Clinical Aspects of Fungal Infection in Organ Transplant Recipients

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Fungal infections following solid organ transplantation remain a major cause of morbidity and mortality. *Candida* species and *Aspergillus fumigatus* continue to account for the majority of these infections, although the attack rate is higher among recipients of organs other than kidneys because those patients receive more immunosuppressive therapy. Although amphotericin B remains the drug of choice for treatment of invasive aspergillosis, its toxicity profile limits its widespread use. Recent experience suggests that fluconazole may be a safe and effective alternative for the treatment of fungal infections caused by *Candida* species or *Cryptococcus neoformans*. Prevention of fungal infections remains one of the most important goals in the field of transplantation. New approaches—such as the use of “preemptive therapy,” or prophylaxis, for patients at greatest risk of developing infection—may assist in attainment of this goal.

The success of organ transplantation has created an ever-increasing patient population that is at risk for invasive, and frequently life-threatening, fungal infection. Fungal infection occurs in zero to 14% of renal transplant recipients [1-6] and in as many as 32% of heart transplant recipients [7-10], 35% of heart-lung and lung recipients [10-12], 42% of liver recipients [13-16], and 38% of pancreas recipients [17-18]. The differences in attack rates among recipients of various transplanted organs are largely due to technical issues related to the transplant procedure and the tendency to administer more immunosuppressive therapy to recipients of organs other than kidneys (i.e., patients who have no alternative life support system, such as dialysis, if their allografts fail). The fungal infections that occur in these patients are due to five major pathogens: *Candida* species, *Cryptococcus neoformans*, the filamentous fungi (predominantly *Aspergillus* species and organisms of the Mucoraceae family), *Pneumocystis carinii*, and the agents causing geographically restricted systemic mycoses (i.e., histoplasmosis, coccidioidomycosis, and blastomycosis).

The incidence of fungal infection following organ transplantation, like that of other forms of opportunistic infection in this patient population, is largely determined by the interaction between epidemiological (exposure) factors and the net state of immunosuppression [19-21]. These two elements interact in a semiquantitative fashion: if the exposure is great enough, even patients who have a normal immune system may become ill; conversely, if the net state of immunosuppression is great enough, even minimal exposure to potential pathogens will result in life-threatening infections [22].

The epidemiological, or exposure, factors of importance can be divided into two categories: those occurring within the community and those occurring in the hospital setting. In the community, the most important exposures are to endemic mycoses. Both recent and remote exposures are important, since three forms of infection are recognized: (1) reactivated infection, in which infection acquired even many years prior to the transplantation may reactivate from a dormant focus because of the waning of previous immunity (as a result of the initiation of immunosuppressive therapy); (2) primary infection, in which an immunosuppressed transplant recipient develops progressive infection due to a fungal pathogen (first exposure); and (3) reinfection, in which pretransplantation immunity (acquired after previous exposure[s]) has been attenuated by immunosuppressive therapy such that new exposure to the same fungal pathogen results in invasive infection. Regardless of the type of infection, the net result is invasive disease, frequently with systemic dissemination.

Exposures within the hospital are even more important than those occurring within the community. Invasive aspergillosis is the most significant nosocomial fungal infection, predominantly because of the high case fatality rate among organ transplant recipients [23]. Although *Aspergillus* species are ubiquitous in the environment and may cause disease in patients who live in or visit farming communities, construction and renovation as well as contaminated air conditioning systems in the hospital environment have been associated with epidemics of invasive aspergillosis in immunosuppressed patients, particularly organ transplant recipients [24]. Two patterns of nosocomial outbreaks are recognized: (1) domiciliary, in which exposure occurs in the room or on
the ward where the patient is housed within the hospital (this type of outbreak is relatively easily identified because of the clustering of cases in time and space), and (2) nondomini­
ciary, in which exposure occurs as the patient travels within the hospital for essential procedures (this type of outbreak is probably more common than the domiciliary type but is more difficult to recognize because there is no clustering of cases in time and space). Reported nondomini­
ciary outbreaks of invasive aspergillosis in immunosuppressed patients have stemmed from exposure in a radiology suite, exposure in an operating room, and even travel through a hospital area un­
dergoing intensive construction [24]. Although high-effi-
ciency particulate air filtering systems prevent domiciliary exposure, efforts for prevention of nondomini­
ciary exposure are unsatisfactory in many transplantation centers. Recently, emphasis has been placed on the development of protective masks and transportational devices for protecting transplant recipients from nondomini­
ciary exposure [25].

