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Fungal infection in solid organ recipients

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ABSTRACT

In solid organ recipients, as with other immunosuppressed patients, infections by *Candida* spp. and *Aspergillus* spp. are the most frequent invasive mycoses. Infections by *Cryptococcus* spp. and fungi of the Mucorales order are less common. Infections by *Fusarium* spp. and *Scedosporium* spp. are very uncommon, except in patients undergoing hematopoietic stem cell transplant and patients with prolonged neutropenia. The risk factors for fungal infection are immunosuppression, surgery, viral co-infection, and environmental exposure. Diagnosis is challenging: blood culture is of little use, except in candidiasis and cryptococcosis, and the poor accuracy of antigen-based techniques, except in cryptococcosis, favors widespread use of empirical therapy. A delay in the initiation of therapy increases the already high mortality of these infections. The agents used to treat fungal infection are azoles, echinocandins, and lipid amphotericin. Administration depends on antifungal activity, drug-drug interactions with calcineurin inhibitors, and safety profiles (effects on grafts and other side effects).

Infección fúngica en los receptores de órgano sólido

Palabras clave:
Infección fúngica
Receptores de órgano sólido
Trasplante

RESUMEN

En los receptores de órgano sólido, y en otros pacientes inmunodeprimidos, las infecciones por *Candida* spp. y *Aspergillus* spp. son las micosis invasivas más frecuentes. Las infecciones por *Cryptococcus* spp. y por hongos del orden Mucorales son menos frecuentes. Las infecciones por *Fusarium* spp. y *Scedosporium* spp. son muy infrecuentes, excepto en pacientes sometidos a trasplante de células madre hematopoyéticas y pacientes con neutropenia prolongada. Los factores de riesgo para infección fúngica son la inmunosupresión, cirugía, coinfección viral y exposición al entorno. El diagnóstico constituye un reto: la poca utilidad del hemocultivo, excepto en la candidiasis y la criptococcosis, y la poca precisión de las técnicas basadas en antígeno, excepto en la criptococcosis, favorecen el uso extendido del tratamiento empírico. El retraso en el inicio del tratamiento aumenta la ya alta mortalidad de estos procesos. Los fármacos utilizados para tratar las infecciones fúngicas son azoles, equinocandinas y amfotericina asociada a lípido. La administración depende de la actividad antifúngica, las interacciones farmacológicas con los inhibidores de la calcineurina y el perfil de seguridad (efecto sobre el injerto y otros efectos secundarios).

Epidemiology of Fungal Infection in Transplant Recipients

Invasive fungal diseases (IFD) represent a serious threat for patients undergoing solid organ transplant (SOT). In epidemiological terms, IFD in this population can be divided into 2 groups: opportunistic and endemic fungi. IFD caused by opportunistic fungi are universally distributed and are caused mainly by *Candida* spp., *Aspergillus* spp., and to a lesser extent, *Cryptococcus* spp., fungi of the Mucorales order, as well as other filamentous fungi. IFD by endemic fungi are usually reactivations but may occasionally occur as primary infections in patients who live in or visit highly endemic areas.[1] This document discusses IFD caused by opportunistic fungi.

Table 1 shows the frequency of infections caused by *Candida* spp. and *Aspergillus* spp. included in the database of RESITRA (Red Española para el Estudio de Infecciones en Trasplantados [*Spanish Network for the Study of Infections in Transplants*]), which recorded

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Table 1
Invasive fungal infections in transplant recipients in Spain (01/09/2003 to 01/03/2005)

Type, No.	*Candida* spp.	*Aspergillus* spp.
Kidney transplant, 1330	41 (3%)	2 (0.15%)
Liver transplant, 979	30 (3.1%)	5 (0.5%)
Heart transplant, 283	11 (3.8%)	3 (1%)
Lung transplant, 167	6 (3.6%)	10 (5.9%)
Pancreas transplant, 53	2 (3.7%)	2 (3.7%)
Bone marrow transplant, 944 (autologous and allogenic)	34 (3.6%)	56 (5.9%)

Data from Garrido et al.[2]

more than 3500 solid organ and/or bone marrow transplants in Spain during the period 2003-2005.[2]

In its follow-up of more than 16,000 SOT in the USA, the Transplant-Associated Infection Surveillance Network (TRANSNET) recently confirmed an incidence of IFD of 3.1% during the first year after transplant, with a mortality rate of around 60%. The frequency of invasive candidiasis (IC), invasive aspergillosis (IA), cryptococcosis, and endemic mycosis was 53%, 19%, 8%, and 5.3%, respectively.[3]

Risk Factors for IFD in Solid Organ Recipients (Table 2)

Environmental factors

Patients who live in or visit areas of endemic mycoses should be warned about risk behaviors associated with acquisition. Recipients should also be informed about the risks associated with work or leisure practices such as farming, gardening, and moving soil.

