Evaluating the risk of transmission of infection from donor to recipient of a solid organ transplantation

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A B S T R A C T

In the context of solid organ transplantation, screening of potential organ donors is crucial, and should be performed with great rigor to minimize the risk of transmission of certain infectious processes. This review aims to update understanding of the possible pathologies involved, as well as of emerging infections that, as a result of globalization, are gaining increasing prominence on a daily basis.

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Evaluación del riesgo de transmisión de infección procedente del donante al receptor de un trasplante de órgano sólido

Palabras clave:
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R E S U M E N

En el contexto del trasplante de órgano sólido, la evaluación previa del donante representa una actuación muy importante que se debe efectuar con sumo rigor, para minimizar al máximo el riesgo de transmisión de ciertos procesos infecciosos. Esta revisión pretende actualizar los conocimientos sobre las posibles patologías implicadas así como el conjunto de infecciones emergentes que, como consecuencia de la globalización, adquieren día a día un creciente protagonismo.

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Introduction

Donor-transmitted infections are both a common and potentially serious complication of solid organ transplantation (SOT). Rigorous screening of the donor for latent infections is essential for optimizing outcomes after transplantation, serves to prevent the inadvertent use of unsuitable organs and prompts strategic anti-infective prophylaxis or infection surveillance measures post-transplantation.

This chapter provides a clinical resource for evaluating the infection risks of potential organ donors. It also provides the basis for understanding geographically restricted donor infections, an increasingly important consideration in transplantation medicine.

We direct the reader to a number of recent publications that discuss guidelines for the pre-transplantation infection screening of organ donors and recipients.[1-6] A comprehensive review on the transmission of tropical and geographically restricted infections during SOT has also been published.[7]

Screening Potential Organ Donors for Infection

History and physical examination

Donor infection screenings begin with thorough reviews of medical and social histories and physical examinations. These examinations may provide evidence of active infection, injection drug use, (nonprofessional) tattoos and stigmata from (undiagnosed) infection such as viral exanthem. Important historical data includes potential endemic, travel-related, occupational and recreational exposures to infection, social and behavioral risk factors, and past and current infections. It is of paramount importance to ask about and report transmissible donor infections to the transplant center, including bacterial infections, fungal infections and suspected sepsis; tuberculosis; central nervous system infections; active viral infections; serologic evidence of HIV and human T lymphotropic

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virus I/II (HTLV I/II) infection, and parasitic and protozoal infections.[8] Emerging infections represent special challenges in the transplantation setting,[9-11] and are therefore important events that need to be communicated to the transplant center.

Screening for specific pathogens

The serological and microbiological tests for donors, as recommended by regulatory bodies and professional transplant societies, are summarized in Table 1.

Human immunodeficiency virus

The transmission of HIV via organ transplantation is well documented, and policies regarding HIV testing of all donor candidates have been in place since 1985.[12] Many countries have policies and regulations that prohibit organ donation from HIV-infected persons, although recently, use of HIV-infected organs for HIV-infected kidney recipients has been performed in South Africa.[13] For donor screening, an enzyme-linked immunoassay (EIA) for HIV-1/2 testing is the preferred initial test, and repeatedly reactive results are confirmed by Western immunoblot assay (WB). It should be noted that the average window period from infection to a reactive EIA result is 22 days (range 6-38 days).[14] For HIV nucleic acid testing (NAT) considerations, see the section on high-risk donors below.

Hepatitis viruses

Organ donors are screened for serologic evidence of hepatitis B virus (HBV) infection with immunoassays for HBV surface antigen (HBsAg) and total core antibody (HBcAb). HBsAg+ donor organs are generally reserved for life-threatening cases. HBsAg+ organs may be considered for use in recipients who are HBsAg+, have protective immunity to hepatitis as a result of immunization (HBsAb titer ≥10 mIU/ml) or natural infection, or who are from geographic locations with HBV hyperendemicity. Post-transplantation, hepatitis B immune globulin and an antiviral agent are administered to recipients of HBsAg+ organs, regardless of immune status, although prophylaxis does not prevent transmission of infection in all cases. All recipients require laboratory monitoring for acquired HBV.[15,16]

