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REVIEW

Selecting suitable solid organ transplant donors: Reducing the risk of donor-transmitted infections

Christopher S Kovacs Jr, Christine E Koval, David van Duin, Amanda Guedes de Morais, Blanca E Gonzalez, Robin K Avery, Steven D Mawhorter, Kyle D Brizendine, Eric D Cober, Cyndee Miranda, Rabin K Shrestha, Lucileia Teixeira, Sherif B Mossad

Christopher S Kovacs Jr, Christine E Koval, Steven D Mawhorter, Kyle D Brizendine, Eric D Cober, Cyndee Miranda, Rabin K Shrestha, Lucileia Teixeira, Sherif B Mossad, Department of Infectious Diseases, Medicine Institute, Cleveland Clinic, Cleveland, OH 44195, United States
David van Duin, Division of Infectious Diseases, Immunocompromised Host Infectious Disease Program, University of North Carolina, Chapel Hill, NC 27599, United States
Amanda Guedes de Morais, Infectious Disease and Internal Medicine, Augusta Health, Fishersville, VA 22939, United States
Blanca E Gonzalez, Department of Pediatric Infectious Diseases, Cleveland Clinic Children's, Cleveland, OH 44195, United States
Robin K Avery, Division of Infectious Disease (Transplant/Oncology), Johns Hopkins, Baltimore, MD 21205, United States
Author contributions: Avery RK created the idea of an institutional approach for donor suitability; Koval CE, van Duin D, Mawhorter SD, Brizendine KD, Guedes de Morais A, Gonzalez BE, Cober ED, Miranda C, Shrestha RK, Teixeira L and Mossad S wrote material from which sections were synthesized and reviewed and approved the final draft; Kovacs Jr CS and Mossad SB coordinated and synthesized data, wrote, and compiled the final submitted draft.
Correspondence to: Sherif B Mossad, MD, Department of Infectious Diseases, Medicine Institute, Cleveland Clinic, 9500 Euclid Ave, Mailstop G-21, room 131, Cleveland, OH 44195, United States. mossads@ccf.org
Telephone: +1-216-4452572 Fax: +1-216-4459446
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Abstract

Selection of the appropriate donor is essential to a successful allograft recipient outcome for solid organ transplantation. Multiple infectious diseases have been transmitted from the donor to the recipient *via* transplantation. Donor-transmitted infections cause increased morbidity and mortality to the recipient. In recent years, a series of high-profile transmissions of infections have occurred in organ recipients prompting increased attention on the process of improving the selection of an appropriate donor that balances the shortage of needed allografts with an approach that mitigates the risk of donor-transmitted infection to the recipient. Important advances focused on improving donor screening diagnostics, using previously excluded high-risk donors, and individualizing the selection of allografts to recipients based on their prior infection history are serving to increase the donor pool and improve outcomes after transplant. This article serves to review the relevant literature surrounding this topic and to provide a suggested approach to the selection of an appropriate solid organ transplant donor.

Key words: Donor selection; Infection; Transplantation; Mass screening; Treatment outcome

Core tip: The literature surrounding preventing donor-transmitted infections in solid organ transplant recipients has increased greatly in the last decade. Increased emphasis has been placed on improved diagnostics for screening of deceased donors. Importance has been placed on using donors who were previously thought to be high risk for transmitting infections to recipients and mitigating the risk to such recipients in an effort to increase the donor pool. Initiating the discussion around using human immunodeficiency virus (HIV) infected donors for HIV infected recipients has important implications for addressing the problem of allograft shortages.

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INTRODUCTION

Selection of the appropriate donor is the cornerstone of achieving a positive outcome after solid organ transplantation (SOT). This selection requires screening potential donors for infectious diseases that can be transmitted to the allograft recipient[1]. Screening for transmissible infections allows timely disqualification of a donor if the risk of developing illness in the recipient is deemed prohibitive. Screening also allows risk reduction by identifying and actively treating infection in the donor prior to procurement or preemptively treating the recipient following transplantation. Selecting the suitable donor is of paramount importance to reducing the risk of infectious morbidity and mortality from donor-transmitted infections (DTI).

