Fungal Infections in Solid-Organ Transplantation

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Fungal infections following solid-organ transplantation remain a major cause of morbidity and death. Their incidence ranges from 5% among recipients of kidney transplants to as high as 40% among recipients of liver transplants. Species of Candida and Aspergillus account for more than 80% of fungal episodes. Moreover, more than 80% of fungal infections occur within the first 2 months after transplantation, with a resulting mortality of 30%-100%. The pathogenesis of infection and the risk factors involved depend on the type of transplant and the infecting microorganism. Cyclosporine has not significantly reduced the incidence or severity of fungal infections in this population. The value of surveillance cultures and fungal antigen detection in solid-organ transplant recipients remains to be determined. Amphotericin B is still a first-line drug, but its potential nephrotoxicity makes its use problematic, especially in renal transplant recipients. Fluconazole is a potential alternative for the treatment of infections due to Candida species and Cryptococcus neoformans. The role of antifungal compounds in the prophylaxis of fungal infection in recipients of solid-organ transplants needs to be established.
most bacterial infections, develops early after transplantation (median, 23 days), while candidal infection occurs later (median, 44 days) [3]. A constant finding, common to all types of solid-organ transplants, is the almost universally fatal outcome of aspergillus infection despite treatment with amphotericin B [3, 23].

**Heart-lung and lung transplantation.** Recipients of combined heart-lung transplants or of lung transplants alone develop fungal infection at a higher rate than do recipients of heart transplants alone; rates were 22% and 5%, respectively, in one series from the same institution [4], and the overall incidences range for both groups from 15% to 35% [6, 7] (table 1). Most infections are caused by Candida species (60%–100%). Other frequent causes are Aspergillus species (20%–27%) and Cryptococcus neoformans (19%–20%) [4, 6, 7]. Not uncommonly, aspergillus infection can occur concomitantly with candidal infection (range, 22–77 days) [4, 7] during the early to intermediate posttransplantation period, although aspergillus infection usually presents later (9–90 days after transplantation) [7]. Candidal infection after heart or heart-lung transplantation may be a cause of sudden death resulting either from rupture of the aortic anastomosis secondary to mycotic aneurysm [24] or from mediastinal abscesses secondary to dehiscence of airway anastomosis [7]. The overall mortality of fungal infection in heart-lung and lung transplant recipients ranges between 40% and 70% [4, 6, 7]. Donor organs are potential sources of posttransplantation pathogens, and lungs can be a reservoir of pathogenic fungi (dimorphic fungi and C. neoformans). However, infection with these organisms has seldom been described after lung transplantation [4, 6, 7]. The few cases of cryptococcal infection in one series of heart-lung and lung transplant recipients were thought to be related to inhalation of the organisms after transplantation [7].

**Liver transplantation.** Orthotopic liver transplant recipients—together with pancreas transplant recipients—have a higher incidence of severe fungal infection (especially that due to Candida) than do recipients of other types of solid-organ transplants [10, 12]. The incidence ranges between 4% and 50% [8–12, 25, 26], with fungal infections accounting for 20%–30% of all severe infections in most series [8, 11, 25, 27] (table 1). The clinical presentation differs from that described in heart or heart-lung recipients in that there is a higher incidence of intraabdominal infections (intraabdominal abscesses, peritonitis) that subsequently disseminate. In one large series 52% of fungal episodes were either intraabdominal or disseminated, while only 16% of episodes were localized to the lungs [11]. This higher incidence of intraabdominal infection correlated with the microbiology of fungal infection in these patients: Candida species caused 88.5% of infections and Aspergillus species caused 14% [16]. Similar Candida-to-Aspergillus ratios have been noted in other series [8–10, 25, 27]. Most fungal infections (85%–100% of episodes) develop within the first 2 months after liver transplantation, with high mortality (50%–77%) overall; 100% in aspergillus infection) [8, 10, 11]. As in heart and heart-lung transplantation, many of these infections are diagnosed postmortem [11].