Immunosuppression

The impact of immunosuppression is generally greater during the early stages of the post-transplant period; however, some patients with repeated rejection episodes or chronic rejection should maintain high levels of immunosuppression for prolonged periods. It is worth remembering that certain immunosuppressants have an antifungal effect and are therefore protective.[1] Table 3 shows the effect of immunosuppressants on fungal infection.

Surgery

Disruption of the skin and mucosal barriers during surgery predisposes patients to infection. Fluid collection (blood, biliary fistula), surgical drainage, and catheters favor excessive growth of fungi. Transmission during transplant by a graft infected with fungi has been reported with *Coccidioides immitis*, *Histoplasma capsulatum*,[4] *Cryptococcus* spp., and *Aspergillus* spp.

Table 2
Risk factors associated with invasive fungal infection in transplant recipients

Environmental	Agriculture, gardening, ventilation systems, water distribution, exposure to building materials
	Prolonged intubation
	Marijuana
	Acquired myelosuppression
	Diabetes, malnutrition, under-nutrition
	Ventricular assistance (heart transplant)
	Bronchiolitis obliterans (lung transplant)
	Traveling to or residence in endemic areas
Immunosuppression	Pre-transplant immunosuppression
	Chronic rejection, multiple episodes of acute rejection, high doses of corticosteroids
	Broad-spectrum antibiotics
	Myelosuppressive agents (ganciclovir, cotrimoxazole)
	Lymphocyte depletion (antithymocyte globulins, muromonab CD3, alemtuzumab)
	Renal insufficiency, dialysis
Surgery	Primary graft dysfunction, retransplantation
	Reoperation, high transfusional requirements
	Multivisceral transplant
	Intestinal transplant (proximal colon)
	Contamination of graft
	Surgical drainage, catheters
Virus	Co-infection with viral immunomodulators (CMV, HSV, HHV-6, HHV-7, HCV)

CMV: cytomegalovirus; HCV: hepatitis C virus; HHV: human herpesvirus; HSV: herpes simplex virus.

Viral infections

Infections by cytomegalovirus, human herpesvirus types 6 and 7, and hepatitis C virus are associated with an increased risk of IFD.

A recent study in Spain of 156 transplant recipients with IA and 300 controls showed that 57% of cases of aspergillosis occur during the first 3 months after transplant and that the remainder occur late.[5] A two-phase (early and late) presentation of aspergillosis has also been described in other studies.[6,7]

In lung transplants, the only independent factor associated with early aspergillosis was colonization of the airway by *Aspergillus* spp. during the 6 months before transplantation. Late-onset aspergillosis

Table 3
Impact of immunosuppressants on fungal infections in transplant recipients

Immunosuppressants with antifungal activity	
Calcineurin inhibitors	Calcineurin phosphatase affects the growth and virulence of some fungi.
Mycophenolate	They are active against *Cryptococcus* spp., *Candida* spp., and *Aspergillus* spp.
Sirolimus/everolimus	They seem to be active against *Pneumocystis jiroveci* by inhibiting inosine monophosphate dehydrogenase TOR inhibitors have potent antifungal activity. TOR kinase is involved in the proliferation of several fungi, including *Candida, Cryptococcus, Fusarium, Penicillium, Saccharomyces*, and *Schizosaccharomyces*
Immunosuppressants that increase the risk of fungal infection	
Lymphocyte depletion inducers	There is a risk of invasive fungal infection, especially aspergillosis
Corticosteroids	Inhibit the activity of macrophages and increase the risk of invasion in patients colonized by *Aspergillus* spp.
Myelosuppressants	Development of neutropenia associated with some drugs used in transplant patients (azathioprine, ganciclovir, cotrimoxazole) increases the risk of invasive fungal infection

in lung recipients was only associated with chronic rejection.[5] However, colonization by other filamentous fungi does not seem to be associated with a high risk of invasive disease, even in the absence of prophylaxis.[8]

In liver transplant recipients, renal insufficiency (especially in patients undergoing dialysis) and retransplantation are 2 of the main risks; however, other studies have also associated an increased risk of IFD with the following conditions: fulminant hepatitis, high transfusional requirements, biliary anastomosis by choledochojejunostomy using the Roux-en-Y technique, and reoperation in the immediate post-transplant period.[6]

In pancreas transplants, the risk factors for IFD (mainly by *Candida* spp.) include bladder drainage (as opposed to enteric drainage), graft thrombosis, fistulization of pancreatic fluid to the peritoneum, infection by cytomegalovirus, and donor age greater than recipient age.[9]

Causal Agents

Candida spp.

