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Consensus Document of the *Grupo de Estudio de la Infección en el Trasplante* (GESITRA) of the *Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica* (SEIMC) and the *Organización Nacional de Trasplantes* (ONT) on the Selection Criteria of Donors of Solid Organs in relation to Infectious Diseases

2019

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ABBREVIATIONS AND ACRONYMS:

DAA: direct-acting antivirals

DNA: deoxyribonucleic acid

RNA: ribonucleic acid

AGREE II: Appraisal of Guidelines Research and Evaluation

CVA: cerebrovascular accident

Anti-HBc: antibody to hepatitis B core antigen

Anti-HBs: antibody to hepatitis B surface antigen

Anti-HCV: HCV antibodies

CHIKV: Chikungunya virus

CLIA: chemiluminescent immunoassay

CMV: cytomegalovirus

CR: carbapenem-resistant

D+/R-: seronegative recipients of organs from seropositive donors

EIA: enzyme immunoassay

FTA-Abs: Fluorescent Treponemal Antibody Absorption

GESITRA: Grupo de Estudio de la Infección en Trasplante [Transplant Infection Study Group] (GESITRA)

HbsAg: HBV surface antigen

HTLV-1: Human T-lymphotropic virus 1

MSM: men who have sex with men

IDSA: Infectious Diseases Society of America

IIF: indirect immunofluorescence

Anti-HB Ig: specific anti-HB immunoglobulin

IGRA: interferón gamma relay assay

LTBI: latent tuberculosis infection

CSF: cerebrospinal fluid

MDR: multi-resistant

WHO: World Health Organization

ONT: Organización Nacional de Trasplantes [National Transplant Organization]

OPNT: Organ Procurement and Transplantation Network

PCR: polymerase chain reaction

PPD: Tuberculosis Skin Test

RPR: Rapid Plasma Reagin

SEIMC: Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica [Spanish Society of Infectious Diseases and Clinical Microbiology]

CNS: central nervous system

SOT: solid organ transplantation

TPHA: *T. Pallidum* Haemagglutination Assay

TPPA: *T. Pallidum* Particle Agglutination

ICU: intensive care unit

EU: European Union

LCMV: lymphocytic choriomeningitis virus

VDRL: *Venereal Disease Research Laboratory*

EBV: Epstein-Barr virus

HBV: hepatitis B virus

HCV: hepatitis C virus

HDV: delta hepatitis virus

HHV-6: human herpesvirus type 6

HHV -7: human herpesvirus type 7

HHV-8: human herpesvirus type 8

HSV: herpes simplex virus

HIV: human immunodeficiency virus

WNV: West Nile virus

VZV: varicella-zoster virus

XDR: extremely resistant

WB: Western Blot

ZIKV: Zika virus

I.   ABSTRACT

The immunosuppressive treatment that recipients receive from a solid organ transplantation hinders the defensive response to infection. Its transmission from the donor can cause dysfunction or loss of the graft and even death of the recipient if proper preventive measures are not established. This potential risk should be thoroughly evaluated to minimise the risk of infection transmission from donor to recipient, especially with organ transplantation from donors with infections, without increasing graft dysfunction and morbidity and mortality in the recipient. This document aims to review current knowledge about infection screening in potential donors and offer clinical and microbiological recommendations about the use of organs from donors with infection based on available scientific evidence.

II.   INTRODUCTION

Infectious complications remain the main cause of morbidity and mortality after organ transplantation. Many of these complications have an exogenous origin that includes those caused by pathogens transmitted by the transplanted organ and by substances that are exposed to the organ before or during its implantation (e.g. preservation fluids). The transmission of donor-derived infections in solid organ transplantation (SOT) recipients is a rare complication, the incidence of which ranges from less than 1% to 1.7% but is associated with significant morbidity and mortality.[1–3] Strict evaluation of latent and active infections in the donor is essential to optimise transplantation results and serves to avoid the accidental use of unfit organs or initiate preventive and/or therapeutic measures in a streamlined way after performance of the procedure.

The need to review a previous document named "Criterios de selección del donante respecto a la transmisión de infecciones"[4] has arisen because of changes regarding the treatment of certain infections such as hepatitis C virus (HCV) or multidrug-resistant bacteria, the increasing geographic mobility of the population, which brings about imported pathologies. In addition, the appearance and development of new diagnostic techniques such as the detection of nucleic acids by polymerase chain reaction. Conversely, the new document is not only aimed at facilitating decision-making regarding the donor's suitability to accept the donation but also at offering monitoring, prophylaxis and/or treatment guidelines for the recipient to ensure transplantation success rates.

As for the transmission of the donor's infection to the recipient, other factors should also be taken into account, such as assuming that the risk of transmission will never be

"zero". There are time limitations from the moment of evaluation of a donor and proceeding to the transplantation as information exchange between laboratories and the professionals ultimately in charge of the procedure must be fast, efficient and safe.

Finally, the evidence to recommend different interventions in this field is limited and is usually based on communications of cases and cohort studies. In any case, local epidemiology should always be considered before making any decision about the risk of transmission of an infectious disease.

Thus, several professionals with experience in the field of infection and organ donation have developed this consensus document sponsored by the *Grupo de Estudio de la Infección en Trasplante* [Transplant Infection Study Group] (GESITRA), *Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica* [Spanish Society of Infectious Diseases and Clinical Microbiology] (SEIMC) and *Organización Nacional de Trasplantes* [National Transplant Organization] (ONT).

The target populations of this document are organ donors and their recipients. The document is addressed to all professionals involved in the donation and transplantation process, especially those who have to make decisions about the donor's suitability, such as transplant coordinators, the ONT staff (as ONT staff advises other professionals on several occasions regarding the viability of the donation, by taking into account all the background information). This includes the professionals working in transplantation teams (the ones who ultimately decide on the use of the organ and are in charge of the selection of a suitable recipient by considering the characteristics of both the donor and recipient).

Here we demonstrate a consensus from an infection transmission perspective from donor to recipient in order to evaluate the available evidence and propose recommendations on the following key sections:

1. What information should be collected regarding the medical history of the potential solid organ donor?
2. Does the prior administration of vaccines contraindicate donation?
3. What infections should be forcefully ruled out in order to assess the suitability of a donor of solid organs?
4. What chronic or latent infections should be screened to assess the risk of transmission?
5. Should hidden infections in the donor be ruled out?
6. What clinical situations should be assessed for the donation of a solid organ?
7. How important is the place of origin of the donor?

III.   METHODOLOGY

A systematic review of the literature has been conducted to evaluate the potential transmission of any infection from a donor to a recipient of a solid organ transplantation and the measures to prevent it. The necessary data were identified by search in PubMed and the search terms used in each section were specified to answer the target question. The search criteria included articles in English or Spanish in which humans had participated without a time limit.

The Notify project database (www.notifylibrary.org), an initiative of the World Health Organization, was also consulted. Experts from across the globe collaborate to share educational information on documented adverse outcomes, associated with the clinical use of human organs, blood, tissues and cells.

Each question included, if applicable, first, the assessment of the risk of transmission of the infection according to Alliance-O (Annex 1)[5] and, secondly, the list of recommendations and grading of their strength and quality according to the table in annex 2. The document has been written in accordance with the Appraisal of Guidelines Research and Evaluation (AGREE II) recommendations. The authors met on one occasion to discuss the final recommendations. The coordinators and authors agreed on the content and the conclusions. The consensus was sent to the members of GESITRA-SEIMC and the ONT, the Donation and Transplantation Network and the *Comisión de trasplantes de Consejo Interterritorial de Trasplantes del Sistema Nacional de Salud* (Transplantation Committee of the Inter-Territorial Transplantation Council of the National Health System) for independent peer review and institutional adoption.

IV.   WHAT INFORMATION SHOULD BE COLLECTED REGARDING THE MEDICAL HISTORY OF POTENTIAL DONORS OF SOLID ORGANS?

A. Recommendations
- All potential donors of solid organs should be screened concerning their medical and social history along with a physical examination. AIII.

B. Note
A search was made in PubMed with the following terms: donor-derived infection, donation, transplantation, transmission recipient, screening, solid organ transplantation, donor infection.

Even though it is impossible to completely eliminate the risk of transmission of an infection, a correct evaluation of potential donors before organ transplantation is

essential to rule out the presence of latent infections that require treatment or infections that contraindicate the performance of a transplant or modify the criteria for assigning organs[5–8]. This evaluation begins with the medical and social history and physical examination of the potential donor[9,10]. It should be borne in mind that the donation interview is conducted with the family members of the potential donor at a time of intense grief and heightened emotions.

The recommended information to be included in the medical history is as follows (table 1):

- Cause of death. It should be documented, especially to rule out infectious or neoplastic causes. In this sense, it is important to identify donors at risk of transmission of pathogens associated with central nervous system (CNS) infections, mainly meningoencephalitis[3]. The risk of rabies transmission, West Nile virus, lymphocytic choriomeningitis virus and parasitic diseases of donors killed by encephalitis is well known. In this regard it is advised to indicate:
  - The cause of death and whether there is any comorbidity that can lead to a cerebrovascular accident (CVA) a.k.a. stroke (e.g., diabetes, heart disease, high blood pressure, previous stroke) versus meningoencephalitis
  - If fever was present in the potential donor at the onset of the disease
  - If the potential donor had undergone computed tomography or brain magnetic resonance imaging or lumbar puncture with data compatible with infectious processes
  - If the potential donor is immunosuppressed
- Family history (dementia, degenerative diseases, etc.)
- Work history
- Previous diseases, in particular, neoplasms, autoimmune diseases, neurodegenerative diseases, intoxications, etc.
- Concomitant medication: antibiotics, immunosuppressive treatment (corticosteroids, monoclonal antibodies)
- Risk behaviours for the acquisition of communicable diseases by blood or sex: risky sexual behaviour in the last 5 years, use of non-medical intravenous drugs in the previous 5 years, sexual intercourse in the last year with persons displaying the abovementioned behaviours, imprisonment in in the last 12 months, exposure to blood infected by human immunodeficiency virus (HIV) through an open wound in the last year, percutaneous inoculation, injured skin or mucous membranes[9].
- Other symptoms or signs suspected of HIV infection such as unexplained weight loss, night sweats, skin lesions or mucous membranes suggestive of Kaposi's sarcoma, nonspecific lymphadenopathy lasting more than 1 month, persistent cough or diarrhoea of unknown cause or signs of parenteral drug abuse[6].
- Exposure to mycobacterial infection, especially *Mycobacterium tuberculosis*, living with patients with tuberculosis, tuberculosis skin test (PPD) result or interferon gamma relay assay (IGRA) if performed[11].
- Hospital admissions and previous surgical interventions.

- Country of birth of the donor and of their mother.
- History of travel and/or residence in parts of the world affected by endemic infections: *Strongyloides stercolaris*, *Trypanosoma cruzi*, *Schistosoma* spp, *Leishmania* spp, *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, malaria, hepatitis virus or mycobacteria[12].
- Contact with wild or domestic animals, pets, stray dogs, rodents, birds such as parakeets, bats and exposure to unpasteurized products and other zoonoses (*Brucella* spp, *Cryptosporidium*, *Listeria monocytogenes, Salmonella* spp*, toxoplasmosis)
- Previous infections. If known, the sensitivity pattern of isolated microorganisms and administered treatment should be collected. In addition, there are donors with anatomical abnormalities that predispose to infectious complications that must also be registered in the medical history (*e.g.,* sinus obstruction, vesicoureteral reflux, pathological heart valves, joint prosthesis, vascular graft, dialysis fistula or catheters).
- Tattoos and piercing, as well as the time of its performance and place (authorised centre)
- Blood transfusion history and treatments with human blood derivatives that can transmit infections (*e.g.*, haemophilia treated with human factor VIII or IX concentrates)
- History of anogenital carcinoma associated with papillomavirus or nasopharyngeal carcinoma or Burkitt lymphoma related to Epstein-Barr virus (EBV).
- Vaccinations and past diseases in paediatric age.

The physical examination should be performed in a systematic and standardized manner and should collect data about the presence of jaundice, hepatomegaly, scars, wounds, rashes, venepuncture or injection points, tumours or adenopathies, tattoos, piercing, genital lesions, etc[13].

Table 1. Data to be collected in the donor's medical history

Previous infections
Vaccination history
Occupational exposure
Travel history
History of blood transfusions or derivatives
Risk contact with people infected with HIV, HBV and HCV
Tattoos and piercing
Drug addiction parenterally or via intranasal route
Sexual behaviour
Imprisonment
Contact with animals

This information will allow us to define the studies necessary to rule out the existence of potentially transmissible infectious diseases as it will be analysed in the following chapters.

V. DOES THE PRIOR ADMINISTRATION OF VACCINES CONTRAINDICATE DONATION?

A. Transmission risk

- Prior administration of inactivated vaccines in the potential donor does not pose a risk to the recipient. RL5.
- The administration of live virus vaccines in the potential donor more than 30 days before the donation does not pose a risk to the recipient. RL4.
- The administration of live virus vaccines in the potential donor within 30 days prior to the donation may pose a risk to the recipient. RL2-3.

B. Recommendations

- Prior administration of inactivated vaccines in the potential donor does not contraindicate the donation. CIII.
- A donor's organs can be accepted for transplantation if such a donor received a live virus vaccine in case it has been administered more than 30 days before the donation. CIII.
- The organs of people who have been administered live virus vaccines within 30 days prior to donation can be accepted for transplantation in case the recipient has confirmed immunity (natural or acquired) against the vaccine virus. CIII.
- Donors vaccinated with live virus vaccines within 30 days prior to donation can only be accepted for non-immune recipients if the health conditions of the recipient are extremely sever and upon signing of the informed consent form. CIII.

C. Note

A search was made in PubMed with the following terms: attenuated live vaccine AND donor, attenuated live vaccine AND transmission, varicella AND donor AND transmission, rubella AND donor AND transmission, measles vaccine AND donor AND transmission, donor vaccination AND transmission. In addition, a search has been made in the MedDRA dictionary with the term 'Infection by a vaccinated person', since no term is contemplated in case of transmission of an infection through a transplanted organ from a previously vaccinated donor. A general consultation to the database of the Spanish Pharmacovigilance System has been carried out on March 1, 2017, on any notification related to infection transmission mechanism associated with vaccinations.

Furthermore, the publicly available information on adverse reactions of an infectious nature contained in the European Pharmacovigilance Database (http://www.adrreports.eu/es/search_subst.html) and in the database of the International Centre for Pharmacovigilance of the World Health Organization (WHO) (http://www.vigiaccess.org/) have been consulted, in relation to vaccines for measles, mumps, rubella, chicken pox, yellow fever, cholera and typhoid fever.

Even with the consultation limitations in these publicly accessible databases, no case has been found related to the transmission to recipients of viruses contained in live vaccines administered to donors.

There is no possibility of transmission of infections secondary to vaccinations by non-living microorganisms. Thus, the problem lies in donors who have received live attenuated vaccines (table 2).

Virus transmission from the donor is a known fact for many viral infections including cytomegalovirus (CMV), EBV or BK virus. Cases of chickenpox transmission by a donor to SOT recipients have also been described[14].
Although immunization with selected live attenuated vaccines has been proven safe in some studies conducted on non-severely immunosuppressed recipients, usually 1 or 2 years after transplantation[15,16], cases of clinical infections with varicella zoster virus after vaccination have been described, at 14-24 months after transplantation, in SOT recipients with two or three immunosuppressive drugs[17,18]. In addition, in severely immunocompromised subjects who have been inadvertently inoculated with measles-containing vaccines, cases of encephalitis by inclusion bodies associated with measles, pneumonitis and fatal outcome have been reported as a direct consequence of the spread of viral infection by the measles vaccine[19].

