutropenic patients, but several studies did not demonstrate a protection against deep mycoses (303, 383). Interpretation of these results, including empirical amphotericin B use in fluconazole prophylactic studies, is difficult to assess, because no consensus exists between the United States and Europe regarding the optimal time of amphotericin B initiation for persistent fever. In the American study reported by Winston et al. (383), 64% of patients received empirical amphotericin B (383) compared with 24.2% in the European study by Philpott-Howard et al. (261). The optimal daily dose of fluconazole for prophylaxis in neutropenic patients has not yet been clearly defined; it varies between 50 and 400 mg for adults and between 1 and 4 mg/kg in children (48, 175). In the United States, higher doses are used for prophylaxis than in Europe, but no cost-effectiveness study is yet available. There is no conclusive evidence to favor high doses of fluconazole (400 versus 50 to 100 mg/day). The Working Party recommended a dose of 50 mg/day in 1993 (386). As recommended for the HIV-infected population, a careful follow-up of the susceptibility of C. albicans strains is required in this population (379). It has recently been reported that patients with an indwelling central venous catheter and under fluconazole prophylaxis can develop fluconazole-susceptible candidemia, thereby suggesting that this regimen fails to prevent catheter colonization and subsequent dissemination (107).

Although the activity of fluconazole against C. albicans was demonstrated in the reported studies, its use also potentially led to the selection of resistant strains, such as C. krusei, responsible for colonization and infection (5, 50, 187, 256, 380), and less susceptible strains, such as C. glabrata (143, 381). The epidemiology of such non-albicans Candida strains is variable, since some centers using fluconazole have not reported an increase in the number of such strains (165) and other centers had observed these infections before fluconazole was introduced. It is also possible that elimination of other fungal infections by prophylactic fluconazole (53, 383) leaves these fungi as persistent pathogens without necessarily increasing their absolute incidence. Finally, intravenous amphotericin B should be promptly administered to persistently febrile neutropenic patients who are colonized at multiple sites by any Candida spp., whether or not they had recently received any antifungal prophylaxis.

(iv) Itraconazole. Itraconazole is highly lipophilic and binds strongly to proteins. Its degree of absorption varies as a function of gastric acidity, which may lead to reduced levels in serum and tissue and, consequently, to therapeutic failures in some cases. Because intestinal absorption can be impaired, itraconazole levels should be measured after 1 week of treatment in all patients and regularly thereafter in patients with dysphagia, gastrointestinal damage, or GVHD or those taking antacids, H₂-receptor antagonists, or drugs that enhance hepatic drug metabolism (355, 386). It is the only commonly availableazole active in vitro against Aspergillus spp., and its activity against various forms of aspergillosis has been demonstrated (177).

When itraconazole (200 mg/day) was first compared versus no treatment in a study involving a small number of neutropenic patients, there was no difference in terms of the total numbers of episodes of invasive fungal infections (270). Itraconazole (100 mg twice a day [b.i.d.]) was also investigated in a noncomparative study: 18% of the subjects developed micro-biologically proven fungal infections, 12.5% of which were fatal (32). In that study, itraconazole was not effective when the levels in plasma were below 250 ng/ml.

A prospective, randomized, double-blind, placebo-controlled study reported a lower incidence of C. albicans infections in patients treated with itraconazole (200 mg b.i.d.) than in those given a placebo, but the treatment had no significant effect on the overall incidence of fungal infections, the duration of fever, or the use of intravenous amphotericin B (348). The bioavailability of itraconazole was not monitored in that trial. Superinfections with C. krusei and C. glabrata have also been reported in patients treated with itraconazole (32).

Systemic azoles versus oral polyenes. (i) Azoles versus nystatin. Studies with ketoconazole are described and their findings are summarized in Table 3. Table 4 gives the major findings from several studies comparing fluconazole with oral polyenes. For itraconazole, one study demonstrated that the prophylactic use of 400 mg of drug/day in neutropenic patients reduced the incidence of invasive fungal infections when compared with a recent historical control group receiving nystatin (327).

(ii) Azoles versus oral amphotericin B. The results derived from one study of ketoconazole are reported in Table 3. The results of the ketoconazole study did not demonstrate sufficient efficacy against mucosal Candida infections and indicated no role for the prevention of deep mycoses. The available data for fluconazole are summarized in Table 4. In most of these stud-

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**TABLE 3. Studies on ketoconazole prophylaxis versus oral polyenes in neutropenic patients**

<table>
<thead>
<tr>
<th>Population</th>
<th>No. of patients</th>
<th>Method</th>
<th>Regimen</th>
<th>Main results for azoles</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological or solid-organ</td>
<td>72</td>
<td>Randomized</td>
<td>Keto (400 mg/day) versus Ny + AmB</td>
<td>Less OPC and genital candidiasis</td>
<td>131</td>
</tr>
<tr>
<td>malignancies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematological malignancies</td>
<td>36</td>
<td>Randomized</td>
<td>Keto (200 mg/day) versus Ny</td>
<td>Less fungal esophagitis and vaginitis; no disseminated candidiasis in either group; no better prevention against OPC</td>
<td>152</td>
</tr>
<tr>
<td>Leukemia</td>
<td>51</td>
<td>Randomized</td>
<td>Keto (400 mg/day) versus Ny</td>
<td>No reduction of OPC; no significant reduction of IFI (23 versus 33%)</td>
<td>346</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>32</td>
<td>Randomized</td>
<td>Keto (200 mg/day) versus Ny</td>
<td>Less mucosal fungal infection (8 versus 16%)</td>
<td>338</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>48</td>
<td>Randomized</td>
<td>Keto (400 mg/day) versus AmB</td>
<td>No reduction of fungal colonization</td>
<td>83</td>
</tr>
</tbody>
</table>

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### References

1. Keto, ketoconazole; Ny, nystatin; AmB, oral amphotericin B; OPC, oropharyngeal candidiasis; IFI, invasive fungal infections.
2. Except in allogeneic BMT recipients (due to decreased bioavailability in this population).
3. Ketoconazole was administered in comparison or in association with oral amphotericin B.
ies, fluconazole was reported to lower the incidence of colonization and sometimes of mucosal candidiasis but did not reduce invasive fungal infections and empirical amphotericin B use. The apparent inefficacy of low doses of fluconazole to prevent systemic yeast infections in neutropenic patients may reflect the protective effects of polyenes given to the control group. According to Preston and Briceland, for neutropenic, non-BMT recipients, fluconazole at high doses provides no benefit over lower doses and is far from being cost-effective (272). Finally, low-dose fluconazole is appropriate in high-risk neutropenic patients colonized at multiple sites by C. albicans.

