8
Donor-Derived Infections: Incidence, Prevention, and Management

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8.1 Introduction

Solid organ transplantation is an ever evolving field, with significant advances in the management of recipients of solid organ transplantation, including enhanced immune suppression and antimicrobial prophylaxis for at-risk patients [1, 2]. In order to increase the number of available organs, and, in turn, save more lives of those on the transplant wait list, the donor pool must continue to expand [3]. Donors reflect the diverse US population; there are an increasing number of donors born in, who have resided in, or who have traveled to underdeveloped areas of the world or areas with geographically restricted infections [4]. As such, these donors are exposed to pathogens that can potentially be transmitted to recipients of the donor's organs. Additionally, there are newer techniques to identify many pathogens that may be transmitted from the donor to the transplant recipients [5, 6]. Finally, high-profile reports of several donor-derived infections have heightened awareness of donor-derived infections and have likely contributed to increased recognition [7–19]. In this chapter, the incidence, methods of identification and prevention, and management of unexpected donor-derived infections will be reviewed. Often, donors are expected to transmit infection (i.e., CMV donor seropositive, recipient seronegative) because of information known by the transplant team posttransplant. In most cases, such information will lead to interventions to reduce the incidence and severity of transmitted disease and is reviewed elsewhere in this text.

In the United States, the Organ Procurement and Transplantation Network (OPTN) policy sets up the framework for minimizing and tracking cases of donor-derived infection transmission. This policy includes language that defines donors at enhanced risk of disease transmission (Table 8-1); the need to obtain special informed consent before using organs from donors with known transmissible disease or risk factors for disease transmission; the need to develop local polices for screening recipients for transmitted disease posttransplant, if appropriate; and the need to report proven or potential disease transmission; policy also defines the requirements for living and deceased donor screening (http://optn.transplant.hrsa.gov/governance/policies/). The Council of Europe has also developed a similar guidance document that is updated regularly to provide similar guidance on donor screening and risk mitigation (https://www.edqm.eu/en/organ-transplantation-mission-67.html). Likewise, the European Union and national governments have established laws and directives that regulate these same functions outside the United States.

8.2 Donors at Increased Risk of Infectious Disease Transmission

Experience has demonstrated that donors with documented infections pose a risk of transmission of the infection from the donor to the recipient. While the risk of transmission varies (i.e., low risk with appropriately treated documented bacterial meningitis or *Naegleria* encephalitis, high risk with active HIV infection), the fact that there is a risk of disease transmission requires several key steps:

1. The organ procurement organization must inform the recipient center of the potentially transmissible infection.
2. The recipient center must assess if the benefit of transplantation outweighs the risk of disease transmission.
3. The recipient center must obtain special informed consent to use the organ from the donor with recognized risk of disease transmission.
4. The recipient center must develop a plan to treat the recipient, if appropriate, to prevent disease transmission and monitor the recipient for evidence of transmitted infection.

Specific details of these key steps will be discussed in greater detail later in the chapter.

Some donors do not have documented infection but instead have engaged in behaviors or have other characteristics

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TABLE 8-1. Known conditions that may be transmitted by the donor organ that must be communicated to the transplant center prior to transplantation

- Infections
  - Syndromes
    - Unknown infection of central nervous system (encephalitis, meningitis)
    - Multisystem organ failure due to overwhelming sepsis
  - Bacterial infections
    - Bacterial meningitis
    - Bacteremia
    - Pneumonia
    - Syphilis
    - Tuberculosis
  - Fungal infections
    - Endemic mycoses: blastomycosis, histoplasmosis, coccidioidomycosis
    - Cryptococcal infection
    - Fungal sepsis (e.g., *Candidemia*)
  - Parasitic infections
    - *Trypanosoma cruzi*
    - *Leishmania*
    - *Naegleria fowleri*
    - Strongyloides
    - Toxoplasmosis
  - Prion disease, including Creutzfeldt–Jakob disease
  - Viral infections
    - Active hepatitis A, B, or C
    - Herpes simplex encephalitis or documented viremia
    - Human immunodeficiency virus/AIDS
    - HTLV-I
    - History of JC virus infection (progressive multifocal leukoencephalopathy)
    - West Nile virus infection
    - Cryptococcal infection of any site
    - Rabies
    - SARS, MERS-CoV, influenza
    - Malignancies
  - Any known or history of malignancies
  - Melanoma, Merkel cell, and Kaposi's sarcoma
  - Hodgkin's disease and non-Hodgkin's lymphoma
  - Multiple myeloma
  - Leukemia
  - Aplastic anemia agranulocytosis
- Inborn errors of metabolism
- Drug or food allergies

TABLE 8-2. Risk factors for recent HIV, HBV, or HCV infection/increased risk donor criteria [20]

Criteria	Characteristics
Behavior and history	1. People who have had sex with a person known or suspected to have HIV, HBV, or HCV infection in the preceding 12 months
	2. Men who have had sex with men (MSM) in the preceding 12 months
	3. Women who have had sex with a man with a history of MSM behavior in the preceding 12 months
	4. People who have had sex in exchange for money or drugs in the preceding 12 months
	5. People who have had sex with a person who had sex in exchange for money or drugs in the preceding 12 months
	6. People who have had sex with a person who injected drugs by intravenous, intramuscular, or subcutaneous route for nonmedical reasons in the preceding 12 months
	7. People who have injected drugs by intravenous, intramuscular, or subcutaneous route for nonmedical reasons in the preceding 12 months
	8. People who have been in lockup, jail, prison, or a juvenile correctional facility for more than 72 consecutive hours in the preceding 12 months
	9. People who have been newly diagnosed with, or have been treated for, syphilis, gonorrhea, *Chlamydia*, or genital ulcers in the preceding 12 months
Pediatric only criteria	1. A child $\leq$ 18 months of age and born to a mother known to be infected with, or at increased risk for, HIV, HBV, or HCV infection
	2. A child who has been breastfed within the preceding 12 months and the mother is known to be infected with, or at increased risk for, HIV infection
HCV risk only	1. People who have been on hemodialysis in the preceding 12 months
Laboratory and other	1. Screening specimens are hemodiluted
	2. Donor medical/behavioral history is unavailable

