Cadaver Donor Screening for Infectious Agents in Solid Organ Transplantation

Francis L. Delmonico

New England Organ Bank and Harvard Medical School, Newton, Massachusetts

The transmission of infection by a cadaver donor organ can result not only in loss of the allograft but also in death of the immunosuppressed recipient. Despite the shortage of cadaver organ donors, every donor must be evaluated thoroughly for the potential transmission of infectious disease, because the consequences of the organ donor events can have a profound effect on the transplant outcome. This review summarizes current knowledge about serological screening of organ donors to determine the suitability of organs from cadaver donors for transplantation.

Evaluation of a Cadaver Organ Donor

A medically suitable cadaver organ donor is a brain-dead individual <80 years of age who has no history of hematologic or visceral malignancy. Allografts recovered from cadaver donors can transmit infection to an immunosuppressed recipient; thus, the Organ Procurement Organization (OPO) must determine the risk of such infectious transmission by a thorough evaluation of the potential donor. Because the OPO coordinator requests family permission for organ donation, a blood sample is also obtained from the donor, to perform bacteriologic and serological screening for infectious disease. This serological sample is usually sent to a central available laboratory that performs such testing on a 24-h basis; however, once the sample arrives at the laboratory, it takes 6 h for the results to be determined. Usually, the donation coordinator is aware of the serological results as the offers for organ-specific recovery are made.

Serological screening for HIV, human T lymphotropic virus (HTLV), hepatitis B virus (HBV), hepatitis C virus (HCV), and cytomegalovirus (CMV) is routinely performed in the United States (table 1); however, the practices among OPOs vary widely around the world [1]. The testing laboratories usually employ ELISA to determine the presence of antibodies (with the exception of antibody to hepatitis B surface antigen [anti-HBs]) in a peripheral blood sample from the prospective donor. The determination of an active viral infection in the form of encephalitis or meningitis, varicella-zoster virus infection, or HIV infection is an absolute contraindication to organ donation because of the hazard each of these clinical situations pose to the allograft recipient.

Although the United Network for Organ Sharing (UNOS) policy regarding HTLV type I (HTLV-I) screening is the same as it is for HIV screening (infected organ donors are not suitable), not all OPOs reject a cadaver donor whose serological screening reveals antibodies to HTLV-I. HTLV has been transmitted to recipients of contaminated blood transfusions [2]. A patient infected with HTLV-I by blood transfusion is at risk for the development of either adult T cell leukemia or neurological disorders. Thus, the report of a positive HTLV serology would be provided by the donation coordinator with every allograft offer to the transplant surgeon. However, because the risk of transmission of HTLV-I by solid organ transplantation has not been clearly defined, it remains the discretion of the transplant surgeon to review information regarding HTLV infection with the potential allograft recipient. If a decision were made to proceed with transplantation, it would seem appropriate to perform follow-up HTLV screening for the recipient after transplantation.

HBV

Serological evaluation of a prospective donor includes the detection of antibody to hepatitis B core antigen (anti-HBc) and anti-HBs. In addition, the blood sample from the donor is directly analyzed for hepatitis B surface antigen (HBsAg). The implications of donor infectivity vary according to the
serological profile and the organ to be donated (table 2). The following review is categorized by the possible results of serological screening for hepatitis B that are reported by an OPO to the transplant center.

**HBsAg positivity:** HBsAg may be identified in the serum of an infected patient within 30–60 days of exposure. HBV transmission has been documented to occur through organ transplantation [3]. Thus, detection of HBsAg in the donor blood sample indicates that the donor is at risk for transmitting HBV. However, the OPO should verify the quality of the serum sample, since a false-positive test result can arise from a hemolyzed sample of donor blood. A false-positive test result because of a hemolyzed sample may be suspected if the donor’s social history gives no risk exposure to HBV. In that instance, another blood sample could be carefully obtained from the donor for HBsAg testing.

Liver allografts from HBsAg-positive donors have been transplanted successfully to critically ill HBsAg-negative recipients in life-threatening clinical situations [4]. Transplantation of renal allografts from HBsAg-positive donors to HBsAg-negative recipients has also been done without development of HBV infection in the recipient; however, the satisfactory clinical course may have been influenced by previous HBV immunization [5].