The net state of immunosuppression is a complex function that is determined by the interaction of a number of factors: the doses of and duration of therapy with different immuno-
suppressive drugs and the sequence in which they are admin­
istered; the presence or absence of granulocytopenia, foreign bodies such as catheters, and devitalized tissue or undrained fluid collections (e.g., blood, urine, bile, or lymph) as a consequence of the transplantation operation; compromise of the primary mucocutaneous barrier to infection: the presence of such metabolic factors as protein-calorie malnutri­
tion, uremia, and hyperglycemia; and the presence of infec­
tion with viruses, such as cytomegalovirus (CMV). The importance of infection with these viruses in regard to the net state of immunosuppression is demonstrated by the follow­ing observation: over the past 10 years in the Massachusetts General Hospital Transplantation Unit, >90% of the opportu­
tunistic infections due to Aspergillus species, P. carinii, and C. neoformans occurred in patients with active or recent infection due to viruses such as CMV [22]. The majority of cases of invasive aspergillosis have been due to unsuspected excessive exposure.

Fungal Infection and the Timetable of Infection After Transplantation

As immunosuppressive regimens have become standard­
ized, the time at which different infections occur after transplan­
tation has become predictable (figure 1). According to this timetable, the posttransplantation course can be divided into three phases: the first month, the period from the first month through the sixth month, and the late period (beyond 6 months post-transplantation).

In the first month after transplantation, infectious disease syndromes that occur are of three types: those present in the transplant recipient prior to transplantation; those conveyed with the allograft; and the usual wound, pulmonary, urinary, vascular-access-device, and drainage-catheter infections that occur in any patient undergoing comparable amounts of sur­
gery (although in immunosuppressed transplantation pa­
tients the infections are associated with greater morbidity and mortality). The following observations are specific to fungal infections.

1. Although any active fungal infection present in an allograft recipient at the time of transplantation could be exacerbated by immunosuppression and the operative proce­
dure, actively infected patients rarely receive transplants. A more frequent clinical challenge is the transplant recipient who is heavily colonized with a fungus at the time of transplan­
tation. In such a setting, the combination of the trans­
plant operation and initiation of immunosuppressive therapy permits colonization to become invasive disease. For exam­
pole, there is an increased risk that invasive aspergillosis will occur during the first month after lung, heart, heart-lung, and occasionally liver transplantation for recipients whose respiratory tracts were colonized with an Aspergillus species before the procedure. Likewise, there is an increased risk of deep candidal wound infection in female recipients of pan­
creas transplants whose vaginas are heavily colonized with a Candida species at the time of transplantation [22]. Both disruption of the primary mucocutaneous barrier (via place­
ment of the pancreas in the pelvis and drainage of exocrine secretions into the bladder) and presence of a foreign body (the bladder catheter) may assist in the pathogenesis of the wound infection by permitting translocation of vaginal can­
didal organisms to the bladder and the pancreatic allograft.

Similarly, excessive colonization of the gastrointestinal tract may predispose liver transplant recipients to deep wound infection.

