Fungal Infections in Solid Organ Transplant Recipients

Peter G. Pappas

Organ transplantation is an effective life-sparing modality for thousands of patients with organ failure syndromes. In spite of important advances in surgical technique and immunosuppressive regimens that have made organ transplantation a safer procedure today when compared to previous decades, there remain substantial risks of infection and other complications related to these procedures. Among the infectious complications of organ transplantation, none is associated with a greater impact on morbidity and mortality than invasive fungal infections (IFI) [1–5]. Fungal infections in organ transplant recipients (OTRs) vary in frequency, etiology, and pathogenesis according to the type of organ transplant procedure. Variations in immunosuppressive regimens, surgical technique, infection control, and exposure history further complicate evaluation of these patients. Moreover, the incidence of IFIs among this group of patients varies considerably from center to center [6].

The clinician is faced with a number of diagnostic and therapeutic challenges in approaching a transplant recipient who has a possible IFI. First, there is a lack of sensitive and specific diagnostic assays that might lead to early intervention. Second, antifungal therapy is frequently associated with dose-limiting toxicity. Third, significant potential for drug–drug interactions exists between existing antifungal agents and immunosuppressive agents. Fourth, only limited data are available that facilitate early identification of patients who are at the highest risk for IFI within each transplant group. This chapter describes risk factors for developing IFIs among OTRs, reviews the specific fungal pathogens, and discusses an approach to the diagnosis, therapy, and prevention of these potentially devastating infections.

P.G. Pappas (✉)
Division of Infectious Diseases, University of Alabama at Birmingham School of Medicine, Birmingham, AL USA
e-mail: pappas@uab.edu

Determining the "Net State of Immunosuppression"

As advanced by Rubin [7] and Fishman [8], the concept of "net state of immunosuppression" is a useful, albeit vague, assessment of the overall risk of infection in the OTR. Quantitation of this risk in a reliable and reproducible manner is difficult. Assessing the net state of immunosuppression encompasses a number of host and environmental factors, each of which can impact host defense (Table 1). Included among these factors are dose, duration, and temporal sequence of specific immunosuppressive agents; underlying immune deficiency such as autoimmune disease and other functional immune deficits; integrity of the mucocutaneous barrier; anatomic abnormalities, such as devitalized tissue and fluid collections; neutropenia and lymphopenia; underlying metabolic conditions, such as renal insufficiency, malnutrition, diabetes mellitus, hepatic failure; and infection with immunomodulating viruses such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis B and C viruses, human herpes virus (HHV-6), and human immunodeficiency virus (HIV) [7, 8].

While this approach is a useful guide to the assessment of risk for infection in OTRs, it does not take into account specific risk factors related to different organ transplants and/or to variations in surgical technique, intraoperative time, and use of blood products. A gross estimate of overall immunologic impairment can be made, but it does not provide a specific means by which the physician might more accurately determine the risk of IFI.

Specific Factors Associated with Invasive Fungal Infection in Organ Transplant Recipients

The development of IFI following solid organ transplantation is influenced by a number of different variables. These include the type and timing of the organ transplant; the

C.A. Kauffman et al. (eds.), *Essentials of Clinical Mycology*,
DOI 10.1007/978-1-4419-6640-7_30,

Table 1 Factors influencing the net state of immunosuppression in solid organ transplant recipients (Adapted from [8])

Immunosuppressive therapy
Dose and duration of individual agents
Recent rejection episodes
Use of antithymocyte globulin, total nodal irritation
Underlying immune disorders
Autoimmune disease
Antibody deficiency, complement deficiency, and other functional immune defects
Integrity of mucocutaneous barrier
Devitalized tissue, undrained fluid collections, hematomas
Neutropenia, lymphopenia
Metabolic conditions
Acute or chronic renal failure
Hepatic failure
Malnutrition
Diabetes mellitus
Alcoholism
Metabolic acidosis
Chronic viral infections
BK virus
Cytomegalovirus
Epstein-Barr virus
Hepatitis B and C viruses
Human herpesvirus 6
Human immunodeficiency virus types 1 and 2
Human T cell lymphotrophic virus type 1

specific immunosuppressive regimen, including the timing and frequency of rejection episodes; donor-transmitted infections; comorbid conditions and coinfections in the recipient, especially viral infections; perioperative fungal colonization; and other factors, including previous exposure and recent epidemiology. Each of these variables is discussed below.

Type of Solid Organ Transplant

The risk of IFI depends on the organ transplanted. Moreover, distribution of causative organisms also varies with the type of transplant [1–6, 8, 9]. Some risk factors, such as retransplantation, prolonged ICU stay with mechanical ventilation, requirement for surgical reexploration, primary graft nonfunction, and active CMV infection, are common to all OTRs. Other risk factors are specific to the type of transplant, and may relate to the type of anastomosis, differences in intensity of immunosuppression, or other variables. The distribution of infection by type and proportion of individual IFI according to the type of transplant for the TRANSNET prospective surveillance study conducted from 2001 to 2006 is demonstrated in Table 2 [6].

Kidney

Kidney transplantation is associated with the least risk of IFI. The published cumulative incidence of IFI following renal transplantation varies between 2% and 14% [10–12], but the most recent data from the multicenter TRANSNET surveillance study suggests that the 12-month cumulative incidence for IFI is 1.3% [6]. The most common fungi causing infection in renal transplant recipients are *Candida* species, *Aspergillus* species, and *Cryptococcus neoformans* [6, 10–12]. In geographic regions in which *Histoplasma capsulatum* and *Coccidioides* species are endemic, these organisms can also be important pathogens in the posttransplant period [13–15]. The TRANSNET study and sporadic reports support a significant role for infections due to *Fusarium* species and other hyalohyphomycetes, the zygomycetes, *Trichosporon asahii* and other pathogenic yeasts, and the dematiaceous fungi [6, 16–19].

Candida infection may be mucocutaneous, urinary, or deeply invasive. Factors predisposing to urinary tract infection include bladder catheterization, structural abnormalities or disruption of urinary flow, corticosteroids, and diabetes mellitus. Asymptomatic urinary tract colonization with *Candida* species is particularly common in renal transplant recipients and can be associated with significant consequences. Renal parenchymal disease may result from ascending infection from the bladder [20]. Rarely, urinary tract colonization can be associated with the development of a ureteral fungus ball, leading to obstruction of urinary flow and threatening allograft survival. Nosocomial candidemia in renal transplant recipients is most commonly associated with recognized risk factors, such as indwelling venous catheters, that are related to infection among nontransplanted patients and can occasionally lead to secondary involvement of the allograft from hematogenous spread [20].

Risk factors for the development of invasive aspergillosis are less well established in renal transplant patients. Underlying diabetes mellitus, cadaveric allograft, increased corticosteroid usage, retransplantation, and recent CMV infection have been associated with invasive aspergillosis [21–23]. Involvement of the lungs or disseminated multiorgan disease is most common, but focal extrapulmonary disease, e.g., cerebral abscess [24, 25], endocarditis [26], tuboovarian abscess [27, 28], and focal prostatic or ureteral involvement, [29, 30], has been reported.

C. neoformans is the third most common invasive fungal pathogen reported among renal transplant recipients, occurring in as many as 2% of patients [6, 31, 32]. Zygomycoses, phaeohyphomycoses, and hyalohyphomycoses are much less commonly reported. Risk factors for the development of these infections are poorly defined, but most occur beyond 4–6 months posttransplantation and are often associated with chronic allograft rejection and intense immunosuppression [1–6, 10].

Table 2 Percent of invasive fungal infection cases stratified by organism/group, according to transplant type in the surveillance cohort [6]

IFI type	Kidney	Liver	Pancreas	Lung	Heart	Sm. bowel
Candidiasis	164 (49)[a]	255 (68)	97 (76)	56 (23)	48 (49)	19 (85)
Aspergillosis	47 (14)	42 (11)	6 (5)	109 (44)	23 (23)	0 (0)
Zygomycosis	8 (2)	9 (2)	0 (0)	8 (3)	3 (3)	0 (0)
Other moulds	10 (3.0)	9 (2.4)	4 (3.1)	49 (19.8)	7 (7.1)	0 (0)
Unspecified moulds	7 (2.1)	8 (2.1)	0 (0)	7 (2.8)	2 (2.0)	0 (0)
Cryptococcosis	49 (15)	24 (6)	6 (5)	6 (2)	10 (10)	1 (5)
Endemic mycoses	33 (10)	17 (5)	8 (6)	3 (1)	3 (3)	0 (0)
Pneumocystosis	5 (1)	0 (0)	1 (1)	4 (2)	3 (3)	0 (0)
Other yeast	6 (1.8)	9 (2.4)	5 (3.9)	0 (0)	0 (0)	1 (4.6)
Unspecified yeast	3 (0.9)	5 (1.3)	1 (0.8)	6 (2.4)	0 (0)	1 (4.6)
Total IFI cases	332	378	128	248	99	22

[a]Number in parentheses represent percent of total for each organ type

Pancreas and Kidney–Pancreas

Invasive fungal infections among pancreas and kidney–pancreas transplant recipients occur much more frequently than among renal transplant recipients. Historically, the cumulative incidence of IFIs in this group has ranged between 6% and 38% [1–5]; TRANSNET demonstrated a 4% incidence in this group [6]. Most of these infections are due to *Candida* species [1, 6, 33, 34], with a much smaller proportion secondary to cryptococcosis, aspergillosis., and non-*Aspergillus* moulds [6, 33, 35].