Azoles versus intravenous amphotericin B. Amphotericin B administered intravenously three times a week at individual doses of 0.5 mg/kg was compared with fluconazole (400 mg/day) in 90 patients with acute leukemia (30). Efficacy against fungal infection was similar in both groups, but there were more side effects in the amphotericin B-treated group than in the fluconazole cohort. Indeed, 58% of patients assigned to the amphotericin B group successfully completed prophylaxis compared with 80% assigned to receive fluconazole.

Azoles in association with oral or intravenous amphotericin B. At present, no clear recommendation has been formulated concerning the combination of azoles and amphotericin B in clinical practice, especially in prophylactic regimens. Oral amphotericin B and systemic azoles need to be specifically studied in combination in the light ofazole selection of resistant C. kruzie and C. glabrata strains (386). Caution is advised because antagonism between ketoconazole and amphotericin B has been demonstrated in vitro and in neutropenic mice (302).

Comparison of oral azoles. Table 5 describes the observations made in clinical trials of oral azoles in neutropenic patients. They suggest that itraconazole may lower the invasive fungal infection rate in comparison with ketoconazole.

Specific Prevention of Invasive Aspergillosis

Oral decontamination with polyenes or nonabsorbable azoles or administration of ketoconazole or fluconazole does not prevent invasive aspergillosis.

As respiratory colonization is known to precede invasive aspergillosis (3), inhalant forms of amphotericin B have been developed and were reported to be effective in rat models of pulmonary aspergillosis (239, 305). In humans, nasal instillation of 10 mg of amphotericin B was first reported by Meunier-Carpentier et al. to control an epidemic of aspergillosis (214). Since then, others have reported results on aerosol administration with conflicting results in controlled trials (150, 153). In a placebo-controlled trial, colonization (but not invasive aspergillosis) was decreased by intranasal amphotericin B spray (66). The efficacy of such prophylactic procedures has not been clearly proven (19, 25, 26, 63, 122, 136, 228), and the optimal daily dosage for both efficacy and patient tolerance has not been determined. Thus, in the absence of a definitive demonstration of efficacy in randomized trials, no recommendation can be advanced for the application of these regimens in neutropenic patients. Furthermore, some side effects, such as cough, bad taste, and nausea, were reported and led to termination of aerosol administration with conflicting results in controlled trials (150, 153). In a placebo-controlled trial, colonization (but not invasive aspergillosis) was decreased by intranasal amphotericin B spray (66).

Table 4. Studies on fluconazole prophylaxis versus oral polyenes in neutropenic patients

<table>
<thead>
<tr>
<th>Population</th>
<th>No. of patients</th>
<th>Method</th>
<th>Regimena</th>
<th>Main results of study</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Hematological malignancies or BMT</td>
<td>248</td>
<td>Comparative</td>
<td>Flu (50 mg/day) versus polyenes</td>
<td>Less suspected fungal infection (27 versus 45%)</td>
<td>35</td>
</tr>
<tr>
<td>Hematological or solid-organ</td>
<td>536</td>
<td>Randomized</td>
<td>Flu (50 mg/day) versus polyenes</td>
<td>Less OPC (1.6 versus 8.6%); no change of fungal colonization, IFI, and AmB use</td>
<td>261</td>
</tr>
<tr>
<td>malignancies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hematological or solid-organ</td>
<td>502</td>
<td>Randomized</td>
<td>Flu (3 mg/kg/day) versus polyenes</td>
<td>Reduction of mucosal infection; no reduction of IFI and colonization</td>
<td>240</td>
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<tr>
<td>malignancies in children</td>
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<td></td>
<td></td>
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<tr>
<td>Hematological malignancies</td>
<td>69</td>
<td>Randomized</td>
<td>Flu (100 mg/day) versus Ny</td>
<td>Reduction of OPC (3 versus 16%); new oropharyngeal candidiasis; no reduction of AmB use</td>
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<td>Hematological malignancies or BMT</td>
<td>89</td>
<td>Randomized</td>
<td>Flu (400 mg/day) versus Ny + aer Mic</td>
<td>Delayed AmB use; no reduction of OPC, IFI, and AmB use</td>
<td>91</td>
</tr>
<tr>
<td>Hematological malignancies</td>
<td>51</td>
<td>Randomized</td>
<td>Flu (200 mg/day) versus AmB</td>
<td>No reduction of fungal infection and AmB use</td>
<td>4</td>
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<tr>
<td>Hematological malignancies or BMT</td>
<td>59</td>
<td>Randomized</td>
<td>Flu (200 mg/day) versus AmB</td>
<td>No reduction of fungal infection and AmB use</td>
<td>210</td>
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<tr>
<td>Acute leukemia</td>
<td>50</td>
<td>Randomized</td>
<td>Flu (50 mg/day) versus AmB</td>
<td>Less fungal colonization of the oropharynx but not of the lower digestive tract; no reduction of severe local fungal infection and IFI</td>
<td>289</td>
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<tr>
<td>Acute leukemia</td>
<td>820</td>
<td>Randomized</td>
<td>Flu (150 mg/day) versus AmB</td>
<td>No reduction of OPC, AmB use, and IFI</td>
<td>206</td>
</tr>
</tbody>
</table>

a Flu, fluconazole; Ny, nystatin; aer Mic, aerosolized miconazole; AmB use, empirical administration of intravenous amphotericin B; OPC, oropharyngeal candidiasis; IFI, invasive fungal infections.
164 patients with hematological malignancies (328). In that study, which included recent untreated historical controls, the incidence of proven aspergillosis was lower, as was the mortality rate. However, more experience is needed before this drug combination can be recommended for daily clinical practice because, as reported above for ketoconazole, antagonism between itraconazole and amphotericin B has also been noted (301).

