Is This Organ Donor Safe?

Donor-Derived Infections in Solid Organ Transplantation

Staci A. Fischer, MD[a,b,*]

KEYWORDS

• Transplant infections • Donor-transmitted infections • Donor-derived infections
• Organ donor screening • Lymphocytic choriomeningitis virus

KEY POINTS

- Organ donor–derived infections are uncommon but may cause significant morbidity and mortality in transplant recipients.
- Diagnosis of infection in deceased donors may be challenging due to reliance on next of kin to provide critical medical and social history, the short time available for evaluation and testing, and the lack of rapid, sensitive assays for uncommon organisms.
- Growing experience with the use of donors at increased risk for infection with human immunodeficiency virus, hepatitis B virus, and hepatitis C virus suggests that these donors may be used with caution and informed consent of the recipients.
- Donors with unrecognized meningoencephalitis may transmit multiple infections including viruses, for which limited therapies exist.
- Careful screening of donors is paramount to improving the safety of organ transplantation.

In 2017, more than 10,000 deceased donors provided organs for more than 28,000 patients in the United States.[1] Although advances in critical care and immunosuppressive therapy have facilitated the use of more deceased donors and improved the outcomes of many transplant procedures, infection remains a common and significant complication of solid organ transplantation (SOT).[2] Causes of post-transplant infection include health care–associated infection during hospitalizations, community-acquired infection, and reactivation of latent infection in the recipient. Transmission of infection from donor to recipient, although less common than the other etiologies, ranges from the routine to the devastating. Although donor-derived infections, such as cytomegalovirus (CMV), are well-studied, anticipated, and able to be prevented in most

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[a] The Warren Alpert Medical School of Brown University, 222 Richmond Street, Providence, RI 02903, USA; [b] Accreditation Council for Graduate Medical Education, 401 North Michigan Avenue, Suite 2000, Chicago, IL 60611, USA
* 470 North Lane, Bristol, RI 02809.
E-mail address: sfischer@acgme.org

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cases, the number and variety of pathogens transmitted with transplantation continue to grow (**Box 1**).[3–31]

RISK OF INFECTION IN ORGAN DONORS

Most organs transplanted in the United States are from deceased donors, who often require intensive medical care prior to becoming candidates for donation, with mechanical ventilation, indwelling vascular and urinary catheters, and administration of broad-spectrum antimicrobials. As a result of intensive care, donors may become colonized or infected with resistant bacterial pathogens as well as fungi, including *Candida* and *Aspergillus*. In many cases, donors with documented bacterial infections on effective antimicrobial therapy may be used when the recipients are also treated; caution should be used with multidrug resistant organisms and infections of the allograft itself. Donors may also harbor latent infections (eg, *Histoplasma*, *Coccidioides immitis*, *Mycobacterium tuberculosis*, and strongyloidiasis), based on their epidemiologic exposures. When transplanted into a recipient on immunosuppressive therapy, these latent infections may reactivate, causing disseminated disease. Because 1 donor may provide organs to as many as 8 recipients, who may be scattered across multiple transplant centers, states, and regions, prompt recognition of donor-derived infections and communication between transplant centers and organ procurement organizations (OPOs) is critical to improving outcomes of these often devastating infections.

WHEN TO SUSPECT DONOR-DERIVED INFECTION

In most cases, infections transmitted from an organ donor present early post-transplant, often in the first 6 weeks. Some pathogens with long incubation periods or latent infection, however, may take months to even years to present in the immunocompromised transplant recipient. Most outbreaks of infection have been identified when more than one recipient of an organ from a common deceased donor develops similar symptoms and signs.[8–12] Because recipients are often hospitalized in different transplant centers and may be under the care of different teams within the same institution, recognition of a pattern of clinical findings may be difficult. If a recipient develops fever, leukocytosis, leukopenia, or other potential signs of infection early post-transplant, and donor-derived infection is considered a possibility, the responsible OPO should be contacted to discuss the findings and determine whether other recipients of organs from the same donor are experiencing similar illnesses. State public health departments and the Centers for Disease Control and Prevention (CDC) can also be of assistance in investigating the cause of an outbreak of infection.

