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Special Article

Donor-Derived Infections in Solid Organ Transplantation

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Key words: Donor infection, donor-to-host transmission, donor screening, testing, latent infection

Abbreviations: CMV, cytomegalovirus; CNT, Centro Nazionale Trapinti; CSF, cerebrospinal fluid; D.R.IN, donor risk infection; DTAC, Disease Transmission Advisory Committee; ELISA, enzyme-linked immunosorbent assay; FDA, US Food and Drug Administration; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IWDT, intervention without disease transmission; LCMV, lymphocytic choriomeningitis virus; MSM, man who has sex with another man; MRSA, methicillin-resistant *S. aureus*; NAT, nucleic acid test; OPTN, Organ Procurement and Transplantation Network; PCR, polymerase chain reaction; REDS, Retrovirus Epidemiology Donor Study; UNOS, United Network for Organ Sharing; VRE, vancomycin-resistant *Enterococcus*; WNV, West Nile virus.

Introduction and Definitions

Advances in surgical technique, immunosuppression and antimicrobial prophylaxis have resulted in significantly reduced morbidity and mortality following organ transplantation. As a result, transplantation is currently considered the definitive therapy for individuals with end-organ failure. Despite these advances, unexpected transmission of infections from the donor to the recipient remains a rare complication of transplantation; when it does occur, the event is frequently associated with significant morbidity and mortality (1,2). In this chapter, the epidemiology of unexpected donor-derived infectious diseases transmissions, risk mitigation strategies and general approach to a patient with possible donor-derived infection will be reviewed.

Definitions

Most donor-derived disease transmissions are expected. Such expected transmissions, including cytomegalovirus (CMV) and hepatitis B virus (HBV), result with the knowedge that the transmission will occur; the donor is known to be infected with the pathogen and virological monitoring with preemptive therapy and/or universal prophylaxis are utilized to minimize the impact of the disease transmissions (I) (1,2). This guideline will not discuss such expected disease transmissions as they are reviewed elsewhere in this supplement. Instead, this guideline will focus exclusively on unexpected transmissions, such as Chagas, HIV, HCV, lymphocytic choriomeningitis virus (LCVM), *Mycobacterium tuberculosis*, multidrug-resistant (MDR) bacteria, rabies and West Nile virus (WNV), which may occur despite current screening strategies and are not expected in the donor at the time of organ placement (3–16). In some of these transmission events, clinical disease in the donor was not recognized at the time of donor death (14,16), while in other cases, screening, although available, was not performed for the pathogen of interest (4–6). Although most disease transmissions have involved deceased donors, recent transmissions of HIV and HCV showed that recipients of living donors may also be at risk (7,17).

Recently, international consensus definitions of donor-derived infections agreed upon (Table 1) (18). These definitions should optimally be utilized to faciliate comparison of data between published studies and reports collected globally.

Epidemiology of Donor-Derived Infectious Disease Transmissions

There are currently few robust systems to assess the epidemiology of donor-derived infectious disease transmissions. Currently, systems are well established in France (Agence de la Biomédecine) and the United States (Organ Procurement and Transplantation Network (OPTN)'s *Ad Hoc* Disease Transmission Advisory Committee) with a more recently established system in Italy (DRIN) (2,19). Additionally, there was a research infrastructure that tracked disease transmission for a finite period in Spain (RESITRA) (20). The French, Italian and US systems require recognition that the disease in the recipient is potentially of donor origin and then the disease must be reported to the national registry. As such, underrecognition and

Table 1: Definitions of imputability for donor origin infectious diseases transmissions (18)

Term	Definition
Proven	Clear evidence of the same infection disease in the donor and at least one of the recipients
Probable	Strong evidence suggesting but not proving a disease transmission
Possible	Used for all situations where data suggest a possible transmission but are insufficient to fulfill criteria for confirmed transmission (proven and/or probable) and transmission cannot be formally excluded
Unlikely	Used for situations where it is possible that the disease in question could have been transmitted from the donor to at least one of the recipients but the available data suggests that donor origin is unlikely
Excluded	Clear evidence of an alternative, nondonor origin of disease
Intervention without Documented Transmission (IWDT)	All or some of the recipients received an intervention (i.e. antimicrobial therapy, specific immunoglobulins or organ removal) and no disease was recognized in any of the recipients
Positive assay without apparent disease transmission	Used for instances in which a donor assay is positive for infection (i.e. coagulase negative *Staphylococcus* in perfusate culture) that is felt by the clinicans not to be clinically significant, is not treated and not associated with disease transmission
Not assessable	When there are insufficient data available to assess imputability of the disease transmission (either from insufficient data being provided in a published document or sufficient donor and/or recipient testing)

