Recommendations for Management of Endemic Diseases and Travel Medicine in Solid-Organ Transplant Recipients and Donors: Latin America

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Abstract: The Recommendations for Management of Endemic Diseases and Travel Medicine in Solid-Organ Transplant Recipients and Donors: Latin America clinical practice guideline is intended to guide clinicians caring for solid-organ transplant (SOT) donors, candidates and recipients regarding infectious diseases (ID) issues related to this geographical region, mostly located in the tropics. These recommendations are based on both systematic reviews of relevant literature and expert opinion from both transplant ID and travel medicine specialists. The guidelines provide recommendations for risk evaluation and laboratory investigation, as well as management and prevention of infection of the most relevant endemic diseases of Latin America. This summary includes a brief description of the guideline recommendations but does not include the complete rationale and references for each recommendation, which is available in the online version of the article, published in this journal as a supplement. The supplement contains 10 reviews referring to endemic or travel diseases (eg, tuberculosis, Chagas disease [ChD], leishmaniasis, malaria, strongyloidiasis and schistosomiasis, travelers diarrhea, arboviruses, endemic fungal infections, viral hepatitis, and vaccines) and an illustrative section with maps (http://www.pmourao.com/map/). Contributors included experts from 13 countries (Brazil, Canada, Chile, Denmark, France, Italy, Peru, Spain, Switzerland, Turkey, United Kingdom, United States, and Uruguay) representing four continents (Asia, the Americas and Europe), along with scientific and medical societies.

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Transplantation is increasing throughout the world, and immigration and travel to and from developing countries and tropical areas are bringing new challenges for the management of transplant recipients. In Latin America (LA), in addition to the usual transplant clinical issues (ie, immunosuppression management, procedural complications, risk of rejection, and infections), endemic diseases can significantly impact donor and candidate screening, donor allocation, and recipient prophylaxis and infections. Independent of where the transplant procedure is done, or the residence of donors and recipients at the time of transplant, endemic infections represent a potential risk in the posttransplant period.[1-4] Furthermore, international travel is predicted to increase and expand to include more volunteerism, medical tourism, and visiting friends and relatives, besides usual business and pleasure travel.[5]

Anywhere from 16% to 48% of solid-organ transplant (SOT) recipients have traveled to tropical regions and other areas with an augmented risk of acquiring IDs. Although rates of infection are not known to be higher in immunosuppressed travelers, severity of illness can be markedly increased.[4]

Numerous factors contribute to an increased exposure of both donors and recipients to tropical and endemic diseases, including immigration from LA to other continents,[6] the rising number of transplant procedures taking place in LA countries,[7,8] and transplant tourism (defined as when the donor or recipient/organs) travel to a foreign country for transplant purposes).[9] Additionally, common endemic IDs of these regions are frequently underestimated and remain the most understudied infections with few prospective trials and no randomized studies in the transplant setting.[6,10] For this reason, recommendations in this review are based on an amalgam of smaller and/or uncontrolled studies, opinions of respected authorities, clinical experience, descriptive case studies, and/or reports of expert committees.

This consensus document is intended to assist the clinician in the clinical approach to the transplant patient who originated from countries in LA, received an organ from a donor originating from countries in LA, and/or those transplant recipients or candidates who will or did travel to these areas.

RESULTS

We present the recommendations for transplant setting regarding the most relevant endemic or travel diseases in LA, including tuberculosis, ChD, leishmaniasis, malaria, strongyloidiasis and schistosomiais, traveler's diarrhea, arboviruses (with Dengue, Zika, Chikungunya, and Yellow Fever [YF]), endemic fungal infections (eg, histoplasmosis, paracocidiodomycosis, coccidioidomycosis, cryptococcosis, and sporotrichosis), viral hepatitis, and guidance for vaccination.[11-20] The rationales for the recommendations and discussion of each endemic disease are provided in the online version of the guideline.

The guideline recommendations for screening donors and candidates aim to strike a balance between minimizing the risk of endemic disease and maximizing the transplant activity with quality, cost-effectiveness, and safety. In this context, the screening procedure recommendations should evaluate the epidemiological risk, the strengths and limitations of screening tests, and the rates of transmission or reactivation and consequences for the recipient.

Given the difficulties in obtaining an accurate epidemiological history for some of the endemic diseases in SOT scenario, there have been numerous failures of the donor and candidate screening process. In addition, screening candidates for the all of the relevant latent endemic diseases is usually not feasible. Therefore, clinicians should be aware that unexplained fever or illness in SOT recipients could be a manifestation of their prior exposure to endemic disease (or in their donor).

Knowledge of the epidemiological exposure of donors, candidates, and recipients is mandatory to investigate the possibility of endemic diseases as a consequence of donor-derived infection (DDI), reactivation, and/or de novo exposure posttransplant. Laboratory clues are also relevant to permit a more rapid and focused diagnosis. For example, with the right epidemiologic exposures, unexplained fever with anemia or pancytopenia should necessitate investigation for ChD or leishmanial infection, whereas unexplained fever with arthralgia, conjunctivitis, and rash may trigger testing for arboviruses infection.

Transplant recipients who travel to endemic regions should seek consultation with an ID specialist well versed in travel medicine and familiar with transplant medicine, to provide advice to this unique population of travelers, both before and after travel; such pretravel consultation can prevent potentially devastating infections.[4] These guidelines provide information on ID prevention for clinicians, including a pretravel checklist for the assessment of traveler health, risk of disease exposure, vaccines, prophylaxis, and use of immunoglobulin, medical care, and overall health guidance (see Appendix 1—Predeparture Medical Questionnaire and Maps at http://www.pmourao.com/map).

GUIDELINE RECOMMENDATIONS

1. TUBERCULOSIS

Donors from an endemic region

A) What are the risks?

Donors originating from endemic countries have a higher risk of both latent and active tuberculosis (TB). The risk of TB transmission when the donor has active disease has been estimated to be approximately 30%. Donors with untreated latent TB infection (LTBI) may also be a source of TB transmission, although the actual risk of transmission from such donors remains undetermined.

B) Which tests should be performed?

Living donors should undergo the same evaluation as candidates, described below, with the exception that the cut-off for tuberculin skin test (TST) should be ≥ 10 mm.

The evaluation of the deceased donor for TB relies on:

- The medical history. The history of untreated or insufficient treated TB should be investigated, as well as previous reactive TST or interferon-gamma release assay (IGRA).
- Endemic exposures. Travel to or residence in highly endemic areas, exposure to active TB in the household or workplace within the last 2 years, homeless or refugee status, incarceration, and alcoholism may be associated with LTBI.
- Radiographic findings, such as apical fibronodular lesions, calcified solitary nodules, calcified lymph nodes, or pleural thickening.

Time does not allow for a TST, and IGRAs have not been validated in deceased donors. Active TB should be ruled out in donors at increased risk by obtaining samples, for example, sputum or bronchoalveolar lavage, to test for the presence of *Mycobacterium tuberculosis*. Because the results of microbiological investigation will more often be available after procurement, it must be ensured that all data will be forwarded to transplant teams as soon as possible to enable appropriate actions.

C) Donor acceptance criteria:

Organs from donors with active TB infection should be discarded. Organs from donors with a history of TB successfully treated for at least 6 months can be transplanted. Lungs with residual tuberculous lesions should not be used for transplantation. A history of LTBI without evidence of active infection is not a contraindication to donation.

D) If you accept the organ donor, how do you manage it?

If the microbiologic diagnosis of active TB in the donor becomes available only after organ transplantation, therapy for active TB should be immediately started in the recipient according to local guidelines.

Recipients who receive a graft from a donor with a history of untreated or incompletely treated LTBI or TB should be treated for LTBI. Results of drug susceptibility testing should be conveyed to the team treating the recipient, especially if drug resistance is detected, for guiding optimal preventive treatment.

Recipients from an endemic region

A) What are the risks?

Despite the current trend for a decline in the incidence of TB in LA, active disease is still moderate to highly endemic in most countries of the region. Transplant candidates originating from such endemic areas have a higher prevalence of LTBI and are, hence, at an increased risk of developing active TB after SOT.

