

Screening of Donor and Recipient Prior to Solid Organ Transplantation

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Background

Pretransplant screening of potential organ donors and recipients is essential to the success of solid organ transplantation (1–4). The goals of pretransplant infectious disease screening are: (1) to identify conditions which may disqualify either donor or recipient, (2) to identify and treat active infection pretransplant, (3) to define the risk of infection and determine strategies for preventing and mitigating posttransplant infection and (4) to implement preventative interventions, such as updating of vaccination status. Although there is general agreement on the major infections for which screening is performed, there is some variation between centers in the types of screening used and actions taken as a result.

In the course of pretransplant evaluation, recipients should be evaluated for infection risk by obtaining a thorough infection and travel history, as well as history of animal and environmental exposures. The pretransplant period is an ideal time for detailed counseling of the recipient and his/her family about safe food handling and the risk of infection associated with pets, travel, and hobbies such as gardening and woodworking. Infection prevention approaches including hand hygiene, prophylactic antimicrobials, postexposure prophylaxis, and updating of immunizations should be addressed as well.

A variety of pathogens may be transmitted by transplantation (5) (Table 1). Guidelines for pretransplant screening have been the subject of several publications including a consensus conference of the Immunocompromised Host Society (ICHS) (6,7), the American Society for Transplantation (AST) Clinical Practice Guidelines on the evaluation of

renal transplant candidates (8), and the ASTP Clinical Practice Guidelines on the evaluation of living renal transplant donors (9). Recommendations regarding hepatitis status of the donor have been summarized in the March 2001 Crystal City Meeting (10) and in a review by Chung, Feng and Delmonico (11). In addition, the Centers for Disease Control and Prevention (CDC), the Infectious Diseases Society of America (IDSA) and the American Society for Blood and Marrow Transplantation (ASBMT) have published guidelines in 2000 for prevention of infection in hematopoietic stem cell transplant recipients (12), and the CDC has published guidelines for the prevention of HIV transmission through transplantation (13).

While traditional screening strategies are very effective in most cases, they are not a guarantee against donor-derived infections. There have been a number of high-profile donor-derived transmission incidents over the last several years, including rabies (14), lymphocytic choriomeningitis virus (15), West Nile virus (WNV, 16), HIV (17–19) and hepatitis C (HCV) (18–20), which have renewed discussion of the issues surrounding donor screening. The recently formed United Network for Organ Sharing (UNOS) Donor Transmission Advisory Group (DTAG), the Transplantation Transmission Sentinel Network of the CDC (21) and other new initiatives have been formed to address donor-transmitted infection and current screening practices (21–23).

After a discussion of the differences in screening between living and deceased donors, this review will summarize current opinion on screening for bacterial, mycobacterial, fungal, parasitic and viral infections in the donor and recipient (Table 2). More detailed discussions of these infections, posttransplant monitoring, prophylaxis, and treatment are found in other sections of these guidelines. Because issues concerning the viral serologies of donor and recipient are intertwined, these will be discussed together.

Given the limited pool of donors, it has become necessary to consider marginal candidates, including those with infection at the time of donation, higher-risk serologic profiles, or a social history indicating potential exposures to blood-borne pathogens such as HIV or HCV. The nature of any potential donor infection, the severity of end-stage organ disease in the recipient, and the likelihood of another organ offer for the patient on the transplant waiting list are important considerations when determining the acceptability of the potentially infected donor.

Table 1: Pathogens transmitted with solid organ transplantation

Bacteria	Mycobacteria
<i>Staphylococcus aureus</i>	<i>Mycobacterium tuberculosis</i>
<i>Klebsiella</i> species	Nontuberculous mycobacteria
<i>Bacteroides fragilis</i>	
<i>Pseudomonas aeruginosa</i>	Parasites/Protozoa
<i>Escherichia coli</i>	<i>Toxoplasma gondii</i>
<i>Salmonella</i> species	<i>Strongyloides stercoralis</i>
<i>Yersinia enterocolitica</i>	<i>Plasmodium</i> species
<i>Treponema pallidum</i>	<i>Trypanosoma cruzi</i>
<i>Brucella</i> species	
<i>Bartonella</i> species	Viruses
<i>Enterobacter</i> species	Cytomegalovirus
<i>Acinetobacter</i> species	Epstein-Barr virus
	Herpes simplex virus
Fungi	Varicella-zoster virus
<i>Aspergillus</i> species	Human herpesvirus-6
<i>Candida</i> species	Human herpesvirus-7
<i>Histoplasma capsulatum</i>	Human herpesvirus-8
<i>Cryptococcus neoformans</i>	Hepatitis B, D
<i>Coccidioides immitis</i>	Hepatitis C
<i>Scedosporium apiospermum</i>	Human immunodeficiency virus
<i>Prototheca</i> species	Parvovirus B19
	Rabies
	Lymphocytic choriomeningitis virus
	West Nile virus
	BK virus

Donor Screening: Living Donor versus Deceased Donor

The differences in screening of the living donor and the deceased donor are largely based on the different time frames during which the evaluation must take place. For the living donor, it is often possible to treat active infection and delay transplantation until the infection resolves. If there is a significant delay between donor evaluation and transplantation, interim evaluation may be indicated to rule out recently acquired infection. Clinical reassessment of the prospective living donor is indicated if clinical signs or symptoms of possible infection occur, particularly any unexplained febrile illness between the time of initial screening and the planned date of transplantation. Repeat serologic testing and nucleic acid amplification testing (NAAT) for HIV, hepatitis B virus (HBV) and/or hepatitis C virus (HCV) may be indicated, since antibody seroconversion may not yet have occurred with recent exposures.