It has become necessary to consider donors who may have active infection, high-risk infectious serologic profile, or high-risk behavior for human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) infection at the time of donation due to an inadequate supply of needed allografts[2]. As more patients rely on organ transplantation to manage end-stage disease processes, the available donor pool will only shrink further. Important, evidence-based, decisions regarding risk stratification and risk *vs* benefit analyses are needed in order to increase the donor pool. The risk of death while on the waiting list for many organs needs to be cautiously weighed with the risk for mortality after transplant when considering using expanded donor criteria in order to first do no harm to the recipient (Table 1)[3-8].

A number of incidents of DTI have brought this topic to the forefront of attention, as renewed evaluations of the donor screening process have been undertaken. Recent cases of rabies, lymphocytic choriomeningitis virus (LCM), West Nile virus (WNV), HIV, and HCV have all been confirmed as donor transmitted[9-13]. In 2005, the Disease Transmission Advisory Committee (DTAC) was created to aid the Organ Procurement and Transplantation Network/United Network for Organ Sharing in identifying and reviewing potential DTI. This committee has served an essential role in systematizing the collection and evaluation of nationwide information about suspected DTI. This includes: a thorough review of each case by an expert appointed by the committee, facilitation of communication between centers, and tabulating information to a growing database that provides critical information about donor derived risks[14-16]. Extensive deceased donor testing is often not feasible given the time constraints in which such screening must be carried out. Concerns exist regarding sensitivity of tests used for pathogens such as HIV and HCV, which may be negative prior to antibody production[17]. Infections that are reliant on microbiologic methods to diagnose, such as donor blood and urine cultures, may not be resulted until after transplant has taken place. New technologies and donor screening strategies using nucleic acid amplification testing (NAAT) may help provide important information earlier, but developing approaches on how best to utilize these tests has been controversial[1,18,19].

Multiple pathogens have been shown to have the potential to be transmitted by SOT[20,21]. DTIs are estimated to occur in 0.2%-1.7% of all transplant procedures, with varying morbidity and mortality[22,23]. Bacterial, mycobacterial, viral, fungal, and parasitic pathogens all need to be contemplated by the transplant physician when called for opinion regarding donor suitability. This article serves to summarize the current literature about commonly encountered DTI and to offer an approach for decisions regarding donor suitability (Table 2).

BACTERIAL INFECTIONS

Transplantation of allografts taken from donors with underlying sepsis syndrome of unknown etiology is not recommended. Bacterial DTIs have been linked to increased morbidity and mortality as well as allograft loss[24-26]. As previously mentioned, however, underlying bacteremia in the donor may not be recognized until after transplantation has occurred. In one study, 60% of bacteremic donors were afebrile during the 24-h period prior to organ procurement[27]. The outcome of allograft donation from a bacteremic donor depends on the type of bacteria causing infection, previous antimicrobial therapy in the donor prior to organ procurement, and timely recognition of donor bacteremia so therapy can be instituted in the recipient[28,29].

An estimated 5% of organ donors have unrecognized bacteremia at the time of donation[27,30]. Some studies have shown that use of organs from bacteremic donors, especially when the organism is community acquired and not highly resistant to antimicrobials, is not associated with higher incidence of allograft dysfunction[27,30,31]. Thirty-day graft and patient survival for recipients of organs from bacteremic donors were not significantly different than those who received organs from non-bacteremic donors[30]. Recipients included in these series had been given broad-spectrum antibiotics during the perioperative period and were given tailored antibiotic therapy once donor bacteremia was identified. This suggests that allografts from bacteremic donors are suitable for transplantation if the donor is on appropriate antibiotic therapy for $\geqslant$ 24 h and if tailored antibiotic therapy can be initiated in the recipient in a timely manner. Recipients should be treated for a minimum of 7 d, depending on the posttransplant course and perhaps longer if the pathogen has the potential to disrupt an anastomosis or seed an endovascular source. In the event a donor is being treated for endocarditis, the recipient should receive organism-specific antimicrobial therapy for at least 2 wk, and if the organism is *Staphylococcus aureus*, 6 wk of therapy is appropriate[32]. If donor cultures are repeatedly positive for pathogenic bacteria or yeast, then additional consent from the recipient and/or family should

