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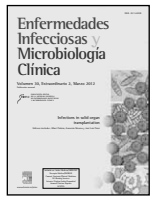

Infections in solid organ transplantation in special situations: HIV-infection and immigration

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ABSTRACT

With the advent of highly active antiretroviral therapy in 1996, patients infected with HIV are now living longer and are dying from illnesses other than acquired immunodeficiency syndrome (AIDS). Liver disease due to chronic hepatitis C is now a leading cause of mortality among HIV-infected patients in the developed world. The prevalence of end-stage kidney or heart disease is also increasing among HIV-infected patients. For these patients, solid organ transplantation (SOT) is the only therapeutic option and HIV infection alone is not a contraindication. Accumulated experience in North America and Europe in the last few years indicates that 3- to 5-year survival in liver recipients coinfected with HIV and HCV is lower than that of HCV-monoinfected recipients. Conversely, 3- to 5-year survival of non-HCV-coinfected liver recipients and kidney recipients was similar to that of HIV-negative patients. Infections in the post-transplant period in HIV-infected recipients are similar to those seen in HIV-negative patients, although the incidence of some of them (e.g. tuberculosis and fungal infections) is higher. In the USA and Europe the number of immigrants from areas with endemic geographically-restricted infections has increased significantly in recent years. These changes in the population profile have led to an increase in the percentage of foreign-born transplant candidates and donors. Organ transplant recipients may develop endemic diseases in four ways: Transmission through the graft; *de novo* infection; reactivation of dormant infection; and reinfection/reactivation in a healthy graft. In foreign-born recipients, there is the possibility of endemic infections manifesting in the post-transplant period as a consequence of immunosuppression. These issues are modifying the criteria for donor selection and have also expanded pre-transplant screening for infectious diseases in both donors and transplant recipients. Some infectious diseases such as Chagas disease, endemic fungal infections, tuberculosis (which could be multidrug- or extensively drug-resistant according the origin of the recipient), leishmaniasis and other viral and parasitic diseases should always be considered in the differential diagnosis of post-transplant infections in foreign-born recipients.

Infecciones en el trasplante de órgano sólido en situaciones especiales: infección por el VIH e inmigrantes

Palabras clave:
Enfermedad de Chagas
Enfermedades parasitarias
Infección por hongos endémicos
Infección fúngica invasiva
Infección por el VIH
Infecciones postrasplante
Inmigración
Leishmaniasis
Nacidos en el extranjero
Profilaxis de las infecciones oportunistas
Sida
Tratamiento antirretroviral
Trasplante hepático

RESUMEN

Con la introducción de la terapia antirretroviral de gran actividad en el año 1996, los pacientes infectados con el VIH están viviendo más tiempo y mueren por otras enfermedades que el síndrome de inmunodeficiencia adquirida (sida). La cirrosis hepática debida al virus de la hepatitis C es ahora la principal causa de mortalidad entre los pacientes coinfectados por el virus de la inmunodeficiencia humana (VIH) y el virus de la hepatitis C (VHC) en el mundo desarrollado. La prevalencia de la enfermedad en fase terminal renal y cardíaca también está aumentando entre los pacientes infectados por VIH. Para estos pacientes, el trasplante de órgano sólido (TOS) es la única opción terapéutica y la infección por VIH por sí sola no es una contraindicación. La experiencia acumulada en América del Norte y Europa en los últimos años indica que a los 3-5 años del trasplante la supervivencia en los receptores de hígado coinfectados por el VIH y el VHC es menor que la de los monoinfectados por el VHC. Por el contrario, la supervivencia a los 3-5 años de los trasplantes de hígado en pacientes no coinfectados por el VHC y de los trasplantes de riñón es similar a la de los pacientes VIH negativos. Las infecciones en el período postrasplante en los receptores infectados por

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Trasplante renal
Trasplante de corazón
Tuberculosis
Virus de la hepatitis C
Virus de la hepatitis B

el VIH son similares a las observadas en los pacientes VIH negativos, aunque la incidencia de algunas de ellas (p. ej., la tuberculosis y las infecciones por hongos) es mayor. Por otro lado, en EE.UU. y Europa, el número de inmigrantes procedentes de zonas endémicas con infecciones geográficamente restringidas se ha incrementado significativamente en los últimos años. Estos cambios en el perfil de la población han dado lugar a un aumento en el porcentaje de candidatos a trasplante y de donantes nacidos en el extranjero. Los receptores de órganos trasplantados pueden desarrollar enfermedades endémicas debido a cuatro causas: la transmisión a través del injerto, la infección de novo, la reactivación de la infección latente y la reinfección/reactivación de un injerto sano. En el receptor de origen extranjero se deben considerar las infecciones endémicas en el período postrasplante como consecuencia de la inmunosupresión. Estos temas están modificando los criterios de selección de donantes y también se ha ampliado el cribado pretrasplante de enfermedades infecciosas tanto en los donantes como en los receptores de trasplantes. Algunas enfermedades infecciosas como la enfermedad de Chagas, las infecciones por hongos endémicas, la tuberculosis (que podría ser multirresistente o extremadamente resistente, según el origen del receptor), la leishmaniasis y otras enfermedades virales y parasitarias se deben considerar siempre en el diagnóstico diferencial de las infecciones en el postrasplante en los receptores nacidos en el extranjero.