The increased risk of IFI in this group largely relates to surgical and technical issues. Specifically, the type of surgical anastomosis can be associated with local complications and *Candida* superinfection [34–37]. Bladder-drained pancreas transplants are associated with a much higher incidence of urinary tract infections due to all causes, but especially due to *Candida* species. In contrast, enterically drained pancreatic transplants are much more likely to develop enteric leaks leading to polymicrobial intraabdominal infections in which *Candida* is an important pathogen [37]. Some experts disagree as to which of these two anastomotic and drainage procedures leads to fewer postoperative fungal infections, as the published data vary according to center. As with other OTRs, the risk of IFI is significantly greater among patients with recent CMV infection, graft rejection or failure, surgical reoperation, higher dose immunosuppression (especially corticosteroids), and bacterial coinfection.

Liver

The risk of IFI among liver transplant recipients has traditionally been very high, with a cumulative incidence of up to 42% [38]. The incidence of IFI has declined in recent years [5, 9], and the TRANSNET study demonstrated a 12-month incidence of only 4.7% [6]. Improvements in surgical technique, immunosuppressive regimens, and improved patient selection have contributed to this decrease. The majority of IFIs in liver transplant recipients are caused by *Candida* species with the peak incidence in the first month posttransplant [5, 6]. Aspergillosis, cryptococcosis, and mucormycosis also are commonly recognized in this population [12, 39–46].

Risk factors for the development of IFI have been best defined in the liver transplant population. In the study by Collins and colleagues, several important and independent variables were related to increased risk of fungal infection in the posttransplant period [47]. These included baseline creatinine >3 mg/dL, operative time >11 h, retransplantation, active CMV infection, and an intraoperative requirement of >40 units of blood products. The risk of fungal infection was 1% without any risk factor, compared to 67% among patients with two or more of these risk factors [47]. In addition, choledochojejunostomy anastomosis and early colonization with a fungal pathogen were strongly associated with the development of IFI in this study. Others have identified similar trends among liver transplant recipients and have consistently related prolonged intraoperative time, requirement for a large number of blood products, CMV infection, and choledochojejunostomy anastomosis to an increased risk of developing IFI [48, 49].

Heart

There is a modest risk of IFI following heart transplantation. The reported rate of occurrence ranges from 4% to 35% [50, 51], although recent reports consistently demonstrate an overall rate <10% [52]. TRANSNET observed an incidence of 3.4% [6]. *Candida* species account for at least two-thirds of the fungal infections; invasive aspergillosis is somewhat more common in heart compared to liver and kidney transplant recipients for reasons probably related to the increased intensity of immunosuppression [52].

Invasive *Candida* infections among heart transplant recipients are usually limited to candidemia and its complications. In addition, preexisting colonization with *Candida* species of ventricular assist devices is an established risk factor for the subsequent development of invasive *Candida* infection

[53, 54]. Mediastinitis due to *Candida* is an uncommon postoperative complication. Active CMV infection, the use of antilymphocyte antibodies, and treatment for rejection are the most common risk factors associated with IFI in heart transplant recipients.

Lung and Heart-Lung

In most recent studies, the incidence of IFI in lung and heart-lung transplant recipients is among the highest of all OTRs [55–57]. The cumulative incidence among this group of transplant recipients from smaller studies ranged between 10% and 36%; the TRANSNET data demonstrated a 12-month incidence of 8.6% [6]. *Aspergillus* species have emerged as dominant pathogens in this population [55–59]. In the TRANSNET study, invasive aspergillosis accounted for 44% of IFIs among lung and heart-lung recipients [6].

Invasive aspergillosis occurs in between 3.3% and 16% of lung and heart-lung recipients in different studies [55–61]. The enhanced risk of developing invasive aspergillosis among lung transplant recipients probably relates to several factors: prior airway colonization with *Aspergillus* species [60]; CMV infection [61]; environmental exposure through routine daily activities; and hypogammoglobulinemia [62]. Smoking substances such as marijuana is an additional risk [63]. Furthermore, patients with single lung transplants appear to have a greater risk of invasive aspergillosis than double lung transplants, a risk that is likely due to colonization with *Aspergillus* species in the remaining native lung [59]. Interestingly, preexisting *Aspergillus* species and *Scedosporium* colonization among patients with cystic fibrosis is not associated with a significantly increased risk of IFI due to these organisms posttransplantation [64, 65]. In fact, among all lung transplant recipients, those with cystic fibrosis appear to be at somewhat less risk of invasive mould disease than other lung transplant recipients.

Candida infections complicating lung transplantation include candidemia, mycotic aneurysm involving the vascular anastomoses, mediastinal wound infection, and necrotizing bronchitis at the tracheal anastomotic site [51, 66–68].

Pneumocystis jiroveci pneumonia (PCP) can occur in all OTRs, but appears to be most common in lung and heart recipients [69]. *P. jiroveci* pneumonia has become uncommon owing to the widespread use of trimethoprim/sulfamethoxazole (TMP/SMX) prophylaxis.

Small Bowel

The highest risk of IFI following organ transplantation occurs among small bowel recipients, with an incidence ranging from a low of 11.6% in TRANSNET [6], to as high as 59% [70, 71]. In addition to risk factors common to other OTRs, intraoperative complications include small bowel anastomotic leaks as a unique risk factor associated with this type of transplantation. Not surprisingly, *Candida* species constitute the majority of fungal pathogens in small bowel transplant recipients, with *Aspergillus* and other moulds playing less of a role. Prospective data among small bowel transplant patients are limited given the relative rarity of this transplant procedure, which has largely been limited to children with congenital small bowel disorders and highly selected adult patients.

Timing of Invasive Fungal Infection Following Organ Transplantation

In spite of differences in frequency and distribution of pathogens among the various transplant groups, the timing of these infections following organ transplantation is similar. As such, the posttransplant period can be generally divided into three intervals when assessing the risk and type of IFI: 0–1 month, 1–6 months, and beyond 6 months posttransplant. Understanding the temporal relatedness of the posttransplant interval to the risk and type of IFI can be very useful to the clinician in formulating a diagnosis and guiding empiric therapy. It also highlights the differences in pathogenesis for IFI during these intervals [1, 6, 8, 9].

Infections in the first month posttransplant are dominated by *Candida* species and are usually related to technical and surgical issues in addition to traditional nosocomial risk factors. Thus, anastomotic leaks, early graft failure, reoperation, central venous catheter–associated fungemia, and catheter-associated urinary tract infections are common. In one study among liver transplant recipients, over 50% of IFIs occurred within the first 10 days posttransplant, almost all of them caused by *Candida* species [47]. In the absence of early graft failure, retransplantation, significant pretransplant immunosuppression, or other mitigating circumstances, mould infections, especially those due to *Aspergillus* species, are uncommon during this period. Donor-related infections, especially those due to *Candida* species and *Aspergillus* species, often present during this first interval, 0–1 months posttransplantation.

During the second interval, 1–6 months posttransplantation, the effects of intense immunosuppression become manifest as the impact of nosocomial and surgical-related infections diminish. This second phase is dominated by mould infections, especially aspergillosis, zygomycosis, scedosporiosis, and less common mould diseases. *P. jiroveci* pneumonia is also common during this period among patients not receiving TMP/SMX prophylaxis. The peak incidence of aspergillosis is between 1 and 4 months posttransplantation, but there continues to be small risk of invasive aspergillosis throughout the posttransplant period

[5, 6, 8, 22]. The development of IFI during this time interval often follows evidence of active disease with an immunomodulating virus, such as CMV, HHV-6, EBV, hepatitis B, or hepatitis C.

The interval beyond 6 months posttransplantation is generally considered to be the period during which IFI is least likely to occur. Nonetheless, especially among patients with chronic rejection, graft dysfunction, late CMV infection, and other transplant-associated viral infections, IFI do occur. The late posttransplant period is dominated by fungal infections due to *C. neoformans*, regionally endemic mycoses, and some of the more unusual pathogens, including the dematiaceous fungi [6, 19, 31, 72–74]. However, mould infections due to *Aspergillus* species and the agents of zygomycoses may occur at any time in the posttransplant period [6, 75].

Immunosuppressive Regimen

The most important factor affecting the risk of IFI after the first month of transplantation is the intensity and duration of immunosuppressive agents that prevent organ rejection. Immunosuppression is initiated at high levels in the immediate posttransplant period when the risk of graft rejection is greatest. Most OTRs currently receive either a cyclosporine- or tacrolimus-based immunosuppressive regimen, usually in combination with mycophenylate mofetil. A growing number of patients receive antithymocyte globulin (ATG), alemtuzumab, basiliximab, daclizumab, or other monoclonal antibodies in the immediate posttransplant period to decrease the risk of rejection and minimize the need for glucocorticosteroids [76]. Reduction in overall glucocorticosteroid exposure has significantly decreased the overall incidence of IFI among OTRs. In an uncomplicated posttransplant setting, these regimens are continued at higher doses in the early posttransplant period, and are gradually tapered to a chronic maintenance regimen within 6 months in the absence of significant rejection. Undoubtedly the approach to immunotherapy in OTRs will continue to evolve as safer and more effective agents are developed.

