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Donor Issues in Organ Transplantation

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This is to acknowledge that Suzanne Wada, M.D. has disclosed that she does not have any financial interest or other relationships with commercial concerns related directly or indirectly to this program. Dr. Wada will not be discussing off-label uses in her presentation.

Biosketch:

Dr. Wada is an Associate Professor in the division of Infectious Diseases. She serves as the UTSW Clinical Director of Transplant Infectious Diseases. Dr. Wada completed her undergraduate degree in musical performance at the Boston University School of Music. Dr. Wada received her medical degree from Temple University School of Medicine in Philadelphia, PA. Dr. Wada completed her Transplant Infectious Diseases Fellowship at the University of Pittsburgh.

Purpose and Overview:

To review aspects of Transplant Infectious Diseases, with an emphasis on donor-derived infections.

Objectives:

1. To review aspects of why transplant recipients are vulnerable to infection.
2. To review the different mechanisms why transplant recipients get infections.
3. To review the phenomena of donor-derived infections.

Transplantation, An ID Physician's Perspective and Donor Issues

Transplantation continues to be an ever evolving medical field that involves a multitude of medical disciplines to ensure the success of an organ transplant. Patients continue to battle chronic illnesses with organ transplantation a viable option for many. Unfortunately, organ shortage continues to be a major hindrance. Because of organ shortage, the field of transplant continues to push the envelope by now considering organs from donors that perhaps in the past, would not be considered because of, for example, donor age, donor medical condition(s).

I hope in this presentation to review: the approach to infectious diseases in solid organ transplantation, with an emphasis on infections, both expected and unexpected, that donor organs from both, deceased and living donors, may transmit to the organ recipient.

History and Transplant Statistics

In 1954, in the USA, the first successful living-related kidney transplant took place, led by Dr. Joseph Murray and Dr. David Hume at the Brigham Hospital in Boston, MA. A kidney was transplanted from Ronald Herrick into his identical twin, Richard. This was followed in 1962, with the first successful kidney transplant from a deceased donor, again led by Dr. Joseph Murray and Dr. David Hume at the Brigham Hospital in Boston. (1)

In 1963, in the USA, the first successful lung transplant was led by Dr. James Hardy at the University Of Mississippi Medical Center in Jackson, MS. (1)

In 1966, in the USA, the first successful kidney pancreas transplant was led by Dr. Richard Liullehei and Dr. William Kelly at the University of Minnesota, in Minneapolis, MN. (1)

In 1967, in the USA, the first successful liver transplant was led by Dr. Thomas Starzl at the University of Colorado in Denver, CO. (1)

In 1967, Dr. Christiaan Barnard led the first successful heart transplant at Groote Schuur Hospital in Cape Town, South Africa, followed by in 1968, in the USA, the first successful heart transplant led by Dr. Norman Shumway at Stanford University Hospital in Palo Alto, CA. (1)

These were pioneering physicians who showed the world how organ transplantation was a viable option for terminal end stage organ failure.

In 2013, in the USA, 16,895 renal transplants occurred, 762 renal pancreas transplants occurred, 6,455 liver transplants occurred, 1.923 lung transplants occurred and 2,531 heart transplants occurred. (2) Organ shortage is reflected in the significant numbers of those on the waiting list, for all organ transplants. (3) Table 1, Organ Transplant Survival Statistics, from 2007, at one year and five years are shown, implying the superior quality of living donor organs. (2)

Table 1

Survival Statistics

	One year	Five years
Renal transplants	dd: 96.5% ld: 98.9%	dd: 81.9% ld: 91%
Renal pancreas transplants	96.7%	87.2%
Liver transplants	dd: 89.4% ld: 91.7%	dd: 73.8% ld: 79%
Lung transplants	82.7%	54.4%
Heart transplants	90.3%	44.9%

The ID Approach

In evaluating a solid organ transplant patient, assessing the degree of immunosuppression is of paramount importance. The main determinant of immunosuppression being the immunosuppressive therapies given to prevent organ rejection. Often a transplant recipient is on a combination of immunosuppressive agents. Certainly, in the first year post organ transplantation, the type of antilymphocyte therapies (T-lymphocyte depleting agents, nondepleting costimulatory blockade therapies, CTLA-4 antagonists and B-cell depleting agents) can have long lasting effects on the immune system as reflected in the description of the commonly used T-lymphocyte depleting agent, thymoglobulin.