Table 2: Summary of potential donor-derived infectious disease transmissions reported to the United States organ procurement and transplantation network 2005–2011 (2)

Infection type	Number of donor reports	Number of recipients with confirmed transmission	Number of DDI-attributable recipient deaths
Viruses[1]	166	48	16
Bacteria[2]	118	34	9
Fungi[3]	75	31	10
Mycobacteria[4]	53	10	3
Parasites[5]	35	22	7

[1]Viruses: adenovirus, HBV, HCV, HEV, HIV, HTLV, herpes simplex, influenza, LCMV, parainfluenza (PIV)-3, parvovirus B19, rabies, West Nile virus.
[2]Bacteria: *Acinetobacter, Brucella, Enterococcus* (including VRE), *Ehrlichia* spp, *E. coli*, Gram-positive bacteria, *Klebsiella, Legionella, Listeria, Borrelia burgdorferi, Nocardia, Pseudomonas,* Rocky Mountain Spotted Fever, *Serratia, S. aureus* (MRSA), *Streptococcus* spp, *Treponema pallidum, Veillonella*; bacterial meningitis & bacterial emboli.
[3]Fungi: Aspergillus spp, Candida spp, Coccidioides imitis, Cryptococcus neoformans, Histoplasma capsulatum, Scopulariopsis, zygomyces.
[4]Mycobacteria: tuberculosis, non-TB mycobacteria.
[5]Parasites: Babesia, *Balamuthia mandrillaris*, Chagas (*Trypanosoma cruzi*), *Naegleria fowleri*, schistosomiasis, strongyloides.

underreporting of cases is likely and limits current data; Italian system (DRIN) is collecting reports of all recipient infections.

Despite these limitations, it is possible to draw several generalizations. It appears that donor-derived infectious diseases complicate approximately 0.2% of deceased organ donor transplants (details from the OPTN data are in Table 2) (2,19); it should be noted that a slightly higher rate (1.7%) was noted during the RESITRA study period (20). When an infection is transmitted, it is typically associated with significant morbidity and mortality (2,19,20); there is likely underrecognition and therefore underreporting of cases that are associated with less severe disease (i.e. transient bacteremia that responds quickly to therapy but was likely of donor origin). Further, there are variable rates of transmission likely related to inoculum of pathogen, organ transplanted and type of immune suppression used (i.e. lymphocyte depletion) (2,19,20).

Risk Mitigation

Although it is impossible to completely remove the risk of disease transmission through solid organ transplantation, there are a number of ways to mitigate against disease transmission (2). Basically, these can be classified as follows:

(1) Risk stratification from the donor medical and social history.
(2) Careful physical assessement of the donor and the donor organs.
(3) Laboratory screening of the donor for infection.

The limitations and benefits of each risk mitigation strategy must be understood by the accepting center to properly inform the risk of donor-derived infectious disease transmission. Lastly, care must be taken to find the appropriate balance between minimizing the risk of disease transmission and organ wastage in making decisions utilizing these risk mitigation strategies (2,21). Currently, there are many more individuals who could benefit from organ transplantation than there are available organs. As such, discarding organs from donors with risk factors needs to be minimized when utilizing these risk mitigation strategies.

Table 3: Behavioral risk factors for a donor to be at increased risk of transmitting human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV)

- High risk sexual contacts:
  - Persons who have had sex with a person known or suspected to have HIV, HBV or HCV infection in the preceeding 12 months
  - Men who have had sex with another man (MSM) in the preceeding 12 months
  - Women who have had sex with a man with a history of MSM behavior in the preceeding 12 months
  - Persons who have had sex in exchange for money or drugs in the preceeding 12 months
  - Persons who have had sex with a person who injected drugs by intravenous, intramuscular or subcutaneous route for nonmedical reasons in the preceeding 12 months.
- Birth to a mother infected with HIV, HBV or HCV (for infant donors $\leq$ 2 years of age)
- Persons who have injected drugs by intravenous, intramuscular, or subcutaneous routes for nonmedical reasons in the preceeding 12 months
- Inmates of a correctional facility (e.g. jail, prison, or juvenile detention) for $>$ 3 days in the preceeding 12 months
- Persons who have or have been treated for syphilis, gonorrhea, chlamydia, or genital ulcers in the preceeding 12 months
- Persons who have been on hemodialyalsis in the preceeding 12 months

Based on proposed US Public Health Services Guideline which are currently under revision. Consult current US Public Health Service Guideline for current criteria.