The screening of a prospective living donor takes place in the transplant center and includes a thorough medical and social history, physical examination, laboratory studies including serologic testing (Table 2) and radiographic studies as indicated by history or the procedure to be performed. The medical history should include an assessment of previous infections, vaccinations, travel and occupational exposures, as well as the presence of risky behaviors (e.g. drug use, sexual practices and incarceration). Living donors should be screened for syphilis, HIV, hepatitis B and C and

Table 2: Frequently utilized serologic tests for screening of donor and recipient prior to transplantation

Tests Commonly Obtained in Both Donor and Recipient

Human immunodeficiency virus (HIV) antibody
 Human T-cell lymphotropic virus (HTLV)-I/II antibody
 HSV (herpes simplex) IgG antibody (at some centers)
 Cytomegalovirus (CMV) IgG antibody
 Hepatitis C (HCV) antibody
 Hepatitis B (HBV) surface antigen (HBsAg)
 Hepatitis B core antibody (HBcAb IgM and IgG, or total core)
 Hepatitis B surface antibody (HBsAb) at some centers
 Rapid plasma reagin (RPR)
Toxoplasma antibody (especially in heart recipients)
 Epstein-Barr virus (EBV) antibody (EBV VCA IgG, IgM)
 Varicella-zoster virus (VZV) antibody

Other Screening Measures for Infectious Diseases

PPD or interferon gamma release assay (IGRA) for latent TB infection in recipients and living donors
Strongyloides serology (for recipients from endemic areas)
Coccidioides serology (for recipients from endemic areas)
Trypanosoma cruzi serology (for donors and recipients from endemic areas)
 Serologies for tetanus, diphtheria, measles, mumps and pneumococcal titers as an aid to pretransplant immunization (at some centers)

Optional Screening Measures

West Nile virus serology or NAAT
 HHV-8 serology (KSHV)
 Nucleic acid amplification testing (NAAT) for HIV, HCV, HBV, particularly in donors with high-risk social histories

tuberculosis via a tuberculin PPD skin test or interferon-gamma release assay (IGRA) (II-2). If there is a suspicious donor history, additional testing may be warranted.

By contrast, the time frame for deceased donor evaluation is typically hours. Serologies are performed in laboratories associated with organ procurement organizations (OPOs) or other reference laboratories, which operate on a 24-hour basis to generate the data needed to determine donor suitability. Because of time constraints and the extensive geographic areas covered by some OPOs, testing is often limited to serologic methods that are rapid and routinely available. Because more sensitive testing may not be available, some infections, such as HIV and HCV, may be difficult to diagnose at an early stage, before the development of specific antibody (17,20). Thus, a detailed social and medical history on the donor is required to identify potential infections that might not be detected by serologic testing. Furthermore, certain infections may come to light only after the transplant has been performed, when results of routine procurement cultures of blood, urine, and sputum become available. Increasingly, some OPOs are utilizing rapid molecular testing, particularly in high-risk potential donors, for rapid detection of viral genetic material (NAAT), particularly for viral infections such as HCV, HBV and HIV. Testing for certain pathogens with particular geographic significance such as *Trypanosoma cruzi* (Chagas disease) and WNV may be performed by some

OPOs. If a deceased donor with uncertain infection risk is to be used, informed consent of the recipient should include the risk for infection transmission.

Donor Screening: Bacterial Infections

The evaluation detailed above will reveal most active bacterial infections present in the living donor. Infections of the respiratory tract, urinary tract or other focal sites should be thoroughly treated with documentation of resolution of infection prior to donation. The potential kidney donor with urinary tract infection should be investigated to rule out upper tract involvement. In the potential donor with a history or suspicion of prior bloodstream infection, a thorough investigation should be performed to insure that the target organ has not been seeded.

Syphilis may be latent and asymptomatic and requires therapy if time permits. Syphilis has rarely been transmitted by transplantation, but it is not a contraindication to organ donation if the recipient is treated posttransplant with an appropriate course of benzathine penicillin (24) (II-3). Standard regimens for late latent syphilis would be appropriate in this situation (e.g. three weekly doses of 2.4 million units of intramuscular benzathine penicillin).

Deceased donors may harbor known or unsuspected bacterial infections (5,25,26). They should be evaluated for these by review of medical records, detailed history from the donor family, temperature chart, radiography, and cultures when available. Blood cultures should be obtained to rule out occult donor bacteremia. Bacteremia with virulent organisms such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* may result in early posttransplant sepsis or mycotic aneurysm formation at the site of vascular anastomoses in the recipient (27,28). Although a review of 95 bacteremic donors found no evidence of transmission when recipients were given antimicrobial therapy for a mean of 3.8 days posttransplant (29), it is prudent to employ longer courses of therapy in the recipient (e.g. 2–4 weeks) if the donor is known to have been bacteremic with a virulent organism (II-2).

In general, there is no reason to treat the recipient of an allograft from a deceased donor with nonbacteremic, localized infection not involving the transplanted organ, with the exception of meningitis, in which occult bacteremia frequently occurs (III). Organs have been successfully transplanted from donors with bacterial meningitis when appropriate antimicrobial therapy was administered to both the donor and recipients (30).