The prophylactic prescription of itraconazole could be expanded if it were adapted to an intravenous formulation involving beta-hydroxycyclodextrins. Such an innovation could favor itraconazole as prophylaxis against fungal infections in allogeneic BMT recipients for whom amphotericin B is of limited value for treatment of or even prophylaxis against aspergillosis (223). The new oral solution formulation of itraconazole is absorbed much better and can be used in BMT recipients (271). A large, double-blind, multicenter study comparing itraconazole solution plus placebo in tablets versus placebo in solution plus oral miconazole has now been completed in Europe, but the data are still being analyzed.

Although no definitive data are available suggesting that itraconazole may be an effective primary prophylaxis against aspergillosis, the administration of the drug to untransferable patients managed without laminar-flow air purification (386) should be considered in centers where there is a high incidence of aspergillosis or where building construction or renovation is in progress or about to be undertaken.

The development of new antifungal agents active against Aspergillus spp. will diminish the possible contribution of aerosolized amphotericin B for the prophylaxis of invasive aspergillosis. Unfortunately, the studies published to date have included relatively small numbers of patients and, at present, provide insufficient data for definitive recommendations concerning systematic primary prophylaxis (44). Nevertheless, neutropenic patients with any Aspergillus-positive culture should probably be given early curative antifungal treatment.

**Hematopoietic Growth Factors and Other Cytokines**

Prophylactic granulocyte transfusions are no longer used in neutropenic patients and give only moderate results. Cytokines, by stimulating the natural host defenses, offer new therapeutic approaches to fungal infections (29, 135, 231). Their effects on fungal infections have been widely studied in vitro and in animal models. Whether the stimulation of normal granulocyte donors with granulocyte colony-stimulating factor (G-CSF) before leukophereses (22) can be used to prevent invasive fungal infections has not been studied. G-CSF (68), macrophage-colony stimulating factor (M-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) (178) stimulate the production and/or improve the function of the polymorphonuclear and mononuclear phagocytic cells. They cannot prevent neutropenia but can shorten its duration and attenuate the nadir of the neutropenic episode following myeloablation. These factors have been shown to lower the number of bacterial infectious episodes, but there is no clear evidence that any impact on the incidence of fungal infections, especially candidiasis or aspergillosis in cancer patients. However, in one recent study, the use of growth factor was associated with a decrease in the number of fungal infections in autologous BMT recipients (224).

Interleukin-1, interleukin-3, tumor necrosis factor alpha, and gamma interferon have been shown to be effective against fungal infections in vitro and in animal models. A recent paper suggested a protective role for GM-CSF, G-CSF, or interleukin-3 in preventing fungal infections in 145 patients who received high-dose chemotherapy with or without stem cell transplantation (257). Further controlled clinical trials of these cytokines should be encouraged in humans to assess their preventive effects and also as potential curative therapies (24, 232, 233).

**Prophylaxis against Relapse**

The prevention of relapse is mostly discussed for hosts who are persistently immunocompromised (by diseases or drugs) and who previously experienced an episode of invasive aspergillosis. In fact, there is a risk of reactivating a previous fungal infection, primarily aspergillosis (282), during subsequent chemotherapy of cancer patients.

Secondary prophylaxis against aspergillosis must be systematically used for patients who will undergo subsequent anticancer treatments. High doses of amphotericin B have classically been given during all neutropenic episodes (157, 205, 339). Surgical excision of a persistent fungal lesion is advised for patients who undergo additional cycles of chemotherapy with

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**TABLE 5. Studies comparing oral azoles in neutropenic patients**

<table>
<thead>
<tr>
<th>Population</th>
<th>No. of patients</th>
<th>Method</th>
<th>Regimen*</th>
<th>Main results*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>88</td>
<td>Randomized</td>
<td>Mic (1 g/day) versus Keto (200 mg/day)</td>
<td>No difference in fungal colonization; withdrawal for digestive intolerance in 7% (Keto) and 15% (Mic)</td>
<td>213</td>
</tr>
<tr>
<td>Hematological malignancies and BMT</td>
<td>90</td>
<td>Randomized</td>
<td>Flu (200 mg/day) versus Clotrim + Ny</td>
<td>Less fungal colonization with Flu; less severe fungal infection with Flu; increased chance of survival with Flu</td>
<td>92</td>
</tr>
<tr>
<td>Hematological malignancies</td>
<td>97</td>
<td>Comparative</td>
<td>Itra (400 mg/day) versus Keto (400 mg/day)</td>
<td>Fewer deaths due to IFI (particularly aspergillosis) with Itra*</td>
<td>333</td>
</tr>
<tr>
<td>Hematological and solid-organ malignancies in children</td>
<td>81</td>
<td>Comparative</td>
<td>Itra (50 to 100 mg/day) versus Keto (10 mg/kg)</td>
<td>No difference in colonization and infection</td>
<td>241</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>82</td>
<td>Historical comparison</td>
<td>Itra (200 mg/day) versus Keto (200 mg/day)</td>
<td>Less IFI with Itra*</td>
<td>335</td>
</tr>
</tbody>
</table>

* Mic, oral miconazole; Keto, ketoconazole; Flu, fluconazole; Clotrim, clotrimazole; Ny, nystatin; Itra, itraconazole; IFI, invasive fungal infections.

* In this study, itraconazole protection against fatal fungal infection was significantly better among patients who were neutropenic for more than 25 days and among patients with acute lymphoblastic leukemia.
or without BMT (46, 180, 193, 221, 304). For patients for whom surgery or prolonged amphotericin B is contraindicated, itraconazole may be used successfully (177), although the number of reported cases is still small (64, 180, 199). Itraconazole levels in serum should also be monitored in these patients.

**AUTOLOGOUS OR ALLOGENEIC BONE MARROW RECIPIENTS**

**Low-Dose Intravenous Amphotericin B**

Amphotericin B deoxycholate. A total of 182 patients undergoing autologous BMT received low-dose intravenous amphotericin B (0.1 mg/kg/day) or placebo when their leukocyte counts dropped below 1,000/mm³ (255). Oropharyngeal yeast colonization was lower and survival evaluated 6 weeks posttransplantation was longer in the amphotericin B group than in the placebo group, but they could not be attributed to the prevention of fungal infections. The need for treatment of oropharyngeal candidiasis and the frequency of isolation of fungi from normally sterile sites did not differ between the groups. In that study, infusion-related adverse events were higher in the amphotericin B group but the incidence of systemic toxicities was similar in both groups.