Introduction

This manuscript reviews infections in solid organ transplant recipients in two scenarios that have become more common in Western countries in the last decade: HIV/AIDS and immigration. Hospitals wishing to carry out transplants in HIV-infected patients and immigrants must have a multidisciplinary team that can regularly evaluate these patients during the pre- and post-transplant periods. The team should include members from the transplant unit (medical, surgical, social work and psychological/psychiatric), experts on alcoholism and drug abuse, HIV/Infectious disease specialists and tropical medicine specialists, in order to perform the appropriate prevention, early diagnosis and therapy for infections that may be life-threatening.

Infections in Solid Organ Transplant HIV-Infected Recipients

With the advent of highly active antiretroviral therapy in 1996, patients infected with HIV are now living longer and are dying from illnesses other than acquired immunodeficiency syndrome (AIDS).[1] Liver disease due to chronic hepatitis C is now a leading cause of mortality among HIV-HCV coinfected patients in the developed world.[3,4] The prevalence of end-stage kidney disease is also increasing among HIV-infected patients.[5] For these patients, solid organ transplantation (SOT) is the only therapeutic option and HIV infection alone is not a contraindication.[6] Accumulated experience in North America and Europe in the last few years indicates that 3- to 5-year survival in HCV/HIV coinfected liver recipients is lower than that of HCV-monoinfected recipients.[7,8] Conversely, 3- to 5-year survival of non-HCV-coinfected liver recipients and kidney recipients was similar to that of HIV-negative patients.[9,10] Experience with heart,[11] pancreas,[12] and lung[13] transplantation in HIV-infected patients is very limited. Infections are one of the main problems in the post-transplant period, together with pharmacokinetic and pharmacodynamic interactions between antiretrovirals, immunosuppressors and antimicrobial agents; high rates of acute rejection; and HCV re-infection in HIV-infected liver transplant recipients, which is the main cause of mortality.

Magnitude of the problem in Spain

End-Stage Liver Disease (ESLD)

According to current estimates, there are approximately 140,000 HIV-infected patients in Spain.[14] The prevalence of HCV and HBV coinfection in Spanish HIV-infected patients was 55% and 5%, respectively,[15] making the estimated number of HCV and HBV co-infected patients approximately 77,000 and 7,000, respectively. In a cross-sectional study performed in Spain,[15] 8% of co-infected patients had clinical or histological criteria for liver cirrhosis, and 17% met the Spanish criteria to be added to a liver transplantation (OLT) waiting list. Therefore, there could be approximately 1,100 potential candidates to be evaluated for liver transplantation.

Magnitude of other end-stage organ diseases

The prevalence of HIV infection in dialysis units varies widely between countries, and even within the same country. In the era of combination antiretroviral therapy (cART), information on prevalence in European countries is scarce. A recent Eurosida survey revealed a prevalence of 0.46% among the HIV-infected population with end-stage renal disease in Europe.[16] In Spain, the prevalence of HIV-infection in dialysis was 0.54%.[17] Therefore, there could be approximately 100 potential candidates to be evaluated for kidney transplantation.[17]

The prevalence of other end-stages organ diseases in Spanish HIV-infected patients is unknown, although ischemic end-stage cardiovascular disease, and therefore heart transplantation, may increase in the future.

HIV criteria for solid organ transplantation

There are three different classes of criteria for including HIV-positive patients on the SOT waiting list: organ disease, HIV infection and other criteria.[6]

Organ disease criteria

These are the same as for the non–HIV-infected population.[6]

HIV infection criteria

Most transplant groups from Europe and North America are using similar HIV criteria. These are summarized in Table 1.[6,18-21]

- Clinical criteria: ideally, no patients should have had AIDS-defining diseases, as this may lead to greater reactivation risk. However, some opportunistic infections (tuberculosis, esophageal candidiasis, and *Pneumocystis jiroveci* pneumonia) have been withdrawn as exclusion criteria in most countries, as they can be effectively treated and prevented. In fact, an NIH-sponsored study[21] has recently updated the inclusion criteria for opportunistic complications, and only untreatable diseases are criteria for exclusion from SOT (e.g., progressive multifocal leukoencephalopathy, chronic cryptosporidiosis, multidrug-resistant systemic fungal infections, primary CNS lymphoma and visceral Kaposi's sarcoma).

Table 1
HIV criteria for SOT in some European countries and the USA

	Spain[6]	Italy[19]	UK[18]	USA[20,21]
Previous C events				
Opportunistic infections	Some*	None in the previous year	None after HAART-induced immunological reconstitution	Some**
Neoplasms	No	No		No
CD4 cell count/mm^3				
Liver Transplantation	>100***	>200 or >100 if decompensated cirrhosis	>200 or >100 if portal hypertension	>100***
Other SOT	>200	>200	>200	>200
Plasma HIV-1 RNA viral load BDL on HAART****	Yes	Yes	Yes	Yes

BDL: below detection levels (<50 copies/ml).
*In Spain, patients with previous tuberculosis, *Pneumocystis jiroveci* pneumonia (PCP) or esophageal candidiasis can be evaluated for OLT.
**In the US, only untreatable diseases are exclusion criteria for SOT (e.g., progressive multifocal leukoencephalopathy, chronic cryptosporidiosis, multidrug-resistant systemic fungal infections, primary CNS lymphoma, and visceral Kaposi's sarcoma).
***Patients with previous OIs should have >200 CD4 cells/mm^3.
****If plasma HIV-1 RNA viral load (PVL) was detectable, post-OLT suppression with cART should be provided for all patients.

