Pretransplant Evaluation for Infections in Donors and Recipients of Solid Organs

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The risk of infectious disease reactivation in recipients of and transmission by solid-organ transplants remains, and thorough screening and testing of recipient and donor is especially important. In conceiving screening strategies, it is crucial to consider the sensitivity and specificity of individual diagnostic tests in the context of their use. Furthermore, recognition of special risks for infectious complications of transplantation will help to guide preventive, diagnostic, and therapeutic steps in the control of infectious complications in individual patients. The acceptability of risks for infectious complications after transplantation depends also on the urgency of transplantation of a vital organ as well as the availability of organs. Although these principals are well accepted, standards for the extent of screening and criteria for inappropriate donors and exclusion of unfit recipients remain controversial to some extent.

It is universally accepted that donors and recipients of solid organs should be screened for infections, to eliminate unsuitable donors and recipients who would not appropriately gain from transplantation. Furthermore, recognition of special risks for infectious complications of transplantation will help to guide preventive, diagnostic, and therapeutic steps in the control of infectious complications in individual patients. Although these principles are well accepted, standards for the extent of screening and criteria for inappropriate donors and exclusion of unfit recipients remain controversial to some extent.

Various factors affect the screening strategy in organ donors (table 1) and recipients (table 2) and the decision on when not to perform a transplantation. The acceptability of risks for infectious complications after transplantation depends also on the urgency of transplantation of a vital organ as well as the availability of organs.

In conceiving screening strategies, it is also important to consider the sensitivity and specificity of individual diagnostic tests in the context of their use. In screening donors, it might often be preferable to use a test with a high sensitivity, in order to avoid an inadvertent transmission by transplantation. On the other hand, a test with a high specificity might be more appropriate in recipients, in order not to dismiss the possibility of a primary infection on the basis of false-positive test results.

DONOR SCREENING

General measures. A complete medical history of the donor should be obtained by the organization procuring the organs, with a particular focus on vaccinations, infections, and unusual exposures (residence in endemic areas, travel, drug use, risky sexual behavior, incarceration). Viruses, bacteria, fungi, parasites, and prions have all been transmitted from the donor to the

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Clinical Infectious Diseases 2001; 33(Suppl 1):S9–14

1058-4838/2001/3301S1-0003$03.00

Table 1. Factors governing screening of solid-organ donors.

Agent	Prevalence in donors	Screening efficient	Transmission rate	Potential damage	Preventive/ therapeutic options
Cytomegalovirus	0.5	Yes	>80% in R−	Low to high	Both
HIV	Low[a]	Yes	>90%	High	Limited
Human T cell lymphotropic virus type 1	Low–15%[a]	50% false positive	Not shown; very likely	High	Experimental
Toxoplasma gondii	10%–75%	Yes	Heart ~50% in R−	Low to high	Both
Epstein-Barr virus	>90%	Yes	>80% in R−	None to high	Experimental
Hepatitis B virus	Low[a]	Yes	High	Low to high	Limited
Hepatitis C virus	1%–7%	Yes, false positive	50% or 100%	None to high	Limited
Syphilis	Low[a]	Yes	Not shown; likely	? to low	Both
Mycobacterium tuberculosis	Low[a]	No	Shown	Low to high	Both
Prions	Very low[a]	No	?	High	None

NOTE. R−, seronegative recipient; ?, no data available.

[a] Low, <1%.

host with the transplant. Actual clinical infections should be sought aggressively, including microbiologic documentation and, where appropriate, drug-susceptibility testing. Geographic diseases (e.g., endemic mycoses, schistosomiasis, malaria, and babesiosis) require special attention. Donor infections do not automatically preclude transplantation [1] but should be treated adequately before and, in some instances, after transplantation [2–4]. Of particular concern is the presence of infection or colonization with multiresistant pathogens, particularly methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci. Blood cultures should be obtained from cadaveric donors at the time of organ taking (B-II) [5]. For a useful interpretation of serologic results, serum samples should be obtained before mass transfusions of potential organ donors, and the number of transfusions given before collection of the samples should be recorded. It has been advised to perform autopsies on all cadaveric donors, in order to document occult infection in addition to neoplastic disease (B-II) [6, 7].

HIV. Among the most detrimental infections transmitted from the donor to the recipient is the HIV type-1 (HIV-1) infection. The transmission rate is high, regardless of the transplanted organ. By serology, only 1 of 34 recipients of a kidney from an HIV-infected donor remained seronegative 6 months after transplantation. The 5-year survival was 50% for the 61 recipients of HIV-infected kidneys, compared with 85% in uninfected patients, and 35% for 24 reported patients receiving an HIV-infected liver, compared with 63% in the other recipients [8]. Screening of donors with a highly sensitive assay for the presence of HIV antibodies is therefore routine in all centers and is part of all regulations on donor screening (A-II) [9, 10].