B) Which tests should be performed?

A history of clinical or radiological TB and the treatment received should be assessed in all recipients. If there is no history of past TB or treatment for LTBI, candidates should undergo evaluation for LTBI. TST is the standard method to identify LTBI and is considered positive when induration at 48 to 72 hours is 5 mm or greater. Candidates with negative TST should immediately undergo an IGRA test to avoid TST-mediated boosting of subsequent IGRA responses. If the IGRA test is not available, a second TST should be performed 7 to 10 days after the first one to evaluate a boosted-related skin conversion. Candidates vaccinated with BCG should be evaluated by IGRA. All candidates with a positive test result should be evaluated to rule out active TB before treating LTBI.

C) How do you manage it?

If active disease is diagnosed in the candidate, transplantation should be postponed until the disease is well controlled with adequate treatment and smears are negative. Nevertheless, active disease may not be considered an absolute contraindication to transplantation for candidates who urgently need it.

Therapy for LTBI is an effective strategy for the prevention of active TB in transplant recipients. LTBI therapy is recommended for transplant candidates with a positive TST or IGRA who have not been previously treated. Those with high-risk pretransplant TB exposure should be considered for therapy even if the TST or IGRA is not positive, as should those with a history of active TB that was inadequately treated. Chest imaging suggestive of previous untreated TB should prompt consideration for therapy, especially in areas where endemic mycoses, which could simulate TB, are uncommon.

The preferred regimen is oral isoniazid (INH) 300 mg/d for 9 months, along with oral pyridoxine 25 to 50 mg daily. Patients should be monitored for hepatotoxicity with at least serum alanine aminotransferase checked every 2 weeks for 6 weeks, and monthly thereafter. Alternative regimens containing other rifamycins (rifabutin or rifapentine) can be considered pretransplant, but should be avoided posttransplant due to immunosuppressive drug interactions. These regimens include rifampin 600 mg daily for 4 months or INH and rifapentine weekly for 12 weeks. For patients who cannot tolerate INH after transplantation, fluoroquinolones (± ethambutol) may be an alternative.

The timing of latent TB treatment requires balancing risks and benefits for each patient. When possible, treatment for LTBI should be started before transplant and can often be completed while the patient is on the waiting list. This issue remains especially controversial in liver transplantation. Although, in several small studies, INH has been shown to be safe in those with compensated cirrhosis awaiting transplant with careful monitoring, some experts do prefer waiting until after transplant to begin INH as once liver function has normalized.

Recipients who travel to an endemic region

A) What are the risks?

Recipients from low incidence countries who travel to endemic areas are exposed to primary infection with *M. tuberculosis*. The risk is higher for travelers involved in healthcare, academic medical exchange programs, and humanitarian work with high-risk populations, such as prisoners and homeless people. The risk increases significantly with a cumulative history of more than 3 months of travel to high-incidence areas.

B) What are the pretravel recommendations (pretravel counseling)?

Transplant recipients who are traveling to TB endemic areas to provide medical or humanitarian care should follow standard precautions to prevent nosocomial acquisition of TB infection.

C) *How to prevent infection or disease development and how to follow-up?*

There is support for the use of universal prophylaxis during the period of highest immunosuppression in the first year after transplantation in highly endemic areas given the higher rates of primary TB acquisition. If recently transplanted patients are planning to move to an endemic area, INH prophylaxis during the first year should be considered.

BCG vaccine is contraindicated in transplant recipients. Those with possible TB exposure should be evaluated on return, and anyone with symptoms of infection should seek medical evaluation immediately.

2. CHAGAS DISEASE

Donors from an endemic region

A) What are the risks?

ChD is endemic in LA, where 6 to 7 million people are infected. Imported ChD is increasing recognized as an emerging problem in the USA and Europe due to immigration from LA. It is estimated that there are over 80 000 cases in Europe and over 300 000 cases in the USA. Donors from endemic regions, or who spent significant time in endemic regions, are at risk for potential infection and transmission of ChD and systematic screening before transplant should be done.

B) Which tests should be performed?

Chronic ChD is defined by having a positive epidemiology and serology, using at least 2 serological methods. Conventional serological techniques are enzyme-linked immunosorbent assay, indirect immunofluorescence and indirect hemagglutination. In case of inconclusive serology (ie, both a positive and a negative test), a third test is required. Inconclusive serologic results can be confirmed by PCR, which is able to detect low parasitemia in chronic patients. PCR should not be used as a screening test in chronic patients, however, beacuse its sensitivity ranges between 40% and 95% in chronic phase because of the intermittent parasitemia.

C) Donor acceptance criteria:

The literature data support the use of kidneys and livers from chronically infected donors, and defer the use of hearts and intestines. The decision to accept an organ from an infected donor is a balance between urgency of need for the organ and the acceptance of the risk of possible infection in the recipient, both by the medical team and the recipient through informed consent, along with the ability to diagnose and treat infection if it occurs. Organs from donors with acute infection (albeit rare) should be deferred. The risk of DDI through the use of kidneys and livers from chronically infected donors is about 10% to 20%, and rates of transmission after heart transplant are 75% or more.

D) If you accept the organ donor, how do you manage it?

Careful monitoring with clinical and parasitological evaluation during the first 6 to 24 months posttransplant for seronegative recipients from infected donors should be done. There is no study to validate a specific monitoring program, but the majority of studies monitor the patients during the first 2 years after transplant. Routine parasitological tests may detect subclinical infection before any symptoms or organ dysfunction occurs; such testing includes direct parasitemia analysis (ie, Strout method), molecular methods, pathological detection of parasites in tissues, and serology. If transmission occurs, tests should be performed weekly while on treatment until (at least) 2 negative results are obtained. Systematic data on the efficacy of prophylaxis for recipients after transplant to prevent *Trypanosoma cruzi* transmission from positive donors to negative recipients are lacking. The transplant team should consider pretransplant treatment of the living donor, and donaton should be take place as soon as possible after completion of treatment. In special situations requiring transplantation before completing treatment, the transplant should not be performed before 14 days of therapy. Monitoring for evidence of transmission infection is generally preferred over the use of prophylactic therapy. Current treatment options for ChD are limited to only 2 old nitroheterocyclic drugs: benznidazole and nifurtimox. Benznidazole is the generally preferred option for treatment given its better tolerability and the absence of an interaction with immunosuppressant drugs. The standard dose is 5 to 7 mg/kg per 24 hours divided in 2 doses, and the treatment is usually 60 days. The average cure rate among acute cases is 80%.

Recipients from an endemic region

A) What are the risks?

Chronic ChD candidates can reactivate the disease after transplant in the context of immunosuppression and the risk is highest in the first year after transplant, and subsequently with intensification of immunosuppression. The risk of reactivation is highest after heart transplant, ranging from 27% as high as 90%, although overall transplant outcomes are usually similar to those without ChD. The incidence of reactivation in kidney transplant recipients is estimated at 8% to 22%, and the reactivation after liver transplant has not been well described.

B) Which tests should be performed?

Candidates with chronic ChD diagnosis should undergo the same evaluation as donors. Negative seroconversion (defined as conversion from positive to nonreactive testing results) in individuals with chronic ChD has been reported after transplant, related to the immunosuppressed status.

C) How do you manage it?

Careful monitoring posttransplant for seropositive candidates is similar with that for seronegative recipients from infected donors, because reactivations as well acute manifestations predominantly occur within this period and when immunosuppression is intensified. Serology has no utility in the diagnosis of reactivation. Other diagnostic methods, discussed above in the section "Donors from endemic regions", could be used to diagnose reactivation infection. However, with reactivation, an increase in parasitic load as measured by RT-PCR can allow an earlier identification of reactivation parasitemia.

Monitoring seropositive recipients after heart transplan-tation.

For the diagnosis of acute chagasic myocarditis in the graft, close parasitologic monitoring, including immunohistochemistry on endomyocardial biopsies, is recommended with the following proposed schedule: weekly during the first 2 months, every 2 weeks through months 3 to 12, every 3 months through the months 13 to 24, and every 6 months thereafter. Reactivation therapy follows the recommendations for acute disease treatment. The average cure rate is less than 20% among chronic and reactivation cases.