Table 4: Residual risk of undiagnosed human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection per 10 000 donors at increased risk of infection (24,25)

	HIV		HCV	
Risk factor	Serology alone	Serology + NAT	Serology alone	Serology + NAT
Men who have sex with men	8.3	3.4	36.0	3.8
Nonmedical intravenous, intramuscular or subcutaneous drug use	12.9	5.3	350.0	37.8
Hemophilia	0.05	0.02	0.46	0.05
Persons who have had sex in exchange for money or drugs	2.9	1.2	107.8	11.5
Partners with any of the above risk factors	2.7	1.1	126.2	13.5
Individuals who have been exposed to blood or blood products from someone with HIV or HCV	1.3	0.5	22.0	2.3
Incarceration	1.5	0.6	68.6	7.3

As a point of reference, in the United States there is a 0.34% (34/10 000) risk of developing hepatitis C per year while on dialysis.

Donor risk assessment

Risk stratification is commonly achieved through careful review of the donor's medical and social history (22). The donors chart should be screened carefully to identify cultures and other assays (e.g. serology and nucleic acid testing (NAT; sometimes also referred to as PCR or viral load testing) that were ordered by the team caring for the patient to diagnose infections (22). Positive results should be interpreted by the accepting teams to match the risk of disease transmission with the risk tolerance and medical status of the recipient. Most importantly, some cultures or other assays may yield results well after the organs have been placed (i.e. mycobacteria cultures frequently take up to 8 weeks) (2,22). The organ procurement organization and recipient center should be aware of the pending results and have a plan for information transmission and recipient management (III). Additionally, the social history is optimally obtained from an individual who knows the patient well (2,22). Attention to travel history is critical to identify donors at risk of endemic infections (such as histoplasmosis, blastomycosis, coccidiomycosis, Chagas disease, strongyloides and tuberculosis, to name just a few). If risk factors for exposure to endemic infections are identified, consideration of additional screening or use of recipient preventative strategies should be considered (III). These will be discussed in further details in later sections. A uniform donor health questionaire is currently being developed by the American Association of Tissue Banks with the goal of standardizing the acquisition of the medical and social history from the next-of-kin or friends who are available. It is important to recognize that the historian may not be aware of all of the donor's risk behaviors and attempts to assess how well the historian knows the donor should be undertaken. Results of the review of the medical history and collection of the social history can be used to identify patients at increased risk of transmitting HIV, HBV and HCV (see Table 3) (2,23). Recipients of organs from donors at increased risk of transmitting HIV, HBV and HCV should be informed of the risk and alternatives to use of organs from the increased risk donors, and should be screened posttransplant for acquisition of these infections. (residual risk of infection despite serologic and/or NAT screening associated with specific behaviors is listed in Table 4 and below) (III) (24,25).

Currently, there are two ways in which organ donors are risk stratified: In the United States, donors are dichotomized as being either at increased risk or without identified risk for transmission of infectious diseases; while

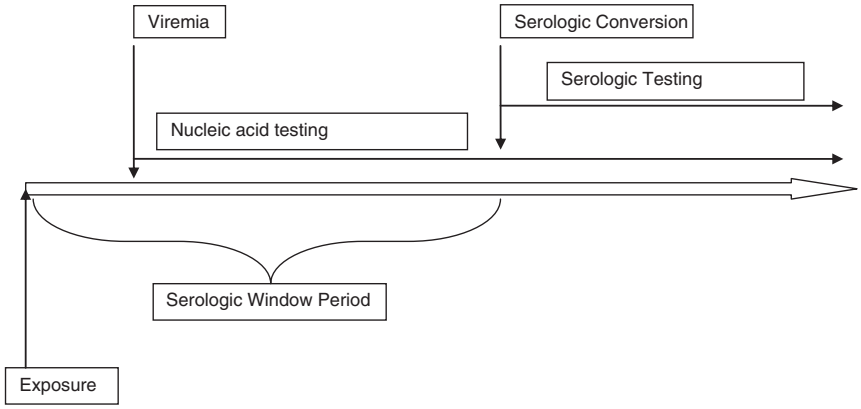

Figure 1: Schematic of viral infection and detection by serology and nucleic acid testing.