**Pancreatic transplantation.** Pancreatic transplantation is becoming a therapeutic alternative for diabetic patients. The number of recipients and the number of medical centers performing this type of transplantation are still lower than the corresponding figures for other types of solid-organ transplantation; therefore, reports of infectious complications are sparse. Two special features of pancreatic transplantation influencing the development of fungal infection are underlying diabetic disease and the fact that the pancreas is occasionally transplanted into patients with functioning renal grafts who are already immunosuppressed. As expected, posttransplantation morbidity and complication rates are higher in combined pancreas-kidney transplantation than in kidney transplantation alone [28]. Of a series of 98 patients who underwent a total of 116 pancreatic transplantations (performed by different surgical techniques), 26 (27%) developed intraabdominal infections of all etiologies [14]. Infection with Candida species was associated with 10 (38%) of these episodes, and enteric drainage was the surgical technique followed by the highest incidence. Infection-related mortality

### Table 1. Relative incidence and microbiological features of fungal infection in solid-organ transplantation.

<table>
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<th>Parameter</th>
<th>Percentage of recipients of indicated type of transplant [reference(s)]</th>
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* Number of severe fungal infections/total number of fungal infections.
† Number of fungal infections/total number of patients.
‡ Percentage of all fungal infections.
§ Reflects only the patients in the control group and not the immunoglobulin-treated group.
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Aspergillus is unclear [14]. Intraabdominal infection led to removal of the graft in 18 of the 26 patients and resolved without graft removal in 5. In a smaller series of 16 cases of pancreatic transplantation (all performed by bladder drainage), three patients (19%) developed severe fungal infection [13]. The only fungal organism isolated in this series was Candida species, and the clinical presentations consisted of fungemia (one case) and deep abdominal wound infection requiring surgical debridement (two cases). No deaths related to fungal infection were reported in these series [13]. A constant feature of candidal infection in these patients was the high incidence of urinary tract colonization [13]. The relevance and role of such colonization in subsequent dissemination remain to be studied.

Renal transplantation. Renal transplantation is presently associated with the lowest incidence of fungal infection of all solid-organ transplantation procedures: fungi account for 5% of all infections in renal transplant recipients [29]. Three decades ago, 50% of deaths in this population were associated with this type of infection [30]. Candida species, Aspergillus species, and C. neoformans are most frequently isolated, although nearly all other types of fungal infection have also been described [31-35]. The urinary tract is the most common site of fungal infections (especially those caused by Candida)—a feature that distinguishes renal from other types of transplantation [29, 36-38]. Candidal infections may appear at any time throughout the postoperative period but are most frequent during the initial 6 months [37]. The clinical presentation is mainly one of fungemia associated with urinary tract infection, catheter-related sepsis, or esophagitis [29]. Aspergillus and Cryptococcus cause opportunistic infections during the early and later posttransplantation periods [37]. Aspergillus infection affects primarily the lungs (with occasional dissemination) and the CNS. Aspergillus, Cryptococcus, and Listeria monocytogenes account for three-quarters of all infections of the CNS in kidney recipients [37, 39].

Aspergillus infection carries the highest associated mortality in this population [30, 31, 40, 41]. In fact, the overall mortality from aspergillus infection has been 100% in large series of solid-organ transplant recipients. However, exceptions have been described in isolated case reports. In addition, the prognosis in aspergillus infection may differ with the infecting species. For example, in our liver transplantation program, we have successfully used a surgical and medical approach to treat pulmonary infection due to Aspergillus terreus but have been unsuccessful in curing infection due to Aspergillus fumigatus.