Candida spp. is the most common cause of IFD in solid organ recipients. The incidence of candidiasis in this group is highly variable and is higher in abdominal transplants.[9] Most cases of candidiasis occur during the first 2 months after surgery. The main portal of entry is the gastrointestinal tract, followed by endovascular catheters and the urinary tract. The most common clinical forms are mucocutaneous, mainly oropharyngeal and esophageal candidiasis and vulvovaginitis.[9] Candidemia is the most common clinical presentation among the invasive forms.

Cryptococcus spp.

The incidence of infection by *Cryptococcus* spp. is low, although mortality in SOT is close to 40%.[10] Infection is more common in kidney recipients. The antifungal activity of calcineurin inhibitors may explain this low incidence.[11,12] Most reported cases in transplant recipients occur more than 1 year after transplant. The main symptoms are neurological, generally leading to meningoencephalitis and, more rarely, brain abscesses. The skin and soft tissues are affected in 13% of recipients. A recent study analyzing cryptococcosis in transplant recipients has confirmed the presence of positive and high titers in extrapulmonary forms, fungemia, non-nodular fungal forms and lung recipients.[13]

Aspergillus spp.

Infection by *Aspergillus* spp. is acquired by inhalation of spores. Many outbreaks of aspergillosis in transplant recipients occur during building work involving extensive movement of materials in areas near the hospital or in the hospital itself. Once the tissue is infected, the vascular system is invaded, resulting in infarction, hemorrhage, and hematogenous seeding. Mortality depends on the type of transplant, but is greater than 50%. The clinical forms of aspergillosis in transplant recipients differ little from those observed in other immunosuppressed patients. The most common manifestation is pulmonary, in which case presentation is usually acute and invasive.

Other filamentous fungi

The incidence of infections by filamentous fungi in transplant recipients has increased in recent years.[14] Most are caused by fungi of the Mucorales order (zygomycosis), although infections by *Fusarium* spp. and *Scedosporium* spp. are also relevant. Two recent American series on fungal infections in solid organ recipients reported a frequency of zygomycosis lower than 3% among all patients with IFD.[3,15] A case-control study of 50 solid organ recipients with zygomycosis confirmed renal insufficiency, diabetes, and previous administration of voriconazole or caspofungin as independent risk factors.[16] The most common form of zygomycosis in solid organ recipients affects the lungs,[16,17] with a mortality of 45-50%. Mortality can reach 70-93% in cerebral forms.[18]

Infection by *Scedosporium apiospermum* accounts for 25% of invasive mycoses caused by filamentous fungi other than *Aspergillus* in lung recipients.[19] Patients undergoing unilateral lung transplant are more susceptible, as the native lung acts as a reservoir.

In recent years, the frequency of infections by dematiaceous fungi (black fungus infection also known as phaeohyphomycosis) has increased in transplant recipients. These fungi are ubiquitous, are found in decomposing material, and are usually contaminants. Although the group comprises several species, *Exophiala* spp. and *Alternaria* spp. are the most widely documented. These species produce 2 very different clinical patterns: soft tissue infection (skin, subcutaneous, and joints), accounting for 90% of cases, and invasive infections, which mainly produce brain abscesses and account for 10% of cases. Pulmonary and esophageal involvement are less common.