that place the donor at increased risk of infection with pathogens, such as HIV, hepatitis B, and hepatitis C, that can, in turn, be transmitted to the recipient. These donors have been defined by the OPTN and US Public Health Services (PHS) as donors at increased risk of disease transmission, termed increased risk donors. The PHS updated their guidance related to increased risk donors in 2013, and this guidance has been adopted as the standard for most transplant systems globally [20]. This updated guideline refined prior guidance taking into account current knowledge of the epidemiology of HIV, HBV, and HCV in the community and the limitations of our contemporary screening practices (Table 8-2). The guideline focuses on three key core recommendations:

1. Screening:
   (a) There is no single standardized and validated tool for collecting the donor's medical and social history, although many US OPOs are utilizing the Uniform Donor Risk Assessment Interview Tool (http://www.

aatb.org/DRAI-Documents). Although living and deceased donors are considered to be equal risk in the guidelines, living donors are able to provide their own history, while histories from deceased donors are obtained from friends and relatives. These individuals may not know the fine details of the donor's social situation (e.g., the mother of a college student who does not live at home). As such, the guideline recognizes these limitations and places donors with incomplete donor histories in the increased risk category as risks may be present but unrecognized.

(b) The 2013 guidelines newly recommend that all donors be screened with serology and nucleic acid testing (NAT) for hepatitis C, regardless of risk factors, and that all increased risk donors be screened with HIV NAT in addition to routine serology. At the present time, only serology is mandated for hepatitis B screening, although this serologic assessment includes hepatitis B surface antigen (HBsAg) which allows for direct detection of the virus. The addition of NAT screening to serology will allow increased detection of acute infections as NAT decreases the length of time between initial infection and the ability of the test to detect the infection, referred to as the window period (Figure 8-1).

(c) The guideline also recognizes that living donors may continue to engage in behaviors that place them at increased risk of disease transmission between screening and donation. As such, the guidelines recommend that living donors are screened as close to the donation procedure as possible, not to exceed 28 days. The feasibility of this recommendation has been demonstrated clinically [21].

2. Consenting: Any patient who is to receive an organ from a patient with risk factors should understand the risk and agree to receive the organ based on that risk assessment. A specialized informed consent for increased risk donor organ use is mandated by policy.

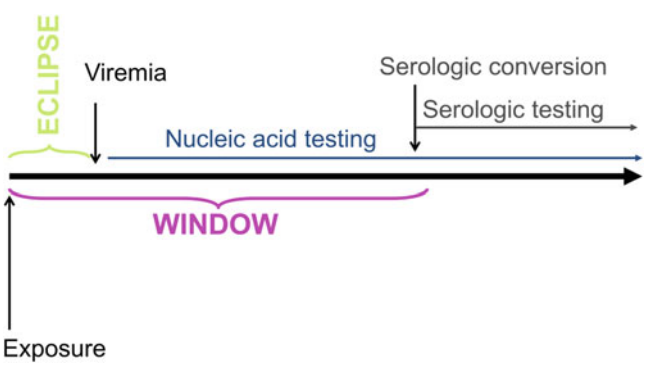

FIGURE 8-1. Interval between infection, detection of virus, and detection of antibody response to infections.

3. Follow-up testing: Perhaps one of the most important recommendations of the PHS guidelines is the need to do posttransplant testing of recipients that received increased risk donor organs to ensure that a disease transmission has not occurred. Early testing may affect outcomes if a transmission is identified, as available effective therapy can be introduced sooner after transmission. Recommendations include HIV NAT (or combined antibody–antigen assay), HCV NAT, HBV NAT, and HBsAg at 1–3 months posttransplant and HBV serology at 12 months posttransplant (including hepatitis B surface antibody, hepatitis B core antibody, and either HBV NAT or HBsAg) [20]. However, data as of 2011 show that posttransplant testing is not reliably performed [22]. Using assays that directly detect the virus in the posttransplant period is critical, and serology may not be reliable because recipients frequently fail to seroconvert due to transmitted infections. In all cases of HCV transmission identified in the United States, for example, all recipients have been seronegative but NAT positive even when tested nearly 1 year posttransplant [23, 24].

These guidelines are helpful in defining donors at increased risk of disease transmission by identifying donors with higher likelihood of HIV, HBV, and HCV infections. Review of existing data clearly demonstrates that the risk of HIV and HCV infection varies significantly by risk behavior (Table 8-3). Given the enhanced risk, it is important to realize that patients may acquire infection in the NAT window, the period of time between infection and when NAT can detect infection (see below). As such, while NAT decreases the risk of disease transmission, residual risk remains and has clearly been demonstrated by three recent transmissions of HCV from donors engaged in nonmedical drug use prior to death with negative donor NAT testing [23].

8.3 Incidence of Unexpected Donor-Derived Infections

To date, there are limited prospectively collected data on the incidence of donor-derived infections. Prior to the establishment of the OPTN/United Network for Organ Sharing (UNOS) Ad Hoc Disease Transmission Advisory Committee (DTAC) in 2005, there were no systems in place to prospectively collect data to estimate the incidence of donor-derived infections; data was only available from published case reports. Underreporting to DTAC was common initially, but recent data show a substantial increase in the numbers of reports (Table 8-4 and Figure 8-2) [24, 25]. In the era of current screening, the following unexpected transmissions have been reported: numerous bacterial species (including gram-positive cocci and gram-negative rods), *Ehrlichia chaffeensis*, legionella, syphilis, *M. tuberculosis, Candida* spp.,

Table 8-3. Residual risk of undiagnosed human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection per 10,000 donors at increased risk of infection [60, 61]

	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

Residual risk is the rate of undetected infection depending on risk factor and testing strategy.