SCREENING ORGAN DONORS FOR INFECTION

Screening potential donors for infection remains crucial to improving the safety of organ transplantation. The United Network for Organ Sharing is contracted by the Department of Health and Human Services to serve as the Organ Procurement and Transplantation Network (OPTN), responsible for policy development and oversight of SOT in the United States. The policies of the OPTN and the experience of the transplant infectious disease community have resulted in recommendations for routine screening of potential donors for several pathogens (**Box 2**).[32–35] Screening for antibodies to HTLV types I and II had been routine for many years, but with the prevalence

Box 1
Pathogens reported to be transmitted via solid organ transplantation

Bacteria

Acinetobacter species
Bartonella species
Brucella species
Ehrlichia species
Enterobacter species
Enterococcus species
Escherichia coli
Klebsiella species
Legionella pneumophila
Listeria monocytogenes
Mycoplasma hominis
Nocardia species
Pseudomonas aeruginosa
Salmonella species
Serratia species
Staphylococcus aureus
Streptococcus species
Treponema pallidum
Veillonella species
Yersinia enterocolitica

Fungi

Aspergillus species
Blastomyces dermatiditis
Candida species
Coccidioides immitis
Cryptococcus neoformans
Histoplasma capsulatum
Prototheca
Scedosporium apiospermum
Zygomyces
Microsporidia
Encephalitozoon cuniculi

Mycobacteria

Mycobacterium tuberculosis
Nontuberculous *Mycobacteria*

Parasites/protozoa/prions/amebae

Babesia species

Balamuthia mandrillaris
Creutzfeld-Jakob disease
Naegleria fowleri
Plasmodium species
Schistosoma species
Strongyloides stercoralis
Toxoplasma gondii
Trypanosoma cruzi

Viruses

Adenovirus
BK virus
CMV
Epstein-Barr virus
HBV
HCV
Hepatitis D virus
Hepatitis E virus
Human herpesvirus 6
Human herpesvirus 7
Human herpesvirus 8
HIV
Human T-lymphotropic virus
Influenza virus
Lymphocytic choriomeningitis virus
Parainfluenza virus
Parvovirus B19
Rabies virus
Varicella-zoster virus
West Nile virus

Data from Refs.[3–31]

of infection in the United States and few donor-transmitted events, serologic screening for this viral pathogen is no longer indicated.[36]

All potential donors should be screened for blood-borne pathogens, such as HIV, hepatitis B, and hepatitis C; those living in endemic areas should also be tested for hepatitis E, an increasingly recognized pathogen in transplant recipients. Serology for CMV and Epstein-Barr virus should be performed to predict the risk of transmission and guide post-transplantation monitoring and CMV prophylaxis. Donors with specific epidemiologic risk factors for infection with endemic fungi, *Strongyloides*, *Trypanosoma cruzi*, *Cryptococcus*, West Nile virus, and other pathogens should be screened for infection with these organisms; in some cases, prophylactic therapy may be

Box 2
General screening for potential organ donors

Required by OPTN policy
- Serology for HIV, hepatitis B, and hepatitis C (repeat within 28 days of donation in living donors)
- CMV IgG
- Epstein-Barr virus IgG
- HIV-1/2 antibody or HIV antigen/antibody assay
- Hepatitis B surface antigen and core antibody; consider NAT
- Hepatitis C NAT
- Syphilis screening
- Toxoplasma IgG
- Blood, urine, and sputum cultures

Recommended additional screening:
- Tuberculosis screening (purified protein derivative or interferon-γ release assay)
- Testing based on prior history of living in an endemic area
  - *Strongyloides* antibody
  - *Trypanosoma cruzi* antibody
  - *Histoplasma* antibody
  - *Blastomyces* antibody
  - *Coccidioides immitis* antibody
  - Hepatitis E antibody
- Testing based on epidemiologic exposures
  - *Brucella* antibody
  - *Cryptococcus* antigen
  - West Nile virus antibody

Organ-specific testing: urine culture for kidney donors, bronchoalveolar lavage fluid/sputum culture for lung donors

Data from Refs.[32–35]

indicated.[18,31–35] The risk of infection is related to the tissue tropism of specific pathogens (eg, *Toxoplasma* and *Trypanosoma* in heart transplants and BK virus in kidney transplants) as well as viability of the organisms.