When HBsAg positivity is verified by repeated testing of a donor blood sample for HBsAg, organ procurement would probably be considered either for heart transplant recipients in a life-threatening emergency situation or, perhaps, for transplant candidates who are anti-HBs-positive (by virtue of immunization or natural immunity).

**Isolated anti-HBs positivity, HBsAg negativity, and anti-HBc negativity:** The serological profile revealing isolated anti-HBs positivity could be observed after hepatitis B vaccination, administration of hepatitis B immune globulin, transfusion of a blood product from an immunized donor, or previous HBV infection. Anti-HBs, unlike anti-HBc, does not arise during acute infection but rather during convalescence. Thus, ≤6 months may elapse before anti-HBs may be detected after HBV infection. The organ donor with anti-HBs is not likely to transmit HBV infection because there is no active viral replication; however, the exception is a liver allograft which can harbor HBV indefinitely.

**HBsAg negativity, anti-HBs positivity, and anti-HBc positivity:** Anti-HBc (IgM) is the earliest antibody detected after HBV infection (10–14 days). Anti-HBc (IgG) can persist for the lifetime of a previously infected patient. Although it has been generally accepted that a serological profile of HBsAg negativity, anti-HBs positivity, and anti-HBc positivity reveals recovery and immunity to HBV infection, HBV may still reside in the patient’s liver, regardless of anti-HBs positivity [6, 7]. Although the presence of anti-HBs may suggest donor immunity to HBV, detection of anti-HBs does not necessarily reduce the hazard of HBV transmission from donors who are anti-HBc-positive. After transplantation, HBV can replicate in the newly immunosuppressed environment. Van Thiel et al. [8] detected HBV DNA by PCR analysis in the livers of patients for whom serological results were positive for HBV. These data suggested an 8%–12% putative risk of HBV transmission through the liver.

Thus, pretransplantation liver biopsy should be performed for all anti-HBc-positive donors, to examine for portal piecemeal necrosis consistent with active hepatitis [7]. This biopsy can be performed at the time of organ recovery, and the biopsy specimen can be examined by an on-call pathologist at the donor hospital. Nevertheless, many transplant surgeons will return to the recipient transplant center with the biopsy specimen (and the liver allograft) so that a transplant pathologist can evaluate the specimen before a final decision to transplant is made. If the biopsy reveals hepatitis, the risk of HBV transmission is evident. De novo HBV infection after transplantation can result in patient death [9].

**Isolated anti-HBc positivity, HBsAg negativity, and anti-HBs negativity:** A serological profile of isolated anti-HBc positivity may reflect the window of time in which anti-HBc has yet to be serologically detectable in an HBV-infected individual. An insufficient period has elapsed for anti-HBs to become positive. Anti-HBc may be the only marker for current HBV infection, since HBsAg has decreased in the peripheral blood to levels

### Table 1. Routine serological screening for organ donors.

| Antibody to HIV | Antibody to human T lymphotropic virus | Antibody to hepatitis B surface antigen | Antibody to hepatitis B core antigen | Antibody to hepatitis C virus | Antibody to cytomegalovirus | Treponemal antigen (syphilis) | Antibody to Toxoplasma |

### Table 2. Relative risk of hepatitis B virus (HBV) transmission from organ donors to transplant recipients.

<table>
<thead>
<tr>
<th>Donor serological profile</th>
<th>Risk of HBV transmission to liver transplant recipients</th>
<th>Risk of HBV transmission to thoracic and kidney transplant recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg-positive</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>HBsAg-negative, anti-HBc-positive</td>
<td>Yes, irrespective of donor anti-HBs positivity</td>
<td>Yes (see table 4)</td>
</tr>
<tr>
<td>HBsAg-negative, anti-HBc-negative</td>
<td>Yes, because HBV may be retained in the liver</td>
<td>Small (see table 3)</td>
</tr>
</tbody>
</table>

**NOTE:** If the donor has a history of hepatitis B vaccination, there may be no restriction to organ recovery when serology reveals anti-HBs. Anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; HBsAg, hepatitis B surface antigen.
that are no longer detectable and anti-HBs has yet to increase in sufficient titer to be detectable. The determination of anti-HBc is not influenced by exposure to hepatitis B vaccine.