Table 8-4. Summary of reported cases to the OPTN/UNOS Ad Hoc Diseases Transmission Advisory Committee, 2005–2014

Disease type	# of donor reports	# of recipients with confirmed transmission	# of donor-derived disease-attributed recipient deaths
Malignancies	374	79	28
Viruses	366	80	18
Bacteria	313	55	13
Mycobacteria	95	11	3
Fungi	165	45	15
Parasites	62	41	14
Other diseases	73	6	1
Total	1448	317	92

histoplasmosis, zygomycosis, *Aspergillus* spp., scedosporiosis, coccidioidomycosis, cytomegalovirus, HIV, HBV, HCV, adenovirus, coxsackievirus, human T-lymphotropic virus, lymphocytic choriomeningitis virus and a related arenavirus, West Nile virus (WNV), rabies, schistosomiasis, strongyloides, *Trypanosoma cruzi*, microsporidiosis, and *Balamuthia* spp. [7–9, 11–13, 15–19, 23–38]. From the available data from the US and French systems, donor-derived disease is transmitted in less than 1% of transplants, with approximately 0.03% of recipients dying from the transmitted disease [24, 25].

There are several key points that can be learned from the data collected to date. While confirmed bacterial transmissions are not the most commonly reported transmission, they likely represent the most common form of disease transmission. Most of the confirmed cases of bacteria transmissions involve highly resistant gram-positive and gram-negative infections. From a series of historical studies, 5–9% of abdominal organs and up to 63% of thoracic organs appear to be contaminated with bacterial pathogens at the time of procurement [25, 39–42]. Use of perioperative antibiotics reduces the risk of disease transmission, although under-recognition and underreporting of bacterial transmissions are likely. Given the high rate of contamination and the increasing prevalence of highly resistant bacteria in hospitals globally, bacterial transmissions will increase over time [25, 39–42]. As such, diligence is important among transplant teams.

Although there have been attempts to estimate the risk of donor-derived infections, none can be considered accurate as there is no formal screening process to identify potential transmissions, and the issues of under-recognition and underreporting of transmissions remain. It is critical, and required by current UNOS Policy, that everyone caring for transplant recipients considers the potential of donor origin in all infections, particularly early posttransplant, and has a plan in place to report this concern to the local OPO and to UNOS [43]. Organ vigilance systems, similar to the OPTN/UNOS Patient Safety System, contribute to more rapid communication. Efficient and timely communication is associated with a lower rate of recipient adverse events, including death [44]. As such, regions without organ vigilance systems should establish formal systems, as has recently been required by the EU directive, to improve patient outcomes and potentially improve the safety of the transplant system.

8.4 Prevention of Infectious Transmissions

The mainstay of infection prevention in organ transplantation is the use of donor and recipient screening. Despite best efforts to screen for potential infections and in a timely manner, the transplanting physicians and organ recipients must understand there always remains a risk for infectious transmission. The goals of screening donors and recipients prior to transplant are to identify conditions that disqualify the donor or recipient from the transplant, to identify and treat active infections pre-transplant, and to allow for risk mitigation strategies to minimize posttransplant infections. Screening occurs in many forms including acquisition of a careful history, detailed physical examination, detection of latent or unknown active infections by laboratory testing, examination

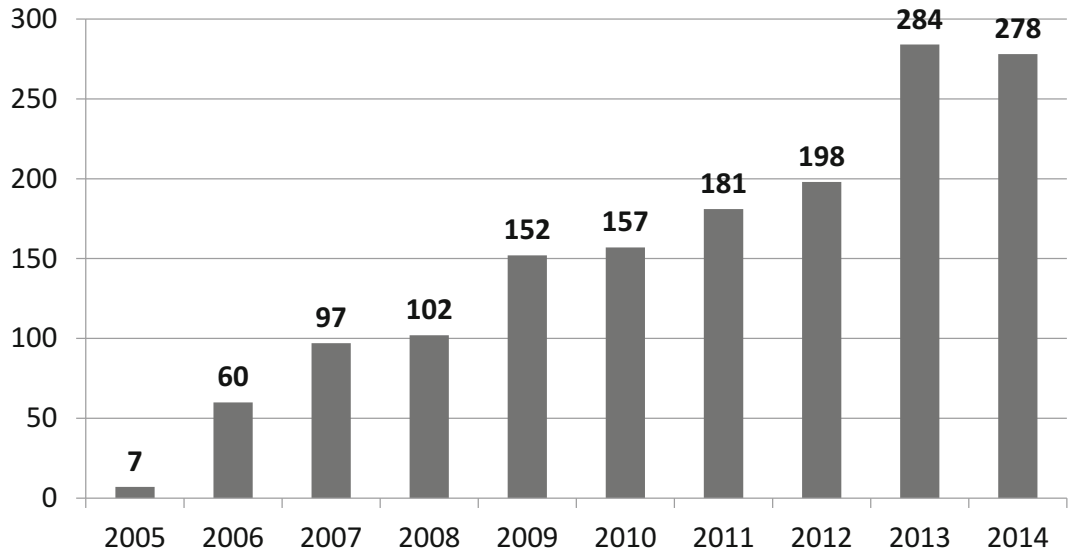

FIGURE 8-2. Potential donor-derived disease transmission reports to the OPTN/UNOS Ad Hoc Disease Transmission Advisory Committee.