In the first year post organ transplant, when organ recipients are on multiple immunosuppressive agents at higher dosages, the signs and symptoms of infection may be blunted, minimal and atypical. Conventional radiology studies may not be

adequate and more sensitive imaging techniques such as computed tomographic (CT) scans and magnetic resonance imaging (MRI) are often essential for assessing the presence of infectious processes. Early and specific microbiologic diagnosis is critical in treating the organ recipient appropriately. This often necessitates aggressive invasive procedures that provide tissue for culture and histology. In addition, early, aggressive surgical debridement of fluid collections, blood or devitalized tissue is critical.

Table 2 (4), is the Infectious Diseases Screening Tests for Solid Organ Transplant (SOT), pre-transplant. These labs and tests are done pre-transplant and are essential in predicting what infections the organ recipient may be at risk for post-transplant. Table 2 (4) reflects the importance of epidemiologic risk factors as reflected in the endemic fungal pathogens, parasitic pathogens and viral pathogens listed.

Table 2

Infectious Diseases Screening for SOT

Routinely Administered Testing	Other Potential Tests (Based on hx or clinical/lab/XR findings)
• CMV antibody	• Blood cultures
• EBV antibody panel	• Chest imaging
• HBV antibody panel	• Coccidioides antibody
• HCV antibody panel	• Cryptococcal antigen
• HIV-1/2 antibody	• Histoplasma antibody/antigen
• HSV antibody	• Respiratory viral antigen panel
• HTLV-I/II antibody	• Schistosoma antibody
• PPD	• Strongyloides antibody
• RPR	• Trypanosoma cruzi antibody
• Toxoplasma antibody	• UA/urine culture
• VZV antibody	• WNV antibody or NAT

Bowden, Transplant Infections, 3rd Ed., 2010

Fishman describes the Net State of Immunosuppression, which is a description of all the factors that contribute to the individual organ recipient's risk for infection. (7,17) these factors include: dose/duration/sequence of immunosuppressive therapies; the presence of: organ dysfunction, underlying immune deficits, tissue ischemia, metabolic derangements, leukopenia/neutropenia; as well as the presence

of: postoperative fluid collections, vascular catheters, surgical drains and tissue ischemia. (7,17)

In addition, the type of transplant, the presenting signs and symptoms, the temporal occurrence in relation to the transplant, preoperative evaluation of the organ recipient, organ recipient exposures both in/out of the hospital and the infectious history of the donor also contribute to the individual's organ recipient's risk for infection.

Figure 1 (26) Timeline of Infection Following Solid Organ Transplantation, by Fishman and Rubin, in 1998, is the classic original timeline for infections post-transplant in the first year post solid organ transplantation. Figure 2 (17) Fishman, in 2007, makes adjustments to the original 1998 timeline, taking into account donor-derived infections.

