

Update on the infection of the immunocompromised patient

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Infection in the process of organ donation

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ABSTRACT

The difference between demand and supply has led transplant organizations to look for marginal donors, including those who could transmit infections to their recipients. This potential risk must be thoroughly evaluated to optimize the use of such organs without increasing the incidence of graft dysfunction and the morbidity and mortality of the recipient. This article aims to provide a general and up-to-date overview of this issue.

Keywords: organ transplantation, donor, transmission, infection

INTRODUCTION

Solid organ transplantation (SOT) is the treatment of choice for many patients with terminal diseases. Although the number of patients on the waiting list has more than doubled since 1998, the number of transplants has increased by only about 30% [1]. Therefore, there is a need to increase the number of donors. On the other hand, infectious complications continue to be the main cause of morbidity and mortality after SOT. Some of these complications are caused by pathogens transmitted by the transplanted organ. In fact, transplant physicians have traditionally avoided the use of donor organs with a known transmissible infection or with an increased risk of carrying it despite negative serological tests. However, with the increased availability of tests based on the detection of nucleic acid in real time, the period during which an early viral infection could be overlooked has been greatly reduced and, so, the possibility of transmission. The underutilization of such organs seems to be even more relevant given the fact these

donors are frequently younger and with lower comorbidity than other donors. In any case, the rigorous examination of the donor to detect latent and active infections is essential to optimize the results after the transplant and serves to prevent the involuntary use of inadequate organs and the prophylaxis directed against the infection or the preventive therapy or the surveillance measures of infections after transplant.

EPIDEMIOLOGY

There are two types of transmission of an infection from the donor to the recipient: the expected and the unexpected one. The expected one is frequent, it is known before the procedure, we have prophylaxis for it or, in any case, it is controllable. An example would be the transmission of cytomegalovirus from a seropositive donor to a seronegative recipient. On the other hand, we have the unexpected transmission. It is infrequent, we do not recognize it before the transplant, we do not usually have effective treatment or prophylaxis for it and, therefore, it has high morbidity and, even, mortality. An example of this would be the transmission of a West Nile virus infection from a donor who died of encephalitis without diagnosis prior to transplantation. It is on the unexpected transmission that we have to concentrate all our efforts to avoid it. However, and to start with, the information that we have about this concern is limited. First, there are no universal standards for donor evaluation and each society publishes its own recommendations [2–4]. Second, sometimes, it is difficult to differentiate the infection derived from the donor from the recipient's own, especially in the case of latent infections. Third, not all the cases of donor-derived infection (DDI) are published. Since there are no protocols or mandatory reporting systems, there is publication bias. Physicians tend to publish the cases of transmission but not the cases of donors with infection, but without transmission. Finally, most publications are case reports and retrospective literature reviews. The few cohort studies, whether prospective or retrospective, place the

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transmission of the infection from the donor to the recipient around 1% but with a lethality of 40% [5, 6].

CAUSES OF UNEXPECTED TRANSMISSION OF INFECTION

There are several causes that lead to the unexpected transmission of an infection. The first one is the asymptomatic latent infection not diagnosed in the donor. It usually happens when an adequate screening is not performed. As an example, with the current migratory movements, we should not neglect the screening of geographically restricted infections to which the transplant physicians are not familiar [3, 7]. On other occasions, it is the screening tests that fail. The result of a given serology is affected by the haemodilution that potentially donor patients suffer when they require infusion of crystalloids or blood products. In some cases, the haste of the donation decreases the time available to perform the screening tests. In no case should confirmatory diagnostic tests be used as screening because, although they increase specificity, they lack sensitivity enough to rule out infection. Finally, the tests will not be positive immediately after infection. It will take several days from the contact to the detection of the infection. In the case of the serology, that determines the production of antibodies, this time is called the window period. Currently the possibility of identifying the presence of nucleic acids of microorganisms by polymerase chain reaction reduces this time. This is what is called the viral eclipse phase. Thus, the possibility of diagnosing an infection by the human immunodeficiency virus (HIV) decreases from 22 to 9 days and that of the hepatitis C virus (HCV) from 66 to 7 days [8].

The second cause of unexpected infection transmission is the absence of diagnosis of an active infection as the cause of death. This situation is especially worrying and mostly related to the absence of diagnosis of deceased donors with encephalitis. Transmission of rabies virus, lymphocyte choriomeningitis virus or West Nile virus usually leads to the death of the recipient due to the lack of an early diagnosis and the absence of targeted treatment [9]. In parallel, the donor may suffer an infectious complication during admission to the intensive care unit that is not diagnosed prior to transplantation in relation to the invasive procedures to which they are subjected. An example of this situation would be occult bacteraemia [10]. Hence, it is essential to obtain blood cultures at the time of donation. In case of positivity, it is compulsory to prescribe antibiotic treatment in the recipient with the intention of minimizing the possibility of DDI.