in Europe, a more graded risk assessment is utilized. In the US system, which has traditionally focused on HIV, HBV and HCV, behavioral risk factors (see Table 3), hemodilution and lack of donor social history have been utilized to classify a donor as increased risk of transmitting blood-borne infections while all other recipients are not further classified (2,22,23). The European classification system was initially developed in 2002 by Italian National Center for Transplantation (CNT) but has been more broadly applied throughout Europe to evaluate the safety and acceptability of donors (26). The CNT/European risk classification system (http://www.edqm.eu/en/Search-519.html) defines donors as follows:

(1) *Unacceptable risk* includes absolute contraindication, with the exception of some life-saving transplantation procedures in the absence of other therapeutic options on a case-by-case basis.
(2) *Increased but acceptable risk* includes cases where transmissible organisms or diseases are identified during the evaluation process of the donor, but organ utilization is justified by the specific health situation of the recipient or the severity of their clinical condition.
(3) *Calculated risk* (criteria referring to protocols for elective transplants) includes all cases where, even in the presence of transmissible diseases, transplantation is allowed for recipients with the same disease or with a protective serological status; this risk applies also to donors with documented bacteremia and/or bacterial meningitis provided that the donor was on targeted antimicrobial treatment for a minimum duration of 24–48 h.
(4) *Not assessable risk (RL 4)* includes cases where the evaluation process does not allow an appropriate risk assessment for transmissible diseases.
(5) *Standard risk (RL 5)* includes cases where the evaluation process did not identify a transmissible disease.

With both systems, it is recommended that a specific informed consent is obtained from every recipient if there is defined risk identified in the donor.

Physical asssessment

Careful physical assessment of the donor's body should be conducted by both the organ procurement team and the procuring surgeon, who should evaluate the explanted organs and vessels. The body should be assessed for evidence of infections, including abscesses, ulcers, genital or anal trauma, lymphadenopathy, in addition to looking for evidence of recent drug use, such as the presence of track marks. The examination should also assess for evidence of other underlying disease, such as cirrhosis or other surface manifestations of infections or malignancies. The explanting surgeon should make sure that there is no free spillage of intestinal contents and that there is no obvious pus or infection of the organ or vessel, including lymphadenopathy.

Donor serologic and nucleic acid testing

Following viral infection, the virus may initially be detected in the blood prior to the infected individual developing antibodies; this is termed the serologic window (see Figure 1). Once the patient develops antibodies directed against the infecting virus, serologic testing will detect the infection in the donor. Several donor-derived infection transmissions have resulted from window period infections missed by serologic screening of donors only (7,14). The period from HIV exposure to the development of HIV antibodies is approximately 22 days, but can be up to 6 months. Thus the donor may be seronegative while potentially infectious. The use of individual donor NAT would reduce the window period for HIV to between 5.6 and 10.2 days (i.e. 4–15 days in which infection is detected by NAT but not ELISA (27–31). A fourth-generation HIV antibody-antigen combination serology diagnostic test was recently approved in the United States and may reduce the window period to 1–2 weeks; it should be noted that the assay is not approved for screening blood or plasma donors and there are limited data on its efficacy in deceased organ donor screening. Recent data estimated incidence of undetected HIV infection by serologic screening was 1 in 50 000 for normal risk potential donors and 1 in 11 000 for OPTN-defined increased risk potential donors (32). HBV surface antigen (HBsAg) ELISA assays have a window period of 38.3–49.7 days,

with NAT in the 20.4–25.7 day range (27,33–36). The use of HBV NAT testing may detect viral replication in hepatitis B core antigen positive who are HBsAg negative. HCV ELISAs have a window period of between 38 and 94 days which is reduced significantly to 6.1–8.7 days by the use of NAT (24,31,32). Recent data estimated incidence of undetected HCV infection by serologic screening was 1 in 5000 for normal risk potential donors and 1 in 1000 for OPTN-defined increased risk potential donors (32). There is a fourth-generation HCV antibody screening assay that is available outside the United States but is not yet approved for use in the United States; it has a reduced window period compared to currently approved assays in the United States.