The yellow fever vaccine is an attenuated vaccine in which cases of neurotropic disease have been seldom reported after vaccination, with sequelae or fatal outcome in some cases. To date, most of these cases have been notified in first vaccinations with an onset within 30 days after vaccination. Congenital or acquired immunodeficiency has been recognised as a potential risk factor. Viscerotropic disease associated with the yellow fever vaccine has been rarely reported after vaccination, and resembles a fulminant infection by the wild-type virus, with a mortality rate of approx. 60%. To date, most cases have been notified in first vaccinations with an onset within 10 days after the vaccination[20].

In relation to the rotavirus vaccine, cases of gastroenteritis associated with the vaccine virus have been reported in children with severe combined immunodeficiency[21] in the post-marketing stage.

Although the transmission of measles and mumps viruses between vaccinated persons and their susceptible contacts has not been documented, it is known that the pharyngeal excretion of measles and rubella viruses occurs approximately between 7 and 28 days after vaccination, with an excretion peak by day 11. However, there is no evidence of the transmission of excreted vaccine viruses to susceptible contacts. Transmission of the rubella vaccine virus to children through breast milk, as well as

transplacental transmission, has been documented, though without any evidence of clinical disease[19]. Transmission of the chickenpox vaccine virus is possible from vaccinated healthy individuals, who may develop a varicella type rash, to susceptible healthy contacts, pregnant and immunocompromised women[22].

In relation to the varicella zoster vaccine, transmission of the vaccine virus has not been reported. However, experience after the marketing of chickenpox vaccines suggests that transmission of the vaccine virus may rarely occur between vaccinated subjects, who develop a varicelliform eruption, and susceptible contacts[23].

In clinical trials after rotavirus vaccination, the virus was excreted in the faeces of 8.9% of those vaccinated subjects, almost exclusively in the week after the first dose and only in one vaccinated subject (0.3%) after the third dose. The maximum excretion occurred within 7 days after the administration of the dose. Post-marketing transmission of vaccine virus strains to unvaccinated contacts has been observed[21].

According to what has been described in relation to viral elimination periods and the chronology of clinical infections secondary to live virus vaccination, it seems reasonable not to contraindicate donation in donors who have received the vaccine within more than one month leading to the donation.

In those patients with confirmed specific immunity, either natural or secondary to prior vaccination, organs from donors, who were vaccinated with live attenuated viruses in the month prior to donation, could also be implanted.
Only in extremely severe situations could organs from donors, who were vaccinated with live viruses in the month prior to donation, be accepted for non-immune recipients.

Table 2. List of vaccines with live attenuated microorganisms

Varicella zoster
Rotavirus
Measles
Rubella
Parotitis
Oral polio
Yellow fever
Smallpox
BCG
Oral *Vibrio cholerae*
Oral *Salmonella typhi*

VI. WHAT INFECTIONS SHOULD BE FORCEFULLY RULED OUT IN ORDER TO ASSESS THE SUITABILITY OF A DONOR OF SOLID ORGANS?

1. WHAT SHOULD BE DONE IN RELATION TO AN HIV-POSITIVE DONOR?

A. Transmission Risk

- The risk of transmission of HIV infection is well documented. RL1-2.

B. Recommendations

- HIV infection in all donors should be ruled out using chemiluminescent immunoassay (CLIA) techniques that include simultaneous detection of antibodies (anti-HIV-1 and anti HIV-2) and HIV-1 p24 antigen. According to the result, the algorithm of Figure 1 will be followed. AI.
- For potential high-risk donors (see below) with negative serology, the detection of nucleic acids would be indicated to reduce the window period. AII.
- The organs of a donor with HIV infection will not be accepted for a seronegative recipient. AII.
- The organs of a donor with HIV infection could be considered as suitable for a seropositive recipient, although the current regulatory framework does not allow so in our country. BII.
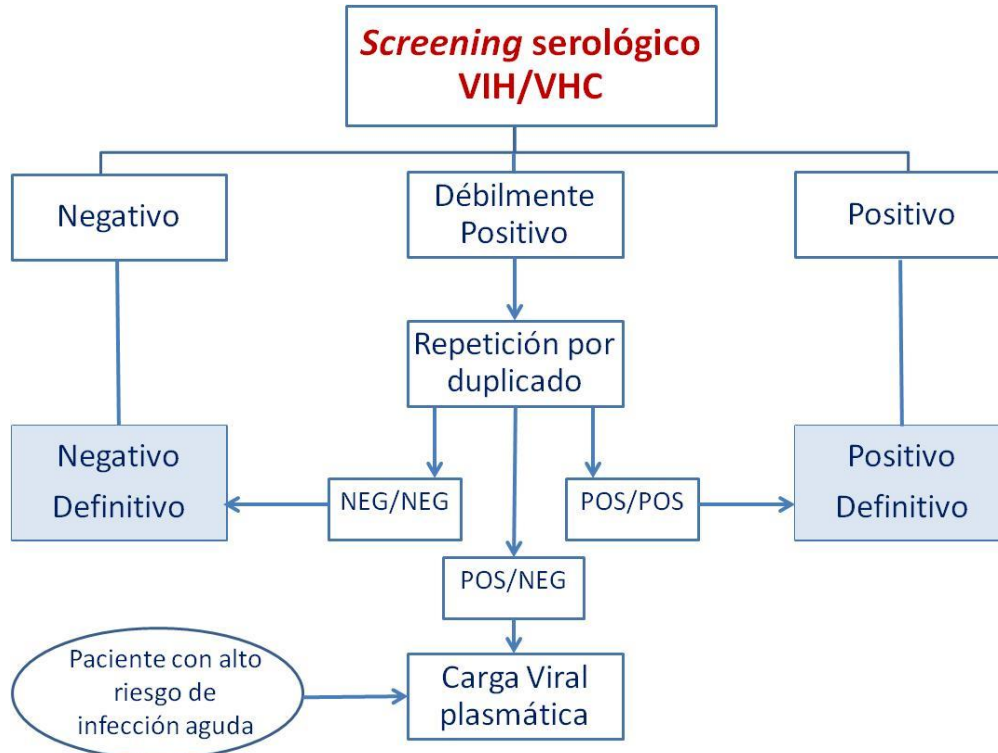
Figure 1. Algorithm screened for HIV and HCV infection

C. Note

A search was made in PubMed with the following terms: donor-derived infection, donation, transmission, solid organ transplantation, donor infection and human immunodeficiency virus or HIV.

Screening for HIV infection is mandatory (Table 3) and should be performed using fourth-generation CLIA techniques that include simultaneous detection of antibodies (anti-HIV-1 and anti HIV-2) and HIV-1 p24 antigen that markedly decrease the window period. The technique to detect HIV-1 viral load should have a lower detection limit of <40 copies/mL. It is well known that the transmission of HIV virus from seropositive donors to seronegative recipients is very high, as cases have been reported in the 80s and early 90s[24]. However, transmission of serologically negative donors has also been shown, but with positive viral load (demonstrated after transplantation) during the window period[25–27]. HIV serology is performed in all US centres to evaluate organ donors, but only 44% of the centres determine the viral load to reduce the window period[28].

In recent years, kidney and liver transplants have been performed from HIV-positive donors to HIV-positive recipients. One of the renal series with the highest number of patients (27 patients) is that reported by Muller E et al[29] in the South African population. The survival of patients at 1, 3 and 5 years was 84%, 84% and 74% respectively, and graft survival of 93%, 84% and 84%. The rejection per year was 8% and at 3 years 22%. HIV infection was controlled and the viral load remained undetected. However, no studies on virus resistance were performed in donors, although the authors assume that the resistance is low (less than 5% in that population according to a study by Nwobegahay J et al).[30] The Swiss Federal Act on the Transplantation of Organs, Tissues and Cells agreed in July 2007 to authorise the transplantation of HIV-positive donor organs to HIV-positive recipients[31] and in the United States by the HOPE Act in November 2013.[32] The first liver transplant from one donor to recipient, both HIV-positive, was performed in Switzerland.[33] The transplanted patient evolved well after 5 months of follow-up. The authors recommend transplantation whenever effective antiretroviral treatment is available. Boyarsky BJ et al[34] have made a series of recommendations for the acceptance of a seropositive donor with a lower risk of superinfection and resistance. The donor with the best options would be the one with a ribonucleic acid (RNA) <200 copies/ml, with a first-line antiretroviral regimen, tropism R5, and elevated CD4. Donors with RNA> 200 copies/ml, evidence of virologic failure, 2nd line antiretroviral treatment, X4 tropism, history of viral resistance, regimens based on low protease/ritonavir and CD4 inhibitors pose a high transmission risk of superinfection and resistant virus.[34] In recent months, patients with the same characteristics have been transplanted in Baltimore. In

spite of this data, currently, the regulatory framework in Spain does not allow the donation of organs and tissues from HIV-positive people, both for a seronegative and HIV-positive recipient.

Table 3. Recommended study in the donor[237]

|	Pre-transplant	Post- transplant
HIV	Anti-HIV-1 and -2 and p24 Ag	
	HIV-1 viral load in high-risk donor with negative serology	
HBV	HBsAg	
	Anti-HBc	
	Anti-HBs if anti-HBc positive	
HDV	Anti-HDV in case of positive HBsAg	
HCV	Anti-HCV	
	HCV viral load in high-risk donor with negative serology	HCV viral load in all donors with anti-HCV positive
HTLV-I/II	CMIA	
CMV	IgG antibodies	
EBV		IgG antibodies
Syphilis	Treponemal Antibodies	
Toxoplasmosis		IgG antibodies
Chagas disease	*Trypanosoma cruzi* antibodies in heart donors from Central or South America	*Trypanosoma cruzi* antibodies in non-heart donors from Central or South America
Geographically Restricted Infections		See text

CMIA: chemiluminescent microparticle immunoassay

2. WHAT SHOULD BE DONE IN RELATION TO AN HBV-POSITIVE DONOR?

A. Transmission risk

- The risk of transmission is well documented in donors with positive HBV surface antigen (HbsAg) or positive viral load. RL1-2.
- The transmission of HBV infection from donors with positive core antigen (anti-HBc) antibodies and reactive surface antigen (anti-HBs) antibodies (> 10 IU/L) is exceptional. RL3.
- The risk of donor transmission with isolated anti-HBc positive will depend on the immunological status of the recipient and the type of transplanted organ. RL3.

B. Recommendations

- For hepatitis B screening, HBs Ag and anti-HBc should be determined by CLIA techniques. AI.
- Transplantation from an HBsAg-positive donor to an HBsAg-negative and anti-HBs-negative recipient is not recommended except in cases of emergency. AII.
- Transplantation from an HBsAg-positive donor to an HBsAg-positive recipient or with anti-HBs> 10 IU/ml can be performed. BII.
- A transplantation from an anti-HBc-positive and HBsAg-negative donor can be performed pursuant to the recommendations in Tables 4 and 5. BII.

C. Note

A search was made in PubMed with the following terms: donor-derived infection, donation, transmission, solid organ transplantation, donor infection and hepatitis B or HBV.

The risk of HBV transmission with the transplant is well known and serological screening is mandatory to avoid so (table 3). Currently, organs from donors with certain positive markers for HBV can be considered for use as the risk of transmission or its consequences (in case of transmission) can be significantly reduced with antiviral treatments.

According to ONT data, the current prevalence of HBsAg-positive donors is 0.1% and of anti-HBc-positive donors is approx. 10%[35].

Infectivity is variable depending on the serological pattern of the donor and the recipient (immune status with respect to HBV), and of the organ to be transplanted. Classically speaking, the infection marker used has been HBsAg. In recent years, the risk of HBV transmission by organs from HBsAg-negative donors has been clarified, with other serological markers of HBV-positive infection, particularly anti-HBc.

HBsAg is the marker of disease activity and infectivity. It is a very early marker that can be detectable in the incubation period. It is also detected in the acute phase and in the chronic stage. Generally, it produces high readings and rarely generates false positive results; when this happens, it is nearly always with low rates. These low results should be confirmed by neutralisation techniques (inhibitions greater than 50% are deemed positive). If they come out as positive, it would be considered as a definitive positive result.

Transplantation from an HBsAg-positive donor carries a high risk of transmission (≈100%) and our community has routinely ruled out its use. Its use has only been considered in exceptional cases of patients in situations of extreme urgency and

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without other possibilities. Notwithstanding, recently with the proper management of antiviral treatments of HBV in the recipient (lamivudine, tenofovir, entecavir) and the use of specific anti-HB immunoglobulin (anti-HB IgG) the scenario has changed. Experiments have been published in countries with a high prevalence of HBV whose results are encouraging.

In kidney transplants, the successful use of HBsAg-positive donors in 104 immune recipients (anti-HBs positive) with different prophylactic measures has been described[36]. Another study in the same population also shows, in well-immunized recipients, the same survival rate at 5 years of HBsAg-negative donors[37]. In addition, in a retrospective analysis of 92 liver transplant recipients performed with HBsAg-positive donors, with adequate antiviral treatment, there were no differences in graft or patient survival compared to those made with an HBsAg-negative donor[38]. Nor did it increase postoperative morbidity and mortality in another liver transplantation study[39].

If organs from HBsAg-positive donors are used, prophylaxis with entecavir or tenofovir should be performed on the recipient with/without anti-HB Ig. It will preferably be carried out in HBsAg-positive or immunized recipients and with informed consent. Periodic monitoring of HBV deoxyribonucleic acid (DNA) will be performed.

Anti-HBc is always detectable after infection, but its presence does not always indicate active infection. In some patients, anti-HBc may be the only visible marker. This situation may indicate: cure of the disease and that other markers have disappeared over time; a prolonged stage of seroconversion, in which HBsAg is negative because it occurs in quantities that the diagnostic test cannot detect or appear in chronic infected replicating patients that produce very little HBsAg. In addition, an anti-HBc false positive result must be considered. Thus, against an isolated anti-HBc positive result, anti-HBs antibodies will be determined, which can be positive after vaccination or viral infection.

The risk of HBV transmission from anti-HBc-positive and HBsAg-negative donors occurs mainly in liver transplant recipients[40–42]. Transmission is significantly lower in kidney transplant recipients[43,44]. The risk seems very low in heart or lung transplants, although there is very little data available.

The risk of transmission by these donors also depends on the HBV immune status of the recipient (serological pattern) and the use of prophylactic antiviral strategies. Table 4 summarises the transmission data of an anti-HBc-positive donor in a liver transplant (taken from [40–42]).

In relation to liver transplantation, the use of organs from anti-HBc-positive donors is preferred in HBsAg-positive recipients (which already require anti-HBV prophylaxis, in any case) or in recipients with natural and/or vaccination immunity from HBV infection. Table 4 also shows the proposed prophylactic recommendations. Current data do not recommend the use of anti-HB Ig in this case (anti-HBc positive/HBsAg negative)[45,46]. Existing data with prophylactic antivirals other than lamivudine (tenofovir or entecavir) are scarce (it is not clear whether they are cost-effective). Discontinuation of prophylaxis can be considered after one year in recipients with persistent immunity (anti-HBs> 10 IU/ml)[46]. HBV DNA monitoring with/without HBsAg should be performed every 3 months for one year and then every 3-6 months indefinitely [46].

In recipients of a non-liver transplant from an isolated anti-HBc-positive donor, the risk of transmission is lower and negligible if the recipient is immune, which highlights the importance of HBV vaccination of recipients before the transplant. Table 5 summarises the transmission data in kidney transplants[43,44] and the prophylaxis proposed in each case. Other organs (heart, lung) could be assimilated in terms of risk given the lack of data. In any case, and similar to liver transplantation, its use is preferred in HBsAg-positive recipients (which already require anti-HBV treatment, in any case) or to recipients with natural and/or vaccination immunity from HBV infection.