Table 1 Mortality figures by type of transplant for 2010 according to the Scientific Registry of Transplant Recipients 2011 Annual Report[1]

Organ tansplanted[2]	Waiting list mortality incidence density[3] (deaths per 1000 patient-years)	1 yr posttransplant mortality incidence density (deaths per 1000 patient-years)
Kidney	56.5	34.9
Liver	115.6	123.7
Intestine	71.6	193.5
Heart	115.8	91.8
Lung	154.1	164.2

[1]The data and analyses reported in the 2011 Annual Data Report of the United States Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients have been supplied by UNOS and the Minneapolis Medical Research Foundation under contract with HHS/HRSA. The authors alone are responsible for reporting and interpreting these data; the views expressed herein are those of the authors and not necessarily those of the United States Government; [2]Data reported in table is for deceased donor only; [3]Incidence is reported as deaths per 1000 patient years at risk.

be obtained. Surveillance blood cultures of the recipient after transplant are prudent in this situation. Most studies evaluating donor bacteremia excluded donors with sepsis. This may have biased the data by selectively removing pathogens more likely to contribute significantly to post-transplant morbidity and mortality.

An emerging concern is the transmission of multi-drug resistant (MDR) bacteria. Management strategies for dealing with these donor-transmitted resistant infections, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococcus (VRE) species, and MDR gram-negative bacteria are not well established[33]. Resistant gram-positive bacteria are frequently encountered in the donor prior to organ procurement. Although less virulent gram-positive bacteria, such as coagulase-negative staphylococci are seemingly less likely to be transmitted from bacteremic donors and are less associated with poorer outcome after transplant, other more virulent gram-positive organisms such as VRE and MRSA do remain a source of concern regarding donor suitability[28]. MRSA colonization of an individual has been shown to increase their risk for infection[34]. Risk factors for MRSA infection and colonization include prolonged hospitalization, exposure to broad-spectrum antibiotics, intensive care unit (ICU) admission, and the presence of a central venous catheter, all of which are often present in deceased organ donors[35]. MRSA colonization in a donor should not prevent acceptance of the allograft; however, perioperative antibiotics should be adjusted to account for the potential increase in recipient infection risk. Mortality from deep-seated MRSA infection associated with bacteremia after transplant has been in excess of 80%[29]. Allografts from donors with deep-seated MRSA infections should only be accepted if the donor has been on appropriate antibiotic therapy for $\geqslant$ 48 h. If the potential allograft is the site of infection, the organ should be rejected. Vancomycin-intermediate *Staphylococcus aureus* and vancomycin-resistant *Staphylococcus aureus* infections in the transplant population have not yet been reported[36]. Donor infection with these isolates should exclude them from donation. VRE is another common pathogen, specifically in the setting of transplantation of an intra-abdominal organ. Risk factors for VRE are similar to MRSA, and general guidelines for donor suitability pertaining to MRSA should be applied to reduce recipient risk for VRE infection[37].

Table 2 Approach to selecting suitable donors for solid organ transplantation

Infections	Diagnostic tools	Treatment considerations
Bacteremia	Blood cultures Antibiogram	Treat donor 24 h Tailored recipient therapy in posttransplant period
Resistant bacteria	Blood cultures Sterile site cultures Antibiogram	Tailored donor and recipient therapy
Meningoencephalitis	CSF analysis CSF culture and stain Cryptococcus antigen NAAT	Tailored therapy if meningitis only
Syphilis	Treponemal testing Nontreponemal testing	Treat recipients as late latent syphilis
Viral hepatitis	Serologic evaluation NAAT	Prophylaxis Tailored therapy HBIG Antivirals
Influenza	Influenza testing Respiratory virus PCR	Neuraminidase inhibitor
HTLV 1/2	Routine screening not recommended	No effective treatment, surveillance for recipients of positive donors
Candida infection	Blood cultures Sterile site cultures Antibiogram	Antifungal treatment of donor Treat colonization in certain settings
Cryptococcosis	CSF cryptococcal antigen Serum cryptococcal antigen	Antifungal treatment of donors prior to donation
Endemic fungi	Urine antigen testing Serologic evaluation Sterile site culture Histologic evaluation	Antifungal treatment of donors prior to donation
Schistosomiasis	Stool examination Serologic evaluation Rectal biopsy	Treat living donor successfully prior to donation
Strongyloidiasis	Serologic evaluation Stool examination	Treat recipients from positive donors
Chagas disease	Enzyme immunoassay Radioimmune precipitation assay	Treat recipient for positive surveillance testing