Pathogenesis

The pathogenesis of fungal infections in solid-organ transplant recipients is incompletely understood. Underlying mechanisms depend on the type of fungus, the type of transplant, the surgical technique, underlying metabolic defects, and specific immunosuppression. Aspergillus infection is acquired mainly by the inhalation of spores. Several nosocomial infections in solid-organ recipients have been associated with construction work in the immediate hospital area and with contaminated ventilation systems [3, 42-46]. Alveolar macrophages (inhibited by the administration of steroids) normally suppress the germination of inhaled spores, while functioning neutrophils eliminate residual hyphae (reviewed in [47]). Thus, both the neutropenia and the dysfunction of neutrophils and macrophages that are often documented in solid-organ transplant recipients favor the development of aspergillosis. Cell-mediated immunity, which is also affected by immunosuppressive therapy, plays a major role (together with macrophage-neutrophil function) in defense against candidal infections [48, 49]. Furthermore, conditions leading to increased candidal colonization, such as treatment with antibiotics, use of indwelling bladder or intravenous catheters, and disruption of the intestinal mucosa by surgical transplantation procedures, profoundly affect the pathogenesis of infection due to Candida species. Since most cases of candidiasis arise from endogenous sources, substantial efforts are made to eliminate or decrease the degree of colonization in solid-organ recipients. For example, heart-lung transplant recipients have a high incidence of candidal colonization of tracheal and bronchial secretions; this condition probably originates from the donor trachea. Measures reducing such colonization result in a decreased incidence of severe candidal infections [8]. Likewise, colonization of the gastrointestinal tract is a potential source of intraabdominal or disseminated infection in those patients whose organ transplantation surgery requires disruption of the intestinal mucosa (i.e., those undergoing orthotopic hepatic or pancreatic transplantation). The donor duodenal segment is frequently colonized with Candida [50] and thus is a possible source of infection for both liver and pancreas recipients.

In the case of pancreatic transplantation, pancreatic exocrine secretions into the bowel are potential sources of infection with enteric flora [51, 52] and serve as a good culture medium for certain microorganisms [53]. This situation could explain the high incidence of urinary candidal colonization in pancreas recipients, whose pancreatic exocrine secretions drain into the bladder, creating a nonacidic environment that favors candidal colonization [13]. However, this possible effect may be difficult to disentangle from the role played by indwelling bladder catheters. The defective killing of C. albicans by granulocytes in diabetic patients [54] aggravates the problem. Therefore, pancreatic transplant recipients are highly susceptible to candidal infection [31].

In liver transplantation, surgery disrupts the biliary tract and small bowel, allowing the release of Candida microorganisms [10]. Fungal translocation across the intestinal mucosa is also a source of endogenous contamination [55-57]. In experimental models, obstructive jaundice is associated with increased candidal dissemination [58]. Antifungal prophyl-
Catheter-related sepsis is a common presentation of fungal infection in recipients of solid-organ transplants. Once more, the data available on this topic are mainly for neutropenic recipients of bone marrow, in whom the underlying risk factors for development of catheter-related sepsis may be somewhat different from those affecting solid-organ transplant recipients. Prolonged periods of neutropenia and long-term indwelling central venous catheterization are unusual in the latter group. Catheter-related sepsis of fungal etiology (Candida species) in solid-organ recipients is most often associated with prolonged hospitalization (especially in intensive care units) and originates from short central venous catheters rather than from Hickman catheters. As in other types of immunocompromised patients [60–62], management should include prompt removal of the suspect catheter and antifungal therapy with amphotericin B or fluconazole.

The significance of fungemia in solid-organ transplant recipients also remains to be studied. Candidemia in immunocompromised patients is associated with mortality of >50% [63–65]. Prompt initiation of antifungal therapy has improved the outcome of fungemia in some studies [63, 64]. In others the outcome of candidemia has been the same with or without treatment [66]. (The promptness with which therapy is initiated may play a significant role in the differences observed among these studies.) The clinical relevance of in vitro susceptibility testing of Candida isolates from the blood remains unknown. Blood isolates for which MICs of amphotericin B are >0.8 μg/mL are associated with higher mortality [67, 68]. The use of liposomal amphotericin B or fluconazole in the treatment of fungemia involving “resistant” isolates warrants further study. Because candidemia in immunocompromised individuals can involve not only C. albicans but also Candida kruzei or Candida tropicalis [69], therapy with fluconazole (which is relatively inactive against C. kruzei) should not be started unless the fungus has been identified. Surveillance cultures [70] may be useful in decisions about whether to start antifungal therapy for certain types of candidal infections. A single episode of fungemia should not be disregarded because it is considered to represent transient colonization or contamination. In one study of immunocompromised patients (not solid-organ recipients), fungemia documented by a single isolate of Candida species carried the same prognosis as fungemia documented by multiple positive blood cultures [69]. Again, relevant information is lacking for the solid-organ recipient population, and information for other immunocompromised patients must therefore serve as a general guideline.