The third cause of unexpected transmission of infection from the donor is the contamination of preservation fluids. A recent meta-analysis has shown that the contamination of the preservation fluid can reach 90% [11] but with a low transmission incidence, around 1%. However, such transmission may compromise the functionality of the graft and the life of the patient, especially in the case of the transmission of yeasts or multidrug resistant microorganisms [11, 12].

PREVENTION

It is very important to get a good clinical history of the donor that includes the occurrence of previous infections, vaccination, travel, transfusions of blood products, contact with

Test	Before transplant	Comments
HIV p24 Ag	Always	
HIV Ab	Always	
HBs Ag	Always	
HDV Ab	If HBs Ag +	
HBe Ab	Always	
HBs Ab	Always	
HCV Ab	Always	
Syphilis (CLIA)	Always	If +, perform reagin and treponemal tests
HTLV I/II Ab	Always	If +, confirm by Western-Blott
<i>Trypanosoma cruzii</i> Ab	Selected	In donor of risk zone or descendant in case of heart transplant
CMV Ab	Always	
HIV NAT	Selected	High-risk donor
HCV NAT	Selected	

Ab: antibody; Ag: antigen; CLIA: chemiluminescent immunoassay; CMV: cytomegalovirus; HBs: hepatitis B surface; HBe: hepatitis B core; HCV: hepatitis C virus; HDV: hepatitis delta virus; HIV: human immunodeficiency virus; HTLV: human T-lymphotropic virus; NAT: nucleic acid testing

people with transmissible diseases such as HIV or HCV, sexual habits, and the use of illicit drugs, among others. This information is not always easy to obtain given the circumstances of the act of the donation and that the interview, mostly, will be made to relatives. In any case, this information is required to define a donor as "high risk" [13]. In this type of donor, it is essential to expand the range of diagnostic tests initially recommended for the assessment of the suitability of the procedure (table 1). If, finally, we decide to go ahead, we must inform the recipient of the risks, request an informed consent and closely monitor the recipient in the event of a probable unexpected transmission [14].

Present. As experience is continuously accumulating, better results are observed with donor organs that, in the past, were considered contraindicated. Nowadays, donors with septic shock or multi-organ dysfunction of bacterial origin can be considered, including the heart, provided donors receive adequate antibiotic treatment for a minimum of 24 hours that it is continued in the recipient [15]. Donors with HIV infection can donate their kidneys to recipients with HIV infection as long as the infection is controlled and there are different choices for HIV treatment [16]. Donors with viremic HCV infection can donate kidneys, lungs and heart with similar results to donors without HCV infection because recipients can now be treated with the new direct-acting antiviral agents against HCV infection which are pangenotypic and without interactions with immunosuppressants (calcineurin and mTOR inhibitors) [17, 18]. To update the information in relation to this topic, the Spanish Organización Nacional de Trasplantes (ONT) has published on its website a consensus document in collaboration with different Spanish Scientific Societies [19].

Future. In order to continue advancing in the prevention of DDI we can act on different directions. By improving the screening of infections in donors with the use of faster and more sensitive and, at the same time, more specific tests, such as techniques based on the polymerase chain reaction or mass spectrometry (MALDI-TOF). By shortening the response times of the tests from obtaining the sample to its result with the implementation of point-of-care tests. By involving all the professionals in the decision making related to the transplant in a multidisciplinary team that includes the specialist in Infectious Diseases. By improving communication between all the levels involved (coordination, microbiology, transplant teams) in case of recognizing a risk in a specific donor-recipient procedure so that the information arrives without loss of time to the rest of the related transplantations. And, finally, by creating standardized and mandatory notification systems with the intention of obtaining the maximum possible information that allows us to convert the transmissions of infection not expected into preventable ones. In that sense, initiatives such as the Notify Library (www.notifylibrary.org) promoted by the Centro Nazionale

Trapianti di Italy in collaboration with the World Health Organization (WHO) are essential.

CONCLUSION

Although the infection derived from the donor is an infrequent event, its severity is potentially high. The improvement of screening tests is vital to advance in the prevention of transmission. However, once it occurs, the best way to improve its prognosis is to recognize it as soon as possible. And, for this, it is essential to have the mechanisms that ensure the communication within and among transplant teams in a timely manner. However, in spite of everything, the risk of transmission will never be zero.

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