Recipients who travel to an endemic region

A) What are the risks?

De novo ChD infection posttransplant can occur from travel or residence in endemic regions and blood transfusions. Risk of acquiring ChD from routine travel to endemic regions is quite low; risk factors include prolonged stays, rural areas, staying in thatched huts, and lower socioeconomic situations.

B) What are the pretravel recommendations (pretravel counseling)?

Transplant recipients who are traveling to ChD endemic areas should be educated about the risk of bites from reduviid

(kissing) bugs. Oral transmission has been reported (ie, contaminated guava juice, açaí products); safe food precautions should be observed in endemic regions.

C) How to prevent infection or disease development and how to follow-up?

If transplanted patients are exposed to *T. cruzi*, management should include screening for acute active disease.

3. LEISHMANIASIS

Donors from an endemic region

A) What are the risks?

Leishmaniasis is a rare disease among transplant recipients. Infection may cause cutaneous, mucocutaneous, or visceral leishmaniasis (VL). VL is the predominant form described in SOT recipients. Transplant patients can develop leishmaniasis by (i) primary infection via a vector, (ii) reactivation of a latent infection, or (iii) DDI (organ or blood). Donors originating from endemic countries have potential risk (although undetermined) for transmission. Up to date, on the best of our knowledge, there is no proved DDI reported. Despite this, recipients of organs from donors with VL should be clinically monitored for infection after organ transplantation, especially during the first year after transplantation.

B) Which tests should be performed?

To date, donor screening is not recommended.

C) Donor acceptance criteria:

Living donors with active disease should be treated before donation. Positive serology or other markers of previous exposure, without evidence of active infection, is not a contraindication to donation. Given the limited data on DDI and considering the high prevalence of asymptomatic infected donors with no proven transmission, organs should not be discarded.

D) If you accept the organ donor, how do you manage it?

Recipients should be monitored closely for signs and symptoms of disease; sequential PCR may be useful for monitoring.

Recipients from an endemic region

A) What are the risks?

Annually, there are 1.3 million new cases of leishmaniasis worldwide, predominantly in tropical and Mediterranean regions (>1 000 000 new cases are cutaneous leishmaniasis [CL] and 200 000 to 400 000 new cases are VL). VL prevalence among SOT recipients range from 0.1% to 0.5% in endemic countries, and CL is rarely reported among these patients. The higher prevalence of latent infection is related to an increased risk of developing active disease after SOT.

B) Which tests should be performed?

CL can manifest through a wide range of presentations, from a self-limiting cutaneous lesion to severe mucocutaneous ulcerations. Atypical features include parasite dissemination with multiple lesions, clinical polymorphism and visceralization. VL should be suspected in patients from endemic region that presents fever, weight loss, splenomegaly and/or hepatomegaly, progressive anemia or pancytopenia, and hypergammaglobulinemia. Fever is the most common symptom of VL in SOT recipients, whereas organomegaly may be less frequent than in immunocompetent individuals. However, only one-third of patients exhibit the triad of fever, visceromegaly and cytopenia. Disease presentation can be atypical, with dissemination through all tissues, including the oral cavity, intestines, lungs, and skin.

Ideally, the combination of multiple methods is recommended for diagnosis. For CL, if microscopy is negative, PCR, which may permit species identification, could be used. Parasite culture tends to present low sensitivity and to provide variable results. For VL, if clinical and epidemiological evidence suggests disease, serological tests may be performed; if these tests are negative, microscopic examination of bone marrow sample should be conducted, although PCR can be considered, even in peripheral blood.

C) How do you manage it?

The treatment for CL and VL in SOT recipients are diverse and depend on various factors, such as patient characteristics (eg, age, immune status and renal/liver function), *Leishmania* species, disease extent, drug availability, concomitant infections and previous treatments, number and size of skin lesions. Immunosuppressant dose reduction has been recommended, but such decisions must be made on an individual basis. No experiences regarding the use of topical treatments as the sole therapeutic measure for CL in SOT recipients have been reported. Therefore, systemic treatment (as used for the treatment of VL) is recommended. Therapeutic options include amphotericin B, pentavalent antimoniates, miltefosine and paromomycin, among others.

Patients with known or suspected CL or VL pretransplant have been reported to develop recurrent disease post-SOT. Relapsed VL occur in approximately 30% cases and can be early as 1 month and as late as 5 years posttransplantation. Therefore, patients with known prior CL or VL should be clinically monitored for evidence of infection after organ transplantation, especially during the first year. The usefulness of monitoring the parasite load with PCR to predict relapses or treatment failure has not yet been established, but PCR monitoring can be helpful for patients with a partial response to treatment or after the first relapse. Because relapse is common in the presence of continued immunosuppression, secondary prophylaxis may need to be used for prolonged periods.

Recipients who travel to an endemic region

A) What are the risks?

Transplant candidates can acquire leishmaniasis from a bite of an infected sand fly.

B) What are the pretravel recommendations (pretravel counseling)?

When visiting endemic areas, transplant candidate, recipient or living potential donor should minimize outdoor activities, especially during dusk hours, when sand flies generally are the most active. These individuals should also wear protective clothing, apply insect repellent (ie, DEET) to exposed skin, use pyrethroid-treated bed nets, and spray dwellings with residual-action insecticides.

C) How to prevent infection or disease development and how to follow-up?

As in any vector-transmitted disease, transplant travelers should avoid exposure to mosquito bite. Those with possible exposure (endemic area) should be evaluated on return, and oriented. Anyone with symptoms of infection should seek medical evaluation immediately.

4. MALARIA

Donors from an endemic region

A) What are the risks?

Malaria should be considered in any individuals who have resided or traveled to malaria endemic areas. Malaria is transmitted to humans by the bite of infected Anopheles mosquitoes in tropical areas of sub-Saharan Africa, Asia, Oceania, and LA. Ten percent of malaria cases in the world occur in LA, and about 90% of malaria cases in the Americas occur in the Amazon basin shared by Brazil, Bolivia, Colombia, Ecuador, French Guiana, Peru, Suriname, and Venezuela, whereas the other 10% occur in non-Amazon regions, mainly along the coastal areas and lowland Andean valleys, as well in some North and Central American countries, from Mexico to Panama.

B) Which tests should be performed?

If the donor is from endemic regions, epidemiological and laboratorial screening should be done. Because the donor may be apparently healthy and/or may also have been exposed to malaria in the distant past, an epidemiological history relevant for malaria must be routinely investigated. For symptomatic infections, laboratory confirmation should be obtained. Giemsa-stained thick blood smear microscopy remains the gold standard for malaria diagnosis. Rapid diagnostic test can be an alternative testing in remote areas. For asymptomatic infections, if the history suggests malaria risk or is unclear, laboratory confirmation should be obtained. The challenge, however, is the detection of low-level parasitemia in donors from malaria areas who were at risk of repeated exposures, resulting in a semi-imune status and an asymptomatic infection with low-level parasitemia. In this scenario, the best screening option is the detection of Plasmodium DNA or RNA by the PCR aiming at the detection of submicroscopic parasitemia to decrease the risk of donor derived malaria. Alternatively, serologic tests could also be used, but detection of antibodies does not necessarily indicate the presence of parasitemia but rather indicate exposure with the risk of organ exclusion of some donors with no parasitemia. Serology testing, however, may be considered if the donor exposure history is uncler. In liver transplantation scenario, the presence of a latent hepatic phase in *P. vivax* and *P. ovale* infections after successful treatment represents an additional risk for malaria transmission at transplantation. Pretransplant screening of blood smears will not identify hypnozoites, because these infect liver cells only. An epidemiological history, therefore, is mandatory to identify the risk.