A common scenario is for the potential donor to be HBcAb+. The HBV serologic profiles, HbsAg–, HBcAb+ and HbsAb–, may appear with early HBV infection or later (resolved) infection. Alternatively, these profiles can sometimes represent a false positive result, especially if risk factors for HBV are absent. Results demonstrating HBcAb+ or HBsAb+ are consistent with resolved infection, although HBV may persist in the liver. The risk of transmission of infection from a HbsAg–, HBcAb+ or HBsAb+/– donor to a susceptible non-hepatic organ recipient is low.[16,17] Recipients with protective immunity require no post-transplantation therapy. HBV non-immune recipients, however, should undergo serial laboratory testing for HBV infection or receive antiviral prophylaxis with an agent such as lamivudine or hepatitis B immune globulin.[15,16] Donor NAT for HBV may be useful in assessing the risk of transmission and for the management of recipients.[16]

For hepatitis C virus (HCV), the risk of viral transmission from an infected donor to a seronegative recipient is substantial, ranging from 25%-100%,[18-20] and recipients with acquired HCV are at risk for chronic infection and progressive liver disease, the course of which may be accelerated by immunosuppressive therapy, especially mycophenolate mofetil.[19] To prevent inadvertent transmission of HCV, donors are screened with an EIA for HCV, and HCV+ organs are generally excluded from transplantation with the exception of emergency situations, often with preferential allocation to HCV-infected recipients.[21] False negative test results can occur with HCV antibody testing, and the mean window period from infection to seroconversion is 66 days. As a consequence, transmission events involving HCV seronegative donors have occurred.[22,23] HCV NAT

Table 1
Recommended infection screening of potential organ donors

Medical evaluation and studies
Medical and social history
Physical examination
Chest radiograph
Bronchoscopy with bronchoalveolar lavage[a]
Tests for bacterial infection
Rapid plasma reagin (RPR) or other serologic test for syphilis
Blood cultures
Urine culture
Sputum gram stain and culture[a]
Tests for viral infection
Human immunodeficiency virus types 1 and 2 (HIV-1/2) antibody
Human T-cell lymphotropic virus I/II (HTLV-I/II) antibody
Cytomegalovirus IgG antibody
Epstein-Barr virus IgG antibody
Herpes simplex virus types 1 and 2 (HSV-1/2) IgG antibody[b]
Hepatitis B surface antigen (HBsAg)
Hepatitis B total core antibody (HBcAb)
Hepatitis B surface antibody (HBsAb)[b]
Hepatitis C antibody
Nucleic acid testing for HIV[c]
Nucleic acid testing for hepatitis C virus (HCV)[c]
Tests for parasitic infection
Toxoplasma IgG antibody[d]

[a]Recommended for prospective lung donors.
[b]Test not routinely performed.
[c]Increasingly utilized for prospective donors with high risk features.
[d]Test recommended for prospective heart donors, especially in areas of high endemicity.

testing of donors may detect infection in cases of negative antibody testing, but is not routinely performed at the present time. See the section on high-risk donors below.

Herpesviruses

Cytomegalovirus (CMV) donor positive/recipient negative (D+/R–) serostatus is the greatest risk factor for CMV infection post-transplantation, although CMV R+ may develop reactivation disease (D+ or –/R+) or donor-related infection (D+/R+). Therefore, organ donors are tested for prior (latent) CMV infection by EIA as part of the SOT risk assessment so that appropriate surveillance and/or antiviral prophylaxis can be instituted after transplantation.[2,4,6,24]

Epstein-Barr virus (EBV) infection is associated with the development of post-transplant lymphoproliferative disorders (PTLD). The greatest risk factor for PTLD is D+/R– serostatus. Thus, donors are serologically screened so that risk can be assessed and the EBV D+/R– recipient can be appropriately monitored post-transplant. Donor screening is most important in the setting of pediatric transplantation, as younger recipients may not have naturally acquired the infection yet. The seroprevalence of EBV exceeds 90% in the adult population, and so the donor is presumed positive if serology is not performed.[2,4]

Other than that based on past medical history and physical examination, donors are not routinely screened for other herpesvirus infections, such as herpes simplex virus, varicella zoster virus and human herpesviruses 6, 7 and 8.