HTLV: Human T-lymphotropic virus; NAAT: Nucleic acid amplification testing; PCR: Polymerase chain reaction; HBIG: Hepatitis B immunoglobulin.

Impact of infection with MDR gram-negative bacteria in transplant recipients is of special concern. Literature suggests that survival in transplant recipients with such infections is decreased[38]. These infections are problematic given limited antimicrobial options, need for potentially more toxic antimicrobials, more potential drug interactions, and fewer drugs in the developmental pipeline[33].

Transplant patients are especially vulnerable to infections with these organisms given end-stage disease processes, extensive healthcare contact before and after transplant, and the need for immunosuppression after transplant to maintain graft function. The most common MDR gram-negative infections encountered in the transplant population are carbapenem-resistant *Enterobacteriaceae* (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and *Pseudomonas* species resistant to at least two different classes of antimicrobials (MDR). Donors with long-term stay in ICU, vasopressor requirement, and prolonged hospitalization are at increased risk for colonization and infection with MDR organisms that can be transmitted to the recipient, even in the absence of overt signs of infection in the donor[39-43]. Studies have shown that using an allograft from a donor with a deep-seated infection from MDR organisms can result in transmission to the recipient even when pathogen directed therapy is used in the recipient[39]. Horizontal transmission within a transplant unit can occur with devastating results. High rates of 30-d mortality have been reported when transplant recipients develop infection with carbapenem-resistant *Klebsiella pneumoniae,* with infection being a predictor of time-to-death[44,45]. The critical information involves whether the infection is sensitive to a carbapenem. If a donor is colonized with a MDR gram-negative organism that remains sensitive to a carbapenem, he may remain a candidate for donation. A donor with a deep-seated infection involving an organ not being transplanted can be considered only if treated with appropriate antibiotics for $\geqslant$ 48 h. Additional consent should be obtained from the recipient and/or family and a plan made to treat the recipient for $\geqslant$ 2 wk depending on the clinical course. As a general rule, donor bacteremia with CRE, CRAB, or MDR *Pseudomonas* infection should eliminate that donor from consideration. Infections stemming from MDR gram-negative organisms no longer susceptible to carbapenems should preclude donation. If a clear case of asymptomatic colonization with a MDR organism is identified in the donor, the allograft may be acceptable, unless noted in the urine or rectal swab of a planned kidney transplant or small bowel transplant, respectively. DTI with these organisms remains an area for study and optimal management strategies for MDR organisms are still to be defined.

Bacterial meningitis and syphilis may be present in a potential organ donor and, as such, may be transmitted to the allograft recipient. The disparity between available allografts and those awaiting transplantation has grown, such that, these two conditions are no longer deemed absolute contraindications for organ donation. Multiple cases of donor-transmitted syphilis have been reported[46-48]. The estimated prevalence of syphilis among potential organ donors based on the incidence in the general population is 0.15%[49]. Transmission of syphilis is a rare event, but if a donor tests positive for this organism additional consent from the recipient and/or family should be obtained. Most experts agree that if the organ is accepted the recipient should be treated with a regimen for late latent syphilis consisting of benzathine penicillin 2.4 million units intramuscularly every week for a total of 3 wk[1]. Syphilis IgG of the recipient should be assessed at time of transplant and at 1, 3, 6, and 12 mo. Patients with documented bacterial meningitis are also no longer considered to be excluded from organ donation, provided that pathogen-directed treatment has been initiated. Several instances of successful allograft procurement have been reported in the literature from donors with microbiologically proven bacterial meningitis[50-54]. Guidelines now recommend accepting an organ if the etiology of the meningitis is *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Escherichia coli*, or group B streptococcus. Meningitis must be confirmed as the sole site of infection in the donor and acceptance of donor allografts infected with highly virulent organisms such as *Listeria* species should be rejected. Ideally, the donor should be receiving appropriate therapy for 48 h prior to procurement with signs of clinical improvement. Additional consent from the recipient and/or family should be obtained and pathogen-directed therapy of the recipient should be continued for at least 2 wk[1].