While these data suggest that NAT will detect infections missed by routine serologic screening of organ donors, many in the transplant community have only advocated for the use of NAT for OPTN-defined increased risk donors because of concern of loss of uninfected organs from false-positive testing (III) (21). More recently, data suggested that organs may be successfully placed from donors with proven or suspected false-positive NAT results (37,38). Further, another group demonstrated that there was a substantial proportion of donors who were seropositive but negative by NAT for HIV, HBV and HCV (38). Such donors could be used in selected transplant candidates (i.e. HBV infected or vaccinated candidates) or in appropriately consented candidates. It should be noted that current US law does not allow use of donors who are known to be infected with HIV. If there is clear evidence suggesting that results are likely false positive (i.e. + serology but negative NAT in donor without risk factors for HIV infection), use of organs can be considered as long as all details of these testing results are clearly disclosed to the recipient and recipient center (III).

There has been recent attention on screening donors for other transmissible infections, such as tuberculosis, Chagas Disease and West Nile virus; these will be discussed in detail in later sections, but key features will be summarized here. Screening of donors for tuberculosis is challenging and supported by limited data. Use of the PPD is not currently an option because there is typically insufficient time to place the antigen and await a response; additionally donors may be rendered anergic by the underlying cause of brain death and/or steroids used for donor stabilization. Use of interferon-gamma release assays is currently under study and therefore cannot be advocated for wide use in screening donors. Donors with risk factors for tuberculosis (exposure to a moderate to high endemicity nation, homelessness, drug abuse, or incarceration) should be screened for active tuberculosis; donors with active tuberculosis should not be used (III). Further details can be found in a recent consensus paper (39). Targeted *T. cruzi* screening of potential donors born in Mexico, Central America and South America has been advocated by a recent group of experts (10). It should be noted that most currently available donor screening assays have a high rate of false-positive results and confirmatory testing is recommended for all positive results. Such confirmatory testing is typically not available in time for the donor offer but can direct posttransplant interventions. Given the relative low rate of transmission, kidneys and livers from *T. cruzi*-infected donors or donors with positive initial screening results should be considered for use with informed consent from recipients (II 3). Hearts from infected or screen-positive donors should not be utilized because of the high rate of disease transmission (10). West Nile virus also represents an infection that can be transmitted from donor to recipient for which screening assays are currently available. Existing data suggest that if donors are to be screened, serum WNV NAT should be utilized; screening of urine by NAT or serum for serology is not recommended at this time. Since WNV NAT will generally yield false-positive results when there is limited WNV in the donor service area, screening is only recommended when there is active disease in the region where that donor has come from; collaboration with local blood banks to determine when screening should be considered has been recommended (III).

Special circumstances

Hemodilution of donor blood samples: Massive blood loss followed by intravascular volume replacement with blood products or infusions of colloids and crystalloids can cause hemodilution and result in unreliable donor test results for infectious diseases (40). The US Food and Drug Administration (FDA) has guidelines for how to assess hemodilution for tissue donors and these can be used to estimate the degree of hemodilution in organ donors (40,41). Hemodilution currently classifies donors as increased risk for disease transmission by the current OPTN definition. As such, care should be utilized in interpreting serologic screening results and recipients of organs from donors with significant hemodilution should be informed about the risk of false-negative testing in the setting of hemodilution (III).

Testing of newborns: In general, maternal antibodies may pass from the mother to the child and last anywhere from 6–15 months of age. Interpretation of antibody results should take this into consideration. Some advocate for testing of infant urine for CMV to confirm infection.

Live donors: A recent transmission of HIV from a live donor to his recipient highlighted the need for testing of live donors close to the time of organ procurement (7). Current guidance suggests that all live donors should be tested for HIV, HBV and HCV (7). Additional testing, within 28 days of procurement but optimally within 14 days, has been recommended for all live organ donors (AHRQ-funded consensus conference available at http://www.feinberg.northwestern.edu/transplant/Increased%20Risk%20Consensus%20Conference/index.html). This additional late testing should include HIV and HCV NAT and hepatitis

B surface antigen (HBsAg) to directly detect the presence of the virus in the donor (III) (7). Lastly, donors should be educated about ways in which they can avoid acquisition of infections between the time of screening and donation.