TABLE 8-5. Infectious disease screening tests recommended for all organ donors

Required by OPTN policy	HIV 1/2 antibody *or* HIV antigen/antibody combination test[a]
	Cytomegalovirus (CMV) antibody[b]
	Hepatitis B surface antigen (HBsAg)[a]
	Hepatitis B core antibody (HBcAb)[a]
	Hepatitis C antibody[a]
	Hepatitis C NAT
	Syphilis test[b]
	Epstein–Barr virus (EBV) antibody[b]
	Blood and urine cultures
	Sputum gram stain (lung transplant donors only)
	Toxoplasma antibody test result or appropriate donor sample to be tested at transplant hospital (heart donors only)
Recommended donor screening	Coccidioidomycosis serology[c]
	Strongyloides[c]
	TB screening (PPD or interferon-γ release assay)[c]
	Trypanosoma cruzi serology[c]
	West Nile virus testing[c]
	Serologies to help guide pre-transplant vaccination: tetanus, diphtheria, measles, mumps, and *S. pneumoniae*

[a]Must be an FDA-approved, cleared, or licensed donor screening tests.
[b]Can be donor screening *or* diagnostic test.
[c]See text for detailed recommendations on testing situations.

TABLE 8-6. Infectious disease screening tests recommended for all organ recipients

Recommended recipient screening tests for all donors	HIV 1/2 serology[a]
	Anti-cytomegalovirus antibody
	Hepatitis B surface antigen (HBsAg)
	Hepatitis B surface antibody (HBsAb)
	Hepatitis B core antibody (HBcAb)
	Hepatitis C antibody
	VDRL or RPR
	EBV serology
	Varicella-zoster virus antibody
	Toxoplasmosis antibody (for heart recipients)
	TB screening (PPD or interferon-γ release assay)
Recommended recipient screening tests for selected donors	HSV 1/2 IgG antibody
	Trypanosoma cruzi serology
	Strongyloides serology
	Coccidioidomycosis serology

and pathologic evaluation of the organ at the time of procurement and implantation, and posttransplant monitoring of recipients. There are policies that have been developed by the OPTN that mandate which screening tests must be done in all donors and recipients (see Tables 8-5 and 8-6). A number of guidelines and consensus conferences have further refined the screening of donors and recipients [20, 45–55].

8.4.1 Donor Screening Methods

While donors undergo a range of screening, including review of the donors' medical and social history and physical examination of the donor and their organs, most attention is paid to tests that are performed on the donors blood to risk stratify the donor. Mandated screening of blood has traditionally focused on detection of antibodies or antigens present in donors, typically using enzyme-linked immunosorbent assays (ELISA) for most infectious disease screening. As of 2011, molecular screening methods using NAT for HIV, HBV, and HCV screening had been implemented by most US organ procurement organizations [56]. In 2014, OPTN policy was updated to mandate HCV NAT for all deceased donor screening and HIV NAT for screening of increased risk organ donors [20, 57].

The indirect ELISA is used to detect antibodies (i.e., HBcAb) while the sandwich ELISA is used to detect antigens (i.e., HBsAg). In the indirect ELISA (http://www.paho.org/hq/index.php?option=com_topics&view=article&id=10&Itemid=40743), a known antigen is fixed to the bottom of a plastic surface, usually a multi-well plate. Serum is then added and if antibodies that react to the antigen are present, they bind to the antigen. The plates are then washed and a detection antibody (usually an anti-IgG or anti-IgM antibody) that is conjugated to a substrate-specific enzyme is applied to each well. After washing, a substrate is then applied and is converted by the enzyme conjugated to the detector antibody, typically resulting in a colorimetric change. The intensity of this change provides a semiquantitative measurement of the presence of the antigen-specific antibody. To detect an antigen, a sandwich ELISA is used in which a capture antibody (one which is specific for the antigen of interest) is bound to the plates. The patient's serum is applied and if antigen is present, it is bound by the capture assay. The plates are then washed and antigen-specific antibodies are applied—creating an antibody–antigen–antibody sandwich. Detection antibodies and substrate are added as above and the resultant colorimetric change is read. Both of these methods have relatively rapid turnaround times, are not subject to a significant risk of contamination, and can usually be done by either an automatic machine or with minimal technical skills.

As discussed below, there are clear challenges to these serological assays. To detect infection earlier, before antibodies have been created, NAT is used for screening of certain infections. NAT refers to a wide range of polymerase change reaction (PCR), transcription amplification testing (TMA), and branched DNA tests. PCR is the most widely used test in which primers that code for complimentary regions of a pathogen-specific gene of interest are selected. For RNA viruses, the RNA is first reverse transcribed to create a complementary DNA (cDNA) based on the RNA template. At this point, PCR for both RNA and DNA viruses are the same. The source nucleic acids are then mixed with the selected primers, DNA polymerase, deoxynucleoside triphosphates, and buffer materials. An initialization step activates the polymerase, and then a denaturation step melts the DNA into two single strands so that the primers may anneal. Extension or elongation then occurs and repeated cycles proceed to amplify the presence of the gene of interest. The presence of DNA can be detected in one of several ways. In real-time PCR, fluorescent dyes are used to intercalate into the double-stranded DNA to quantitatively detect the target DNA. NAT is challenged by longer turnaround time than serologic tests, greater technical expertise to perform the test, and risk of contamination that may result in false-positive test results, especially in low-volume laboratories.

8.4.2 Challenges to Current Screening Techniques

Once an individual is infected with a viral infection, there is typically local replication of the virus with subsequent viremia (see Figure 8-1) [58]. The period of time between initial infection and detectable viremia is referred to as the eclipse period. Once viremia is present, the immune system can recognize the virus and produce neutralizing antibodies to components of the virus [58]. The period between initial infection and the first detection of these antibodies is referred to as the window period [59]. Transmission of both HIV and HCV from donor to recipient has been reported to UNOS during both the eclipse and serologic window periods [17, 23, 24]. The window period differs for each virus and has been shortened over time with improved serologic tests that are able to detect antibodies earlier after initial infection (Table 8-7) [60, 61].

