Transmission of infectious agents from the donor to the recipient.

Do we need a change in the risk assessment?

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The article discusses possible risks of bacterial, fungal, and viral infections for a recipient through organ transplants. The paper defines the infectious diseases being contraindications to an organ donation and the recipient and donor diseases in which the donor organs can be used.

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One of the most important tasks in the prevention of infectious complications in a recipient is to eliminate the transmission of infectious agents through donor organ transplantation. The solution of this task is someway difficult due to limited chances to take a detailed medical history and make a broad spectrum of laboratory diagnostic tests in a potential donor. Standardized common approaches to assess potential organ and tissue donors would provide an effective tool for preventing donor-derived infectious diseases in transplant recipients.

Specifically, the implementation of an established set of serological tests may eliminate the risk of infection transmission to the recipient via parenteral route [1–4].

According to the National Clinical Guidelines "Postmortem Organ Donation" adopted in 2013, obligatory tests to be made in a potential donor include: tests for antibodies to human immunodeficiency virus (anti-HIV), for hepatitis C virus (anti-HCV), for the surface antigen of hepatitis B virus (HBsAg), for antibodies to cardiolipin (RPR-screening test for the diagnosis of syphilis), and for total antibodies to Treponema pallidum antigen (EIA Ig M + Ig G) [4].

The risk of infecting a recipient is associated with both the host tropism of a pathogen, and vector-borne infectious strains, however, available data on pathogens (even the known ones) are limited to determine accurately the probability of their infecting a recipient. Therefore, it is necessary to use the most informative advanced microbiological techniques for the diagnosis of infections caused by pathogenic microorganisms.

Timely diagnosis of pyo-septic complications in potential donors being in the ICU is of great importance both for their effective treatment, and for determining contraindications to organ donation in case of stating their brain death [4].

Bacterial and fungal infections

Absolute contraindications to using donor organs for transplantation include the presence of the following in a potential donor:

- Active tuberculosis;

- Unknown CNS infections, encephalitis or meningitis;

- Invasive fungal infection.

The fungal infection is the most dangerous. If it is diagnosed retrospectively, this information should be immediately reported to the transplant center. In this case, the recipient must be administered an

antifungal therapy with echinocandins or amphotericin B lipid complex [5–7].

In pancreas transplantation, the duodenum is a part of the graft complex and may often be contaminated with fungi of *Candida spp.,* especially in patients who have long stayed in an Intensive Care Unit (ICU). Donors staying in an ICU for over 5 days should be considered as potential sources of fungal infection. Candidiasis infections in recipients are rather frequent and aggressive. Aimed at reducing the risk of their development in the postoperative period, most transplant centers have established protocols dictating the donor's duodenum shall be washed with amphotericin B through nazointestinal tube during organ explantation. A preventive irrigation of the recipient's abdominal cavity with this agent is also performed prior to surgery completion [8, 9].

Given a potential donor stay in the ICU (especially for over 5 days) is always associated with pathogenic contamination, bacteriological cultures are strongly recommended. In this case, broad spectrum antibiotics should be administered to the recipient from the start of surgical procedure, without waiting for bacteriological culture results.

Currently, hospital ICUs are facing the increase in the number of patients with infections caused by Gram-negative pathogen strains with multiple drug resistance. In case of such infections, the post-transplant recipient mortality rates may exceed 70% [10]. Therefore, when detecting an asymptomatic contamination of donor with carbapenem-resistant strains one must carefully assess the appropriateness of organ harvesting. During organ transplantation from the donor contaminated with these pathogens, the antibacterial therapy is recommended to the recipient and must be performed with this regard [11].

When a potential donor is diagnosed with the bacteremia caused by low-virulent microorganisms, the organs can be safely harvested for transplantation [12].