– Immunological criteria: for liver transplantation, all groups agree that the CD4+ lymphocyte count should be above 100 cells/mm^3,[6,18-21] This figure is lower than that recommended for other SOT (CD4 >200 cells/mm^3), because patients with cirrhosis often have lymphopenia due to hypersplenism, which leads to a lower absolute CD4+ count, despite high CD4 percentages and good virologic control of HIV.[6] On the other hand, in Spain and the US, in patients with previous opportunistic infections the CD4+ count must be greater than 200 cells/mm^3.[6,20,21] In Italy[19] and the UK,[18] the CD4+ cut-off is 200 cells/mm^3, unless patients have decompensated cirrhosis or portal hypertension. In these scenarios, they use the same CD4+ cell threshold as in Spain and the US (>100 cells/mm^3).
– Virological criteria: the ideal situation is one in which the patient tolerates cART before transplantation with an undetectable HIV viral load in plasma using ultra-sensitive techniques (<50 copies/mL).[6,18,21] In some cases (e.g., patients who remain viremic with antiretroviral medication), it is essential to carry out antiretroviral sensitivity testing to ascertain the real therapeutic options. Some patients do not have an indication for cART, as they are long-term non-progressors or do not fulfill the immunological and clinical criteria to start antiretroviral treatment and, therefore, have viremia that is detectable in plasma. In this setting, it is unknown whether and when (pre- or post-transplant) it would be beneficial to initiate cART although the authors of this review recommend that these patients should start cART after transplantation in order to achieve complete suppression of viral replication.

Other criteria

The candidate must have a favorable psychiatric evaluation.[6] Patients who actively consume drugs or alcohol will be excluded.[6] In Spain, a consumption-free period of 2 years is recommended for heroin and cocaine, and 6 months for other drugs such as alcohol.[6] Patients who are on stable methadone maintenance programs are not excluded. Finally, patients must show an appropriate degree of social stability to ensure adequate care in the post-transplant period.

Post-transplant infections in SOT HIV-infected recipients

It is generally accepted that the incidence and etiology of infections in the early post-transplant period of HIV-infected patients are similar to those reported in HIV-negative recipients;[8,22] however, information regarding non-AIDS-related infections in HIV-infected transplant recipients is scarce. Most published results of the analysis of HIV-1-infected transplant recipients do not provide details of non-AIDS-related infectious events after transplantation. Post-transplant infections may have three origins: a) surgical (e.g., biliary tract, urinary tract, etc.) and health-care related infections; b) infections due to immunosuppressive drugs; and c) infections related to complications from end-stage graft disease (e.g., liver cirrhosis, dialysis, etc.). All cases received post-SOT and HIV infection antimicrobial prophylaxis in order to prevent these infections.[23,24] HIV-infected recipients generally received the same immunosuppressive regimens as HIV-negative patients. In order to suppress the plasma HIV RNA viral load, cART was administered until the day of surgery and was resumed once the patient was stable and oral intake was reintroduced, as recommended in national guidelines.[25]

The characteristics of infections according to the type of SOT are as follows:

Liver transplantation

HIV is not a direct cause of liver disease. Clearly, the most significant morbidity associated with liver transplantation in HCV/HIV co-infected patients is post-transplant HCV recurrence;[7,8] however, the recurrence of HBV infection is easily prevented in the post-transplant period[9].

In a Spanish study[26] evaluating 84 consecutive HIV/HCV-coinfected liver recipients, bacteria were the principal etiological agent of post-transplant infections. Forty-six percent of patients developed a bacterial infection during follow-up, and 9.5% had bacteremia.[26] The incidence of surgical site infection was 2.3% (similar to that observed in the HIV-negative population), but the incidence of intra-abdominal infections was slightly more frequent in HIV-positive recipients (8% vs. 4%).[27] Most cases of early bacterial infection were related to surgery and invasive procedures. Data from recent US studies reported that 70/125 (56%) of liver recipients had 243 serious infections (71% bacterial, 7% fungal, 5% viral, 1% protozoa, 17% culture negative or not done). The most common sites of infection were respiratory (17%), blood (17%) and genitourinary (12%).[28] These results are similar to infections in HIV-negative transplant recipients. Nevertheless, a significantly higher mortality due to infectious complications has been reported in HIV-infected recipients (4 out of 15 between 1999 and 2006).[29]

In a Spanish study,[26] severe infections increased mortality almost 3-fold (HR 2.9; 95%CI 1.5-5.8). Independent factors for severe infection included pre-transplant MELD score >15 (HR 3.50; 95%CI 1.70-7.10), non-tacrolimus based immunosuppression (HR 2.5, 95%CI

1.3-4.8) and a history of AIDS-defining events prior to transplantation (HR 2.5; 95%CI 1.5-5.1). The latter is an important finding, as it identifies a subset of patients with a high risk of dying from severe infection. Opportunistic infection before transplantation is not an exclusion criterion if the infection can be prevented or treated;[6,18-21] however, if this finding is confirmed in larger studies, a pre-transplant AIDS-defining opportunistic infection could become an exclusion criterion. In addition, effective antiretroviral treatment has been found to have a protective effect.[26]

Kidney transplantation

In the US, results have been published of the largest prospective, non-randomized trial of kidney transplantation in 150 HIV-infected patients.[10] In 57 cases (38%) 140 infections requiring admission were reported. Of these, 69% were bacterial, 9% fungal, 6% viral and 1% protozoan. The three most common sites of infection were the genitourinary tract (26%), respiratory tract (20%) and blood (19%). Sixty percent of serious infections occurred within the first 6 months after transplantation.[10] Polyomavirus (BK virus) nephropathy was reported in five patients.[10] Results were similar in French (27 cases)[30] and Spanish (20 cases)[31] studies, with no more complications from infection in HIV-infected renal transplant recipients.

