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Donor Infection: An Opinion on Lung Donor Utilization

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Multiple risks are assumed in the process of delivering a lung transplant, including the potential transmission of infectious agents. This study reviews the current information available with regard to risk of donor-related infections. This investigation does not attempt to cover other areas of donor risk management, such as malignancy or primary organ failure. It can be helpful to try to categorize infectious risk by timing related to transplantation, as well as type of infection. Both are covered here. The intent is to summarize the available data in a way that is useful to the clinician.

BACTERIAL INFECTIONS

In terms of timing related to the transplant, the most immediate risk to the recipient is probably transmission of bacteria. In the early post-operative period, the agents the recipient carries can be very important, especially when noxious, such as with methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enteroccoccus (VRE) or *Burkholderia cepacia*. Likewise, the donor can add complexity by contributing both known and unsuspected agents.

Traditional division of bacteria into gram-positive and -negative staining has apparent validity in transplantation. Donor organs infected, even if bacteremic, with gram-positive agents seem to be usable despite the apparent risk, whereas those with proven gram-negative infections should be studiously avoided. In one report of 15 patients who received hearts from donors infected with gram-positive organisms, none developed infection with the agent of concern.[1] Conversely, 2 of 3 donors with gram-negative infections transmitted infection to the recipient, with 1 death.[1] The risk has been seen more often in other solid organ transplants, with similar results.[2] There are no specific data from lung transplantation experience, but local experience from one center detailed the results of 2 lung recipients from 1 donor infected with *Serratia marcescens*: 1 died of septic shock, whereas the other developed acute respiratory distress syndrome (ARDS) due to sepsis but survived a further 9 years.

Mycobacterial infections pose a potentially difficult problem due to the difficulty in assessing the activity of disease, and also because they are known to be transmitted.[3] In lung transplantation, the difficulty is partly eased because of the use of chest X-rays to assess donors, with abnormal films often leading to exclusion of donor organs. Multiple reports have documented transmission of *Mycobacterium tuberculosis*, especially in more endemic areas. Confounding the potential problem is the fact that acid-fast staining of donor secretions is not routine, and would further delay in organ placement if widely practiced. Fortunately, the apparent risk is small, and the disease is largely treatable. Recommending more extensive testing is not likely to be helpful.

FUNGAL INFECTIONS

Difficult early lung transplant experience has led to increased awareness of common fungi due to the serious complications associated with these agents.[4] Although more recent experience has shown increased promise, fungal infections remain a problem. Of the 2 environmental fungal genera encountered commonly in lung transplantation, *Aspergillus* and *Candida* species, it appears that the latter is more likely to be transmitted from donor to recipient. This concern arises from early problems with airway anastomoses, and dissemination from the lung. Due to advances in operative management, preservation, anti-microbial therapy and immunosuppression, the incidence of major airway dehiscence has declined along with reports of serious airway infection with *Candida* species. Although this was a recognized problem in the early history of lung transplantation, serious *Candida* infections have become uncommon, and donation should not be ruled out based on presence of *Candida* species alone. There are no convincing reports of *Aspergillus* transmission to recipients of solid organ transplants.

VIRAL TRANSMISSION: HEPATITIS

Hepatitis viruses may be transmitted with transplanted organs, and the transplant outcome may be affected by the infection. In kidney transplantation, de novo viral infection from the donor does not seriously impact outcome at up to 10 years, but has a significant effect on recipient survival by 20 years.[5] If the recipient has

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serologic evidence of previous viral infection, the outcome after renal transplantation is even more in doubt, but is considered better than the alternative of permanent dialysis.[6] Other investigators have found evidence that recipient-positive status leads to increased risk of graft loss, death and death due to sepsis.[7,8] That viral transmission occurs with solid organ transplants is clear, but the outcome is less so. One group addressed more directly the issue of risk of transmission when they assessed the likelihood of serum and liver tissue virus from liver biopsy patients.[9] Their study showed that the risk of hepatitis B transmission from a core antibody-positive liver was small, and the risk of finding virus in the blood was negligible.

Although few data exist in the lung transplantation literature to address the aforementioned problems, we can derive help for our clinical practice from the experience of others. We believe that donors positive for hepatitis C should not be used for lung transplantation, unless grave circumstances demand it, and the recipient gives approval before transplantation. In the case of hepatitis B, donor surface antigen–positive status should lead to exclusion of the lungs. If the donor is hepatitis B core antibody positive, however, the risk of transmission of hepatitis B to the recipient is very small, and thus donor lungs can be utilized, if appropriate.[9]

With regard to other viruses, information ranges from extensive, in the case of cytomegalovirus (CMV), to theoretical and almost non-existent, in the case of Creutzfeldt–Jakob disease (CJD). This study does not address further the issues surrounding CMV, but attempts to rationalize donor issues related to other viruses.