Diagnostic Procedures

Blood culture is the diagnostic procedure with the highest yield in clinically suspected candidiasis. Most currently used automated systems reveal the presence of candidemia without the need for prolonged incubation periods. If candidemia is not present, the diagnosis of candidiasis is more complicated and requires staining techniques and sample culture. Compared with blood culture, sensitivities and specificities of almost 90% have been obtained with mannan antigen-based techniques and anti-mannan antibodies in serum (Platelia Candida®, Bio-Rad) or with techniques based on detection of antimycelium antibodies to *Candida* spp. (Candida albicans IFA IgG®; Vircell). All of the above techniques are used in immunocompetent patients; however, their diagnostic yield decreases in transplant recipients and immunosuppressed patients.[20] The mannan-antimannan detection technique has shown very good performance in the diagnosis of chronic disseminated candidiasis, as it is able to detect the infection 16 days in average prior culture.[21]

Serial detection of β-D glucan (Fungitell®, Cape Cod Incorporated; or Wako WB003 test®, Wako Pure Chemical Industries) has revealed predictive values >90%, although this approach is not specific for candidiasis (the component is panfungal), it is technically difficult to apply, and experience with transplant recipients is limited.[22] False-positive results have been described in patients with *Pseudomonas aeruginosa* bacteremia[23] and in patients receiving treatment with fungus-derived antibiotics.[24] Finally, promising real-time PCR methods have been developed for the detection of *Candida* spp. in clincial samples. A meta-analysis published recently including 963 cases of invasive candidiasis reported 95% sensitivity for PCR-based tecniques. However, standardization processes and third party validation should be carried out to evaluate the accuracy of those methods in clinical practice.[25]

The diagnosis of IA is problematic because of the risk of colonization and contamination and the low predictive value of respiratory sample culture (mainly sputum). The European Organization for the Research and Treatment of Cancer and the American Mycosis Study Group drew up a series of guidelines for the treatment of IFD;[26] these guidelines have recently been revised.[27] Three diagnostic criteria were established: proven infection, probable infection, or possible infection. These 3 categories are established after analyzing 3 patient characteristics, including underlying condition, clinical (and radiological) presentation, and microbiological or histological reports (Table 4). Together with computed tomography,

Table 4
Diagnostic criteria for invasive fungal infection

A) Underlying condition
Recent episode of neutropenia (<500/mm^3) for >10 days
Allogenic bone marrow transplant
Prolonged use of corticosteroids at mean doses of >0.3 mg/kg/day of prednisone equivalent for >3 weeks (except for allergic bronchopulmonary aspergillosis)
Treatment with T-cell immunosuppressants, such as cyclosporine, tacrolimus, TNF-α blockers, specific monoclonal antibodies (e.g., alemtuzumab), or nucleoside analogs for the last 90 days
Severe innate immunodeficiency (e.g., chronic granulomatous disease or severe combined immunodeficiency)
B) Clinical (and radiological) criteria
Lower respiratory tract infection with the presence of 1 of the following signs:
Dense, well delimited lesions (with/without halo sign)
Signs of air trapping
Cavitation
Tracheobronchitis (ulcer, nodule, pseudomembrane, plaque, or erosion in bronchoscopy)
Infection of the nasal sinuses associated with 1 of the following signs:
Localized acute pain
Nasal ulcer with black eschar
Disruption of the bone barrier, including the orbit
Central nervous system infection, with the presence of 1 of the following signs:
Focal lesion in image tests
Meningeal thickening (computed tomography or magnetic resonance)
C) Microbiological (mycological) criteria
Direct analysis (cytology, direct microscopy, or culture)
Filamentous fungus in sputum, bronchoalveolar lavage, bronchial brushing, or aspiration of paranasal sinuses, indicated for:
Presence of hyphae
Culture of filamentous fungi (eg, *Aspergillus* spp., *Fusarium*, *Zygomycetes*, or *Scedosporium* spp.)
Indirect analysis (detection of antigens)
Aspergillosis: serum galactomannan, plasma, bronchoalveolar lavage, or cerebrospinal fluid
Invasive fungal infection (noncryptococcal or by Mucorales): β-D-glucan in serum

Proven infection: confirmation by histology or sterile tissue culture.
Probable infection: A + B + C (at least 1 factor from each group).
Possible infection: A + B (at least 1 factor from each group).
Modified from De Pauw.[27]

detection of galactomannan (GM) is one of the non-culture-based tests that most contributes to the diagnosis of IA. It has proven highly useful in monitoring patients with a hematological malignancy.[28] Our group found a sensitivity of 56% in the diagnosis of IA in liver recipients.[29] The specificity of GM is reduced by potential false positives, which are usually associated with the use of β-lactams.[30] Our group has confirmed a high frequency of false positives for GM during the first week after liver transplant, and this finding was associated with β-lactam prophylaxis.[31]