Cyclosporine and tacrolimus have not demonstrated any clear difference with respect to incidence of IFI [77]. Similarly, studies among renal transplant recipients comparing regimens utilizing mycophenolate mofetil or azathioprine have not demonstrated any significant difference in rate of IFIs [78]. Moreover, recent data suggest that use of the calcineurin inhibitors (cyclosporine and tacrolimus) has led to decreased rates and severity of IFI because of their modest in vitro antifungal activity [79]. Thus, the recent reduction in IFIs associated with the calcineurin inhibitors may not only relate to a glucocorticosteroid-sparing effect, but also to modest antifungal activity.

The timing and frequency of rejection episodes as they relate to intensification of immunosuppressive regimens are also important factors associated with IFIs in OTRs. Pulse-dose glucocorticosteroids are commonly administered in this setting, usually coupled with an overall intensification of immunosuppressive therapy. In addition, specific antilymphocyte therapy with ATG or monoclonal antibodies is often administered in this setting. These interventions are associated with higher rates of CMV reactivation, which leads to an increased risk of IFI [76].

Donor-Related Fungal Infections

The vast majority of donor-related transplant infections are viral in origin. Well-documented donor-related infections are CMV, EBV, hepatitis B, hepatitis C, and HIV. Donor-related fungal infections are much less common; often the source of the pathogen is suspected to be the donor, but convincing proof is lacking. Nonetheless, several well-documented cases of donor-transmitted fungal infections have been described, including cases of histoplasmosis [80, 81], coccidioidomycosis [82–84], cryptococcosis [68], candidiasis [85, 86], and aspergillosis [87]. A recent French study found that graft site candidiasis could be traced to donor transmission, and occurred in 1 per 1,000 renal transplant recipients [86].

Among donors from endemic areas for histoplasmosis and coccidioidomycosis, a suspicion for latent disease must be maintained. Donor transmission of these two pathogens, *H. capsulatum* and *C. immitis*, is uncommon, and it remains difficult to accurately discern the source of these pathogens with certainty. Donor-derived *Aspergillus* infection among lung transplant recipients, while theoretically common because of frequent airway colonization, is rarely demonstrated [87]. Similarly, donor-derived cryptococcosis is infrequently recognized.

Comorbid Illnesses

Underlying diseases in the host contribute to the "net state of immunosuppression," and no doubt influence the risk of IFI. Factors that have most commonly been associated with an increased risk include renal dysfunction and the need for peritoneal or hemodialysis, diabetes mellitus, neutropenia, malnutrition, mechanical ventilation, admission to an intensive care unit, and chronic immunosuppressive therapy pretransplant [7, 8]. The degree to which these factors individually influence risk is uncertain.

Several viral infections increase the risk of IFI in the transplant recipient. CMV is the most commonly recognized

immunomodulating viral infection in this population. Ample evidence from large retrospective studies relate active CMV disease to increased risk of fungal infection in OTRs [47, 48, 61]. Additional data suggest that active hepatitis B and C, HHV-6, and HIV infection are important risk factors for posttransplantation IFI [8].

Specific Fungal Pathogens

Candida Species

Candida species are the commonest invasive fungal pathogens among OTRs. Virtually all of the more common *Candida* species, particularly *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. lusitaniae*, and *C. guilliermondii*, have been reported in this population. *Candida albicans* is the commonest species, followed by *Candida glabrata*, *C. tropicalis*, and *C. parapsilosis* [6]. In contrast to hematopoietic stem cell transplant recipients, *Candida krusei* is an uncommon pathogen in OTRs [6, 41, 66]. Reflecting a similar trend among nontransplant hospitalized patients, the broad use of prophylactic and empiric antifungal therapy, particularly with the azoles, has probably played an important role in the emergence of non-*albicans Candida* species in this population. Factors leading to candidemia are similar among OTRs and nontransplant patients, but the rate of complicated infection as evidenced by disseminated disease appears to be greater among OTRs than among nontransplanted patients [41]. Candidemia is the most common manifestation of invasive candidiasis in the transplant population, accounting for at least 60% of all episodes [6].

Intraabdominal infections secondary to *Candida* infections are significantly more common among liver, pancreas, and small bowel transplant recipients compared to other OTRs. These patients undergo disruption of the normal anatomy of the small bowel, common bile duct, and/or pancreatic duct with the potential for intraabdominal anastomotic leakage. Intraabdominal infectious complications frequently occur within the first month posttransplant and are often polymicrobial. Sternal wound infections among heart and heart-lung transplants due to *Candida* species have been reported, and can be associated with significant morbidity and mortality [67]. Among lung transplants, bronchial anastomotic infections secondary to *Candida* species have been reported [68].

Urinary tract infections due to *Candida* are common among OTRs owing to the need for bladder catheterization during the period of hospitalization, particularly in the immediate postoperative period. Candiduria can be a harbinger of complicated upper tract disease, but in a large prospective study of candiduria in renal transplant recipients, patients who received treatment with fluconazole did not have better outcomes than those who were not treated [88]. An unusual complication of *Candida* urinary tract infection in OTRs is the development of a ureteral fungus ball due to *Candida* species [89]. This complication is most often seen in renal transplant recipients, but it is also seen in other OTRs, and may clinically mimic fungus ball due to less common urinary pathogens such as *Aspergillus* species

A rare but important syndrome due to *Candida* species relates to vascular anastomotic infections. True "mycotic" aneurysms occurring at the site of the vascular anastomosis due to *Candida* species have been reported among pancreatic [90], renal [86, 91], and heart-lung transplant recipients [92]. Among renal transplant recipients this manifestation has been associated with donor origin of the organism [86]. These represent a very significant and highly lethal postoperative complication. Less common complications of *Candida* infection include septic arthritis, chronic meningitis, endocarditis, and rarely, pneumonia [93, 94].

Aspergillus

Invasive aspergillosis is reported among all transplant groups; however, lung transplant recipients seem to be particularly predisposed to infections with *Aspergillus* species. As many as 10% of lung transplant recipients will develop significant infection with *Aspergillus* and another 10% will develop *Aspergillus* colonization posttransplantation [21, 22]. Among non-lung OTRs, the overall risk of invasive aspergillosis is substantially less [6]. *Aspergillus fumigatus* is the most common causative species; however, infections due to *A. flavus*, *A. niger*, *A. terreus*, *A. nidulans*, *A. glaucus*, *A. ustus*, *A. versicolor*, and other less common species have been reported. Moreover, multiple species may be isolated from the same patient. Newer molecular techniques have provided the means of identifying several less common *Aspergillus* species, including *A.lentulus*, *A. calidoustus*, and *A. tubingensis* [95].

Aspergillus spores are ubiquitous in the environment, and infection usually begins as a result of inhalation, resulting in lower respiratory tract colonization. Disease may be confined to the lungs or may disseminate to virtually any organ, most commonly the skin, central nervous system, heart, and the endocrine glands, especially the thyroid. Disseminated disease is associated with a mortality rate of greater than 80% [96, 97]. Ulcerative tracheobronchitis due to *Aspergillus* is a well-described syndrome among lung transplant recipients that is characterized by superficial invasion of the tracheobronchial tree, typically at the site of an anastomosis, but it may occur anywhere within the proximal airway [98]. The disease has been reported among other transplant groups [99], but is distinctly uncommon outside of lung transplant recipients. Patients with this ulcerative tracheobronchitis

may be asymptomatic or minimally symptomatic with chronic nonproductive cough. Bronchoscopy reveals single or multiple ulcerative lesions at the anastomotic site.

Aspergillus species frequently colonize the upper airways, making it difficult to distinguish between invasive disease and asymptomatic colonization. However, the detection of significant *Aspergillus* colonization in the upper airways is strongly predictive of invasive disease in most OTRs with a positive predictive value of at least 60% [60, 100–102]. Recently, the measurement of *Aspergillus* galactomannan by EIA in bronchoalveolar lavage fluid has proven to be a sensitive indicator of pulmonary invasive aspergillosis and should become an important component of the evaluation of patients with suspected disease [103].

Other manifestations of invasive aspergillosis in OTRs include sinusitis, thoracic empyema, and angioinvasion at virtually any site. *Aspergillus* has been reported as a cause of urinary tract fungus ball and prostatic abscess in renal and liver transplant recipients [28, 29]. Invasive aspergillosis may occur several years following transplantation, especially among patients undergoing intensification of immunosuppressive therapy or receiving higher-dose corticosteroids for allograft rejection [6, 22, 75]. Additional risk factors for invasive aspergillosis include CMV infection, renal failure, and early graft failure [22, 61].

The source of *Aspergillus* infection can be difficult to discern. Recent studies have suggested that nosocomial transmission occurs, although the frequency of this event is unclear [104]. Also, the recipients may serve as their own reservoirs for *Aspergillus*, especially those with single lung transplants [59]. Community-acquired infection occurs, but its relative importance compared to nosocomial acquisition and donor transmission remains unknown [87].

Cryptococcus

Cryptococcus is overall the third most common IFI in OTRs, and usually occurs relatively late in the posttransplant period [31]. In the TRANSNET study, the median time to development of cryptococcosis was 575 days posttransplantation [6]. Disease is usually due to *C. neoformans*, although disease due to *C. gattii*, *C. albidus*, and *C. laurentii* is reported. Manifestations of cryptococcal disease are similar among OTRs and HIV-infected individuals. Primary infection usually occurs following inhalation [105] although there are sporadic reports of direct primary cutaneous disease possibly resulting from direct inoculation [106, 107]. Most patients present with nonspecific respiratory symptoms, unexplained fever, or an asymptomatic nodule on chest roentgenogram. Asymptomatic infection with *C. neoformans* is common; thus, it is unclear how often extrapulmonary dissemination occurs in OTRs. The central nervous system (CNS) is the most common extrapulmonary site of cryptococcal disease in OTRs, followed by involvement of the skin and subcutaneous tissue, bones, and prostate. Necrotizing cellulitis is a common cutaneous manifestation in this population, and must be distinguished from cellulitis due to common bacterial and mycobacterial pathogens [108–110]. Based on data from TRANSNET and other studies, there seems to be little predilection for the type of organ transplant and the development of cryptococcosis [6]. Cryptococcemia is especially common in this group and is generally associated with a worse clinical outcome [111].

