Donor Infections

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Transmission of infection via transplantation of allografts is uncommon but potentially life-threatening events. There are two major types of donor-derived infections that are transmitted: those that are unexpected despite routine donor screening and those that would be expected secondary to donor and recipient screening.
In the present chapter, donor screening and the most challenging unexpected donor-derived infections will be described, including the new challenging organ transplantation from HIV-positive individuals to HIV-positive recipients.

10.1 Introduction

Over the years, an improving liver transplantation (LT) survival rate (1- and 5-year survival of greater than 90% and 75%, respectively) [1] has been instrumental in establishing transplant surgery as a durable therapy for all forms of end-stage liver disease and for some malignant conditions. The success of such treatment has resulted in a progressively increasing demand for LT. Each year more than 20,000 livers are transplanted worldwide [2]. However, at the same time the number of potential recipients for LT is now exceeding organ supply. The growing gap between the number of patients waiting for transplantation and available organs

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continues to be the number one issue facing the transplant community. As a consequence, the major focus in liver transplantation has been developing strategies to increase available donors through the use of live donor liver segments and splitting deceased donor grafts for two patients. In addition, several groups continue to explore ways in which outcomes can be improved utilizing organs from "extended criteria" donors, including donors with infections or malignancies [3].

In spite of significant benefits derived from the clinical application of LT, there is an inherent risk of disease transmission or other negative outcomes. Transmission of infection via transplantation of allografts is uncommon but potentially life-threatening events. The precise rate of disease transmission from donors to recipients and the effectiveness of current donor screening protocols are currently unknown. There are two major types of donor-derived infections that are transmitted: those that are unexpected despite routine donor screening and those that would be expected secondary to donor and recipient screening. Unexpected donor-derived disease transmissions occur when infections are not recognized by history, physical examination, or laboratory assessment in the donor before procurement of the organs. Available data suggest that unexpected transmission events occur in <1% of solid organ transplant recipients [4–9]. Disease can be severe carrying a particularly high risk of adverse outcomes. In most cases, this risk is managed by a combination of clinical assessment and pre-procurement donor testing. However, most donor-derived disease transmissions are expected. In some cases (e.g., cytomegalovirus, Epstein–Barr virus), organs from infected donors into seronegative recipients and organs from donors with some infections (e.g., bacteremia, bacterial meningitis, etc.) are knowingly transplanted recognizing that the donor-derived infection can be managed with monitoring and/or preventive strategies.

Infectious agents transmissible by organs belong to five groups of pathogens:

- **Viruses:** By infection in the tissue of donors with or without current viremia. Thereby, Deoxiribonuceic acid (DNA) virus may persist latently in the tissues without detectable viremia; Ribonucleic acid (RNA) viruses usually cause direct infection and disease. Compartmentalization of an infectious pathogen can also lead to transmission in the absence of detectable viraemia.
- **Bacteria:** By bacteremia or colonization/infection of organs.
- **Fungi:** By fungemia or colonization/infection of organs.
- **Parasites:** By acute or latent infection.
- **Prions:** By infection.

Over the past decade, the solid organ transplant community has focused increased attention on minimizing the risk associated with unexpected transmissions from organ donor to recipients and to mitigate the consequences of such transmissions.

This chapter will not discuss expected disease transmissions and will be limited to what is unusual and has been recently reported and on what the author believes are the future challenges transplant surgeons and physicians are going to face.

10.2 Basic Screening for Infections in Organ Donors

The approach to microbiologic screening of organ donors varies with national and regional regulations and the availability and performance of microbiologic assays used for potential donors. Donor screening has been addressed by many excellent reviews and guidelines [10–14]. However, the basic screening for infections in deceased and living organ donors must include the following serological tests, with results being provided within the time frame specified in Table 10.1.

Screening should be extended to Nucleic acid test (NAT) for donors with an increased risk of Human Immunodeficiency Virus (HIV)-1, hepatitis B virus (HBV), or hepatitis C virus (HCV) infection [14–16]. The results of these tests must be made available before organ recovery or transplantation. However, during the eclipse phase, NAT may also fail to detect the pathogen in the blood or plasma (≈ 5–7 days for HIV and HCV, and ≈ 20 days for HBV), and infection may be transmitted even with a non-reactive NAT. Accordingly, recipients should be tested in the post-transplant period to rule out transmissions.

Screening protocols must be reviewed regularly because of the rapid development in testing repertoires.