Treponema pallidum

Transmission of *T. pallidum* by organ transplantation has been documented,[25] although syphilis is not a contraindication to organ donation. Donors are screened for serologic evidence with a non-treponemal assay, such as the rapid plasma reagin test or a treponemal immunoassay, so that treatment may be administered to recipients of serologically reactive donor organs.[3,5]

Mycobacterium tuberculosis

Although most cases of tuberculosis (TB) are attributed to the reactivation of latent infection in the recipient, donor-derived tuberculosis has occurred.[26] Therefore, all living donors should undergo PPD skin testing. If the result is positive, active TB should be ruled out.[27] The donor evaluation for TB in cadaveric donors relies on medical history, endemic exposures and radiographic findings. Organs from donors with known active TB infection are generally discarded, and lungs with residual tuberculous lesions should not be used for transplantation.[28] A history of latent TB without evidence of active infection is not a contraindication to donation, but the administration of preventive therapy to the recipient should be considered. Interestingly, there are no proven cases of transmission of mycobacteria other than tuberculosis.

Other bacterial and fungal pathogens

Sepsis, bacterial and fungal infections are frequently identified in potential organ donors as a consequence of intensive care and invasive resuscitative efforts. Donor bacteremia is common, with reported rates of up to 16%.[29,30] These infections can be transmitted to the recipient and result in potentially fatal early post-transplant complications, such as bacteremia, myocarditis and mycotic aneurysms.[31,32] *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida* spp., in particular, have a propensity to cause these serious complications. Sepsis and infections are not absolute contraindications to organ donation; rather, antimicrobial therapy is administered to the donor (if the infection is identified pre-mortem) and the recipient to reduce the risk of transmission.[4,30] Similarly, organs from donors with bacterial meningitis have been used successfully as long as the donor received appropriate antibiotic therapy pre-mortem.[30] To identify subclinical infections, blood and urine are often collected at the time of organ donation, especially if the donor has been hospitalized for more than 48 hours. Generally, recipients who receive organs from bacteremic or fungemic donors receive directed anti-infective therapy for a period of 7-14 days.[29,30,33]

The lung is the most common site of infection in donors.[30] When lung transplantation is under consideration, bronchoalveolar lavage (BAL) and gram stain and culture of respiratory secretions is performed.[34] Donors with evidence of gram-positive bacterial infections (bloodstream or pneumonia) are often used. Use of lungs with gram-negative infections is more controversial; some experts favor discarding these organs, while others advocate their use with aggressive antibiotic therapy.[34,35] Supporting the latter argument, a recent retrospective study demonstrated a high rate of transmission of respiratory tract pathogens to lung recipients (>40%), but overall patient survival was no different from that of recipients of uninfected lungs.[35]

Toxoplasma gondii

Infection with the protozoan *T. gondii* is extremely common, with seroprevalence rates of 50%-80% in Europe and Central and South America.[36,37] Transmission of an infection with *T. gondii* occurs most commonly when a seronegative recipient receives an organ from a seropositive donor. Whereas the occurrence of toxoplasmosis following abdominal organ transplantation is low, the prevalence in D+/R– heart and heart-lung recipients in the absence of antimicrobial prophylaxis ranges from 17%-75% due to the transmission of cysts present within cardiac tissue.[38] Less commonly, seropositive recipients may manifest a reactivation of latent infection. To assess the risk of transmission, organ (especially heart) donors should be screened for serologic evidence of infection, although this is not a consistent practice across health centers, especially in regions with low endemicity, or if anti-infective prophylaxis with trimethoprim-sulfamethoxazole is routinely provided.[4,37,39]