Recent experience among OTRs with cryptococcosis suggest that outcomes are at least as good as outcomes among patients who are otherwise normal hosts [45, 111]. This paradox is not well understood, but could relate to the intensity of patient follow-up after organ transplantation and the ability to make a diagnosis earlier in the course of infection. Corticosteroids may have an ameliorating effect early in the course of cryptococcosis, particularly when the CNS is involved. The calcineurin inhibitors, especially tacrolimus, possess not only modest in vitro antifungal activity, but also excellent CNS penetration, and may have a beneficial effect on the natural history and severity of CNS cryptococcosis in OTRs [79, 112]. Investigators also suggest that a relative increase in cutaneous expression of disease may be the result of poor antifungal activity of tacrolimus at lower temperatures found in cutaneous tissue [31].

Transplant-related immune reconstitution inflammatory syndrome (IRIS) has been best described among patients with cryptococcosis and relates to the rapid withdrawal of immunosuppressive therapy from patients with active infection. The clinical manifestation of IRIS is a paradoxical worsening of disease, relating to the rapid conversion from a TH2 to a TH1 host immunologic response [113–116].

Mucorales (Zygomycetes)

Mucormycosis or zygomycosis, has been reported in all OTRs. Disease has been reported due to several genera, most commonly *Rhizopus* species, *Mucor* species, *Cunninghamella bertholletiae*, and *Absidia* species. Risk factors for invasive disease include neutropenia, ketoacidosis, renal failure, and treatment of chronic rejection, especially with higher-dose steroids.

Clinical disease often involves the paranasal sinuses, leading to destructive lesions and CNS involvement by direct extension. The lungs are also a commonly involved site, although virtually any organ can be involved [42–44, 49, 117–119]. Multiple organ involvement consistent with hematogenous dissemination is reported, but is less common

than that due to invasive aspergillosis, even though the pathogenesis of both disorders involves angioinvasion. *Conidiobolus coronatus*, an organism infecting patients living in tropical areas, has been reported as a cause of disseminated disease in a renal transplant recipient [120].

The typical clinical finding associated with mucormycosis is a necrotizing, locally invasive process. Necrotizing wound infections have been described [119], as has infection of a renal allograft [17]. In addition, localized gastrointestinal mucormycosis, characterized by giant gastric and/or colonic ulcers, has been reported [121–123].

Phaeohyphomycoses

The agents of phaeohyphomycosis consist of over 100 pigmented moulds (dematiaceous fungi), and a growing number of these species have been reported to cause disease among OTRs [19, 74]. The clinical spectrum of these infections includes invasive sinusitis, pneumonia, endophthalmitis, skin and musculoskeletal involvement, CNS disease, gastrointestinal involvement, and disseminated disease. Infections due to *Exophiala* species, *Dactylaria constricta*, *Alternaria* species, *Bipolaris spicifera*, *Curvularia* spp., *Cladophialophora bantiana*, *Colletotrichum crassipes*, *Phaeocremonium parasiticum,* and *Fonsecaea pedrosoi* have been reported [124–131]. In one review of disseminated phaeohyphomycosis in OTRs, only 16% of patients survived, even with therapy [19]. In another review, Singh and colleagues noted that cutaneous and synovial involvement was usually caused by *Exophiala* species, whereas systemic infections, including CNS involvement, were caused by less common organisms, such as *Ochroconis gallopavum* and *Cladophialophora bantiana* [74]. Phaeohyphomycosis is usually late-occurring, and specific risk factors for development have not been clearly delineated.

Endemic Fungi

Infections due to *C. immitis* and *H. capsulatum* are not uncommon among OTRs who have lived in endemic areas. The true incidence of these infections is unknown, but estimates range between 0.2% and 6% [72, 73, 132–139]. Endemic fungal infections tend to occur late in the posttransplantation period, with a median time of greater than 1 year posttransplant. In the TRANSNET cohort, infections with the endemic fungi occurred a median of 343 days following transplantation [6]. Transmission from the donor organ has been documented in several of these cases [81–83, 138], but a history of prior infection without evidence of active disease should not exclude potential donors or recipients. Nonetheless, the potential for donor-related transmission with these organisms remains a concern in endemic areas. Several recent reports clearly document donor-related *H. capsulatum* and *C. immitis* transmission to recipients residing in nonendemic areas for these organisms, underscoring the need to consider the donor as a potential source of infection in patients with undifferentiated fever [81–83].

Histoplasmosis is the most commonly reported endemic mycosis among OTRs. Most reports have involved renal transplant recipients, although disease has been described in liver, heart, and lung recipients [135–141]. Histoplasmosis in OTRs usually presents as disseminated disease, although focal involvement of the CNS, skin, renal papilla, and gastrointestinal tract has been described. In addition, cecal and ileal perforation associated with gastrointestinal histoplasmosis has been described.

Coccidioidomycosis following organ transplantation has been reported in up to 6% of OTRs living in the endemic desert areas in the southwestern USA [142]. Disease is due to either recent environmental exposure or to reactivation of a latent infection; there is less documentation of donor-related transmission. Clinical features of coccidioidomycosis in this population vary from pneumonia to disseminated disease involving skin, musculoskeletal structures, and the CNS [15, 132–134]. The majority of cases of posttransplant coccidioidomycosis have been reported among renal, heart, and liver transplant recipients.

Blastomycosis is distinctly uncommon among OTRs, even among patients residing in endemic areas [143–145]. There has been no evidence to suggest donor-related transmission of *B. dermatitidis* to date. Disease manifestations in this group tend to parallel those of the normal host; however, disseminated disease, including involvement of the CNS, is more commonly observed in OTRs. Overall, the mortality rate among OTRs and other immunocompromised hosts with blastomycosis has been significantly higher than among otherwise normal patients [145].

Sporotrichosis due to *Sporothrix schenckii* and *S. cyanensis* has been reported sporadically among OTRs [146]. There is no evidence to suggest donor-transmitted infections, and most cases have been reported in conjunction with recognized environmental exposure. Disease has been limited to the skin and subcutaneous tissue in most cases, although pulmonary and disseminated disease has been reported [147].

Other Fungi

Disease due to other pathogenic yeasts and moulds has been reported sporadically among OTRs. Fusariosis due to *F. solani*, *F. oxysporum*, *F. moniliforme*, and *F. sacchari* has been

reported [16, 148, 149]. Infection due to *Fusarium* species is often associated with prolonged periods of neutropenia, although fusariosis can present among OTRs without neutropenia. Patients with fusariosis are frequently fungemic [150]. Localized infection involving the sinuses, lungs, skin, and soft tissue, as well as disseminated disease, are reported. Another ubiquitous hyalohyphomycete, *Paecilomyces lilacinus*, is a cause of cutaneous and sinus disease in OTRs [151–153].

Trichosporonosis due to *T. asahii*, a pathogenic yeast often associated with intravenous catheter-related infections, may cause disseminated disease in OTRs. In addition, funguria due to *T. asahii* has been reported among OTRs [18]. Fatal fungemia due to *Trichoderma harzianum* has also been observed [154].

Pneumocystis jiroveci

Infection due to *Pneumocystis jiroveci* is reported in all organ transplant recipients, although it is most commonly reported among lung and heart-lung transplant recipients [69]. The incidence of *Pneumocystis* pneumonia (PCP) is greatest within the first year after transplantation. Gordon and colleagues suggested an eight-fold higher incidence of PCP in the first year following transplant compared to the combined incidence in all subsequent years among OTRs at one institution [155].

For patients with PCP associated with transplantation, recent receipt of antithymocyte globulin, CMV infection, and therapy for organ rejection are considered important risk factors [69]. Extrapulmonary disease similar to that seen among patients with AIDS can occur. Antimicrobial prophylaxis with trimethoprim/sulfamethoxazole or sulfadoxine/pyrimethamine in the first 6–12 months posttransplantation is highly effective in preventing PCP [156]; dapsone, atovaquone, and inhaled pentamidine are reasonable alternatives to these agents.

Approach to Diagnosis

A diagnosis of IFI in OTRs is frequently challenging, relating in part to the relative paucity and nonspecificity of the signs and symptoms associated with IFI in immunocompromised patients in general and in OTRs, specifically. Thus, a high index of suspicion and an aggressive approach to diagnosis is warranted in clinically compatible situations. The recently revised EORTC/MSG criteria for the diagnosis of IFI [157] are based on the following criteria: (1) the isolation of a pathogenic organism from a properly obtained clinical specimen, associated with clinical or radiographic evidence of disease, (2) the demonstration of fungal organisms in cytologic or histopathologic studies, or (3) serologic detection of a specific antibody or fungal antigen from blood, serum, urine, cerebrospinal fluid, or bronchoalveolar lavage (BAL) fluid. These definitions are categorized as proven, probable, or possible based on the strength of the host, clinical, radiographic, and microbiologic criteria.