In addition to national guidelines, locally applicable current and updated epidemiology of infectious diseases should be taken into account. Recent experience with emerging local or geographically restricted and pandemic infections highlights the changing nature of risk, and this risk is best addressed by ad hoc action plans on a national or international level (e.g., for Trypanosoma cruzi, chikungunya virus, West Nile virus, Zika virus, Yellow fever virus, Ebola virus, or the 2009 pandemic influenza H1N1 virus [17–21]).

Screening should be performed with the latest-generation assay available, according to the manufacturer's instructions and as licensed by the national health authorities. Each center should have a plan for how to handle reactive or unexpected results. For basic screening, serologic tests should detect IgG antibodies. Only in special cases is IgM detection necessary. The use of IgM for donor screening is not advocated on the basis of the little information gained and the high rate of false-positive results. Donor sera or plasma samples should be stored for at least 10 years by the organ procurement organization, according to the methods available and national recommendations.

Table 10.1 Basic screening for infections in organ donors

Before organ recovery or transplant (1–3 h)	As soon as possible (not necessarily before organ recovery and transplant)	Retrospectively after transplant, if indicated at the recipient transplant center
• Anti-HIV-1/2 (incl. HIV-1 p24-Ag) • HBsAg and anti-HBc • Anti-HCV	• Anti-CMV-IgG • Anti-EBV-VCA-IgG • Anti-Treponema pallidum ELISA (enzyme-linked immunosorbent assay or VDRL/RPR) • Anti-Toxoplasma-IgG	Additional tests can be performed according to the recipient profile for targeting specific prophylaxis

10.3 Unexpected Donor-Derived Infections

10.3.1 Viral Infections

Although a wide spectrum of viral infections have been transmitted through organ transplantation, only HIV, Human T-Lymphotropic Virus 1 (HTLV-1), Hepatitis E Virus (HEV), Arboviruses, Lymphocytic Choriomeningitis Virus (LCMV), Rabies, and Human Herpes Virus 8 (HHV-8) will be discussed in detail.

10.3.2 HIV

Until recently, anti-HIV-1/2 reactive status in potential donors has been regarded as absolutely contraindicated for organ donation in the United States and in all European countries. However, transmission of HIV through solid organ transplantation (SOT) has been reported sporadically. Most cases involved renal transplants prior to 1985 [22–29], before HIV antibody donor screening was implemented by the US Public Health Service. Three recent clusters of donor-derived infections due to HIV have been reported. HIV-infected donors have been inadvertently used after false-negative reporting or testing, resulting in unintended transmission into previously uninfected recipients [30–32]. Although most disease transmissions have involved deceased donors, recent transmission of HIV and HCV has shown that recipients of living donors may also be at risk [33]. Donor-derived HIV transmission has been associated with bad outcome in the US cluster; however, the three recipients of the Italian cluster are still alive with undetectable HIV-RNA, good CD4 count, and functioning grafts more than 10 years after organ transplantation. No data are available about the outcome of the five recipients from Taiwan.

Organs from donors with HIV infections have been utilized intentionally in a limited number of cases as part of an experimental protocol for HIV-infected recipients in South Africa, United States, Canada, Switzerland, United Kingdom, and Italy [34–39].

Allowing transplantation of organs from HIV+ donors might reduce the discard of organs due to false-positive results from viral antibody and nucleic acid testing. Although limited data quantify the number of lost organs due to unconfirmed testing for HIV [40], deceased HIV-infected patients in the United States represent a potential of approximately 500–600 donors per year that could be used for HIV-infected transplant candidates [41]. The HIV Organ Policy Equity (HOPE) Act [29] together with the current legislation in some European Countries allowing scientists to carry out research into organ donations from one person with HIV to another could lead to life-saving organ donations for people living with HIV while ensuring the safety of the organ transplant process and strengthening the national supply of organs for all who need them.

Very recently, for the first time, South African Surgeons reported a successful liver transplant from an HIV-positive individual, in this case the recipient's

mother, to an HIV-negative child [42]. This report raises the question of whether, under circumstances of well-controlled HIV replication in the living or deceased donor and well-defined prophylactic measures for the recipient, HIV transmission may be prevented. This type of transplant could potentially open up new therapeutic options for HIV-negative individuals urgently awaiting organ transplantation.

10.3.3 Arboviruses

A multitude of arthropod-borne viruses (Arboviruses) associated with human disease may circulate in tropical and subtropical regions [43]. Changes in climate or weather conditions may impact infectious diseases by affecting the pathogens, vectors, hosts, and their living environment. Studies have found that long-term climate warming tends to favor the geographic expansion of several infectious diseases and that extreme weather events may help create the opportunities for more clustered disease outbreaks or outbreaks at non-traditional places and times [44].