C) Donor acceptance criteria:

All potential donors with evidence of active infections should be deferred from donation until diagnosed and treated. After treatment, the deferral period should follow local guidelines. Although the recommendations about the deferral period for malaria risky donors vary among regions and countries, based on endemicity, availability of donor screening, and the level of risk of malaria transmission we would like to avoid, donor deferral time in endemic countries is usually shorter compared to nonendemic countries. A permanent deferral for donors with a history of *P. malariae* infection is recommended.

D) If you accept the organ donor, how do you manage it?

Based on reported cases of transmission of malaria after transplant in SOT recipients, both living donors and recipients should be monitored by clinical and laboratory tools prospectively posttransplant, ideally for a period of 2 months. Detection of Plasmodium DNA or RNA by the PCR is the best choice.

Preemptive therapy of malaria for transplant recipients has not been formally recommended. However, in case of high-risk DDI due to recent donor exposure or infection, preemptive therapy may be considered.

Recipients from an endemic region

A) What are the risks?

Organ transplant recipients can either present with a de novo infection or a reactivation of a previous infection. The risks are the same of donors from an endemic region.

B) Which tests should be performed?

All transplant candidates originating from endemic areas should be screened by epidemiological history and laboratory testing (are the same described for donors from an endemic region).

C) How do you manage it?

Based on reported cases of recrudescence of malaria after transplant in SOT recipients, recipients should be monitored by clinical and laboratory tools prospectively posttransplant, ideally for a period of 2 months. Ideally, detection of Plasmodium DNA or RNA by the PCR is the best choice.

Recipients who travel to an endemic region

A) What are the risks?

Infection risk is associated with travel to areas of malaria transmission.

B) What are the pretravel recommendations (pretravel counseling)?

Transplant recipients travelling to malaria endemic areas should consult specialists before their travel to be informed about mosquito exposure prevention measures and preventive medication (chemoprophylaxis), depending on the malaria risk in the area to be visited.

The recommendations for malaria prophylaxis for transplant recipients are the same as for general population travelers; the drug of choice varies according to the country of destination. Potential drug interactions should be taken into account as special concerns for posttransplant travellers under immunosuppression medications.

C) How to prevent infection or disease development and how to follow-up?

Travellers should prevent mosquito bites with barriers methods, such as insect repellents and long-sleeved clothing. They should also limit outdoor activities, particularly from dusk-to-dawn, and sleep in a well-screened, or preferably, air-conditioned room.

5. SCHISTOSOMIASIS AND STRONGYLOIDIASIS

Schistosomiasis in organ transplantation

Donors from an endemic region

A) What are the risks?

Schistosomiasis should be considered in any individuals who have resided or travel to endemic areas with significant freshwater contact. Countries reporting active transmission are Brazil, Venezuela, Dominican Republic, Guadeloupe, Martinica, Puerto Rico, St. Lucia and Suriname. Transmission of *Schistosoma* via a liver allograft can cause infection

after transplantation but overall, good long-term outcomes are observed.

B) Which tests should be performed?

If the donor is from endemic region, screening should be done by stool examination, serological tests or histological examination of the explanted organ, which can demonstrate granulomatous reaction and/or the presence of *S. mansoni* eggs. In most cases, schistosomiasis in the donor is not diagnosed before transplantation because donors were asymptomatic and parasitological tests were falsely negative or not done. PCR is highly sensitive and may offer added value in diagnosis of schistosomiasis if available.

C) Donor acceptance criteria:

Infected donors should be accepted and if possible, treated before donation, with a single dose of praziquantel (20 mg/kg/dose 2 or 3 times daily, for 1 day).

D) If you accept the organ donor, how do you manage it?

The recipient should be monitored by stool examination, serology or any complication but treated only if active egg excretion or seroconversion is found. Preemptive therapy of recipients remains controversial because of the lack of effect of therapy on the eggs and immature worms.

Recipients from an endemic region

A) What are the risks?

Organ transplant recipients can either present with a *de novo* infection or a reactivation of a previous infection however, literature is scarce regarding to *Schistosoma* infection after SOT. Recipients usually present mild hepatic or intestinal schistosomiasis and long-term survival of patients/grafts are observed.

B) Which tests should be performed?

All transplant candidates originating from endemic areas should be screened by stool examination. Serology assays presents high sensitivity for screening, however, antibodies remain detectable for a long period after infection, and consequently serology tests does not differentiate between current and past infections. In immunosuppressed patients, seroconversion can be delayed or never occur. Histological examination of the explanted organ can demonstrate granulomatous reaction or the presence of *S. mansoni* eggs.

C) How do you manage it?

Recipients should be treated before transplantation. First-line therapy is oral praziquantel given at a dose of 20 mg/kg per dose 2 or 3 times daily, for 1 day. Oxamniquine and antimalarial artemether can be used as alternative therapies.

Recipients who travel to an endemic region

A) What are the risks?

Consider screening transplant travelers that refers contact with natural waters in endemic areas of Brazil, Venezuela, Dominican Republic, Guadeloupe, Martinica, Puerto Rico, St. Lucia, and Suriname.

B) What are the pretravel recommendations (pretravel counseling)?

Uninfected transplant patients or candidates travelling to endemic areas should strongly be advised not to bathe in fresh water reservoir.

C) How to prevent infection or disease development? How to follow-up?

Health education practices should be taken, such as avoiding contact with contaminated water (this includes swimming, bathing, or wading in rivers, lakes, ponds or irrigated fields). The physician should be aware of the pruriginopapulous rash (swimmers itch), fever, cough and abdominal pain (associated to acute disease - Katayama syndrome) and hypereosinophilia. Schistosome antibodies do not appear until at least 2 to 8 weeks of infection and it may be longer to eggs appear in stool. In asymptomatic travelers, latent infection can be detected by serology, anyway seroconversion occurs within months.

Strongyloidiasis in organ transplantation

Donors from an endemic region

A) What are the risks?

S. stercoralis transmission by an infected organ donor has been well documented in recipients of all organs and unfortunately, this occurs not infrequently. High-risk donors are those who were born or those who have lived in endemic areas for a significant period of time.

B) Which tests should be performed?

Transplant physicians should be vigilant in looking for deceased donors with epidemiological risk factors or eosinophilia. High-risk donors should be screened for *S. stercoralis* infection before donation and treated with ivermectin before transplantation. Enzyme-linked immunosorbent assays for *Strongyloides* immunoglobulin G (IgG) antibodies are the most frequently test used for this purpose, although in certain regions false positive reactions due to other nematodes makes interpretation difficult. For potential living donors, either serology and/or stool for O&P can be performed. Deceased donors can have serological testing done, although this cannot distinguish between active and prior infection in endemic areas, and results may not be available at the time of donation.

C) Donor acceptance criteria:

Infected donors should be accepted and, if possible, treated before donation.

D) If you accept the organ donor, how do you manage it?

Infected donors should be treated with ivermectin before transplantation. If it is not feasible to screen the donor before transplantation, it is recommended to empirically treat the recipient with ivermectin (1 to 2 day course) after transplantation and be followed up. In hyperendemic areas, with wide access to ivermectin, donors and recipients could receive a 1- to 2-day course of universal prophylaxis, given the low cost and toxicity of the drug.

Recipients from an endemic region

A) What are the risks?

Strongyloides affects 100 to 370 million people worldwide and underdiagnosis/poor reporting is an important issue. In the Americas, infection rates over 15 % were recorded in Brazil, Peru, Venezuela, Argentina and Ecuador. Most infected patients are asymptomatic; however, immunocompromised patients are at risk of life-threatening dissemination in the setting of immunosuppression. Strongyloidiasis in SOT organ recipients has been attributed both to reactivation of latent disease, as well as donor-derived transmission.

B) Which tests should be performed?

Patients who have emigrated from or lived in an endemic region should be screened before the onset of immunosuppression. Veterans who fought in endemic countries are also at risk and should be screened. As the infection can last

decades, there is no time limit on how long it has been since exposure. Screening should include a check for eosinophilia and at least 1 stool specimen for ova and parasites. In nonendemic settings, serology can be used for screening.

C) How do you manage it?