This serological profile of anti-HBc positivity is a potential concern for all allograft recipients; however, the risk of HBV transmission from such HBsAg-negative, anti-HBc-positive donors has been thought to be mainly for the liver allograft recipient (vs. recipients of extraliver organs) [7]. In the review from the University of California, San Francisco [7], only 1 of 42 kidney transplant recipients and 0 of 7 heart allograft recipients became HBsAg-positive after transplantation of organs from 25 HBsAg-negative, anti-HBc-positive donors, whereas 3 of 6 liver transplant recipients became HBsAg-positive after transplantation. All of these recipients were HBsAg-negative before transplantation.

To determine the impact of an anti-HBc-positive donor on the development of antibodies to HBV in heart and kidney transplant recipients within 1 year of transplantation, stepwise multivariate logistic regression analyses was done on data for cadaver heart and kidney transplantations from the UNOS database that were performed from 1 April 1994 through 30 June 1997. The results of these analyses are displayed in table 3; 12%–15% of recipients of heart and kidney allografts from anti-HBc-positive donors were reported to develop antibodies to HBV by 1 year after transplantation, in comparison with only 2%–3% of recipients of transplants from HBsAg-negative donors (P = .001, χ² test). The results of multivariate logistic regression analyses indicated that when donors were positive for anti-HBc, the OR for developing antibodies to HBV within 1 year after transplantation was 6.16 for heart transplant recipients and 5.16 for kidney transplant recipients. The UNOS database does not provide information pertaining to the development of hepatitis in recipients in either group, but there are data on mortality in recipients of transplants from donors with positive HBV serology. Donor positivity to anti-HBc and antibody to HCV did not affect 1-year allograft or patient survival; however, recipients of kidney transplants from donors who were positive for both anti-HBc and antibody to HCV had a 170% increase in the odds of 1-year mortality. Because HBsAg-negative, anti-HBc-positive donors can transmit HBV to renal allograft recipients [10], perhaps the most appropriate use of kidneys obtained from cadaver donors whose serological results reveal isolated anti-HBc reactivity is transplantation to recipients who have been immunized to HBV or who have an extenuating need (table 4).

Some OPOs do not assay for anti-HBs in routine serology assessment of a prospective donor and rely only on determination of anti-HBc. If the donor is HBsAg-negative and anti-HBc–negative, there are no restrictions to organ recovery. If the serological profile for the donor reveals HBsAg negativity and anti-HBc positivity, the anti-HBc–positive result is further defined by testing for IgM versus IgG. Organs from IgM-positive donors would not likely be recovered, because the IgM-positive result indicates recent HBV exposure. However, organs from IgG-positive donors may be recovered for HBsAg-negative recipients in life-threatening situations, HBsAg-negative recipients, or recipients who have been immunized to HBV (table 4). Prophylactic treatment with hepatitis B immune globulin would be a useful adjunct to prevent the development of hepatitis in allograft recipients who have not been immunized to HBV; lamivudine treatment should be reserved for those who develop hepatitis after transplantation.

Finally, it should be noted that as many as 30% of positive test results may be false-positive for anti-HBc (by ELISA) because of the testing methodology [12].

Table 3. Antibody to hepatitis B core antigen (anti-HBc) status 1 year after transplantation, compared with donor anti-HBc status for heart and kidney transplant recipients who were anti-HBc–negative at the time of transplantation.

<table>
<thead>
<tr>
<th>Donor anti-HBc status</th>
<th>No. (%) of transplant recipients with anti-HBc status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heart</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>Negative</td>
<td>657 (98)</td>
</tr>
<tr>
<td>Positive</td>
<td>21 (88)</td>
</tr>
<tr>
<td>Unknown</td>
<td>222 (97)</td>
</tr>
<tr>
<td>Total</td>
<td>900 (97)</td>
</tr>
</tbody>
</table>

HCV

The hazard of HCV transmission from a previously infected organ donor is a concern for all allograft recipients. Approximately 5% of all organ donors are positive for antibody to HCV [13, 14]. The presence of antibody to HCV is indicative of HCV infection, because antibody to HCV appears in peripheral blood within 2 months of HCV exposure. Most OPOs have adopted a policy of screening organ donors for antibody to HCV. IgG antibody to HCV does not protect against donor organ contamination; however, it is also important to emphasize that detection of antibody to HCV by serological screening of the donor is not predictive of HCV transmission [15].

Table 4. Suggested thoracic and renal candidates for a transplant from a donor with isolated antibody to hepatitis B core antigen (anti-HBc) positivity.