Figure 1

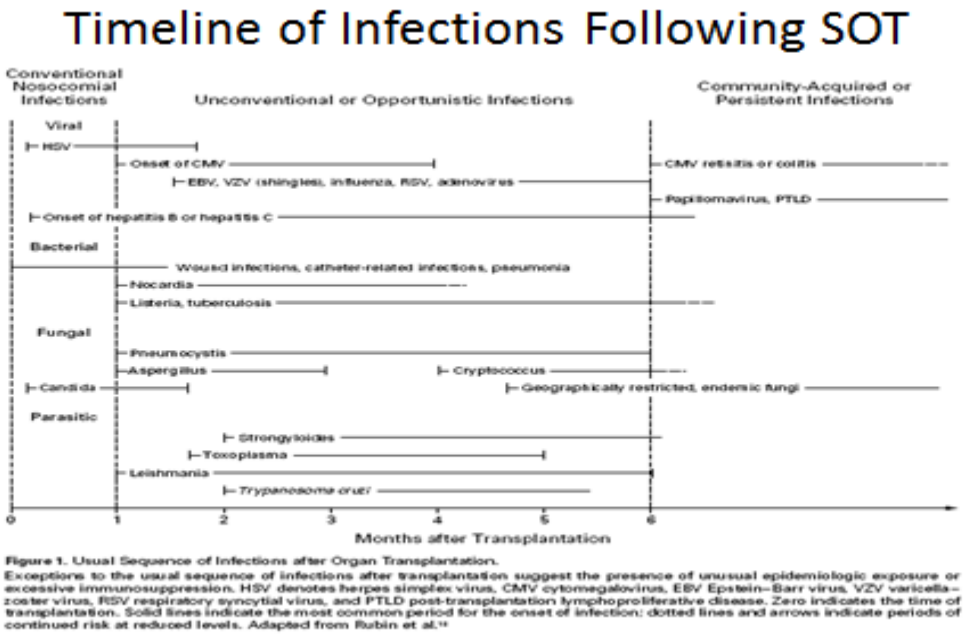
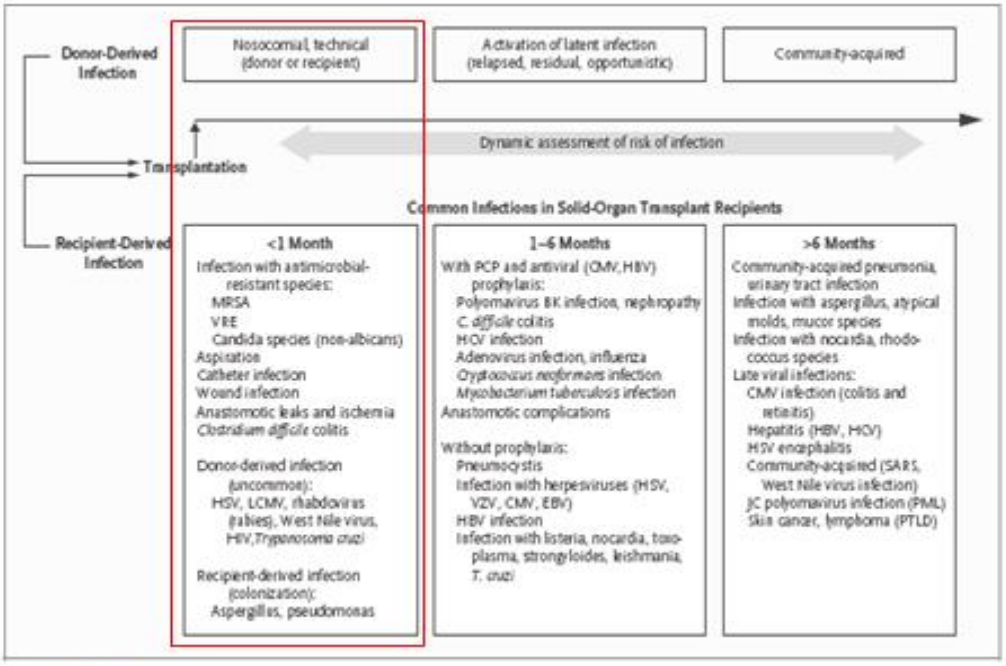


Figure 1. Usual Sequence of Infections after Organ Transplantation.
Exceptions to the usual sequence of infections after transplantation suggest the presence of unusual epidemiologic exposure or excessive immunosuppression. HSV denotes herpes simplex virus, CMV cytomegalovirus, EBV Epstein–Barr virus, VZV varicella–zoster virus, RSV respiratory syncytial virus, and PTLD post-transplantation lymphoproliferative disease. Zero indicates the time of transplantation. Solid lines indicate the most common period for the onset of infection; dotted lines and arrows indicate periods of continued risk at reduced levels. Adapted from Rubin et al.[19]

Fishman and Rubin, NEJM 1998

Figure 2



Fishman, *NEJM* 2007

In the first month after solid organ transplant, there are 2 major causes of infection in all forms of solid organ transplantation; infection derived from either the donor or recipient and infectious complications of the transplant surgery and hospitalization. (17) The major effects of exogenous immunosuppression are not yet evident. Immediate common postoperative infectious complications include: aspiration pneumonitis, surgical site (wound) infections, line sepsis, urinary tract infections. Organ recipients are at unique risk for superinfection of ischemic or injured graft tissues (eg, anastomotic suture lines) and/or fluid collections (eg, hematomas, lymphoceles, pleural effusions, urinomas). The organ recipient is at increased risk for infection associated with indwelling vascular access catheters, urinary catheters and surgical drains. The organisms responsible for postoperative complications are often the bacteria and fungi that have colonized the organ recipient or organ donor prior to the transplantation and the local flora of the hospital. The microbiologic history of the organ recipient and the organ donor are important factors in deciding on initial emperic antimicrobial therapy.