2. Fungal infection can be transmitted with the allo­
graft. Rare cases of histoplasmosis [26] and cryptococcosis [27] in recipients of renal allografts, secondary to unsus­
pected systemic infection in the donor, have been reported. More commonly, donor organs are contaminated with Can­
dida species secondary to unsuspected candidemia in the do­
nors that is associated with preterminal care (e.g., the use of a vascular access device, bladder catheters, and ventilatory support via an endotracheal tube). The recipient may de­
velop infection (and myotic aneurysm) at the vascular su­ture line [28–31]. Careful assessment of potential donors for both focal and systemic fungal infection is as important as evaluation for other pathogens.

3. More than 95% of the infections during the first month after transplantation are the result of technical prob­
lems associated with the surgical procedure and postopera­
tive management [19, 20]. The majority of fungal infections are due to Candida species.

4. Opportunistic fungal infections such as those caused by Aspergillus species (unless colonization occurred before transplantation), C. neoformans, and P. carinii are notably absent during the first month after transplantation. The oc-
currence of such infections during this time period (when the net state of immunosuppression is usually insufficient for opportunistic fungal infections to occur) suggests an unusually intense environmental exposure [24].

In the period from the first month through the sixth month after transplantation, the dominant infections are those caused by "immunomodulating" viruses (i.e., those that add to the net state of immunosuppression), particularly CMV. The combination of viral infection and immunosuppressive therapy results in a net state of immunosuppression great enough for opportunistic infection, particularly with *P. carinii*, to occur in the absence of specific anti-*Pneumocystis* prophylaxis. Protection of patients from exposure to environmental risk factors (particularly those in the hospital) during this time is of paramount importance because of their high state of immunosuppression.

Patients with a functioning allograft >6 months after transplantation can be divided into two groups on the basis of their risk for opportunistic fungal infection: those with satisfactory allograft function whose conditions are being maintained only with baseline immunosuppressive therapy (these patients are at minimal risk of acquiring opportunistic fungal infection unless subjected to unusually intense environmental exposure) and those with a history of significant acute and chronic allograft rejection, who have received significantly more immunosuppressive therapy and frequently have chronic infection with the immunomodulating viruses. Patients in this latter group (termed the "chronic ne'er-do-wells") are at increased risk for life-threatening opportunistic infection.

**Fungal Infections of Particular Importance in the Organ Transplant Recipient**

**Candidiasis**

*Candida* species are by far the most common cause of fungal infection in the organ transplantation patient; the clinical syndromes they cause range from the trivial (mucocutaneous thrush) to the life-threatening (candidal sepsis with visceral seeding) [6, 20]. The forms of candidal infection that occur and their incidence vary according to the type of organ transplanted (figure 1). The patterns may be summarized as follows.

1. The incidence of candidal infections in the renal transplant recipient is between 3% and 5% [1–6]. Oral and esophageal candidiasis (particularly in diabetic patients and in those receiving broad-spectrum antibacterial therapy without concomitant antifungal prophylaxis), vascular access device–related sepsis, and candidal urinary tract infection are the most frequent forms of infection. Deep wound infection is uncommon but may occur in diabetic patients, frequently as a mixed fungal and bacterial process [18]. Isolation of a *Candida* species from the sputum is common; however, candidal pneumonia almost never occurs. The important result of colonization of the respiratory tract by these organisms is concomitant colonization of the skin, which increases the risk of vascular access–related candidemia. Candiduria in the renal transplant recipient with diabetes or compromised bladder function is associated with an increase in obstructive uropathy caused by fungus balls, which may form at the ureteropelvic junction [20]. In addition, candidal...
pyelonephritis of the allograft may be associated with subsequent candidemia.

2. Fungi account for 20%-30% of life-threatening infections in the liver transplant recipient; >85% of these infections are candidal [13-16]. Although the types of infections include vascular access device-related sepsis and biliary tract infection, intraabdominal infection adjacent to the hepatic allograft is of greatest significance [14]. The pathogenesis of deep wound infections involves the following stages: first, candidal colonization of recipient's small bowel (which is manipulated during the transplantation procedure) provides an opportunity for direct inoculation of the abdominal cavity; second, intraabdominal bleeding and the formation of a hematoma during the operative procedure provide a fertile ground medium for candidal and other pathogens; third, candidal growth is promoted by peritransplantation antibacterial therapy; and, ultimately, the host defense mechanism is impaired by the immunosuppressive regimen.