CREUTZFELDT–JAKOB DISEASE

In the era of mad cow disease, and a better understanding of prion transmission, CJD has become a potential concern.[10–12] Variant CJD has been transmitted with brain tissue and dura mater, and appears to have traveled with the liver in at least 1 case.[11–16] Theoretically, it can transported with other tissues, including lung.[15] Although infectivity appears to be low with non-brain tissue, it seems advisable to avoid donors potentially infected with variant CJD, because there are no screening tests available, no disinfectant mechanism, and no treatment for the infection itself.[12,15]

HUMAN IMMUNODEFICIENCY VIRUS AND ORGAN TRANSPLANTATION

The main consideration in the use of human immunodeficiency virus (HIV)-positive donors has been the risk of transmission of HIV infection and the largely historic experience with immunosuppression in acquired immunodeficiency syndrome (AIDS) for organ transplantation. Accidental transmission of HIV to transplant recipients by organs or blood products was generally associated with an accelerated course of AIDS.[17,18] Although the use of HIV-positive organs is likely to result in transmission of HIV to the recipient, the precise risk remains unclear because the numbers of recipients who have received such organs, but who have not subsequently seroconverted, are not known.[19–24]

The use of "highly active anti-retroviral therapies" (HAART) has transformed AIDS into a long-term–manageable disease, with extended survival. As a result, an increasing number of HIV-positive patients are being considered for (or have received) renal or hepatic transplantation, usually because of AIDS-associated glomerulopathy or co-infection with hepatitis C. Transplantation of these patients has been associated with short- and medium-term results similar to those in HIV-negative recipients.[23–29] In this setting, it may be appropriate to expand the donor pool to include HIV-positive donors in select circumstances.[29–31] Although it is highly likely that patients receiving an organ from such donors will develop HIV/AIDS, the counter-argument is that AIDS is a manageable problem and the use of such organs may offer survival opportunities to critically ill patients.[24–28]

RISK OF INFECTIONS/CANCER

Several recipients of organs from HIV-positive donors have developed prolonged fever associated with splenomegaly, lymphadenopathy, abnormal liver function and cytopenia. The differential diagnosis includes CMV infection, but often no cause is found, suggesting that this syndrome reflects seroconversion to HIV. This syndrome is self-limiting and should be considered in the differential diagnosis of unexplained fever in the first 2 months post-transplantation.[24]

The risk of opportunistic infections and cancer is increased in both AIDS and after organ transplantation. Highly active anti-retroviral therapy (HAART) has reduced the risk of serious infections in AIDS. However, Epstein–Barr virus (EBV)-associated lymphoproliferative disease has been seen with both AIDS and organ transplantation and the incidence does not appear to be reduced by HAART.[32,33] Furthermore, human herpesvirus (HHV)-8 may be related to the development of Kaposi's sarcoma.[34,35]

CONCOMITANT RISK OF REJECTION

It has been demonstrated that some degree of immunosuppression is necessary to prevent graft rejection in HIV-infected individuals receiving renal and hepatic transplantation.[28] However, there is evidence that infection with HIV does not adversely affect rates of rejection in renal, hepatic and cardiac transplantation.

Furthermore, several patients have maintained normal allograft function despite a significant reduction (occasionally total discontinuation) in immunosuppressive medication.[30,31] The use of HAART does not appear to increase the rate of rejection.[29–31,36,37]

Therefore, to balance the risk of infection and rejection, it is advisable to reduce the dose of immunosuppression in symptomatic HIV-infected recipients. It is not known whether this reduction should begin in asymptomatic patients with a low CD4 count.