Lung transplantation deserves special attention (31). Donor bacterial colonization is common, as the lungs are in contact with the external environment, and the mouth and upper airways are a site for colonization with multiple organisms. Donor bronchoscopy with cultures performed at

the time of evaluation and/or procurement allows for the administration of antibiotics directed at these colonizing organisms, and can prevent invasive infection in the recipient (III) (31).

Allograft contamination may occur during procurement or processing (32). Rubin recommends treatment of the recipient if organisms are isolated in perfusates or organ transplant medium, citing the risk of mycotic aneurysm formation (28), although culture contamination must be considered as well (33). Antibiotics should be administered for at least 14 days for Gram-negative bacilli, *S. aureus* or *Candida* species (II-3). A shorter course of therapy may be considered for less virulent organisms (III). A more recent study of kidney preservation fluid contamination with *Candida* species in eight recipients demonstrated that the risks of mycotic aneurysm rupture can be mitigated with appropriate antifungal therapy (34).

Donor Screening: Mycobacterial Infections

Mycobacterium tuberculosis has been transmitted by transplantation; donor transmission accounted for approximately 4% of reported posttransplant TB cases in a review of 511 patients by Singh and Paterson (35). Potential living donors should have PPD testing performed (a two-stage tuberculin skin test if from an endemic area) or TB IGRA testing (36); if either test is positive, additional testing should be performed to rule out active infection (III). If there are symptoms or chest radiograph findings suggestive of active disease, sputum AFB cultures should be performed; chest computed tomography (CT) may be helpful in assessing adenopathy. Urine microscopy and AFB cultures, excretory urogram and abdominal CT scanning may be useful in PPD-positive prospective kidney donors. If there are no signs or symptoms of active disease and the chest radiograph is normal, sputum AFB cultures are very low-yield. Management of the prospective living donor with latent TB infection (LTBI) differs in areas of differing endemicity. Delay of transplant until the living donor is treated for LTBI (with isoniazid for 9 months or rifampin for 3 months) is appropriate, should another suitable donor not be available. In TB endemic areas, where as many as 30–40% of donors have LTBI, it may be difficult to avoid the use of infected donors. One cohort study from an endemic area demonstrated no benefit to treating the prospective living donor with LTBI prior to transplantation (37). Isoniazid prophylaxis of the recipient is an option but controlled studies are needed to determine the efficacy of this practice.

In deceased donors, time does not allow for tuberculin skin testing, and the IGRA is not yet logistically practical in this situation. Donors in whom active tuberculosis is a clinical possibility should not be utilized (II-2). In cases where a potential donor is known to have a recent PPD skin test conversion, transplantation should be approached with caution due to the risk of dissemination in the recipient. Donors with a history of a positive PPD but without evidence

of active disease are acceptable, but warrant consideration of treatment of the recipient with isoniazid (INH) (III) (35,38).

Donor Screening: Fungal Infections

Active systemic fungal infection in the donor is a contraindication to transplantation. The endemic mycoses in particular may be present in dormant form. Transmission of histoplasmosis by transplantation has been described (39), but most cases appear to be the result of reactivation of past infection in the recipient. In many individuals from the Midwestern United States, calcified pulmonary, hilar and splenic granulomata on X-ray may be the visible residua of old *Histoplasma* infection, but such radiographic signs have not traditionally been considered a contraindication to donation (III). Transmission of coccidioidomycosis by lung transplantation has been reported in the Southwestern United States (40), although reactivation of coccidioidomycosis in the recipient appears to be far more common (41). As yet, uniform recommendations for donor screening for endemic mycoses have not emerged.

Donor Screening: Parasitic Infections

Toxoplasmosis is a major concern particularly in heart transplantation, where the *Toxoplasma*-seronegative recipient of a *Toxoplasma*-seropositive heart is at highest risk for developing active toxoplasmosis posttransplant (42). Toxoplasmosis has also rarely been transmitted to liver and kidney recipients (43). Donor seropositivity is not a contraindication to heart donation but allows for appropriate prophylaxis to be administered to the recipient; routine trimethoprim-sulfamethoxazole prophylaxis against *Pneumocystis jiroveci* is effective in preventing toxoplasmosis and may negate the need for serologic testing in areas of low prevalence (44). Screening of donors for *Toxoplasma* is not routinely performed for noncardiac donors but may be part of the screening panel at some centers.

Transmission of Chagas disease (*T. cruzi*) by transplantation is a significant problem in endemic areas (South and Latin America) but has rarely been reported in the United States (45). Routine screening is not yet mandated in the United States. Further discussion of these issues is found in the Parasitology section of these Guidelines.

Donor and Recipient Screening: Viral Infections

The following sections will discuss both donor and recipient screening for viral infections as the serologic status of both donor and recipient is often crucial in determining the risk of infection (Table 3). Each of the viruses mentioned here are discussed in more detail in other sections of these Guidelines.

