3 Pre- and Peri-transplant Period: Screening and Treatment of Infections in the Pretransplant Period, Donor-Derived Infection

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3.1 Introduction

Optimal donor and recipient screening and selection must minimize the risk of disease transmission from donor to recipient and avoid unnecessary rejection of uninfected donors due to false-positive testing. False-positive tests become more likely when applied universally to a population at low risk of the tested infection. Risk mitigation relies on more than laboratory testing, and a comprehensive strategy is ideally based on three aspects:

- Donor medical, social, and epidemiological history
- Physical and radiological donor examination
- Microbiological testing

A previously proposed risk grading system for both donor and potential recipient factors classified the risk of donor-derived infection into one of five categories globally [1] (modified from Len and Garzoni, with permission [2]:

- Unacceptable risk includes absolute contraindication, with the exception of some lifesaving transplantation procedures in the absence of other therapeutic options on a case-by-case basis.

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- Increased but acceptable risk includes cases where transmissible microorganisms 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 its clinical condition.
- Calculated risk 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, in cases with broad-spectrum antibiotic therapy of a minimum duration (24 h) and those with documented bacteremia who have started targeted antibiotic therapy.
- Not assessable risk includes cases where the evaluation process does not allow an appropriate risk assessment for transmissible diseases.
- Standard risk includes cases where the evaluation process did not identify a transmissible disease.

Recently, both the European and the US approaches are abandoning this "grading system," and donors are classified using a dichotomous system:

– Standard risk donor: donor with no evidence of increased disease transmission risk beyond the average population-adjusted risk for undetectable disease.
– Nonstandard or increased risk donor: donor presents an increased risk for disease transmission beyond the average population-adjusted risk for undetectable diseases.

In the case of the nonstandard risk donor, an individualized risk-benefit analysis is needed to decide if transplantation of a given organ into a given recipient is justifiable. In this circumstance, informed consent of the recipient is mandatory, and all reasonable strategies for risk reduction should be employed.

This chapter will discuss mandated screening protocols for donor-derived infection in both the USA and Europe, as well as discuss potential screening for geographically and seasonally limited diseases in both deceased and living donors. Further, we will discuss important selected potential donor findings (either on screening or clinically) and discuss treatment intended to mitigate risk and help readers classify into the categories described above.

3.2 Definitions and Epidemiology

Expected donor-derived disease occurs frequently, with Epstein-Barr virus (EBV) and cytomegalovirus (CMV) being the most common pathogens, and defined management strategies are employed. Unexpected donor-derived disease transmission, the focus of this chapter, is rare complicating less than 1% of transplants [3]. Outcomes can be poor, with mortality rates of up to 25% in affected recipients [3]. In a 10-year review of donor-derived infections reported to the US Organ Procurement and Transplantation Network (OPTN) and Disease Transmission Advisory Committee (DTAC), which manages a required but passive reporting system, viral

infections accounted for 24% of infected recipients, bacteria 19%, mycobacteria 2.4%, fungus 16%, and parasites 12%. The remaining donor-transmitted diseases—malignancies and other non-infectious conditions—accounted for 34% of infected recipients [3]. Epidemiology will vary from region to region based on screening practices and the prevalence in the donor population of transmissible infection. For example, the transmission of intermediate stage Chagas disease would be much more likely in South America than in Europe, and cases of donor-derived infection with West Nile virus (WNV) would be seasonally limited. Most disease transmissions are caused by infections that may be difficult to screen for or recognized in the infected donor, including rabies virus, WNV, lymphocytic choriomeningitis virus, tick-borne encephalitis, as well as parasitic pathogens such as *Balamuthia mandrillaris*.