Hepatitis delta virus (HDV) is a defective virus that needs the presence of HBV to cause infection. Thus, it should not be sought in the absence of HBV. In those cases with HBsAg positive, detection of HDAg and anti-HDV will be neccessary (Table 3).

Table 4. Summary of the transmission data of anti-HBc+ donors in liver transplantation

DONOR Serology	RECIPIENT Serology	Transmission **without prophylaxis**	Transmission **with prophylaxis**	**Treatment recommendation**
HBsAg +		100 %		Undefined. Recipient oriented (ENT or TDF) ± HB Ig
Anti-HBc + (HBsAg -)	Anti-HBs -/anti-HBc -	58-77 %	11-12 %	LAM non-defined?
	Anti-HBs -/anti-HBc +	13-15 %	3-4 %	LAM non-defined?
	*anti-HBs +/anti-HBc -	10-18 %	0-2 %	LAM non-defined?
	Anti-HBs +/anti-HBc +	0-4 %	0%?	No prophylaxis

*vaccinated; LAM: lamivudine; ENT: entecavir; TDF: tenofovir

Table 5. Summary of the transmission data of anti-HBc+ donors in kidney transplantation. Other organs (heart, lung) could be assimilated in terms of risk, given the scarcity of data.

DONOR Serology	RECIPIENT Serology	Transmission **without prophylaxis**	Transmission **with prophylaxis**	Treatment recommendation
HBsAg +		100 %		Undefined. Recipient oriented (ENT or TDF) ± HB Ig
Ac HBc + (HBsAg -)	Anti-HBs -/anti-HBc -	0-27 %		LAM non-defined?
	Anti-HBs -/anti-HBc +			Consider LAM for 1 year
	*anti-HBs +/anti-HBc -	Seroconversion: HBsAg 0.28%		No prophylaxis
	Anti-HBs+/anti-HBc+	Anti-HBc 3.24%		No prophylaxis

* vaccinated; LAM: lamivudine; ENT: entecavir; TDF: tenofovir

3. WHAT SHOULD BE DONE IN RELATION TO AN HCV-POSITIVE DONOR?

The information in this section is an excerpt from the consensus document promoted by the ONT that can be accessed on the following website: http://www.ont.es/infesp/DocumentosDeConsenso/Documento%20Consenso%20Valoración%20Donantes%20Virus%20C_ABRIL2019.pdf

It is worth mentioning that rapid advances in this field and ongoing studies could modify these recommendations in the forthcoming months.

A. Transmission risk

- The transmission of infection from an anti-HCV+ non-viremic donor is exceptional.
- Anti-HCV+ viremic donors transmit HCV infection to almost all patients, regardless of the transplanted organ. RL1-3.

B. Recommendations

- HCV serological screening should be performed in all donors based on the detection of HCV antibodies (anti-HCV) using CLIA techniques (Figure 1). AII.
- HCV RNA screening should be performed to rule out viremia in all anti-HCV+ donors during the donation process. CIII
- In potential high-risk donors (see below) with negative serology, HCV-RNA detection would be indicated to reduce the window period. AII.
- The organs of an anti-HCV+ non-viremic donor (after effective treatment or spontaneous clearance) may be used in anti-HCV positive recipients without restrictions. CIII.
- The organs of an anti-HCV+ non-viremic donor (after effective treatment or spontaneous clearance) may be used in anti-HCV negative recipients that

accept the risk after informed consent and undergo close monitoring and treatment in case of infection. CIII.

- Donation of organs from an anti-HCV+ viremic donor can be performed in HCV viremic recipients who receive early or post-exposure treatment. CIII.
- Donation of organs from anti-HCV+ viremic donors can be performed in an anti-HCV negative recipient who agrees to the risk after informed consent and undergoes post-exposure treatment. CIII
- In the case of liver transplantation of an anti-HCV+ donor, the liver fibrosis stage should be established by elastography or biopsy. BII.

C. Note

A search was made in PubMed with the following terms: donor-derived infection, donation, transmission, solid organ transplantation, donor infection and hepatitis C or HCV.

In Spain, according to preliminary data from the National Survey of Seroprevalence of hepatitis C, HCV antibody prevalence is estimated at 0.8% and viremia prevalence is estimated at 0.17% in the population aged between 2 and 80 years.

According to ONT data, effective donors with HCV positive serology account for about 1% of the total sample of effective donors[47].

The establishment of Direct-Acting Antiviral (DAA) therapy has resulted in a dramatic shift in the management of HCV infection. The high effectiveness and safety of these treatments in the treated population in general, and particularly in the population of transplanted patients, provide the opportunity to assess the transplantation of organs from donors with positive serology for HCV (anti-HCV+). This not only includes anti-HCV+ recipients with HCV-PCR positive (classical recommendation), but also anti-HCV negative recipients, which increases transplantation options.

Since the experience is still limited, the use of organs from HCV positive donors in anti-HCV negative recipients must be performed with the informed *consent* of the patient and must involve a thorough follow-up of the recipients that contribute to solving any pending issues.

HCV serological screening should be performed in all donors (table 3). It is based on the demonstration of anti-HCV antibodies by CLIA techniques. It is recommended to use third-generation immunoassays capable of detecting antibodies to core recombinant antigens (NS3, NS4 and NS5), with high sensitivity and specificity (approx. 99%) and with a window period around 6-7 weeks[48] (Figure 1).

In all anti-HCV+ donors and high-risk anti-HCV negative donors or in situations with the possibility of a false negative test, the determination of HCV-RNA by PCR is recommended since it allows reducing the 40-50-day window period (from the infection to anti-HCV Ac positivity) at 3-5 days of the eclipse period (from the infection to HCV-RNA positivity). When that is not possible, the determination of antigenemia (more feasible and less expensive both economically and logistically) is considered a valid option given its evasive sensitivity. In any case, PCR should always be requested even if the result to be obtained after the transplant is different.

In anti-HCV+ donors, given that the donor's infectivity depends on existing replication, detection of HCV-RNA by PCR/Antigenemia also allows for distinguishing HCV+ viremic donors from non-viremic ones. Hence, the risk of transmission is better estimated and pairing with the recipient and its subsequent management can be adjusted since the course of action would be treatment with DAAs in case of a viremic donor (HCV-RNA positive) and specific monitoring in the case of a non-viremic donor (HCV-RNA negative), regardless of the organ to be transplanted.

The determination of the *genotype* in viremic donors, given the current availability of pan-genotypic DAAs, is indicated in all cases for a correct follow-up of the recipients although results are not necessary before transplantation.

In the case of liver transplantation, it is also necessary to assess the liver fibrosis stage of the donor (by elastography or biopsy, preferably reperfusion as fresh tissue biopsy does not allow to precisely defining the stage of fibrosis). Scientific evidence supports the acceptance of donors with a liver fibrosis stage of <2[49] although it is estimated that, by combining an adequate evaluation of the liver by the surgeon and the result of liver biopsy, livers with stage 2 liver fibrosis could also be acceptable. There is sufficient scientific evidence to always rule out liver donors with higher liver fibrosis stages (F3-F4).

HCV infection in the transplanted patient is described as having a more rapid evolution than in immunocompetent patients due to immunosuppression. However, DAA treatment with pan-genotypic guidelines has shown high efficacy and safety in liver, kidney, heart and lung post-transplantation[50-60]. From the viewpoint of the recipient, it is necessary to distinguish a liver transplant (which involves implanting an organ potentially damaged by HCV) from a non-liver transplant, in which the risk is limited to the possible transmission of the infection.

Table 6 summarises the selection and post-transplant management algorithms according to the organ and serological profile of the donor and recipient in relation to HCV.

In general, treatment of the recipient is recommended in case of a viremic donor as long as clinical conditions and the immunosuppression regimen are stable, which usually happens in the first month after transplantation with profiled DAA guidelines, depending on kidney function, history of previous exposure to DAAs and possible pharmacological interactions.

If the donor's viral load is unknown, the donor should be deemed viremic until viral load results are available.

Recipients of organs from HCV negative donors but with risk factors should be monitored after transplantation by serial assay of HCV-RNA (1 week, 1 month, 3 months) to detect possible HCV transmission and act accordingly[61,62].

Table 6. Recommendations regarding transplantation of organs from donors with HCV infection

Donor	Non-liver recipient		* Liver recipient	
	Anti-HCV -	Anti-HCV +	Anti-HCV -	Anti-HCV +
anti-HCV + RNA-HCV-	Accepted Close monitoring of recipient by PCR	Accepted	Accepted Close monitoring of recipient by PCR	Accepted
anti-HCV + RNA-HCV +/unknown	Accepted Close monitoring of recipient by PCR Recipient's treatment	Accepted Recipient's treatment	Accepted in patients at risk of clinical deterioration Close monitoring of recipient by PCR Recipient's treatment	Accepted in RNA-HCV + recipient Not accepted in RNA-HCV – recipient, except in urgent situations according to risk-benefit ratio Recipient's treatment

* Donor with fibrosis stage <2

4. WHAT SHOULD BE DONE IN RELATION TO A HIGH-RISK DONOR?

A. Transmission risk

- Transmission of HIV, HBV or HCV infection from a high-risk donor to a recipient is well documented. RL1-3.

B. Recommendations

- In high-risk donors, testing for nucleic acids is recommended in the case of negative serology for HIV-1/2 and/or HCV. AII.
- Donation can be accepted if there is prior acceptance by the recipient upon signing the informed consent form and in case of emergency. BII.

C. Note

A search was made in PubMed with the following terms: donor-derived infection, donation, transmission, solid organ transplantation, donor infection and high-risk donor.

There are factors associated with an increase in which donors potentially infected with HIV, HBV or HCV could be subject to, during the window period, regarding serological tests. Therefore, an unintended transmission could occur in the following cases:

- People who have had sex with strangers or with people with suspected HIV, HBV or HCV infection during the previous 12 months
- Men who have had sex with men (MSM) during the previous 12 months
- Women who have had sex with MSM during the previous 12 months
- People who have practiced prostitution during the previous 12 months
- People who have had sex with people who have prostituted themselves during the previous 12 months
- Drug addicts who have taken drugs via parenteral or intranasal route during the previous 12 months
- People who have sex with drug addicts who have taken drugs via parenteral or intranasal route.
- People who have been in prison or in a correctional institution for more than 72 hours during the previous 12 months
- People diagnosed or treated for a sexually transmitted disease or genital ulcer during the previous 12 months
- Children under 18 months of age of a mother with a potential risk of HIV infection or breastfed by a woman with HIV risk in the last 12 months[63]

The risk period considered is 12 months prior to the potential donation according to the recommendations of the American Society for Transplantation[10]. In these cases, detection of the viral load for HIV-1 and HCV is recommended (Figure 1). This goes from a window period of 7 to 16 days for HIV infection and 40 to 50 days for HCV

infection to an eclipse period (from infection to positive results by nucleic acid detection techniques) of 5 to 6 days for HIV and 3 to 5 days for HCV. In the case of HBV infection, reduction of the window period from 35 to 44 days and the eclipse period from 20 to 22 days is not as marked. In addition, it poses a logistical problem in its detection regarding the time availability of the technique. In any case, given this circumstance, acceptance by the donor (with informed consent) and the emergency itself must be evaluated[63].

In relation to HIV, HBV and HCV serological assays, a series of common considerations must also be taken into account:

- the appearance of false positives after a blood transfusion.
- In the case of one-month old infants or younger, serologic tests are not advised due to the passage of antibodies from the mother and the immature immune system of the newborn. In this case, viral load detection is recommended.
- samples that give a non-reactive result will be considered negative; however, in case of suspicion of risk factors for acute infection, viral load detection techniques should be performed, since the window period decreases significantly.

VII. WHAT INFECTIONS OR LATENT INFECTIONS SHOULD BE SCREENED IN ORDER TO ASSESS THE RISK OF TRANSMISSION?

1. WHAT DECISION SHOULD BE MADE IN RELATION TO A DONOR WITH LATENT SYPHILIS?

A. Transmission risk
- There is a risk of transmission of *Treponema pallidum* from donors with positive luteal serology. RL3.

B. Recommendations
- It is recommended to routinely perform serologic tests for *T. pallidum* in both the recipient and donor. AII.
- Treatment (syphilis patterns of undetermined evolution) should be administered in recipients from donors who have been tested positive for *T. pallidum* (positive treponemal test accompanied or not by positive reaginic test). AIII.

C. Note
A search was made in PubMed with the following terms: donor-derived infection, transmission, solid organ transplantation, and syphilis or *Treponema pallidum*.

Transmission of *T. pallidum* by solid organ transplantation has been documented in the form of seroconversion in previously seronegative recipients, although early administration of treatment prevented the development of clinical manifestations of syphilis in the cases described in literature[64–66]. Thus, and thanks to the wide availability of serological diagnostic techniques and the effectiveness of antibiotic treatment, the diagnosis of syphilis in the donor should not be deemed a contraindication for transplantation, although screening should be performed in all donors (table 3).

The classic diagnostic algorithm for syphilis involves first performing a reaginic or non-treponemal test (Rapid Plasma Reagin [RPR] or Venereal Disease Research Laboratory [VDRL]) whose positive result must be subsequently confirmed by a specific treponemal test (*T. Pallidum* Haemagglutination Assay [TPHA], *T. Pallidum* Particle Agglutination [TPPA] or Fluorescent Treponemal Antibody Absorption [FTA-Abs], among others)[67]. In recent years, many laboratories are implementing reverse screening algorithms based on a first automated treponemal technique (enzyme immunoassay or chemiluminescence), followed in the case of a positive result by reaginic test confirmation. This approach has shown a higher cost-effective ratio in populations with low prevalence, in addition to allowing the detection of situations in which the reaginic tests yield false negatives (pre-reaginic syphilis or prozone phenomenon)[68]. Notwithstanding, it involves the detection of numerous serodiscordant cases (positive treponemal test accompanied by a negative or positive reaginic test at very low titres) that usually reflect past syphilis episodes (treated or not) or even false positives of the treponemal test.

Although the real risk of *T. pallidum* transmission from donors with serodiscordant results in the serologic test is low, its theoretical possibility requires the early administration of treatment to recipients in the presence of any positive treponemal test performed on the donor (that is, regardless of the reaginic test result)[8]. Due to the practical impossibility of specifying the chronology of infection in the donor, treatment guidelines for syphilis of undetermined evolution should be used, based on intramuscular Penicillin G benzathine (3 weekly doses 2.4 million units) or, in case of allergy, doxycycline (100 mg/12 hours for 4 weeks) (AIII). It is necessary to carry out serological monitoring of the recipient every 3 months throughout the first post-transplant year to detect a possible seroconversion (BIII).

2. WHAT DECISION SHOULD BE MADE IN RELATION TO A DONOR WITH LATENT TUBERCULOSIS?

A. Transmission risk
- There is a risk of tuberculosis transmission from donors with latent tuberculosis infection (LTBI), particularly in lung transplant recipients. RL3.

B. Recommendations
- LTBI screening in living donors is recommended by performing PPD and/or interferon-γ release assay (IGRA); in case they are positive, the presence of

active tuberculosis disease should be systematically ruled out before the transplant. AII.