One potential advance in the diagnosis of IA is the use of GM in bronchoalveolar lavage. In a study performed at the University of Pittsburgh, Husain et al[32] assessed the role of GM in bronchoalveolar lavage in 116 lung recipients. Based on a cut-off of 0.5, the authors found a sensitivity of 60% and specificity of 95%; when the cut-off was raised to 1.0, sensitivity was 60% and specificity was 98%. Similarly, for a GM >1.0 in bronchoalveolar lavage in lung recipients, a group from the University of Florida, USA, found a sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 90.8%, 41.7%, and 100%, respectively.[33]

In the application of PCR to *Aspergillus fumigatus*, different primers, extraction and amplification protocols, and reagents make it difficult to reproduce and validate results between laboratories. A study carried out in Madrid confirmed that serial detection of *A. fumigatus* using PCR in serum (by amplifying the ribosomal ITS1 region and using beacon molecular probes) had a sensitivity and specificity >90% in the diagnosis of IA in patients with hematological malignancy.[34] A recent study reported favorable results after applying PCR to detect *Aspergillus* mitochondrial DNA in liver recipients with positive GM titers: PCR was positive in 8 out of 13 patients with probable or possible aspergillosis and in none of the 12 patients with a false positive for GM.[35]

Sensitivity and specificity for the detection of cryptococcal antigen in serum and cerebrospinal fluid (CSF) are very high (close to 100%). Together with blood cultures, this technique is the main diagnostic tool in patients with suspected cryptococcosis, including transplant recipients. However, diagnosis can also be established by India ink staining of yeasts (usually in CSF) or by culture of sterile samples.

Treatment

Candida spp.

The usual treatment of *Candida* infections in transplant recipients is no different from that administered to other types of patients. The Infectious Diseases Society of America has updated its guidelines on management of patients with candidiasis.[36] The Spanish Society for Infectious Diseases and Clinical Microbiology (Spanish initials, SEIMC) recently published its guidelines for the treatment of candidiasis, with a specific section on treatment of transplant recipients.[37]

The first measure to be adopted, where possible, is withdrawal of central venous catheters. This measure has been associated with lower mortality in neonates and non-neutropenic patients;[38] an appropriate ophthalmological examination is also recommended in patients with candidemia.

Although randomized clinical trials have shown polyenes, triazoles, and echinocandins to be efficacious in IC, the initial choice of treatment (pending species identification and sensitivity) usually involves fluconazole and echinocandins.[36,37] The advantages of fluconazole include its low cost, low toxicity, and its oral and intravenous bioavailability; however, its activity against *Candida glabrata* is poor. Echinocandins are expensive, although they are subject to fewer interactions, have fewer side effects, and are very active against azole-resistant strains.

Administration of certain antifungals is limited in solid organ recipients. Amphotericin B deoxycholate should not be used in SOT, due to its nephrotoxicity, especially in patients receiving calcineurin inhibitors. All the azoles interact with calcineurin inhibitors because their metabolism depends on cytochrome P450; therefore, it is very important to determine plasma levels of both azoles and immunosuppressive agents. Echinocandins (caspofungin, anidulafungin, and micafungin) generally have few side effects and fewer interactions in solid organ recipients than the other antifungals mentioned.

In non-neutropenic transplant recipients who have not recently received azoles, fluconazole can be administered at ≥6 mg/kg/d to treat candidiasis. However, fluconazole is frequently used as prophylaxis in transplant recipients. In such cases, or in patients with moderate-to-severe infection, an echinocandin (caspofungin, anidulafungin, or micafungin) should be used.[36,37] If the causal agent is *C. albicans*, or *C. parapsilosis*, the recommended treatment is fluconazole; if it is *C. glabrata* or *C. krusei*, an echinocandin is the best option. Lipid amphotericin and voriconazole can be used as

alternatives in cases of intolerance or when it is impossible to use other antifungals. In patients with candidemia, treatment should be maintained for 2 weeks after the last sterile blood culture and until symptoms have resolved. If the strain is sensitive to fluconazole, then treatment can be completed with this drug. In cases of infection by *C. glabrata* with dose-dependent sensitivity to fluconazole (MIC, 16-32 μg/ml), fluconazole should be used at 12 mg/kg/d. In patients infected with *C. krusei*, sequential treatment can be administered with voriconazole.

Although neutropenia is uncommon in solid organ recipients, if candidemia occurs in this context, then the recommended treatment is an echinocandin or lipid amphotericin B (3-5 mg/kg/d), given the fungicidal character of these treatments.