Several instances of HIV transmission by transplants from individuals who had not yet seroconverted and were antibody-negative in early primary infection have been reported [8]. Therefore, screening for HIV-1 p24 antigen has been proposed in addition to testing for antibody to HIV-1/HIV-2 [11]. On the basis of the available data, the panel recommends testing for both antigen and antibody (A-II). The diagnostic window can, however, be shortened by p24 antigen testing by only ~6 days. PCR would further shorten this window by another 5 days [12]; however, at least for cadaveric donors of solid organs, the time frame required for PCR frequently does not permit application of this technology. Nevertheless, the panel proposes to test donors for antibody, p24 antigen, and HIV RNA whenever possible (A-III). By applying multiple tests for HIV screening, the problem of false-positive results increases, which leads to a waste of perfectly suitable organs. In an analysis of 500,000 blood donations tested for antibody and p24 antigen, the majority of patients testing positive for p24 antigen were shown to be false-positive [13]. To supplement laboratory testing, the Centers for Disease Control and Prevention guidelines [9] recommend use of the past history of donors to apprehend further the risk of HIV infection escaping laboratory screening (risky sexual behavior, hemophilia, incarceration). These recommendations foresee the information for potential recipients of the possibility of an increased risk of HIV transmission.

Cytomegalovirus (CMV). CMV has been shown to be transmitted by all solid-organ transplants from seropositive donors [14, 15]. The vast majority of seronegative (i.e., immunologically naive) recipients will acquire CMV from kidneys, hearts, lungs, pancreas, or small bowel, procured from seropositive donors, and are at high risk to develop CMV disease within the first months after transplantation or to bear other consequences of CMV infection. Superinfection by CMV from the organ donor to seropositive recipients has been documented by molecular methods [16, 17]. Serologic testing for CMV infection, preferably by IgG ELISA, is regarded as mandatory by all authorities (A-II). The ELISAs or latex agglutination tests used are very sensitive but are hampered by a high rate of false-positive test results, which are estimated to occur in 10%–15%

Table 2. Factors governing screening of solid-organ recipients.

Agent	Prevalence in recipients	Screening efficient	R+/− affects susceptibility	Reactivation or affecting prognosis	Preventive/ therapeutic options
Cytomegalovirus	0.5	Yes	Yes	Low to intermediate	Both
HIV	Low[a]	Yes	No	Intermediate	Limited
Toxoplasma gondii	15%–70%	Yes	Yes	? to low	Both
Hepatitis B virus	Low[a]	Yes	Yes	Low to high	Both
Hepatitis C virus	Intermediate	Yes	Not documented	Intermediate	Limited
Epstein-Barr virus	>90%	Yes	Yes	None	Experimental
Human T cell lymphotropic virus type I	Low–15%[a]	False positive	?	? to low	Experimental
Mycobacterium tuberculosis	Low[a]	No	?	Low to intermediate	Both

NOTE. R+/−, serostatus of recipient; ?, no data available.

[a] Low, <1%.

of cases [11]. Although, in terms of prevention, misclassifying seronegative donors as positive might be preferable over the opposite error, false-positive tests cause unnecessary costs and toxicity of superfluous preventive therapy. The risk of donors acquiring CMV by blood products shortly before organ procurement has been regarded as small (<1%) [11]; however, anti-CMV immunoglobulins passively transferred might taint test results if blood samples are drawn after blood products are given to organ donors. The use of IgM anti-CMV in donor screening has been considered but is not advocated on the basis of the little information gained and the high rate of false-positive results (E-III) [11].

Epstein-Barr virus (EBV). Primary EBV infection through infected organs or transmission of latently EBV-infected blood donor lymphocytes to EBV-negative recipients increases their risk of developing EBV-associated lymphoproliferative disease manifold. Because of the high prevalence of latent EBV infection in the adult population with a pretest probability of a positive test result for EBV IgG of >90%–95%, the increment of information by EBV screening is small. The positive predictive value of anti–Epstein-Barr Virus Nuclear Antigen–1 IgG testing is so high (≤99.8%) [18] that screening can be recommended (A-III).