- The administration of chemoprophylaxis in living donors with untreated LTBI, AII, and ideally, deferring transplantation for at least 2 months is recommended. AIII.
- Although LTBI screening in deceased donors has practical difficulties, the previous history of untreated tuberculosis, the epidemiological risk profile (countries of origin with high incidence) and/or the presence of residual lesions in chest X-Rays should be considered on a case-by-case basis. AIII. It is also possible to consider the performance of IGRA, although the experience in this regard is limited. CIII.
- The administration of chemoprophylaxis in recipients of organs from donors (living or deceased) with documented LTBI (or high suspicion) that have not been previously treated or with insufficient information is recommended. AIII.
- The administration of chemoprophylaxis in recipients of organs from donors (living or deceased) with a prior history of properly treated LTBI is not recommended. AIII.

C. Note

A search was made in PubMed with the following terms: donor-derived infection, transmission, solid organ transplantation, and latent tuberculosis.

The latent infection by *Mycobacterium tuberculosis* in the solid organ donor can be reactivated in the recipient.[69,70] This risk appears to be greater in lung transplant recipients. However, the presence of LTBI in the donor should not be considered a contraindication for the transplant.

LTBI screening is easier from a logistic point of view in living donors. In this situation, PPD and/or IGRA must be performed. Any positive results should systematically rule out the presence of active tuberculosis by means of targeted anamnesis, chest X-Ray and, if appropriate, smear microscopy, culture and/or nucleic acid quantification techniques in the relevant biological samples (AII).[70] Except in cases where the correct prior treatment could be adequately documented, LTBI treatment (chemoprophylaxis) should be administered in living donors (AIII). Ideally, and if the clinical situation of the recipient allows so, the transplant should be delayed for at least 2 months to ensure that the donor receives an acceptable course of LTBI treatment before the procedure[11].

In the case of deceased donors, LTBI screening is imbued with practical and logistical difficulties. For obvious reasons, PPD is not applicable in this scenario and there is no information to recommend the performance of IGRA systematically (brain death can depress cell-mediated immunity, thus compromising the ability to respond to the antigen).[71] In any case, the IGRA result would not be available until 24 hours after the donor's blood sample was collected. Therefore, the donor's medical history must be analysed individually (with special consideration for LTBI history or incorrectly treated active tuberculosis), epidemiological risk profile (countries of origin with high incidence

[> 100 annual cases/100,000 inhabitants]) and/or presence of residual lesions on the chest X-Ray (AIII)[71].

LTBI detection in the donor (or the presence of a high clinical, epidemiological and/or radiological suspicion) justifies the administration of chemoprophylaxis (also called LTBI treatment) in the recipient (AIII). The regimen of choice is the administration of isoniazid (5 mg/kg/day [maximum: 300 mg/day] for 9 months) (AII). Alternatively, rifampicin (10 mg/kg/day [maximum: 600 mg/day] can be used for 4 months, in cases of resistance to isoniazid), although there is limited information on its efficacy and safety in the context of solid organ transplantation. In general, the regimen based on the combination of rifampicin and pyrazinamide (for 2 months) is not recommended due to the high risk of liver toxicity[70].

3. WHAT DECISION SHOULD BE MADE IN RELATION TO A DONOR WITH CMV INFECTION?

A. Transmission risk
- There is a high risk of CMV transmission from seropositive donors to seronegative recipients (D+/R-) with potentially serious consequences. RL3.

B. Recommendations
- It is recommended to routinely perform serologic tests for CMV in both the recipient and donor. AII.
- The application of specific prevention strategies is recommended in recipients with D+/R- serological status for CMV. AI.

C. Note
A search was made in PubMed with the following terms: donor-derived infection, transmission, solid organ transplantation, and cytomegalovirus or CMV.

CMV transmission by the donor is widely documented, in both seropositive (superinfection) and seronegative (primary infection) recipients. Thus, its detection is recommended (Table 3). The clinical implications, however, are fundamentally limited to this latter scenario. The presence of a D+/R- serological status for CMV constitutes the main risk factor for the development of clinical manifestations in the post-transplantation period in the form of both direct and indirect effects, with potentially serious consequences on the recipient and the graft. Hence, the application of specific prevention strategies is recommended in this subgroup of patients. This may be based on the administration of antiviral prophylaxis for a variable period according to the type of recipient or on the systematic monitoring of viral replication followed by the establishment of early treatment in the presence of asymptomatic infection (universal prophylaxis and early treatment, respectively). Details about its application and the advantages and disadvantages of each approach are contained in the recent SET/GESITRA-SEIMC/REIPI consensus document[72].

4. WHAT DECISION SHOULD BE MADE IN RELATION TO A DONOR WITH EPSTEIN-BARR VIRUS (EBV) INFECTION?

A. Transmission risk
- There is a high risk of EBV transmission from seropositive donors to seronegative recipients (D+/R-) with potentially serious consequences. RL3.

B. Recommendations
- Systematic monitoring of EBV viremia by viral load detection is recommended in recipients with D+/R-serological status for EBV. BII.

C. Note
A search was made in PubMed with the following terms: donor-derived infection, transmission, solid organ transplantation, and Epstein-Barr virus or EBV or mononucleosis.

Primary EBV infection is the most important risk factor for the development of post-transplant lymphoproliferative syndrome[73]. Therefore, it is necessary to determine the serological status of both donor and recipient (Table 3). In fact, viral load detection is especially indicated for this subgroup of SOT recipients[73,74].

5. SHOULD INFECTION BY OTHER HERPESVIRUS, PARVOVIRUS B19, BK VIRUS OR HEPATITIS E VIRUS (HEV) BE RULED OUT?

A. Transmission risk
- The risk of transmission from donors with chronic herpes simplex virus (HSV) infection, varicella-zoster virus (VZV), human herpes virus type 6 (VHH-6), 7 (VHH-7) and 8 (VHH-8), parvovirus B19 and BK virus is considered of low probability and/or with little clinical impact. RL5.
- Although HEV transmission by liver graft has been described with severe ramifications, there is not enough information to systematically assess this risk. RL4.

B. Recommendations
- It is not recommended to routinely perform the serologic tests for these viruses in the donor. AIII.

C. Note
A search was made in PubMed with the following terms: donor-derived infection, transmission, solid organ transplantation, and human herpesvirus or BK virus or hepatitis E virus or HEV or parvovirus B19.

Although isolated cases of possible HSV transmission by solid organ transplantation have been published[75,76], the exceptionality of this complication coupled with the high frequency of seropositive adults has deemed HSV serology as not necessary in donors[8].

VZV transmission is equally exceptional, and it has only been described among donors with acute or very recent VZV infection and seronegative recipients[14]. Serology for VZV in donors is assumed to be frequently positive and its systematic evolution is not currently recommended, given that donors with chronic infection without an associated clinical condition do not pose a risk of transmission.

However, in order to assess the need for HSV prophylaxis or treatment in the recipient, when the latter is seronegative, some centres recommend retrospective HSV lab tests in donor serum.

No prevention strategies have been defined for other herpesviruses such as HHV-6 and HHV-7, assuming that a percentage of adults is seropositive and that no cases of transmission have been described outside of acute donor infection situations[8].
In the case of HHV-8, seroprevalence in the general population is low and, although a seroconversion rate of approx. 20-30% has been observed between D+/R-, the clinical implications are anecdotal. Hence, HHV-8 serologic tests in donors are not advised in the meantime[77].

Parvovirus B19 transmission by solid organ transplantation has not been described to date, so serologic tests in donors and recipients are not recommended.

Although the BK virus transmission from donors has been proven with molecular biology methods (particularly in kidney transplant recipients)[78], the clinical implications are unclear and, as most adult patients are seropositive for BK viruses, serologic tests in donors and recipients would not assess the risk of developing BK virus-associated nephropathy, so it should not be routinely performed.

In the case of HEV, transmission by liver grafts has been reported occasionally resulting in the death of the recipient[79] and seroprevalence in some geographical locations such as Catalonia can be up to 20%[80]. However, the natural history of transmission by solid organ transplantation remains unclear; hence, no specific recommendations can be made in this regard.

6. WHAT DECISION SHOULD BE MADE IN RELATION TO A DONOR WITH *TOXOPLASMA GONDII* INFECTION?

A. Transmission risk
- There is a risk of *Toxoplasma gondii* transmission in (D+/R-) with potential clinical implications, particularly in heart transplant recipients. RL3.

B. Recommendations
- It is recommended to routinely perform serologic tests for *T. gondii* in both recipient and donor, especially in heart transplant recipients. AII.

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- In heart transplant recipients with D+/R- serological status, *T. gondii* treatment should be administered at full doses during the first three months after transplantation. AIII.

C. Note

A search was made in PubMed with the following terms: donor-derived infection, transmission, solid organ transplantation, and toxoplasmosis or *Toxoplasma gondii*.

T. gondii transmission in (D+/R-) is clearly described, although the assumed clinical impact is generally low. Heart transplant recipients are an exception, as transmission through the persistence of the trophozoites included in the heart graft tissue occurs in up to 75% of cases and is often associated with early severe disseminated disease[81–83]. Thus, treatment with pyrimethamine (200 mg on the first day followed by 75 mg/day [weight> 60 Kg] or 50 mg/day [< 60 Kg]) and sulfadiazine (2-4 g/day) during the first three months after transplantation, followed by prophylaxis with trimethoprim/sulfamethoxazole at low doses (AIII). Proposed alternative regimens are trimethoprim/sulfamethoxazole at a double dose every 8 or 12 hours daily, dapsone (50-100 mg/day) or atovaquone (1500 mg/day) with pyrimethamine (50 mg/8-12 hours)[84] (BIII). In D+/R- transplants of organs other than the heart, the associated risks have not been established and there are no recommendations beyond prophylaxis against *Pneumocystis jirovecii* with trimethoprim/sulfamethoxazole at low doses, which is supposed to present some efficacy to avoid the disease associated with primary infection by *T. gondii*. In any case, the serological status of risk of primary infection by *T. gondii* should be considered when assessing any suspected infection immediately after transplantation of these patients (Table 3).

VIII. SHOULD HIDDEN INFECTIONS IN THE DONOR BE RULED OUT?

1. IS IT NECESSARY TO RULE OUT BACTERAEMIA IN THE DONOR?

A. Transmission risk
- The risk of transmission of bacteraemia from donor to recipient is due to the identified microorganism and its susceptibility to antibiotics. RL2-3.

B. Recommendations
- Blood donor cultures should be obtained routinely at the time of donation. AII.
- All the necessary organisational measures must be taken to ensure that the information on the result of the blood culture collected in the centre, where the donor is located, arrives to the centre where the recipient is located in the shortest time possible and with the highest quality (in case these centres are different). AII.

- The organs of a donor with bacteraemia can be safely used for transplantation if the following conditions are met. AII.
    - absence of signs of sepsis in the donor
    - if the donor has been treated with an effective antibiotic, at least for 24-48 hours
    - prompt transmission of information on blood culture isolation to the centre where the recipient is located
    - continuity of an effective antibiotic treatment in the recipient for 7-14 days (depending on the microorganism pathogenicity and the characteristics of the antimicrobial treatment)

C. Note

A search was made in PubMed with the following terms: donor bacteraemia, donor-derived bacteraemia, organ transplantation.

It is estimated that 5% of donors have bacteraemia at the time of donation, but the transmission of infection to the recipient is low[2,85]. This has been described mainly in donors with bacteraemia by microorganisms resistant to antibiotic prophylaxis used in transplantation. The risk of infection transmission varies by microorganism. It is low with little virulent microorganisms such as coagulase-negative staphylococci and higher with gram-negative bacilli[86].

There is sufficient evidence in the literature on the transmission of bacterial infections from a donor with bacteraemia with serious consequences for the recipient in the form of bacteraemia, sepsis, vascular graft complications resulting in transplantectomy and death[87]. Additionally, there are controversial information on the relationship between bacteraemia in the donor and a worse graft function[85,88,89].

Similarly, there is evidence that mostly demonstrates that the administration of an effective antimicrobial treatment in both donor and recipient, during the donation process, dramatically decreases (but does not eliminate) the risk of transmission, until this practice becomes reasonably safe[1,7,8,85,86,89,90]. An exception to this rule could be, at the present time, in situations in which bacteraemia is caused by a multidrug-resistant microorganism against which there is no antibiotic treatment, or if any, the risk of its administration in a transplant recipient is very high.[91] It seems clear that a correct communication in time and form between the centre where the blood cultures are collected from the donor and the centre that performs the transplant is a critical factor to ensure the safety of this practice[92].

2. SHOULD URINARY TRACT INFECTION (UTI) IN THE DONOR BE RULED OUT?

A. Transmission risk
- The presence of a positive urine culture in the donor represents a risk of transmission in kidney transplant recipients. RL3

B. Recommendations
- The systematic performance of urine culture in a SOT donor other than kidney transplant is not recommended. AIII.
- The presence of a positive urine culture in a SOT donor other than kidney transplant is not deemed a contraindication for the transplant. AIII.
- The presence of a positive urine culture (including candiduria without candidemia) in a deceased kidney transplant donor is not considered a contraindication for transplantation, as long as it corresponds to a mild urinary tract infection or asymptomatic bacteriuria. The recipient must receive antibiotic treatment according to the donor's urine culture antibiogram for at least 10 days. AII.

C. Note
A search was made in PubMed with the following terms: donor; urinary tract infection; pyuria; bacteriuria; pyelonephritis.

The published scientific information on positive urine culture in SOT donors is very scarce, so evidence quality is deemed low. However, clinical experience and the absence of publications on post-transplantation complications in relation to this type of infection, allows for strong recommendations in this regard. There are only two published studies that have studied the donor's urinary tract infection in kidney transplants and their conclusions are that there are no complications in the recipients as long as proper antibiotic treatment is administered to the recipient in the immediate post-transplantation period[93,94].

3. SHOULD RESPIRATORY INFECTION IN THE DONOR BE RULED OUT?

A. Transmission risk
- The risk of transmission of infection from donor to recipient is well documented in lung transplantation. Its consequence will depend on the identified microorganism and its susceptibility to antibiotics. RL2-3.

B. Recommendations
- A bronchial aspirate should be performed in the donor and in the lung transplant recipient at the time of the procedure. AII.
- The lung donor with an active bacterial infection should receive antibiotic treatment before the donation of the organ (preferably for more than 48 hours). Treatment should continue in the recipient. AII.

- In the case of lung transplantation, colonisation by microorganisms with low therapeutic reserves (*Klebsiella pneumoniae* or *Acinetobacter baumanii* resistant to carbapenems, extremely resistant (XDR) *Pseudomonas aeruginosa*, *Burkholderia cenocepacia*, *Mycobacterium abscessus*) should be considered a relative contraindication. The lungs should be used based on the urgency of the transplant and post-transplant therapeutic possibilities. AIII.
- • Donor organs with positive respiratory secretion cultures, including microorganisms with different antibiotic resistance patterns, can be considered for transplantation. Recipients should be monitored. AIII.

C. Note

A search was made in PubMed with the following terms: donor respiratory infection, antibiotic resistance, organ transplantation.

Lungs are the most common site of infection in donors. Most deceased donors require emergency tracheal intubation. Aspiration and consequent pneumonia should be ruled out and treated. Concomitantly with the time spent in an intensive care unit (ICU), confirmed bronchopulmonary infections range from 10% to 40%.[8] In case of a non-long transplantation, there is not enough information in the literature to rule out any organ based on colonisation or respiratory infection. The use of lungs with gram-negative bacteria or fungal infections is controversial. Some experts prefer to rule out these organs, while others advocate their use with aggressive antibiotic therapy. After at least 48 hours of proper antibiotic treatment (or at least the unaffected lobes) they should be considered for donation. Currently, an increasing number of patients in ICU are exposed to infections by multidrug-resistant bacteria, in particular, strains of clonal complexes of XDR *P.aeruginosa*, and *K. pneumoniae* or *A. baumanii* resistant to carbapenems (CR). These strains imply a difficult treatment and a significant increase in morbidity and mortality, especially among SOT recipients[95–97]. We have not been able to find valuable risk factors to predict this type of infection by multidrug-resistant (MDR) bacteria. It has been published that prolonged stay (> 7 days) in ICU, together with the use of vasopressors and the need for cardiopulmonary resuscitation, are independent risk factors for predicting donors potentially infected by MDR bacteria[98]. However, others have shown that a hospitalization period as short as 2 days is sufficient to acquire a nosocomial MDR pathogen that can be transmitted through transplantation[99]. The limited experience available suggests that, under well-defined conditions, organs from donors that are positive for a CR strain in respiratory secretions can be considered for transplantation. Close monitoring of the recipient is mandatory to validate this approach. In this context, the possibility of not having a lung transplant seems prudent if the lungs are colonised by *K. pneumoniae* or *A. baumanii* resistant to carbapenems.