The High-Risk Donor

Due to the rare occurrence of HIV seronegative donor transmission of HIV, regulations and guidelines were put in place to further reduce the transmission of HIV (and other blood-borne viruses) by organ donation. Guidelines provide social, behavioral, medical and laboratory criteria by which to identify donors who have the potential for recent HIV infection but are in the "window period" prior to seroconversion or in whom the possibility of infection cannot be adequately assessed due to hemodilution or lack of medical history (Table 2). Organ donors who meet any of these criteria are generally considered only for recipients in life-threatening situations, and additional consent must be obtained from the recipient. Some experts advocate the use of viral NAT to supplement serologic testing of high-risk donors.[41,42] With NAT, the window period from infection to viral detection can be reduced to 5-10 days for HIV, 3-5 days for HCV, and to a lesser extent, 20-22 days (from 44 days) for HBV.[14,43] Negative NAT results may provide further information about the risk of donor viral infections and maximize organ utilization. The disadvantages of NAT are the expense, time requirements for additional testing, geographically limited availability and false positive tests resulting in the loss of organ donors.

Geographically Restricted Donor Infections

The main information about geographic distribution is collected in Table 3, and a brief summary of each particular approach is provided in the text.

Histoplasma capsulatum

Transmission of histoplasmosis has been described,[44] but most cases appear to be the result of reactivation of past infection in the recipient. Serological testing should be performed on potential donors living in areas of endemicity with a history of pulmonary disease within the past 2 years or radiographic findings suggestive of active or past histoplasmosis, such as calcified pulmonary, hilar and splenic granulomata. In non-endemic areas, serological testing is recommended in cases where there is past history of travel to, or residence in, endemic areas. Serology results from complement fixation (CF) and immunodiffusion (ID) should not affect the indication for transplantation. If acute histoplasmosis is suspected then detection of antigens in urine, BAL fluid or CSF may offer a rapid diagnosis. NAT for detecting *H. capsulatum* in blood and tissue samples is in development. The use of itraconazole prophylaxis in recipients whose donors had a past history of histoplasmosis is controversial. Nevertheless, a course of at least 3 to 6 months should be offered, at least to lung recipients.

Coccidioides immitis

Transmission of coccidioidomycosis by lung transplantation has been reported,[45] although reactivation of latent infection in the recipient appears to be far more common. Serological screening by EIA, CF and ID is recommended in donors coming from, or residing in, areas of endemicity. If the donor has a history of remote coccidioidomycosis, radiological changes of prior coccidioidomycosis or has lived in, or traveled to, areas of endemicity, then the recipient

Table 2
Donor exclusionary criteria from the 1994 U.S. Public Health Service/Centers for Disease Control and Prevention *Guidelines for Preventing Transmission of Human Immunodeficiency Virus Through Transplantation of Human Tissue and Organs*[40]

Exclusion from donation based on	Criteria
Behavior and history	Men who have had sex with another man in the preceding 5 years
	Persons who report nonmedical intravenous, intramuscular or subcutaneous injection of drugs in the preceding 5 years.
	Persons who have received human-derived clotting factor concentrates.
	Men and women who have engaged in sex in exchange for money or drugs in the preceding 5 years.
	Persons who have had sex in the preceding 12 months with any person described in items above or with a person known or suspected to have HIV infection.
	Persons who have been exposed in the preceding 12 months to known or suspected HIV-infected blood through percutaneous inoculation or contact with an open wound, non-intact skin or mucous membrane.
	Inmates of correctional systems.
Additional pediatric donor features	Children meeting any of the exclusionary criteria listed above should not be accepted as donors.
	Children born to mothers with HIV infection or mothers who meet the behavioral or laboratory exclusionary criteria for adult donors (regardless of their HIV status) should not be accepted as donors unless HIV infection can be definitively excluded in the child as follows:
	Children >18 months of age who are born to mothers with, or at risk for, HIV infection, who have not been breast-fed within the last 12 months, and whose HIV antibody tests, physical examination and review of medical records do not indicate evidence of HIV infection, may be accepted as donors.
	Children ≤18 months of age who are born to mothers with or at risk for HIV infection or who have been breast-fed within the past 12 months should not be accepted as donors regardless of their HIV test result.
Laboratory and other medical characteristics	Persons who cannot be tested for HIV infection because of refusal, inadequate blood samples (e.g., hemodilution that could result in false-negative tests) or any other reason.
	Persons with a repeatedly reactive assay for HIV-1 or-2 antibody, regardless of the results of supplemental assays.
	Persons who have a history, physical examination, medical records or autopsy reports that reveal other evidence of HIV infection or high-risk behavior, such as diagnosis of:
	AIDS
	Unexplained weight loss
	Night sweats
	Blue or purple spots on the skin or mucous membranes typical of Kaposi's sarcoma
	Unexplained lymphadenopathy lasting >1 month
	Unexplained temperature >100.5 °F (38.6 °C) for >10 days
	Unexplained persistent cough and shortness of breath
	Opportunistic infections
	Unexplained persistent diarrhea
	Male-to-male sexual contact
	Sexually transmitted diseases
	Needle tracks or other signs of parenteral drug abuse