In the first month after solid organ transplantation, infections that have been transmitted from the donor (eg, donor-derived infections) to the organ recipient,

can include: bacterial (eg, vancomycin-resistant enterococci, methicillin resistant staph), viral (eg, LCMV, West Nile virus, rabies, HIV) and parasitic (eg, trypanosoma cruzi) pathogens. (17)

In the first month after solid organ transplantation, recipient-derived infections where the source is the organ recipient have included: Aspergillus, pseudomonas.

From one through six months after solid organ transplant, immunosuppression is most intense and in general, this is the period when organ recipients are most at risk for the development of opportunistic infections. Viral infections including: HBV, HCV, HSV, CMV, BK may reactivate. Recipient-derived mycobacterium tuberculosis, toxoplasma gondii, cryptococcus, histoplasmosis, coccidioides immitis, strongyloides stercoralis, trypanosoma cruzi also tend to reactivate more than one month after transplantation. (17) Prevention of the infections observed during this period is the basis of prophylactic antimicrobial strategies.

More than 6 months after transplantation, most patients are receiving stable and reduced levels of immunosuppression. (17). These organ recipients are living active lives and are prone to community-acquired pneumonias (eg, pneumococcus, legionella). However, there is a subset of organ transplant recipients with less than optimal graft function on higher than usual immunosuppressive therapy. As a result, they are at the highest risk for rare opportunistic infections (eg, nocardia, molds). Chronic viral infections, with cytomegalovirus being the biggest culprit, can contribute to allograft injury and allograft rejection.

Organ recipients at particular risk for nosocomial infections are those requiring prolonged ventilatory support or those with diminished lung function, those with persistent ascites/fluid collections, those with stents of the urinary tract or biliary ducts, and those with intravascular clot or ischemic graft tissue. (17) Organ recipients with delayed graft function or who require early reexploration or retransplantation are also at increased risk for infection, often with fungi or bacteria with antimicrobial resistance. (17)

Certainly each type of solid organ transplant comes with its own inherent infectious propensity (eg, urinary tract infection and Bk virus infection in kidney transplant recipients; intraabdominal abscess and wound infection in liver transplant recipients; pneumonia in lung transplant recipients; and a plethora of infectious possibilities in heart transplant recipients). (4)

The source of infection in solid organ transplant recipients can be from the: environment (-nosocomial), the recipient, the community and from the donor. If one is faced with an unexplained infectious syndrome, then one should consider a donor-derived infection(s). (7)

Donor-derived Infections

There are 2 major types of donor-derived infections, the expected secondary to donor and recipient screening and the unexpected despite routine screening. (6) The most common expected donor-derived infection is caused by the human herpes virus, cytomegalovirus (CMV). CMV donor-derived infection is most likely to occur when the organ donor is CMV IgG positive and the organ recipient is CMV IgG negative. Clinically, we refer to this as a CMV mismatch. CMV can infect multiple organ systems and cause significant morbidity. CMV is one of the most important infections affecting all organ transplant recipients. CMV and associated viruses play a role in allograft injury/rejection and other concomitant infections. (7)

High profile unexpected donor-derived infections have included: HIV, West Nile virus and rabies, etc. (5, 10, 22)

The medical/social history of the donor is of paramount importance in helping determine whether or not the donor is an increased risk donor. An increased risk donor has a lifestyle that exposes them to infection at a higher rate than the general population. Sexual history, exposure to blood products, illicit drug use, prior incarceration, etc., are explored for both the deceased donor and the living donor. (15, 19) It can be family or friend(s) who may provide the social history information for an individual whose organ(s) will be procured prior to death. This is a difficult time for family or friend(s) and obtaining reliable medical and social information may be challenging. (14) Donor screening labs are also obtained prior to organ procurement. (6, 15)

Increased Risk Donors (15) include:

- Men who have sex with another man in the preceding 5 years.
- Persons who report nonmedical intravenous, intramuscular or subcutaneous injection of drugs in the preceding 5 years.
- Persons with hemophilia or related clotting disorders who have received human derived clotting factor concentrates
- Men and women who have engaged in sex in exchange for drugs or money in the preceding 5 years.