In addition to West Nile virus donor-derived transmission [45], Dengue virus, Zika virus (ZIKV), Chikungunya virus, and Yellow Fever virus have recently emerged as potential threat in solid organ transplant recipients and organ donors [46, 47]. Dengue virus has been shown to be transmitted from donor to recipient, but immunosuppression does not seem to have any major adverse effect on the evolution of dengue fever within the recipient [48, 49]. However, in the possible organ transmission, more severe cases have been reported [50, 51]. In endemic regions, it is important to suspect and screen for dengue in febrile and thrombocytopenic recipients in the postoperative period. The first case series of ZIKV infection in solid organ recipients, with a description of clinical and laboratory features and therapeutic management, has been recently published [52]. This report did not demonstrate more severe disease in transplant recipients. A case of transfusion-transmitted Zika virus infection in a liver transplant recipient has been published in 2016 with no indication of a more severe course of infection [53]. The risk of transmission by SOT is currently unknown, but theoretically possible.

Physicians should be aware that symptoms of fever, joint pain, and rash of undetermined origin in donors, and transplant candidates and recipients could be related to unusual arboviruses, particularly because recent epidemics have significantly expanded the regions of potential exposure risk. Arbovirus infections should be included in the differential diagnosis of infection in transplant patients so that appropriate testing and treatment can be offered. Based on current epidemiologic data, the recommendation is to rule out acute infection in donors living or coming from regions with ongoing outbreaks. Organs from these donors might be used before the results of the tests are available. However, in this case, it is recommended to perform monitoring of recipients of organs from donors with documented infection according to updated protocols in order to identify future risks due to this emerging pathogen.

10.3.4 Kaposi Sarcoma Herpesvirus (KSHV) or HHV-8

Kaposi sarcoma herpesvirus (KSHV) is a γ-herpesvirus that is homologous but different from the Gammaherpesvirinae Epstein–Barr virus and Herpesvirus saimiri. Several seroepidemiologic studies suggest that KSHV may be sexually transmitted. Unlike most herpes viruses, human infection with KSHV is not ubiquitous. Seroprevalence rates vary widely, depending on the geographic region. Besides having different prevalence rates in different geographic regions, the specific risk groups for seropositivity appear to be quite different, depending upon the location. Seroprevalence is estimated to be between 0% and 5% in North America, northern Europe, and Asia, between 5% and 20% in the Mediterranean and Middle East, and > 50% in some parts of Africa [53]. Epidemiologic and virologic data suggest that the virus may be transmitted through saliva, and salivary spread could explain both the sexual and horizontal transmissions of KSHV. Transmission of KSHV from organ donor to recipients has been documented through assessment of serostatus before and after transplantation and by molecular epidemiologic studies [54–60]. In SOT recipients, fever, splenomegaly, lymphoid hyperplasia, pancytopenia, and occasionally rapid onset Kaposi sarcoma (KS) have been described in association with apparent primary KSHV infection [57]. A very severe clinical picture associated with primary KSHV infection has recently been observed in a series of liver transplant recipients [58, 60]. This syndrome resembles the so-called KSHV associated inflammatory cytokine syndrome (KICS), which was recently described in patients positive for HIV [61] and more recently in a solid organ transplant recipient with donor-derived primary KSHV infection [62]. The clinical picture is characterized by unexplained fever, markers of severe systemic inflammation, and elevated HHV-8 viral load, similar to the KICS originally described in HIV-infected patients.

The optimal serologic assay technique cannot be determined at present. It has been suggested that a combination of whole-virion ELISA and lytic indirect immunofluorescent assay may be the most sensitive method for diagnosing KSHV. A recent prospective multicenter Italian study suggested that two lytic antigen-based indirect immunofluorescent assays are the best methodological approach to identify HHV8-infected SOT donors and recipients [63]. A commentary to the Italian study highlights the strengths and limitations of the currently available screening tools [64].

The question of screening donors and recipients for KSHV, even in low-KSHV infection prevalence countries, is still debated, and prospective studies are needed to evaluate the benefit of pre- and post-transplantation strategies. However, the potential risk of KSHV transmission with organ transplantation must be taken into account particularly if the donor originates from country with high prevalence.

10.3.5 HTLV

Retrovirus infection by Human T-Lymphotropic Virus-1 (HTLV-1), an RNA virus, results in insertion of the viral genome into T-lymphocytes. HTLV-1-associated

T-cell leukemia develops in 2–5 percent of the cases usually 20–30 years after infection. During a shorter timeframe, HTLV-1 may also cause spastic tropical paraparesis (also called HTLV-Associated Myelopathy or HAM) in 0.25–4 percent of cases. HTLV-2 has not been definitively associated with human disease. No proven treatment for HTLV exists, although the combination of zidovudine and raltegravir has in vitro activity against HTLV-1 and chemotherapy may treat associated leukemia [65].