Heart, pancreas and lung transplantation

The largest US heart transplantation study[32] describes the intermediate-term outcome of only five HIV-infected recipients. Post-operative treatment was similar to HIV-negative heart recipients. No surgical wound infection was reported.[32] At least three similar cases have been reported in Europe.[11] Miro et al.[12] reviewed cases of simultaneous pancreas-kidney transplantation in HIV-infected patients. In one case, the pancreas graft failed at 2 weeks and the patient died at 9 months because of a relapsing multidrug-resistant *Pseudomonas aeruginosa* infection. The three additional cases reported in the study survived, despite the failure of both the pancreas and kidney grafts in one subject. Grossi et al[13] reported a case of a double lung transplant performed on an HIV and HBV co-infected patient with cystic fibrosis and end-stage respiratory failure. The operation was successful and the patient recovered rapidly after surgery. After two years of follow-up, the avoidance of major infectious complications and rejection has thus far been avoided due to cautious infectious and immunosuppressive management.

Generally SOT recipients with HCV/HIV coinfection had a higher average rate of serious infections.[10,26]

Opportunistic (AIDS related and non-AIDS related) infections in SOT HIV-infected recipients

It is difficult to separate the complications caused by particular opportunistic infections associated with HIV infection from the complications associated with the immunosuppression required for transplantation. Cellular immunity is affected in both cases. In patients on cART with suppressed viral replication, the CD4+ cell counts are stable or increase and opportunistic infections go down.[33] Since all HIV transplant programs require full control of HIV viral replication and a determinate CD4 cell threshold,[6,18-21] it is more likely that opportunistic infections will be related to the post-transplant immunosuppressive state than to HIV infection. There are solid data showing that HIV-infected patients do not have any significantly increased risk of opportunistic infections or tumors than HIV-negative patients using current-day prophylaxis, monitoring and treatment.[22,34,35] However, opportunistic infection rates are generally not reported properly in either the HIV-infected or HIV-negative cohorts.

In a Spanish study,[26] approximately 11% of HIV/HCV-coinfected liver recipients developed an opportunistic infection (CMV disease, disseminated herpes simplex, invasive fungal infection or tuberculosis). In 44% of cases they were late infections (>6 months post-transplant). In another large Spanish cohort study of HIV-negative solid organ transplantation recipients, the incidence of opportunistic infections was only 6%.[36] In the previous study of HCV/HIV coinfected patients,[26] 4/10 had an opportunistic infection; at the time of infection the CD4+ T-cell count was under 200 cells/ml and plasma HIV-1 RNA viral load was undetectable. This higher proportion is similar to that reported in solid organ transplantation recipients treated with alemtuzumab (humanized monoclonal anti-CD52 antibody). [37] Invasive fungal infections occurred in 7% of patients.[26] The authors report two episodes of zygomycosis (rhinocerebral and involving surgical site). Another single case of zygomycosis has been published.[38] Ragni et al.[39] found an 8% incidence of invasive fungal infection in the late post-transplant period among 24 HIV-1-infected liver recipients. Incidence of invasive fungal infection is slightly higher in HIV-1 infected transplant recipients and should be carefully prevented.[26] The incidence rate and incidence of tuberculosis were 2.4% and 3,140 cases per 100,000 transplants/year,[26] respectively, 4- to 5-fold higher than in HIV-negative transplant recipients.[40]

The incidence of opportunistic infections was higher, as reported in other liver transplant studies with a combined HIV-infected sample size of 39 patients (20.5%).[41,42] Overall, the incidence of post-transplant opportunistic infections was low when plasma HIV RNA viral replication was controlled and CD4+ cell count was higher than a determined threshold.

In a US study[10] of 150 recipients of kidney transplantation, there was no evidence of accelerated HIV disease progression, despite an initial decline in the CD4+ T-cell count. HIV replication remained under control despite challenging interactions with immunosuppressive drugs. There were two cases of newly diagnosed cutaneous Kaposi's sarcoma and one case each of candida esophagitis, presumptive *Pneumocystis jiroveci* pneumonia, and cryptosporidiosis.[10] The two patients with newly diagnosed Kaposi's sarcoma were successfully treated with sirolimus, which has been reported to control human herpesvirus-8 infection.[43] Two patients had biopsy-proven newly diagnosed HIV-associated nephropathy in the absence of detectable HIV viremia.[10] There was a trend toward reduced rates of survival among patients with HCV co-infection that may be related to an increased risk of other serious infections. Patients treated with anti-thymocyte globulin therapy had profound and long-lasting suppression of their CD4+ T-cell counts, which was associated with an increased risk of infections requiring hospitalization.[10,44,45]

Opportunistic infections in 275 HIV-infected transplant recipients from the US (the previously-discussed 150 kidney transplant and 125 liver transplant recipients) have recently been reported.[28] Only 13 cases of opportunistic infections were described: 4 cutaneous Kaposi's sarcoma, 2 *Pneumocystis jiroveci* pneumonia, 1 cryptosporidiosis and 6 subjects with candida infections, mostly esophageal. These results show a low incidence similar to that previously described. Most importantly, there were no recurrences of opportunistic infections, and no differences in survival were based upon these infections.