Because screening for many infections is based on serology, the sensitivity and specificity of the assays used must be considered in choosing a donor screening methodology. Results of these tests may also be affected by dilution from transfusion of multiple blood products and crystalloid into deceased donor candidates.

The key to assessing the risk of infection from a particular donor is obtaining an accurate history of exposures. OPOs are responsible for reviewing available medical records and interviewing family members to ascertain this information. Questionnaires used to guide next of kin discussions are not standardized across the United States but generally address medical and social factors to help assess organ quality and the risk of infection. The information gathered is dependent on the accurate knowledge of those questioned with the prospective donor's circumstances. In evaluating potential living donors, transplant centers have time to assess medical, social, and exposure histories and treat any identified infections prior to donation to prevent transmission.

SELECTED PATHOGENS THAT CAN BE DONOR TRANSMITTED

Balamuthia mandrillaris

Two outbreaks of donor-transmitted *Balamuthia mandrillaris* have recently been described.[20,21] This free-living ameba, known to cause granulomatous amebic

encephalitis, is found in soil in multiple areas of the world, including the United States, where infection seems more common in patients of Hispanic ethnicity. Infection is believed to result from inhalation or inoculation into broken skin, with spread to the brain and spinal cord. In both transplant-related clusters, the organ donor presented with headache and focal brain lesions on CT or MRI; 1 donor had a several month history of neurologic symptoms. One donor had fever; the other was afebrile but demonstrated lymphocytic pleocytosis on cerebrospinal fluid (CSF) testing. In both cases, some recipients developed neurologic symptoms (eg, headache, blurred vision, and ataxia), whereas others were asymptomatic; fever was variably present. CSF revealed lymphocytic pleocytosis and MRI demonstrated multiple ring-enhancing lesions in some of the recipients. Histopathologic testing of brain tissue from symptomatic recipients at the CDC revealed evidence of *Balamuthia* infection, for which therapy was initiated with combinations of flucytosine, pentamidine, sulfadiazine, fluconazole, azithromycin, and miltefosine, with variable outcomes, including infection clearance, significant neurologic sequelae, and death.[21]

Coccidioides immitis

Coccidioides immitis is an endemic fungus in the southwestern United States, Mexico, and parts of Central and South America, which can be transmitted with transplantation. Deceased or living donors who have visited or lived in an endemic area may have viable organisms that reactivate in the setting of immunosuppression in the recipient, regardless of whether they or their families recall previous infection, which is usually asymptomatic. Guidelines for treatment of exposed recipients recommend fluconazole, 400 mg daily for 3 months to 12 months, for nonlung recipients and lifelong therapy for lung transplant recipients when the donor has evidence of pulmonary coccidioidomycosis.[34] Screening of potential donors from endemic areas has been recommended to guide informed consent and treatment of the recipients.

Lymphocytic Choriomeningitis Virus

Multiple outbreaks of donor-derived infection with lymphocytic choriomeningitis virus (LCMV) and related arenaviruses have been described in recent years.[8–10] Because infection is most commonly asymptomatic, recognition of donor infection is difficult. Some donors may present with aseptic meningitis; the timeframe for deciding whether to use a deceased donor generally precludes CSF testing (eg, by culture, polymerase chain reaction [PCR], and/or enzyme immunoassay), which is available through the CDC and some state health departments. Exposure to wild or pet mice or hamsters, which may harbor lifelong asymptomatic infection, may be an important clue to the possibility of LCMV infection, for which no screening tests are routinely available. Decreasing immunosuppressive therapy and administration of ribavirin may be of use in treating infected recipients, in whom the mortality rate has been high.[8,10]

Strongyloides stercoralis

Strongyloides stercoralis is endemic in tropical and subtropical areas, including the southern United States. Infection may be asymptomatic, with reactivation causing disseminated disease (termed, *hyperinfection syndrome*) in immunocompromised hosts. Most donor-derived infection cases present within the first 6 months after transplantation, with variable symptoms; fever and eosinophilia, hallmarks of infection in immunocompetent hosts, are often absent.[18,19] Screening donors who have traveled to or lived in endemic areas with serology may be useful in preventing infection, by treating the living donor prior to procurement and/or treating the recipients with ivermectin and/or albendazole.[19]