Low-dose intravenous amphotericin B administered during the pretransplantation and peritransplantation periods lowered the incidence of and the mortality attributable to aspergillosis in 186 allogeneic BMT patients compared with historical controls (287). Intermittent intravenous amphotericin B combined with nasal instillation of amphotericin B also compared favorably with historical controls in pediatric BMT recipients (334). Low-dose intravenous amphotericin B continuing for 2 to 3 months posttransplantation was reported to decrease the incidence of all fungal infections in allogeneic BMT recipients from 30 to 9% (244). In that study, those who received amphotericin B also had lower cyclosporine levels, which led to an increased rate of GVHD. Within the first 30 days after transplantation, no systemic fungal infection developed in 17 BMT recipients blindly randomized to receive amphotericin B (0.1 mg/kg/day) (281). In the placebo group, 5 (28%) of 18 patients developed documented systemic fungal infections, but 1 case of invasive aspergillosis developed in the amphotericin B-treated group after 56 days. Patients treated prophylactically with low-dose intravenous amphotericin B required fewer days of high-dose amphotericin B and fewer days of antibiotics. Low-dose amphotericin B was associated with significantly prolonged survival among the subgroup of allogeneic transplant recipients (281). In one study, prophylactic amphotericin B was prescribed for all patients with GVHD (205). Low-dose intravenous amphotericin B (0.2 mg/kg/day) was also compared to fluconazole (400 mg/day) in 190 patients undergoing BMT. There was no significant difference in the incidence of invasive fungal infections among these patients (385). The doses used for prophylaxis during these clinical studies were often too low to eradicate pathogens, such as Aspergillus spp., for which a minimal dose of 1 mg/kg/day is required (43).

The role of low-dose intravenous amphotericin B in primary prophylaxis remains undetermined, since no study has demonstrated that it was able to lower the subsequent need for higher doses of the drug to treat fever of unknown origin (343, 377). Its use as a prophylactic agent is also limited by its toxicity in allogeneic BMT recipients, in whom deep mycoses may be observed during GVHD.

**Lipid formulations of amphotericin B.** Lipid formulations were recently reviewed (34, 140) and reported to be valuable for curative treatment of fungal infections in neutropenic patients (45, 220). Liposomal amphotericin B showed a protective effect against C. albicans infection in neutropenic mice (179). In a study of patients undergoing BMT, Tollemar et al. reported that significantly fewer patients were colonized by fungi in an AmBisome-treated group (1 mg/kg/day) compared with placebo (33 and 62%, respectively), but AmBisome afforded no significant reduction of the incidence of invasive fungal infections (330). However, no definitive conclusion can be drawn from this paper, because only 76 patients were evaluated.

To date, the efficacy of AmBisome as a prophylactic agent has not been sufficiently investigated in humans. The optimal dosage for such an indication remains unknown (perhaps 1 mg/kg/day), and these drugs are expensive (322) and are not available in all countries.

**Azoles**

Ketoconazole. Ketoconazole (400 mg/day) was tested versus nystatin in 56 allogeneic BMT recipients (309). Ketoconazole more effectively lowered the number of positive cultures from the mouth, genital tract, and rectum and reduced the incidence of oral mucositis. Two nystatin-treated patients developed disseminated invasive fungal infections. Tolerance to and compliance with the drug regimen was better in the ketoconazole group. Ominously, however, C. glabrata colonization of the rectum and vagina increased in ketoconazole-treated patients (309).

In a randomized, double-blind, placebo-controlled trial, ketoconazole administration to children with yeast colonization of the digestive tract led to higher percentages of yeast eradication. Children who were not initially colonized had lower rates of colonization, but there was no difference in terms of documented fungal infection and the percentage of children who required intravenous amphotericin B was similar in the two groups (21). Administration of a multiagent regimen containing povidone-iodine, nystatin, and ketoconazole to 16 consecutive pediatric BMT recipients resulted in less oropharyngeal colonization, and none of the patients developed oropharyngeal candidiasis or invasive fungal infections (23).

Fluconazole. According to the two largest studies shown in Table 6 (117, 313), which were also well designed, fluconazole (400 mg/day) was able to decrease both the number of systemic fungal infections and the overall mortality or death due to fungal infection. However, as mentioned above for neutropenic non-BMT recipients, the optimal dose of fluconazole for antifungal prophylaxis has not yet been determined. Indeed, at low doses, it has been reported to significantly lower the incidence of fungemia, C. albicans colonization, and the need for empirical amphotericin B in BMT recipients (6), but some authors have noted colonization and occasional fungemia caused by C. glabrata when 100 mg/day was used (6, 218). A retrospective study described the increased frequency of colonization and infection by C. krusei and C. glabrata in BMT patients who were receiving fluconazole prophylaxis (380). In the study by Goodman et al., fluconazole prevented infections with all strains of Candida except C. krusei (117). These observations could be due to the eradication of the more pathogenic fungal organisms, mainly C. albicans and C. tropicalis, and overgrowth by the other yeasts. Lam and Althaus (171) suggested in their review that C. krusei and C. glabrata generally do not contribute to increased mortality and that most patients infected by these organisms recover after prompt initiation of intravenous amphotericin B treatment.

In the studies by Goodman et al. and Slavin et al., the...
incidence of GVHD was higher in the fluconazole-treated group; this can be explained by the longer survival of these patients (117, 313). Fluconazole levels in serum following a dose of 400 mg/day were comparable in BMT recipients and healthy volunteers. No increase in cyclosporine toxicity was recorded with prolonged administration of fluconazole (400 mg/day) (313). Because of greater efficacy and better tolerance, oral fluconazole should be preferred to topical antifungal agents in this population (274).

**Itraconazole.** In one small study, itraconazole concentrations in the serum of BMT patients appeared to be below the average MIC for *Aspergillus* spp. That result led the authors not to recommend itraconazole for the prevention of aspergillosis in BMT recipients (326). However, it must be kept in mind that the efficacy-MIC relationship remains to be elucidated. However, there is still no definitive answer regarding the effectiveness of itraconazole in this high-risk population.