Hepatitis B virus (HBV). HBV can be transmitted by all solid-organ transplants, but the transmission rate depends on the stage of HBV infection in the donor, the presence or absence of viremia, and/or replication of virus in the liver and presumably on the anti-HBs (antibodies to HB virus surface antigen) immune status of the recipient. Several markers, which reflect the stage and course of HBV infection, permit definition of the risk of transmission. There is agreement that all donors should be tested for HBs antigen (A-I) based on the observation that HB surface antigen (HBs Ag)–positive donors regularly [19, 20], but not always [21], transmit the infection to the recipient. Because anti-HB core antibody (HBc) might be the only marker of early HBV infection or of a continuous circulation of HBV DNA and/or of infective virus in the liver [22], and because anti–HBc-positive donors cannot whereas HBs antigen-negative donors can transmit HBV, even with organs other than the liver [23–25], anti-HBc antibody should be routinely tested in all organ donors (A-I). Some experts also recommend the routine testing of anti-HBs antibody in order to supply further information on the true nature of a positive anti-HBc test and because of a reduced risk of transmission by extrahepatic organs by HBs Ab–positive donors [11] (B-II). Others have found that, regardless of the anti-HBs antibody status, kidneys from anti–HBc IgG-positive, anti–HBc IgM-negative HBs antigen–negative donors can safely be used in recipients with a history of HBs vaccination (even if they are anti-HBs–antibody negative) or HBV infection [24] (B-II). It is intriguing, however, that these authors have noted that, even in the absence of clinically overt HBV infection, several of their patients seroconverted with respect to their anti-HBs status. If time permits PCR for HBV, DNA should be considered in unclear situations [26].

Hepatitis C virus (HCV). HCV is transmitted by 50%–100% of organs from anti–HBC-positive donors to HBC-negative recipients [27–31]. HCV infection usually takes a chronic indolent and slowly progressive course, with cirrhosis and liver failure or liver cancer not developing before 5–20 years after infection [32]. Therefore, the ultimate consequences of transplantation acquired HCV might not yet be evident because the first documented transplantation-associated HCV infection antedates this study by only a few years [33]. Nevertheless, it has been found in a cohort of 29 anti-HCV–negative recipients that received organs from HCV-positive (by first-generation ELISA) donors that graft survival and mortality were not worse after a follow up of 5–9 years than in a control group receiving HCV-negative organs [27]. The risk for chronic liver disease was, however, 4.4 times higher after transplantation of HCV-positive organs, and 1 death occurring among the 29 recipients was attributed to HCV hepatitis and rejection of the transplanted liver. Another caveat stems from the observation by the authors that patients with preexisting HCV infection, an-

tedating transplantation by many months and years, had a worse prognosis, presumably because of the longer duration of their hepatitis. In similar studies based on a more specific, second-generation ELISA for donor screening, albeit with shorter observation periods, virtually all seronegative recipients were infected through HCV-positive organs [28, 30] and ~50% developed liver disease [31]. In 1 study, 1 of 15 patients with transplantation-acquired HCV infection died from liver failure 55 months after renal transplantation [31]. Because of an absent or delayed antibody response to HCV, diagnosis of transplant-transmitted infection cannot be based solely on antibody testing but frequently requires assays for HCV RNA [28, 30, 31, 34]. On the basis of the transmissibility and the consequences of HCV infection, all donors should be screened for anti-HCV antibodies. Although a second-generation ELISA is more specific (98%) than its predecessor, its positive predictive value nevertheless remains low in donor populations with a low prevalence of HCV (55.1% in a large US collaborative study [29]), which results in an unnecessary waste of organs. HCV RNA assays are better predictors of transplant-transmitted, HCV-associated liver disease, but a negative PCR does not exclude HCV transmission [29], and, again, PCR is not practical for screening cadaveric donors. The panel recommends screening of all donors by (a second-generation) ELISA (A-I).

Toxoplasma gondii. *T. gondii* can be transmitted by solid-organ transplants to the recipient, the result being potentially fatal infections in seronegative recipients. Because of the propensity of *Toxoplasma* to persist in its encysted form in the heart muscle, recipients of heart transplants are particularly prone to transplant-acquired toxoplasmosis [35, 36], but fatal cases have also been observed after renal [37, 38] or liver transplantation [39]. Without prophylaxis, ~50% of seronegative heart recipients, 20% of liver recipients, and <1% of kidney recipients acquire toxoplasmosis through the organ of a seropositive donor. With a prevalence of *T. gondii* in the general population of 10%–75%, depending on the geographic area, a mismatch in the serostatus of donor and recipient is common. Prophylaxis for *Pneumocystic carinii* with cotrimoxazole appears to have eliminated much of the toxoplasmosis problem [40, 41]. Because not all patients receive or tolerate cotrimoxazole or another effective prophylactic regimen (i.e., pyrimethamine), all donors should be screened for the presence of *Toxoplasma* antibody (A-II).

Human T cell lymphotropic virus type 1 (HTLV-1)/HTLV-2. HTLV-1 virus infection is endemic in Japan, the Caribbean, Australia, and parts of Africa, with a seroprevalence of ≤15%–18% [42]. Most infections remain clinically quiet, but some infections have been associated with adult T cell leukemia or chronic neurologic diseases. HTLV-2 infection has not been definitely associated with any disease. Screening tests usually detect cross-reacting antibodies to HTLV-1/2. Seroprevalence in Europe and the United States in blood donors is <0.5%. A French study found in potential organ donors a frequency of Western blot–confirmed HTLV-1/2 positivity of 0.47% [43].