3.3 Timelines

In general, most donor-derived infections cause symptoms early after transplantation. In one report, 67% developed symptoms within 30 days of transplantation and 88% within 90 days [4]. Bacterial infections are almost always recognized within 30 days and rarely become apparent after 45 days. Nonetheless, some pathogens, particularly those with a long clinical latency, may present months after transplantation, including *M. tuberculosis*, *Strongyloides*, *Toxoplasma*, *Balamuthia*, *Histoplasma*, human immunodeficiency virus (HIV), viral hepatitis, *Microsporidium*, and rabies [5]. Early recognition and notification is critical to allow preventative measures to be instituted to protect other recipients of the source donor.

3.4 Diagnosis and Screening

3.4.1 Clinical Screening

In addition to the required and targeted screening tests discussed above, careful clinical screening is essential to identify donor risk factors for infection with a transmissible pathogen. For deceased donors, the cause of death should be reviewed to determine if an unidentified but transmissible pathogen may be present. For example, a number or clusters of potentially fatal donor-derived disease have involved donors with meningoencephalitis of unknown etiology. Transmitted pathogens have included *Balamuthia mandrillaris*, *Cryptococcus neoformans*, and lymphocytic choriomeningitis virus [6]. Generally, a potential donor with meningoencephalitis of unknown cause should be rejected. In addition to reviewing the cause of death, other clinical information should be considered. For example, the presence of multidrug-resistant organism in certain circumstances (e.g., sputum of a lung transplant donor, blood of any organ donor, urine of a kidney donor) may be transmitted to the recipient, and careful management strategies are required to mitigate risk.

3.4.2 Required Donor Laboratory Screening

Required screening strategies differ slightly between the USA and different European countries. In the USA, the OPTN sets required minimum standards for screening (Table 3.1). Further, the Public Health Service (PHS) classifies some donors as increased risk for undetected infection with HIV, hepatitis B, or hepatitis C based on behaviors or other exposures that put the patient at risk for recent or "window period" infection with the aforementioned blood-borne viruses (Table 3.2) [7]. In addition to the required serologic and nucleic acid testing (NAT) for hepatitis C, these donors must undergo NAT or antigen-antibody combination testing for HIV. As a practical matter, nearly all donors in the USA are tested by NAT for HIV, hepatitis C, and hepatitis B. The NAT window, or "eclipse," period, where tests may be negative but transmission of virus possible, is about 5–10 days for HIV, 6–9 days for HCV, and 20–26 days for HBV. Up to 25% of donors in the USA are identified as increased risk donors, but the risk of window period infection is likely less than 1%, and a thoughtful informed consent process is necessary to ensure that potential recipients understand the meaning of increased risk donor and of the generally low risk associated with these donors [8, 9].

Table 3.1 Routine donor screening tests (living and deceased)

Condition	Test	Comment
Human immunodeficiency virus	Antibody p24 or NAT	HIV+ donors may be eligible for donation to HIV + recipients NAT reduces window period to 5–10 days
Hepatitis C	Antibody and NAT	HCV+ may be used in HCV + recipients and investigational use in HCV− NAT reduces window period to 6–9 days
Hepatitis B [1]	Surface antigen Core antibody HBV NAT	NAT-negative core antibody-positive non-hepatic organs at low risk for transmission
CMV	IgG antibody	Needed to plan preventative strategy
EBV	IgG antibody	Needed to plan preventative strategy
Bacteremia	Blood cultures	Bacteremia typically not a contraindication, treat recipient
Urinary tract infection	Urine culture	UTI not a contraindication, treat kidney recipients
Pulmonary infection	Sputum culture BAL with culture Chest radiograph	Most relevant for lung recipients
Syphilis	Treponemal or non-treponemal test	No contraindication to transplant, treat recipient
Toxoplasmosis	IgG antibody	Prophylaxis in heart D+R−

HIV human immunodeficiency virus, *NAT* nucleic acid test, *HCV* hepatitis C virus, *HBV* hepatitis B virus, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *UTI* urinary tract infection, *BAL* bronchoalveolar lavage, *D+R−* donor positive-recipient negative

Table 3.2 Public Health Service criteria defining donors at increased risk for recent infection with HIV, HBV, and HCV