3. The incidence of candidal infection in pancreas transplant recipients approaches 10% [17, 18]. As indicated above, the predominant infection is of the deep wound variety and is associated with heavy vaginal colonization with Candida species.

4. In lung and heart-lung transplantation, candidal colonization may affect healing of the bronchial anastomosis and may increase the risk of candidal mediastinitis [10, 11]. Ulcerative tracheobronchitis with formation of a pseudomembrane following lung transplantation has been reported [32].

5. Candidal infection in the heart transplant recipient is similar to that observed in renal transplant recipients: it is primarily mucocutaneous candidiasis and related to contaminated venous access devices and drainage catheters. Thus, the majority of candidal infections in transplant recipients are the result of technical mishaps during the surgical procedure or are related to the postoperative management of vascular-access, bladder, or drainage catheters.

Aspergillosis

Invasive aspergillosis is the most important cause of life-threatening fungal infection in the organ transplant recipient [23]. In >90% of cases the lungs are the portal of entry, although the sinuses and skin damaged by other processes can also be the sites of invasion [23, 33]. Ulceration, necrosis, cartilage invasion, and formation of a pseudomembrane may occur in lung and heart-lung transplant recipients who have histologic evidence of invasive aspergillosis [32]. Once tissue infection develops, invasion of blood vessels is the rule, accounting for the three cardinal features of invasive aspergillosis in the organ transplant recipient: tissue infarction, hemorrhage, and dissemination with metastatic seeding. The presence of disseminated disease is closely related to mortality. More than 50% of transplant recipients without disseminated disease may respond to therapy with amphotericin (particularly when localized invasive aspergillosis is recognized early, immunosuppression is reduced, and the allograft is functioning) [23]. Once the infection has metastasized, however, it is almost uniformly fatal (even with the addition of rifampin to the therapeutic regimen) [23]. The risk of developing invasive aspergillosis is primarily determined by epidemiologic (exposure) factors, but the attack rate is higher in patients who have previously had CMV infection and those requiring antirejection therapy (with additional steroids or with antilymphocyte antibody).

Cryptococcosis

For unclear reasons, cryptococcal infection rarely occurs during the first 4-6 months after transplantation [19]. The portal of entry for C. neoformans is the lung, from which it hematogenously disseminates, particularly to the skin and the CNS and less frequently to such sites as the urinary tract and skeletal system. Most cryptococcal pulmonary disease is asymptomatic or associated with flu-like symptoms. These infections may be diagnosed only after a routine chest radiograph shows either an infiltrate or an asymptomatic nodule. Metastatic infection of the skin (resulting in papules, cellulitis, or non-specific lesions) is the first sign of disseminated cryptococcal infection in up to 30% of patients [22]. Early biopsy of unexplained skin lesions is encouraged, because treatment of cryptococcal infection is more frequently successful when it has not yet metastasized to the CNS [34]. The presence of cryptococcal antigen in the blood (or the isolation of the organism in blood cultures) may also indicate disseminated infection.

C. neoformans is the classic cause of subacute-chronic meningitis in transplant recipients. Focal disease may also be present, usually in association with meningitis. The most common presenting symptoms are headache and fever; less common are an altered state of consciousness and meningeal signs (in contrast to the presenting symptoms and signs of human immunodeficiency virus [HIV]-infected patients). The CSF-related findings of lymphocytic pleocytosis, hypoglycorrhachia, and an elevated protein concentration are common, although the presence of cryptococcal antigen of the organism in culture confirms the diagnosis. The cryptococcal antigen test is quantitative and useful not only for initial diagnosis but also as a means of serial measurement of titers for determining the patient's response to therapy [35].