Cultures of organ procurement fluid (OPF) have been studied as a potential source of DTI. OPF cultures are commonly positive for the growth of bacteria, with low-virulence bacteria such as coagulase-negative staphylococcus and *Corynebacterium*[55-60]. Studies are variable on whether positive OPF cultures portend an increased risk for posttransplant infection. Cultures of the OPF are rarely available to make donor suitability decisions, but should not prevent organ donation. The exception to this is OPF cultures growing *Candida*, which may be an important risk factor for graft-transmitted candidiasis[61-64]. The optimal strategy for managing recipients of allografts with positive OPF cultures is not known, but brief tailored treatment of the recipient for growth of virulent organisms is likely indicated[60].

TUBERCULOSIS

Almost 10000 cases of *Mycobacterium tuberculosis* (TB) infection were reported in the Unites States in 2012. The majority of these cases were in patients who were not born in the United States, but have emigrated from highly endemic areas, highlighting the need for close attention to donor demographics and travel history. It is estimated that rates of tuberculosis in patients from highly endemic areas are 20-74 times the general population with the prevalence of posttransplant tuberculosis approaching 12%[65,66]. Management of tuberculosis in transplant recipients is challenging on many fronts. Diagnosis can be difficult because disease presentation can be atypical, despite ongoing active disease, sputum smears can be negative with low mycobacterial burden, and tuberculin skin testing (TST) and interferon gamma release assays (IGRA) may be falsely negative in the setting of immunosuppression end-stage disease processes[65,67-69]. Treatment is also difficult with concerns for drug toxicity, interactions with immunosuppressive medications, and potential develop-

Table 3 Suggested approach to donor-transmitted *Mycobacterium tuberculosis*

[1]TB Risk	[2]Suggestive radiology	[3]Donor testing	[4]Donor treated	Accept allograft	Additional consent	[5]Recipient treatment	Additional recipient testing
Deceased donors							
Low	No	Negative	N/A	Yes	None	None	None
Low	Yes	Negative	No/Yes	Yes	Yes	Chemoprophylaxis	None
Low	Yes	Pending	No/Yes	No	N/A	N/A	N/A
Elevated	No	Negative	No/Yes	Yes	Yes	Chemoprophylaxis	None
Elevated	Yes	Negative	No/Yes	Yes	Yes	Chemoprophylaxis	None
Elevated	Yes	Pending	No/Yes	No	N/A	N/A	N/A
Elevated	Yes	Positive	No/Yes	No	N/A	N/A	N/A
Prior active TB	Yes	Negative	Yes	Yes	Yes	Chemoprophylaxis	None
Prior active TB	Yes	Pending	Yes	Yes	Yes	Chemoprophylaxis	None
Prior active TB	Yes	Positive	No/Yes	No	N/A	N/A	N/A
Prior active TB	Yes	Positive	No	No	N/A	N/A	N/A
Active TB	Yes	Positive	No/Yes	No	N/A	N/A	N/A
Living donors							
Low	No	Negative	N/A	Yes	No	None	None
LTBI	No	Positive	Yes	No	Yes	None	None
Active TB	No	Positive	No	No	N/A	N/A	N/A
Elevated	Yes	Negative	No/Yes	Yes	Yes	Chemoprophylaxis	None

[1]Based on history and physical examination; [2]Apical fibrosis and/or pleural thickening on chest radiograph or computerized tomography scan; [3]Sputum acid fast bacilli (AFB) smear and culture; molecular testing on smear-positive sputum; [4]Must be documented treatment with appropriate anti-TB therapy; [5]Refers to accepted regimen for treatment of latent tuberculosis infection (LTBI). TB: Tuberculosis; N/A: Not applicable.

ment of drug-resistant tuberculosis. *Mycobacterium tuberculosis* infection after transplant is associated with 20%-30% mortality rate[67,70].