Unfortunately, even once antibodies are formed, it may be challenging to detect these antibodies. First, some donors require transfusion of blood and blood products or receive large volumes of fluids to replete their intravascular compartments. This may dilute the concentration of the antibodies, antigens, or viral particles to below the limit of detection; this process is referred to as hemodilution [62]. There are a number of ways in which hemodilution can be assessed, and no one method is currently considered the gold standard; a simple guideline is that testing may be less reliable if the donor has received greater than 2 L of blood or crystalloid within 48 h of blood sampling or greater than 1 L of crystalloid within 1 h of sampling in adults; recommendations are more strict for pediatric donors [62, 63]. Second, some donors may lose their serologic response to certain infections over time, particularly if they are immunosuppressed. Thirdly, in infant donors, serologic testing may detect the presence of maternal antibodies without active infection of the child [64].

8.4.3 Donor Types

The type of donor affects testing as well. In general, there are two types of donors: living and deceased donors. The major differences between these donor types are the potential quality of the donor history and the time frame during which

Table 8-7. Interval between initial infection and detection of infection by current molecular and serologic testing methods [136, 137]

Pathogen	First detection by NAT (days)	First detection by serology (days)
HIV	7	22
HBV	20	59
HCV	7	70

donor screening may take place. In the case of living donation, the actual donor is interviewed, which may allow for collection of a more accurate medical and behavioral history. The quality of the medical and behavioral history is more challenging in deceased donation in which the histories are obtained from friends and family members who may not know all of the medical or behavioral details—especially if there was limited contact between the donor and the historian. Often, the clinical circumstances leading to the death of the deceased donor may contribute to this limitation—often donors are found down and accurate history about the preceding events may be limited [13, 15]. Likewise, donors may have undergone extensive resuscitation and/or a prolonged hospitalization that will affect donor screening and infectious risk—secondary to hemodilution as discussed above or by introduction of infection at the time of transfusion [7, 11]. There may be a significant time frame between initial screening and organ donation in the case of a living donor. As such, consideration of repeat testing closer to the time of the transplantation should be considered, and current policy recommends that HIV, HBV, and HCV screening of all living donors be performed within 28 days of the transplant [65]. When time allows, donors may be treated for potentially transmissible infections, such as latent TB, prior to the transplant, decreasing the transmission risk. Lastly, the period of time between initial evaluation and transplantation allows one to screen living donors with risk factors for contracting blood-borne viral infections, such as HIV, HBV, and HCV. In increased risk living donors, as defined by the 2013 Public Health Services Guidelines [20], counseling to abstain from the increased risk behaviors and repeat NAT and serologic testing over a period of time similar to the window period for the virus of interest should be considered to minimize the risk of an occult transmission [20].

8.4.4 Universal Donor Screening

As previously stated, screening of the potential organ donor is critical to identify pathogens that can be transmitted to a recipient. Current OPTN policy requires that screening be done for certain pathogens (see Table 8-5) and that enhanced cultures be obtained in the setting of hospitalization of ≥72 h [66]. Current policy requires only sputum gram stain and description of sputum for lung donors and does not require collection of BAL specimens for cultures (although only bacterial cultures are frequently done by some OPOs, viral, fungal, and mycobacterial cultures are typically not obtained) [66]. As of December 2014, NAT is required for HCV screening of all donors and for HIV screening of increased risk donors only. Positive NAT results suggest active viremia; as such appropriate measures need to be in place for appropriate consent and prophylaxis of and follow-up of recipients for transmission events if viremic donor organs are to be used. Negative NAT does not rule out infection, although it may suggest a lower risk of transmission.

8.4.5 Donor Screening for Endemic Infections

Over time, new pathogens have become significantly prevalent and recognized as having transmission potential via organ transplantation. Screening for these types of pathogens should be considered based on local prevalence of the disease. Endemic pathogens that have increasingly been recognized to result in disease transmission and likely should be screened for in donors from endemic regions include: Chagas disease (*Trypanosoma cruzi*), coccidioidomycosis, strongyloides, and WNV.

8.4.5.1 Chagas Disease (Trypanosoma cruzi)

Chagas disease is caused by the parasite *Trypanosoma cruzi* and is endemic to regions of Central and South America [67, 68]. Since testing for Chagas is required for all blood donors, seroprevalence in the United States is known, and significant geographic variability is recognized [53]. Available US guidelines recommend targeted *T. cruzi* screening of potential donors born in Mexico, Central America, and South America. Given the high rate of false-positive results, donors with initially reactive results should have confirmation with a second test. These guidelines suggest that programs can consider transplantation of kidneys and livers from *T. cruzi*-infected donors with informed consent from recipients but do not recommend the use of heart transplantation from infected donors [53]. Recipients of *T. cruzi*-infected donors should be monitored posttransplant with PCR-based screening with institution of antitrypanosomal treatment if recipient infection is detected [53].

8.4.5.2 Coccidioidomycosis

While there is a low but true risk of disease transmission with all endemic fungal infections, the risk appears highest for coccidioidomycosis. This is likely because of the risk of donor transmission as well as recipient reactivation of disease. Coccidioidomycosis is endemic to the Sonoran desert in the Southwest of the United States and Northwest of Mexico in addition to Central and South America. Donors and recipients from endemic regions should be screened for seropositivity by enzyme immunoassay (EIA), complement fixation (CF), or immunodiffusion (ID). If the donor or recipient is seropositive, prophylaxis with fluconazole, typically 400 mg initially (3–12 months) followed by 200 mg daily, is recommended [69].

8.4.5.3 Strongyloides

There have been an increasing number of donor-derived strongyloides transmissions in the United States, likely secondary to a large pool of potential donors with latent infection and increasing use of steroids for donor maintenance

[27]. Strongyloides is endemic in tropical or subtropical regions of the world, where seropositivity may exceed 80% in some locations. Historically, high rates of strongyloides (~3.8%) have been documented in Appalachia and the southeastern United States. Current guidelines recommend routine screening of donors from endemic regions for strongyloides IgG. Living donors should be treated with ivermectin 200 μg/kg daily on two separate days prior to donation, whereas recipients of deceased donors with positive strongyloides antibodies should receive ivermectin posttransplant [54, 70].