<table>
<thead>
<tr>
<th>Life-threatening situation in an anti-HBs–negative transplant candidate treated with HBIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HBs–positive heart or lung transplant candidate</td>
</tr>
<tr>
<td>Anti-HBs–positive renal transplant candidate with extenuating need (i.e., highly sensitized, elderly, or access failure)</td>
</tr>
</tbody>
</table>

NOTE. Anti-HBs, antibody to hepatitis B surface antigen; HBIG, hepatitis B immune globulin.
Approximately 50% of patients positive for antibody to HCV have detectable hepatitis C viremia by PCR analysis of peripheral blood [13]. All organ donors for whom PCR analysis is positive for HCV will transmit HCV to allograft recipients [13]. However, the risk of HCV transmission from an organ donor for whom PCR analysis is negative (positive for antibody to HCV) is unclear [16]. Unfortunately, the use of PCR testing cannot be accomplished within the time constraint of the preservation period necessary for the release of the donor organs. Thus, exclusion of all organ donors positive for antibody to HCV would eliminate the possibility of HCV transmission; however, such an indiscriminate policy would unnecessarily discard some organs that are not infected with HCV.

The transmission of HCV through a kidney transplant may be affected by the method of preservation. Roth et al. [14] used pulsatile machine perfusion and found that a standard perfusion of 20 h reduced the HCV load in the renal allograft by 75%.

The consequence of receiving an organ from a donor who is positive for IgG antibody to HCV is as follows: ~50% of the recipients have detectable antibody to HCV; 24% have detectable hepatitis C viremia by PCR analysis; and 35% may develop liver disease [13].

The following data were derived from analyses of data on cadaver heart and kidney transplantations from the UNOS database that were performed from 1 April 1994 through 30 June 1997; the analyses assessed the outcome of HCV-negative recipients of transplants from donors positive for antibody to HCV (table 5). Among donors who were positive for antibody to HCV, the OR for developing antibodies to HCV within 1 year of transplantation was 31.83 for heart transplant recipients and 12.94 for kidney transplant recipients. Analysis of post-transplantation outcomes for heart transplant recipients suggested that donor positivity to antibody to HCV increased the statistical reference of OR of 1-year mortality by 126% and the odds of 3-year mortality by 214%. As noted above, recipients of kidney transplants from donors who were positive for both anti-HBc and antibody to HCV had a 170% increase in the odds of 1-year mortality.

However, notwithstanding the high risk of transmission of HCV to allograft recipients, a positive screening result does not necessarily rule out organ donation [16]. Fishman et al. [16] suggested a selective strategy of reserving organs from HCV-positive donors for recipients with previous HCV exposure and detectable antibody to HCV. There is evidence in both animal models and human studies that “superinfection” with donor strains can occur in HCV-positive transplant recipients [17, 18]; therefore, this approach is not without risk. However, transplantation of a liver from a donor positive for antibody to HCV to a recipient positive for antibody to HCV does not appear to cause increased morbidity or mortality [19]. Transplantation of an HCV-positive heart allograft when a HCV-negative recipient’s life is in danger may be the only alternative to immediate death.

### CMV

The seminal work of Ho et al. [20] established the cadaver organ donor as a most important source of CMV infection in the organ recipient >2 decades ago [20]. More than 2 decades later, CMV disease remains a major complication of organ transplantation. Approximately 50%–75% of allograft recipients will have evidence of CMV replication after transplantation, because the transplanted allograft becomes the ongoing reservoir of infection [21]. The development of CMV disease has been associated with increased morbidity and cost of transplantation, because of an increased risk of organ rejection, allograft loss, and death [22].

Thus, all prospective organ donors and recipients should be routinely tested for antibody to CMV. Transplantation of an organ from a CMV-positive donor can result in subsequent reactivation of latent virus and replication in the immunosuppressed host. The specific CMV serological status of the donor and recipient has implications for prophylaxis, the highest risk group being CMV-seronegative recipients of CMV-seropositive donor organs (i.e., the so-called primary infection group).