Culture of certain fungi from any site virtually always suggests disease, even in the absence of clinical signs and symptoms. Examples include *H. capsulatum*, *C. immitis*, *B. dermatitidis*, *S. schenckii*, and *P. brasiliensis*. Isolation of *C. neoformans* from specimens other than sputum is always indicative of invasive disease. In rare circumstances, isolation of *C. neoformans* from the sputum can represent colonization only, but the recovery of this organism from respiratory secretions in an OTR must always be accompanied by an aggressive diagnostic approach, including chest CT scan and/or bronchoscopy, directed at evaluating the possibility of parenchymal lung disease.

Isolation of *Candida* species from the blood, regardless of whether it was obtained from a peripheral site or an intravascular catheter, should always be considered a true infection, even in the absence of clinical signs and symptoms. Isolates of *Candida* from other normally sterile sources should similarly be regarded as indicative of invasive disease. *Candida* species isolated from drains, urinary catheters, sputum, and other nonsterile sites often represent colonization only, and must be interpreted in the clinical context of the individual patient. The main value of isolation of *Candida* from a nonsterile site is to help predict the future development of invasive candidiasis and guide empiric therapy in patients who are perceived to be at high risk.

Isolation of *Aspergillus* species from blood cultures is rare. By comparison, *Fusarium* species, *Scedosporium* species, *P. lilacinus*, and other rare moulds are frequently isolated from blood cultures among patients with disseminated disease. The isolation of a mould from other clinical specimens such as sputum, BAL fluid, or tissue biopsy are best interpreted with clinical, radiographic, and histopathologic correlation [57, 60, 100, 102].

Direct visualization of an organism on a histopathologic specimen is an indispensable means of establishing tissue invasion. The demonstration on biopsy of fungal elements invading tissue often distinguishes a proven from a possible or probable case of invasive mould disease in an immunocompromised patient. Special stains such as Gomori's methanamine silver, periodic acid–Schiff, and Fontana-Masson can help to demonstrate fungal organisms in tissue.

Several serologic tests have been used successfully in the early detection of fungal infections. Among the approved tests, detection of cryptococcal antigen in serum or cerebrospinal fluid remains the most reliable of these serologic assays, maintaining a high sensitivity and specificity.

The measurement of *Histoplasma* antigen in serum and urine has also been extremely useful in the diagnosis of histoplasmosis in immunocompromised patients. The urine *Histoplasma* antigen assay has a sensitivity of at least 90% among immunocompromised patients with disseminated disease. In addition, among AIDS patients with disseminated histoplasmosis, serial urine *Histoplasma* antigens have been utilized to follow response to therapy and to predict relapse. Among the other endemic fungi, reliable serologic testing is available for *C. immitis*. The detection of antibodies to *Coccidioides* is a sensitive and specific marker of coccidioidomycosis.

Serologic assays for detecting early evidence of invasive candidiasis and invasive aspergillosis are available [158, 159]. The serum 1–3 beta-D-glucan is approved as an adjunctive assay for the diagnosis of invasive candidiasis. The test is approved but not widely utilized due to cost and technical factors. The *Aspergillus* galactomannan EIA is approved for use in serum and BAL, but has proven to be less useful in OTRs than in patients with hematologic malignancies and in stem cell transplant recipients. Nonetheless, this assay is an important step forward in the earlier diagnosis of invasive aspergillosis.

Prophylactic Antifungal Therapy

Antifungal prophylaxis is widely practiced but inadequately studied in liver, pancreas, lung, and heart-lung transplant recipients. With the exception of liver transplant recipients, there are limited studies of targeted prophylaxis in OTRs. The largest study to date compared fluconazole 400 mg daily to placebo given for the first 70 days posttransplant among 212 liver transplant recipients in a randomized, double-blind study. In this study, 6% versus 23% of fluconazole and placebo recipients, respectively, developed IFI, but neither regimen demonstrated reduced mortality rates [160]. In a small, randomized, double-blind study of 86 liver transplant patients, 0% versus 16% (p, 0.01) of recipients of a lipid formulation of amphotericin B versus placebo, respectively, developed an IFI in the first month posttransplant [161].

In an observational study of 200 low-risk liver transplant recipients who did not receive antifungal prophylaxis, the incidence of IFI was 3.6% during the first 100 days posttransplant, suggesting that antifungal prophylaxis in a low-risk population is unnecessary [162]. A recently published study comparing 71 high-risk liver transplant recipients who received either fluconazole (400 mg/day) or liposomal amphotericin (2 mg/kg/day) as posttransplantation prophylaxis both given for 14 days, demonstrated a low incidence of IFI and no differences between the two arms [163].

Some authors have advocated targeted prophylaxis and/or preemptive therapy in selected clinical situations. These include early posttransplant pulmonary colonization with *Aspergillus* species, the discovery that removed focal pulmonary nodules contain *C. neoformans* or *H. capsulatum* without evidence of extrapulmonary disease, and asymptomatic candiduria in the renal transplant recipient [164].

Recent studies among lung transplant recipients have examined the use of inhaled amphotericin B preparations for primary prophylaxis of invasive fungal pneumonia and bronchitis. These uncontrolled studies demonstrate the safety of a nebulized lipid agent and amphotericin B deoxycholate and efficacy in preventing IFI in the early postoperative period [165, 166]. Aside from these studies, there are few data that address the best approach to antifungal prophylaxis in OTRs. As such, antifungal prophylaxis is largely practiced in a center-to-center approach based on local experience, epidemiology, and perceived risk of IFI.

References

1. Paya CV. Fungal infections in solid-organ transplantation. Clin Infect Dis. 1993;16:677–88.
2. Hibberd PL, Rubin RH. Clinic aspects of fungal infection in organ transplant recipients. Clin Infect Dis. 1994;19 Suppl 1:33–40.
3. Hadley S, Karchmer AW. Fungal infections in solid organ transplant recipients. Infect Dis Clin N Am. 1995;9:1045–74.
4. Dictar MO, Maiolo E, Alexander B, Jacob N, Veron MT. Mycoses in the transplanted patient. Med Mycol. 2000;38:251–8.
5. Silveira FP, Husain S. Fungal infections in solid organ transplantation. Med Mycol. 2007;45:305–20.
6. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients in the United States: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis. 2010;50:1101–12.
7. Rubin RH. Infection in the organ transplant recipient. In: Rubin RH, Young LS, editors. Clinical approach to infections in the compromised host. 3rd ed. New York: Plenum; 1994. p. 629–705.
8. Fishman JA. Infection in solid-organ transplant recipients. N Eng J Med. 2007;357:2601–14.
9. Patel R, Paya CV. Infections in solid organ transplant recipients. Clin Microbiol Rev. 1997;10:86–124.
10. Patel R. Infections in recipients of kidney transplants. Infect Dis Clin N Am. 2001;15:901–51.
11. Abbott KC, Hypolite I, Poropatich RK, et al. Hospitalizations for fungal infections after renal transplantation in the United States. Transpl Infect Dis. 2001;3:203–11.
12. Singh N. Fungal infections in the recipients of solid organ transplantation. Infect Dis Clin N Am. 2003;17:113–34.
13. Cuellar-Rodriguez J, Avery RK, Lard M, et al. Histoplasmosis in solid organ transplant recipients: 10 years of experience at a large transplant center in an endemic area. Clin Infect Dis. 2009; 49:710–6.
14. Wheat LJ, Smith EJ, Sathapatayavongs B, et al. Histoplasmosis in renal allograft recipients: two large urban outbreaks. Arch Intern Med. 1983;143:703–7.
15. Blair JE. Coccidioidomycosis in patients who have undergone transplantation. Ann NY Acad Sci. 2007;1111:365–76.
16. Heinz T, Perfect J, Schell W, Ditter E, Ruff G, Serafin D. Soft tissue fungal infections: surgical management of 12 immunocompromised patients. Plast Reconstr Surg. 1996;97:1391–9.