### SOLID-ORGAN TRANSPLANT RECIPIENTS

**Kidney**

The risk of aspergillosis is low in the kidney transplant recipient population, and probably only patients given bolus corticosteroids for acute rejection would benefit from protection against environmental contamination during high-dose steroid therapy. Regarding the low incidence of *Candida* infections in this population, no recent study on theazole prophylaxis of such infections has yet been undertaken.

Initial studies reported that clotrimazole troches were more effective than placebo in a placebo-controlled, double-blind study of the prevention of oropharyngeal candidiasis (246). These troches were also compared to nystatin suspension (1.5 MU 6 times/day). No patient in either group developed mucosal candidiasis, but patient compliance was much higher in the clotrimazole group (113). A prospective trial of anti-CMV immune globulin showed a decrease in the number of invasive fungal infections (318).

For the time being, in the light of the low incidence of severe *Candida* infections in this population and the lack of experimental data, no systematic antifungal prophylaxis can be recommended.

### Liver

Given the high incidence of invasive fungal infections in liver transplant recipients, the choice of appropriate agents for prophylaxis and therapy becomes particularly relevant. Because candidal infections occurred early in the postoperative period, institution of selective digestive decontamination preoperatively may be of value (250), and liver transplant recipients may benefit from systemic prophylaxis with fluconazole. However, the risk of infection with species resistant to fluconazole needs to be prospectively evaluated. Selective decontamination with oral polynene plus fluconazole might reduce intestinal colonization, including that due to *C. glabrata* or *C. krusei*; such a study would be worthwhile.

Nystatin suspension may be useful in reducing *Candida* colonization (374). One study reported that selective bowel decontamination with quinolones and nystatin may prevent invasive candidal infections (119). Oral clotrimazole and nystatin appeared equally effective for the prevention of mucosal candidiasis in these transplantees (291).

Others advocate the peritransplantation use of low-dose intravenous amphotericin B (10 mg/day) (219), oral amphotericin B (6,000 mg/day), or oral or intravenous fluconazole (200 mg/day) (345). However, failures of low-dose intravenous amphotericin B (0.5 mg/kg/day) have been reported with the simultaneous occurrence of aspergillosis and candidemia (312). A randomized, placebo-controlled study demonstrated that AmBisome (1 mg/kg/day) administered for 5 days starting during the transplant surgery completely protected the patients against invasive fungal infections during the first month, whereas 16% of the patients in the placebo group developed such infections. Furthermore, prophylaxis with AmBisome was much less expensive than treatment of proven deep mycoses in the placebo group (329). Four recent studies documented the efficacy of fluconazole in this population (Table 7). However, only one was randomized (191).

A prospective trial of anti-CMV immune globulin adminis-
The use of effective air filtration is reasonable, but no data exist about the potential protective efficacy of aerosolized amphotericin B or oral itraconazole. How- ever, no consensus has been reached on the usefulness and the time of high risk after transplantation. It remains to be evaluated in prospective randomized trials.

Fungal infections in 6 of 26 recipients of left ventricular transplantation in 6 of 26 recipients of left ventricular transplantation showed a decrease in the number of cases of invasive fungal infections (317). The exact role of itraconazole in the prevention of fungal infections after liver transplantation remains to be evaluated. In addition, the absorption of itra- conazole, which is a lipid-soluble azole, is less predictable in this population because the bile is often drained by a T-tube during the first few weeks posttransplantation (71). Therefore, no definitive recommendations can be advanced for liver transplant recipients at this time (250, 275, 316), but fluconazole might be given during the first month post transplant.

**Pancreas and Kidney-Pancreas**

Research of infection in pancreas and kidney-pancreas transplant recipients is greatly lacking. Nonetheless, the general rule for *Aspergillus* prophylaxis applies to these patients, who should avoid exposure to contamination by environmental sources. Because fungal prophylaxis applied universally to all pancreas and kidney-pancreas patients is costly and bears the risk of allowing the emergence of resistant strains, epidemiological studies are needed to better identify the patients at risk and the time of high risk after transplantation.

**Heart, Lung, and Heart-Lung**

In heart, lung, and heart-lung transplant recipients, the prevention of fungal infections requires technically impeccable surgery, precisely managed immunosuppression, and preventive antifungal regimens. The use of effective air filtration is reasonable, but no data exist about the potential protective efficacy of aerosolized amphotericin B or oral itraconazole.

Lung transplantation for patients suffering from cystic fibro- sis is of particular concern when the patients are colonized by *Aspergillus* spp. prior to transplantation. Success has been reported in such a setting in patients treated prophylactically with intravenous amphotericin B or oral itraconazole. However, no consensus has been reached on the usefulness and the choice of antifungal prophylaxis.

Fungal infections in 6 of 26 recipients of left ventricular assist devices have recently been described (112). Three of these six patients died, and the other three underwent orthotopic heart transplantation. The authors demonstrated that the combination of fluconazole prophylaxis (200 mg/day), daily nystatin, empirical fluconazole treatment for culture-negative sepsis, and daily dressing changes around drivelines successfully treated the three recipients monitored over the short term.

In their analysis of a series of 25 cases of invasive *Aspergillus* infection between 1985 and 1991 (6% incidence), Hummel et al. (144) concluded that repeated microscopic findings of typical septated and dichotomously branched hyphae in bronchial or tracheal secretions are an indication of endobronchial colon- ization and are usually associated with invasive aspergillosis. Thus, treatment is indicated to prevent or, more precisely, to cure the early invasion.

Oropharyngeal *Candida* infections can be avoided by the use of prophylactic medication, either fluconazole or amphotericin B suspension when available (144). Although some authors recom- mended topical agents such as nystatin (162) and amphotericin B to prevent oral candidiasis, the efficacy of these agents remains to be evaluated in prospective randomized trials.

Itraconazole was reported to be effective for prophylaxis against aspergillosis in lung transplant recipients (229). In this population, monitoring of drug levels in serum is also man- datory (252). In addition to difficulty in obtaining an early diag- nosis, a major concern is the use of certain antifungal drugs because of their toxicity or interaction with immunosuppressive drugs, particularly cyclosporine.