Trypanosoma cruzi

Chagas disease, caused by *Trypanosoma cruzi*, is endemic throughout much of Mexico, Central America, and South America. Several outbreaks of donor-derived infection have occurred in the United States.[17] The risk of transmission is highest in heart and intestine recipients, due to chronic infection of myocardial and enteric tissues, although recipients of liver and kidney transplants have also developed infection. Donors from endemic areas should be screened for infection with serologic testing, and caution used when considering heart or intestinal transplantation. Monitoring noncardiac recipients with PCR and serology may be of assistance in diagnosing donor-derived infection. Treatment with nifurtimox and/or benznidazole may be challenging in the United States, where these agents are not readily available.

USE OF DONORS AT RISK OF HEPATITIS B VIRUS, HEPATITIS C VIRUS, OR HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Transplantation of organs from donors at risk for HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) poses inherent risk of transmission of infection to recipients. With increasingly effective therapies now available against these pathogens, centers are gaining experience with transplantation of organs from donors with treated (nonviremic) infection in selected recipients.[37–40]

All potential organ donors, regardless of risk, should undergo testing for HIV (anti-HIV 1/2 or HIV antigen/antibody), HBV (hepatitis B surface antigen and core antibody), and HCV (anti-HCV antibody and HCV-RNA by nucleic acid testing [NAT]), with results available prior to procurement. For potential living donors, testing should be repeated within 28 days of donation.

Although NAT has improved the sensitivity of testing potential organ donors for infection with these viruses, those with recent infection in the window period of current diagnostic testing may transmit infection. The US Public Health Service has developed guidelines for the testing and use of organs from donors at higher than average risk of infection with hepatitis B, hepatitis C, and HIV, which are termed, *increased risk donors* (*IRDs*) (**Box 3**).[41] It has been estimated that approximately 30% of donors in the United States and Canada meet these criteria.[42,43] As the opioid epidemic spreads in the US, more donors meet these criteria.

Those potential organ donors meeting criteria for increased risk should undergo more sensitive testing (eg, HIV NAT) prior to procurement, although results may not be available prior to transplantation from deceased donors. Living IRDs should undergo repeat testing using NAT within 28 days of surgery. Informed consent of recipients accepting organs from IRDs is critical, as is rigorous post-transplant NAT testing. Use of IRDs has been successful in many centers, proving an important resource in the current organ shortage. A recent registry review demonstrated a significant long-term survival benefit for recipients who accepted IRD kidneys, in which only 31% of those who declined an IRD offer had undergone transplant with a non-IRD donor after 5 years.[44]

MENINGOENCEPHALITIS

In recent years, outbreaks of donor-derived infections, such as rabies, West Nile virus, LCMV, and *Balamuthia*, have emphasized the difficulty in diagnosing encephalitis in potential deceased organ donors and the risk of transmission of infection if undetected (**Box 4**).[45,46] Donors with bacterial meningitis may be used if antimicrobial therapy is administered to the donor and all recipients. Undiagnosed meningoencephalitis of viral etiology may pose the greatest risk of donor-derived infection, due to high rates

Box 3
The US Public health service–defined increased risk donors

Men who have had sex with a man (MSM) in the past 12 months

Nonmedical injection drug use in the past 12 months

Having sex in exchange for money or drugs in the past 12 months

Having sex with a person known or suspected to have HIV, HBV, or HCV infection in the past 12 months

Women who have had sex with a man with a history of MSM behavior in the past 12 months

Having sex with a person who had sex in exchange for money or drugs in the past 12 months

Having sex with a person who injected drugs by intravenous, intramuscular, or subcutaneous routes for nonmedical purposes in the past 12 months

A child less than or equal to 18 months of age born to a mother known to be infected with or at increased risk for HIV, HBV, or HCV infection

A child who has been breastfed in the past 12 months whose mother is known to be infected with or at increased risk for HIV infection

In lockup, jail, prison, or a juvenile correctional facility for more than 72 consecutive hours in the past 12 months

Newly diagnosed with, or previously treated for, syphilis, gonorrhea, *Chlamydia*, or genital ulcers in the past 12 months

On hemodialysis in the past 12 months (HCV only)

When a deceased potential organ donor's medical/behavioral history cannot be obtained or risk factors cannot be determined, the donor should be considered at increased risk for HIV, HBV, and HCV infection because the donor's risk for infection is unknown.