• Any of the following behaviors in the preceding 12 months
– Men who have had sex with men
– Drug injection by intravenous, intramuscular, or subcutaneous route for nonmedical reasons
– Sex in exchange for money or drugs
– People who have had sex with partners meeting any of the above criteria
– People who have had sex with persons known or suspected to have HIV, HBV, or HCV infection
– New diagnosis with or treatment for syphilis, gonorrhea, chlamydia, or genital ulcers (with the exception of known recurrent HSV)
– People who have been on hemodialysis
– Child 18 months or younger born to a mother known to be infected with or at increased risk for HIV, HBV, and HCV
– Child who breastfed from a mother known to be infected with or at increased for HIV infection

3.4.3 Geographically or Seasonally Limited Infections

In addition to required testing for routine infections (e.g., blood and urine cultures) and blood-borne viruses, screening for geographically or seasonally limited infections may be appropriate in certain circumstances [10]. For example, during an outbreak of WNV, screening deceased donors with NAT may be reasonable. Such testing optimally would utilize highly specific assays to avoid false-positive tests which could lead to wastage of uninfected organs since confirmatory testing generally cannot be performed routinely given the time constrains of organ donation. Further, application of screening tests that have not been tested or approved in deceased donors, such as interferon-gamma release assay testing for TB, may provide tests with unexpected high false-positive or false-negative results. Even when the results of testing performed on deceased donors cannot reliably be obtained prior to the decision to procure the organ, the test may still be useful. For example, a positive donor serology for *Strongyloides* would prompt recipient treatment even if the result is learned after the transplant procedure has occurred. For living donors, there is a much greater opportunity to obtain a careful history of geographic risk, occupational risk, hobbies, and exposures to zoonotic infections. Appropriate testing can then be obtained including confirmatory tests if required. Table 3.3, adapted from an OPTN guidance document, lists some of agents for which testing could be considered in living donors [11].

3.5 General Approach

The following sections will discuss considerations for use and risk mitigation strategies for various categories of organisms and associated clinical situations.

Table 3.3 Screening for seasonally and geographically limited diseases

Disease	Signs/symptoms in potential donor	Known risk factors	Potential testing	Use in deceased donors
Human T-cell lymphotropic virus (HTLV-1)	Most asymptomatic, T-cell leukemia, or myelopathy	Residence in Asia (particularly Japan), Caribbean, South America, West Africa	Serology – Confirmatory testing required	False-positives common
Histoplasmosis	Fever, night sweats, lymphadenopathy, cough, noncalcified pulmonary nodules or cavities	Residence in Midwestern states, Mississippi, or Ohio river valleys	Serology – Complement fixation – Immunodiffusion – EIA – Urine or serum antigen testing	Consider if evidence of histoplasmosis (lung nodule with organism)
Coccidioidomycosis	Fever, joint pains, cough, neck stiffness, headaches, pulmonary nodules or cavities, reticulonodular infiltrates	Residence in desert areas of the southwestern USA	Serology – Enzyme immunoassay – Complement fixation – Immunodiffusion – Urine or serum antigen testing	Universal testing may be appropriate in endemic areas
Chagas	Most asymptomatic; symptomatic chronic infection may present with cardiomyopathy, cardiac conduction abnormalities, megaesophagus, megacolon	Born or resided in endemic areas of South and Central America, child of woman who lived in endemic area, received blood transfusion in endemic area	Serology testing	Consider if risk factors
Strongyloides	Donors may have chronic abdominal pain, intestinal symptoms, and/or eosinophilia, or could be entirely asymptomatic	Soil exposure in tropical/warm climates. Walking barefoot, contact with human sewage, or contaminated soil. Exposure risk may persist for decades	Donors could be tested by serology (preferable) and/or stool examination, specifically looking for *Strongyloides*	Consider if epidemiological risk factors