- Persons who had had sex in the preceding 12 months with any person described in items above or with a person known as suspected to have HIV infection.
- Persons who have been exposed in the preceding 12 months to known or suspected HIV-infected blood through percutaneous inoculation or through contact with an open wound, nonintact skin or mucous membrane
- Current or recent inmates of correctional systems

The increased risk donor is described as: HIV positive, Hep Bs Ag positive, Hep Bcore Ab positive and Hep C Ab positive. Currently, HIV positive patients do not donate: blood products, tissue or solid organs. Each transplant center has their own protocol on accepting or not accepting the increased donor who is: Hep Bs Ag positive, Hep Bcore Ab positive or Hep C Ab positive. The transmission rate of either Hep B or Hep C is considerable, depending upon how active the Hep B or Hep C is in the donor, but in the case of Hep B transmission, the immunity of the organ recipient to Hep B, through prior exposure or vaccination, may be protective. (5)

Figure 3 (16), Schematic of viral infection and detection by serology and nucleic acid testing depicts viral exposure and the window period where antibodies are not yet detected, though nucleic acid testing may reveal evidence of viral replication, thus detecting infection.

Figure 3

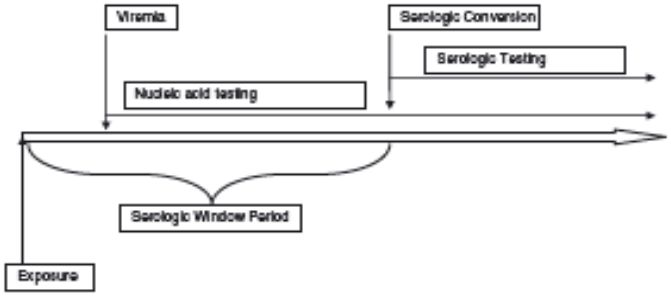


Figure 1: Schematic of viral infection and detection by serology and nucleic acid testing.

Several donor-derived infection transmissions have resulted from window period infections missed by serologic screening of donors. (16) Therefore, nucleic acid testing (NAT; sometimes referred to as PCR or vial load testing) has become an important pre-transplant screening test for both decreased and living organ donors.

The period from HIV exposure to the development of HIV antibodies is approximately 22 days, but can be up to 6 months. (16). Thus the potential donor may still be seronegative while potentially infectious. The use of donor NAT reduces the window period for HIV to between 6 and 10 days. (15) Hep Bs Ag Elisa assays have a window period of 38 to 50 days. Use of donor NAT reduces the window period for HBV to between 20 to 26 days. (15) Hep C Elisa assays have a window period of 38 to 98 days. Use of donor NAT reduces the window period for HCV to between 6 to 9 days. (15)

The use of organs from hepatitis Bcore Ab positive donors has been controversial, but the risk of hepatitis Bs Ag negative/hepatitis Bcore Ab positive donors is low in nonhepatic recipients, especially if the transplant candidate has been effectively vaccinated. (8) But, due to the shortage of transplantable organs (-livers) and the development of prophylactic strategies (eg, hepatitis B Ig, epivir, entecavir), the majority of transplant centers do accept livers from donors who are hepatitis Bcore antibody positive. (8) An emerging threat both to the efficacy of HBV vaccination and of hepatitis B Ig post-transplant prophylaxis is the existence of escape mutants of HBV for which hepatitis Bs Ab does not provide protective immunity. (8)

The first documented case of HIV transmission in the USA from a living donor was in 2009, despite screening of the donor with serologic testing. (23) The organ recipient had ESRD and received a kidney transplant from a living donor in NYC in 2009. (23) The organ recipient did not have any high-risk behaviors. One year after transplant, the organ recipient developed refractory oral/esophageal candidiasis and was found to be HIV positive. The living donor was known to have a h/o syphilis as well as a h/o of having sex with male partners. (23) Seventy-nine days prior to the transplant, the living donor was tested with results: HIV Ab negative, Hep Bs antigen negative, Hep C Ab negative and RPR 1:1. (23). One year after the transplant, the living donor tested positive for HIV. (23)

An investigation ensued. Stored organ donor and organ recipient serum were analyzed at the CDC. HIV NAT testing was done on all specimens. Living organ donor results at 57 days pre-procurement: HIV NAT negative, and 11 days pre-procurement: HIV NAT positive for 3 HIV genes. Organ recipient results at 11 days pre-transplant: HIV NAT negative and 12 days post-transplant: HIV NAT positive.(23)