Transmission of HTLV by blood or organs has been reported in a few cases globally. The natural history of HTLV-1 transmission from donor to recipient is unknown in this setting, because available screening platforms are suboptimal in low-prevalence areas and there is a lack of long-term follow-up. Minimizing organ wastage due to false-positive screening and avoiding donor-derived HTLV-associated diseases remain the goal. To date, only six HTLV-naive organ recipients from four donors (only one had confirmed HTLV) have developed HTLV-associated disease after transplantation. All of these cases were described in countries or from donors from HTLV-endemic regions. The first definitive case of solid organ donor-derived HTLV-1-associated disease emerged from Spain [66, 67]. All three recipients (two kidneys and one liver) were seronegative at transplantation, received cyclosporine, and developed HAM within 2 years of transplantation. The single donor who died of brain injury was previously infected by vertical transmission from his Venezuelan mother but was an asymptomatic unknown carrier at the time of donation. These three recipients are unique, in that they are the only reported cases of HAM after transplantation with homologous DNA sequencing to the infections origin to the donor's mother. Another cluster of donor-derived HTLV-1 transmission with organ transplantation has been reported from Germany [68, 69]. Proviral HTLV-1-DNA was detected in all blood samples of three organ recipients (one liver and two kidneys), but seroconversion was delayed for up to 2 years in screening assays and more than 6 years in the confirmatory assay. In two of three organ recipients, a cutaneous T-cell lymphoma was diagnosed 2 and 3 years after infection, respectively. There have been no reported cases of donor-derived HTLV-1-associated death after organ transplantation in the world. Based on data from low-prevalence countries (Europe and the United States) and the current shortage of donor organs, it appears plausible to authorize the decision to transplant an organ without the prior knowledge of the donor's HTLV-1 status. Unfortunately, current screening methods cannot differentiate between HTLV-1 and HTLV-2 infections. Furthermore, many screening methods have a high rate of false-positive results, and confirmatory tests are time-consuming [70]. HTLV screening can only be recommended for endemic areas and in endemic populations. Because of the limited follow-up on recipients of HTLV-infected organs, no conclusive recommendations are possible. In donor populations where HTLV is endemic, the risk assessment for donor-derived HTLV infection should balance the likelihood of true HTLV-1 infection, the low likelihood of subsequent disease in recipients of such organs, the general shortage of organs, and the specific needs and wishes of patients. An European Center for Diseases Control (ECDC) ad hoc expert panel recently suggested that if HTLV-1/2 screening is implemented in a member state or its regions for blood donations (e.g., due to

high prevalence of HTLV-1/2 infections, exceeding 1 percent in the general population or 0.01 percent in first-time blood donors), it should also be implemented for tissue and cell donations. However, any initial reactive test result must be confirmed as a true positive before further conclusions can be drawn [71].

10.3.6 HEV

HEV is a single-stranded RNA virus containing a 7.2-kilobase-long genome that belongs to the genus *Hepevirus* in the Hepeviridae family. Four major genotypes have been described. HEV genotypes 1 and 2 have been mainly found in humans in Asia (HEV1) and in Africa and Mexico (HEV2), and both cause epidemics in the developing world. HEV3 and HEV4 have been found in humans and various animal species. Cases of HEV3 have been mainly reported in western countries, whereas HEV4 is mainly found in China, Japan, and Taiwan [72, 73]. Acute HEV infection is a self-limiting symptomatic or asymptomatic disease. Sources of infection are unsanitary water and contaminated food; materno-fetal (vertical spread) and parenteral routes are less common modes of infection. However, as recently observed, HEV infection can manifest as chronic hepatitis in patients receiving SOT as well as in patients with HIV infection or severe hematologic disorders [74–76]. Chronic HEV infection can be defined as persisting HEV replication beyond 3 months after infection, at least in SOT recipients [77].

Currently, the relevance of HEV infection cannot be assessed due to the low endemic occurrence in European organ donor population. A rather low-level HEV carrier state may be partially attributable to the low sensitivity of the current anti-HEV assays. However, HEV transmission from a donor with occult HEV infection leading to chronic HEV infection in a liver transplant recipient has been recently reported [78].