In addition to the risk of Kaposi's sarcoma (the most common neoplasm in HIV-infected SOT recipients), concerns have been raised about the risk of other malignancies in the long-term (e.g., lymphoma, human papillomavirus-related cancers). Currently there are insufficient data, which makes it difficult to pinpoint the real problem. The concern for these malignancies may be unfounded, at least in the short term. Long-term reporting of this outcome is required in order to obtain accurate data.[46] Interestingly, melanoma, known to be exacerbated by an immunosuppressed state, is more frequent in non-HIV transplanted recipients than in non-transplanted HIV-infected patients.[47] No cases of post-transplant lymphoproliferative disease have been reported in the US studies of renal and liver transplantation[10,28] or the Spanish study of liver transplantation;[26] however, one case was reported in the Spanish study of renal transplantation.[31] Other newly-diagnosed

Table 2
Post-transplant opportunistic diseases in HIV-infected liver and kidney transplant recipients

	Liver transplant recipients			Kidney transplant recipients	
Country (reference)	Spain (26)	France (49)	USA (28)	Spain (31)	USA (10,28)
No. of patients	84	105	125	20	150
Follow-up (mo)	24	36	32	40	28
No. of cases with at least one opportunistic disease	9 (11%)	5 (5%)	6 (5%)	ND	7 (5%)
Opportunistic infections					
Tuberculosis	2	1	0	0	0
Pneumocystis jiroveci pneumonia	1	0	1	0	1
Esophageal candidiasis	2	2	3	0	2
Other invasive fungal infections	3*	0	0	1	0
CMV disease	2	1	0	1	0
Other opportunistic infections	0	1**	1†	2††	1‡
Neoplasms					
Kaposi's sarcoma	0	ND	1	0	3
Non-Hodgkin lymphoma	0	ND	0	1	0

ND: No data.
*Two mucormicosis and one aspergillosis.
**Non-tuberculous mycobacteria.
†Bronchial candidiasis.
††Other viruses.
‡Chronic cryptosporidiosis.

cancers were observed at rates consistent with kidney transplantation.[48]

Table 2 summarizes the opportunistic infections that were diagnosed in the major studies of liver and kidney transplantation in HIV-infected patients.[10,26,28,31,49]

Infections in Immigrant Recipients of Solid Organ Transplantation

Magnitude of the problem in Spain

In recent years, Spain has received a large influx of immigrants. Of the 47 million people living in Spain in 2011, approximately 5 million were of foreign origin (around 12%) and most were from the European Union, Latin America (Ecuador, Bolivia, Colombia) and Africa (Morocco). A change in the characteristics of transplant donors and recipients has also been observed. Data presented by the National Transplant Organization (ONT) in 2009 reveal how immigrants have contributed to the transplant system: out of approximately 4000 transplants performed in Spain during the year 2008, 10% were from foreign donors (up to 19% in the main cities) and the percentage of foreign recipients was 3% (up to 9% in the main cities). Most foreign-born recipients were from European countries (47%) and Latin America (44%), with the remainder coming from Africa (4%) and Asia (4%). Nearly 40% of foreign donors and recipients were of Latin American origin, from countries where transmission of Chagas disease, amongst others, may occur.

In foreign-born recipients, there is a possibility of endemic infections manifesting in the post-transplant period as a consequence of immunosuppression. The majority of imported parasitic tropical infections tend to disappear after 3-5 years because environmental conditions, intermediate hosts and the specific vectors required may be absent, but some geographically-restricted infectious diseases may occur after transplantation. Organ transplant recipients may acquire significant tropical diseases in four ways: a) Transmission with the graft (e.g., HTLV-1); b) *de novo* infection (e.g., visceral leishmaniasis); c) reactivation of dormant infection (e.g., histoplasmosis); and d) reinfection/reactivation in a healthy graft (e.g., Chagas disease).

These issues are modifying the criteria for donor selection and have also expanded pre-transplant screening for infectious diseases in both donors and transplant recipients.[50-52]

Endemic opportunistic infections

Characteristics of post-transplant immunosuppression and recommendations for candidates

Cell-mediated immunity is important for the control of these infections; therefore, organ transplant recipients have a high risk of severe, disseminated infection or relapses, with increased associated mortality.

In addition to the fungal and parasitic infections considered in this review, there are many other pathogens, including viruses, such as HTLV-1 and rabies, and bacteria with geographic restriction, which would merit special considerations in the context of organ transplantation. These have been extensively reviewed elsewhere[53]. Tuberculosis also has a specific worldwide distribution with areas of higher prevalence and guidelines for the management of tuberculosis reactivation in solid organ transplantation have been published recently.[40] In Table 3 the recommendations for screening and management of fungal and parasitic geographically-restricted infections in the transplant candidate with epidemiological risk factors are summarized.