Donors With Documented Infections at the Time of Procurement

Decisions regarding the use of organs from donors with active or suspected infection should be based upon the urgency of transplantation for the recipient, the availability of alternative organs and recipient informed consent. Care should be taken in carefully assessing all available data about the donor and the infection present in the donor, including susceptibility testing, antimicrobial therapy utilized and evidence of clinical response to therapy in the donor (III) (22). Consultation of specific guidance documents may help in determining donor suitability and risk mitigation strategies posttransplant (9,22,39,42,43). In general, any active bacterial or fungal infection in the donor or recipient should be treated and, ideally, resolved prior to transplantation *(II-3)*; organs known to be infected with pathogens likely to be transmitted to the recipient should not be transplanted *(II-3)*.

Bacteremic donors

It has been estimated that 5% of organ donors have bacteremia at the time of organ procurement (2,44,45). Transmission has been described, typically involving bacteria that were not susceptible to typically utilized perioperative antibiotics. When transmissions occur, there is frequently significant graft loss, morbidity and mortality (2,44–46). Although bacteremia and bacterial infections in the donor pose a potential risk for the transmission of infection to the recipient, discarding organs from such donors could further compromise the already limited donor pool and aggravate the organ donor shortage. The risk of donor-transmitted infection varies with the type of bacteria causing the infection. Among Gram-positive bacteria, there is a low risk of transmission with relatively avirulent bacteria, like coagulase-negative staphylococci. Gram-negative bacilli in the donor appear to pose a greater risk for transmission and is associated with poorer outcomes than that caused by Gram-positive bacteria (47–54).

Of greatest concern is the ever-increasing challenge of multiresistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococcus (VRE) and multidrug-resistant Gram-negative rods. The problem is particularly serious with Gram-negatives producing carbapenemases, which usually exhibit extended-drug resistant phenotypes and remain susceptible to only a few antibiotics. There have been only a few reports related the optimal evaluation and risk mitigation management related to these highly resistant bacteria (51,54–57). Open and rapid interinstitutional and -agency communication, antibiotic prophylaxis based on *in vitro* susceptibility testing and careful infection control practices are rational approaches to minimize the impact of donor transmitted bacteria following organ transplantation (57). Further work is needed to identify when organs can be safely used from potential donors with MDR Gram-negative infections, how to prospectively identify donors that may harbor subclinical infection and how to best manage recipients at risk for donor derived infections following transplantation (57).

Emerging data suggest that bacteremic donors may be utilized in certain circumstances (II-2) (44,45,47,51,58,59). Generally, it is recommended that the infected donor receives targeted antimicrobial treatment for at least 24–48 h, optimally with some degree of clinical response (improved white blood cell count, improved hemodynamics, defervescence) (22). In addition, it is recommended that the recipient is treated with a 7- to 14-day course of antibiotics targeted to the organism isolated from the donor (III) (22).

Donors with bacterial meningitis

There are significant data suggesting that donors with proven bacterial meningitis can be safely used for organ donation (II-2). Documentation of bacterial meningitis is essential since transmission of infections and malignancies have been documented from donors with presumed, but not proven bacterial meningitis. Kidneys, livers and thoracic organs from donors with bacterial meningitis due to *Neisseria meningitidis*, *Streptococcus pneumoniae, Haemophilus influenzae* and *Escherichia coli* have been successfully transplanted (60–67). Generally, donors are treated for 24–48 h with antibiotics directed at the identified bacteria prior to procurement, optimally with evidence of clinical improvement. The recipient is typically treated for 7–14 days posttransplant with antibiotics directed at the cultured bacteria (II-2) (22). Meningitis caused by highly virulent or intracellular organisms such as Listeria species are still considered a contraindication by many transplant centers.