8.4.5.4 West Nile Virus

All US blood donors are screened for WNV. The presence of antibodies to WNV does not predict risk of infection, as they are present in those with prior WNV infection or related flaviviruses. As such, detection of virus in the blood by molecular testing predicts increased risk of transmission, although there have transmissions with negative NAT [7, 11, 71]. A 2008 survey revealed that 11/58 OPOs were currently testing donors for WNV by PCR, typically performing testing in seasons when virus would be predicted in the donor service area [72]. Universal testing may be associated with loss of organs and net loss of life in transplant candidates [73]. A more effective screen is to avoid the use of donors with unexplained encephalitis or unexplained mental status change, but unfortunately donors may be completely asymptomatic and carry the infection [7, 11, 68]. Since transmission of other neuropathogens and malignancies has been associated with patients with unexplained encephalitis, avoidance of these donors is prudent in general [13, 15, 16, 31, 74, 75]. If donor testing is utilized, it should be restricted to NAT of the donor blood during periods of time when there are WNV cases in the region from which the donor resided [54]. Use of donor WNV serology or testing of urine for WNV is not recommended at this time.

8.4.6 Recipient Screening

Just as donor screening is critical to minimize the risk of posttransplant infectious complications, recipient screening may contribute to prevention of donor-derived disease transmission (Table 8-6). This is particularly important for CMV and, in the case of potential heart recipients, toxoplasmosis, where the risk of disease and prophylactic plans are frequently determined by donor and recipient serostatus. In addition, all potential recipients should be screened for tuberculosis using medical history (to assess for potential exposure, prior testing, and prior treatment), radiologic examination (baseline chest radiograph), and testing for latent tuberculosis using either the PPD, with a 5 mm cutoff for positivity, or a TB-specific interferon-γ release assay (such as QuantiFERON-TB Gold, Cellestis Inc., Victoria, Australia) [51, 76, 77]. All potential recipients should also be screened either clinically or serologically for a history of exposure to varicella-zoster virus to allow pre-transplant vaccination of unexposed candidates [51, 78].

Recipients may have been exposed to pathogens with regional endemicity. Careful travel and residence history should be obtained from all potential recipients to determine if specialized testing is indicated. Chagas disease can reactivate in asymptomatic, latently affected recipients [67]. Since Chagas is endemic throughout much of Mexico and Central and South America, consideration of screening potential candidates from affected countries should be considered. Since the approved serologic tests lack specificity, confirmatory testing is recommended; patients with confirmed positive serologic screening should be evaluated by an expert in Chagas disease before proceeding for transplantation [53, 67]. Strongyloides is a parasitic infection that is endemic to tropical and subtropical regions of the world. Infection may remain latent after initial infection with risk of potentially lethal hyperinfection in immunosuppressed patients, particularly those who receive steroids [79]. Reactivation with associated mortality has been well described in the setting of solid organ transplantation [79, 80]. As a result, serology for strongyloides and/or testing of stool for ova and parasites should be considered in all at-risk transplant candidates [80]. Lastly, some centers test patients who have lived in areas with high endemicity for *Coccidioides immitis* for serologic exposure to the fungus [81]. There is no role in testing recipients by serology for histoplasmosis or blastomycosis [82].

Certain transplant candidates may have underlying organ diseases that predispose to pathogens that warrant special screening—this is especially true among lung transplant candidates. Patients with a history of cystic fibrosis may be colonized with pathogens that are highly resistant to usual antibiotics; as such, regular screening cultures from BAL and nasal washes may allow the tailoring of specific perioperative antibiotic regimens to minimize the risk of posttransplant infections with these resistant pathogens [83, 84].

8.5 Management

8.5.1 Vaccination

Recipient serology should be a strong driver of pre-transplant vaccination. Detailed recommendations about transplant candidate and recipient vaccination are made elsewhere (see Chap. 48). Patients who do not have evidence of hepatitis B immunity should receive three doses of HBV vaccine unless contraindicated. Although the traditional regimen of vaccination at months 0, 1, and 6 is used by most centers, there is evidence that an accelerated regimen using double doses of vaccine (at days 0, 7, and 21 or weeks 0, 2, 4, and 6 or months 0, 1, and 2) may provide similar efficacy in a shorter period of time [85–87]. Serologic evidence of protection, as

demonstrated by HBs antibody seropositivity, would potentially allow the use of a core-positive alone or HBV-infected organ in a protected recipient. Likewise, patients without prior exposure to varicella-zoster virus are at increased risk of severe infection if exposed posttransplant. Nonimmune transplant candidates should be vaccinated against varicella unless they have a contraindication to vaccination. Lastly, although there are not a lot of data regarding measles and mumps posttransplant, given recent outbreaks of these diseases in the United States and abroad, measles and mumps immunity should be ensured prior to transplantation, especially in candidates born after the vaccine era (after 1963).