4. SHOULD BILE DUCT INFECTION IN THE DONOR BE RULED OUT?

A. Transmission risk
- The risk of transmission of a donor with positive bile duct culture is unknown. RL4.

B. Recommendations
- Systematic culture of donor bile in liver transplantation is not recommended. AII.

C. Note
A search was made in PubMed with the following terms: bile; transplant; donor; cholangitis; bactibilia; culture; transmission.

The published scientific information on bile culture of the liver transplant donor is limited to a study in which a systematic culture of the bile of the deceased liver transplant donor[98] was performed. The study was conducted in Taiwan between 2002 and 2007, with the inclusion of 59 liver transplant donors (aged between 9 and 59 years) who were systematically subjected to blood cultures as well as sputum, urine and bile cultures. In this study, all bile cultures were sterile. The publication of this study, together with the absence of publications that have detected post-transplant complications in relation to the alleged infection of the donor's bile, allows for strong recommendations in this regard, although the degree of evidence is moderate.

5. SHOULD PRESERVATION FLUID–RELATED INFECTION BE RULED OUT?

A. Transmission risk
- The transmission of preservation fluid-related infection is well documented. Its impact will depend on the identified microorganism and its susceptibility to antibiotics. RL2-3.

B. Recommendations

- Although there is no ambiguous evidence that systematic culture of preservation fluids should be a routine practice in organ transplantation, the panel recommends its practice. CIII.
- A positive culture of preservation fluid for potentially pathogenic bacteria would require the administration of proper antimicrobial treatment in the recipient for not less than two weeks. BIII.
- In the presence of *Candida* spp in the preservation fluid it is advisable to obtain blood cultures, urine culture and drainage and fungal biomarkers in the recipient, as well as assess the start of antifungal treatment. In these cases, a baseline Doppler ultrasonography should be performed due to the risk of vascular involvement by *Candida* spp. BIII.

- When the result of the preservation fluid culture is positive for low virulence bacteria (negative *staphylococcus* plasmocoagulase, *Corynebacterium* spp, etc.) antibiotic treatment in the recipient does not seem to be necessary. BII.

C. Note

A search was made in PubMed with the following terms: infection, organ transplantation, preservation fluid contamination, donor-derived infection, organ preservation solution, adverse effects.

There is little information on the efficiency of systematic culture of preservation fluids at the time of transplantation. The most comprehensive thereof, shows that preservation fluids are frequently contaminated by bacteria (generally gram positive) of low virulence[100]. The absence of specific treatment for the recipients of these organs does not seem to lead to transmission of the infection to recipients. In fact, this practice is not supported by most of the authors[8].

There are isolated cases and small series of cases that unequivocally demonstrate the transmission of *Candida* spp infections from the contamination of the graft preservation fluid. In several of these cases, the donor has presented vascular complications in the form of fungal aneurysms of the graft resulting in transplantectomy and/or death of the patient [101–105].

The administration of antifungal prophylaxis upon detection of *Candida* spp culture in the preservation fluid has been reported by some groups, with variable results. In many cases, no transmission of the pathogen has occurred, while in others the event has occurred despite the administration of the antifungal drug[102–106].

Finally, a recently published meta-analysis concludes that the incidence of positive cultures in the preservation fluid reaches 37% with an incidence of related infection in the recipient of 10% in the case of isolation of pathogenic microorganisms and an associated mortality of 35%. This would recommend the performance of preservation fluid culture and close monitoring of the recipient in case of a positive culture[107].

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IX. WHAT CLINICAL SITUATIONS SHOULD BE ASSESSED FOR THE DONATION OF A SOLID ORGAN?

1. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN THE CASE OF A POTENTIAL DONOR WITH ACTIVE TUBERCULOSIS?

A. Transmission risk
- Transmission from a donor infected with active tuberculosis has been documented. RL1.

B. Recommendations
- It is recommended to contraindicate solid organ transplantation in cases of active tuberculosis and in cases of justified suspicion. AII.

C. Note
A search was made in PubMed with the following terms: donation, donor infection, transmission, solid organ transplantation, and tuberculosis or *Mycobacterium tuberculosis*.

Organs from donors with known active tuberculosis should be ruled out, as well as lungs with residual tuberculous lesions[70]. Organs from donors with a history of tuberculosis treated for a minimum of 6 months have been transplanted without problems[108]. Organs from donors with tuberculous meningitis can only be considered for transplantation in exceptional cases, as the infection may already be disseminated.

2. WHAT SHOULD BE DONE IN RELATION TO A POTENTIAL DONOR WITH PNEUMONIA?

A. Transmission risk
- Acute pneumonia without systemic dissemination does not constitute a contraindication for transplantation (RL5) except for both single and double lung transplant. RL1-3.

B. Recommendations
- Donors with pneumonia should receive effective antibiotic treatment before the organ removal (preferably for more than 48 hours) and present hemodynamic stability. AII. Treatment should be continued in the recipient for a period of 7-14 days. AII.

C. Note
A search was made in PubMed with the following terms: donation, donor infection, transmission, solid organ transplantation, and pneumonia.

Deceased donors require tracheal intubation, which favors the presentation of ventilator-associated pneumonia. This risk increases with the time that the patient remains in ICU so that the bronchopulmonary infection rate increases from 10% to 40%. Therefore, this situation should be ruled out and treated before considering donation[8]. In the case of pneumonia with unilateral involvement, the use of contralateral lung for transplantation is not recommended.

3. WHAT SHOULD BE DONE IN THE CASE OF A POTENTIAL DONOR WITH INFLUENZA?

A. Transmission risk
- Donors with influenza virus infection can transmit the infection to the recipient. RL1-3.

B. Recommendations
- The deceased subjects with suspected or confirmation of influenza virus infection, whether they have received antiviral treatment or not, can be considered as SOT donors provided that the recipient is treated prophylactically with neuraminidase inhibitors. BIII.
- Deceased subjects with suspected or confirmed influenza virus infection should be ruled out as lung or bowel donors. AIII.
- Transplantation from a living donor with influenza should be postponed until the infection is resolved. AIII.

C. Note
A search was made in PubMed with the following terms: donation, donor infection, transmission, solid organ transplantation, and flu or influenza virus.

Potential donors with upper or lower respiratory tract infection symptoms should undergo microbiological tests to rule out influenza virus infection during the annual epidemic of this virus. Donors with confirmed or suspected influenza virus infection, whether they have received antiviral treatment or not, can be considered for SOT if the recipient is prophylactically treated with neuraminidase inhibitors. These donors should be ruled out in the case of lung or bowel transplantation even if they have been previously treated with neuraminidase inhibitors[109].

4. WHAT SHOULD BE DONE IN THE CASE OF A POTENTIAL DONOR WITH ACUTE PYELONEPHRITIS?

A. Transmission risk
- Acute pyelonephritis without systemic dissemination does not constitute a contraindication for transplantation (RL5) except for transplantation of any of the two kidneys. RL1-3.

B. Recommendations

- The potential donor with acute pyelonephritis should receive effective antibiotic treatment before removal of the organ (preferably for more than 24-48 hours) and present hemodynamic stability. AII. Treatment should be continued in the recipient for a period of 7-14 days. AII.
- Acute pyelonephritis or renal abscesses at the time of the donor's death are considered a contraindication for kidney transplantation. AIII.
- Any type of urinary tract infection (high or low) in a living donor is considered an indication to delay the transplant until it has been resolved. AIII.

C. Note

A search was made in PubMed with the following terms: donation, donor infection, transmission, solid organ transplantation, and acute pyelonephritis.

Lower urinary tract infections and pyelonephritis are common in deceased donors given the presence of bladder catheterization. In the case of cystitis or low UTI, the kidneys can be transplanted as long as they are not infected. Once the microorganism causing the urinary tract infection is known, antimicrobial treatment should be administered until clinical stability is achieved, and the same should be maintained in the recipient for an adequate period[110]. In the case of pyelonephritis of one kidney, use of the non-affected kidney is not recommended.

5. WHAT SHOULD BE DONE IN THE CASE OF A POTENTIAL DONOR WITH MENINGITIS?

A. Transmission risk

- Acute meningitis without systemic dissemination does not constitute a contraindication for transplantation. RL2-3.

B. Recommendations

- The donor with bacterial meningitis should receive effective antibiotic treatment before the organ removal (preferably for more than 24-48 hours) and present hemodynamic stability. Treatment should be continued in the recipient for a period of 7-14 days. AII.

C. Note

A search was made in PubMed with the following terms: donation, donor infection, transmission, solid organ transplantation, and meningitis.

Bacterial meningitis does not constitute an absolute contraindication for organ donation if the causative agent (*Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae, Listeria monocytogenes*) has been identified and adequate donor antimicrobial treatment has been administered for at least 24- 48 hours and infection is clinically controlled[2]. Caution should be exercised in donors supposedly affected by bacterial meningitis with cultures in both blood and cerebrospinal fluid (CSF) and negative polymerase chain reaction (PCR) in CSF. In addition, donors who

died from meningoencephalitis caused by *Cryptococcus neoformans* or *Mycobacterium tuberculosis* should be ruled out given the possibility of widespread infection[111–113].

The presence of a brain abscess does not contraindicate donation per se. However, it would be necessary to study the potential causes of its presence before accepting the donor organs.

6. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN THE CASE OF A POTENTIAL DONOR WITH ENCEPHALITIS?

A. Transmission risk

- The transmission of viral encephalitis (West Nile virus, lymphocytic choriomeningitis, rabies, etc.) from donor to recipient with a fatal outcome has been documented. RL1.

B. Recommendations

- Organs from donors with encephalitis without etiologic diagnosis should not be used for transplantation due to the high transmission risk of infection in the recipient. AII.
- Organs from donors with encephalitis of known etiology (herpes simplex virus) will be assessed individually. CIII.

C. Note

A search was made in PubMed with the following terms: donation, donor infection, transmission, solid organ transplantation, and encephalitis.

The organs of donors with encephalitis without etiological diagnosis have frequently been associated with transmission of infection to recipients. Transmission of rabies virus, West Nile virus, lymphocytic choriomeningitis virus, and parasitic infections such as *Balamuthia mandrillaris* has been described[114–116]. Hence, organs from donors with encephalitis without clarified etiology should not be accepted for transplantation[7,8,117]. However, in the case of known etiology and proper treatment in both donor and recipient, the rate of adverse effects is low[118].

In the case of herpetic encephalitis treated etiologically, organs can be donated, after individual assessment, since viremia is rare in this entity and most recipients are seropositive. If the recipient is seronegative, specific antiviral prophylaxis (acyclovir) is recommended for 6 months.

Progressive multifocal leukoencephalopathy caused by the CJ virus, typical of patients with cellular immunosuppression, usually occurs without viremia despite high loads in CSF and urine. Given the lack of data about the safety of donation in this situation, it is recommended not to use the organs from these donors.

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7. WHAT SHOULD BE DONE IN THE CASE OF A POTENTIAL DONOR WITH A PRION DISEASE?

A. Transmission risk

- The transmission of diseases caused by prions from donor to recipient is well documented. RL1. AII.

B. Recommendations

- The organs of donors diagnosed with prion diseases should not be used for transplantation. RL1. AII.

C. Note

A search was made in PubMed with the following terms: donation, donor infection, transmission, solid organ transplantation, and prion disease.

Cases of transmission of prion diseases such as Creutzfeldt-Jakob disease and spongiform encephalopathy have been documented, mainly in cornea and dura-mater graft recipients and more rarely in solid organ recipients[119]. Patients with prion disease they should not be considered as organ donors because of the risk of transmission of irreversible diseases to the recipient[7,8,117].

8. WHAT SHOULD BE DONE IN THE CASE OF A POTENTIAL DONOR WITH ENDOCARDITIS?

A. Transmission risk

- Endocarditis does not constitute a contraindication for transplantation, except for heart transplantation. RL1-3.

B. Recommendations

- In the patient with endocarditis, heart donation is contraindicated. AII.
- Patients with endocarditis can be accepted as donors of other organs if they have received proper antibiotic treatment prior to donation (preferably a minimum of 48 hours), if they have been tested negative for bacteraemia and there is no evidence of embolic phenomena that have damaged the organs to be transplanted. Targeted antibiotic treatment should be continued in the recipient. AII.

C. Note

A search was made in PubMed with the following terms: donation, donor infection, transmission, solid organ transplantation, and endocarditis.

Endocarditis is not an absolute contraindication for organ donation except for heart transplants, although some cases of transmission of infection in the recipient have been described, especially of resistant and virulent pathogens such as methicillin-resistant *Staphylococcus aureus*[120]. Patients with endocarditis can be accepted as

donors if they have received appropriate treatment for a minimum of 24-48 hours and have been tested negative for bacteraemia. It is recommended to maintain a targeted antibiotic treatment in the recipient, although its duration is not well established[7,8,117,121].

9. WHAT SHOULD BE DONE IN THE CASE OF A POTENTIAL DONOR WITH OTHER LOCALISED INFECTIONS: CHOLECYSTITIS, CHOLANGITIS, ARTHRITIS, OSTEOMYELITIS, CELLULITIS, ABSCESSES, ETC.?

A. Transmission risk

- There is transmission risk if the infected organ is transplanted. RL1.

B. Recommendations

- The organ affected by the infection should not be transplanted. AII.
- The donor with localised bacterial infection must have received adequate treatment prior to donation (preferably a minimum of 24-48 hours). Targeted antibiotic treatment should be continued in the recipient. AII.

C. Note

A search was made in PubMed with the following terms: donation, donor infection, transmission, solid organ transplantation, and acute cholecystitis or cholangitis or septic arthritis or skin and soft tissue infection or abscess.

Donors with localised bacterial infection do not have an absolute contraindication for donation, as long as the infection is in a different site from the donation organ and they have received proper antibiotic treatment for a minimum of 24-48 hours. It is recommended to maintain a targeted antibiotic treatment in the recipient, although its duration is not established [2,7,8,117].

10. WHAT SHOULD BE DONE IN THE CASE OF A POTENTIAL DONOR WITH SEPTIC SHOCK?

A. Transmission risk

- The donor suffering from septic shock of unknown origin can transmit the infection to the recipient. RL1.

B. Recommendations

- Septic shock of unknown origin and even its well-founded suspicion should, in principle, contraindicate the use of organs for transplantation. AIII.
- If the septic shock origin is fungal or related to tuberculosis, the use of organs for transplantation should be contraindicated. AII.

C. Note

A search was made in PubMed with the following terms: donation, donor infection, transmission, solid organ transplantation, and septic shock.

Organs from donors with uncontrolled septic shock should be ruled out, except for patients whose microorganism etiology and sensitivity that causes the infection is known, the cultures have been tested negative and the shock is in resolution phase[2,122,123].