Table 3. Criteria for rejecting or accepting solid-organ transplantation in infected cadaveric donors and/or recipients.

Infection	Donor status	Recipient status	Recommendation regarding transplantation	Special aspects
HIV	Positive	Negative	Reject	
	Irrelevant	Positive	Experimental	? D+/R+
Cytomegalovirus	Positive	Positive	Accept	Antiviral strategy
		Positive	Accept	
Toxoplasma gondii	Positive	Negative	Accept	Prophylaxis after heart and liver transplantation
Hepatitis B virus	HB surface antigen–positive	Negative	Reject	
		Positive	Experimental	Accept for lifesaving transplantation
	Anti-HB core–positive, HB surface–antigen–negative	Negative	Accept extrahepatic organs	Consider liver in desperate situations
Hepatitis C virus	Positive	Negative	Decision depends on urgency of SOT and age of recipient	Accept only for urgent SOT and/or elderly recipients
	Positive	Positive	Accept	
Human T-cell lymphotropic virus type 1/type2	Positive	Negative	? Accept only for urgent SOT	No transmission documented by SOT, but very likely
Epstein-Barr virus	Positive	Negative	Accept	? Future antiviral strategy

NOTE. HB, hepatitis B; HC, hepatitis C; SOT, solid-organ transplantation; ?, no data available.

Four of 6 positive screening results were considered false-positive. HTLV-1 and HTLV-2 are transmitted sexually, by breast-feeding, and by cellular components of blood products (T cells). Transmission through solid-organ transplantation has not been documented and reported, but concern arises from reports of HTLV-1–associated myelopathy in a heart transplant patient acquiring the retrovirus from a blood transfusion [44] and a report of a T cell leukemia/lymphoma in an HTLV-1–positive renal transplant patient [45]. For these reasons, HTLV-1/2 screening is performed in many countries not only in blood but also in solid-organ donors, and in some countries screening is mandatory. Most experts of the panel recommend HTLV-1/2 screening (C-III).

RECIPIENT SCREENING

The aims of screening the potential recipient of a solid-organ transplant are 4-fold:

(1) To determine the immune status of the recipient against common pathogens that can be transmitted by transplants. This is because established immunity against pathogens such as CMV, *T. gondii,* and possibly HBV protects the recipient from severe sequelae of a primoinfection with these agents.

(2) To permit the allocation of organs from donors infected with a certain pathogen to recipients who are already carriers of this agent, such as HCV infection.

(3) To recognize and possibly treat infections that can be expected to exacerbate or reactivate after immunosuppression such as tuberculosis, the endemic dimorphic mycoses such as coccidioidomycosis and histoplasmosis, or strongyloidiasis.

(4) To avoid transplantation in patients with a poor prognosis after transplantation, such as HIV infection or colonization with certain panresistant bacteria.

A clinical and radiological workup for the detection of occult or latent infection should, in addition to a thorough history and physical examination, include in all patients a chest film in 2 planes for detection of infiltrates and residues of chronic infections such as tuberculosis, coccidioidomycosis, or histoplasmosis (B-III), a tuberculin skin test (C-III), and stool examinations for parasites (C-III).

Despite being performed often in transplant recipients, there is no evidence that radiographic evaluation for dental foci and their eradication is necessary (D-II). A case-control study in cases with untreated dental foci had results comparable to those without dental foci [46].

There is no evidence for the necessity of routine radiographic evaluation of the paranasal sinuses in solid-organ transplant (SOT) recipients (E-III), except in patients with cystic fibrosis awaiting a lung transplant and those with clinical sign or symptoms of sinusitis. In these cases direct sagittal computed tomography imaging is the procedure of choice (B-II).

SUMMARY

On the basis of this concept, the panel recommends screening for anti–HIV-1/HIV-2 (A-III), anti-CMV IgG (A-II), anti-*Toxoplasma* IgG (A-II), anti-Epstein-Barr Virus Nuclear Antigen IgG (A-II), HBs antigen, anti-HCV antibodies (A-II), anti-HBs antibodies, anti-HBc antibodies (A-III), and, at least in hemodialysis patients, HCV PCR (A-II). The reasoning of these recommendations is given in table 2 and the Donor Screening section.

Criteria formulated by the consensus panel for accepting or rejecting transplantation on the basis of infections in donors and recipients are summarized in table 3. Not included in the table are guidelines for transplantation of organs from donors that have infections with bacteria that can easily controlled with antibiotics, such as meningitis caused by *Neisseria meningitis* or penicillin-susceptible pneumococci [1]; however, infections with multiresistant microorganisms such as MRSA, vancomycin-resistant enterococci, or *Burkholderia cepacia* might be an insurmountable obstacle to transplantation. Transplantation of organs from patients with invasive fungal infections might similarly pose a problem.

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