Transplant candidates who found to be infected, should be treated before transplant with a 1- to 2-day course of ivermectin. Some clinicians repeat this at 2 weeks (1 autoinfection cycle). If hyperinfection or disseminated Strongyloidiasis is diagnosed in an SOT recipient, treatment is recommended until visible organisms are cleared and then for 7 to 14 additional days, with close monitoring for relapse.

In hyperendemic regions where treatment is easily accessible, centers may choose to treat all candidates before transplant without screening because there is a risk of false-negative testing. Retreatment is also recommended to recipients who are treated for rejection, considering reactivation or de novo infection. In the posttransplant period, surveillance stool exams may be done on a routine basis (eg, annually) or repeated courses of ivermectin may be given at predetermined intervals. The optimal strategy depends on local epidemiology, laboratory capabilities, and drug availability.

Recipients who travel to an endemic region

A) What are the risks?

There is a very small risk of acquisition of *S. stercoralis* with usual leisure or business travel. The risk is highest in recipients who stay for prolonged periods (>3 months) in endemic regions. Travellers who visit friends and relatives fall into this category because they may not seek pretravel advice and may stay in more remote settings.

B) What are the pretravel recommendations (pretravel counseling)?

The best measure for preventing infection with *S. stercoralis* is to wear shoes in endemic areas, particularly where there is inadequate human waste disposal.

C) How to prevent infection or disease development and how to follow-up?

Strongyloidiasis may persist lifelong through endogenous reinfection and in SOT recipients, and immunosuppression can facilitate progression to hyperinfection/disseminated disease. When traveling, patients should be advised to always wear footwear in endemic environments. Screening may be necessary after travel if there is a suspicious history of itching and/or hypereosinophilia. The sensitivity of single stool test is low; it increases by repeating stool examinations. Serology can also be used in nonendemic areas. In case of doubt, the recommendation is empiric treatment.

6. TRAVELERS DIARRHEA

Donors from an endemic region

A) What are the risks?

Donors from endemic region are under risk of traveler's diarrhea, caused by viral, bacterial and parasitic organism usually transmitted by food and water. The risk is highest in regions where sanitation and hygienic practices are poor, particularly if from resource-rich to source-limited regions of the world. The incidence of traveler's diarrhea is approximately 10% to 40%, depending on the travel destination. South and Central America, and Mexico are considered high risk (incidence greater than 20%), and the Caribbean Islands are considered moderate risk (10 - 20%).

B) Which tests should be performed?

Living donors from endemic regions with diarrhea should be screened before donation for intestinal parasites and enteropathogenic bacteria, by stool examination, blood, and fecal culture.

C) Donor acceptance criteria:

Donors with diarrhea have the potential risk for transmission of enteropathogenic strains of *Salmonella* spp., *Shigella* spp., enterotoxigenic *Escherichia coli* (ETEC) (or any, bacterial enteric pathogens). Although the actual risk of transmission from such donors remains undetermined, organ donation from donors with unexplained diarrhea should be deferred until the diagnosis and appropriate treatment.

D) If you accept the organ donor, how do you manage it?

Recipients should be monitored closely for signs and symptoms in posttransplant period.

Recipients from an endemic region

A) What are the risks?

Causes of diarrhea in SOT recipients are similar to those in the general population, enhancing a higher incidence of drug-induced diarrhea and opportunistic infections. As in the general population, bacterial agents are the most frequent cause of traveler's diarrhea associated to ETEC and enteroaggregative *E. coli*, followed by *Shigella* spp., *Salmonella* spp., *Campylobacter* spp., *Aeromonas* spp., noncholeric vibrios, and *Plesiomonas* spp. Other pathogens include protozoan infections (*Cryptosporidium* spp, *Cystoisospora belli, Cyclospora* spp., Microsporidia, *Giardia duodenalis*), and *Strongyloides stercoralis*.

B) Which tests should be performed?

Diagnosis and management of posttransplant diarrhea should include stool culture and parasitological examination of stools, stool *Clostridium difficile* assessment, and blood cytomegalovirus quantitative viral load.

C) How do you manage it?

The majority of traveler's diarrhea is self-limited, and requires mainly supportive management and fluid replacement. Empiric antibiotic therapy is recommended for moderate to severe cases of traveler's diarrhea, and for those with invasive symptoms (eg, bloody stools), and systemic illness (eg, fever). Transplant recipients suffering from diarrhea refractory to standard treatment, especially those at risk for additional waterborne diseases, should undergo a full evaluation for intestinal parasitic infection.

Empiric and targeted antibacterial therapy options are: ciprofloxacin 500 mg PO BID for 1 to 3 days, ciprofloxacin 500 mg PO single dose, levofloxacin 500 mg PO QD for 1 to 3 days, levofloxacin 500 mg PO single dose, azithromycin 500 mg PO QD for 1 to 3 days, or azithromycin 1000 mg single dose).

Empiric and targeted antiparasitic therapy options are: metronidazole 500 to 750 mg PO TID for 5 to 10 days (amebiasis) or 250 mg TID for 5 to 7 days (giardiasis), tinidazole 2 gram PO single dose (giardiasis) or once daily for 3 days (amebiasis), nitazoxanide 500 to 1000 mg PO BID for 14 days or until diarrhea resolves (amebiasis, cryptosporidiasis, giardiasis), paromomycin 25 to 35 mg/kg/day PO TID for 5 to 10 days (amebiasis), or trimethoprim-sulfamethoxazole, 1 double-strength tablet PO BID for 7 to 10 days (cyclosporiaisis, cystoisosporiasis).

Recipients who travel to an endemic region

A) What are the risks?

The risks for traveler's diarrhea are likely to be similar to those associated with general population travelling to endemic regions. In transplant recipient travelers, however, the severity of illness can be increased.

B) What are the pretravel recommendations (pretravel counseling)?

Most evidence about prevention and treatment of TD in SOT are extrapolated from other groups of nonimmunosuppressed travelers. Individualized risk assessments should be made about potential hazards for all travelers, particularly those with immunosuppression. Transplant patients who already have gastrointestinal problems and/or whose hydration status is in fine balance may need special counseling about the wisdom of travel to high-risk settings.

C) How to prevent infection or disease development and how to follow-up?

Advice should be provided about personal hygiene and dietary precautions. The conventional advice is to avoid all foodstuffs that have not been freshly prepared or properly cooked. The evidence base for effectiveness of prebiotics and probiotics is poor, and they are not widely recommended. There is no evidence to support the use of loperamide or similar antimotility agents in prevention (as opposed to treatment). Bismuth salicylate has moderate efficacy in preventing travelers diarrhea but has to be taken frequently and should be avoided by people with salicylate allergy and toxicity has been reported in patients with renal insufficiency, Short-term chemoprophylaxis with systemically absorbed antibiotics is highly effective in preventing travelers diarrhea, but prophylaxis has to be balanced against the risk of side effects of medication and drug-drug interactions. The systemic agents usually recommended are quinolones, such as ciprofloxacin taken in standard doses for short periods.

7. ARBOVIRUSES: CHIKUNGUNYA, DENGUE, YELLOW FEVER, AND ZIKA

Donors from an endemic region

A) What are the risks?

Chikungunya virus (CHIKV), dengue virus (DENV), and Zika virus (ZIKV) are arboviruses transmitted by urban *Aedes* species, predominantly *Aedes aegypti* and *Aedes albopictus*, globally distributed in the world.

YF is an endemic hemorrhagic fever in tropical areas of South-Central America and Africa. In most of the Americas, the virus is transmitted via a sylvatic cycle, in which jungle or savannah mosquitoes transmit the virus.

Donors originating from endemic countries of CHIKV, DENV and ZIKV have a higher risk of previous infection, which may potentially be transmitted through blood, tissue, or transplanted organs during this time. To date, there are no reports of YF transmission by organ or blood transplant, so this remains a theoretical risk. Transfusion related transmission of YF vaccine-virus has been reported, which necessitates careful screening and deferral of recently vaccinated blood donors.

B) Which tests should be performed?