**Risk Factors**

Identification of specific risk factors predisposing to fungal infection in solid-organ recipients is of critical importance. This information would facilitate the selective targeting of certain patients for specific prophylaxis, thereby reducing the incidence of fungal infection and its resultant morbidity and mortality. In several studies of bone-marrow transplant recipients, risk factors for severe fungal infections have been identified [71–73]. Such information is not widely available for solid-organ recipients other than those undergoing orthotopic liver transplantation, in whom the following risk factors were identified by means of univariate statistical analysis: preoperative administration of steroids and antibiotics, prolonged duration of surgery, administration of steroid boluses for the treatment of allograft rejection during the first 2 months after transplantation, and prolonged antibiotic use after transplantation [10]. In a study of 101 liver transplant recipients, all 18 fungal episodes (14 caused by Candida) developed in patients whose duration of surgery was >12 hours and who received prolonged antibiotic therapy after—but not before—transplantation [8]. In another study of 42 liver transplant recipients, additional risk factors were identified for the 9 cases of severe fungal infection: high preoperative serum albumin level, biliary atresia, prolonged mean time in the intensive care unit after transplantation, gastrointestinal or vascular complications, age of >20 years, and hemodialysis after transplantation [25]. In yet another study of risk factors, 355 liver transplantations were analyzed: 91 fungal infections developed in 72 patients [11]. By univariate analysis, 23 risk factors (out of a possible 38 pre-, intra-, and posttransplantation factors) were identified. These included some factors already mentioned. However, this study provided novel confirmatory data obtained by multivariate analysis. Of the 23 variables identified as significant by means of univariate analysis, only the following were also identified in the multivariate analysis: retransplantation, reintubation, urgent clinical status at the time of transplantation, high risk score, requirement for intraoperative transfusion, method of biliary reconstruction, steroid use after transplantation, bacterial infections after transplantation, antibiotic use after transplantation, and vascular complications [11]. Since the majority (88.5%) of fungal infections were caused by Candida species, these risk factors are probably applicable mainly to the development of candidiasis.

In other types of solid-organ transplantation, extensive studies of risk factors are lacking. Prolonged antibiotic use favors the development of fungal infection in heart-lung transplant recipients [4], as do bacterial infections in heart recipients [3] and antirejection treatment and underlying diabetes mellitus in kidney recipients [31]. These identified risk factors contrast with those in other immunocompromised patients; for example, in leukemic patients undergoing bone marrow transplantation, the duration of neutropenia is a primary risk factor for infections due to Aspergillus and Candida [69, 71–73].

**Immunosuppressive therapy.** The immunosuppressive therapy that has been administered may be a possible additive risk factor for fungal infection. Since the introduction of
cyclosporine, survival after and outcome of solid-organ transplantation have significantly improved [74, 75]. However, it is still uncertain whether these improvements are due to a decrease in the incidence of severe infection, especially fungal infection. A review of 10 series of cases (nine consisting of kidney recipients and one consisting of heart recipients) indicated that, compared with azathioprine and prednisone with or without antithymocyte globulin or antilymphocyte globulin, cyclosporine results in a lower incidence of bacterial and viral infections but not of fungal infections [76]. Heart transplant recipients treated with cyclosporine—compared with matched controls given a conventional regimen of azathioprine, prednisone, and antithymocyte globulin—had an overall reduction in the rates of bacterial, viral, and protozoan infections as well as in infection-related mortality. However, no statistically significant difference in the incidence of fungal infections (all caused by Aspergillus and Candida) was found [3]. Results have been similar in other studies of heart transplantation [15, 16, 77].

Muromonab-CD3 is currently being used as a prophylactic immunosuppressive agent. Preliminary reports have not documented an increase in fungal infection with its use [17].