Due to low prevalence and incidence, organ donors are not routinely screened. In cases of acute infection in the donor with viremia, organs should not be transplanted. However, after recovery from HEV infection, organs can be transplanted without restriction.

10.3.7 LCMV

Lymphocytic choriomeningitis virus (LCMV) is a rodent-borne, Old World arenavirus that has been reported to cause asymptomatic or mild, self-limited illness in otherwise healthy humans. It is a known cause of aseptic meningitis, but fatal infection is rare. Humans are primarily infected by inhaling infectious aerosolized particles of rodent secretions (saliva, urine, or droppings). In addition, contact with infectious rodent excreta, ingestion of contaminated food, rodent consumption, and rodent bite have all been known to cause infection in humans.

To date, five clusters of transmission of LCMV, including an LCMV-like arenavirus, via organ transplantation [79–83] have been described. Fourteen of the 17

recipients died of multisystem organ failure, with LCMV-associated hepatitis as a prominent feature. A common donor was recognized in each cluster. Diagnosis of LCMV should be strongly considered in organ transplant recipients presenting with aseptic meningitis and encephalitis, especially with unexplained fever, hepatitis, or multisystem organ failure. Supportive care with meticulous fluid balance and electrolyte management is the mainstay of therapy in arenavirus infection. One surviving transplant patient in the 2005 cluster of donor-transmitted cases was treated with ribavirin and reduction of immunosuppressive therapy. However, in the 2011 cluster, two of the four infected recipients survived without receiving treatment with ribavirin.

The Food and Drug Administration has not approved any diagnostic tests for LCMV infection. Furthermore, the sensitivity of currently available assays is not adequate for routine donor screening, as demonstrated by the negative results of tests on a wide array of clinical specimens from the donors involved in the clusters.

10.3.8 Rabies

Rabies is an acute encephalitis caused by viruses in the genus *Lyssavirus*, family Rhabdoviridae, that is nearly uniformly fatal in unvaccinated hosts. Although the virus is present in animal reservoirs, infection in humans is rare in the United States and Europe. The primary mode of transmission is through the bite of an infected animal, most commonly a dog or a bat in the United States. Despite raccoons being the most frequently reported rabid animal in the United States, only one human rabies case associated with the raccoon rabies virus variant has been reported [84].

Rabies virus transmission has occurred through tissue and SOT. In two clusters of rabies virus transmission through organ transplantation, which were attributed to a bat and a canine rabies virus variant, respectively, all recipients except 1 who was previously vaccinated had rabies symptom onset within 6 weeks of transplantation and died [85, 86]. These observations suggest a high infectivity rate and an incubation period of approximately 6 weeks in unvaccinated immunosuppressed recipients of solid organs from donors with rabies. In February 2013, a man who received a deceased donor kidney transplant in September 2011 died 22 days after admission. The deceased kidney recipient and donor were infected by the raccoon rabies virus variant [87]. The symptomatic recipient's incubation period is the longest documented in a transplant recipient who had not received prior rabies vaccination. The deceased kidney recipient had in fact an unexpectedly long incubation period, and the three other solid organ recipients were unvaccinated but remained asymptomatic for an 18-month period between transplantation and administration of post-exposure prophylaxis with vaccination. More recently, clusters of rabies transmission have been reported from China and Kuwait [88–91].

In summary, rabies in the setting of SOT can be transmitted variably and may have a long incubation period. Although recognition of rabies is challenging and solid organ transplant transmission of infectious encephalitis is rare, further education to increase awareness is needed.

10.3.9 Bornavirus

Germany very recently reported four human cases of acute encephalitis or encephalopathy caused by infection with Borna disease virus 1 (Borna Disease Virus 1, BoDV-1; species Mammalian 1 Bornavirus) [92]. This virus is clearly distinct from VSBV-1 (Variegated Squirrel Bornavirus 1; species Mammalian 2 Bornavirus). The first investigations started at the end of 2016, and an official notification of human cases was started in March 2018. Three of the cases belong to a cluster of solid organ recipients. The donor was from southern Germany, and his cause of death was unrelated to neurological disease. At present, BoDV-1 disease among humans seems to be a rare event. However, further investigations into the frequency of such events are needed. In the transplant recipients, immunosuppression therapy likely has enabled and/or enhanced infection. The routes of transmission pertaining to the organ donor and the additional case remain unknown at this time. This is the first time that a possible BoDV-1 transmission through organ transplantation has been reported [93].