Mucormycosis

Mucoraceae are uncommon causes of fungal infection in the organ transplantation patient and produce either a rapidly progressive necrotizing pneumonia or rhinocerebral disease. There are too few cases of mucormycosis to know which species are the most likely to cause invasive disease.
Although classically associated with diabetic ketoacidosis, mycoses has been observed in transplant recipients who were euglycemic but acidotic (e.g., because of uremia or a bicarbonate leak via the bladder following pancreatic transplantation).

**P. carinii Pneumonia**

Now classified as a fungus, *P. carinii* is the most common cause of opportunistic pneumonia in transplant recipients; *P. carinii* pneumonia occurs in ~10% of transplant recipients during the first 6 months, if no prophylaxis is administered [36-40]. It primarily occurs 1–4 months after transplantation in association with CMV infection or in the late period in the “chronic ne'er-do-wells.” The relationship between CMV and *Pneumocystis* may be related to effects of CMV on alveolar macrophage function. The presentation of pneumocystic pneumonia is subacute and chest radiographs typically show bilateral basilar interstitial infiltrates. As in the HIV-infected patient, extrapulmonary pneumocystosis in the transplantation patient is uncommon [38-40]. Pneumocystic pneumonia is thought to result from reactivation of dormant infection. Because of the possibility of person-to-person spread, isolation of patients with this infection seems prudent.

**Endemic, Geographically Restricted Systemic Mycoses**

Histoplasmosis is the most frequently reported of the three major endemic mycoses occurring in transplant recipients. Patients living in regions of endemicity (the Mississippi and Ohio River valleys and much of the Midwest and south-central United States) tend to develop primary disease, while patients living in regions where histoplasmosis is not endemic tend to have reactivated disease. Outbreaks during which the attack rate among renal transplant recipients in regions of endemicity rose from 0.5% to 2.1% have been reported [41]. Risk factors for the development of invasive disease, in addition to environmental exposure, include anti-rejection therapy. The relationship between CMV disease and histoplasmosis is unclear. Although progressive disseminated disease develops in most transplant recipients, 66% have the chronic form, presenting with nonspecific complaints such as prolonged fever and skin lesions. CNS involvement is uncommon and, surprisingly, the chest radiograph may be normal for ~50% of patients. Cultures of specimens from pulmonary and extrapulmonary sites are diagnostic, but results may not be available for 3 weeks. Fungal staining (of bone marrow aspirates, for example) may provide a more rapid diagnosis. Serology is usually unhelpful. The potential role of the radioimmunoassay for serum and urine antigen in transplant recipients is under investigation.

Coccidioidomycosis occurs less frequently than histoplasmosis and has occurred mostly in renal and cardiac transplant recipients [42]. Variable incidence rates occur in the regions in which it is endemic (southwestern United States). Like histoplasmosis, reactivated disease tends to occur in regions of nonendemicity and primary disease in regions of endemicity. Again, disseminated disease is the rule (the CNS and genitourinary, splenic, hepatic, and joint sites are commonly involved). The associated mortality rate is >60%. Diagnosis depends on either culture or detection of spherules in tissues. Bronchoscopy greatly improves the diagnostic yield from pulmonary specimens. The high mortality rate despite therapy (see below) and the risk of relapse after apparently successful therapy have resulted in an ongoing controversy: should transplantation continue in regions of endemicity, and should prophylaxis (e.g., with ketoconazole) be administered to transplant recipients in whom prior infection with *Coccidioides immitis* is evident?

Blastomycosis is rare, and experience with the disease in transplant recipients is therefore limited [43]. It most frequently occurs as disseminated disease, although patients usually present with more subacute pulmonary symptoms than are observed with histoplasmosis or coccidioidomycosis. Diagnosis is by means of culture or histopathology. Serological testing of transplant recipients is unhelpful.