Infection with cytomegalovirus (CMV). Infection caused by CMV leads to superinfection with other opportunistic organisms in transplant recipients [18, 19, 71] and in animal models [20, 21] and therefore may be an added risk factor for fungal infection. Measures reducing the incidence of CMV infections after transplantation may indirectly reduce the incidence of fungal infections as well. Studies in which prophylaxis with immunoglobulin is given in an attempt to reduce the incidence of CMV infection show a decrease in the rate of fungal infection among bone marrow and kidney recipients [22, 78]. Whether this decrease is due to a decrease in the rate of some forms of CMV infection (as seen in these studies) or to an effect (direct or indirect) of γ-globulin on fungal infection remains unknown. Studies of prophylaxis with antiviral compounds that decrease the incidence of CMV infections have not yet addressed the issue of possible reductions in the incidence of other opportunistic infections, such as those caused by fungi.

Diagnosis

Since in a large number of cases the diagnosis of severe fungal infection is established only post-mortem, the clinician must maintain a high index of suspicion and, in the face of appropriate evidence, consider starting empirical therapy with antifungal agents [79, 80]. The relative value of the different techniques, such as open-lung biopsy, bronchoalveolar lavage, and fine-needle aspiration, for the diagnosis of pulmonary fungal infection in the immunocompromised host (reviewed in [42, 43, 48, 73, 81]) has not been formally evaluated in solid-organ recipients; the guidelines established for other types of immunocompromised patients are followed and will not be discussed here.

The development of new diagnostic methods that detect fungal antigen in serum and other body fluids at an early stage of fungal infection has so far had little impact on the clinical management of solid-organ recipients. The detection of Candida antigen in the serum of immunocompromised patients (bone marrow transplant recipients or neutropenic patients) and in burned patients has so far had relatively low utility [82-84]. The latex test has a sensitivity of 54% and a specificity of 29% [82]. The Cand-tec detection test (Ramco Laboratories, Houston) in neutropenic patients has a sensitivity of 76% and a specificity of 93% [83]. In one study of bone marrow recipients, the positive and negative predictive values of Candida antigen detection were 100% and 97%, respectively [85]. With regard to solid-organ recipients, Candida antigen was detected in eight of nine liver transplant patients with deep fungal infection and in none of the 20 patients who were not infected [86]. The clinical usefulness of Aspergillus antigen detection in serum is being studied, mainly in bone marrow recipients and neutropenic patients. Its sensitivity and specificity are 75% and 100%, respectively [87], and its positive and negative predictive values for pulmonary and disseminated aspergillosis are ~95% [88, 89].

Surveillance Cultures

Surveillance cultures are routinely undertaken in some solid-organ transplantation programs; however, their predictive value, especially in fungal infection, remains unknown. Heart-lung, pancreas, and liver recipients are often colonized with Candida organisms; even though most patients who develop a deep candidal infection are known to have been previously colonized, many colonized patients do not develop infection. The clinical value of surveillance cultures for the early diagnosis of deep candidal infection has been studied primarily in bone marrow recipients. The results indicate a good negative predictive value but a poor positive predictive value for C. albicans infection [85, 90] as well as good negative and positive predictive values for infection with other species, such as C. tropicalis [85]. In liver transplant recipients, colonization with C. albicans in three or more sites does not appear to correlate with deep fungal infection: surveillance cultures were positive in eight of 11 cases in which deep candidal infection developed but also in eight of 16 cases in which it did not—for a sensitivity of 78% but a specificity of only 50% [86]. Strain typing by DNA fingerprinting has indicated that the isolate causing infection is previously present in the colonizing flora [70].

Treatment

Treatment of deep fungal infections in solid-organ recipients does not differ significantly from that in other types of immunocompromised hosts, although special considerations apply. Except for candidiasis and aspergillosis, fungal infections (mucormycosis, cryptococcosis, blastomycosis, and his-
Amphotericin B. Intravenous amphotericin B has been the mainstay of treatment for deep candidal infection, aspergillosis, and cryptococcosis [94, 95]. Although this agent is effective in certain cases, its use in solid-organ transplantation is associated with undesirable side effects. In addition to bone marrow toxicity (which may aggravate or be confused with that caused by azathioprine or CMV infection), nephrotoxicity is common. This condition is reversible by means of drug discontinuation or salt loading in other immunosuppressed patients [96, 97], but solid-organ transplant patients requiring treatment with amphotericin B may already have impaired renal function and may already be receiving a variety of drugs (such as cyclosporine) that—by themselves or in association with amphotericin B—can potentiate renal toxicity. The interaction of cyclosporine and amphotericin B has been associated with acute renal failure [76, 98], and amphotericin B may increase plasma levels of cyclosporine [99]. This situation is especially important in kidney recipients, who are more vulnerable than other types of solid-organ recipients to renal dysfunction caused by allograft rejection. Thus nephrotoxicity secondary to treatment with amphotericin B needs to be differentiated from that induced by drugs such as cyclosporine, by allograft rejection, and occasionally by CMV infection.