Blood specimens from both the organ donor and organ recipient were obtained on post-transplant day 404. HIV DNA sequences from donor and recipient peripheral blood lymphocytes collected on day 404 were amplified and sequenced; sequences from these 2 specimens were analyzed phylogenetically together with HIV

sequences from the donor's frozen leukocyte specimen collected 11 days pre-transplant , with greater than 98% identity and tight phylogenetic clustering, highly suggestive that the 2 viruses were highly related. (23)

Donor-derived transmission of both HIV and HCV occurred in a 66 yr old cirrhotic female who had a liver transplant in 1/2007. (25) In 11/2007, the Organ Procurement Organization (OPO), contacted the institution where the transplantation occurred to inform them that the donor of the liver graft was both HIV and HCV positive. (25) The liver transplant recipient was tested for HIV and HCV and was found to be positive for both with: HIV-1 Ab positive, HIV-1 RNA greater than 500,000 copies/ml, CD4 ct 34 cells/mm3 and HCV RNA greater than 5 million IU/ml. (25) The liver transplant recipient was started on HAART with some improvement in her CD4 ct (eg, 112 cell/mm3) but her clinical course was complicated by: depression, urosepsis, cmv viremia, renal failure, multiple ring enhancing brain lesions and she ultimately expired on 1/2008, one year post liver transplant. (25) The institutions of the liver transplant learned from media reports that the heart and kidney organ recipients from the same donor also had become HIV and HCV positive. (25) The organ donor was a male who had h/o sex with men who had previously tested negative for HIV. The organ donor had predonation, pretransfusion and posttransfusion serologic testing with negative HIV Ab and HCV Ab results. Stored preoperative donor serum testing was found to be: positive for both HIV NAT and HCV NAT. (25)

Donor-derived bacterial infections can be transmitted via the allograft, donor bacteremia and the preservations fluid. (8). An estimated 5% of deceased organ donors are bacteremic at the time of organ procurement. (13) Donor bacteremia does not prevent theses organs from being successfully used in transplantation, however, ideally the donor would have received antimicrobial therapy prior to organ procurement and the organ recipient will receive a course of antibiotic(s) post transplantation using the deceased donor cultures as a guide to appropriate antimicrobial(s). (13) Organ donors with documented treatable bacterial meningitis can be successfully used for transplantation. (16) Donor bronchoalveolar lavage cultures at the time or organ procurement, should be used to guide appropriate post-transplant antimicrobials for the lung transplant recipient. Depending upon the geographic and epidemiologic risks, transplant programs need to be aware of certain endemic mycoses that their organ recipients may be at particular risk for.

West Nile Virus (WNV) transmission from donor to organ recipient has been documented. On 8/2/2002, 4 organs (eg, heart, liver, 2 kidneys) were transplanted

into 4 recipients. Within two to three weeks of the transplants, all 4 organ recipients presented with fever and neurologic symptoms with laboratory confirmation of WNV infection. (17) Testing of the donor's serum revealed positive WNV pcr and viral culture. (17) One of the four organ transplant patients died from WNV infection. (17)

Rabies was transmitted from donor to 4 organ/tissue recipients in 2004. (26) Four organ/tissue recipients (eg, 2 kidney transplant, 1 liver transplant, 1 arterial segment transplant) developed rapid neurologic deterioration (eg, agitated delirium, seizures, respiratory failure and coma)/encephalitis within 30 days of transplantation. All 4 organ/tissue recipients died. The donor had been a healthy young male who died with a subarachnoid hemorrhage. The donor had told others of being bitten by a bat. (26)

Sequence of Events

There is a sequence of events that occurs where a donor-derived infection is thought to have occurred. Transplant centers are required to report a confirmed or suspected donor-derived disease transmission to that transplant center's Organ Procurement Organization (OPO). (5,22). The OPO then reports the case to the Organ Procurement Transplantation Network (OPTN), who then reports to the: Disease Transmission Advisory Committee (DTAC) of the United Network of Organ Sharing (UNOS) and the Centers for Disease Control and Prevention (CDC).