Tuberculosis	Fever, night sweats, weight loss, cough, recurrent pneumonia, exudative pleural effusion of unknown etiology, lymphadenopathy, noncalcified pulmonary nodules or cavities	Born outside USA/Europe, prolonged residence outside USA/Europe, homeless, alcohol or other substance abuse, jail/prison time, healthcare worker, known TB exposure	Positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA); sputum/BAL AFB smear, culture, nucleic acid amplification, TB PCR; AFB smear, culture, PCR on tissue	Performance of latent TB testing in deceased donors unknown
West Nile virus	Often asymptomatic; 20% develop acute febrile illness; <1% encephalitis, myelitis	Mosquito exposure, blood transfusion; risk varies by season and location	Nucleic acid test (NAT) and IgM serology	Consider during outbreak

Adapted from Recognizing Seasonal and Geographically Endemic Infections in Organ Donors: Considerations during Living Donor Evaluation, OPTN Guidance Document) https://optn.transplant.hrsa.gov/media/1138/seasonal_disease_guidance.pdf

3.5.1 Bacterial Organisms

3.5.1.1 Routine Bacterial Infections

Bacterial infection or colonization is commonly detected in potential donors. While bacterial infections can be transmitted to recipients, most routine donor infections are not considered to be contraindications to transplantation. For example, kidney recipients of donors with bacteria isolated in the urine can generally be treated with 5–7 days of antibiotics based on resistance testing with no clinically significant transmission of infection. Similarly, most lung transplant centers treat recipients with 7–14 days of antibiotics guided by donor sputum or bronchoalveolar lavage culture results. In the case of donors with bacterial meningitis, organ procurement is considered safe after at least 48 h of effective antibiotic therapy, and recipients should receive 7 days of treatment posttransplantation. Donors with bacteremia due to *Staphylococcus aureus*, coagulase-negative *Staphylococcus*, and gram-negative organisms can often be used with donor and recipient treatment.

3.5.1.2 Multidrug-Resistant Bacteria

Colonization or infection of donors with gram-negative or gram-positive multidrug-resistant bacteria (MDR) presents a unique challenge. In one report, a donor with methicillin-resistant *Staphylococcus aureus* (MRSA) receiving appropriate antibiotics and with resolution of bacteremia transmitted recurrent and difficult to treat MRSA to two recipients despite prophylactic antibiotics [12]. In that case, however, the donor had endocarditis, and the extensive seeding of the organs likely played a role in the recalcitrant nature of the infection. Major complications may occur when donors infected or colonized with vancomycin-resistant enterococci (VRE), carbapenemase-producing bacteria, pan-resistant *P. aeruginosa*, and other pan-resistant gram-negative bacteria are used, and reports described poor outcomes in this circumstance [13]. In some cases, abdominal organs can be soiled with MDR organisms in donors with trauma and open abdomens. Knowledge of potential MDR colonization is highly relevant to target peri-transplant antibiotic prophylaxis, and one report does describe successful use of donors with MDR gram-negative organisms with careful application of active antibiotics after transplant [14]. In general, these donors should be used very cautiously in conjunction with transplant infectious disease consultation.

3.5.2 Fungal Organisms

3.5.2.1 Candida

As is the case for routine bacterial organisms, colonization of donors with *Candida* is common. Donor urinary colonization with *Candida* is typically treated with 7–14 days with an antifungal drug (typically fluconazole if sensitive) for kidney recipients. While no consensus exists on the need to routinely culture

preservation fluid, if cultures are done and *Candida* has grown, 7–14 days of antifungal treatment would be reasonable. There have been few reports describing recipients outcomes in donors with candidemia. These donor should be used with caution, and the recpient should be treated with an appropriate antifungal for 7–14 days. *Candida* can occasionally infect the bronchial anastomotic site of lung transplant recipients, and *Candida* is a frequent colonizer of sputum in potential donors. Many lung transplant centers routinely use antifungal prophylaxis after lung transplantation.