8.5.2 Recipients of Organs from Increased Risk Donors

As of 2015, 19.5% of all organ donors in the United States are at increased risk of having undetected HIV, HBV, and/or HCV (increased risk donors) [88]. The 2013 PHS guidelines suggest that "even though attempts should be made to ensure the highest level of safety, organ donor and recipient selection practices and policies should not be restrictive, considering the clinical need… informed decision-making is an important part of this process for transplant clinicians and their patients" [20]. Data suggest that there may be net benefit to using increased risk donor organs, especially in patients on hemodialysis who have a risk for acquiring these infections already, particularly when further screened using NAT [89]. Per current OPTN policy, "if additional donor disease or malignancy transmission risk is identified pre-transplant, the transplant program must … explain the risks and obtain informed consent from the potential transplant recipient … before transplant, document this consent in the potential recipient's medical record and follow any recipient of the deceased or living donor organs for the development of potential donor-derived disease after transplantation" [43]. Policy also states that "if a donor is found to have an increased risk for transmitting blood borne pathogens, the transplant program must offer recipients of the donor organs…., additional post-transplant testing for HIV, hepatitis C, and hepatitis B as appropriate … [and] every transplant hospital must develop and implement a written protocol for post-transplant testing … [as well as] treatment of or prophylaxis for the transmissible disease, when available" [43]. Policy also requires that the host OPO maintain "blood specimens appropriate for serologic and … NAT, as available, for each deceased donor for at least 10 years after the date of organ transplant, and ensuring these samples are available for retrospective testing" [66]. The 2013 PHS guidelines outline how recipients of increased risk donor organs should be followed and recommend that baseline serology be drawn immediately pre-transplant and the following tests at 1–3 months posttransplant: HIV NAT (or combined antibody–antigen assay), HBV NAT and HBsAg, and HCV NAT [20]. Additionally, the following tests are recommended at 12 months posttransplant: HBsAb, HBcAb, and either HBV NAT or HBsAg [20].

Transmission without seroconversion, especially in the case of HCV, has occurred in the majority of the donor-derived transmissions to date, and therefore, posttransplant testing of recipients of increased risk donor organs must use both serologic and molecular methods [17, 20, 23]. Any documented disease transmission must be reported to the local OPO and to UNOS and should warrant further evaluation as well as referral for management of the transmitted infection [43].

8.5.3 Recognition and Management of Potential Donor-Derived Infection Transmissions

There are currently a number of limitations to the recognition of potential donor-derived transmission events. Often, a single donor provides organs to recipients at multiple different centers or recipients that are cared for by different management teams at the same center. As a result, multiple recipients may present with similar clinical illnesses, but the clustering of this illness goes unrecognized [16]. Likewise, pathogens that are commonly recognized as causing nosocomial infections may not be recognized as a potential donor-derived infection [41, 42]. Finally, onset of disease may be of variable severity in individuals and may present with variable onset posttransplant, further challenging the recognition of donor-derived transmission [11, 15, 90]. To overcome these challenges, it is critical that all transplant centers:

1. Maintain a high level of suspicion for donor-derived infection in all early infections or unexplained clinical illnesses. Any early infection or unexplained clinical illness should lead to an inquiry as to the clinical status of other recipients. This is most easily done through contact with the local OPO. This is especially true for patients with unexplained neurological or severe illness within the first 30–60 days posttransplant.
2. Develop a plan for reporting concern for a potential donor-derived infection transmission. This plan should include a local contact at the transplant center and at the OPO when there is concern for a potential donor-derived infection transmission. Likewise, it is important to consider the transplant center's risk management policies to determine if others within your institution need to be alerted. This plan should also include whom the OPO should contact at your center if there are questions about the status of recipients based on queries generated from other centers. Some have found appointing a specific surgeon and transplant infectious disease consultant as the early points of contact facilitate the clear transmission of data.

3. Provide timely feedback about your patients when information is requested by the OPO.
4. Seek outside expertise, through your local health department, UNOS's Disease Transmission Advisory Committee, and the Center for Disease Control's Office of Blood, Organ, and other Tissue Safety. These groups can advise on optimal testing, help collect appropriate specimens, and may provide insight into similar cases that allow the local center to make more informed treatment decisions.

8.5.4 Management of Recipients of Organs from Infected Donors

As previously discussed, all organ donors are currently screened with serology for HIV 1/2, CMV, EBV, HBV, and HCV and also with HCV NAT as currently required by OPTN policy [66]. Although the recent passing of the HIV Organ Policy Equity Act allows for research to be performed in using organs from donors that are HIV-1/2 infected, the use of these organs for transplant is not yet allowed outside of a research protocol in the United States [66, 91].

Donors seropositive for CMV and EBV are universally used, although donor and recipient serologic status may determine monitoring and prophylaxis plans. The risk of developing CMV viremia and diseases is greatest in seronegative recipients of seropositive organs as described later in this text [92, 93]. Universal prophylaxis and preemptive therapy can reduce the risk of viremia and disease in at-risk patients [92, 93]. Development of posttransplant lymphoproliferative disorder (PTLD) has been described, particularly in young EBV seronegative recipients of EBV seropositive donors [94–96]. Careful monitoring and intervention, as described later in this text, may reduce the risk of PTLD in this setting [94–96].

Current mandated donor screening for hepatitis B includes detection of HBV surface antigen (HBsAg) and core antibody (HBcAb). HBsAg is a marker of active viremia while HBcAb is a marker of exposure to hepatitis B virus. Since HBV vaccine only contains hepatitis B surface antigen, vaccinated donors should only have HBV surface antibody (HBsAb), but not HBcAb. If HBsAg is measured early after vaccination, it can be detected in the blood [97, 98]. The risk of transmission of HBV to a nonimmune recipient is high in HBsAg-positive donors [99]; use of these organs is discussed further in the chapter on Hepatitis B. Although HBsAg-positive donors may have been deferred in the past, advances in the use of hepatitis B immune globulin and anti-HBV antivirals now allow the selective use of these organs [99]. Donors that have isolated HBcAb positivity may represent latently infected individuals or a false-positive result. The risk of transmission of HBV in liver transplant recipients is higher than in non-liver recipients [100]. The risk of transmission of HBV from a donor with and isolated HBcAb is estimated to be less than 5% for non-liver recipients [55, 101, 102]. Additional testing of these donors with HBcore IgM and HBV DNA NAT would further stratify the risk of transmission, with the highest risk in the IgM+ and NAT+ donor [55]. Some centers use these organs, particularly in patients who have been vaccinated against hepatitis B [55]. When used in nonimmune patients, posttransplant vaccination is often combined with the use of either anti-HBV antiviral prophylaxis or hepatitis B immune globulin infusions [55]. All recipients, especially liver recipients, of HBsAg+ or HBcAb+ donors should be monitored closely for the presence of active viral replication with expansion of therapy based on these results [55, 103, 104].