RISK OF PROGRESSION TO AIDS

It is unclear if the use of immunosuppressive medication would modify the course of infection with HIV. In the HAART era, experience from renal and hepatic transplantation suggests that the use of calcineurin inhibitors is not associated with either an accelerated or delayed development of AIDS.[29,36]

In terms of other immunosuppressants, clinical experience is limited. Azathioprine has been associated with exacerbation of HIV replication, whereas mycophenolate mofetil has been shown to reduce HIV replication in vitro.[30] The use of anti-lymphocyte antibodies has been associated with severe exacerbation of HIV replication and should be avoided. Similarly, corticosteroid dose should be limited whenever possible.[24,26,27]

Finally, the use of HIV-positive donors would probably result in a small increase in the donor pool, but transplantation would result in increased risk and complexity of post-operative care. If such donors are to be considered, then clear guidelines should be established detailing the situations in which such organs could be used. Furthermore, the process of informed consent should be transparent and perhaps even standardized. It should deal with the issues of likely HIV transmission, HIV as a contagious disease, and that transplantation outcome is unclear. Until these issues are addressed, we believe that use of organs from HIV-positive donors should be avoided.

HERPESVIRUSES

It is clear that nearly all herpesviruses can exist in one or more tissues in a non-apparent and often latent form after initial infection. All herpesviruses be transmitted either by the allograft or by transfusion of blood or blood components.[38,39] Seroconversion or DNA detection after transplantation (Tx) is equated with transmission of the virus in most instances. Furthermore, especially with regard to the newly recognized human herpesviruses (HHV 6–8), most studies have explored reactivation without differentiating between transmitted or endogenous reactivation.[34–37]

It is believed that the presence of antibodies against these agents in donor serum indicates latent infection, but cross-reaction is possible, at least with HHV 6, HHV 7 and CMV.[38] Furthermore, some studies have found higher incidence rates of CMV or dual infections (CMV + HHV 7)[39] under more potent immunosuppression (i.e., when MMF has replaced azathioprine). Therefore, the role of clearly transmitted disease is uncertain, at least for HHV 6 and HHV 7.[38–46]

CMV

Large numbers of publications have dealt with CMV reactivation. However, studies concerning transmission or reactivation in untreated patients have been performed only in the early history of solid organ transplantation, showing infection rates between 19% and 90% and disease rates between 26% and 90%, with the latter frequently occurring in the graft.[47,48] For lung transplantation, more recent publications have most often compared different prophylactic and immunosuppressive treatment strategies for achieving better long-term survival, especially regarding the development of bronchiolitis obliterans syndrome/obliterative bronchiolitis (BOS/OB). Results for CMV infection have been between 0% and 59%.[44,49]

HHV 6

Seroprevalence before liver or kidney transplantation is 88%, with infection (diagnosed by virus isolation) in 31%.[50–53] Infection/reactivation occur in 20% to 50% of patients 2 to 3 weeks after transplant. Major symptoms include unexplained fever and/or bone marrow suppression, but mental status changes, encephalitis, skin rash, pneumonia and rejection have also been described. Coincident infections with HHV 7 and CMV have been noted.[53]

No studies were found concerning HHV 6 in lung transplantation.

HHV 7

Coincidental infection with HHV 7 and CMV is common, and HHV 7 reactivation occurs before CMV in most patients.[45,54] Detectable DNA in plasma seems to correlate with severity of disease, such as encephalitis. Both latent infection and reactivation are common among recipients of kidney, liver and bone marrow transplants.

No studies were found concerning HHV 7 in lung transplantation.

HHV 8

HHV 8 is the agent of Kaposi's sarcoma (KS).[34,35,55] Prevalence of latent infection with HHV 8 shows strong geographic variation among blood donors from France, Italy, Uganda and the USA.[55–57] Seroprevalence increases post-transplant, and the incidence of KS has been noted to be up to 8% to 12%. Transmission is apparently common during transplantation, but it ap-

pears that de novo infection infrequently leads to KS, as the risk seems to reside in those seropositive pre-transplant.[56,58]

No studies were found concerning HHV 8 in lung transplantation.

EBV

EBV transmission is associated with post-transplant lymphoproliferative disease (PTLD).[59–61] This virus has been clearly linked to the development of PTLD in bone marrow transplant and solid organ recipients, including lung transplant patients.[62–71] B- and T-cell–derived non-Hodgkin's lymphoma, as well as immunoblastic lymphoma and Hodgkin's disease, have been reported.[62,63,72] The incidence of PTLD in liver Tx is reportedly 5% to 12% overall, but as high as 40% in seronegative patients/seroconverters, whereas in seropositive patients it is only 1% to 2%.[65–68] The relative risk of PTLD by EBV-negative serostatus is about 20 in seronegative vs seropositive recipients.[67,69] In addition, EBV infection (as PTLD or atypical viral infectious disease) usually occurs in the first post-operative year and is associated with a higher degree of immunosuppression.[73,74] Therefore, caution is warranted when seropositive organs are to be used for seronegative recipients, but no clear-cut preventive strategies are available at present. Work continues on a potential vaccine.