Table 3: Interventions related to donor screening results

Serologic finding	Action
Antibody to HIV	Exclude from organ donation
Antibody to HTLV I/II	Generally exclude from organ donation (may be used in life-threatening situations, with informed consent)
Antibody to HCV	If used, usually reserve organ for recipient with antibody to HCV or severely ill recipient
Antibody to CMV	Use information to determine prophylaxis (in conjunction with recipient serology)
Antibody to EBV	Consider PCR monitoring posttransplant if donor seropositive, recipient seronegative
Hepatitis B surface antigen (HBsAg+) or HBcAb IgM+	Exclude from organ donation (possible use in life-threatening situations with preemptive treatment of the recipient)
Hepatitis B surface antibody (HBsAb+)	Generally safe for organ donation
Hepatitis B core antibody IgG (HBsAg-, HBcAb IgG+)	High-risk for transmission if liver used for donation, but used at some centers with intensive prophylaxis; nonhepatic organs carry a small risk of transmission of HBV and are used for vaccinated recipients or with prophylaxis
RPR +	Not a contraindication to donation. Recipient should receive benzathine penicillin
Antibody to <i>Toxoplasma</i>	Not a contraindication to donation. Sulfa-allergic, seronegative heart transplant recipients with a seropositive donor should receive pyrimethamine prophylaxis

Any donor with evidence of active rabies, lymphocytic choriomeningitis virus, West Nile virus or other encephalitis should not be used.

Cytomegalovirus (CMV)

The CMV serologic status of donor and recipient is an important predictor of posttransplant infection, with the CMV seronegative recipient of a CMV seropositive donor organ (D+/R-) being at highest risk for development of tissue-invasive CMV, recurrent CMV and ganciclovir-resistant CMV (46-48). Consequently, all donors and recipients should be tested for CMV infection using commonly available serologic techniques. While not a contraindication to transplantation, D+/R- status is an indication for more intensive monitoring and prevention strategies posttransplant than in donor/recipient pairs with a lower risk of CMV

infection (II-2). The seropositive recipient, regardless of donor status, is at risk for CMV reactivation and usually receives either prophylaxis or preemptive monitoring and therapy. There are many different protocols in use; a full discussion of CMV prevention methods is found in another section.

Epstein-Barr virus (EBV)

Posttransplant lymphoproliferative disease (PTLD) is a feared complication of transplantation. The highest PTLD risk is in the EBV seronegative recipient of an EBV seropositive graft, which most commonly occurs in pediatric recipients (49,50). PTLD can also develop in the seropositive recipient under the influence of augmented immunosuppression. Awareness of pretransplant serologies can target the highest risk group for close monitoring by EBV-PCR and preemptive interventions such as decreasing immunosuppression (II-2) (49,51). In pediatric transplant centers, EBV serology should be performed on donors and recipients (II-2). As approximately 90% of adults are seropositive for EBV, when EBV serology is not available, the adult donor should be presumed to be seropositive.

Other herpesviruses

Other herpesviruses of clinical importance in the transplant recipient include herpes simplex virus (HSV-1 and HSV-2), varicella-zoster virus (VZV), human herpesvirus-6 and 7 (HHV-6 and 7) (52) and HHV-8 (KSHV) (53). HSV screening is performed by some centers, whereas other centers administer universal antiviral prophylaxis for at least the first month posttransplant. As primary varicella infection posttransplant can be fatal, VZV screening of the recipient is extremely important, with vaccination of the seronegative recipient pretransplant if at all possible (III). In addition, knowledge of VZV serostatus after transplant is important in the management of VZV exposures.

Recent awareness of the possible roles of HHV-6 and HHV-7 as cofactors for CMV effects, fungal infections and possibly allograft dysfunction has led to increasing interest in these viruses (52). Since almost all adults are seropositive, however, donor and recipient screening for these viruses has not generally been recommended. Whether or not such screening would be helpful in pediatric transplant programs is as yet unknown. HHV-8, the agent of Kaposi's sarcoma, can reactivate after transplantation and may be transmitted by transplantation (53,54); it may also be associated with EBV-negative lymphoproliferative disease (55). The seroprevalence varies widely according to the population studied. Optimal strategies for prevention of reactivation have not been defined, thus definitive recommendations for pretransplant screening can not be made at the present time.

Hepatitis B virus

All donors and recipients should be tested for hepatitis B using standard serologic techniques. The complex issues

surrounding HBV and transplantation are discussed in more detail in the hepatitis section of these Guidelines. Donor screening usually includes at least hepatitis B surface antigen (HBsAg) and HBV core antibody (HBcAb, which is most useful when performed as IgG and IgM). Donor HBsAg positivity or HBcAb-IgM positivity indicates active HBV infection. HBsAg negative, HBcAb-IgM positive persons may be in the 'window period'; such donors have generally not been utilized, although some centers have used these donors in recipients with evidence of immunity to hepatitis B (+ HBsAb) and/or with intensive posttransplant prophylaxis and monitoring. Isolated HBsAb positivity usually indicates prior vaccination or resolved infection and is not generally considered a risk for HBV transmission.

The most complex question is the use of the HBsAg negative, HBcAb-IgG positive donor ('core-positive donor') (56,57). This may represent either a false-positive test (if isolated HBcAb positive) or persistent HBV infection. If the latter, there is a significant risk of transmission of HBV to a liver transplant recipient, and therefore these livers were often not utilized in the past (II-2); however, it has now become more common to transplant livers from HBcAb positive donors with intensive posttransplant prophylaxis (58). The risk for transmission to nonhepatic recipients appears to be low but not zero (56,57); this risk can be further diminished by pretransplant HBV vaccination of the recipient. Some centers restrict the use of such organs to life-threatening situations and/or vaccinated recipients, or would utilize posttransplant prophylaxis with hepatitis B immune globulin (HBIG) and/or lamivudine if transplanted into a nonimmune recipient (II-3) (11). Because of the possibility of being offered such an organ, it is prudent to vaccinate all seronegative transplant candidates with HBV vaccine, although the response to this vaccine in patients with end-stage organ disease may be suboptimal, and higher or additional dosing strategies may be required (III). A donor HBV-DNA level provides helpful information for designing prophylactic strategies, even if the result is received after transplant (11). Detailed recommendations for posttransplant prophylaxis can be found in Chung et al. (11), and in the Hepatitis section of these Guidelines.