The liposomal form of amphotericin B appears to have fewer adverse effects at equivalent doses and thus can be allowed to reach presumably much higher serum and tissue concentrations [100]. No difference between in vitro susceptibility to conventional amphotericin B and that to the liposomal drug has been found for the different fungal strains [101, 102]. Open trials of liposomal amphotericin B in neutropenic patients and bone marrow recipient show—in comparison with the conventional drug—a similar or improved efficacy profile with a lower incidence of side effects in the treatment of infections due to Candida and Aspergillus species [100, 103–110]; in contrast, descriptions of isolated cases of cryptococcal meningoitis in patients with AIDS indicate that the efficacy of liposomal amphotericin B is not ideal [111]. Its safety profile in solid-organ transplantation and its expected efficacy in the treatment of severe infections caused by Aspergillus, Candida, and Cryptococcus species remain to be evaluated. Preliminary reports indicate that this agent may be clinically useful in some types of solid-organ transplantation ([112, 113] and author's unpublished observations). Liposomal amphotericin B may be a valid alternative for the treatment of candidal urinary tract infection [114] in recipients of renal and pancreatic (bladder drainage) transplants.

5-Fluorocytosine combined with amphotericin B for 6 weeks is indicated for the treatment of cryptococcal meningitis [115, 116], which—after candidiasis and aspergillosis—is the most common type of fungal infection among organ transplant recipients. The role of fluconazole as an alternative to this combination therapy is currently being evaluated. Ketoconazole, itraconazole, and fluconazole. Ketoconazole, an oral broad-spectrum antifungal drug, has little role in solid-organ transplantation since it is not indicated for the treatment of invasive candidiasis or aspergillosis in immunocompromised patients [92]. This drug is effective in therapy for North American mycoses (blastomycosis, coccidioidomycosis, and histoplasmosis), but these infections are not predominant among transplant recipients. Moreover, the use of ketoconazole in the treatment of the latter fungal infections in immunocompromised patients is associated with an increased rate of relapse as compared with amphotericin B [117]. Ketoconazole can cause liver dysfunction [118–120]; this complication is encountered especially often in the management of liver transplant recipients. Ketoconazole also interacts with cyclosporine, increasing the plasma levels of the latter drug by blocking the cytochrome P-450 system or by displacing the protein-bound fraction [121–124].

Itraconazole, another oral imidazole, is active against Aspergillus species but exhibits poor CNS penetration (reviewed in [125]). Itraconazole interacts with cyclosporine to a lesser degree than does ketoconazole [76], although it has been reported to increase plasma levels of cyclosporine [126]. In preliminary, unrandomized clinical trials, itraconazole has appeared to be somewhat efficacious against aspergillosis infections in immunocompromised patients [94, 127, 128]. Studies comparing itraconazole with liposomal amphotericin B in terms of safety and efficacy for the treatment of aspergillosis in solid-organ transplant recipients remain to be done.