17. Chkhotua A, Yussim A, Tovar A, et al. Mucormycosis of the renal allograft: case report and review of the literature. Transpl Int. 2001;14:438–41.
18. Lussier N, Laverdiere M, Delorme J, Weiss K, Dandavino R. *Trichosporon beigelii* funguria in renal transplant recipients. Clin Infect Dis. 2000;31:1299–301.
19. Revankar SG, Patterson JE, Sutton DA, Pullen R, Rinaldi MG. Disseminated phaeohyphomycosis: review of an emerging mycosis. Clin Infect Dis. 2002;34:467–76.
20. Nampoory MR, Khan ZU, Johny KV, et al. Invasive fungal infections in renal transplant recipients. J Infect. 1996;33:95–101.
21. Paterson DL, Singh N. Invasive aspergillosis in transplant recipients. Medicine (Baltimore). 1999;78:123–38.
22. Singh N, Paterson DL. *Aspergillus* infections in transplant recipients. Clin Microbiol Rev. 2005;18:44–69.
23. Patterson JE, Peters J, Calhoon JH, et al. Investigation and control of aspergillosis and other filamentous fungal infections in solid organ transplant recipients. Transpl Infect Dis. 2000;2:22–8.
24. Carlini A, Angelini D, Burrows L, DeQuirico G, Antonelli A. Cerebral aspergillosis: long term efficacy and safety of liposomal amphotericin B in kidney transplant. Nephrol Dial Transplant. 1998;13:2659–61.
25. Garcia A, Mazuecos A, Flayo A, et al. Isolated cerebral aspergillosis without a portal of entry-complete recovery after liposomal amphotericin B and surgical treatment. Nephrol Dial Transplant. 1998;9:2385–7.
26. Marin P, Garcia-Martos P, Carcia-Doncel A, et al. Endocarditis by *Aspergillus fumigatus* in a renal transplant. Mycopathologia. 1999;145:127–9.
27. Viertel A, Ditting T, Pistorius K, Geiger H, Scheuermann EH. Just-Nubling G. An unusual case of *Aspergillus* endocarditis in a kidney transplant recipient. Transplantation. 1999;68:1812–3.
28. Kim SW, Nah MY, Ueum CH, et al. Pelvic aspergillosis with tubo-ovarian abscess in a renal transplant recipient. J Infect. 2001;42:215–7.
29. Shirwany A, Sargent SJ, Dmochowski RR, Bronze MS. Urinary tract aspergillosis in a renal transplant recipient. Clin Infect Dis. 1998;27:1336.
30. Kaplan-Pavlovcic S, Masera A, Ovcak Z, Kmetec A. Prostatic aspergillosis in a renal transplant recipient. Nephrol Dial Transplant. 1999;14:1778–80.
31. Husain S, Wagener MM, Singh N. *Cryptococcus neoformans* infection in organ transplant recipients: variables influencing clinical characteristics and outcome. Emerg Infect Dis. 2001;7:1–14.
32. Singh N, Dromer F, Perfect JR, Lortholary O. Cryptococcosis in solid organ transplant recipients: current state of the science. Clin Infect Dis. 2008;47:1321–7.
33. Lumbreras C, Fernandez I, Velosa J, Munn S, Sterioff S, Paya CV. Infectious complications following pancreatic transplantation: incidence, microbiological and clinical characteristics, and outcome. Clin Infect Dis. 1995;20:514–20.
34. Benedetti E, Gruessner AC, Troppmann C, et al. Intra-abdominal fungal infections after pancreatic transplantation: incidence, treatment, and outcome. J Am Coll Surg. 1996;183:307–16.
35. Smets YF, van der Piji JW, van Dissel JT, Ringers FJ, de Fijter JW, Lemkes HH. Infectious disease complications of simultaneous pancreas kidney transplantation. Nephrol Dial Transplant. 1997;12:764–71.
36. Hesse UJ, Sutherland DER, Najarian JS, Simmons RL. Intra-abdominal infections in pancreas transplant recipients. Ann Surg. 1986;203:153–62.
37. Pirsch JD, Odorico JS, D'Alessandro AM, Knechtle SJ, Becker BN, Sollinger HW. Post-transplant infections in enteric versus bladder-drained simultaneous pancreas-kidney transplant recipients. Transplantation. 1998;66:1746–50.
38. Wajszczuk CP, Dummer JS, Ho M, et al. Fungal infections in liver transplant recipients. Transplantation. 1985;40:347–53.
39. Singh N, Pruett TL, Houston S, et al. Invasive aspergillosis in the recipients of liver retransplantation. Liver Transpl. 2006;12:1205–9.
40. Singh N, Avery RK, Munoz P, et al. Trends in risk profiles for and mortality associated with invasive aspergillosis among liver transplant recipients. Clin Infect Dis. 2003;36:46–52.
41. Husain S, Tollemar J, Dominguez EA, et al. Changes in the spectrum and risk factors for invasive candidiasis in liver transplant recipients: prospective, multicenter, case-controlled study. Transplantation. 2003;75:2023–9.
42. Stelzmueller I, Lass-Floerl C, Geltner C, et al. Zygomycosis and other rare filamentous fungal infections in solid organ transplant recipients. Transpl Int. 2008;21:534–46.
43. Sun HY, Singh N. Emerging importance of infections due to zygomycetes in organ transplant recipients. Int J Antimicrob Agents. 2008;32 Suppl 2:S115–8.
44. Sun HY, Aguado JM, Bonatti H, et al. Pulmonary zygomycosis in solid organ transplant recipients in the current era. Am J Transplant. 2009;9:2166–71.
45. Davis JA, Horn DL, Marr KA, Fishman JA. Central nervous system involvement in cryptococcal infection in individuals after solid organ transplantation or with AIDS. Transpl Infect Dis. 2009;11:432–7.
46. Sun HY, Wagener MM, Singh N. Cryptococcosis in solid-organ, hemtopoietic stem cell, and tissue transplant recipients: evidence-based evolving trends. Clin Infect Dis. 2009;48:1566–76.
47. Collins LA, Samore MH, Roberts MS, et al. Risk factors for invasive fungal infections complicating orthotopic liver transplantation. J Infect Dis. 1994;170:644–52.
48. Patel R, Portela D, Badley AD, et al. Risk factors of invasive *Candida* or non-*Candida* fungal infections after liver transplantation. Transplantation. 1996;62:926–34.
49. Singh N, Aguado JM, Bonatti H, et al. Zygomycosis in solid organ transplant recipients: a prospective, matched case-control study to assess risks for disease and outcome. J Infect Dis. 2009; 200:1002–11.
50. Waser M, Maggiorini M, Luthy A, et al. Infectious complications in 100 consecutive heart transplant recipients. Eur J Clin Microbiol Infect Dis. 1994;13:12–8.
51. Kramer MR, Marshal SE, Starnes VA, Gamberg P, Amitai Z, Theodore J. Infectious complications in heart-lung transplantation analysis of 200 episodes. Arch Intern Med. 1993; 153:2010–6.
52. Grossi P, Glaudio F, Fiocchi R, Dalla Gasperina D. Prevalence and outcome of invasive fungal infections in 1,963 thoracic organ transplant recipients. Transplantation. 2000;70:112–6.
53. Goldstein DJ, El-Amir NG, Ashton RC, et al. Fungal infections in left ventricular assist device recipients: incidence, prophylaxis, and treatment. ASAIO J. 1995;41:873–5.
54. Argenziano M, Catanese KA, Moazami N, et al. The influence of infection on survival and successful transplantation in patients with left ventricular assist devices. J Heart Lung Transplant. 1997;16:822–31.
55. Gordon SM, Avery RK. Aspergillosis in lung transplantation: incidence, risk factors, and prophylactic strategies. Transpl Infect Dis. 2001;3:161–7.
56. Singh N, Husain S. *Aspergillus* infections after lung transplantation: clinical differences in type of transplant and implications for management. J Heart Lung Transplant. 2003;22:258–66.
57. Mehrad B, Giusppe P, Martinez FJ, Clark T, Iannettoni MD, Lynch JP. Spectrum of *Aspergillus* infection in lung transplant recipients. Chest. 2001;119:169–75.
58. Yeldandi V, Laghi F, McCabe MA, et al. *Aspergillus* and lung transplantation. J Heart Lung Transplant. 1995;14:883–90.