Fungal infections

Coccidioides immitis: Coccidioidomycosis is an infection caused by *Coccidioides* species, endemic in the Southwestern United States and parts of Central and South America. Residence or travel to these endemic areas is a risk factor for infection. Transplant recipients who travel to or reside part- or full-time in endemic areas are at risk for both primary coccidioidomycosis and reactivation of latent coccidioidal infection. Coccidioidomycoses complicating the post-transplant period have been reported in several types of organ

Table 3
Recommendations for screening and management of fungal and parasitic geographically-restricted infections in transplant candidates with epidemiological risk factors

Infectious agent	Geographic distribution	Recommendations
Coccidioides immitis (coccidiomycosis)	Southern USA, México, Central America (Guatemala, Honduras, Nicaragua) and South America (Argentina, Paraguay, Venezuela, Colombia)	Serological screeening if epidemiological risk. Radiological studies. Rule out active infection. If positive serology: prophylaxis with FLU recommended during 1st year and 200-400 mgs thereafter for the duration of immunosuppression. If active infection 1-2 years before Tx or at time of evaluation: Infection should be resolved before Tx (clinically, serologically and Rx), then FLU as secondary prophylaxis.
Histoplasma capsulatum (histoplasmosis)	USA (Mississippi Valley) and Latin America (Mexico, Panama, Guatemala, Venezuela)	If donor or recipient born or resident in endemic areas, post-transplant anti-fungal prophylaxis with itraconazole recommended (3- 6 months).
Paracoccidioides brasiliensis (paracoccidiomycosis)	Restricted geographic distribution: only present in Latin America, mainly in Brazil	Screening and restrictions unnecessary
Blastomyces dermatitidis (blastomycosis)	Endemic in the southern USA (Mississippi, Ohio River Valley), Canada (Great Lakes), Mexico and Central America	Screening and restrictions unnecessary
Plasmodium sp (malaria)	*P. falciparum* in Sub-saharan Africa (not present in North Africa), Southeast Asia, Indian subcontinent, South America, Haiti, Dominican Republic and Oceania. *P. malariae* and *P. ovale* in Subsaharan Africa. *P. vivax* in areas of Southeast Asia and the Indian subcontinent; *P. Knowlesi* in Southeast Asia	Screening is indicated for immigrants and travellers (5 preceding years) from endemic areas. Screening should include thick and thin blood films. Other techniques: HRP-2 (immunochromatography), PCR. If donor is positive organs need not be rejected but treatment should be commenced promptly. Organs should be rejected if death due to malaria
Leishmania sp. (leishmaniasis)	Southern Europe, Indian subcontinent, Amazon basin, Ethiopia, Sudan	Cases described have been related to post-transplant reactivation or primary infection. No clear recommendations on pretransplant screening: If positive serology, strict monitoring post-transplant in order to start treatment early if necessary.
Trypanosoma cruzi (Chagas disease)	From North México to South America	Pre-transplant screening 2 serology-based tests should be performed in candidates with epidemiological risk of Chagas disease. Parasitological and molecular tests to rule out active disease. Targeted prophylaxis: controversial data. Probably improve outcome of chronic and indeterminate phase. Post-transplant follow-up of recipients with Chagas disease Follow-up and testing with parasitological tests to detect parasitemia (Strout, microhematocrit, PCR) Weekly (1st month); biweekly (2-6 months); monthly therafter until 1 year, then annually. If suspect reactivation perform parasitological tests (blood and tissues). Specific treatment if reactivation confirmed. In a heart recipient with chronic chagasic disease specific pre and post transplant therapy may be recommended.
Strongyloides sp. (strongyloidiasis)	Southeast Asia, Subsaharan Africa, Brazil, Southern USA, certain areas of Spain (Safor, Valencia)	If recipient from endemic area: empirical treatment with pre-transplant ivermectin.
Clonorchis sp., *Opisthorchis* sp., *Schistosoma* sp., *Paragonimus* sp., *Fasciola* sp.	Varies depending on species	Screening with stool, urine or sputum examination (depending on species) for ova in donors from endemic areas, or if peripheral eosinophilia. If recipient infected transplantation not contraindicated if treatment administered pre-transplant.

transplant recipients, and most occurred in endemic areas or involved patients who had been former residents in these areas.[54,55] Most cases are diagnosed in the first year post-transplantation (70%), with 50% occurring during the first 3 months. These patients frequently have evidence of prior infection, indicating post-transplantation coccidioidomycosis probably results from reactivation rather than *de novo* infection following transplantation. The main risk factor for developing coccidioidal infection is anti-rejection therapy (high-dose corticosteroids or antilymphocyte antibodies). Dissemination (up to 75%) and mortality (up to 30%) are significant.

Preemptive screening of recipients who may be at risk and targeted antifungal prophylaxis decrease the risk of reactivation after transplantation.[56,57]

Recommendations

Serological screening for coccidioidomycosis in transplant donors or recipients from, or residing in, endemic areas should be recommended. The patient's travel history to endemic areas should be established. In cases of potential risk, a *Coccidioides* serological test must be performed at local reference laboratories. The available serological tests are EIA for IgG and IgM, complement fixation for IgG and immunodiffusion for IgM and IgG. Recipients with positive serological results undergo further evaluation, including CT, bone scan or CSF analysis to rule out active infection, after which prophylaxis should be started with 400 mg daily fluconazole.[55,57] After transplantation, all patients should be monitored serologically every 3-4 months during the first year, and yearly thereafter.