**HIV-INFECTED INDIVIDUALS**

**Mucosal Candidiasis**

Mucosal candidiasis is the most common opportunistic infection in HIV-infected patients, occurring in up to 90% of these patients at some time during the course of their disease (276). It is often a consequence of low CD4 counts (< 200 cells/μL).

**Primary prophylaxis.** Mucosal candidal lesions are not targets for primary prophylaxis, because they are easily treated with topical or oral antifungal agents with no important consequences (101) and because the possible risk of selecting resistant strains is high. Primary prophylaxis cannot be prescribed in a general manner, although one recent prospective study demonstrated that oral fluconazole (200 mg/day), as opposed to clotrimazole troches, was associated with fewer episodes of esophageal candidiasis (3 of 217 versus 17 of 211 patients) and oropharyngeal candidiasis (5.7 of 100 versus 38.1 of 100 patient-years) over a mean follow-up period of 35 months (266). Results of a double-blind, randomized study of weekly (400 mg) versus daily (200 mg) oral fluconazole showed similar effectiveness for deep fungal infections in AIDS pa- tients, but a weekly regimen was less effective than a daily regimen in suppressing thrush (63.7 and 28.4 episodes per 100 patient years, respectively) (133).

**Suppressive therapy.** Relapses are common after a first epi- sode of mucosal candidiasis, and several studies have proven the efficacy of maintenance treatment with 50 mg (93, 154) to 100 mg (321) of oral fluconazole per day or 150 mg of oral

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Method</th>
<th>Regimen</th>
<th>Main results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>Prospective</td>
<td>Flu (200 mg/day) versus oral AmB (6 g/day)</td>
<td>Better prevention and clearance of <em>Candida</em> colonization with Flu; no effect of Flu on <em>C. glabrata</em> and <em>C. krusei</em> colonization; administration of Flu more convenient</td>
<td>331</td>
</tr>
<tr>
<td>117</td>
<td>Historical comparison</td>
<td>With and without Flu (100 mg/day)</td>
<td>Reduction of fungal deaths with Flu</td>
<td>164</td>
</tr>
<tr>
<td>75</td>
<td>Retrospective</td>
<td>AmB + selective digestive decontamination + Flu (200 mg/day)</td>
<td>Only 1 case of <em>C. glabrata</em> fungemia</td>
<td>71</td>
</tr>
<tr>
<td>143</td>
<td>Prospective randomized</td>
<td>Flu (100 mg/day) versus oral Ny</td>
<td>Less <em>Candida</em> colonization with Flu; less superficial and invasive candidiasis with Flu</td>
<td>191</td>
</tr>
</tbody>
</table>

* Flu, fluconazole; AmB, oral amphotericin B; Ny, nystatin.
fluconazole per week (176). The risk of selecting fluconazole-resistant strains has led other authors to prefer treating each episode with topical agents when possible (when there is no associated esophageal candidiasis). Therefore, systematic lifelong suppressive therapy is not recommended. Anecdotally, central venous catheter infection caused by "Rhodotorula minuta" was reported in a patient taking suppressive doses of fluconazole (110).

For patients experiencing frequent relapses, intermittent treatment with topical clotrimazole (10 mg x 5/day) or nystatin (500,000 U x 5 times/day) or azoles, such as ketoconazole (200 mg/day) or fluconazole (50 to 100 mg/day), can be prescribed. Ketoconazole should be used with caution in this population because of drug absorption problems (170), and fluconazole may increase rifabutin levels in plasma (332) and thus the potential toxicity of rifabutin (245). In a recent trial, long-term continuous therapy with fluconazole was more effective than intermittent therapy (134). As recently emphasized, compliance with prophylactic regimens must be verified in cases of clinical failure (103).

Fluconazole is more effective than ketoconazole in the treatment of esophageal candidiasis (169) and is also effective as secondary prophylaxis (2), but because fluconazole is more expensive, ketoconazole is probably a valid alternative, especially in developing countries. Other antifungal agents under evaluation for the treatment of oropharyngeal candidiasis resistant to azoles may also prove effective for long-term suppressive therapy (120, 121).

Cryptococcosis

Primary prophylaxis. Several studies have recently addressed primary prophylaxis of cryptococcosis. The AIDS Clinical Trial Group demonstrated that fluconazole (200 mg/day) was more effective than clotrimazole troches (10 mg x 5/day) for the primary prevention of cryptococcal meningitis (0.9 and 7.1%, respectively), but there was no influence on survival (266). The benefit obtained with fluconazole was greater in patients with fewer than 50 CD4+ lymphocytes/mm3. The same results were also observed in another case-control study, which found 0.3% cryptococcosis in 329 patients receiving fluconazole (100 mg/day) versus 4.7% cryptococcosis in 337 patients who were untreated for approximately 165 days (238). Another study comparing 18 patients with cryptococcal meningitis to 72 patients without this infection found that fluconazole was effective and significantly protected against this infection (273). Finally, a linear tendency in risk reduction as a function of increasing dosage (>150 mg/day) was demonstrated in a recent case-control study in which 34 matched controls took a significantly higher average daily dosage of fluconazole than did HIV-infected patients with cryptococcosis (9). A retrospective study of 1,200 HIV-infected patients with CD4+ cell counts below 200/mm3 showed a significantly smaller number of patients with cryptococcal infection in a group prophylactically treated with low-dose fluconazole than in an untreated control group (196). Postmortem records of 145 HIV-infected patients showed that there were 15 cases of disseminated cryptococcal infection and that 13 of these occurred in patients who did not receive prophylactic fluconazole (100 mg/week) (235). Recently, Singh et al. demonstrated the efficacy of low-dose fluconazole (200 mg orally three times a week) as primary prophylaxis for cryptococcal infection, with only 1 of 218 patients developing the disease (311). However, it must be noted that 18% of their patients developed mucocutaneous and/or esophageal candidiasis. It must also be stressed that this strategy is very expensive and runs the risk of facilitating the emergence of resistant strains of a variety of fungi; therefore, it cannot be routinely considered in clinical practice.