can be given prophylaxis with oral fluconazole after transplantation until the results of the serological studies become available. If a positive result is obtained and the transplant has already been performed then active illness must be excluded. If no focus is found, prophylaxis with fluconazole or itraconazole should continue for 6 months.

Other fungi

Other regional fungal infections include *Paracoccidioides brasiliensis*, *Blastomyces dermatitidis* and *Penicillium marneffei*. Clinicians and radiologists should be aware of the possibility of *P. brasiliensis* and *B. dermatitidis* infection when evaluating potential donors from Latin America who show lung and skin lesions, particularly when they fail to identify acid-fast bacilli in samples. There are no reported cases of infection transmission via graft. In addition, the routine use of trimethoprim-sulfamethoxazole as

primary prophylaxis for *Pneumocystis jiroveci* pneumonia is also effective against *Paracoccidioides brasiliensis*.

Plasmodium spp.

Screening should be performed on donors from countries of endemicity, or if there is a history of recent travel (two or three preceding years) to these areas, as transmission of malaria to the recipient has been documented.[46] Detection of this infection should not necessarily contraindicate organ donation unless the cause of death is related to the malaria, in which case the organs should be rejected. The diagnostic test that should be performed is examination of thick and thin blood films stained with Giemsa, Field or Wright stain. These techniques are sensitive and allow an estimation of the degree of parasitemia as well as the identification of the infecting species of *Plasmodium*. Immunochromatography-based techniques are useful but do not detect low levels of parasitemia (<300 parasites/