59. Westney GE, Kesten S, de Hoyos A, Chapparro C, Winton T, Maurer JR. *Aspergillus* infection in single and double lung transplant recipients. Transplantation. 1996;61:915–9.
60. Cahill BC, Hibbs JR, Savik K, et al. *Aspergillus* airway colonization and invasive disease after lung transplantation. Chest. 1997;112:1160–4.
61. Husni RN, Gordon SM, Longworth DL, et al. Cytomegalovirus infection is a risk factor for invasive aspergillosis in lung transplant recipients. Clin Infect Dis. 1998;26:753–5.
62. Goldfarb NS, Avery RK, Goormastic M, et al. Hypogammaglobulinemia in lung transplant recipients. Transplantation. 2001;71:242–6.
63. Marks WH, Florence L, Lieberman J, et al. Successfully treated invasive pulmonary aspergillosis associated with smoking marijuana in a renal transplant recipient. Transplantation. 1996;61:1771–83.
64. Nunley DR, Ohori NP, Grgurich WF, et al. Pulmonary aspergillosis in cystic fibrosis lung transplant recipients. Chest. 1998;114:1321–9.
65. Cimon B, Carrere J, Vinatier JF, Chazalette JP, Chabasse D, Bouchara JP. Clinical significance to *Scedosporium apiospermum* in patients with cystic fibrosis. Eur J Clin Microbiol Infect Dis. 2000;19:53–6.
66. Horn DL, Neofytos D, Anaissie EJ, et al. Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. Clin Infect Dis. 2009;48:1695–703.
67. Dauber HJ, Paradis IL, Dummer JS. Infectious complications in pulmonary allograft recipients. Clin Chest Med. 1990;11:291–308.
68. Kanj SS, Welty-Wolf K, Madden J, et al. Fungal infections in lung and heart transplant recipients: report of 9 cases and review of the literature. Medicine (Baltimore). 1996;75:142–56.
69. Rodriguez M, Fishman JA. Prevention of infection due to *Pneumocystis* spp. in human immunodeficiency virus-negative immunocompromised patients. Clin Microbiol Rev. 2004;17:770–82.
70. Reyes J, Abu-Elmagd K, Tzakis A, et al. Infectious complications after human small bowel transplantation. Transplantation. 1992;24:1249–50.
71. Kusne S, Furukawa H, Abu-Elmagd K, et al. Infectious complications after small bowel transplantation in adults: an update. Transplant Proc. 1996;28:2761–2.
72. Freifeld AG, Iwen PC, Lesiak BL, Gilroy RK, Stevens RB, Kalil AC. Histoplasmosis in solid organ transplant recipients at a large Midwestern university transplant center. Transpl Infect Dis. 2005;7:109–15.
73. Peddi VR, Hariharan S, First MR. Disseminated histoplasmosis in renal allograft recipients. Clin Transplant. 1996;10:160–5.
74. Singh N, Chang FY, Gayowski T, Marino IR. Infections due to dematiaceous fungi in organ transplant recipients: case report and review. Clin Infect Dis. 1997;24:369–74.
75. Singh N, Limaye AP, Forrest G, et al. Late-onset invasive aspergillosis in organ transplant recipients in the current era. Med Mycol. 2006;44:445–9.
76. Issa NC, Fishman JA. Infectious complications of antilymphocyte therapies in solid organ transplantation. Clin Infect Dis. 2009;48:772–86.
77. The US Multicenter FK506 Liver Study Group. A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppresion in liver transplantation. N Engl J Med. 1994;331:1110–5.
78. Bernabeu-Wittel M, Naranjo M, Cisneros JM, et al. Infections in renal transplant recipients receiving mycophenolate versus azathioprine-based immunosuppression. Eur J Clin Microbiol Infect Dis. 2002;21:173–80.
79. Kontoyiannis DP, Lewis RE, Alexander BD, et al. Calcineurin inhibitor agents interact synergistically with antifungal agents in vitro against *Cryptococcus neoformans* isolates: correlation with outcome in solid organ transplant recipients with cryptococcosis. Antimicrob Agents Chemother. 2008;52:735–8.
80. Wong SY, Allen DM. Transmission of disseminated histoplasmosis via cadaveric renal transplantation: case report. Clin Infect Dis. 1992;14:232–4.
81. Limaye AP, Connolly PA, Sagar M, et al. Transmission of *Histoplasma capsulatum* by organ transplantation. N Engl J Med. 2000;343:1163–6.
82. Wright P, Pappagianis D, Davis CA, et al. Transmission of *Coccidioides immitis* from donor organs: a description of two fatal cases of disseminated coccidioidomycosis. Clin Infect Dis. 2003;37:1265–9.
83. Brugière O, Forget E, Biondi G, et al. Coccidioidomycosis in a lung transplant recipient acquired from the donor graft in France. Transplantation. 2009;88:1319–20.
84. Tripathy U, Yung GL, Kriett JM, Thistlewaite PA, Kapelanski DP, Jamieson SW. Donor transfer of pulmonary coccidioidomycosis in lung transplantation. Ann Thoracic Surg. 2002;73:306–8.
85. Battaglia M, Ditonno P, Fiore T, De Ceglie G, Regina G, Selvaggi FP. True mycotic arteritis by *Candida albicans* in 2 kidney transplant recipients from the same donor. J Urol. 2000;163:1236–7.
86. Albano L, Bretagne S, Mamzer-Bruneel MF, et al. Evidence that graft-site candidiasis after kidney transplantation is acquired during organ recovery: a multicenter study in France. Clin Infect Dis. 2009;48:194–202.
87. Keating MR, Guerrero MA, Daly RC, Walker RC, Davies SF. Transmission of invasive aspergillosis from a subclinically infected donor to three different organ transplant recipients. Chest. 1996;109:1119–24.
88. Safdar N, Slattery WR, Knasinski V, et al. Predictors and outcomes of candiduria in renal transplant recipients. Clin Infect Dis. 2005;40:1413–21.
89. Gallis HA, Berman RA, Cate TR, Hamilton JD, Gunnels JC, Stickel DL. Fungal infections following renal transplantation. Arch Intern Med. 1975;135:1163–72.
90. Ciancio G, Burke GW, Viciana AL, et al. Destructive allograft fungal arteritis following simultaneous pancreas-kidney transplantation. Transplantation. 1996;61:1172–5.
91. Potti A, Danielson B, Sen K. "True" mycotic aneurysm of a renal artery allograft. Am J Kidney Dis. 1998;31:E3.
92. Dowling RD, Baladi N, Zenati M, et al. Disruption of the aortic anastomosis after heart-lung transplantation. Ann Thoracic Surg. 1990;49:118–22.
93. Ralph ED, Hussain Z. Chronic meningitis caused by *Candida albicans* in a liver transplant recipient: usefulness of the polymerase chain reaction for diagnosis and for monitoring treatment. Clin Infect Dis. 1996;23:191–2.
94. Choi IS, Kim SJ, Kim BY, et al. *Candida* polyarthritis in a renal transplant patient: case report of a patient successfully treated with amphotericin B. Transplant Proc. 2000;32:1963–4.
95. Balajee SA, Kano R, Baddley JW, et al. Molecular identification of *Aspergillus* species collected for the Transplant-Associated Infection Surveillance Network. J Clin Microbiol. 2009;47:3138–41.
96. Patterson TF, Kirkpatrick WR, White M, et al. Invasive aspergillosis: disease spectrum, treatment, practice, and outcomes. Medicine (Baltimore). 2000;79:250–60.
97. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systemic review of the literature. Clin Infect Dis. 2001;32:658–66.
98. Kramer MR, Denning DW, Marshall SE, et al. Ulcerative tracheobronchitis after lung transplantation: a new form of invasive aspergillosis. Am Rev Respir Dis. 1991;144:552–8.
99. Sayiner A, Kursat S, Toz H, Duman S, Onal B, Tumbay E. Pseudomembranous necrotizing bronchial aspergillosis in a renal transplant recipient. Nephrol Dial Transplant. 1999;14:1784–5.
100. Horvath JA, Dummer S. The use of respiratory-tract cultures in the diagnosis of invasive pulmonary aspergillosis. Am J Med. 1996;100:171–8.