Suppressive therapy. The rate of relapse after initial treatment of cryptococcosis in AIDS patients is 50 to 60% (82, 265). The contribution of secondary prophylaxis was demonstrated in a double-blind study versus placebo that evaluated oral fluconazole (100 to 200 mg/day). The relapse rate was 3% in the fluconazole group compared with 37% in the placebo group (33). In addition, fluconazole (200 mg/day) was shown to be more effective than amphotericin B (1 mg/kg/week) (1.8 and 18%, respectively) and generated fewer side effects (268). The same dose of fluconazole has also been recently shown to be more effective than itraconazole (200 mg/day) in preventing relapses of cryptococcal meningitis: (3.8 and 23.6%, respectively) (292). However, the itraconazole dose given was lower than that usually prescribed during HIV infection. A retrospective study indicated that the 400-mg/day dose of fluconazole was probably more effective than the 200-mg/day dose (230).

Taken together, these results demonstrate that fluconazole is currently the prophylaxis of choice against relapsing cryptococcosis during the course of HIV infection (262). Amphotericin B (50 mg administered intravenously once or twice weekly) and itraconazole (>200 mg/day), should be considered as alternatives in cases of intolerance to fluconazole. As reported for other fungal diseases during HIV infection, the potential risk of acquired resistance should not be forgotten.

Histoplasmosis Due to Histoplasma capsulatum

Primary prophylaxis. The benefit of primary prophylaxis against histoplasmosis during the evolution of AIDS has recently been demonstrated by a trial of itraconazole versus placebo (200) conducted in U.S. cities where the incidence of this opportunistic infection is high (Indianapolis, Kansas City, Memphis, and Nashville). In a retrospective study, oral fluconazole (100 mg/day) did not lower the incidence of histoplasmosis in AIDS patients in Dallas (238). Anecdotally, one patient taking fluconazole (50 mg/day) developed histoplasmosis (308) and another patient on maintenance therapy for cryptococcosis developed histoplasmosis (264). In a recent evaluation of oral fluconazole (200 mg/day) prophylaxis during HIV infection, no protective effect against histoplasmosis was observed (266). In France, we have also found that several HIV-infected patients developed histoplasmosis while receiving low doses of fluconazole (182). In addition, the potential risk of selecting Histoplasma strains resistant to azoles must be taken into account in the context of primary prophylaxis (370). Cost-benefit studies should also be undertaken, particularly for the possible application of these therapies in regions of endemic infection in third-world nations.

Suppressive therapy. Relapses without maintenance therapy occur in 35 to 80% of patients with histoplasmosis (300, 371). Thus, lifelong secondary prophylaxis is indicated.

(i) Amphotericin B. Administration of amphotericin B every week or every other week is more effective than administration of ketoconazole (80 to 97% and 50%, respectively) in preventing relapses, with a median survival time of 13 to 17 months (201, 202, 371). Neither amphotericin B nor ketoconazole is indicated as maintenance therapy in patients with central nervous system involvement (14, 366). Bacteremias, catheter infections, and thrombophlebitides often arise during secondary amphotericin B prophylaxis (202). With side-effect and relapse rates as high as 20% during amphotericin B prophylaxis, the evaluation of azoles for this indication was not only needed but highly justified.
(ii) **Itraconazole.** Itraconazole (200 mg b.i.d.) was shown to be well tolerated and highly (95%) effective as maintenance therapy in 42 patients who had received amphotericin B induction therapy (15 mg/kg [total dose]). The median survival time was 109 weeks (369). Indeed, itraconazole represents the maintenance therapy of choice in patients who are able to absorb it (315) and are not taking another medication that could interfere with it. Itraconazole has proven effective as maintenance therapy for especially severe forms of disease, like endocarditis (181) and central nervous system involvement (366).

(iii) **Fluconazole.** In a retrospective study (242), relapses were noted in 12% of 76 patients receiving 100 to 400 mg of fluconazole per day, after induction therapy with amphotericin B, itraconazole, or fluconazole. The relapse rate was higher in those receiving 100 mg of fluconazole per day, but these data were insufficient to establish the optimal dosage of fluconazole for this indication. Survival was longer in patients who had received 1 g of amphotericin B initially. The survival time was shorter in patients receiving fluconazole (94 weeks) than that observed in the study evaluating the efficacy of itraconazole (369). In another study (372), the relapse rate in patients given 400 mg of fluconazole per day was 52% in patients who had received fluconazole as induction therapy. Thus, the majority of reports indicate that fluconazole (≥200 mg/day) is to be reserved for patients who cannot tolerate itraconazole or those with drug interaction problems (130).

**Coccidioidomycosis**

**Primary prophylaxis.** No study has actually proven the usefulness of primary prophylaxis against coccidioidomycosis during HIV infection. Some patients developed coccidioidomycosis while they were receiving ketoconazole for another indication (97). Prophylactic administration of fluconazole (200 mg/day) is currently being evaluated in regions of endemic infection in the United States (367). HIV-infected patients whose coccidioidal serological status is positive are probably good candidates for prophylaxis (203).

**Suppressive therapy.** Lifelong maintenance therapy is indicated for patients with a history of coccidioidomycosis (203). However, treatment modalities have not yet been specified (186). Daily fluconazole (200 to 400 mg/day) or weekly amphotericin B can be prescribed (373). Ketoconazole cannot be used (390), and itraconazole has not been tested for this indication.

**Aspergillosis**

**Primary prophylaxis.** Primary prophylaxis cannot be given to all patients with a low level of CD4+ lymphocytes because of the rarity of the disease. Therapy could be considered for patients in the late stages of AIDS when they are exposed to renovation and/or construction and possibly for patients with a positive sputum or bronchoalveolar lavage sample without evidence of lung invasion.

**Suppressive therapy.** The idea of secondary prophylaxis against invasive aspergillosis during AIDS has not been addressed in light of the poor short-term prognosis of this infection (160, 188). In some cases that are diagnosed early, induction therapy can nevertheless be effective, especially in patients with aspergillosis affecting the sinuses or tracheobronchial tree (160, 184). After at least 14 days of intravenous amphotericin B, long-term itraconazole (400 mg/day) may be prescribed when no concomitant counterindicated medications are being taken. A loading dose of itraconazole (600 mg/day) should be administered for 4 days, and itraconazole levels in serum should be determined after 7 days of treatment.