11. WHAT SHOULD BE DONE IN THE CASE OF A POTENTIAL DONOR WITH DISSEMINATED FUNGAL INFECTION?

A. Transmission risk

- The donor with disseminated fungal infection has a high risk of infection transmission. RL1-2.

B. Recommendations

- It is recommended to rule out the existence of an invasive mycosis in donors with CNS or pulmonary pathology whose origin is not known, especially if they present risk factors such as immunosuppressed donors, prolonged stay in ICU, prolonged mechanical ventilation or drowning victims. BIII.
- Patients with disseminated mycosis or CNS mycosis should not be accepted as donors. In cases of extreme need, transplantation can be assessed if the donor has received prior treatment and microbiological eradication has been documented. BIII.

C. Note

A search was made in PubMed with the following terms: donation, donor infection, transmission, solid organ transplantation, and invasive fungal infection or fungemia.

Patients with disseminated fungal infection should not be accepted as donors, unless microbiological eradication has been documented and the recipient's health condition is extremely severe[124]. In these cases, informed consent will be requested and antifungal treatment will be administered to the recipient.

Donors with neurological conditions (hemorrhage, coma, stroke without risk factors) or lungs conditions whose origin cannot be well defined, who also present risk factors for invasive fungal infection (immunosuppressed donors, prolonged stay in ICU, prolonged mechanical ventilation, drowning victims) should be evaluated by an expert to rule out an invasive fungal infection by filamentous fungus or by *Cryptococcus*[114,125–127].

Living donors with an active endemic mycosis should be treated for 3-6 months before transplantation. In deceased donors from endemic areas, the liver and spleen should be inspected. Granuloma visualization does not constitute an absolute

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contraindication of transplantation. A biopsy will be taken, serology and cultures will be requested and the administration of antifungals to the recipient will be assessed[128–131].

Different emerging fungal infections transmitted from the graft have been documented. *Scedosporium* spp, *Aspergillus* spp, Zygomycetes and other filamentous fungi have been transmitted by donors who have acquired mycosis from nosocomial sources, sometimes after prolonged stays in intensive care units prior to death[124,132]. The use of organs from patients with prolonged immunosuppression or even transplanted ones has been linked to the transmission of mycosis to their recipients.

Transmission of this type of mycosis is especially relevant when deceased donors have died from water diving or semi-drowning accidents[133,134]. In these cases, unlike the usual presentation of opportunistic mycoses in transplant recipients associated with prolonged immunosuppression, the clinical presentation is early, with frequent graft involvement, sometimes with catastrophic vascular phenomena in the graft vasculature and acute graft dysfunction. High clinical suspicion, rapid surgical debridement and early onset of antifungals are determinants for the control of these forms of presentation[124,132].

The transmission of cryptococcosis from the donor has been described, mainly in liver transplants that, unlike the usual cryptococcosis, have an early onset and usually affect the graft itself and even the surgical wound [131].

Finally, a well-documented entity in recent years is the transmission through grafting of *Candida* spp infections to its recipients with special vascular tropism and high morbidity and mortality. In these cases, candidemia or candidiasis had not been documented in the donors, but most had received broad-spectrum antibiotic therapy and there was a disruption of the intestine in the organ removal procedure or in the context of previous polytrauma with *Candida* spp growth in the preservation fluids[135].

12. WHAT SHOULD BE DONE IN THE CASE OF A POTENTIAL DONOR WITH LOCALISED FUNGAL INFECTION?

A. Transmission risk
- Donors with localised fungal infection present a risk of transmission of the infection to the recipient. RL1-2.

B. Recommendations

- In donors with focal lung lesions, a histopathological and microbiological study of the biopsy specimen should be performed. Transplantation of an organ with fungal infection is not recommended, except in situations of extreme urgency and prior documentation of microbiological eradication. BIII.

- Organ transplantation of patients with cryptococcal meningitis is not recommended, except in conditions of extreme urgency. BIII. In donors with pulmonary or extraneural cryptococcosis, lumbar puncture with cryptococcal antigen should be performed, as well as CSF cultures, blood cultures, urine cultures and serum cryptococcal antigen. BII.

C. Note

A search was made in PubMed with the following terms: donation, donor infection, transmission, solid organ transplantation, and fungal infection.

An organ with a filamentous fungal infection or *Cryptococcus* should not be transplanted [124].

Donors with cryptococcal infection in any organ can transmit the disease. This should be considered in donors with neurological disease or with pulmonary nodules of unknown origin.

Donors with active filamentous fungal infection are not deemed acceptable for donation. These infections should be suspected in immunosuppressed donors, drowning victims, donors with liver or kidney failure, with prolonged stays in ICU and who have CNS or lung lesions of unknown origin.

Donors from or with a history of travel or residence in areas with endemic mycoses should be evaluated radiologically and serologically. Recipients of organs from donors with localised mycosis should receive antifungal treatment and be monitored periodically to detect seroconversion.

13. WHAT SHOULD BE DONE IN THE CASE OF A POTENTIAL DONOR WITH FEVER OF UNKNOWN ORIGIN (FUO)?

A. Transmission risk
- There are no data on the risk of infection transmission in donors suffering from fever of unknown origin (FUO). RL4.

B. Recommendations

- Screening of potential donors includes comprehensive medical history and social behaviour, as well as thorough physical examination. It is necessary to perform laboratory analysis, microbiological and radiological tests according to the patient's clinical condition and personal history. AII.
- In addition to the usual tests, specific serologic tests are recommended based on the donor's medical history and clinical suspicion. AII.
- The possibility of an autopsy should be considered in all donors who died with fever in order to diagnose a hidden infection. AII.

- In the event that the subjects have died from a suspected or confirmed infection of unknown origin, informed consent is required by the recipient assuming the risk of transmission of an infection. AIII.

C. Note

A search was made in PubMed with the following terms: donation, donor infection, transmission, solid organ transplantation, and fever unknown.

In donors with fever of unknown origin (FUO), attempts should be made to identify and treat both old and recently acquired infections[10]. In the event that there is sufficient time between the initial assessment of the donor and the removal of the organs, reassessment of the clinical signs or symptoms related to a possible infection is necessary[89].

It is convenient to rule out fever of non-infectious etiology (adrenal insufficiency, drug-induced fever, bruises, inflammatory diseases, etc.).

14. WHAT SHOULD BE DONE IN THE CASE OF A POTENTIAL DONOR COLONISED BY MULTIDRUG RESISTANT MICROORGANISMS?

A. Transmission risk
- There is insufficient data to determine the risk of transmission of infection from a donor colonised by multidrug resistant bacteria to a recipient. RL4.

B. Recommendations

- The use of organs from patients with active systemic infection by multidrug resistant bacteria is not recommended. BIII.
- There is no evidence about the benefit of systematically conducting colonisation investigation by *Staphylococcus aureus* or *Enterococcus* R *to vancomycin* in the donor, since it is not clear what course of action should be taken with the recipient, and if the establishment of empirical antibiotic treatment has any benefit to avoid related infections that may arise during the postoperative period. If colonisation is documented there is no contraindication for the use of these organs. BIII.
- It is recommended to perform a rectal exudate to search for multidrug resistant gram-negative bacteria (carriers of extended-spectrum beta lactamases and carbapenemases). If positive, the use of donor organs is not contraindicated. It is not known if the administration of antibiotic prophylaxis to recipients of organs from donors colonised by these microorganisms has any impact on the prevention of infections arising thereof. However, it is important to have the epidemiological history recorded in the medical history in order to adjust the empirical antibiotic treatment in case of suspected infection immediately after the transplantation period. BIII.

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C. Note

A search was made in PubMed with the following terms: donation, donor infection, transmission, solid organ transplantation, and multidrug resistance.

SOT recipients are at a high risk of infections by multidrug resistant microorganisms[136,137] and donor-derived transmission has been documented[137–140]. In a recent study, up to 14% of SOT recipients received an organ from a donor with infection or colonisation by a carbapenem-resistant gram-negative bacillus, unknown at the time of the transplant[90].

There is not enough evidence to contraindicate the transplantation of organs from donors that are colonised by multidrug resistant bacteria[141], except in the case of uncontrolled infection. It is convenient to investigate the colonisation of donors according to the procedures recommended by the *Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica* [Spanish Society of Infectious Diseases and Clinical Microbiology][142].

X. HOW IMPORTANT IS THE PLACE OF ORIGIN OF THE DONOR?

1. INTRODUCTION

The great boost in international travel and migration in recent decades led to an increase in the number of donors or transplant candidates who have been born or have been overseas. According to data provided by the ONT, in Spain in 2017 about 9% of donors were born overseas. There are infections with geographic restriction, not present in our environment, to which donors may have been exposed, even years before, and that could be transmitted by grafting procedures.

This new reality compels us to assess the performance of extended and targeted screening in donors with risk factors and potential exposures to unusual pathogens. Table 7 summarises the approach to infection screening according to the geographical area of origin of the donor.

In order to identify these risk situations, it is essential to try to collect, as exhaustively as possible, the donor's medical history from their place of origin, trips or stays in areas with infections with geographical restriction or epidemic outbreaks, background screening for zoonosis, sexual habits and relationships, parenteral drug use, blood product transfusions, and symptoms and signs suggestive of active infection in the weeks or months prior to donation.

Moreover, the appearance of emerging infections in recent years, which generate epidemic outbreaks, represents a risk of dissemination to other areas through non-vector transmission routes such as transfusions or transplantation.

The emergence of vector-borne infections is related to multiple factors but mainly to climatic variations and some human activities and behaviours.

The ability of infectious agents to cross interspecies barriers explains why many zoonotic and vector-borne infections affect humans. Among emerging infections, 75% are zoonoses, originating mainly in nature[115].

The review of manuscripts that analyse cases of infections transmitted from donors to recipients shows that, despite existing measures and recommendations, some cases of infection transmission continue to occur[125,143].

Table 7. Screening recommendations for donor-derived infections with geographic restriction according to their geographical origin.

Test	REGION				
	Central and South America	North of Africa	Sub-Saharan Africa	Indian Subcontinent	Southeast Asia
Plasmodium spp PCR	Central America and Amazon	No	Always	Always	Always
Stool parasites	Always	Always	Always	Always	Always
Urine parasites	No	Egypt	Always	No	No
Strongyloides stercolaris Serology	Always	Always	Always	Always	Always
Schistosoma spp Serology	Caribbean, Venezuela and Brazil	Always	Always	No	Always
Trypanosoma cruzi Serology	Always (not necessary for the Caribbean)	No	No	No	No
Paracoccidioides brasiliensis Serology	Brazil	No	No	No	No
Histoplasma capsulatum and *Coccidioides immitis* Serology	Always	No	West Africa (histoplasmosis)	No	No

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2. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN CASES OF SUSPECTED MALARIA?

A. Transmission risk: RL2. If donor dies of malaria: RL1.

B. Recommendations

- It is recommended to screen all immigrant donors or travellers to endemic areas (tropical and subtropical areas, especially sub-Saharan Africa) in the last 3 years by smear and thick peripheral blood drop and detection of antigens by rapid immunochromatography techniques (RDT-malaria). AII.
- It is recommended to performe *Plasmodium* PCR in a deferred way to detect low or mixed parasitaemia. AIII.
- Malaria in the donor is not considered an absolute contraindication for the use of the organs (unless the patient has died of malaria). AIII.
- In the case of a donor with malaria, treatment should be initiated early in the recipient. BIII.

C. Notes

A search was made in PubMed with the following terms: donor derived, donor infection, solid organ transplantation, and malaria or *Plasmodium*.

Malaria in humans is caused by several species of *Plasmodium* spp.: *P. falciparum, P. vivax, P. ovale, P. malariae* and *P. knowlesi*, with *P. falciparum* infections being usually associated with greater morbidity and mortality.

Transmission to humans is usually through the bite of the female *Anopheles* spp. although other less frequent transmission routes have been described, such as vertical transmission, by means of blood transfusions and organ transplantation from an infected donor.

With respect to SOT, *Plasmodium* sp., can survive >24h at 4°C in the blood and therefore cold preservation of the organs does not prevent transmission.

More than 50 cases of transmission have been described in the literature by solid organ transplantation, the majority in kidney transplant recipients, with *P. falciparum* being the most frequently implicated species. In addition, six cases of multiple organ transmission of malaria have been described[144–148]. The prognosis of post-transplant malaria depends on several factors such as the type of transplanted organ (generally the evolution in kidney transplantation is more favorable), the species of *Plasmodium* sp. (*P. falciparum* is less favourable), the immunosuppressive treatment used and the delay in the initiation of anti-malarial treatment.

3. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN CASES OF SUSPECTED *T. CRUZI* INFECTION?

A. Transmission risk: RL2. If donor has acute Chagas disease or if donated organ is the heart/intestine: RL1.

B. Recommendations

- The donor should be screened by serology if there are risk factors for *T. cruzi* (donor residing in endemic area of Latin America, except the Caribbean, even years before, who has received a transfusion in endemic area or son of a mother born in endemic area). AII.
- The use of organs from donors with acute infection is contraindicated and the use of heart/intestine from donors with chronic *T. cruzi* infection is contraindicated. AIII.
- The use of other organs such as liver and kidney (not heart/intestine) from donors with chronic *T. cruzi* infection can be assessed after adequate informed consent and proper post-transplant monitoring. BII.
- In the case of an infected living donor, specific trypanocidal treatment before donation could reduce parasitic load and transmission. AIII.
- Routine treatment/prophylaxis with benznidazole in recipients of organs from donors with positive *T. cruzi* serology is not recommended, but close monitoring (clinical and parasitological) is recommended. AIII.
- Early specific anti-parasitic treatment is recommended in case of recipients affected by acute donor-derived infection with positive *T. cruzi* serology. AII.

C. Notes

A search was made in PubMed with the following terms: donor derived, donor infection, solid organ transplantation, and Chagas or *Trypanosoma*.

In endemic areas of the American continent, transmission is usually vector-borne (by hematophagous bed bugs). Both in endemic areas and outside them, it can also be transmitted vertically, by blood transfusion or organ transplantation from an infected donor, consumption of contaminated food or beverages (oral transmission) and in laboratory accidents.

Several cases of transmission of *T. cruzi* infection by SOT in kidney and liver transplants and cases of multiple organ transmission have been described, and its detection in donors from endemic areas is recommended (Table 3). In endemic areas, positive serology for *T. cruzi* in the donor would not necessarily be a contraindication for transplantation given the high prevalence of the disease in some areas and the shortage of organs. In addition, according to published data, *T. cruzi* transmission from a donor with Chagas disease to a recipient does not occur in most cases and depends on the transplanted organ. This includes a series with an estimated transmission of up

to 20% in kidney transplantation, up to 30% in liver transplantation and up to 75% in heart transplantation (although there are few reported cases)[149].

Although there is little transplantation data, the reduction of parasitaemia (negative *T. cruzi* PCR) has shown a decrease in vertical transmission. In the case of an infected living donor, specific trypanocidal treatment before donation could decrease the parasitic load and transmission.

Routine prophylaxis in a recipient of organs from a donor with Chagas disease is not recommended, as transmission does not occur in all cases and treatment is associated with high toxicity. However, close monitoring is recommended in the post-transplant period and early treatment, if data on acute donor-derived infection with positive *T. cruzi* serology appears[149].

4. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN CASES OF SUSPECTED *STRONGYLOIDES* SPP INFECTION?

A. Transmission risk: RL2.

B. Recommendations
- A targeted screening (serology and stool analysis) will be carried out in donors with risk factors (stays in tropical and subtropical areas, even if that happened years before). AII.
- If the organs of a seropositive donor for *Strongyloides* sp. are accepted, ivermectin treatment of the recipient and close clinical monitoring should be considered in the post-transplant period. AII.