Living and deceased donors from nonendemic areas may be assessed for exposure risk by screening for recent travel. Living donors should be educated to avoid infection before donation. Donors from endemic regions should be deferred if they have a recent history of a febrile illness suggestive of active arbovirus infection, particularly within 30 days. An alternative approach in areas with actively circulating arbovirus infections may be routine viremia screening using nucleic acid testing (NAT). It is possible, however, that these viruses persist in tissue after clearance from blood. For this reason, laboratory screening cannot fully replace epidemiological screening for recent arbovirus infection.

C) Donor acceptance criteria:

Organs from donors with signs and symptoms suggestive of recent arbovirus infection should be discarded. Organs from donors with a previous history of arboviruses can be considered for transplant after a minimum of 30 days quarantine period.

D) If you accept the organ donor, how do you manage their recipients?

Clinicians should be aware of the potential of arboviruses transmission through blood, tissue, or transplanted organs, particularly if the recipient develops an unexplained febrile manifestation after receiving an organ or blood products from donors with potential exposure to endemic areas.

Recipients from an endemic region

A) What are the risks?

The risks are likely to be similar to those associated with donors from an endemic region.

B) Which tests should be performed?

A history of epidemiological exposure to arboviruses should be assessed in all unexplained febrile episodes after transplant. Diagnosis should be suspected clinically based on the presence of signs and symptoms, such as fever, weakness, malaise, headache, conjunctivitis, myalgia, arthralgia, retroorbital pain, nausea, vomiting, and rash. Laboratory confirmation is based on serology and/or molecular testing. Due to possible cross-reactive antibodies produced during previous arboviruses infections and previous YF and Japanese encephalitis vaccines, RT-PCR is considered the gold standard for all arboviruses diagnoses. Viral PCR is positive during the viremic period and is also detectable in tissues, urine, and saliva. IgM antibody detection is a marker for acute infections; it typically becomes positive 3 to 5 days after symptom onset and may remain detectable for 3 to 6 months. In addition, NS1 detection is also an alternative diagnostic test for dengue; it can be detected up to 9 days after the onset of symptoms.

C) How do you manage it?

There are no specific antiviral treatments for CHIKV, DENV, ZIKV, and YF. Therapy consists mainly of supportive care.

Prevention includes mosquito avoidance with insect repellents and long sleeved clothing. In addition to the first licensed DENV vaccine developed by Sanofi Pasteur, multiple clinical trials of DENV vaccine candidates are in progress and may be available soon.

YF is preventable by a single lifetime dose of effective vaccine. Because the YF vaccine is a live attenuated vaccine, it is contraindicated posttransplant. YF vaccine is strongly recommended pretransplant in candidates who can safely receive live vaccines and are likely to be exposed to YF posttransplant.

Recipients who travel to an endemic region

A) What are the risks?

Infection risk is associated with travel to areas with actively circulating arboviruses, especially during the rainy season.

B) What are the pretravel recommendations (pretravel counseling)?

Transplant recipients who are traveling to YF endemic areas require a valid international certificate of YF vaccination (International Certificate of Vaccination) for travel to and from certain countries. Because YF vaccine is a live attenuated vaccine, it is contraindicated after transplant. Unvaccinated transplant recipients should be counseled to avoid travel to YF endemic areas. If this is not possible, they should be strongly educated to avoid mosquito exposure, and they need a physician's letter with a stamp from a YF travel clinic indicating that YF vaccine is contraindicated, to be permitted to travel to some countries.

Dengue vaccine is not currently approved for use in most countries and has not been routinely indicated for travelers.

C) How to prevent infection or disease development and how to follow-up?

Travellers should reduce skin exposure to mosquito bites with barrier methods, such as insect repellents and long sleeved or permethrin-treated clothing.

8. ENDEMIC FUNGAL INFECTIONS

Histoplasmosis

Histoplasmosis is endemic in the Americas and concentrated predominantly in the eastern US and LA.

Donors from an endemic region

A) What are the risks?

Donor-derived infections have been rarely reported.

B) Which tests should be performed?

Routine testing of all donors from an endemic area is not necessary. Deceased donors from endemic areas who have findings that could be consistent with histoplasmosis should undergo testing with cultures, antigen/serologic testing, and tissue histopathology.

C) Donor acceptance criteria:

Deceased donor organ procurement should not be delayed, as results of testing will subsequently guide recipient management. Living donors with active histoplasmosis should be treated for 3 to 6 months before organ donation.

D) If you accept the organ donor, how do you manage their recipients?

The most common scenario is the discovery of granulomas containing yeast morphologically consistent with Histoplasma in the allograft. Management is not well established, but itraconazole prophylaxis may be considered. If active deceased donor infection is confirmed, antifungal treatment of the recipient is advised.

Recipients from an endemic region

A) What are the risks?

Post-SOT histoplasmosis has an estimated incidence less than 1%.

B) Which tests should be performed?

For transplant candidates in endemic areas, routine pretransplant diagnostic testing is not recommended. For patients with any clinical suspicion the same screening described for donors should be performed.

C) How do you manage it?

Patients who have recovered from active histoplasmosis during the last 2 years before transplantation may be considered for itraconazole prophylaxis. Serial monitoring with urine/serum antigen levels can be considered.

Recipients who travel to an endemic region

A) What are the risks?

Exposure to disrupted soil around construction or agricultural areas, caves where bats reside, or buildings inhabited by birds or bats pose particular risk.

B) What are the pretravel recommendations (pretravel counseling)?

Patients should be counseled to avoid the above described high risk exposition.

C) How to prevent infection or disease development and how to follow-up?

Once the recipient returns from an endemic area, the clinician must maintain vigilant to recognize the manifes tations early.

Paracoccidioidomycosis

Paracoccidioidomycosis (PCM) is a systemic fungal infection caused by the dimorphic fungus, *Paracoccidioides brasiliensis*. The infection is endemic in some areas of LA, predominantly in South America, and is more prevalent among rural workers.

Donors from an endemic region

A) What are the risks?

Only 1 case of a kidney donor with an incidental diagnosis PCM has been reported.

B) Which tests should be performed?

Donors who have lived or traveled to rural areas in endemic regions should undergo a chest X-ray, skin testing, and serology. Microbiological tests and biopsy may be necessary if specific organ or tissue involvement is suspected.

C) Donor acceptance criteria:

Using an organ from donor with active disease is not advised. For a living donor with active disease, treatment for at least 6 months is recommended before donation.

D) If you accept the organ donor, how do you manage their recipients?

When using an organ from an infected donor, prophylaxis with itraconazole for 12 months is recommended. In addition the recipient should undergo serial serologic testing for at least 12 months.

Recipients from an endemic region

A) What are the risks?

Transplant candidates who have lived, worked, or traveled in rural areas in endemic regions should be considered at risk.

B) Which tests should be performed?

Recipients at risk should be submitted to the same screening described for donors.

C) How do you manage it?

Patients with active disease should receive treatment, starting at least 6 months before transplantation. For patients with evidence of prior infection without active disease, posttransplant prophylaxis with itraconazole for 12 months should be considered.

Recipients who travel to an endemic region

A) What are the risks?

The risk is associated with activities in rural areas.

B) What are the pretravel recommendations (pretravel counseling)?

Recipients traveling to endemic regions should be counseled to avoid rural areas.

C) How to prevent infection or disease development and how to follow-up?

For recipients exposed, a follow-up with serial serology for at least 12 months is recommended.

Sporotrichosis

Sporotrichosis is acquired mainly by a penetrating trauma with contaminated environmental material or after a cat scratch or bite. Endemic areas include LA.

Donors from an endemic region

A) What are the risks?

No donor transmitted cases have been reported.

B) Which tests should be performed?

Only donors from endemic regions with chronic skin or lymphocutaneous lesions should be screened, with histopathology and culture of tissue biopsy.

C) Donor acceptance criteria:

The decision to use organs from donors with active sporotrichosis should be individualized. Organs from donors with disseminated infection should be deferred.

D) If you accept the organ donor, how do you manage their recipients?

The role of posttransplant recipient antifungal prophylaxis has not been determined.

Recipients from an endemic region

A) What are the risks?

Sporotrichosis has been rarely reported among SOT recipients.