When a deceased potential organ donor's blood specimen is hemodiluted, the donor should be considered at increased risk for HIV, HBV, and HCV infection because the donor's risk for infection is unknown.

From U.S. Department of Health & Human Services Organ Procurement and Transplantation Network. Understanding the risk of transmission of HIV, hepatitis B, and hepatitis C from PHS increased risk donors. Available at: https://optn.transplant.hrsa.gov/resources/guidance/understanding-hiv-hbv-hcv-risks-from-increased-risk-donors/. Accessed January 27, 2018.

Box 4
Central nervous system pathogens transmitted through solid organ transplantation

Aspergillus Species

Balamuthia mandrillaris

Coccidioides immitis

Cryptococcus neoformans

Herpes simplex virus

LCMV and related arenaviruses

Mycobacterium tuberculosis

Rabies virus

West Nile virus

of transmissibility, morbidity, and mortality and the lack of effective antiviral therapies. Recognition of infection may be limited by the myriad etiologies for fever and altered mental status in potential deceased organ donors as well as the limited diagnostic testing available for some of these pathogens (**Box 5**). Guidelines have been developed to assist OPOs in recognizing the potential donor with meningoencephalitis.[46]

When evaluating a potential donor with a presumed cerebrovascular accident (CVA) or stroke, OPOs and transplant centers should consider the following questions:

- Do the donor's age and comorbidities (eg, previous stroke, hypertension, and diabetes mellitus) support a diagnosis of CVA? Meningoencephalitis should be considered in younger donors and those without underlying comorbidities, in whom CVA is less likely.
- Were fever, altered mental status, and/or seizures noted on presentation? If there is not a clear explanation for these symptoms and signs, meningoencephalitis should be considered.
- Is there unexplained CSF pleocytosis, hypoglycorrhachia, or elevated protein (eg, no identified bacterial pathogen prior to initiation of antibacterial therapy)?
- Is there unexplained hydrocephalus, which could be a sign of infection?
- Is the donor immunosuppressed, so that the risk of infection is higher and atypical presentations possible?
- Does the donor have a history of potential environmental exposures to pathogens causing meningoencephalitis (eg, bats, rodents, and mosquitoes) or of living in areas endemic for or in the midst of epidemic spread of CNS pathogens (eg, West Nile virus and *Coccidioides*)?
- Was the donor homeless? This could result in exposure to rodents and their excreta.

In several investigations of transplant-related outbreaks of LCMV and rabies, risk factors for infection were not identified during pretransplant evaluation of the donors.[8,10,12] Caution should be used when the next of kin of a potential deceased donor is unfamiliar with the donor's recent history and exposures so that risk may not be accurately assessed.

INVESTIGATING AND REPORTING DONOR-DERIVED INFECTIONS

Prevention, identification, and treatment of potential donor-derived infections is a fundamental role of the transplant infectious disease specialist. The OPTN/UNOS, which regulates SOT in the United States, has an Ad Hoc Disease Transmission Advisory Committee (DTAC) that investigates possible transmission of infection and diseases (eg, malignancy) from donors to recipients and publishes its findings.[4–6,47]

Box 5
Challenges in recognizing central nervous system infections in potential deceased donors

Suspecting infection
- May be clinically silent
- May be difficult to differentiate from stroke or drug overdose

Diagnosing infection
- Limited time prior to procurement
- Specialized testing (eg, PCR) not available in a timely manner

Lack of effective treatments for many pathogens

When suspicious of donor-transmitted infection, notification of the responsible OPO and DTAC may help facilitate recognition of similar symptoms in other recipients and testing for possible donor-derived infections in the hope of improving outcomes of these uncommon events.

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