C. Notes
A search was made in PubMed with the following terms: donor derived, donor infection, solid organ transplantation, and *Strongyloides*.

Humans become infected after direct contact with soil contaminated with *S. stercoralis* larvae in tropical and subtropical areas. This nematode has the ability to complete its replication cycle in the human host, with the possibility of self-infection and severe hyper-infestation syndrome mainly in immunosuppressed patients. Direct graft transmission has been described.

Several cases of SOT-associated transmission have been described, some with multiple organ transmission (donor infection (by serology) was not confirmed in all cases). Theoretically speaking, the organ of greatest risk is the intestine. Although symptoms usually appear in the first six weeks, in some cases, infections were delayed up to 9 months post-transplant period[150,151].

In a recent review in the United States, eleven cases of donor-derived *Strongyloides* infection in solid organ recipients have been described. None of the seven donors had been screened for this infection prior to transplantation (six of these donors were born in Latin America). Two of the infected recipients died from infection complications[150].

Molecular diagnostic techniques can be performed in stools to detect *Strongyloides* spp. in centres where these techniques are available, in order to identify recipients with donor-derived infection in its early stages (mainly due to the low sensitivity of the direct stool examination for the detection of *S. stercoralis* and the possibility of false negative serologic tests in the acute phase especially in immunocompromised patients)[152].

5. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN CASES OF SUSPECTED *SCHISTOSOMA* SPP INFECTION?

A. Transmission risk: RL2.

B. Recommendations

- Screening with serology is recommended in donors with risk factors (stays in tropical and subtropical areas, especially in sub-Saharan Africa, even if that took place many years before donation). AIII.
- The organs of a donor with positive serology could be used, but correct treatment with praziquantel should be performed on the infected living donor. AII.

C. Notes

A search was made in PubMed with the following terms: donor derived, donor infection, solid organ transplantation, and *Schistosoma*.

Infection by *Schistosoma* spp. (*S. haematobium, S. mansoni, S.mekongi, S.intercalatum, S. japonicum*) is acquired after contact with contaminated fresh water.

SOT associated cases have been described. A recent review identified at least seven cases of transplanted liver grafts infected with *S. mansoni*[153]. Vincenzi et al describe the evolution after transplantation of six liver grafts from a living donor, with liver biopsy in which *Schistosoma* eggs are visualized. In the post-transplant follow-up, the function of the grafts was not affected[154]. Moreover, another article communicates the favourable evolution after transplantation of a biopsied graft with parasite eggs and granulomatous reaction in the biopsy and another case of liver transplantation of a donor with *Schistosoma* in faeces[155]. Previously, four cases of donor-derived transmission had been described, with favourable evolution[156].

The biological cycle of *Schistosoma* explains that treatment of the recipient is not necessary, nor is the graft evolution affected. After the acute phase, *S. mansoni* adults remain in the mesenteric plexus. Eggs surrounded by granulomatous inflammation can be identified in the liver. The presence of *Schistosoma* eggs in the liver is not a contraindication for the donation itself.

6. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN CASES OF SUSPECTED *CLONORCHIS* SPP./*OPISTHORCHIS* SPP. INFECTION?

A. Transmission risk: RL2.

B. Recommendations
- Screening is recommended for donors from risk areas, especially if there is peripheral eosinophilia, by studying faeces to visualize the parasite eggs. AIII.
- Infection with these trematodes would not be an absolute contraindication for transplantation, but specific treatment with praziquantel should be administered to donors and recipients. AII.

C. Notes
A search was made in PubMed with the following terms: donor derived, donor infection, solid organ transplantation, and *Clonorchis* or *Opistorchis*.

Infection with these trematodes is acquired by the intake of contaminated freshwater fish. They usually cause liver and bile duct infection.

Some 20 cases have been described in which liver grafts infected with *Clonorchis* spp. have been used, all from Southeast Asian countries. In some of the cases, specific treatment was given to the donor or recipient[153,157]. A case has recently been reported in which a liver graft of a living donor was used. This donor was from an endemic area infected with *Opisthorchis felineus*. After an early diagnosis and targeted treatment the evolution was good in both recipient and donor[153].

7. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN CASES OF SUSPECTED FILARIAL INFECTION?

A. Transmission risk: RL4.

B. Recommendations
- There are no specific recommendations for screening donors from endemic areas. AIII.

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C. Notes

A search was made in PubMed with the following terms: donor derived, donor infection, solid organ transplantation, and filariasis.

Filarial nematodes have complex biological cycles that include several species of arthropods as vectors. Therefore, transmission to humans occurs after the bite of an infected arthropod.

A possible case of *Wuchereria bancrofti* microfilariae transmission in kidney transplantation from a living donor has been described. Both the donor and the recipient were from endemic areas and microfilariae were identified in the perioperative biopsy[158]. The recipient received specific treatment with good evolution.

In case of suspected infection (clinically compatible eosinophilia), a blood filarial study should be requested and the donor should be treated before transplantation if possible.

8. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN CASES OF SUSPECTED *COCCIDIOIDES* SPP INFECTION?

A. Transmission risk: RL2.

B. Recommendations

- Screening by serological techniques is recommended in donors staying in or travelling to endemic areas. AII.
- In Spanish reference centres, the available serological technique is immunodiffusion (IgG and IgM). AII.
- The use of molecular techniques has been useful in transplants with clinical suspicion of reactivation and negative serology but there is no experience in donor screening. CIII.
- In the case of donors who have lived in endemic areas and especially if they have a history of past infection or suggestive radiological changes, it is recommended to start prophylaxis in the recipient with post-transplant fluconazole pending serological results. BII.
- If these are positive, it is mandatory to rule out active disease. AII. In its absence, prophylaxis with fluconazole, itraconazole or posaconazole should be maintained for at least 6 months and with quarterly serological monitoring during the first year and annually thereafter. BII.

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C. Notes

A search was made in PubMed with the following terms: donor derived, donor infection, solid organ transplantation, and *Coccidioides*.

The geographical distribution of Coccidioides sp. mainly includes semi-desert areas of the south-west of the United States and northern Mexico, but it is also present in several countries of Central and South America.

The estimated risk of coccidioidomycosis in SOT in endemic areas is 2-9%[159,160].
C. immitis transmission by grafting has been well documented in different transplants. However, it is difficult to confirm this relationship in endemic areas. Transmission by grafting has been documented in lung, liver, kidney and heart transplant recipients in four case groups with multiple organ transmission[128,129,161,162], and in four cases of confirmed transmission from the donor to the lung transplant recipient (the recipients had no epidemiological history of stay or travel to endemic areas)[163–165]. Another case includes a kidney transplant recipient, who developed cerebral involvement[166].

In all cases in which donor infection was confirmed to the recipient, it was symptomatic in the first weeks after transplantation (first month). Among six of the eight cases, donors were residents or had traveled to the endemic area. Two of these donors had had previous coccidioidomycosis.

Among the four groups of multiple organ transmission cases (13 recipients from four donors), ten recipients developed the infection in the early stages (first month) with a rapid course causing infection with graft involvement and disseminated forms and death. In three recipients (two kidney transplants and one lung transplant) in which the transmission of the infection was not fatal, antifungal treatment could have been administered early[128,129]. In one of these kidney transplant recipients, in addition to the early use of azoles, favourable evolution was related to a longer period of the graft in cryopreservation fluid[161].

Similar results have been reported in a review of potential or proven donor-derived transmission cases reported to the Organ Procurement and Transplantation Network (OPNT) from 2005 to 2012 in the United States. Six donors were detected with coccidioidomycosis infection. In four of them, the infection was first detected during the recipient's autopsy. In two cases, the donor was first identified. Twenty-one recipients received organs from these six donors. Five of these six donors were from endemic areas.

Transmission occurred in 43% of them with a median of 30 days post-transplant, with a

mortality rate of 28.5% (median: 21 days). The eleven recipients who received early antifungal treatment survived[167].

9. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN CASES OF SUSPECTED *HISTOPLASMA CAPSULATUM* INFECTION?

A. Transmission risk: RL2.

B. Recommendations

- In non-endemic areas, it is important to conduct a correct medical history in donors who have resided in or travelled to endemic areas and screen donors by serology, especially those with a clinical history and/or suggestive chest X-Ray. AII.
- Immunodiffusion is the technique available in Spanish reference centres. II. The result should not rule the indication for the transplant. AII.
- Itraconazole is recommended to recipients of organs from seropositive donors for at least 3-6 months during the period of maximum immunosuppression. BIII.
- Although posaconazole has been proven effective in the treatment of histoplasmosis, there is no experience on its use in prophylaxis. CIII.

C. Notes

A search was made in PubMed with the following terms: donor derived, donor infection, solid organ transplantation, and histoplasmosis or *Histoplasma*.

Although *H. capsulatum* has a widespread distribution, there are high endemic regions, such as the Mississippi and Ohio river valleys in the United States, Central and South America, and certain areas of Asia, and Africa.

Most cases of histoplasmosis in transplant patients are *de novo* reactivations or acquisitions during outbreaks, but there are cases of graft transmission. At least five cases of donor-derived infection transmission have been reported[162,168,169]. In one of the cases the disease did not develop, although the liver biopsy of the graft showed Histoplasma infection, after administering prolonged prophylaxis with itraconazole to the recipient[162].

Two of the cases occurred during a multiple organ donation. Transmission occurred in two recipients who resided in non-endemic areas and developed the disease 8 and 9 months, respectively, after organ transplantation from an asymptomatic donor whose serological study was negative but it was possible to confirm *H. capsulatum* infection by molecular techniques[168].

10. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN CASES OF SUSPECTED *PARACOCCIDIOIDES BRASILIENSIS* INFECTION?

A. Transmission risk: RL5.

B. Recommendations

- Given the low frequency of paracoccidioidomycosis in the post-transplant period and the low utility of serological markers, which are usually negative in this type of patients, there is no special recommendation for follow-up of this disease in transplant patients. CIII.

C. Notes

A search was made in PubMed with the following terms: donor derived, donor infection, solid organ transplantation, and *Paracoccidioides*.

Paracoccidiodes brasiliensis is endemic in Latin America in a region extending from Mexico to Argentina, although the greatest number of cases is reported in Brazil, with annual incidence of 10-30 inhabitants per million inhabitants[170].

Three cases of paracoccidioidomycosis, all of them pulmonary, have been described in three kidney transplants[171–173]. No case of *P. brasiliensis* graft transmission has been documented. It is believed that the systematic use of cotrimoxazole in the prophylaxis of *P. jiroveci* and with activity against *P. brasiliensis* contributes substantially to its control[12].

11. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN CASES OF SUSPECTED *BLASTOMYCES DERMATITIDIS* INFECTION*?*

A. Transmission risk: RL5.

B. Recommendations

- Specific measures for the recipient or donor are not recommended, given the low prevalence of blastomycosis in transplants and the low profitability of antigen and/or antibody detection techniques. CIII.

C. Notes

A search was made in PubMed with the following terms: donor derived, donor infection, solid organ transplantation, and blastomycosis.

Blastomycosis is endemic to central and northern United States, although it has also been occasionally described in areas of the Mediterranean basin and Africa.

No case of blastomycosis graft transmission to recipients has been confirmed to date. A case of a kidney transplant recipient who developed pulmonary blastomycosis secondary to accidental inoculation has been described[174].

12. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN CASES OF SUSPECTED *PENICILLIUM MARNEFFEI* INFECTION*?*

A. Transmission risk: RL4.

B. Recommendations
- No specific measures are recommended for the control of this infection in recipients or donors. CIII.

C. Notes

A search was made in PubMed with the following terms: donor derived, donor infection, solid organ transplantation, and penicilliosis or *Talaromyces* or *Penicillium*.

P. marneffei is endemic to Southeast Asia, primarily southern China, Taiwan and Hong Kong.

P. marneffei is uncommon in transplant patients. Most of these cases have occurred in late periods after transplantation and possibly associated with reactivation of latent infections[175–177]. The first case of *P. marneffei* graft transmission has recently been published in a recipient of Belgian nationality who received a lung transplant from another fellow citizen who had returned from a trip to Southeast Asia (Myanmar) 3 months before his death. The recipient presented, four months after the transplant, after suspension of prophylaxis with inhaled amphotericin B, fever and pulmonary infiltrates with *P. marneffei* isolation in blood cultures and respiratory samples. The evolution was favourable after treatment with Amphotericin B lipid complex, followed by voriconazole[178].

13. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN CASES OF SUSPECTED HUMAN T-LYMPHOTROPIC VIRUS 1 (HTLV-1) INFECTION?

A. Transmission risk: RL1.

B. Recommendations
- Universal screening with serology in all donors through automated, approved tests that are efficient, fast with an adequate cost. AII.
- Screening is especially indicated in: a) donors from or who have lived in endemic areas of HTLV-1 infection; b) donors who are children of mothers born or residing in

endbmic area; c) donors, especially women, whose partners have resided in endemic areas. BII.

- In the case of seropositive donor and seronegative recipient, reject the organ. AII.
- In the case of seropositive donor and seropositive recipient for HTLV-1, assess acceptance of the organ, by considering potential lower risks of associated disease development in already infected subjects. BII.

C. Notes

A search was made in PubMed with the following terms: donor derived, donor infection, solid organ transplantation, and HTLV or tropical spastic paraparesis.

The main routes of HTLV-1 transmission are: vertical transmission, by sexual route (more efficient man to woman) and parenterally.

High endemic HTLV-1 regions are: southwest of Japan, Caribbean, sub-Saharan Africa, South America, and outbreaks in the Middle East and Oceania[179].
In Europe, only Romania represents an endemic HTLV-1 area.

In Spain, the prevalence is less than 0.23%[180]. As of December 2016, 327 cases of HTLV-I infection were described. Eighteen percent (18%) of the cases described correspond to Spanish natives. In 2008, some transfusion centres started to conduct universal screening in blood donors. Since then, there has been a significant increase in the number of cases identified (20-25 cases/year)[181].

In non-endemic countries, including Spain, the main source of HTLV-1 transmission is by people from endemic areas. Transmission occurred sexually (41%), parenterally (12%) and vertically (9%)[181].

Transmission of HTLV-1 infection by transplantation of organs from seropositive donors to seronegative recipients is described in at least 15 cases, on three occasions transmission has been in multiple organs[182–189].
In 10 of the 15 cases (66%), recipients developed some of the diseases associated with HTLV1. After the HTLV-1 seropositive donor-derived transmission to seronegative recipients, the evolution of HTLV1-related myelopathy has been modified, with a shorter period from the infection to the appearance of symptoms (2 months-8 years), compared to the 15-20 years described in the natural evolution of the infection in immunocompetent patients.

Conversely, this rapid evolution after transplantation in seronegative recipients (primary infection) has not been found in pre-transplant seropositive recipients, both in deceased donors and living donors[185].

HTLV-1 infection can be diagnosed by the presence of HTLV-1 antibodies in enzyme immunoassay (EIA), particle agglutination, indirect immunofluorescence (IIF) and Western Blot (WB). Currently, automated detection, based on a double sandwich assay using recombinant proteins and synthetic peptides, has improved serological diagnosis, with a specificity of 99.98% and a sensitivity of 100%. This has justified its majority use as a diagnostic and screening technique[190].

High provirus loads, determined by real-time PCR, are associated with a risk factor for the development of TSP/HAM.

14. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN CASES OF SUSPECTED RABIES VIRUS INFECTION?

A. Transmission risk: RL1.

B. Recommendations
- Draw a history, as detailed as possible, of donor travels, exposures or accidents that occurred during these trips, such as bites, wounds, and a history of previous travel vaccinations. AII.
- Donors with fever and an unexplained CNS event should be evaluated to rule out meningoencephalitis. AIII.
- Reject the donor with unknown encephalitis data. AII.
- In case of transplant transmission, identify and perform early immunisation of the other recipients. AIII.