There are limitations to the donor evaluation, most noteworthy with the deceased donor. There is a narrow time period to: screen, place and procure the organ. (20) Medical and sociobehavioral histories of the deceased donors are indirect; they come from family members and friends and are taken in a very sensitive period, therefore information may be incomplete. (20) Donor screening is heavily reliant on serology, which is susceptible to false-negative results during the window period between initial infection and development of detectable antibodies and if there is significant hemodilution from massive blood products. (20) There is no commercially available screening assays for all recognized infections that are transmissible from donors to recipients and nucleic acid testing (NAT) is not available at all times in all locations. (20)

Use of organs from increased risk donor (eg high risk donor) is controversial. (19) Organs from increased risk donors account for 7% of all transplants. (19) The use of increased risk donors varies among OPOs, anywhere from 0% to 30%. (19) Overall, there is significant under-reporting of events and significant delays between

the transmission event and reporting to the OPTN. (6) In addition, follow up on these events is limited. (6)

If an increased risk donor is used, the organ recipient should have testing at: baseline, 1, 3, 6 or 12 months post-transplant that include: HIV Ab, syphilis titer and nucleic acid testing that includes: HIV-RNA, HCV-RNA and HBV-RNA. (15) Storage of samples of organ donor and organ recipient blood, plasma and cells for future testing is necessary. (15)

In addition, for living organ donors, it is highly recommended that HIV NAT, Hep Bs Ag, and HCV NAT, be done 7-14 days prior to organ procurement. (16, 19) This is not uniformly practiced. (16, 19) It is reasonable to avoid the use of organs from donors with unexplained fever, untreated infectious syndromes or encephalitis.

UTSW St Paul case of: Donor-derived Pulmonary Toxoplasmosis in a Cardiac Transplant Recipient and the Importance of Pre-transplant Serologies

A 52 yr old African American female with sarcoid cardiomyopathy was admitted with: fever, chills, drenching night sweats, overwhelming fatigue, doe, anorexia and diarrhea, one month after having received a cardiac transplant (CMV donor positive/CMV recipient positive). The patient's antirejection regimen was: tacrolimus, mycophenolate and prednisone (20 mg/7.5 mg). The patient had been on prophylactic valcyte and monthly aerosolized pentamidine. The initial ID workup was not revealing. A CT scan of chest was noted for new: nonspecific groundglass nodules bilaterally, most prominent at the lung bases with mild mediastinal lymphadenopathy.

The pt had a number of studies and eventually had a bronchoscopy with biopsies obtained. The lung biopsy revealed a pneumocyte with intracellular parasites in the setting of interstitial pneumonitis. The immunostain for Toxoplasma gondii showed the intracellular tachyzoites. Stored organ donor and organ recipient blood was analyzed. Pre-transplant, our patient had negative Toxoplasma gondii serologies, and post-transplant, her Toxoplasma gondii serologies (eg, both IgM and IgG) became positive. Post-transplant, our patient's Toxoplasma gondii pcr was positive in the serum. The organ donor's Toxoplasma gondii IgG was positive. The organ donor was from El Salvador. Therefore, with confidence, we can say that our patient was infected with Toxoplasma gondii from her organ donor. UTSW now does pre-transplant Toxoplasma gondii serologies in heart transplant candidates.

Toxoplasma gondii is an obligate intracellular protozoan parasite. Cats and other felines are the definitive hosts. Humans acquire infection through ingesting contaminated food or water. Most immunocompetent humans experience asymptomatic infection. (29) Immunocompromised patients may present with fever, malaise, painless lymphadenopathy and can develop: pneumonia, chorioretinitis, brain abscesses and diffuse encephalitis. (29)

In heart transplantation, Toxoplasma gondii infection can occur from the transplanted heart or from reactivation. At Stanford Medical Center in a series of 620 heart transplant patients, 4/16 (25%) of Toxoplasma gondii donor positive/recipient negative heart transplant patients developed and died from toxoplasmosis. None of the patients who died had received toxoplasmosis prophylaxis. Of the patients who received trimethoprim-sulfamethoxazole prophylaxis, none developed toxoplasmosis. (28)

Conclusion

The source of infections in solid organ transplant recipients can be: nosocomial-derived, recipient-derived, community-derived and donor-derived.

Overall , unexpected donor-derived infections are rare, but when they do occur, there can be significant morbidity and some mortality. A high suspicion for a donor-derived infection should occur, if all other more typical infectious disease scenarios have been excluded. It can be a tedious process, but necessary and potentially life-saving in the care of these often complicated organ transplant recipients.

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