In case of diagnosing the donor sepsis caused by multiresistant pathogens (methicillin-resistant Staphylococcus aureus [MRSA], Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa, etc.), the decision is made on an individual basis. Organs may be retrieved for transplantation only in case of a confirmed sensitivity to antibiotics and the administration of an appropriate antibiotic therapy to the recipient. Organ donors should be evaluated for Staphylococcus aureus, specifically the donors staying in the ICUs where the pathogen was a common cause of nosocomial infection. However, the MRSA isolation from cultures without clinical signs of sepsis is not a contraindication to organ donation.

Multiple organ failure due to a severe sepsis in a potential donor is a contraindication to organ retrieval for the transplantation purpose.

The presence of antibodies against Treponema pallidum detectable by enzyme immunoassay used to be a contraindication to donation before [13]. However, the accumulated experimental and clinical experience gave the chance to change this view and to expand the indications to using such donor organs. Most authors consider it acceptable to explant organs from a donor with a syphilis pathogen if the donor's organs are not affected by the disease. In this case, a specific antibiotic therapy with penicillin is obligatory for the recipient starting intraoperatively [14]. F.Caballero (1998) described a safe transplantation of organs from a 63-year-old donor infected with Treponema pallidum (++++) [15]. An empirically assessed risk of transmitting the infection does not exceed 0.15%. However, even such a low risk is practically reduced to zero in the conditions of retrieval and preservation of

donor organs. To date, according to UNOS, there have been no cases of donor-derived syphilis in organ transplant recipients.

Viral infections

Detection of *human immunodeficiency virus* (HIV) antibodies in a potential donor is a contraindication to organ donation.

Herpesvirus types such as *Cytomegalovirus* (CMV), *Epstein-Barr virus* (EBV), and *Varicella-zoster virus* (VZV) are very widespread. Almost the entire adult population of the Earth may get infected with them in their lifetime. In this case, 35–80% of the population have immunoglobulin G (IgG) antibodies to CMV. The presence of these antibodies in a donor indicates that organs can be used for transplantation without restrictions. A potential for the prevention and treatment of CMV-virus infection in a recipient make CMV-infected organs quite eligible for transplantation. At the same time, we should emphasize that the development of CMV-infection after surgery may cause organ dysfunction of the liver, kidney, lung and gastrointestinal tract; and in case of a reduced immunosuppressive therapy it may promote an acute rejection crisis.

As for the EBV, the presence of IgG antibodies to EBV in a donor is not regarded as a serious obstacle to organ transplantation. EBV infection responds well to therapy with either acyclovir, or ganciclovir. An exception may be the donors with an active EBV infection at the moment their brain death is stated if their organs are considered to be used for pediatric transplantation.

Most of the world's population gets VZV infection in early childhood. An active VZV infection in the donor or recipient may lead to such complications as hemorrhagic pneumonia, encephalitis, disseminated

intravascular coagulation, and hepatitis that preclude from using the organs for transplantation; the same regulation is applied to measles and mononucleosis.

If HBsAg is detected in a donor, the organs shall not be used for transplantation. Testing for IgM antibody against hepatitis B core antigen (IgM anti-HBc) is appropriate, and a positive IgM anti-HBc test result must be regarded as a contraindication to liver transplantation, the same shall be applied to the entire spectrum of serological markers of hepatitis B (anti-HBs, IgM anti-HBc, IgG anti-HBc, HBe-Ag, anti-HBe).

Isolated anti-HBs revealed by a virological test in a potential donor means that the person was either previously vaccinated against hepatitis B, or received a therapy with a specific immunoglobulin (HBIg) in the recent past. Such donor organs can be safely used for transplantation.

In cases of a spontaneous recovery from hepatitis B (that happens in about 90% of cases), the patient will be positive for IgG anti-HBc, alongside with positive results for anti-HBs, in the vast majority of cases. If the donor serologic tests are positive for anti-HBc (with or without simultaneously being positive for anti-HBs, the risk of HBV infection to be transmitted to a "liver" or "extrahepatic" organ recipient is rather high.