**Antifungal Therapy for Organ Transplant Recipients**

Treatment of fungal infections in organ transplant recipients is complicated by three factors: the continuing need for immunosuppression (except for recipients of renal and pancreas allografts, whose conditions may be maintained with dialysis and insulin therapy if the graft fails); the requirement for a prolonged course of therapy; and the potential for all currently available antifungal agents to interact with essential immunosuppressive agents, particularly cyclosporine. There are three ways in which antifungal agents may interact with cyclosporine: (1) upregulation of hepatic cytochrome P-450-linked metabolism of cyclosporine (and probably of prednisone), resulting in inadequate cyclosporine levels and an increased risk of allograft rejection; (2) down-regulation of cyclosporine metabolism, resulting in increased blood levels, an increase in the number of toxic effects due to cyclosporine (particularly in the kidneys), overimmunosuppression, and an increased risk of opportunistic infection; and (3) synergistic, idiosyncratic nephrotoxicity.

The azole antifungal agents downregulate cyclosporine metabolism. This effect is most potent with ketoconazole [44-47], less potent with itraconazole [48, 49], and least potent with fluconazole [35, 50, 51]. Appropriate adjustments in the dosage of cyclosporine (usually a reduction, based on serum levels) and/or of the antifungal agent permit use of such agents while preventing toxic effects of cyclosporine. The more challenging problem is use of the combination of cyclosporine and amphotericin (until recently, amphotericin
Antifungal agents, like antibacterial and antiviral agents, can be administered in three modes: as prophylaxis, to prevent an infection that is common and of sufficient clinical impact to justify administration of a nontoxic antimicrobial agent to all transplant recipients; as preemptive therapy, to prevent clinical infection in the subgroup of patients at greatest risk for development of symptomatic disease (as determined by a laboratory finding or a clinical/epidemiological characteristic); and as therapy, to ameliorate and cure established clinical infection.

The most successful form of antifungal prophylaxis in transplant recipients is the use of trimethoprim-sulfamethoxazole to prevent P. carinii pneumonia [36, 56–58]. In addition, trimethoprim-sulfamethoxazole is quite effective in the prevention of urosepsis, listeriosis, and nocardiosis [36]. In many transplantation centers, trimethoprim-sulfamethoxazole (80 mg trimethoprim, 400 mg sulfamethoxazole) is administered daily to all transplant recipients for the first 6 months after transplantation. It is our practice to reinstitute therapy with this agent for patients previously described as “chronic ne'er-do-wells.” The efficacy of nonabsorbable oral antifungal agents such as clotrimazole, nystatin, or amphotericin in the prevention of candidal infection derived from the gastrointestinal tract is less clear [59]. At our institution, nonabsorbable antifungal agents are used to prevent oral and/or esophageal candidiasis in transplant recipients receiving antibacterial therapy and to decrease the colonization of candidal species in the gut of liver transplant candidates. The potential role of fluconazole as a prophylactic agent in liver transplantation is currently under investigation.

There are currently three types of preemptive antifungal therapy in use at our center. Preemptive therapy with itraconazole is used to prevent invasive aspergillosis (by decreasing colonization) in transplant recipients whose respiratory tracts are colonized with an Aspergillus species just prior to transplantation or in the early posttransplantation period. Preemptive therapy with fluconazole or itraconazole is used to reduce the risk of disseminated cryptococcal or Histoplasma capsulatum infection, respectively, which may be triggered by surgical excision of focal pulmonary nodules. Preemptive therapy with fluconazole is used to prevent ascending infection and the formation of obstructing fungus balls in renal transplant recipients with asymptomatic candiduria. Fluconazole is very effective in the treatment of asymptomatic pyuria associated with candiduria that is due to Candida albicans and Candida tropicalis but not with infection due to Torulopsis glabrata [34].