Table 3
Geographic distribution of infectious agents

Infectious agent	Geographic distribution
HTLV-1/2	HTLV-1 seroprevalence: southwestern Japan (up to 10%), Caribbean area (up to 6%), sub-Saharan African countries (up to 5%), and Iran and Melanesia (less than 5%). In Europe and North America, HTLV-1 infection is found in immigrants, their offspring and sexual contacts, sex workers and intravenous drug users (IVDU).
	HTLV-2: IVDU populations of the United States, Europe, South America (Brazil) and Southeast Asia (Vietnam), and their sexual contacts, as well as in populations of native Amerindians.
WNV	Africa, Asia, the Middle East, Europe, North America, the Caribbean Islands and Latin America (212). Seasonal incidence in the temperate zones of North America, Europe and the Mediterranean Basin, with peak activity from July through October.
Rabies virus	Rabies virus-free: islands (e.g., Japan, New Zealand, Barbados, Fiji, Maldives, and Seychelles), parts of northern and southern continental Europe (e.g., Greece, Portugal and the Scandinavian countries) and Latin America (e.g., Uruguay and Chile).
Coccidioides immitis (coccidioidomycosis)	Southwestern United States and northern Mexico, where they are endemic. Also found in parts of Argentina, Brazil, Colombia, Guatemala, Honduras, Nicaragua, Paraguay and Venezuela.
Histoplasma capsulatum (histoplasmosis)	Mississippi and Ohio River valleys, Central America and certain areas of Southeast Asia and the Mediterranean basin.
Paracoccidioides brasiliensis (paracoccidiomycosis)	From Mexico to Argentina (Chile and some of the Caribbean Islands are not affected).
Blastomyces dermatitidis (blastomycosis)	Central United States. Also found in the Mediterranean basin and parts of Africa.
Penicillium marneffei (penicilliosis)	Southeast Asia, southern China, Taiwan and Hong Kong.
Plasmodium spp. (malaria)	*P. falciparum:* sub-Saharan Africa, Southeast Asia and the Indian subcontinent, as well as in South America, Haiti, the Dominican Republic, Jamaica and areas of Oceania.
	P. malariae and *P. ovale:* sub-Saharan Africa.
	P. vivax: Southeast Asia, the Indian Subcontinent and Central and South America.
Leishmania spp. (leishmaniasis)	Southern Europe, India, Kenya, Sudan, Brazil and tropical areas.
Trypanosoma cruzi (Chagas' disease)	From the south of the United States to Argentina and Chile.
Strongyloides spp. (strongyloidiasis)	Southeast Asia, sub-Saharan Africa, Brazil (where prevalence rates are close to 60%) and the southern United States.
Taenia solium (cysticercosis)	Worldwide distribution, predominating in areas where there is porcine livestock, and because of this, it is rare in Islamic countries. Greater incidence in developing countries and endemic in parts of Asia, Africa and Latin America.
Echinococcus spp.	*E. granulosus* (cystic hydatidosis): coastal areas of the Mediterranean, South America, southern areas of Russia, Central Asia, China, Australia and some areas of Africa.
	E. multilocularis (alveolar hydatidosis): northern hemisphere, mainly in Central Europe, Russia, Central Asia, North America (especially in hunters in Canada and Alaska) and West China.
	E. voegeli: Central and South America (Colombia, Venezuela, Brazil, and Panama).
Filariae (filariasis)	North Africa, Caribbean, South America (in certain countries), Yemen, Indian subcontinent, Southeast Asia and Pacific area of Oceania.
Schistosoma spp.	*S. haematobium*, *S. intercalatum*, and *S. mansoni*: sub-Saharan Africa; the latter is also found in Brazil, Venezuela and certain areas of the Caribbean.
	S. japonicum: China, Indonesia and the Philippines.
	S. mekongi: Cambodia and Laos.
Clonorchis spp.	China, Taiwan, Korea and Japan.
Opistorchis spp.	Eastern Europe, countries of the former Soviet Union, India and Thailand.
Paragonimus spp.	Japan, India, islands of the Pacific, West and Central Africa and South and Central America.
Fasciola spp.	Europe, East Asia, South Africa, North and South America, the Caribbean and Australia.
Babesia spp. (babesiosis)	Temperate zones of the United States and Europe, even though isolated cases have also been described in China, Taiwan, Egypt, South Africa, Mexico and, more recently, India.
Entamoeba histolytica (amebiasis)	Central and South America, Africa and the Indian subcontinent.
Free-living amoeba	Widely distributed in the environment, mainly where there is freshwater (rivers, streams, lakes, swimming pools and water treatment systems). Cases peak in the summer months.
Trypanosoma brucei (sleeping sickness)	*Trypanosoma brucei gambiense*: West and Central Africa.
	Trypanosoma brucei rhodesiense: East Africa.

ml). NAT, if available, could exclude cases with low parasitemia. Serology is not useful in this setting.

Trypanosoma cruzi

The transmission of Chagas disease during transplantation has been documented, particularly for heart transplantation.[47] Chagas

disease should be ruled out in all donors who have resided in endemic areas. The use of serological tests should be mandatory. Two positive results using different serological techniques (immunofluorescent antibody tests [IFAT] and EIA) are necessary to consider a patient infected. There are new rapid serological tests that use recombinant proteins in immunochromatography cassette tests, which may be used in emergency situations, such as in the hours preceding a