According to current strategies, donors should be tested for HBsAg and anti-HBc. In case both tests are negative, the donor is considered as being absolutely safe in relation to HBV infection. If the donor is HBsAg-negative, but anti-HBc-positive, additional tests are required. They detect IgM and IgG antibodies to Hepatitis B core antigen. The presence of IgM anti-HBc indicates an acute or recent hepatitis B which is a contraindication to organ donation. In case the IgG anti-Hbc is detected in a potential donor,

then this donor's organ may only be transplanted to a HBsAg-positive recipient.

A liver retrieved from anti-HBc-positive donors should be used for transplantation only in those recipients who are positive for anti-HBs and/or anti-HBc or who are listed as high-urgency UNOS status 1 (critical care patients) on the waiting list, regardless of the presence or absence of hepatitis B markers [16].

Chang et al. reviewed 377 liver transplantations in patients with the terminal stage of hepatitis B-related liver disease. All 377 patients received an allograft from anti-HBc-positive donors. Patient and graft survival rates at 5 years were 73% and 71%, respectively, compared to 81% and 75% survival rates when using the liver grafts from anti-HBc-negative donors. Five-year recipient and graft survival rates among those who received a combination therapy (HBIg and lamivudine) to prevent the graft HBV infection were 88% and 84%, respectively, being significantly higher compared to those survival rates reported for the cases of preventive monotherapy or no therapy [17] .

Liver transplantation from an anti-HBc-positive donor entails the need of a long-term preventive administration of entecavir and HBIg to the recipients having no markers of recent hepatitis B or no post-vaccination protective level of anti-HBs.

Meanwhile, the test for HBs-Ag has been the only test that is obligatory required in the Russian Federation to detect the presence of HBV infection. This implies the use of the entire donor pool of patients, including the donors with a previous history of hepatitis B.

The presence of antibodies against hepatitis C virus (HCV) is a contraindication to organ donation in the Russian Federation; however, in

many countries, these donor organs have been used for transplant recipients infected with hepatitis C, but always with regard to the virus genotype.

A lot of studies have shown that the use of organs from a HCV-infected donor does not adversely affect the outcome and long-term results of liver transplantation [18, 19].

Currently, most of the centers support the possibility of liver transplantation from donors positive for HCV antibodies to recipients with HCV-related liver cirrhosis. A prerequisite for liver transplantation from a HCV-positive donor is a thorough preoperative evaluation, including graft histology to assess the liver parenchyma damage caused by HCV-infection (by Ishak/Knodell Score). Marroquin et al. compared the orthotopic liver transplantation (OLT) outcomes between 96 HCV-positive recipients of HCV-positive grafts and 2827 comparable HCV-positive recipients of HCV-negative grafts. The recipient and graft survival rates in the long-term period after surgery were similar between the groups [20].

Rare infections

Several infections pose risks that may contribute to the development of post-transplant complications in some situations.

In the recent decade, the risk of being infected, including that for potential donors, has grown up due to a rapid development of tourism to regions with endemic foci.

Donor blood tests for malaria antibodies should be considered when retrieving organs from the donor who has recently traveled to a malaria-endemic area. The risk of West Nile virus and Q fever (Coxiella burnetii) transmission is insignificant, so the routine testing of donors is not justified. The exclusion of the donor may be considered in case of an evident clinical

presentation of the disease. Leishmaniasis is a contraindication to organ donation, despite a small risk of transmission [21, 22].

CONCLUSION

Identification of donors having infectious risks for a recipient is a difficult task. The risk of donor-derived infections in organ and tissue transplant recipients exists and that requires an improvement of safety mechanisms including the use of modern laboratory techniques for detecting bacterial, fungal, and viral infections in a potential donor. Meanwhile, organs from infected donors that can be transplanted without the risk to a recipient would increase the number of transplant procedures.

Donor evaluation algorithms should be improved basing on current research findings, and regular changes should be made in organ donor screening programs for an effective use of the donor pool.

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