Oral itraconazole solution has the best bioavailability and needs to be tested for prophylaxis in patients at risk.

**Infection Due to Penicillium marneffei**

The percentage of relapses with *P. marneffei* is high after cessation of antifungal therapy (325), indicating the need for secondary prophylaxis. Itraconazole (200 mg/day) is a valid suppressive therapy. Its use for primary prophylaxis in areas of high endemism, such as Northern Thailand, is under investigation.

**Other Mycoses**

No clear recommendations can be made for rare systemic mycoses, such as blastomycosis, sporotrichosis, and paracoccidioidomycosis, that develop during AIDS (185).

**QUALITATIVE DEFECTS OF NEUTROPHILS**

Of 30 children with chronic granulomatous disease enrolled in one center from 1985 to 1991 who received itraconazole (5 to 10 mg/kg/day), 3 developed pulmonary aspergillosis. This 10% rate of aspergillosis in children taking itraconazole was lower than that observed in a historical untreated group (34.4%) (226).

**CONCLUSION**

Precise guidelines are difficult to draw up from the published literature, because of the lack of international consensus on the definition of fungal disease and end points for antifungal treatments. It is obvious that the best drug regimen has yet to be determined for almost every group of immunocompromised patients at risk of fungal infections. In addition, among the parameters to be considered, cost-effectiveness must also be addressed (353). Without specifying the targets, host, and fungal species, optimal antifungal prophylaxis cannot be obtained. It can even have deleterious effects by increasing the risk of infections caused by resistant fungi and also by lowering the guard of the clinician, who, confident that the patient is protected against fungal infections, fails to monitor drug levels in serum and potential sites of colonization.

The only real consensus in the prevention of fungal diseases is that it is mandatory to control exposure to environmental sources of fungi: hand-washing for *Candida* spp., using efficient air filtration and limiting construction or renovation work near hematology units for airborne fungi like *Aspergillus* spp., avoiding soil heavily contaminated with pigeon droppings for *C. neoformans* and bat guano for *H. capsulatum*, and remaining indoors during dust storms for *C. immitis*.

For HIV-infected patients (Fig. 1), results of well-designed protocols have demonstrated the value of suppressive therapies with fluconazole for cryptococcosis or itraconazole for histoplasmosis. For patients with CD4+ cell counts below 100/μm^2^, primary prophylaxis has recently been demonstrated to be effective in areas of endemic infection (histoplasmosis) or is under investigation (penicilliosis, coccidioidomycosis). For other opportunistic fungal infections, such as mucosal candidiasis or cryptococcosis, at least in Western countries, systematic prophylaxis is of little benefit considering its cost, side effects, and inability to prolong survival. Increased use of new antiretroviral agents including protease inhibitors should lower the incidence of mycoses and contribute to the better control of patients who previously experienced opportunistic fungal infections, particularly those harboring resistant strains.

The most hotly debated topics remain aspergillosis and he-
FIG. 1. Algorithm for the primary prophylaxis and prevention of relapse of fungal infections in patients with AIDS. Under each disease except coccidioidomycosis, left arrows indicate primary prophylaxis and right arrows indicate suppressive therapy for prevention of relapse. For coccidioidomycosis, the top arrow indicates prophylaxis and the bottom arrow indicates suppressive therapy.

Flu: fluconazole - Itra: itraconazole
* Monitor fungal colonization to detect the emergence of azole-resistant Candida spp. strains
** However, some studies showed that Flu reduced the incidence of the disease.
*** When no contraindicated drug is being taken simultaneously.

FIG. 1. Algorithm for the primary prophylaxis and prevention of relapse of fungal infections in patients with AIDS. Under each disease except coccidioidomycosis, left arrows indicate primary prophylaxis and right arrows indicate suppressive therapy for prevention of relapse. For coccidioidomycosis, the top arrow indicates prophylaxis and the bottom arrow indicates suppressive therapy.
matogenous candidiasis in neutropenic patients, BMT and solid-organ transplant recipients and how, when, and how long to prescribe prophylaxis.

In our opinion and from this literature review (Fig. 2), antifungal prophylaxis should be considered in high-risk neutropenic patients (i.e., those with prolonged neutropenia) and prescribed only when *Candida* spp. colonize more than one site. For *C. albicans*, fluconazole is the preferred drug, while for other *Candida* spp., their prevalence and frequency of azole resistance in individual units has to be taken into account. It should be noted that prophylactic fluconazole administration has resulted in a decrease in deaths attributable to invasive *Candida* infections and sometimes overall mortality in malignant hematological diseases including BMT. In general, ketoconazole and oral nonabsorbable polyenes have given disappointing results in severely neutropenic patients or BMT recipients, but the latter should now probably be evaluated on a large-scale basis (123), particularly for the prevention of hematogenous dissemination in patients colonized with non-*albicans* *Candida* species.

Systematic primary prophylaxis against aspergillosis remains investigational, but despite the lack of conclusive data, itraconazole may be considered for patients who cannot be transferred during renovation within the hospital. In the BMT population, prophylaxis should probably also be given to cover the GVHD period and might be prolonged in the setting of CMV disease or steroid therapy. For patients with hematological malignancies receiving extensive chemotherapy, the use of hematopoietic growth factors will also probably reduce the risk of fungal infections.

In solid-organ transplant recipients, abdominal surgery (liver and pancreas transplantations) should probably be associated with fluconazole prescription at least during the first month after grafting. In these patients, colonization of bronchial secretions with *Aspergillus* spp. should prompt the administration of antifungal therapy.

For non-HIV immunocompromised patients who contract noncandidal systemic infections, prophylaxis against relapse should be given until recovery from the immune deficit.

In the future, vaccines (80, 114, 248) may be added to the arsenal of antifungal prophylactics, particularly against endemic mycoses and cryptococcal infection, and new antifungal agents under development (18, 120, 121) and cytokines (41, 59, 149, 163, 190, 232, 233, 284, 319, 342) should be evaluated as alternatives to existing azoles in immunocompromised patients.

Finally, prevention of fungal infections also includes continuing education of physicians and clinical microbiologists to make them aware of emerging fungal species and of the fact that any fungus is a potential pathogen in immunocompromised hosts.

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