Since echinocandins do not cross the blood-brain barrier, the recommended treatment for CNS infections is lipid amphotericin, with or without flucytosine, followed by fluconazole. Echinocandins diffuse poorly to the retina; therefore, in endophthalmitis it is recommended to use amphotericin or fluconazole, combined with surgery in severe forms. Endocarditis and endovascular infections require treatment with fungicidal agents such as lipid amphotericin with or without flucytosine or echinocandins, as well as surgery or valve replacement, when possible. Fluconazole is maintained for sequential treatment in stable patients.[36,37]

Transplant recipients are frequently affected by candiduria, especially in kidney and pancreas transplants. In these and other transplant recipients, as well as in neutropenic patients, ICU patients, and low-birth-weight infants, candiduria can indicate disseminated candidiasis and should be treated for 7-14 days. Urinary catheters should be withdrawn or replaced. Treatment of urinary tract infections caused by *Candida* spp. in a transplant recipient should be based on fluconazole. The high urine concentrations reached by this agent make it very effective, even in isolates with reduced sensitivity. The use of amphotericin B or its derivatives should be restricted to treatment of fluconazole-resistant strains, mainly *C. krusei*. The low levels reached in urine with echinocandins and the scant experience with these agents in urinary tract infections caused by *Candida* spp. lead to a recommendation against using echinocandins —at least as first-line agents— in *Candida* infections.

Fluconazole is the treatment of choice in esophageal candidiasis. Echinocandins are recommended in azole-treated patients or in patients with *C. krusei* infection. Caspofungin, micafungin, and anidulafungin have been analyzed in clinical trials showing efficacy rates similar to those of fluconazole or amphotericin B in esophageal candidiasis.[39-41] Oropharyngeal candidiasis and/or vaginitis can be treated topically with nystatin solution or topical azoles (eg, clotrimazole pessary).

Cryptococcus spp.

There are no specific recommendations for the management of cryptococcosis; treatment should be similar to that established for other immunosuppressed patients, mainly those with HIV infection.[42] Nevertheless, management of transplant recipients with cryptococcosis requires that 2 particular observations be borne in mind: the synergetic interaction between calcineurin inhibitors and antifungal treatment in this population[12,13] and the phenomenon of immune restoration in 5% of transplant patients with cryptococcosis. Immune restoration occurs a mean of 5 weeks after reducing immunosuppression and initiating antifungal treatment and entails a paradoxical worsening of symptoms despite negative cultures.[43]

The lipid formulations of amphotericin B (plus flucytosine) are as effective as amphotericin B (66-75% response) and present less toxicity; therefore, these are the treatment of choice in transplant recipients.

5-flucytosine should be adjusted to renal function or, preferably, by determining serum levels, which should range from 30 μg/ml to 80 μg/ml[9]. Nevertheless, a recent multinational study on 83 transplant recipients and the review of 168 cases published in the literature confirmed that only one-third received concomitant 5-flucytosine and that this was not associated with poorer sterilization of CSF cultures at 2 weeks. In this study, induction treatment was based on a lipid formulation of amphotericin B in 50% of the patients, and induction with fluconazole was reserved for the mildest forms and extrameningeal forms. No significant differences were observed in the outcome of patients who received induction therapy with amphotericin compared to those who received fluconazole.[43]

Maintenance treatment should be with fluconazole (200 to 400 mg/d) or itraconazole (200 mg/d). Some authors recommend lifelong treatment. However, Singh et al[43] confirmed that the median maintenance treatment was 6 months (55% of patients), although in 25% it was maintained for up to 1 year. Therefore, relapse was recorded in only 1% of patients, who were followed for between 2 and 5 years.

In comparison with *C. neoformans*, infection by *C. gatii* is associated with more neurological sequelae, a greater need for surgery, and a poorer response, probably because of the reduced activity of fluconazole and the greater frequency of cryptococcoma, and the use of corticosteroids in the presence of marked perilesional edema. Cryptococcoma must sometimes be removed by surgical resection if they are easily located. In patients with cryptococcosis, intracranial hypertension must be managed appropriately with repeated lumbar punctures or placement of a CSF shunt when necessary.

Aspergillus spp.