B) Which tests should be performed?

Transplant candidates from endemic regions and with chronic skin or lymphocutaneous lesions should be screened.

C) How do you manage it?

Patients with previous history of infection should be evaluated for the early diagnosis of posttransplant sporotrichosis. There is no recommendation for antifungal prophylaxis.

Recipients who travel to an endemic region

The risk is associated with skin trauma and contact with infected animals.

A) What are the pretravel recommendations (pretravel counseling)?

Recipients should be advised to avoid skin penetrating trauma or contact with cats, and to wear appropriate gloves during gardening activities

B) How to prevent infection or disease development and how to follow-up?

Once exposure occurs, close follow-up is recommended, to allow early diagnosis.

Coccidioidomycosis

Areas of high endemicity of coccidioidomycosis include Arizona, California, New Mexico, and Texas, as well as areas of Mexico and Central and South America. Infection is related to outdoor activities.

Donors from an endemic region

A) What are the risks?

Infected donors who live or have lived in an endemic area can transmit the infection with the allograft, even if they were asymptomatic.

B) Which tests should be performed?

Potential living donors should undergo serologic testing, chest imaging, fungal culture of respiratory secretions or tissue specimens as clinically indicated. Serologic testing should be performed on deceased donors with risk factors for infection.

C) Donor acceptance criteria:

Organs from donors with active infection should not be used.

D) If you accept the organ donor, how you manage their recipients?

If a recipient receives an organ from a donor with active disease, therapy must be administered. All recipients should be monitored for symptoms and seroconversion when prophylaxis is stopped.

Recipients from an endemic region

A) What are the risks?

Approximately 1.5% to 8.7% of the transplant recipients in endemic areas may be affected.

B) Which tests should be performed?

Screening of all transplant candidates from endemic regions for prior or present infection as described for living donors.

C) How do you manage it?

Fluconazole is recommended for patients with history of previous disease or positive pretransplant serology for at least 6 months posttransplant. Patients with documented active disease should receive lifelong secondary prophylaxis.

Recipients who travel to an endemic region

A) What are the risks?

Even brief exposures, such as changing planes in an endemic area, have been sufficient to cause infection.

B) What are the pretravel recommendations (pretravel counseling)?

Activities associated with dust exposure must be avoided. Use of masks may be helpful.

C) How to prevent infection or disease development and how to follow-up?

Any sign of disease must be immediately reported. All involved physicians must be aware of the travel history.

Cryptococcus gattii infections

C. gattii is a primary fungal pathogen that affects mostly individuals in tropical and subtropical regions. It is usually recovered from debris found in the hollows of Eucalyptus trees and the soil around trees. Where available, molecular methods (PCR) for diagnosis and MALDI-TOF for species identification may be useful.

Donors from an endemic region

A) What are the risks?

Donors who performed outdoor activities have a theoretical higher risk of transmission.

B) Which tests should be performed?

Donors who performed outdoor activities in the last year in endemic areas should be tested for serum cryptococcal antigen.

C) Donor acceptance criteria:

The decision to use organs from donors who are antigen-positive with no evidence of disease should be individualized. Transplanting organs from donors with active *C. gattii* cryptococcosis should be avoided. Organs from donors with a history of successfully treated cryptococcal infection might be acceptable for transplant, although there may be some risk (depending on organ type, eg, lung) for additional disease; this has not been studied.

D) If you accept the organ donor, how you manage their recipients?

In cases of donors who are antigen-positive, antifungal prophylaxis for recipients may be of benefit. When using an organ from an infected donor, posaconazole prophylaxis could be of benefit. Duration of prophylaxis has not been determined.

Recipients from an endemic region

A) What are the risks?

C. gattii infections remain rare in SOT recipients.

B) Which tests should be performed?

Performing a serum cryptococcal antigen could be considered for individuals from endemic regions who performed outdoor activities in the last year.

C) How do you manage it?

Management of asymptomatic SOT candidates who are found to have cryptococcal antigen in the serum is uncertain. These patients may benefit from careful clinical evaluation and antifungal prophylaxis.

Recipients who travel to an endemic region

A) What are the risks?

Exposure to environmental sources of *C. gattii* increases the risk of aggressive forms of cryptococcosis.

B) What are the pretravel recommendations (pretravel counseling)?

Recipients should be advised to avoid performing outdoor activities. The benefit of wearing masks during such activities is uncertain.

C) How to prevent infection or disease development and how to follow-up?

Once exposure occurs, close follow up is recommended, aiming for an early diagnosis. The utility of serial antigen testing is unknown.

9. VIRAL HEPATITIS

The most important hepatotropic viruses are the hepatitis A—E viruses. Hepatitis A virus (HAV) is mainly transmitted by the fecal-oral route; most countries in LA have an intermediate seroprevalence. Hepatitis B virus (HBV) may be transmitted vertically, by percutaneous or mucosal exposure to infected blood or body fluids, and sexually. The majority of LA countries are considered low prevalence (<2%) regions for HBV. The risk factors for hepatitis C virus (HCV) infection are similar to HBV. The estimated prevalence of HCV infection in LA ranges from 1.4 to 2.9%. Hepatitis D virus (HDV) is a defective virus that requires preexisting or concurrent infection with HBV. The North Region of Brazil and Venezuela, Colombia and Peru have high chronic HDV infection rates. Hepatitis E virus (HEV) occurs predominantly by fecal-oral route, and LA is considered as endemic area, although the prevalence is largely unknown.

Donors from an endemic region

Routine serologic screening is recommended.

A) What are the risks?

There are no reports of HAV transmitted via organ transplantation. Donor transmission of HBV and HCV are well described. Transfusion-transmitted HEV infections have been reported.

B) Which tests should be performed?

Serology for HBV and HCV should be performed in all donors, and serology for HDV in donors coming from high-risk areas. NAT for donor screening may improve sensitivity but it is costly and not always accessible in developing countries. Screening for HAV is not advised. Serological or molecular screening for HEV is not routinely performed, but immunosuppressed patients who receive organ from a positive donor can develop chronic liver disease.

C) Donor acceptance criteria:

Potential donors with positive anti-HBc and negative HBsAg testing are appropriate for organ donation in most settings. There is frequently an option to allocate organs from an HCV positive donor to an HCV positive recipient. Potential donors who test positive for HCV antibody with negative NAT testing may be appropriate for donation Use of organs from HCV viremic donors to HCV-negative recipients is now a consideration with the availability of highly effective treatments.

D) If you accept the organ donor, how do you manage their recipients?

There is a risk of HBV transmission from seropositive anti-HBc donors and recipient prophylaxis with oral antiviral medication is recommended. Recipients from positive HCV donors should be followed with NAT and treatment should be considered if transmission occurs.

Recipients from an endemic region

A) What are the risks?

The highest risk for acquisition of HAV infection in nonimmune individuals is through ingestion of contaminated food or water. Men who have sex with men are also at risk of transmission. HBV and HCV risk factors include exposure to blood products and body fluids from injection and medical equipment, all commonly present in transplant candidates. Consumption of undercooked pork, boar, and deer increases the risk of HEV infection.

B) Which tests should be performed?

All transplant candidates should have serology for HAV, HBV, HCV, and HEV performed. NAT should be done according to serologic status and clinical indication. Serology for HDV is indicated if HBV serology is positive.

C) How do you manage it?

Seropositive HAV recipients do not need any special approach. In seropositive HBV recipients, prophylaxis of reactivation after transplant is recommended. In HCV viremic patients, treatment should be considered before or after transplant. As HEV is known to cause chronic hepatitis in immunocompromised hosts, follow-up with NAT and liver function tests is advised. Treatment of chronic HEV infection in SOT recipients is decreasing immunosuppression and ribavirin.

Recipients who travel to an endemic region

A) What are the risks?

The risks for HAV and HEV infection are associated with water and food consumption in areas without basic sanitation and hygiene practices. Regarding HBV and HCV infection, the magnitude of the risk will depend on the presence of risky behaviors, including sexual activity, which are more common during travel.

B) What are the pretravel recommendations (pretravel counseling)?