Amphotericin B remains the drug of choice in therapy for invasive infection with filamentous fungi such as Aspergillus species [23, 60–64]. In most transplantation centers, the daily dose of amphotericin for the treatment of invasive aspergillosis is at least 0.5 mg/kg and frequently is as high as 1.0 mg/kg. All patients receiving cyclosporine during therapy should be monitored daily for symptoms of cyclosporine toxicity, in conjunction with daily measurement of renal function and frequent determinations of serum cyclosporine levels. Frequent dosage modifications are almost always necessary. Although itraconazole is active against Aspergillus species, its safety and efficacy in treatment of invasive aspergillosis in transplant recipients has yet to be evaluated. At this time, it appears that itraconazole should probably be reserved for the completion of therapy and be given only after administration of at least 1 g of amphotericin, providing the patient has demonstrated adequate clinical response. In contrast to that for invasive aspergillosis, the primary mode of therapy for mucormycosis is ablative surgery, with a goal of excision of the entire infected area. High-dose amphotericin (goal, 1.0 mg/[kg • d]) is administered to control and eradicate only the remaining microscopically evident infection. There is insufficient information regarding whether rifampin is a useful adjunct for the treatment of mucormycoses. Although amphotericin B has been the drug of choice for management of endemic mycoses (histoplasmosis and coccidiomycosis), there are anecdotal reports of effective treatment and suppression with itraconazole and fluconazole.

For invasive candidal and cryptococcal infection, primary therapy with fluconazole appears to be a reasonable alternative to that with amphotericin. Of 74 consecutive recipients of solid organ transplants who received fluconazole for the treatment of candidal and cryptococcal infection, 71% were cured of infection, with minimal toxic effects [34]. Infection in ~50% of the remaining 29% of patients had abated by the time that therapy with fluconazole was discontinued (because of either the presence of a drug rash or the discovery of simultaneous filamentous fungal infection requiring treatment with amphotericin). Therapy with fluconazole was found to be effective, and there was no evidence that its initiation caused worsening of hepatic function in liver transplantation patients (even in patients with significant dysfunction). The most common cause of failure was infection with T. glabrata, a yeast relatively resistant to fluconazole [34].

How, then, should one choose between amphotericin and fluconazole for the treatment of candidal and cryptococcal infection in the organ transplant recipient, and is there a role for flucytosine in combination with either agent? Although a direct comparison of amphotericin and fluconazole in the cyclosporine-treated transplant recipient will probably never
be possible because of the excessive toxicity of amphotericin B in this setting, the findings regarding our uncontrolled case series [34] and the recent demonstration of the comparable efficacy of the two drugs in the treatment of candidemia in immunosuppressed patients are reassuring [65]. The addition of fluconazole to a regimen of amphotericin for the treatment of cryptococcal meningitis and candidal meningitis or arthritis in transplant recipients (as is recommended for other groups of immunosuppressed hosts) has not been widely studied. Although the combination has been used effectively, there is a high risk of severe toxic effects, particularly in patients with significant azotemia and minimal bone marrow reserve.

At our institution, the approach to treatment of candidal and cryptococcal infection is as follows. Amphotericin B (used alone) remains the drug of choice for infection with *T. glabrata* and *Candida krusei* (the most common fluconazole-resistant species). Amphotericin B also is administered as initial therapy for patients who are critically ill with fungal sepsis and at immediate risk of death, but once these patients' conditions have stabilized, the drug is replaced with fluconazole for antifungal therapy. Fluconazole is used as the sole agent for primary therapy for the majority of patients who present with subacute illness. For all patients treated with fluconazole, levels of cyclosporine in the blood are carefully monitored, and the cyclosporine dosage is adjusted when clinically indicated. The appropriate duration of antifungal therapy remains a challenging question. Our approach has been to treat for 2–4 weeks after resolution of clinical signs and symptoms of infection and when there is microbiological evidence that the infection has been eradicated. The availability of fluconazole has made this approach safer, because the drug reduces renal dysfunction and the risk of vascular access device–related infections in organ transplant recipients who require parenteral therapy.

References