Voriconazole is authorized for treatment of IA in solid organ recipients based on the results of a small-scale non-comparative open-label European trial[44] and on a trial that compared voriconazole and amphotericin B deoxycholate as initial treatment in patients with hematological malignancy;[45] however, the latter study only included 11 solid organ recipients. Although the experience of SOT groups with voriconazole is considerable, few data have been published.[46]

The CLEAR (Collaborative Exchange of Antifungal Research) study analyzed 721 immunosuppressed patients with IFI treated with amphotericin B lipid complex. The study included 109 solid organ recipients with IA, of whom 54% had a favorable response.[47]

Caspofungin is the only echinocandin approved by the FDA and EMEA for the treatment of refractory IA. In a study of 12 thoracic organ recipients, this agent was used with 86% efficacy.[48] Maertens et al[49] recently confirmed a favorable response in 6 of 9 solid organ recipients. In an observational study of 19 solid organ recipients, Winkler et al[50] found a favorable response with caspofungin used as first-line treatment in 78% of patients receiving monotherapy and in 70% of those receiving combination therapy.

The role of combination therapy in solid organ recipients with IA has not been defined. One multicenter study analyzed outcomes in 40 patients who received voriconazole and caspofungin as initial treatment for IA.[51] This group was compared with a historic cohort who received a lipid formulation of amphotericin B. The multivariate analysis revealed that combination therapy reduced 90-day mortality in the subgroup of patients with renal insufficiency and IA caused by *A. fumigatus*.[51]

To date, published experience with posaconazole or micafungin to treat solid organ recipients with IA is limited, although results are satisfactory.[52,53] Even fewer data are available for anidulafungin.

In most patients with IA, the primary approach involves voriconazole (4 mg/kg/12 h, with a loading dose of 6 mg/kg/12 h) or liposomal amphotericin (3 mg/kg/d). If voriconazole is used in severely ill patients, the parenteral formulation is recommended in order to ensure bioavailability. If renal impairment is present or the patient is clinically stable, the drug can be administered orally (200

Table 5
Recommendations for the management of fungal infections other than those caused by *Candida* spp., *Cryptococcus* spp., and *Aspergillus* spp. in transplant recipients

Agent	Treatment
Mucorales	Lipid amphotericin 3-5 mg/kg/d (or a higher dose?) Posaconazole 800 mg/d Wide surgical resection. Correction of metabolic deficiency Reduction of immunosuppression (if possible).
Scedosporium apiospermum	Voriconazole 400 mg/d Lipid amphotericin 3-5 mg/kg/d Surgical resection and removal of foreign body Correction of neutropenia when present
Scedosporium prolificans	Multiple resistance Favorable outcome with azoles in some cases (voriconazole) ± terbinafine Surgical resection and removal of foreign body Correction of neutropenia when present
Fusarium spp.	Lipid amphotericin 3-5 mg/kg/d Voriconazole 400 mg/d Posaconazole 800 mg/d Surgical resection and removal of foreign body Correction of neutropenia when present
Phaeohyphomycosis	Voriconazole 400 mg/d Itraconazole 400 mg/d Lipid amphotericin 3-5 mg/kg/d Surgical resection and removal of foreign body
Trichosporon spp.	Fluconazole 400-800 mg/d Voriconazole 400 mg/d
Malassezia spp.	Fluconazole 400-800 mg/d Lipid amphotericin B 3-5 mg/kg/d Removal of intravenous catheters
Histoplasma capsulatum	Lipid amphotericin 3-5 mg/kg/d or amphotericin DC 0.6-0.7 mg/kg/d Itraconazole 400 mg/d
Coccidioides immitis	Lipid amphotericin 3-5 mg/kg/d or amphotericin DC 0.7-1 mg/kg/d (in severe or disseminated pulmonary forms) Fluconazole 800 mg/d (in meningitis and severe forms) Itraconazole 400 mg/d (when meningitis is not present)
Blastomyces dermatitidis	Lipid amphotericin 3-5 mg/kg/d or amphotericin DC 0.7-1 mg/kg/d Itraconazole 400 mg/d (for mild forms) Voriconazole 400 mg/d (for mild forms)
Paracoccidioides brasiliensis	Lipid amphotericin 3-5 mg/kg/d or amphotericin DC 0.7-1 mg/kg/d Itraconazole 400 mg/d Cotrimoxazole (400/80; tid) of sulfadiazine (4 g/d or 60-100 mg/kg/d)
Sporothrix schenckii	Lipid amphotericin 3-5 mg/kg/d or amphotericin DC 0.7-1 mg/kg/d Itraconazole 400 mg/d (in cutaneous forms)

Amphotericin DC: amphotericin deoxycholate; lipid amphotericin: liposomal amphotericin (3 mg/kg/d), amphotericin lipid complex (5 mg/kg/d).

mg/12 h). Plasma concentrations of voriconazole must be monitored in order to maintain the range between 2 μg/ml and 5 μg/ml. Azoles should be administered on an individual basis in solid organ recipients, and, in certain cases (especially liver recipients) their use should be questioned. In patients for whom administration of voriconazole is problematic (risk of liver toxicity, severe drug-drug interaction, intolerance or allergy to azoles), treatment should be with liposomal amphotericin B.