10.4 Bacterial Infections

10.4.1 Multidrug-Resistant Organisms (MDRO)

Bacterial infections remain a significant challenge to SOT recipients. In the early post-transplantation period, SOT recipients are particularly vulnerable to severe bacterial infections due to the complexity of the SOT surgical procedure, use of immunosuppressive drugs, prolonged hospital and intensive care unit (ICU) stay following transplant, exacerbation of pre-existing conditions, and, less frequently, donor-transmitted pathogens [94]. Currently, an increasing number of patients admitted to ICU are exposed to infections with MDR organisms [95–98]. In addition to methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci, extended-spectrum beta-lactamase-producing enterobacteriaceae, carbapenem-resistant *Acinetobacter baumannii*, *Klebsiella pneumoniae,* and other carbapenem-resistant enterobacteriaceae and carbapenem-resistant *Pseudomonas aeruginosa* are increasingly detected in ICU patients. Carbapenem-resistant Gram-negative bacteria are of particular concern because of their difficulty to treat which, in turn, results in significant morbidity and mortality, particularly among solid organ transplant recipients [99–101]. No specific donor risk factor may predict the infection or colonization by MDR organisms. Anecdotal reports suggest that with a prolonged treatment after transplantation, recipients of organs from donors with MDR infection may have a favorable outcome [100]. In addition, the current availability of new drugs with activity against some MDR pathogens might allow in the future a more liberal use of organs from donors with carbapenem-resistant enterobacteriaceae or *P. aeruginosa* [101–107].

10.5 Parasitic Infections

10.5.1 Toxoplasma Gondii

Toxoplasmosis is a worldwide parasitic zoonosis transmitted to humans by ingestion of raw or undercooked meat containing *Toxoplasma gondii* cysts or by ingestion of oocysts from fecally contaminated foods. Seroprevalence of Toxoplasma varies geographically, with lower rates in the United States (3–35%) and higher rates reported in Western Europe, Africa, and South and Central America. The acute infection is followed by a latent chronic phase with persistence of the cysts in tissues, especially in the muscles, brain, eye, and, more rarely, other organs [108]. Toxoplasmosis prophylaxis is standard following heart and heart–lung transplantation, where an increased risk of allograft transmitted Toxoplasma is well recognized. In contrast, prophylaxis and routine serologic evaluation of donors and recipients for Toxoplasma in noncardiac SOT is not recommended [109]. In the absence of prophylaxis, the rate of transmission from a seropositive donor to a seronegative recipient (D+/R−) is maximal after cardiac transplantation but cases have been reported also after liver and kidney and small bowel transplantation. Transmission of toxoplasmosis via LT is extremely uncommon but in most cases results in a fatal outcome [110]. The rarity of the disease and the nonspecificity of the symptoms have led to a general lack of awareness among clinicians and, hence, a high mortality rate among transplanted patients due to the delayed initiation of therapy. Toxoplasmosis is transmitted via an infected allograft from an IgG seropositive donor to a seronegative recipient. The high mortality rate is generally due to a delay in diagnosis and initiation of therapy. The classical diagnosis of toxoplasmosis based on serological tests can be unreliable in transplant patients. Therefore, the diagnosis is usually based on the direct demonstration of the parasite in tissues or biological fluids. However, these techniques are time-consuming and lack sensitivity. The polymerase chain reaction (PCR) technique allows a simple, rapid, and highly sensitive detection of *T. gondii* DNA in various specimens and represents a valuable diagnostic tool for assessing disseminated toxoplasmosis [111]. In a multicenter case–control study from Spain, a negative serostatus prior to transplantation was the only independent risk factor for toxoplasmosis [112]. It has been in fact recently documented that the liver is a frequent site of cyst carriage, confirming that transplantation of an organ from a seropositive donor to seronegative recipient is at high risk for transmitting toxoplasmosis [113]. Seronegative solid organ transplant recipients receiving a graft from a seropositive donor are at high risk for developing toxoplasmosis and should be given prophylaxis with a single tablet of trimethoprim–sulfamethoxazole (double strength) daily and receive careful follow-up. In cases of intolerance to sulphonamides, a possible alternative is the use of 25 mg per day of pyrimethamine alone [109].

10.5.2 Strongyloides Stercoralis

Strongyloides stercoralis is a cosmopolitan parasite that is estimated to affect at least 370 million people worldwide. *S. stercoralis* is endemic throughout the tropics and subtropics and in limited areas in Europe and the United States [114]. It is a 2-mm-long intestinal roundworm. Infection is acquired by percutaneous penetration of intact skin of filariform larvae present in infected soil which are subsequently carried through the bloodstream to the lungs; then they move up the respiratory tree, over the epiglottis and down to the small intestine where female adult worms begin producing eggs.; these open in the mucosa and then are excreted with the feces. Most infected people are asymptomatic or have minor gastrointestinal or respiratory symptoms. Its medical importance lies primarily in its ability to produce overwhelming infection in immunocompromised people, a consequence of its unique ability to replicate and increase in numbers without leaving its host [115].