101. Brown RS, Lake JR, Katzman BA, et al. Incidence of significance of *Aspergillus* cultures following liver and kidney transplantation. Transplantation. 1996;61:666–9.
102. Perfect JR, Cox GM, Lee JY, et al. The impact of culture isolation of *Aspergillus* species: a hospital-based survey of aspergillosis. Clin Infect Dis. 2001;33:1824–33.
103. Husain S, Paterson DL, Studer SM, et al. *Aspergillus* galactomannan antigen in the bronchoalveolar lavage fluid for the diagnosis of invasive aspergillosis in lung transplant recipients. Transplantation. 2007;83:1330–6.
104. Patterson JE. Epidemiology of fungal infections in solid organ transplant patients. Transpl Infect Dis. 1999;1:229–36.
105. Kapoor A, Flechner SM, O'Malley K, Paolone D, File TM, Cutrona AF. Cryptococcal meningitis in renal transplant patients associated with environmental exposure. Transplant Infect Dis. 1999;1:213–7.
106. Hunger RE, Paredes BE, Quattroppani C, Krahenbuhl S, Braathen LR. Primary cutaneous cryptococcosis in a patient with systemic immunosuppression after liver transplantation. Dermatology. 2000;200:352–5.
107. Nosanchuk JD, Shoham S, Fries BC, Shapiro S, Levitz SM, Casadevall A. Evidence of zoonotic transmission of *Cryptococcus neoformans* from a pet cockatoo to an immunocompromised patient. Ann Intern Med. 2000;132:205–8.
108. Anderson DJ, Schmidt C, Goodman J, Pomeroy C. Cryptococcal disease presenting as cellulitis. Clin Infect Dis. 1992;14:666–72.
109. Baer S, Baddley JW, Gnann JW, Pappas PG. Cryptococcal disease presenting as necrotizing cellulitis in transplant recipients. Transpl Infect Dis. 2009;11:353–8.
110. Chandesris LF, MO PS, et al. Cellulitis revealing a cryptococcosis-related immune reconstitution inflammatory syndrome in a renal allograft recipient. Am J Transplant. 2007;7:2826–8.
111. Pappas PG, Perfect JR, Cloud GA, et al. Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. Clin Infect Dis. 2001;33:690–9.
112. Singh N, Alexander BD, Lortholary O, et al. *Cryptococcus neoformans* in organ transplant recipients: impact of calcineurin-inhibitor agents on mortality. J Infect Dis. 2007;195:756–64.
113. Singh N, Perfect JR. Immune reconstitution syndrome associated with opportunistic mycoses. Lancet Infect Dis. 2007;7:395–401.
114. Singh N, Lortholary O, Alexander BD, et al. An immune reconstitution syndrome-like illness associated with *Cryptococcus neoformans* infection in organ transplant recipients. Clin Infect Dis. 2005;40:1756–61.
115. Singh N, Lortholary O, Alexander BD, et al. Allograft loss in renal transplant recipients with *Cryptococcus neoformans* associated immune reconstitution syndrome. Transplantation. 2005;80:1131–3.
116. Singh N, Lortholary O, Dromer F, et al. Central nervous system cryptococcis in solid organ transplant recipients: clinical relevance of abnormal neuroimaging findings. Transplantation. 2008;86:647–51.
117. Demirag A, Elkhammas EA, Henry ML, et al. Pulmonary *Rhizopus* infection in a diabetic renal transplant recipient. Clin Transplant. 2000;14:8–10.
118. Lee E, Vershvovsky Y, Miller F, Waltzer W, Suh H, Nord EP. Combined medical surgical therapy for pulmonary mucormycosis in a diabetic renal allograft recipient. Am J Kidney Dis. 2001;38:E37.
119. Jimenez C, Lumbreras C, Aguado JM, et al. Successful treatment of *Mucor* infection after liver or pancreas-kidney transplantation. Transplant. 2002;73:476–80.
120. Walker SD, Clark RV, King CT, Humphries JE, Lytle LS, Butkus DE. Fatal disseminated *Conidiobolus coronatus* infection in a renal transplant patient. Review. Am J Clin Pathol. 1992;98:559–64.
121. Sheu BS, Lee PC, Yang HB. A giant gastric ulcer caused by mucormycosis infection in a patient with renal transplantation. Endoscopy. 1998;30:S60–1.
122. Ju JH, Park HS, Shin MJ, et al. Successful treatment of massive lower gastrointestinal bleeding caused by mixed infection of cytomegalovirus and mucormycosis in a renal transplant recipient. Am J Nephrol. 2001;21:232–6.
123. Timmouth J, Baker J, Gardiner G. Gastrointestinal mucormycosis in a renal transplant patient. Can J Gastroenterol. 2001;15:269–71.
124. Gold WL, Vellend H, Salit IE, et al. Successful treatment of systemic and local infections due to *Exophiala* spp. Clin Infect Dis. 1994;19:339–41.
125. Salama AD, Rogers T, Lord GM, Lechler RI, Mason PD. Multiple *Cladosporium* brain abscesses in a renal transplant patient: aggressive management improves outcome. Transplantation. 1997; 63:160–2.
126. von Eiff C, Bettin D, Proctor RA, et al. *Phaeocremonium parasiticum* infective endocarditis following liver transplantation. Clin Infect Dis. 1997;25:1251–3.
127. Mesa A, Henao J, Gil M, Durango G. Phaeohyphomycosis in kidney transplant patients. Clin Transplant. 1999;13:273–6.
128. Malani PN, Bleicher JJ, Kauffman CA, Davenport DS. Disseminated *Dactylaria constricta* infection in a renal transplant recipient. Transpl Infect Dis. 2001;3:40–3.
129. Castro LG, da Silva Lacaz C, Guarro J, et al. Phaeohyphomycotic cyst caused by *Colletotrichum crassipes*. J Clin Microbiol. 2001;39:2321–4.
130. Magina S, Libosa C, Santos P, et al. Cutaneous alternariosis by *Alternaria chartarum* in a renal transplanted patient. Br J Dermatol. 2000;142:1261–2.
131. Halaby T, Boots H, Vermeulen A, et al. Phaeohyphomycosis caused by *Alternaria infectoria* in a renal transplant recipient. J Clin Microbiol. 2001;39:1952–5.
132. Blair JE. Coccidioidomycosis in liver transplantation. Liver Transplant. 2006;12:31–9.
133. Blair JE, Logan JL. Coccidioidomycosis in solid organ transplantation. Clin Infect Dis. 2001;33:1536–44.
134. Braddy CM, Heilman RL, Blair JE. Coccidioidomycosis after renal transplantation in an endemic area. Am J Transplant. 2006;6:340–5.
135. Marques SA, Hozumi S, Camargo RM, Carvalho MF, Marques ME. Histoplasmosis presenting as cellulitis 18 years after renal transplantation. Med Mycol. 2008;46:725–8.
136. McGuinn ML, Lawrence ME, Proia L, Segreti J. Progressive disseminated histoplasmosis presenting as cellulitis in a renal transplant recipient. Transplant Proc. 2005;37:4313–4.
137. Bacal F, Andrade AC, Migueletto BC, et al. Histoplasmosis as a late infectious complication following heart transplantation in a patient with Chagas' disease. Arquivos Brasileiors de Cardiologia. 2001;76:403–8.
138. Botterel F, Romand S, Saliba F, et al. A case of disseminated histoplasmosis likely due to infection from a liver allograft. Eur J Clin Microbiol Infect Dis. 1999;18:662–4.
139. Livas IC, Nechay PS, Nauseef WM. Clinical evidence of spinal and cerebral histoplasmosis twenty years after renal transplantation. Clin Infect Dis. 1995;20:692–5.
140. Zainudin BM, Kassim F, Annuar NM, Lim CS, Ghazali AK, Murad Z. Disseminated histoplasmosis presenting with ileal perforation in a renal transplant recipient. J Trop Med Hygiene. 1992;95:276–9.
141. Brett MT, Kwan JT, Bending MR. Caecal perforation in a renal transplant patient with disseminated histoplasmosis. J Clin Pathol. 1988;41:992–5.
142. Cohen IM, Galgini JN, Potter D, Ogden DA. Coccidioidomycosis in renal transplant replacement therapy. Arch Intern Med. 1982;142:489–94.
143. Serody JS, Mill MR, Detterbeck FC, Harris DT, Cohen MS. Blastomycosis in transplant recipients: report of a case and review. Clin Infect Dis. 1993;16:54–8.

144. Gauthier GM, Safdar N, Klein BS, Andes DR. Blastomycosis in solid organ transplant recipients. Transpl Infect Dis. 2007;9:310–7.
145. Pappas PG, Threlkeld MG, Bedsole GD, Cleveland KO, Gelfand MS, Dismukes WE. Blastomycosis in immunocompromised patients. Medicine (Baltimore). 1994;72:311–25.
146. Agarwal SK, Tiwari SC, Dash SC, et al. Urinary sporotrichosis in a renal allograft recipient. Nephron. 1994;66:485.
147. Gullberg RM, Quintanilla A, Levin ML, Williams J, Phair JP. Sporotrichosis: recurrent cutaneous, articular, and central nervous system infection in a renal transplant recipient. Rev Infect Dis. 1987;9:369–75.
148. Guarro J, Nucci M, Akiti T, Gene J, Barreiro MD, Goncalves RT. Fungemia due to *Fusarium sacchari* in an immunosuppressed patient. J Clin Microbiol. 2000;38:419–21.
149. Sampathkumar P, Paya CV. *Fusarium* infection after solid-organ transplantation. Clin Infect Dis. 2001;32:1237–40.
150. Boutati EI, Anaissie EJ. *Fusarium*, a significant emerging pathogen in patients with hematologic malignancy: ten years' experience at a cancer center and implications for management. Blood. 1997;90:999–1008.
151. Clark NM. *Paecilomyces lilacinus* infection in a heart transplant recipient and successful treatment with terbinafine. Clin Infect Dis. 1999;28:1169–70.
152. Blackwell W, Ahmed K, O'Docherty C, Hay RJ. Cutaneous hyalohyphomycosis caused by *Paecilomyces lilacinus* in a renal transplant patient. Br J Dermatol. 2000;143:873–5.
153. Hilmarsdottir I, Thorsteinsson SB, Asmundsson P, Bodvarsson M, Arnadottir M. Cutaneous infection caused by *Paecilomyces lilacinus* in a renal transplant patient: treatment with voriconazole. Scand J Infect Dis. 2000;32:331–2.
154. Guarro J, Antolin Ayala MI, Gene J, Gutierrez-Calzada J, Nieves-Diez C, Ortoneda M. Fatal case of *Trichoderma harzianum* infection in a renal transplant recipient. J Clin Microbiol. 1999;37:3751–5.
155. Gordon SM, LaRosa SP, Kalmadi S, et al. Should prophylaxis for *Pneumocystis carinii* pneumonia in solid organ transplant recipients ever be discontinued? Clin Infect Dis. 1999;28:240–6.
156. Torre-Cisneros J, De la Mata M, Pozo JC, et al. Randomized trial of weekly sulfadoxine/pyrimethamine versus daily low-dose trimethoprim-sulfamethoxazole for the prophylaxis of *Pneumocystis carinii* pneumonia after liver transplantation. Clin Infect Dis. 1999;29:771–4.
157. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of the EORTC/MSG Consensus Group for invasive fungal diseases. Clin Infect Dis. 2008;46:1813–21.
158. Ostrosky-Zeichner L, Alexander BD, Kett DH, et al. Multicenter clinical evaluation of the (1,3) β-D glucan assay as an aid to diagnosis of fungal infections in humans. Clin Infect Dis. 2005;41:654–9.
159. Husain S, Kwak EJ, Obman A, et al. Prospective assessment of Platelia *Aspergillus* galactomannan antigen for the diagnosis of invasive aspergillosis in lung transplant recipients. Am J Transplant. 2004;4:796–802.
160. Winston DJ, Pakrasi A, Busuttil RW. Prophylactic fluconazole in liver transplant recipients: a randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1999;131:729–37.
161. Tollemar J, Hockerstedt K, Ericzon BG, Jalanko H, Ringden O. Liposomal amphotericin B prevents invasive fungal infections in liver transplant recipients. Transplantation. 1995;59:45–50.
162. Pappas PG, Andes D, Schuster M, et al. Invasive fungal infections in low-risk liver transplant recipients: a multi-center prospective observational study. Am J Transplant. 2006;6:386–91.
163. Hadley S, Huckabee C, Pappas PG, et al. Outcomes of antifungal prophylaxis in high-risk liver transplant recipients. Transpl Infect Dis. 2009;11:40–8.
164. Marty FM, Rubin RH. The prevention of infection post-transplant: the role of prophylaxis, preemptive and empiric therapy. Transpl Int. 2006;19:2–11.
165. Palmer SM, Drew RH, Whitehouse JD, et al. Safety of aerosolized amphotericin B lipid complex in lung transplant recipients. Transplantation. 2001;72:545–8.
166. Monforte V, Roman A, Gavalda J, et al. Nebulized amphotericin B prophylaxis for *Aspergillus* infection in lung transplantation: study of risk factors. J Heart Lung Transplant. 2001;20:1274–81.