transplant procedure. Identification of *T. cruzi* in Giemsa-stained thick and thin blood films or by means of concentration techniques such as Strout's method and the micromethod are the tests of choice for the diagnosis of acute infection. NAT may have greater sensitivity and specificity than microscopy in the acute phases and may detect the parasite in the chronic phase, when the circulating parasitemia is low. If the cause of death is deemed to be acute Chagas disease, the donor should be excluded. In the case of cardiac transplantation, the use of a heart from a patient with chronic infection is an absolute contraindication given the risk of development of chagasic myocarditis. There is no consensus on the possible use of organs from infected patients other than the heart. If an organ from an infected donor is transplanted, close follow-up with serological and parasitological methods is recommended. Immediate treatment with benznidazole for 30 to 60 days or nifurtimox for 90 to 120 days should be started upon finding evidence of infection or as prophylaxis.[48]

Strongyloides stercoralis

Diagnostic tests should be performed in donors who have resided in, or traveled to, zones of endemicity, and specific treatment should be recommended prior to transplantation. Diagnosis is obtained following the visualization of larvae in the stool and with larval culture. Examination of several samples is recommended. The use of special microbiological techniques, such as Harada-Mori or larval culture in agar medium with coliforms, increases the sensitivity of diagnosis.[49]

Echinococcus spp.

The discovery of an image suggestive of a hydatid cyst in a prospective organ donor from an area of endemicity should raise suspicion of the diagnosis and should be confirmed with serology. Cysts that are found in the liver or bone tend to produce a positive serology with greater frequency than those located in the lung, brain or spleen. Calcified cysts or those with an intact capsule may be associated with negative serology. Indirect hemagglutination assay (IHA), IFAT and EIA are the most commonly used serological tests. If a patient has negative serology and a suspicious lesion on imaging, puncture and aspiration of the lesion should be performed in order to obtain a definitive diagnosis. An organ infected with hydatid cysts should not be used for transplantation unless the cyst is localized, inactive and calcified, permitting radical excision prior to transplantation. If there is isolated hepatic involvement, other organs may be used if a computed tomography (CT) scan rules out extensive disease.

There are no reported cases of donors infected with *E. multilocularis*, but should the situation arise, the infected organ should not be used in transplantation, as it would be infiltrated by the disease, and a CT scan should be performed to search for disease at other sites.

Trematodes

Clinically relevant trematodes include *Schistosoma* spp. (*S. haematobium*, *S. mansoni*, *S. japonicum*, *S. intercalatum*, and *S. mekongi*), *Fasciola* spp., *Clonorchis* spp., *Opistorchis* spp. and *Paragonimus* spp. Different organs may be involved: *S. mansoni* and *S. japonicum* involve the liver and *S. haematobium* primarily involves the urinary tract and the kidney. *Fasciola* spp., *Clonorchis sinensis* and *Opistorchis* spp. infections affect mainly the liver and bile ducts. Pulmonary involvement is common in *Paragonimus* spp. infection, with extrapulmonary manifestations occurring only rarely. The use of diagnostic tests for all donors from areas of endemicity is recommended, especially in the presence of peripheral blood eosinophilia. Screening tests for intestinal and hepatic trematodiases

(*Clonorchis* spp. and *Opistorchis* spp.) and intestinal schistosomiases (*S. mansoni*, *S. japonicum*, and *S. intercalatum*) are made after direct visualization of the parasite's ova in feces. Paragonimiasis is diagnosed after direct visualization of ova in sputum and stool specimens. In the case of genitourinary schistosomiasis (*S. haematobium*), ova can be visualized in urine specimens. A positive finding would not necessarily contraindicate transplantation, but specific treatment should be administered and cases should be closely monitored due to the risk of possible long-term complications.

Other parasites

Other parasitic pathogens include *Leishmania* spp., filariae (*Wuchereria bancrofti*, *Brugia malayi*, *Onchocerca volvulus*, and *Loa loa*), *Babesia* spp., *Entamoeba histolytica* (amebiasis), free-living amebae, *Trypanosoma brucei* and *Taenia solium* (cysticercosis).

Routine serological screening of organ donors from areas of endemicity would not be advocated due to the lack of definitive evidence of transmission of *Leishmania* spp. through transplanted grafts. If an available donor serology is known to be positive, strict monitoring of the recipient in the post-transplant period would be recommended, rather than rejecting the organ.