C. Notes
A search was made in PubMed with the following terms: donor derived, donor infection, solid organ transplantation, and rabies.

In developing countries, rabies is a common cause of encephalitis.
The most frequent route of rabies virus acquisition occurs after bite or exposure to fluids of animals with rabies infection.

There are no serological techniques regarding donor screening that can identify rabies virus infection.

Rabies transmission by corneal transplantation has been described on at least 8 occasions, but transmission by solid organ transplantation was not described until 2004 [191].

Since that date, four cases of multiple organ transmission by rabies virus to several recipients have been reported. In three of these four cases of multiple organ transmission, it was identified in the epidemiological investigation, that three infected donors had a history of bites by animals infected with the rabies virus[192–195].

The evolution after transmission during organ transplantation (13 recipients from four donors), four of them survived, one of them with a history of vaccination and the other three after being vaccinated for rabies following the abovementioned transmission[193,196].

15. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN RELATION TO A DONOR WITH SUSPECTED WEST NILE VIRUS (WNV) INFECTION?

A. Transmission risk: RL1.

B. Recommendations
- Screening should be based on the donor's epidemiological background (stay in areas where there are cases of WNV transmission to humans in the previous 28 days) since most infections are asymptomatic. BII.
- It is recommended to evaluate PCR screening in those donors with epidemiological risk and/or compatible symptoms, in case of:
    - Stay, travel or blood product transfusions during activity periods in areas with active WNV transmission (May to November in the northern hemisphere). BII.
    - History of febrile syndrome with or without neurological symptoms during stay in areas of active WNV transmission. BII.
    - Donors with fever and encephalopathy at the time of donation and epidemiological history of potential exposure to WNV. AII.
    - History of diagnosis of WNV infection. AII.
- If viremia or documented WNV infection is detected within the previous 28 days, organ donation should be ruled out. AII.
- If screening is not possible and there are epidemiological risk factors or a medical history within the previous 28 days, organ donation should be rejected. BII.

C. Notes
A search was made in PubMed with the following terms: donor derived, donor infection, solid organ transplantation, and West Nile.

The most frequent transmission mechanism to humans is by infected mosquito bites. 80% of infected people remain asymptomatic; only 1% have neuroinvasive disease. In Europe, the WNV circulation season is from June to November, and about 200 cases have been reported annually in European Union (EU) countries, with Italy being the country with the highest number of cases[197].

There are well-documented cases of West Nile virus transmission by organ transplantation.

Transmission by solid organ transplantation was first reported in 2002[198].

To date, more than 20 transmission cases have been reported from donors[199]. Infection through this route of transmission is associated with a high incidence of neuroinvasive disease (70%) and high morbidity and mortality (30%). The median time from transplant to the onset of symptoms was 13 days (range: 5-37 days). The most frequent form of presentation was the onset of unexplained fever and the rapid onset of neurological symptomatology.

The infection was transmitted to 87% of recipients of organs from donors with documented active infection. All donors, except one, were asymptomatic. In retrospect, only four (50%) of the eight donors were positive for serum PCR and only three of them (38%) were positive for WNV IgM[199].

EU screening recommendations have been developed for donors in areas of high WNV prevalence[200,201].

Laboratory studies for diagnosis of infection include WNV detection by serum IgM and IgG and CSF and viral load detection by PCR[202].
The screening technique used for detection of viremia is by means of nucleic acid detection techniques with semi-automatic or automatic systems, although cases of donor transmission and negative blood PCR have been described.
These cases suggest that the virus concentration in the tissues may remain after the viremia has cleared or in case of viremic levels below the detection threshold[203].

16. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN CASES OF SUSPECTED DENGUE VIRUS INFECTION?

A. Transmission risk: RL1.

B. Recommendations
- Adequate donor screening in case of epidemiological risk factors within 28 days prior to transplant. BIII.
- For screening, NS1 antigen detection, PCR and NS1 IgM antibody detection are recommended. AII.
- In the case of a donor with acute dengue infection (NS1 antigen and/or positive PCR), donation should be ruled out. AIII.

- If the donor has positive IgM serology as the only screening marker, the risk-benefit ratio associated with the transplant should be assessed, given the difficulties of interpretation about the time of infection, and inform the recipient about the possible effects. CIII.

C. Notes

A search was made in PubMed with the following terms: donor derived, donor infection, solid organ transplantation, and Dengue.

Dengue virus is a *Flavivirus* with high prevalence in tropical Asia, especially in Southeast Asia and South America. It is estimated that 50-100 million cases of dengue occur annually. It is a vector-borne infection by *Aedes* mosquito bites

Most infections are asymptomatic or cause a febrile syndrome of moderate intensity. A percentage of cases evolve into severe or hemorrhagic forms.

In addition, there are other non-vector transmission routes: vertical transmission, transmission by transfusion of infected blood products, by accidental punctures with infected blood or material and transmission by transplantation[204].

Graft transmission cases are rare, because for the transmission to occur from infected organs, the donor must be in its viremic period, which is very short.

The infection effect on the recipient and on the graft function when the transmission route is through the graft is not well known.

Three cases have been associated with graft transmission, in all cases from living donors. In these cases, the infection was presented right after the transplant, in the first week, and the presentation was with fever and liver disorders. The diagnosis was made by NS1 antigen detection. The evolution was favourable in two cases[205–207].

The interpretation of a positive IgM serology as the only marker of acute infection is complex, as it usually appears after 5 days from the onset of symptoms but remains detectable between 2-3 months.

17. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN CASES OF SUSPECTED LYMPHOCYTIC CHORIOMENINGITIS VIRAL INFECTION?

A. Transmission risk: RL1.

B. Recommendations

- The sensitivity of the tests available for diagnosis is not appropriate for routine donor screening.
- Draw an epidemiological history of the exposure or contact of the donor with rodents and evaluation of clinical symptoms. BIII.
- In case of high suspicion of LCMV infection (previous exposure and compatible symptoms), donor should be excluded. AII.

C. Notes

A search was made in PubMed with the following terms: donor derived, donor infection, solid organ transplantation, and choriomeningitis.

Lymphocytic choriomeningitis virus (LCMV) is an Old World *Arenavirus* transmitted by rodents, which can cause asymptomatic or mild disease in healthy non-immunosuppressed adults.

The infection is sporadic in humans, and usually of benign course. Humans become infected by direct contact with rodents or by aerosols from rodent secretions. Cases of vertical transmission have also been described. In relation to transplantation, five cases have been described so far by multiple organ transmission of LCMV (17 recipients). Of these, ten recipients died from LCMV infection-related causes[208–213].

In all cases of multiple organ transmission, except one of them, it was found that donors had been exposed to rodents in the retrospective epidemiological research.

18. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN CASES OF SUSPECTED CHIKUNGUNYA VIRUS INFECTION?

A. Transmission risk: RL1.

B. Recommendations

- Perform donor screening of tissues (B-II) and organs (B-III) if any of the following situations exist in the previous 28 days: stay in areas affected by the epidemic, previous Chikungunya virus (CHIKV) infection or signs and symptoms of active infection at the time of donation. BII.

- PCR (RT-PCR) should be used as a screening technique (blood and tissues). AII.
- Donors with positive PCR should be excluded from organ and tissue donation. BII.
- Donation should be refused in those cases with a history of previous CHIKV infection in the previous 28 days. BIII.
- People without active infection and epidemiological risk history may be donors if molecular tests have been carried out to rule out the infection. BIII.

C. Notes

A search was made in PubMed with the following terms: donor derived, donor infection, solid organ transplantation, and Chikungunya.

CHIKV is an Alphavirus transmitted by the *Aedes* mosquito. Since 2004, CHIKV has caused outbreaks in the Indian Ocean region and has spread to new areas, such as Europe, the Middle East and the Pacific.

CHIKV infection is benign, with a self-limited febrile syndrome, with headache and myalgia. In addition, it is characteristically associated with osteoarticular manifestations such as arthralgia, arthritis and tenosynovitis.

The evolution of CHIKV infection is usually benign in healthy people although in people with comorbidities or immunosuppression it can take an atypical and serious course with associated mortality[214,215].

During the CHIKV outbreak in the Reunion Island, 69 potential cornea donors were analysed. Seventeen percent (17%) of donors were viremic and/or were positive for IgM and/or IgG. In a third of them, their corneas were infected. CHIKV ocular inoculation caused systemic infection. Transmission of viral infection via the eye was demonstrated in an animal model with human CHIKV infection. The transplanted cornea must contain viral particles for the viral transmission to occur. The usual methods of corneal preservation do not eradicate the viral particles present in the eye tissue[216].

The findings described in the cornea transplant are relevant for organ transplantation and an active screening by PCR should be performed of the organs and tissues in the areas where there is CHIKV activity, in organ donors with a history of travel or recent stay in areas of CHIKV outbreaks.

In 2007, after an outbreak in Italy, the EDCD/WHO developed recommendations for the donation and transplantation of organs and tissues regarding the risk of infection and transmission of CHIKV in situations of epidemic outbreaks[217].

19. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN CASES OF SUSPECTED ZIKA VIRUS INFECTION?

A. Transmission risk: RL1.

B. Recommendations

- Microbiological screening for the donor, given the possible risk of transmission in certain epidemiological contexts. BIII:
  - Within 28 days prior to:
    i. Travel or residence in areas with Zika virus transmission (ZIKV),
    ii. Transfusions of blood products
    iii. Presence of related symptoms.
  - Within six months prior to:
    i. Unprotected sex with people who live or have recently been in areas with ZIKV transmission.
- Microbiological screening, if available, by PCR in blood and urine. BIII, in people with epidemiological risk factors.
- If PCR positive, it is recommended to refuse the donation. AIII.
- In case of documented infection, do not accept organs or tissues for transplantation until 6 months after resolution of symptoms. BIII.
- In the case of negative PCR, but epidemiological risk factors in the previous 28 days, consider donation after risk assessment and benefit of the potential risk of infection derived from the donor and informed consent in the following situations. CIII.
- If it is not possible to perform the screening and in case of the epidemiological factors abovementioned, it is recommended to:
  - In asymptomatic donors, consider donation after risk assessment and benefit of the potential risk of donor-derived infection and informed consent. CIII.
  - In symptomatic donors, whose symptoms cannot be explained by alternative diagnosis, it is recommended to refuse donation. BIII.

C. Notes

A search was made in PubMed with the following terms: donor derived, donor infection, solid organ transplantation, and Zika.

Zika virus is a *Flavivirus* whose main transmission route is vector-borne, through the *Aedes* mosquito bite. The clinical presentation of the infection in most people is asymptomatic. Since 2014, there has been an epidemic originating in Brazil, with local extension and transmission in more than 70 countries in the Western Hemisphere, including South America, Central America, Mexico and the Caribbean[197].

The infection has been spreading and cases appear after trips to areas with ZIKV outbreaks, demonstrating the risk of expansion and introduction into areas with

competent vectors as well as the potential risk of non-vector transmission[218]. Since June 2015, more than 1900 cases have been reported in the EU. Sexual transmission has been documented in five European countries[219].

During the evolution of the epidemic, complications potentially associated with Zika have been described, such as microcephaly in newborn babies or cases of Guillain-Barre syndrome, and encephalopathy [220–224].

Other non-vector transmission routes have been described, such as vertical transmission, sexual transmission[225–227] and cases related to transfusion of infected blood products[228]. During the epidemic in French Polynesia, 3% of blood donors had been tested PCR positive for Zika[229]. Some cases related to transfusion of blood products have been reported[230,231].

No cases of Zika virus have been reported in transplant recipients, although they are likely to appear considering the number of transplants performed in the affected areas and international travel.

The evolution and potential complications that the infection would have in a immunocompromised patient is unknown[232]. A small series of four cases of patients infected with Zika virus after transplantation has been published. All of them were hospitalized, with longer stays than immunocompetent patients and had liver and kidney failure. There was no related death[233].

The potential risk of ZIKV transmission from donors is unknown, and there are no rapid and accessible techniques in most centres that allow screening.

Diagnosis can be made by PCR in blood in the first 5 days from the onset of symptoms and/or in urine in the first 14 days after the onset of symptoms. It is worth noting that the elimination of the virus in semen or urine seems to take longer[234]. The time that the virus persists in the tissues is unknown.

In some countries, different transplantation organisations have developed an informative guide with recommendations on the possibility that there may be donors with Zika virus infection, both deceased donors and living donors[235,236]. Table 8 shows the proposed recommendations for screening and donation of the organs from these donors.

The risk-benefit ratio should be analysed when deciding whether to transplant organs from a donor with Zika infection. It is advisable to discuss the situation of unknown

transmission risk with the recipients, as well as a close follow-up in the first months following the transplant. It is recommended, in case donation takes place, that an informed consent form is signed, given the uncertainties that exist at the present time about risk of transmission, effect of the infection in the recipient and the time that the virus can remain as well as its behaviour.

Table 8. Proposal for screening recommendations in the transplant donor for Zika virus

Deceased donor in areas without active transmission	
Asymptomatic donor with a history of travel to Zika transmission areas in the previous 4 weeks	Consider donation after risk assessment and benefit of the potential risk of donor derived infection and informed consent
Asymptomatic donor with a history of unprotected sex with men who have been in areas of Zika transmission in the previous four weeks	Consider donation after risk assessment and benefit of the potential risk of donor derived infection and informed consent
Donor with symptoms suggestive of Zika infection and travel to area with active transmission in the previous 6 months	Do not use organs of a donor unless the symptoms can be attributed to a condition other than Zika virus and this condition has no contraindications.
Donor with history suggestive of Zika infection and history of unprotected sex with men who have been in areas of active transmission in the previous 6 months	Do not use organs of a donor unless the symptoms can be attributed to a condition other than Zika virus and this condition has no contraindications.
Deceased donor in areas of active transmission	
Asymptomatic donor	Consider donation after risk assessment and benefit of the potential risk of donor derived infection and informed consent

XI. CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest.

XII. ACKNOWLEDGEMENTS

XIII. REFERENCES

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XIV. ANNEX I

Alliance-O classification of risk levels in relation to disease transmission:

1. Unacceptable risk (RL1): absolute contraindication, with the exception of some transplant procedures to save lives in the absence of other therapeutic options based on a case-by-case assessment.

2. Increased but acceptable risk (RL2): includes cases in which microorganisms or communicable diseases are identified during the donor evaluation process, but the use of organs is justified by the specific situation or severity of the clinical situation of the donor. receiver.

3. Calculated risk (RL3): includes all cases in which, even in the occurrence of communicable diseases, transplantation to recipients with the same disease or with a serological protection status is allowed, in cases of infection in the treated donor properly with a minimum duration (24 hours).

4. Non-assessable risk (RL4): includes cases in which the evaluation process does not allow an adequate risk assessment for communicable diseases.

5. Standard risk (RL5): includes cases in which the evaluation process did not identify a communicable disease.

XV. ANNEX II

Classification of the recommendations in the consensus document based on the strength and quality of the analysed evidence:

Recommendation strength

Level A: Good level of evidence to support the recommendation for use.

Level B: Moderate level of evidence to support the recommendation for use.

Level C: Little evidence to support the recommendation.

Recommendation quality

I: Evidence from at least one randomised clinical trial.

II: Evidence from at least one non-randomised, well-designed trial, either from cohort studies, or from case-control analytical studies (preferably from more than one center), or from time series, or from conclusive results obtained in non-controlled experimental studies.

III: Evidence of expert opinions based on clinical experience or descriptive studies.