Donors With Proven or Presumed Infectious Encephalitis

It is important to note that encephalitis, particularly with fever, without a documented source is frequently associated with disease transmission. Transmission of rabies, parasitic infections, lymphomas and leukemias have occurred when donors with encephalitis without a proven cause were accepted as organ donors (2,16). As such, donors dying of encephalitis without a proven cause should likely be avoided (II-3). The two exceptions to this general caution include donors with proven bacterial meningitis (see above) and donors with proven *Naegleria fowlerii* meningoencephalitis. *Naegleria* infection is generally limited to the CNS; even when there is molecular evidence of

the parasite outside the CNS, transmission has not been documented. If the donor has proven *N. fowlerii* meningoencephalitis, the organs can be utilized with a low risk of transmission, as long as the recipients are informed of the risk and monitored closely (II-3) (68,69).

Evaluation of Recipient With Suspected Donor-Derived Infection

Although donor-derived disease transmissions are rare (estimated to involve ~0.2% of all transplants), it is critical to consider the donor as the source of any posttransplant infection or malignancy and report that concern to the local OPO and/or national competent authority (i.e. UNOS in the United States) immediately (II-2) (2). Unfortunately, recipients may be cared for by different teams within the same hospital or in a number of different hospitals; this may hamper recognition of a transmission. Additionally, as has been the case in several recent transmissions, the patients present with clinical symptoms at different times posttransplant; mechanisms to flag all recipients of a single donor with concern about a potential transmission should be in place but typically are not available. The OPO should have a mechanism in place to rapidly assess the status of all other recipients of organs, tissues or vessels from the same donor and report the concern to the OPTN (2,22). The recent allograft recipient with unexplained fever, leukocytosis, altered mental status, or other signs of occult infection is a candidate for donor-derived infection. Likewise, proven infections early posttransplant should prompt a careful review of donor cultures and donor origin of the infection should be considered (II-3). Common processes such as wound or surgical sites infections, graft rejection, anastamotic leaks, vascular compromise, drug toxicity, pneumonia, or *C. difficile* colitis must be evaluated for and treated if present. If donor origin is considered, the case should be immediately reported to the national transplant authority (UNOS in the United States), the local organ procurement organization and, if it is a reportable disease, the local public health authorities. This reporting should be done as early as possible to potentially alert providers of other recipients of the same donor to facilitate evaluation and initiate disease transmission mitigation strategies (III). It should be emphasized that reporting should not await confirmation of transmission. As part of the evaluation, it is prudent to contact the involved laboratory to save any residual blood, serum, CSF and donor tissues (such as vessels) to facilitate the investigation and insure that they will be held and not be inadvertently disposed of.

Lastly, it is critical that the transplant team work collaboratively to develop an evaluation and treatment plan for all recipients of donors with identified risk of infectious disease transmission. This should include a clear plan for who is responsible for follow-up testing (i.e. follow-up cultures or serology/PCR testing of the recipient) and treatment (III). In general, when an infection is identified in the donor, the recipient is treated with appropriate antimicrobial therapy directed against the pathogen for a duration that one would use if the recipient themselves had the infection (2,22). Further, it is currently recommended that all recipients of organs from donors with identified risk factors for HIV, HBV and HCV be tested posttransplant (III). While there is controversy as to the optimal timing of this testing, it is important to utilize assays that directly detect the presence of the virus (i.e. HIV and HCV NAT and HBsAg) since patients frequently fail to seroconvert (2,14,22). Reliance on serology alone may miss acquisition of a donor-derived viral infection.

Future Research

Since the topic of donor-derived infections is still relatively new, there is significant need for additional research. It is critical that more nations establish organ vigilance and surveillance systems to further define the epidemiology of donor-derived infections. This includes evaluation for geographically limited infections that may not have been transmitted in areas where surveillance is currently ongoing. Additionally, the relative importance of specific pathogens and risk mitigation strategies can only be assessed with collection of global data. Prospective studies of organ donors and recipients, similar to what was conducted as part of the Retrovirus Epidemiology Donor Study (REDS) in transfusion medicine, are needed to more completely define the true epidemiology and risk of donor disease transmission. Studies are also needed to assess the wide range of available diagnostic and screening assays that could be utilized to risk stratify potential organ donors. Lastly, specific registries of donors with potentially transmissible infections (i.e. Chagas, encephalitis, or bacteremia) are needed to inform which donors can safely be utilized and what risk mitigation strategies are most effective in prevent disease transmission.

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