Guidelines for the management of coccidioidal infection have been published,[58,59] and posaconazole has recently been accepted by the ATS and EMEA for coccidioidal therapy.[60]

Histoplasma capsulatum

Histoplasma capsulatum is endemic in the Mississippi and Ohio River valleys, Central America, and certain areas of Southeast Asia and the Mediterranean basin. *H. capsulatum* may remain dormant in

tissues and then reactivate years later if the host becomes immunosuppressed. Organ transplant recipients, especially renal allograft recipients, have been observed to be particularly susceptible to disseminated disease. In the cases described in the literature, symptoms started a median of 1 year after organ transplantation, with the majority of cases occurring in the first 18 months post-transplantation. Disease usually develops via reactivation of latent lesions or from new exposure in *Histoplasma*-endemic zones,[61-64] but transmission of histoplasmosis via the graft from donor to recipients has also been described.[65] Some authors postulate that most post-transplant cases are due to exogenous inhalation during outbreaks and not due to reactivation.

Recommendations

Serological testing should be performed in potential recipients from endemic areas, those with a history of pulmonary disease within the past 2 years consistent with histoplasmosis or radiological findings suggestive of active or past histoplasmosis. Complement fixation (CF) and immunodiffusion (ID) assays (or radioimmunoassay RIA, if available) should be performed at reference laboratories. Positive results do not contraindicate transplantation.

Although the risk of developing histoplasmosis is low in these patients, prophylaxis with itraconazole should be offered to recipients with positive serological results or recipients from a positive serological donor. The duration of this prophylaxis has not been established, and although the risk of reactivation is low even in the absence of prophylaxis, a course of at least 3-6 months should be offered during the period of more active immunosuppression.[61,62] Early experience with the use of posaconazole in the treatment of histoplasmosis has been favorable, but further studies are necessary to assess its use in prophylaxis.

Other endemic fungal infections

P. brasiliensis has a restricted geographic distribution. Paracoccidioidomycosis is rare in organ transplant recipients: only three cases of paracoccidioidomycosis in solid organ transplants have been reported.[66,67] *Blastomyces dermatitidis* is endemic in the South Central and North Central United States, in the Mediterranean basin and parts of Africa. Blastomycosis has been reported infrequently in immunocompromised patients, such as solid organ and bone marrow transplantation[68,69] patients receiving long-term immunosuppressive therapy and patients with AIDS.

These fungal infections are rare in transplant patients; therefore specific screening or preventive measures would not be necessary in this setting.

Parasitic infections

Infections caused by Plasmodium sp.

Malaria is currently endemic in more than 100 countries worldwide. The infection is transmitted from the bite of the female *Anopheles* mosquito and is produced by *Plasmodium* species with various geographic distributions.

Malaria may be transmitted in several ways in the context of solid organ transplantation: a) through infected blood products; b) direct transmission via an infected organ; c) reactivation of infection due to post-transplantation immunosuppression[70]; and d) *de novo*; exposed organ recipients have an increased risk of acquiring malaria infection. Anti-malarial prophylaxis should be recommended for patients who are travelling to endemic areas.

Malaria is an infrequent complication of solid organ transplantation in non-endemic countries. In recipients who may have been exposed in endemic areas infection should be excluded in the pre-transplant period (by microscopy and PCR) so that specific therapy may be administered prior to transplantation.[71]

Infections produced by Leishmania sp.

Visceral leishmaniasis (VL) is endemic in approximately 60 countries worldwide. This infection has a high prevalence in Southern Europe, India, Kenya, Sudan, Brazil and tropical areas. The parasite is transmitted to humans through the bite of an infected female *Phlebotomus* fly (or *Lutzomyia* in America). Visceral leishmaniasis is a rare complication of kidney transplantation, with <100 cases reported in the literature. It usually occurs as a late complication after transplantation, after a median period of 18 months. VL affects immunosuppressed patients as a result of direct transmission via the transplanted organ, recrudescence of a dormant infection or *de novo* natural infection.[72,73] It is usually a late complication of solid organ transplantation suggesting primary infection, although some reported cases are considered to occur due to reactivation.[74,75]

Screening of blood or organ donors is not performed even in highly endemic areas because it is unclear whether routine testing of recipients would help identify those individuals with a greater probability of developing leishmaniasis due to reactivation of a latent infection after immunosuppression.[50,75,77]

Infections caused by Trypanosoma cruzi

American trypanosomiasis (Chagas disease), caused by the parasite Trypanosoma cruzi, is naturally transmitted in endemic areas by triatomine vectors. The endemic area for *T. cruzi* spans from the southern US to Argentina and Chile. Between 8 and 10 million people are estimated to be infected worldwide and the disease is one of the leading causes of cardiomyopathy in Latin America. More than 12 million Latin American immigrants currently reside outside endemic areas, which has expanded the disease's geographical limits to include regions where non-vector transmission (blood and organ donation; mother-to-child transmission) may spread the infection. In the US and Europe the number of immigrants from these areas has increased significantly in recent years.[78] Among European countries, Spain has the largest number of migrants from Latin America.[79,80] The number of potential recipients with chronic Chagas infection that could reactivate in the post-transplant period (cardiac and non-cardiac transplantation) due to drug-induced immusuppression has thus increased.[81] Recent data estimate there may be nearly 40,000 patients with chronic Chagas infection in Spain (90% of these are Bolivian). The seroprevalence of Chagas disease in Bolivians is approximately 20%.[80,82,83]

Transplant recipients with chronic *T. cruzi* infection are at risk of reactivation after transplantation. The incidence of reactivation in recipients with Chagas disease varies according to the transplanted organ and the intensity of immunosuppression. Reactivation has been shown to occur mainly within the first year post-transplantation, with an incidence of 15-35%.[84,85] Most of the data available has been reported for kidney transplants and evidence is scarce for other organs.[86] The most frequent features during reactivation are asymptomatic parasitemia and cutaneous/subcutaneous involvement. Myocarditis and encephalitis have been reported less frequently.