Recipient screening for HBV is helpful in posttransplant management. In patients undergoing a liver transplant because of end-stage liver disease due to HBV, there are a variety of posttransplant protocols for prevention of reactivation of HBV, many utilizing HBIG. Nonhepatic transplantation in HBsAg positive recipients has been controversial. In the early days of kidney transplantation, such transplants were performed, with some recipients developing early fulminant liver disease and a greater number developing chronic liver disease. Some have maintained asymptomatic status after many years despite evidence of active viral replication (59). Then, for a period of time, HBsAg positive status was considered a contraindication to nonhepatic transplantation. Now, with more effective therapies such as lamivudine, adefovir and tenofovir available, it

appears theoretically possible to transplant such recipients more safely (60) although antiviral resistance may become an issue (III).

Hepatitis C virus

HCV infection is frequently chronic, and donors and recipients should be tested for the presence of HCV via standard serologic techniques. HCV is a major indication for liver transplantation, and although HCV recurrence is common posttransplant, patient and liver graft survival are not significantly worse than with other pretransplant diagnoses. HCV seropositive renal transplant candidates are at higher risk for liver disease and sepsis after transplant than are their HCV seronegative counterparts, but compared with no transplantation as the alternative, the balance of benefit often falls on the side of transplantation in most cases (61). The role of pretransplant viral load reduction is under study. Strategies for management of HCV in the recipient are discussed in detail in a later section.

Hepatitis C antibody-positive donors have traditionally been considered a dilemma, because of the high risk of transmission of HCV through transplantation of any organ. A positive donor HCV-RNA, indicative of active viral replication, has been associated with a higher risk of transmission, but often this information is not available in the time frame required to utilize a deceased donor. The risks of transmission from HCV-RNA negative, HCV antibody positive donors have not yet been fully defined. In the future, rapid molecular testing will likely be increasingly performed in the time frame needed for donor evaluation.

The 2001 Crystal City Meeting reported that there was no increase in 1- or 5-year mortality or morbidity in transplanting a liver or kidney from an HCV-positive donor versus an HCV-negative donor into an HCV-positive recipient (10). However, a large 2003 study by Abbott and colleagues of over 36 000 adult deceased-donor renal transplant recipients demonstrated an independent risk for increased mortality with HCV-positive donors, even in the subgroup of HCV-seropositive recipients (62). When compared with remaining on the waiting list, there was a survival advantage to receiving a kidney from an HCV+ donor (63). Thus, survival with a kidney from an HCV+ donor, while less than that seen in the setting of an HCV negative donor, appears to be associated with better survival than remaining on dialysis (64).

In recent years, the use of HCV+ organs for life-saving transplants in HCV-negative recipients has also been studied, sometimes with acceptable results. In a survey of lung transplant programs, 55% reported utilizing HCV seropositive donors, in many cases restricted to HCV seropositive recipients (65). A survey of heart transplant programs revealed that most centers use HCV+ donors for status 1 and/or HCV+ transplant candidates; only 26% of centers reported never using HCV seropositive donors. In

that survey, 64% of centers reported listing HCV+ candidates for heart transplantation (66). However, one series identified an excess of rapidly progressive cholestatic hepatitis and an increased mortality overall for HCV- recipients of HCV+ donor hearts on mycophenolate-based immunosuppression (67). Whether specific immunosuppressive regimens are preferred in such situations requires further study. In any event, whenever an HCV seropositive donor is utilized, stringent informed consent is advisable.

As recent transmission events have proven, HCV can be transmitted to multiple organ and tissue transplant recipients from a seronegative donor (19,20). The time between infection and antibody production can vary in HCV-infected individuals, although viral RNA may be present much earlier after acute infection. The efficacy and feasibility of NAAT and other confirmatory HCV RNA testing is being investigated in the hope of decreasing the risk of transmission from donors to recipients.

Human immunodeficiency virus (HIV)

HIV-seropositive donors have traditionally not been utilized in transplantation, due to the known risk of transmission to the recipient. HIV-1 and HIV-2 serologies are required for all potential donors and at least HIV-1 serology on all recipients; HIV-2 is rare in the United States and positive HIV-2 screening serologies are often false-positives. Western blot testing should be obtained for confirmation of any positive screening test for either HIV-1 or 2. In the potential living donor with risk factors for HIV exposure but negative HIV serology, a molecular viral test should be obtained, as these tests become positive prior to the development of a positive antibody test. When available, NAAT for HIV is also desirable for deceased donors with potential exposures identified in their social history. A recent report of HIV transmission from an antibody-negative organ donor underscored the risk of transmission if the donor is in the 'window' period after infection but prior to development of anti-HIV antibody (19).