Nevertheless, transplantation of organs from CMV-seropositive donors has not been considered an absolute contraindication for transplantation [23], because the high seroprevalence of the virus among the general population makes it impractical to rule out such donors. Furthermore, recent evidence suggests that even mismatches between CMV-positive donors and CMV-negative recipients can be successfully overcome by strategies aimed at prophylaxis for CMV infection. Treatment with valacyclovir after renal transplantation has reduced the incidence or delayed the onset of CMV disease in both seronegative and seropositive patients [24]. Treatment with valacyclovir has also decreased the rates of CMV viremia and viruria and herpes simplex virus disease [24].

From a practical standpoint, donor testing for CMV should always be performed before any blood or plasma product transfusion to an organ donor. Testing of organ donors after blood transfusion presents an additional complexity of assessing the risk of CMV transmission in the blood products given to the recipient.

### Table 5

<table>
<thead>
<tr>
<th>Donor anti-HCV status</th>
<th>Heart</th>
<th>Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Total</td>
</tr>
<tr>
<td>Negative</td>
<td>1169 (99)</td>
<td>10 (1)</td>
</tr>
<tr>
<td>Positive</td>
<td>21 (76)</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Unknown</td>
<td>28 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>1158 (98)</td>
<td>19 (2)</td>
</tr>
</tbody>
</table>
donor, even though this risk would be very small (currently, the risk of an organ donor acquiring CMV infection from blood product transfusion is <1%). Furthermore, testing after donor transfusion also introduces the possibility of a false-positive result of CMV for organ donors, because of antibody to CMV that is passively transmitted in the blood products.

Other Viruses: Human Herpesvirus 8 (HHV-8)

HHV-8 has been detected in all forms of Kaposi’s sarcoma, including transplantation-associated Kaposi’s sarcoma. Regamey et al. [25] analyzed serum samples from 220 renal transplant recipients for the presence of antibodies to HHV-8 on the day of transplantation and 1 year later. Within the first year after transplantation, seroconversion was detected in 25 patients. Kaposi’s sarcoma developed in 2 of them within 26 months after transplantation. Of 8 controls who were seronegative at the time of transplantation (and received allografts from HHV-8-negative donors), none underwent seroconversion within 1 year after transplantation. Thus, HHV-8 has been transmitted through renal allografts, and it is a risk factor for transplantation-associated Kaposi’s sarcoma. Nevertheless, the unusual occurrence of Kaposi’s sarcoma in the transplant recipient makes routine screening of all cadaver donors for HHV-8 impractical.

Transmission of other neurotropic viruses, such as rabies virus and the agent of Creutzfeldt-Jacob disease, from tissue donors has been reported [26]. Donor deaths associated with these viruses exclude such a donor from consideration. Although successful transplantation of renal allografts from donors with Reye’s syndrome (encephalopathy and liver failure) was reported several years ago [27], many transplant centers today may be reluctant to expose their recipient to an unknown (presumed viral) etiology of donor death.

Over 95% of potential adult donors are seropositive (IgG antibody) for Epstein-Barr virus (EBV); thus, serological screening of organ donors for EBV has not been routinely performed. However, primary EBV infection (i.e., transplantation of an organ from an EBV-seropositive donor to an EBV-seronegative recipient) is associated with an increased risk of post-transplantation lymphoproliferative disease. Therefore, recognition of this mismatch in a potential allograft recipient known to be EBV-negative may be important prognostic information. Currently, there is no effective means of preventing this complication.

Treponemal Antigen (Syphilis)

The detection of antibody to treponemal antigen by the rapid plasma reagin test is not a contraindication to organ procurement [28], but it is a contraindication to tissue procurement. The rapid plasma reagin test is reactive for >90% of patients with primary syphilis, but it may be negative between 6 and 18 months after primary infection. Although syphilis can be transmitted by blood transfusion, we are unaware of previously described infection in a recipient of a transplant from a syphilitic donor. Moreover, a standard course of penicillin therapy would provide sufficient antibiotic coverage to prevent syphilitic complications in an allograft recipient.

Toxoplasma

The possible transmission of the protozoan Toxoplasma gondii is a concern especially for heart allograft recipients, because of the predilection of this parasite for muscle tissue. Organ procurement from seropositive donors is not contraindicated; however, the detection of seropositivity means that the recipient may be placed at high risk. Fortunately, the use of trimethoprimsulfamethoxazole as prophylaxis for Pneumocystis carinii infection prevents transmission of T. gondii.

Acknowledgment

I wish to express my appreciation to Wilda Cherick of the United Network for Organ Sharing (UNOS) for providing UNOS donor and recipient data.

References