Reactivation in heart transplant recipients with chronic Chagas disease occurs in 20% to 49% of cases. Some authors have linked the high incidence of reactivation to rejection treatment and mycophenolate mofetil use.[87-89]

Transplant candidates with *T. cruzi* infection/Chagas disease with exclusion criteria for transplantation (WHO criteria) are: 1) patients with Chagas disease and miocardiopathy grade 2 or greater (Kuschnir classification) (excluding heart transplant candidates); and 2) the presence of advanced stage megaesophagus or megacolon.[90]

Diagnosis of reactivation is best achieved by direct parasitological tests, preferentially the Strout method. Also all available tissue specimens should be evaluated for the presence of amastigotes, including protocol endomyocardial biopsies. PCR-tests may prove to

be of use, allowing an earlier diagnosis. Diagnosis of reactivation may be achieved by identifying the parasite in the myocardium (72%), in the subcutaneous tissue (25%), in blood (34%) and in the CNS (3%).[85]

Recommendations

Recommendations for the management of Chagas disease in organ and hematopoietic tissue transplantation programs in non-endemic areas have been recently published by a group of Spanish experts[90] and other international consensus groups.[51,52,85]

Pre-transplant

Screening: All transplant candidates from Latin American countries, born to Latin American mothers or who have resided or traveled to a high-risk geographical area for prolonged periods of time (more than 6 months) should be tested for *T. cruzi* infection during the pre-transplant evaluation, using two serological tests using different methods. Overall, enzyme immunoassays (EIAs) perform better than other screening assays. RIPA could be considered a gold standard for evaluating the performance of other assays. PCR should be performed to detect parasitemia.

There is no prospective randomized evidence to support pre-transplant trypanocidal treatment to diminish or prevent post-transplant reactivation, especially if patients have end-stage liver or kidney disease (because of drug toxicities). However, pre-transplant treatment may be considered in some cases as some studies indicate that treatment may affect disease progression in the chronic phase.[91,92]

Post-transplant follow-up

Monitoring reactivation: Reactivation is defined as an increase in parasitemia that may be detectable by parasitological techniques, even in the absence of symptoms. Parasitemia should be monitored weekly for the first 2 months, then every two weeks up to the first six months and monthly thereafter. If immunosuppression is intensified, revert to weekly monitoring for two months.

Preferred laboratory tests for monitoring include those that identify parasites in blood: Strout test, microhematocrit and PCR (most sensitive test for diagnosis of acute infection).[93,94] Amastigotes should be searched for in all protocol biopsy specimens, skin lesions and subcutaneous tissues.[90,95]

Management of reactivation

All patients with reactivation should receive specific treatment for 30-60 days with benznidazole (5 mg/kg/day). Nifurtimox should be reserved for patients with benznidazole side effects or infections with resistant strains.[51,85] During reactivation, parasitological tests should be performed weekly until at least two negative results are obtained.

Strongyloides sp. infections

S. stercoralis is an intestinal nematode with a non-uniform distribution throughout the world in the tropics and other areas, mainly in Southeast Asia, Subsaharan Africa, Brazil and the southern US. Various cases have been reported in renal and heart transplant recipients, and more recently following pancreatic transplantation. Post-transplant strongyloidiasis may develop after primary infection due to auto-infection or transmission via the graft. In the majority of cases, symptoms of strongyloidiasis develop in the first six months following transplantation.[96-98] Diagnosis is achieved by visualisation of larvae in stool and with larval culture.[99] Other diagnostic methods include detection of the parasite in other samples and serological tests.

Strongyloides hyperinfestation syndrome[100,101] occurs due to an accelerated auto-infection cycle and is usually associated with immune suppression (especially suppression of T lymphocyte activity). In this context, steroids may have a role in accelerating the nematode's life cycle. This syndrome has a high mortality rate, which may be close to 75%. Due to immunosuppression, the larvae have a greater capability of penetration through the intestinal wall leading to mucosal ulceration with consequent migration of larvae to the pulmonary circulation leading to respiratory symptoms. Intestinal ulceration favors the development of bacteremia, which can be recurrent, and may lead to serious complications such as sepsis or peritonitis secondary to Gram-negative bacilli or other bacteria from the intestinal flora.

Recommendations

Diagnostic tests to exclude *Strongyloides* should de performed during the pre-transplant evaluation in patients who have resided or travelled to endemic zones. Treatment with ivermectin (3-day regimen) would be recommended prior to transplantation for those patients in whom infection is detected, and maintenance therapy with ivermectin for at least 3-4 months should be considered due to the risk of recurrence. During the first months post-transplantation there is a greater incidence of hyperinfestation coinciding with the period of greatest immune suppression. Although controversial, other authors recommend pre-transplant empirical treatment for all potential candidates with risk factors, regardless of test results.[97,102]

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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