Although previously considered a contraindication to transplantation, HIV seropositivity in the recipient is receiving renewed attention (68). Now that many patients with HIV on highly active antiretroviral therapy (HAART) regimens are living longer and with far less immunocompromise, in some cases it is end-stage organ failure rather than HIV that is the survival-limiting condition. A multicenter trial has been evaluating the feasibility of transplantation in such individuals. Updated results including 1- and 3-year graft and patient survival data indicate that these transplants are well tolerated with meticulous clinical care and careful attention to pharmacokinetics in the setting of significant drug interactions between immunosuppressive agents and HAART (68). The complex issues involved are more fully discussed in the HIV section of these Guidelines.

Human T-lymphotropic virus (HTLV-I/II)

HTLV-I is endemic in certain parts of the world including the Caribbean and Japan, and is often asymptomatic. However, infection with HTLV-I can progress after years or decades to HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP) or to adult T-cell leukemia/lymphoma (ATL); progression occurs in <1% and 2–4% of seropositive individuals in endemic regions, respectively. HTLV-II is a virus that is serologically difficult to distinguish from HTLV-I, although its association with disease processes is less certain. PCR assays can be used to distinguish HTLV-I and II. HTLV-I seropositive donors are often not utilized, although the use of such donors could be considered for a life-threatening situation, particularly in an older recipient, with appropriate informed consent (III). Some experts recommend more widespread use of such donors, citing a review of all recipients from the UNOS registry who received transplants from HTLV-I positive donors between 1998 and 2000; of 22 organs transplanted, no HTLV-I disease was reported in any recipient, with a median followup of 11.9 months (69). However, reports from Spain of donor-derived transmission of HTLV-I with rapid development of myelopathy in the recipients suggest exercising caution in the use of these donors (70–72). In endemic areas, recipients are often tested for HTLV-I/II antibodies, although little is known about the course of infection following solid organ transplantation. No cases of HTLV-I reactivation were observed in a series of Japanese HTLV-I seropositive recipients undergoing renal transplantation (73).

Emerging or unusual viral infections—West Nile virus, lymphocytic choriomeningitis virus, rabies and SARS

In recent years it has been increasingly recognized that emerging viral infections can have an impact in transplantation, through donor-derived transmission and with unusually severe presentations in recipients (74,75).

WNV is a flavivirus which can cause meningoencephalitis, and which has recently appeared in the United States. In the fall of 2002, the CDC's investigation of transmission of WNV from a single donor to four organ recipients was reported, and additional reports of transmission by blood transfusion and liver transplantation have appeared (76,77). It is unclear as yet what the magnitude of the risk of such transmission is, and the pattern of WNV activity is changing on a yearly basis. Serology and PCR for WNV are available but time-consuming. It is prudent to avoid any donor who has had an unexplained febrile illness, unexplained mental status changes, or unexplained meningitis or encephalitis. Since July 2002, all US blood bank products have been tested for WNV using the investigational NAAT performed at specific centers. In the fall of 2003, the US Health Resources and Service Administration (HRSA) issued a Guidance statement regarding donors and WNV, which recommended testing all prospective live donors with NAAT close to the time of transplant; avoiding donors with any form of unexplained or confirmed WNV encephali-

tis; and heightened clinical suspicion on the part of the treating clinician for any febrile illness occurring shortly after transplant. NAAT poses logistical challenges in some UNOS regions and is not mandated or donor screening. There is also concern that false positive NAAT may result in loss of noninfected organs and net loss of life particularly for liver and heart candidates on the waiting list (78). In some regions of Canada, prospective donors are tested for WNV NAAT.

Lymphocytic choriomeningitis virus (LCMV), a rodent-associated arenavirus, has been reported in several clusters of donor-derived transmission to multiple organ recipients, most of whom had fatal infection (15,79). In one cluster, the outbreak originated from a new pet hamster in the donor's home (15). Strikingly, however, the donor's LCMV serology was negative, raising questions as to what kind of screening measures could have detected and prevented this transmission (15). The CDC has issued interim guidelines for minimizing risk of LCMV related to pet rodents (80).

The investigation of this LCMV outbreak involved molecular diagnostic testing for dozens of pathogens, and established the value of cooperation and communication between OPO's, transplant centers, public health departments and the CDC in investigating unusual clinical scenarios in transplant recipients when donor-transmitted infection is suspected (15). The blueprint from this investigation has led to increasing awareness of donor-derived infection and now a comprehensive reporting system introduced by the CDC (21,22). A recent report of donor-derived transmission of a new related arenavirus to multiple recipients has also highlighted the use of new molecular technologies for identification of unknown pathogens (81).

Rabies is another potentially fatal donor-derived infection (14,82). Recipients of transplants from a donor who died of cerebral hemorrhage acquired a rapidly progressive neurologic illness which was found to be rabies; retrospectively, the donor was found to have had a recent bat bite (14,82). In the US, rabies is transmitted most commonly by bites, scratches, or other saliva exposure from bats, raccoons, skunks or foxes. The rabies and LCMV cases raise the question of whether donor evaluations should include information about exposure to animals, bites, and other environmental exposures to supplement the already detailed information obtained. Because of the highly fatal nature of rabies infection, clinicians are encouraged to avoid donors where even a small possibility of rabies is present.

In 2003, a new respiratory pathogen was reported to cause severe disease with rapid international spread. Severe Acute Respiratory Syndrome (SARS) was found to be due to a previously undescribed coronavirus, with nosocomial and household transmission. At least 10% of affected patients required mechanical ventilation; at least one transplant recipient died of SARS (83). While

transmission by transplantation is theoretically possible, the extent of this risk is unknown. Current principles of donor and recipient selection would likely exclude patients with recent acute illnesses meeting SARS criteria; however the consequences of a more remote history of SARS, or a subclinical infection, are unknown. Screening tools for potential adult and pediatric donors were proposed by experts in Toronto (one of the major centers of the 2003 outbreak), which took into account the risk of SARS transmission at the donor's hospital as well as donor symptoms, travel, and contact history (83). If another SARS outbreak should occur, or a similarly transmitted emerging virus, this donor screening algorithm would be very useful.