Recipient travelers to LA should be informed about safe food handling, good hand washing practices and water precautions. Unpurified drinking water including ice cubes, raw or inadequately cooked meat, inadequately washed raw salads, and unpeeled vegetables and fruits should be avoided. It is safe to drink bottled water from reliable manufacturers. Travelers should be counseled on avoiding contact with nonsterile needles, syringes, cosmetic and tattoo procedures, or other risky behaviors, with emphasis of condom use.

Ideally, all SOT recipients over 1 year of age who are susceptible to HAV should be vaccinated before transplant. After SOT, vaccination is recommended only in 6 months. SOT recipients susceptible to HAV infection should receive the HAV vaccine series before travel to moderate- to high-risk infection areas. When feasible, seroconversion should be assessed before departure, and if

TABLE 1.

Recommendation for vaccination in adults transplant candidates or recipients

Vaccine	Recommended before transplant	Recommended after transplant	Vaccination schedule	Comments
Tetanus/diphtheria (Td)	Yes	Yes	1 dose every 10-20 years	
Pertussis (Tdap)	Yes	Yes	1 dose	
Influenza (inactivated)	Yes	Yes	1 dose yearly	Booster dose, intradermal route, high-dose, adjuvanted vaccines not routinely recommended
Influenza (live-attenuated)	Yes	No	1 dose yearly	Temporary contraindication to transplant for 2 weeks after vaccination Contraindicated after transplantation
MMR	Yes	No	1-2 doses	In adult candidates, 1 dose followed by serological testing, with booster administration if no seroconversion Contraindicated after transplant
Pneumococcal				*at least 1-year after any prior PPV23
PCV13*	Yes	Yes	Yes	**at least 8 weeks after PCV13 and
PPV23**	Yes	Yes	Yes	5 years after previous PPV23.
Neisseria meningitidis (MCV4, group B vaccines)	Yes	Yes	2 doses, 0-2 months	Only in patients at high epidemiological risk Consider in transplant candidates who could potentially receive eculizumab after transplant (ie, highly sensitized, atypical HUS, etc)
Varicella	Yes	No*	2-doses 4 weeks apart 1 dose	*Has been given to selected patients posttransplant
Zoster	Yes	No	1 dose	Live viral vaccine contraindicated after transplant. When available, nonlive vaccines may be useful.
Hepatitis B	Yes	Yes	3-dose series at 0, 1, 6 months	High-dose vaccine recommended in patients on dialysis, with organ failure, and posttransplant. Accelerated schedules with 4 doses may be used. Can be administered alone or in combination with the HAV vaccine
Hepatitis A	Yes	Yes	2-doses 6-12 months apart	Administer intramuscular pooled immunoglobulins in case inadequate time from vaccination to travel Can be administered alone or in combination with the HBV vaccine
Polio inactivated	Yes	Yes	1 dose	
Polio (oral, live-attenuated)	Yes	No		Contraindicated after transplantation for recipients and their household contacts
HPV	Yes	Yes	3-dose series	Females 9-45 years and males 9-26 and MSM > 26

HPV, human papillomavirus; MSM, men who have sex with men; MMR, measles, mumps, rubella; PCV, peumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; MCV4, tetravalent meningococcal.

Adapted from:

Danziger-Isakov L, Kumar D, AST Infectious Diseases Community of Practice. Vaccination in solid organ transplantation. Am J Transplant. 2013 Mar;13 Suppl 4:311–7.

Kotton CN, Hibberd PL, AST Infectious Diseases Community of Practice. Travel medicine and transplant tourism in solid organ transplantation. Am J Transplant. 2013 Mar;13 Suppl 4:337–47.

TABLE 2.

Recommendation for vaccination in adults transplant candidates or recipients traveling to LA

Vaccine	Vaccination schedule	Comments
Influenza (inactivated)	1 dose yearly	Should be given to all SOT candidates or recipients who were not vaccinated within the past year, before travel
Neisseria meningitidis (MCV4, group B)	2 doses, 0-2 mo	Not routinely recommended before travel to LA, except in cases of outbreak (update information can be checked at http://www.who.int/wer)
Hepatitis A	2 doses 6-12 months apart	Recommended for susceptible individuals traveling to LA
Polio (inactivated)	1 booster	Not routinely recommended before travel to LA
YF	1 dose	Contraindicated in the posttransplant Some LA countries require proof of YF vaccine or a waiver letter from all arriving travellers or depending of origin of traveller—a list of those countries are available at http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/yellow-fever
Japanese encephalitis	2 doses (0-28 d)	Not routinely recommended before travel to LA
Rabies	Preexposure: 3 doses (plus 1 additional dose at 12 mo if needed) Postexposure; 2-4 doses	Vaccination schedule post exposure to rabies depends on previous pre exposure vaccination. Not routinely recommended before travel to LA. Postexposure prophylaxis (the schedule depends on previous pre exposure vaccination) Control of antibodies titres are needed to potentially administer additional doses of the vaccine
Typhoid fever (inactivated polysaccharide)	1 dose	Indicated for everyone traveling to endemic areas, especially if traveler staying with friends or relatives, visiting smaller cities or rural areas, or if you are an adventurous eater
Typhoid fever (live-attenuated oral)	2 doses at days 1, 3, and 5	Contraindicated for SOT recipients
Cholera (oral vaccines)	2 doses	Not routinely recommended before travel to LA Vaxchora: contraindicated for SOT recipients
Dengue (lived-attenuated vaccine)	3 doses at 0, 6, and 12 mo	Contraindicated for SOT recipients

still seronegative pooled immunoglobulins are recommended. Although the HBV vaccination series should ideally be given before transplantation, it is recommended for all unvaccinated SOT recipients, particularly before travel. When feasible, serologic testing of anti-HBs 1 to 2 months after completion of the vaccine series should be performed. Re-vaccination should be considered if antibody response is suboptimal, potentially with higher-dose HBV vaccine. Traveler may necessitate an accelerated series with variable efficacy.

There is currently no commercially available HCV vaccine. HEV vaccine has been developed but is currently only available in China.

C) *How to prevent infection or disease development and how to follow-up?*

For susceptible recipients returning from travel with risky behaviour history, a follow-up with serial serology during the respective incubation period is recommended.

10. VACCINES

Vaccine-preventable infections represent a significant burden of disease in SOT recipients. Pretransplant vaccination may help mitigate the risk of vaccine-preventable infection. See Table 1 and Table 2.

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APPENDIX 1.

CHECKLIST Pre-travel Questionnaire			
Name:			
Gender:			
For women, are you pregnant, breast feeding or planning pregnancy in the next 6 months?			
Occupation:			
Date of birth:		Country of origin:	
Date of departure and length of stay:			
Itinerary: Rural or urban			
Country	Town	Duration of stay	
		Dates	From to
Purpose of travel:		Volunteer/Mission Medical care Business Adoption	Vaccation Other VFR (visiting friend and relatives)
Accomodation/Travel style/Modes of transportation		Backpacking/Hostels Rural or remote areas Campsite	
Activities planned during travel		Sports and outdoors activities (diving, camping, high altitude)	
Assess traveler's health			
		Time of transplant	
		Immunosuppressive medications (drug and dose)	
		Transplant complications: Graft versus host disease Rejection Opportunistic infections Antimicrobial use in the last 3 months	
		Recent surgery	
Immunization history and vaccine records		Routine vaccines Yellow-fever endemic country: Yes No Provide YF vaccine waiver document Influenza	
Allergies (i. e. eggs, latex, antibiotics, vaccines)			
Prophylaxis: Diarrhea	Malaria		
Pre-travel screening (e.g. previous exams)			
Physical assesment			
List of medication			
Hospital for medical care or insurance			
History of anxiety or depression, Neurological disorders (e.g. epilepsy), Cardiovascular disorders (e.g. thrombosis, arrhythmia), Recent chemo or radiotherapy			
Tunneled catheter, pacemaker or prosthesis			
Counseling checklist:	Food and water advice Travel insurance	Insect and animal avoidance Sexual health	
Post-travel monitoring	Date:		