3.5.2.2 Endemic Fungi and Cryptococcus

Except in extreme cases of recipient need, active infection with endemic fungi should be considered a contraindication to organ donation [15]. Occult and asymptomatic donor infection, however, may be unrecognized with resultant transmission to recipients. Among the endemic fungi, coccidioidomycosis has been the most frequently reported. In the largest available report which included 6 donors, 9 of 21 exposed recipient developed active infection, and 6 of these recipients died. Notably, no recipient receiving preventative or early treatment died of coccidioidomycosis [16]. In endemic areas, prophylaxis is commonly given to recipients of donors with suspected or proven coccidioidomycosis, and many centers practice universal prophylaxis to reduce the risk of both donor-derived and environmentally acquired infection. Histoplasmosis had been less commonly reported, although in endemic areas granulomatous lesions in the lung or mediastinal lymph nodes are common and generally do not require any recipient treatment. When possible, however, serological and antigen testing of the donor can be used to guide therapy with management options including itraconazole treatment or antigen monitoring of the recipient [17]. As is true of donors with active endemic fungi, organ from donors with active infection with *Cryptococcus* should rarely if ever be transplanted. If donor-derived cryptococcal disease is discovered after transplant, all recipients should be tested for cryptococcosis using both antigen testing and culture. In the absence of detection of *Cryptococcus* in the recipient, a minimum 6-month course of fluconazole would be a reasonable course. If recipient disease is detected, guidelines for treatment should be followed [18].

3.5.3 Environmental Molds

Reports of rapid fatal dissemination of *Aspergillus* from colonized or infected donors suggest that potential donors known to be infected with *Aspergillus* or other pathogenic environmental methods should not be used [19]. Sources of these molds may include preservative fluids, environmental contamination during the procurement process, and drowning/submersion victims. Extended treatment with a mold-active antifungal is recommended if donor-derived mold infection (perhaps with the exception of lung colonization) is discovered posttransplant.

3.5.4 Mycobacteria

Medical and epidemiological history and chest imaging are mandatory to determine the risk for tuberculosis. Active disseminated tuberculosis is a contraindication for organ donation. Organs, with the exception of the lung in case of residual visible changes, can be used in cases of past tuberculosis treated for at least 6 months. History of latent TB or positive IGRA test without a sign of active infection is not a contraindication, but preventive therapy for all recipients should be considered (see Chap. 20).

3.5.5 Viral Infections

This chapter will not address *Cytomegalovirus* or EBV as these are expected donor-derived diseases with specific management strategies addressed in Chaps. 6 and 7.

3.5.5.1 Human Immunodeficiency Virus

Since widespread donor HIV testing became available, in the USA only two instances of donor-derived HIV infection have been reported. In one case a living donor contracted HIV between his initial testing and transplant. In the second case, a donor with a history of intravenous drug use in the serological window period transmitted HIV and hepatitis C to multiple recipients [20, 21]. Outside of the USA, a living donor in India likely in the window period transmitted HIV to her recipient, and human error in transcription of a positive HIV donor test result in Italy led to a cluster of donor-derived cases [22, 23]. Early diagnosis of donor-derived HIV is critical as early treatment may be lifesaving; recipients of donors with risk factors for window period HIV infection should undergo NAT testing 1 to 2 months posttransplant. Currently, in several European countries and since the passage of the HOPE Act in the USA, organs from HIV-infected donors who meet certain criteria can be transplanted into HIV-positive recipients, in some countries as part of research protocols. Several guidelines have been published for transplantation in HIV-positive recipients, and generally the following requirement for the recipient should be met: CD4 > 200 ul, efficacious HAART, documented aviremia, and absence of active opportunistic infections. Please refer to national guidelines and legal rules for more details [24].

3.5.5.2 Hepatitis B and Hepatitis C

Donor-derived hepatitis C has occurred from donors in both the serological and NAT window period [25]. While the hepatitis C NAT window period is only 6–9 days, the increase in the number of donors with active intravenous drug results in a larger donor pool with negative screening antibody and NAT tests at risk for recent and transmissible infection with hepatitis C. Modeling studies and limited data from DTAC suggest that the risk of NAT window period donor hepatitis C infection in an intravenous drug user is likely less than 3% [8, 25]. This risk may increase significantly in the setting of a local outbreak of hepatitis C. Similar to HIV, early

diagnosis of donor-derived hepatitis C is critical to avoid fibrosing hepatitis; NAT testing at 1–2 months after treatment will detect virtually all cases, and new antiviral therapy is highly effective. In immunosuppressed patients posttransplant, seroconversion may not occur and thus serologic testing is not reliable.