Peripheral blood smears may be screened by lysis-centrifugation and Giemsa staining if there is a high index of suspicion of infection by filariae. The donor could be treated prior to transplantation if results are positive.

There have been no documented cases of transmission of *Babesia* spp. or *E. histolytica* directly via an infected graft, so screening tests are not routinely necessary.

The risk of transmission of *Naegleria* through organ donation is unknown, possibly because patients who die due to encephalitis are generally rejected as potential organ donors. Until new NAT becomes readily available, there will be no test available to exclude the free-living amebae infections, and currently, no prophylactic treatment regimens have been established.

There have been no described cases of transmission of human African trypanosomiasis through SOT. Due to the severe prognosis of this disease and the toxicity of the treatment, organs coming from a known infected donor should be rejected.

If the donor is from an area of endemicity or has clinical symptoms or signs suggesting cysticercosis, WB may be performed. Serology may be positive in 8% to 12% of patients living in areas of endemicity, reflecting exposure rather than infection, or may be falsely negative due to decreasing sensitivity if cysts are calcified or few in number. The use of organs from a patient with neurocysticercosis would not be contraindicated, given that the cysts occur only in the central nervous, ocular and subcutaneous tissues or skeletal muscle. Nevertheless, cysts may arise in cardiac muscle; thus an imaging technique of the donor heart may be performed, which, together with negative serology, should rule out infection of the organ.

Human T-lymphotropic virus-1/2

The determination of donor HTLV I/II status is based primarily on the results obtained from EIA. Samples that initially test positive are retested in order to decrease the risk of a false-positive result due to technical errors. The timely performance of a confirmatory assay (WB or radioimmunoprecipitation), which is not always readily available, may save organ donations from being rejected because of a false-positive screening test. However, long delays in confirmatory testing may also lead to the loss of grafts. NAT could potentially be more specific in identifying false-positive donors. However, there is currently no commercially available NAT with a turnaround time that is short enough to solve the problem of donors who are HTLV reactive by EIA. In countries with low seroprevalence of HTLV I/II, the current policy of mandatory testing for anti-HTLV antibodies is

applied only to organ donors coming from areas where HTLV I is endemic or with a high suspicion of HTLV I infection. The majority of organ procurement organizations have a policy of rejecting organs from HTLV I/II positive donors. However, the use of such donors may be considered in the case of a life-threatening situation, particularly in an older recipient, with appropriate informed consent. This decision is based on a series with no documented transmission.[50]

West Nile virus

Potential donors with meningoencephalitic or myelitic symptoms of undetermined etiology, who reside in specific geographic areas during periods (usually two weeks) of human WNV activity, should be excluded. Transmission of infection is well documented.[9] Screening tests based on specific antibody detection are not useful, as these antibodies appear 1 to 2 weeks after the infection and can persist for 6 months. Screening methods should be based on NAT as close to the time of donation as possible. Viremic donors should be rejected.

Rabies virus

Rabies virus causes acute encephalitis. Questioning the patient and relatives about the possibility of contact with bats anywhere in the world or any other mammalian bite abroad should identify patients at risk. Also, potential donors with unexplained neurological symptoms should be evaluated for the possibility of CNS infections. If there is even a minimal risk of infection, the donor should be tested for the rabies virus before transplantation (by skin biopsy, saliva test and, preferably, a brain biopsy). Virus-neutralizing antibodies in serum measured using a virus neutralization test, such as the rapid fluorescent focus inhibition test or the fluorescent antibody virus neutralization test, tend to appear on average 8 days after clinical symptoms appear. Viral antigen may also be detected by using the IFAT on skin biopsies. NAT may be performed to detect rabies virus in several biological fluids and samples (e.g., saliva, CSF, tears, skin biopsy sample and urine). If there are time restraints or specific diagnostic tests are not available, anyone with a history of possible exposure to rabies virus should not be accepted as a donor. Transmission of infection with fatal outcomes has been observed.[51]

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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