Other new and emerging, potentially communicable agents may arise which may affect donor acceptability or recipient activation on the transplant list (74,75). It is advisable to avoid transplantation involving individuals with potentially communicable infections for which inadequate information exists to provide appropriate recommendations regarding precautionary measures.

Additional screening tests for emerging pathogens, or more sensitive testing for known pathogens, may be proposed by guidelines committees in the future (22,23,78). Such committees will have to consider the feasibility of testing as well as the risk of false-positive test results which could lead to not utilizing donor organs which otherwise might have been life-saving for some recipients (78).

Recipient Screening: Pretransplant Detection of Active Infection in the Recipient

Transplant recipients are at risk for infections related to complications of organ failure. Patients awaiting renal transplants may have infected hemodialysis or peritoneal dialysis access sites or catheters, or complicated upper- and/or lower-tract urinary infections. Candidates awaiting liver transplants are at risk for aspiration pneumonia, spontaneous bacterial peritonitis, urinary tract infection and infections associated with intravenous catheters. Candidates awaiting heart transplants may have infections related either to indwelling intravenous catheters, or to ventricular assist devices (VADs) utilized as a bridge to transplantation (84). In addition, heart candidates are also at risk for pneumonia in the setting of congestive heart failure and debilitation.

Ventricular assist-device (VAD)-associated infections should be treated prior to transplantation although complete eradication may not be possible until after transplant. These infections are common because the VAD is a large foreign body that may be in place for three months or longer (84). The portal of entry is most frequently the abdominal wall exit site of the driveline. There may be exit site drainage and local infection, more proximal infection

in the VAD pocket, bacteremia, and/or endocarditis. Causative organisms include coagulase-negative staphylococci, *S. aureus*, aerobic gram-negative bacilli, and yeast. Prolonged antibacterial therapy may lead to *Candida* superinfection. These infections are not a contraindication to transplantation, however, as total removal of the VAD at the time of transplant, combined with appropriate posttransplant antibiotic therapy, is often curative (84).

Screening of lung transplant recipients includes an assessment of colonizing airway flora, and careful review of their previous pulmonary infections (85). Cystic fibrosis patients may be colonized with multiresistant strains of *Pseudomonas* and/or *Burkholderia cepacia* as well as other organisms such as *S. aureus*, *Alcaligenes*, *Stenotrophomonas*, *Aspergillus* and *Scedosporium*. Knowledge of the pretransplant colonizing flora can assist in decisions regarding an individualized peritransplant prophylactic antimicrobial regimen. There is controversy as to whether patients colonized with *Burkholderia* should be excluded from receiving lung transplants; molecular typing of *Burkholderia* isolates is a promising method that may be used to define risk in the future, as genomovar 3 (*Burkholderia cenocepacia*) is associated with the highest risk of poor outcomes after transplantation (86).

Recipient Screening: Mycobacterial Infections

All patients should have a PPD (tuberculin skin test) performed prior to transplant, and those who have a positive skin test, or a history of active tuberculosis, should undergo additional screening to rule out active disease (see below) (II-2) (35). Recently, the availability of the IGRA has generated interest (36), particularly with regards to patients who received Bacillus Calmette-Guerin (BCG) vaccination as the IGRA assay has the potential to distinguish PPD positivity related to BCG from that related to LTBI (87).

Isoniazid hepatotoxicity appears to be less of a problem than originally thought in transplant candidates and recipients (35,38), and therefore patients with a history of positive PPD or radiographic evidence of prior TB with no previous treatment should be considered for isoniazid prophylaxis (I). Prophylaxis can be started while the patient is on the transplant waiting list and completed after transplantation if a donor organ becomes available and at least 1–2 months of isoniazid has been administered. The prophylaxis course (9–12 months) can be completed after transplantation. If transplantation is urgently needed or if isoniazid is poorly tolerated prior to transplantation, prophylaxis can begin shortly after transplantation. Alternatives to isoniazid prophylaxis in this population for those who have true allergies or severe intolerance to isoniazid are not clearly defined. Rifampin, another option for prophylaxis, has significant drug interactions with calcineurin inhibitors; if utilized, the course should be completed prior to transplantation.

In transplant candidates with a clinical history, radiographs, and/or cultures suggesting infection with TB or nontuberculous mycobacteria, a thorough evaluation for active disease should be performed, which may include CT scans, bronchoscopy or other tests as deemed clinically necessary. Any mycobacterial infection should optimally be treated with documented microbiologic and radiographic resolution before transplantation is considered.

Recipient Screening: Fungal Infections

Pretransplant colonization with fungi such as *Aspergillus* is common in lung transplant recipients, particularly in cystic fibrosis patients. Such colonization should prompt a rigorous evaluation to exclude active infection. Although posttransplant aspergillosis is a feared complication, transplant clinicians have generally relied more on posttransplant preemptive and prophylactic strategies rather than pretransplant antifungal therapy for colonized patients. A pretransplant candidate with *invasive fungal infection* (rather than colonization) should be treated at least until there is radiographic, clinical and microbiologic resolution in order to minimize the risk of this high-mortality infection posttransplant (III).