Because of its excellent pharmacokinetic properties, its low incidence of side effects, and its minimal interference with cyclosporine, fluconazole is a potentially useful compound in solid-organ transplantation. Unlike the other azoles, fluconazole has a low protein-binding capacity (11%), is excreted mainly via the kidneys, and effectively penetrates the CNS [129]. Its antifungal spectrum, both in vitro and in vivo, covers C. albicans and C. neoformans. Even though fluconazole exhibits poor in vitro activity against Aspergillus species, animal models of disseminated aspergillosis show that this agent is somewhat effective in controlling this infection [130–132]. No clinical data yet support the use of fluconazole in human aspergillosis. Studies of surgical patients and of immunocompromised patients (mainly those with AIDS) show fluconazole to be effective for the treatment of oral and esophageal candidiasis, cryptococcal meningitis, and deep-seated candidal infections [133–138]. The safety and efficacy of this agent in solid-organ transplantation have not been formally evaluated. One report on the administration of fluconazole to two pancreas recipients and one kidney recipient in whom nephrotoxicity was a major block to
the use of amphotericin B indicated that this drug was effective against invasive candidiasis (which developed in two patients), allowing the preservation of the transplanted organ and causing no significant adverse reactions [139]. A major advantage of fluconazole is its minimal interference with cyclosporine; fluconazole has only a very minor effect on the hepatic cytochrome P-450 system [140–142], although increased plasma levels of cyclosporine have been reported with its use [143, 144]. One important issue in the treatment of candidal infection with fluconazole is that certain species, such as *C. krusei*, exhibit a low level of susceptibility in vitro. Although experimental models indicate some efficacy of fluconazole against *C. krusei* [145], emergence of this species after fluconazole treatment has been reported in immunocompromised patients [146]. Because *C. krusei* infections are not uncommon in neutropenic patients [69] and because the incidence of infection caused by this species in solid-organ recipients is unknown, empirical treatment with fluconazole for a presumed candidal infection should be undertaken with caution.

Research on new antifungal compounds continues. Saperconazole, a triazole with potent activity against *Aspergillus* species in vitro and in immunosuppressed animal models [147, 148], is in the preliminary stages of development. The evaluation of cilofungin, another experimental drug with excellent activity against *Candida* species [149], has been discontinued because of the development of hepatocarcinoma in rodents during studies of carcinogenesis (J. Albrecht, personal communication).

Immunotherapy complementing treatment with antifungal drugs needs further evaluation. The activation of macrophages in vitro by interferon γ results in antifungal killing [150]. Although interferon γ is potentially useful against fungal infection, its positive immunomodulatory role—with a subsequent increase in allograft rejection—is a source of concern [151]. Colony-stimulating factors, such as granulocyte-macrophage colony-stimulating factor, can boost the turnover and function of monocytes and neutrophils [152–154]; the role of these factors in vivo in defense against fungal infections needs to be evaluated in immunocompromised patients. Likewise, combinations of antifungal drugs with immunoglobulin preparations or antifungal monoclonal antibodies may merit further study. Experimental models show enhanced efficacy when antibodies to *Candida* are linked to amphotericin B–carrying liposomes [155].

**Prophylaxis**

Prophylaxis of severe fungal infections should be a high priority in the management of solid-organ transplant recipients. Risk factors for fungal infection in each type of solid-organ transplantation need to be identified. Those patients with specific risk factors should be monitored especially carefully, with a high index of suspicion.

Protective isolation has not been as extensively studied for solid-organ recipients as for bone marrow recipients; in the latter patients this type of isolation—together with laminar airflow—reduces the incidence of severe infections, especially those caused by *Aspergillus* species [43, 72, 156, 157]. In one comparative study of renal transplantation, patients hospitalized in areas with high-efficiency particulate air (HEPA) filters had a lower incidence of invasive aspergillosis and of colonization with *Aspergillus* than did control patients (5% vs. 18% and 3% vs. 8%, respectively) [43]. Protective isolation, as the sole prophylactic measure, failed to protect heart transplant recipients from the development of a variety of severe infections, including fungal infections [158].