Drug-drug interactions should be evaluated very carefully in solid organ recipients. Itraconazole increases serum concentrations of cyclosporine A and tacrolimus by 40-83%.[54] If voriconazole is administered, the calcineurin inhibitor dose should be reduced by 50-60%.[55] Co-administration of voriconazole and sirolimus is formally contraindicated, although some authors have used applied this combination by reducing the dose of sirolimus by 75-90%. If the patient is receiving posaconazole, then the dose of tacrolimus or cyclosporine A should be reduced by 60-75%. Few drug-drug interactions affect the echinocandins: most are observed with caspofungin, the fewest with anidulafungin.

Surgery is recommended in patients with massive hemoptysis, endocarditis, sinus node disease, and infection of the pericardium, large vessels, bone, subcutaneous tissue, or central nervous system during treatment. When immunosuppressants are used as an adjuvant to antifungal therapy, the dose should be reduced without jeopardizing the viability of the graft. Although the duration of treatment has not been established, it should be maintained until radiological signs disappear, usually after a minimum of 6 to 12 weeks. Treatment with oral voriconazole could be extended for some weeks in order to treat possible residual microfoci of aspergillosis.

Other filamentous fungi

As with other immunosuppressed patients, management of zygomycosis in solid organ recipients is based on 3 approaches: 1) antifungal treatment with amphotericin B; 2) surgical resection, and 3) reduced immunosuppression. Recent advances in therapy include new lipid formulations of amphotericin B, posaconazole,[53,56] and iron chelators such as deferasirox or deferiprone,[57] as well as echinocandins that can be used in combination with amphotericin B[58] and recombinant cytokines, such as granulocyte colony-stimulating factor and granulocyte macrophage-colony stimulating factor.

High doses of lipid amphotericin B (10-15 mg/kg/d) have been used in refractory forms and/or in cases of CNS involvement, although their efficacy has not been compared to doses of 3-5 mg/kg/d and they are more toxic. Good results have been reported with posaconazole in patients who have previously received amphotericin B;[53,56] nevertheless, the combination of posaconazole and amphotericin B has not proven beneficial in the prevention of murine experimental aspergillosis.[59] Reed et al[58] recently reported their experience with combinations of caspofungin and lipid formulations

of amphotericin B used to treat mucormycosis. An ongoing study is evaluating the efficacy and tolerability profile of deferasirox combined with lipid amphotericin B.

Management of infections by *Scedosporium* spp. is also based on correction of underlying factors. Surgery can improve expectations for therapy, especially in the treatment of processes such as sinusitis, keratitis, arthritis, osteomyelitis, and brain abscess. Voriconazole is the treatment of choice, especially in infections by *S. apiospermum*.[60] In contrast, *S. prolificans* is resistant to most antifungals.[61] A recent multicenter study confirmed the role of voriconazole in the treatment of 107 severe infections caused by *Scedosporium* spp., some of which were in transplant recipients.[60] The study showed that 57% of patients responded to voriconazole and that the response was significantly better in infection by *S. apiospermum* (64%) than in infection by *S. prolificans* (44%). A recent series of 162 cases of infection by *S. prolificans* showed that 9% were solid organ recipients; in addition, mortality in disseminated forms was 87%, although this was mainly associated with prolonged neutropenia, a situation that was not reported in solid organ recipients.[61] *S. prolificans* is uniformly resistant to all common antifungals such as amphotericin B, flucytosine, miconazole, ketoconazole, fluconazole, and itraconazole. In vitro studies reveal a synergy between terbinafine and several azoles (voriconazole, miconazole, and itraconazole), and there is some clinical experience with these combinations.[62]

Infection by *Fusarium* spp. is exceptional in solid organ recipients. It should be treated with high doses of lipid amphotericin (mainly in infections by *F. solanii* and *F. verticillioides*) or voriconazole, together with withdrawal of infected catheters and resection of necrotic material.

Table 5 shows the recommendations for treatment in solid organ recipients with other types of fungal infection.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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