Pretransplant screening for endemic mycoses is most useful in areas endemic for coccidioidomycosis, where a pretransplant history of active disease and/or seropositivity may prompt lifelong azole prophylaxis (II-2) (41). Pretransplant screening for histoplasmosis is of limited value since latent histoplasmosis may be present with a negative serology (III); instead, heightened awareness of the possibility of histoplasmosis is important when investigating a posttransplant febrile illness in a patient from an endemic area.

Recipient Screening: Parasitic Infections

Patients from endemic areas or who have traveled for extended periods of time to endemic areas for strongyloidiasis (including most tropical countries and parts of the southeastern United States) are at risk for development of disseminated strongyloidiasis after transplant. Although some centers screen with stool ova and parasite examinations, some experts favor screening with serology for *Strongyloides*, which is much more sensitive than stool exams (III). For seropositive patients, a short course of ivermectin or thiabendazole is indicated pretransplant, although randomized data are lacking. Regimens utilized include ivermectin 0.2 mg/kg daily for 2 days; some clinicians recommend repeating the same 2-day course one week later. As discussed above, *Toxoplasma* serology is important in heart recipients, and seronegative heart recipients with seropositive donors should receive prophylaxis (II-2) (42). Chagas disease and other parasitic infections are more fully discussed in the Parasitic Infections section of these Guidelines.

Recipient Screening: Viral Infections

Active primary infection with viruses such as CMV, EBV or HBV at the time of transplant is uncommon. Nonetheless, if active viral infection is detected in a potential recipient, transplantation should likely be delayed until the infection resolves in order to allow for development of natural immunity prior to transplant immunosuppression (III). This recommendation also extends to candidates who present for transplantation with clinical symptoms suggestive of an acute community-acquired viral infection. If there is any chance of exposure to HIV pretransplant, the potential recipient should have an HIV molecular detection test as well as HIV antibody testing (III). Viral screening of both donor and recipient is discussed in more detail above.

Pretransplant Immunizations

The pretransplant evaluation presents an important opportunity to update the potential recipient's immunizations, since many vaccinations are more effective when administered prior to the onset of transplant immunosuppression (I). More detailed immunization recommendations are summarized in a later section of these Guidelines.

The varicella-seronegative candidate should ideally be immunized against varicella prior to transplantation (II-3). However, if transplantation is expected imminently, it may be best to withhold it as varicella vaccine is a live attenuated vaccine (III). The zoster vaccine, also a live vaccine, is currently licensed for older adults who are not immunocompromised. Further data are awaited regarding whether pretransplant zoster vaccine prevents posttransplant zoster reactivation, but at the present time it would appear reasonable to administer the zoster vaccine if the transplant candidate meets current criteria for the vaccine and if transplant is not expected within 3 weeks.

Yearly influenza vaccine should be administered to transplant candidates. (II-2). Vaccination of household contacts and health care workers is also very important, as immunocompromised patients may not mount an optimal antibody response to the vaccine (I).

A hepatitis B vaccine series should ideally be administered pretransplant to seronegative individuals (II-2); especially as a potential donor may be found who is HBsAg negative but HbCAb positive. Some clinicians have advocated an accelerated course (e.g. 0, 1, 2 months) rather than the traditional schedule of 3 doses at 0, 1 and 6 months, but further data are awaited (III). The response to the vaccination is diminished in end-stage organ disease, so that early vaccination in the patient who may eventually require transplantation is indicated. Enhanced potency formulations for dialysis patients and others are available.

Patients with advanced liver disease are at particularly high risk for fulminant hepatitis A and should receive hepatitis A

vaccination (II-2). This vaccine is likely more effective when administered early on in liver disease (II-2). The combined hepatitis A and B vaccine is immunogenic but data are awaited in transplant candidates and recipients.

Measles–mumps–rubella (MMR) vaccine contains live virus. Patients born in or before 1956 are presumed to have natural immunity. Patients born after 1956 who have not received a second dose of the MMR vaccine should receive a second dose, given pre rather than posttransplant (III).

The 23-valent pneumococcal polysaccharide vaccine ideally should also be administered to transplant candidates over the age of 2 who have not received it within the past 5 years (III) (please see the Immunizations section for pediatric recommendations). The tetanus–diphtheria toxoid (Td) booster (or now preferably the Tdap or tetanus–diphtheria–acellular pertussis vaccine) should be administered if the potential adult recipient has not had a Td booster within 5–10 years (III).

Pretransplant Counseling

Prevention strategies for infection should not be limited to medications and vaccinations. A thorough education of the transplant recipient and his or her family is a very important preventive tool. Pretransplant classes and printed materials are helpful and should include information on handwashing/hand hygiene, environmental exposures, activities to avoid, food safety and handling, foodborne pathogens, pets and travel. It is also helpful for patients to have a general idea of the infections to which transplant patients are susceptible and the prevention strategies in use at their particular center.

Conclusion

Pretransplant screening of the donor and recipient affords an opportunity to assess the safety of transplantation, to determine the prophylaxis and preventive strategies utilized posttransplant, to detect and fully treat active infection in the potential recipient prior to transplant, to update the vaccination status of the potential recipient, and to educate the patient and family about preventive measures. Future advances will likely include the increasing use of rapid molecular diagnostic testing, and possibly additional testing for emerging pathogens.

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