Immunocompromised patients are at risk of developing hyperinfection syndrome and disseminated strongyloidiasis that can be fatal due mostly to Gram-negative bacteremia and sepsis. Severe strongyloidiasis follows corticosteroid therapy but has also been described in patients with lymphoma, leukemia, human T-cell lymphotropic virus and HIV infection, malnutrition, chronic renal failure and end-stage renal disease, alcoholism, diabetes mellitus, advanced age, and solid organ transplant recipients.

In addition to reactivation in chronically infected recipients, solid organ transplant recipients may acquire this infection through transmission from an infected donor [116–121]. Previous screening recommendations have focused on preventing reactivation by testing for chronic infection in at-risk recipients by stool ova and parasite exams or IgG enzyme-linked immunosorbent assay (ELISA) antibody testing. Individuals at risk are identified by assessing potential exposure to the parasite in endemic areas based on country of origin and travel history [122].

More recently, screening for Strongyloides stercoralis has been recommended in all donors and recipients who have resided in or traveled to areas of endemicity [11, 13, 123]. However, very few organ procurement organizations (OPO) in the United States are currently screening donors. In a recent paper, only 6 out of 58 US OPO (10%) currently screen donors for strongyloidiasis. All used risk-based criteria to determine which donors to screen, though the criteria varied among OPOs [124].

The pathogenesis of Strongyloides dissemination in chronically infected deceased donors is not well defined. Chronic carriers are thought to harbor the parasite in the small intestine and may be at risk for dissemination and hyperinfection when exposed to glucocorticoids. Alternatively, a small number of Strongyloides larvae may be present in organs outside the gastrointestinal tract in the absence of reported symptoms. Further research is needed to better understand the biology of this parasite to allow for more accurate assessment of at-risk patients.

10.5.3 Trypanosoma Cruzi (Chagas Disease)

Chagas disease, caused by the protozoan parasite *Trypanosoma cruzi*, is endemic in many parts of Mexico, Central America, and South America. The most common mode of *T. cruzi* transmission is vector-borne, via the feces of infected triatomine bugs. *T. cruzi* parasites can also be transmitted by congenital and foodborne routes, transfusion and transplantation. Chronic infection persists for life in the absence of treatment, and reactivation in immunosuppressed patients may result in severe disease with increased risk of mortality [125]. Documented human cases of *T. cruzi* infection have been acquired by transplant transmission [126]. Chagas disease is an emerging infection in transplant recipients, particularly due to donor-derived transmission, as donor demographics increasingly include persons with origins in or travel to *T. cruzi*-endemic countries. Although uninfected recipients who receive an organ from a *T. cruzi*-infected donor may develop acute *T. cruzi* infection, transmission under these circumstances is not universal. Intensive monitoring and prompt *T. cruzi* therapy when transmission occurs may be a safe and effective management strategy for recipients of livers and kidneys from seropositive donors. In 2011, published recommendations from the Chagas in Transplant Working Group advised targeted screening of donors from Mexico, Central America, and South America and consideration of transplantation of liver and kidneys from infected donors with prospective monitoring for infection and prompt treatment [127]. Due to significant variability in sensitivity and specificity, appropriately validated tests must be used. Acute parasitemia may be detected by PCR and Strout test (microscopy of blood after blood concentration), but these are generally not sufficiently sensitive for screening of organ donors because of intermittent parasitemia. For screening purposes, serology with validated antibody assays must be used. Recent single-center studies from Spain and Argentina showed excellent results using livers from Chagas-infected donors with a scheduled monitoring and preemptive therapy in the recipients [128, 129]. The reported results are promising but need to be confirmed in larger series.

Prophylactic treatment (benznidazole) in D+/R− combinations is considered controversial but it has had some success [128]. All recipients of organs from Chagas disease-positive donors should be closely monitored for disease transmission by PCR or microscopy of blood [130, 131]. Treatment (benznidazole, nifurtimox) should be initiated promptly upon recognition of parasitemia. Some experts recommend avoiding certain immunosuppressive therapies (e.g., thymoglobulin or mycophenolate) in recipients of organs from Chagas disease-positive donors [132]. Cardiac or intestinal grafts should not be used from donors with a history of Trypanosoma cruzi infection, whereas other organs can be considered.