Detection of HCV antibodies suggests prior infection with hepatitis C, but about 15–20% of those infected with HCV will clear the virus, and the HCV serology test has a relatively high known false-positive rate [105, 106]. Therefore, the use of HCV NAT in donor screening allows for differentiation between prior HCV infection and active infection with viremia. Use of HCV-positive donors for HCV-negative recipients is currently considered only in life-threatening situations; however, HCV-positive donor organs should be considered in HCV-infected recipients [106–109]. Small, likely clinically insignificant, decreases have been found in transplant graft and patient survival when HCV+ organs are used for HCV-infected recipients, but these are offset by the concomitant decrease in transplant waiting list time [108]. Mortality appears to be higher among heart recipients, so the use of HCV seropositive donors is less frequently considered [110–112]. One concern relates to infecting a recipient with an additional HCV genotype that may be less responsive to antiviral therapy, since genotype results are typically not known at the time of transplant. With the advent of new and evolving data regarding direct-acting antivirals and interferon-free HCV regimens, the options to treat HCV before and after transplant are continuously changing.

It should be noted that the only required bacterial screening in organ donors is blood and urine cultures of donors and screening for syphilis. OPOs are required to determine if additional culture-based testing has been conducted on the donors prior to procurement. Unfortunately, there are current challenges to this—once the donor is declared deceased, they are often "discharged" from the hospital and then readmitted under a new account under the care of the OPO until procurement. When cultures come up positive, the laboratory may not realize that the deceased patient has become a donor and that they have to inform the OPOs of the donor result. Some hospitals may stop working up cultures on "deceased" patients so that no further results are obtained. Lastly, follow-up cultures of bacteremic donors may not be available at the time of procurement.

In general, donors with positive blood cultures may be used if they have received an appropriate antimicrobial and have had a clinical response to therapy; often a complete course of therapy is given to the recipient posttransplant.

Transmission of particularly virulent organisms, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*, has been described [37, 40, 113]. Donor bacteremia or candidemia mandates treatment of all recipients with a minimum of 14 days of appropriate, active systemic therapy, and experts recommend 4 weeks of recipient therapy when receiving organs from donors bacteremic with *Staphylococcus aureus* [114]. Non-bacteremic localized infections from other sites only require treatment if transmission in the transmitted organ is plausible (i.e., positive urinary cultures require therapy in kidney recipients; sputum cultures require therapy for lung recipients but not other recipients unless bacteremic; etc.).

In patients with proven bacterial meningitis, even with bacteremia, organs can be safely used as long as the patient has received at least 24 h of appropriate antibiotics and antibiotics are continued in the recipient [115–118]. Donor bacterial colonization of lung donors is common. Donor lung sample, including donor bronchoscopy at the time of lung transplantation, may allow for directed antimicrobial therapy.

All donors are tested for latent infection with syphilis per OPTN policy. A recent survey of OPOs revealed that 87% used RPR for testing and 81% of OPOs confirmed positive initial tests with a confirmatory test; a high rate (41%) of positive RPR results was negative on confirmatory testing [119]. Transmission of syphilis by organ transplantation has been rare and is not a contraindication to organ donation [120–122]. Recipients are typically treated as latent syphilis of unknown duration with 3 weekly 2.4 million unit doses of benzathine penicillin G [51, 122].

Lastly, sometimes perfusate or transport media may become contaminated with bacteria or fungi. As with other infections, this is a risk factor for systemic infection and formation of mycotic aneurysms at the site of vascular anastamoses. A full 14-day course of active antibiotic is recommended for recipients to minimize the risk of transmission [123–125].

In general, screening for *Mycobacteria tuberculosis* is not done in deceased donors, but should be performed in all living donors [51, 54, 126, 127]. Active tuberculosis in any donor is a contraindication to donation; if a deceased donor is thought to possibly have tuberculosis, their organs should not be used unless active TB infection can be definitively ruled out [126, 128–131]. Donor-transmitted TB accounts for 4% of all posttransplant cases of tuberculosis [132]. Testing for TB can be done by the PPD placed using the Mantoux method or via a TB-specific interferon-γ release assay (such as QuantiFERON-TB Gold, Cellestis Inc., Victoria, Australia) [133]. Positive testing by either method should result in careful assessment for active disease, including chest imaging and, if appropriate, sputum and/or urinary AFB cultures. Some centers will provide latent TB treatment to the recipient of organs from these donors; this decision can be individualized as transmission if not universal [77, 129, 132]. If the recipient does not receive treatment for latent TB, a note about the donor's testing should be prominent in the recipient chart to trigger aggressive evaluation with the appropriate clinical presentations (i.e., sterile pyuria, pneumonia).

Toxoplasmosis is a parasite that remains dormant predominantly in muscle tissue. As such, the risk of transmission is greatest in heart donation [68]. Routine screening of all donors for toxoplasmosis is not done at many OPOs, but policy requires that serum is procured at the time of explanting the heart to perform toxoplasmosis serology at the recipient center [66, 134]. Positive serology is not a contraindication for transplantation. In the setting of heart transplantation, donor and recipient toxoplasma serostatus may affect prophylactic and monitoring strategies [134, 135]; generally, prophylaxis is not modified in non-heart recipients of toxoplasmosis seropositive donors [135].

8.6 Conclusion

Donor-derived infections are increasingly recognized as causes of morbidity and mortality that typically present in the early posttransplant period. Careful screening of donors through history, physical examination, and serologic and molecular testing may minimize the risk of infection transmission. It is impossible to screen for all potential pathogens, and our current screening practices have clear limitations. As a result, the possibility of donor origin should be considered for all early infections and patients with atypical clinical courses. Reporting of proven or suspected donor-derived infections is currently mandated as part of OPTN policy.

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