Window period hepatitis B transmission has occurred as well, and screening of recipients of donors at increased risk for recent hepatitis B is reasonable; a second test at 6–12 months is recommended. For HBV NAT-negative donors who are core antibody positive, the risk of transmission from non-hepatic organs is low, particularly if recipients are hepatitis B surface antibody positive. Hepatitis C seropositive donors can be divided into two categories based on NAT status. Those who are NAT positive are likely to transmit hepatitis C to the recipient of hepatic and non-hepatic organs. NAT-negative donors may have naturally cleared hepatitis C virus or received successful medical treatment for hepatitis C. While these donors would generally not be expected to transmit hepatitis C to seronegative recipients, one report describes that 4 of 25 recipients of hepatitis C seropositive/NAT-negative liver donors developed probable donor-derived hepatitis C. All four donors died from drug overdose, and it is unclear whether the hepatitis C transmission was due to occult hepatitis C infection or new donor eclipse period infection [26]. Chapter 10 provides further details on the treatment and prevention of viral hepatitis after transplant.

3.5.5.3 Other Viruses

Human T-cell lymphotropic virus 1 (HTLV-1) is endemic in the Caribbean, parts of South America, West Africa, and parts of Asia particularly Japan. Prevalence is very low in the USA and Europe, and universal screening is not required as false-positive tests resulted in significant organ wastage [27]. Donor-derived cases with the rapid development of HTLV-1-associated disease have been reported, and screening of donors from endemic areas is reasonable [28]. The effect of immunosuppression on the natural history of HTLV-1 remains unclear, and while HTLV-1-positive recipient status is not an absolute contraindication to transplantation, HTLV-1 disease has been reported after transplantation, and no effective antiviral treatment is available [29]. Other viruses associated with encephalitis and without effective treatment with described donor transmission and fatal outcomes in recipients have included WNV, lymphocytic choriomeningitis virus, tick-borne encephalitis virus, and rabies virus, and donors with suspected active infection with these pathogens should not be used [30].

3.5.6 Selected Parasitic Infections

Strongyloides is endemic throughout the world, but more common in tropical regions and the Mediterranean basin. Asymptomatic infection may persist for years, and donor-derived infection often with fatal outcomes has been well described [31]. Recipients with suspected infection or receiving organs from potentially infected donors should receive treatment with ivermectin, and with the exception

of hyperinfection in the donor concern for *Strongyloides*, infection should not delay transplantation or exclude infected donors or recipients.

Prevalence of infection with *Toxoplasma gondii* varies throughout the world but exceeds 70% in some regions. Since the parasite encysts in the heart muscle, the major concern has been transmission from positive heart donors to negative heart recipients, and prophylaxis is recommended in that setting. As disease development has been reported in seronegative non-cardiac recipients not receiving TMP/SMX prophylaxis, awareness of the potential for donor-derived disease in that circumstance is prudent.

Infection with *Trypanosoma cruzi*, the cause of Chagas disease, is endemic in parts of Mexico and much of Latin and South America. Intermediate stage Chagas disease is typically asymptomatic, and transmission to recipients may occur. Recipients of donors seropositive for Chagas disease should receive periodic blood microscopy and if possible, NAT testing available at the CDC (consultation with Division of Parasitic Diseases, CDC 770-488-7775) or local tropical disease reference centers. A suggested protocol for testing and treatment if transmission occurs is available [32].

3.5.7 Selected Relevant Guideline References

Guidelines advising on donor screening and recipient and donor management have been published and serve as an excellent reference [7, 10, 33].

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