10.5.4 Malaria

Malaria poses an immense health problem in developing countries where it is the cause of more than 300 million acute cases and over one million deaths per year. It

is transmitted to humans mostly through the bite of the female Anopheles mosquito; blood transfusions and organ transplantation are responsible for some cases in endemic areas and occasionally in countries with large immigrant populations [133].

As the pool of foreign donors has increased with a corresponding increase in exotic infections, unusual infections such as malaria now represent a threat during the post-transplantation period. Malaria is not a common infection in transplant recipients. In fact, only a few cases have been reported after kidney, liver, heart, and bone marrow transplants. All species of Plasmodium causing human infection (P. falciparum, P. vivax, P. ovale, and P. malariae) can be transmitted by the graft [134–139]. Donors at risk of malaria infection include immigrants from, as well as travelers to, endemic areas [140]. Screening of donors who have recently spent time (preceding 3 years, as suggested by the Council of Europe guidelines) in malarious regions should be considered. Potential screening methods should include thick and thin smear stained with Giemsa, Wright, or Field stains. Rapid diagnostic tests detecting the histidine-rich protein 2 (HRP2) antigen or DNA amplification by PCR can also be considered when expert review of thick and thin smears is not possible. In some donors, symptoms may not be detectable. Parasitemic donors are usually rejected by transplant centers. Grafts can be used after successful treatment and recovery, but it must be remembered that some species (*P. vivax* and *P. ovale*) may survive in the liver. Therefore, differential diagnosis of any fever in the recipient within the first weeks after transplantation should consider reactivation of malaria in recipients of grafts from donors at risk of acquired malaria. Proper treatment of the recipient must be initiated immediately. Treatment recommendations are dependent on the plasmodium species and the geographic region where malaria was acquired. Consultation of a transplant and malaria/tropical medicine specialist is recommended.

10.6 The Donor with Possibly Increased Infectious Risk ("Increased Risk Donor")

One way to expand the donor pool is to use organs from donors with an increased risk of transmission of infection with HIV, HCV, and HBV to transplant recipients. The guidelines for excluding or including donors presenting certain risk behaviors for an increased risk of de novo infections vary between countries and regions. The evidence-based guidelines issued by the United States Public Health Service (PHS) and the American Centers for Disease Control and Prevention (CDC), as updated in 2013, are recommended for assessing individuals at increased or non-standard risk for HIV, HCV, or HBV infections [15]. In the European setting, some deviations from PHS guidelines should be considered, according to the recently published Council of Europe guidelines [14]. Studies aimed to evaluate the actual risk of transmission of blood-borne pathogens using increased risk donors have been recently published [141, 142]. In both studies, the use of organs from increased risk donors was associated with a safe increase in the transplant procedures. No transmission of HIV, HBV, and HCV has in fact been reported. Organ Procurement &

Transplantation Network policy in the United States and Europe requires post-transplant screening of recipients of organs from donors at increased risk for transmission of HIV, HBV, and HCV. However, available data suggest that follow-up testing of recipients is not routinely conducted [143].

10.7 Conclusions and Future Directions

Donor-derived infections continue to be a challenge for solid organ transplant recipients and their physicians. However, the currently available data are insufficient to determine the true incidence of the diseases in transplant recipients. The impact of immunosuppressive therapy on the presentation and outcome of many of these donor-transmitted infections needs to be better defined. The discovery of emerging viruses will probably continue. New agents are currently emerging or re-emerging and for many of these rarely known viruses, screening of donors and candidates to transplant is currently not recommended or unavailable.

This rapidly evolving field requires to improve at international level the surveillance and notification of emerging pathogens to tackle the real burden and impact of these agents in the transplantation scenarios. Given the shortage of organs for transplantation, innovative approaches must be consistently applied to improve the quantity, quality, and allocation of organs for transplantation, and the quality and survival of patients and grafts after transplantation.

Finally, the increased use of HCV- and HIV-infected donors will potentially open a new chapter of donor-derived infections. Awareness of the transplant physicians and surgeons will be key to prevent transmissions and for early diagnosis of donor-derived infections.

Key Points

- Unusual clinical syndromes or clusters of infections in organ recipients receiving organs from single donors should suggest donor-derived infection as a possible source.
- The incidence of unexpected transmission of infection by organ allografts is low but precise data are lacking.
- Donor screening for uncommon pathogens must be guided by knowledge of changes in the local epidemiology of infection.
- The emergence and re-emergence of mosquito-borne disease have attracted interest in recent years due to their increasing incidence and geographical expansion.
- The key element in the detection of donor-derived infection is suspicion by the clinicians caring for organ recipients.

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