Most studies evaluating the safety and efficacy of antifungal drug prophylaxis have involved bone marrow recipients rather than solid-organ recipients (reviewed in [156, 157]). As has already been discussed, special risk factors and underlying pathogenic mechanisms make these two populations different. Nonetheless, transplantation centers have applied the experience gathered from bone marrow recipients and from patients with cancer and have introduced prophylactic regimens into their management programs for solid-organ recipients. Nystatin and amphotericin B are two nonabsorbable antifungal polymers that eradicate colonizing *Candida* from the human gastrointestinal tract. Even though the minimal dose of nystatin reputed to eradicate yeasts from the digestive tract is 4.5 million IU/d, doses as high as 30 million IU/d have sometimes been clinically ineffective [159, 160]. Clearance of yeasts from the oropharynx appears to be easier than clearance from the lower gastrointestinal tract [161, 162]. In one study of liver transplantation, the administration of nystatin as part of a prophylactic program of selective bowel decontamination was associated with a low incidence of fungal infection, correlating with decreased candidal colonization in both the upper and the lower portions of the gastrointestinal tract [59]. Because this study was not randomized, it is difficult to delineate the role of nystatin; the incidence of gram-negative bacterial infections also decreased, and this change probably led to the administration of less antibacterial therapy. Oral amphotericin B gives better results than nystatin in leukemic patients and bone marrow recipients [163]. Doses of amphotericin B as high as 1,500 mg/d may be required to eradicate *Candida* species from the lower gastrointestinal tract [159, 164]; however, both high and low prophylactic doses can fail [164, 165].

Once more, the efficacy of oral agents such as nystatin and amphotericin B in solid-organ transplantation remains to be evaluated in prospective randomized studies, and the data available supporting the use of these agents come from studies of other immunocompromised patients. Intravenous administration of amphotericin B to febrile neutropenic patients who are not responding to antibacterial agents [79, 80] needs to be assessed individually in solid-organ transplant recipients, with special consideration of the time of onset of fever after transplantation and of specific underlying risk fac-
tors. The use of amphotericin B as a prophylactic agent in liver transplantation is currently being analyzed [166].

As prophylaxis of candidal infections, ketoconazole has been evaluated in leukemic patients and bone marrow transplant recipients but not in solid-organ recipients [163, 164, 167–170]. Its need for an acidic gastric pH for absorption and its interaction with cyclosporine make ketoconazole less than ideal for prophylaxis in these groups of patients. Clotrimazole troches have been reported to be effective in preventing oral candidal colonization and infection in renal transplant recipients [171].

Fluconazole, whose use is in many respects more convenient than that of ketoconazole, may be superior for prophylaxis against candidal and cryptococcal infection in solid-organ transplant recipients [172, 173]. Its efficacy in preventing relapse and dissemination of cryptococcal meningitis in patients with AIDS [174, 175] may be of practical importance in certain isolated cases of solid-organ transplantation. Randomized trials are under way to evaluate the safety and efficacy of fluconazole in the prevention of deep fungal infections in orthotopic liver transplantation. Once more, the emergence of Candida species resistant to fluconazole (e.g., C. krusei) is of great concern in any clinical situation in which this drug is being administered prophylactically for prolonged periods to patients with multiple risk factors for severe candidal infections [176]. In a recent randomized, placebo-controlled study of bone marrow recipients, fluconazole was effective for prophylaxis of infections due to all Candida species except C. krusei [177]. However, the increased incidence of C. krusei infections did not result in increased mortality.

Itraconazole has not been evaluated in the prophylaxis of aspergillus infections in solid-organ transplant recipients. However, studies in progress are assessing the efficacy of this agent in the prophylaxis of infections due to Candida and Aspergillus species in cancer patients [178, 179].

New applications of established drugs (e.g., the intranasal administration of amphotericin) are being studied in other types of immunocompromised patients [43, 156, 165, 180] and will need to be evaluated in solid-organ transplant recipients as well. Moreover, the administration of amphotericin B in an aerosol formulation merits further study. Preliminary assessments in experimental models and in granulocytopenic patients suggest that the latter route of administration may be effective in the prophylaxis of aspergillus infection [181, 182]. Other experimental antifungal agents are being evaluated for prophylaxis in animal models [183]. The use of prophylactic immunoglobulin in solid-organ transplantation appears to decrease the incidence of fungal infection. In one study of renal transplant recipients with high titers of antibody to CMV, immunoglobulin administration decreased the incidence of fungal infection [22]; results were similar in a study of bone marrow recipients [78].

Conclusion

In summary, the incidence and severity of fungal infections may decrease in the future as the result of a knowledge of the specific risk factors for each type of transplant recipient; a high index of suspicion of fungal infection, with the application of rapid and aggressive diagnostic methods; and the use of highly specific antifungal prophylactic agents that cause little toxicity and that interact minimally with other drugs given to transplant recipients.

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