Herpes Simplex

Latent infections with herpes simplex virus (HSV) occur in trigeminal and lumbosacral dorsal-root ganglia; therefore, there is usually no transmission through solid organ transplantation. There are reports of HSV 2 transmission from 1 donor to both kidney recipients, without neutralizing antibodies before Tx.[75,76] In another case, liver and heart were transplanted into different recipients: each received early re-transplantation on post-operative Day 1 (heart) and Day 12 (liver), respectively, without evidence of HSV 2 infection.

No studies were found concerning HSV and lung transplantation.

Varicella Zoster

Latent infection occurs in neural ganglia, and therefore it is believed that varicella zoster virus would not be transmitted through transplantation of solid organs unless the donor suffered active varicella infection at the time of brain death. No documentation of transmission could be found.

Parvovirus B19

Transmission of this viral infection has been reported specifically in kidney transplantation and after bone marrow transplant.[77,78] Symptoms include unexpected graft failure, pure red cell aplasia, prolonged anemia, thrombocytopenia, arthralgia and erythema infectiosum after bone marrow transplant. The local experience of one of the present investigators also documented parvovirus B19 infection in 1 lung transplant recipient who had pure red cell aplasia that cleared within 1 year after therapy with intravenous immunoglobulin infusions (unpublished findings).

Adenovirus

In one pediatric study, adenovirus infection was found in 8 of 16 patients, from 1 to 26 months after lung transplantation, and was significantly associated with respiratory failure and histologic diagnosis of obliterative bronchiolitis.[79,80] In 2 patients with early fulminant infection it was also identified in the donor. Therefore, transmission is apparently possible, and knowledge of donor adenovirus infection should result in discarding the lungs.

West Nile Virus

West Nile virus became a well-known entity in 2002, as outbreaks of headaches and central nervous system disease occurred in several parts of the USA, with over 4,000 reported human cases by April 2003.[81,82] It is likely to be a recurrent late summer problem, and therefore is important to organ transplantation.[83]

The virus infects birds and mosquitoes, with humans and horses becoming incidental hosts. Human symptoms may be mild to severe and include fever, headache, body aches, truncal rash and lymphadenopathy.[82] The most serious complications of infection include fever, neck stiffness, stupor, disorientation, coma, tremors, convulsions, muscle weakness, and paralysis, which may lead to death. There is no known therapy. Although little experience exists with transplantation of organs from donors with West Nile infection, it appears that the virus can be transmitted from an asymptomatic host to recipients, which happened with 4 patients last fall in the southeastern USA.[81] With this in mind, it is prudent to avoid use of organs from patients potentially infected with the West Nile virus.

Severe Acute Respiratory Syndrome (SARS)

Since late 2002 and early 2003, SARS has been a constant presence in our newspapers.[84–86] Newly identified as a unique coronavirus, the agent has caused serious disease in Asia and in areas with a high prevalence of travelers from southern Asia. In its most severe manifestation, SARS leads to acute respiratory distress syndrome, respiratory failure and death. There is no proven therapy. No published reports exist to guide our thinking with regard to SARS and transplantation, but manifestations of the disease would likely rule out the use of lungs and other organs from potential donors afflicted by SARS.

Table 1. Summary of Recommendations

Donors should not be used routinely upon evidence of:
Gram-negative bacteremia
Mycobacterial infections of chest
Invasive fungal diseases
Hepatitis C
Hepatitis B surface antigen-positivity
HIV/AIDS
Creutzfeldt–Jakob disease
West Nile virus
Severe acute respiratory syndrome (SARS)
Donors may be used with caution upon evidence of:
Gram-positive bacteremia
Mycobacterial infections outside the chest
Fungal airway colonization
Hepatitis B core antibody
Herpesviruses (HHV 6–8, simplex, varicella)
Cytomegalovirus
Epstein–Barr virus (high risk if donor^{+}/recipient^{-})

SUMMARY

As new information accumulates, the transplant community alters the way in which donors are utilized. Greater effort is being made to better manage the donor and to re-define the so-called marginal donor. A clearer understanding of donor infection and transmission will help in the selection of organs for use by the potential recipient. Continued evolution is expected. We hope that this literature review contributes to the rational use of organs from the potentially infected donor. Transplantation will continue to improve as we attempt to solve the problems inherent in organ donation and donor management, and incrementally improve our evaluation and utilization of this scarce resource (Table 1).

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