Most cases of posttransplant tuberculosis are caused by reactivation of latent infection in the recipient following immunosuppressive therapy[71]. *Mycobacterium tuberculosis* can also be transmitted directly from the allograft to organ recipient[15,72,73]. This fact highlights the necessity of a thoughtful approach to the potential organ donor to limit the risk of a potentially catastrophic posttransplant infectious complication. Table 3 highlights one approach to evaluating the risk of donor-transmitted tuberculosis. There is no firm evidence from randomized clinical trials to make strong recommendations, and each center should factor in the incidence and prevalence of latent TB infection (LTBI) and active TB within their population. Assessment of the donor begins with identifying country of birth, a thorough historical evaluation with emphasis on epidemiological and associated disease-related TB risk factors, prior positive TST/IGRA, review of prior radiographic imaging, and in the case of prior active disease, documentation of completed appropriate anti-tuberculosis treatment. Risk factors for TB in the donor include substance abuse, malnutrition, HIV infection, and close household contact with TB smear-positive individuals[74-77]. Special attention should be paid to donors who have resided in homeless shelters, prisons, or highly endemic areas outside of the United States[78-81]. In donors with low TB risk accompanied by negative radiology, the allograft can be accepted without the need for chemoprophylaxis or additional informed consent on the part of the recipient. Donors, who have had active TB, particularly in the preceding 2 years, have higher relapse potential and increased risk of harboring drug-resistant TB isolates, which, may lead to increased risk of donor-transmitted TB. This should be considered when monitoring and treating recipients of allografts from such donors[69,82].

VIRAL INFECTIONS

Viral infections are a common cause of morbidity and mortality after SOT. Infections that are potentially donor derived include HIV, HCV, HBV, human T-lymphotropic virus (HTLV- 1 and 2), etiologic agents of viral encephalitis, such WNV, LCM and rabies virus, and viral respiratory pathogens. Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) are commonly donor-transmitted but mainly affect outcomes after the initiation of posttransplant immunosuppression and thus are not addressed in this review. Criteria have been established by the CDC which, when present, may increase the risk of donor transmission of HIV, HBV, and HCV (Table 4)[28]. In the past, many centers have often rejected allografts from such high risk donors. However, availability of improved NAAT testing and closer surveillance monitoring of transplant recipients from CDC-defined high risk donors have allowed these transplants to be undertaken. Aiming to match the allograft to the most appropriate recipient to mitigate the overall risk by improved selection and monitoring has been an overall successful strategy. In such scenarios, additional consent and recipient screening at regular intervals during the first year after transplant should be performed[83].

Viral hepatitis is commonly encountered in both donors and recipients of SOT. HBV infects approximately 400 million people worldwide, with prevalence varying by geographic region[84,85]. As mentioned previously, the ever-enlarging pool of patients awaiting lifesaving transplants has necessitated relaxation of exclusion criteria used to

Table 4 Factors associated with increased risk for human immunodeficiency virus, hepatitis B virus, hepatitis C virus infection and potential donor transmission

People who have had sex with person known or suspected to have HIV, HBV, or HCV in the preceding 12 mo
MSM in the preceding 12 mo
Women who have had sex with a man with a history of MSM in the preceding 12 mo
People who have had sex in exchange for money or drugs in the preceding 12 mo
People who have had sex with a person who has had sex in exchange for money or drugs in the preceding 12 mo
People who have had sex with a person who has injected drugs for nonmedical reasons in the preceding 12 mo
A child who is ≤ 18 mo of age and born to a mother known to be infected with, or at risk for HIV, HBV or HCV infection
A child who has been breastfed within the preceding 12 mo and the mother is known to be infected with, or at risk for HIV, HBV or HCV infection
People who have injected drugs for nonmedical reasons in the preceding 12 mo
People who have been in lockup, jail, prison or a juvenile correctional facility for ≥ 72 consecutive hours in the preceding 12 h
People who have been newly diagnosed with, or have been treated for, syphilis, gonorrhea, *Chlamydia* or genital ulcers in the preceding 12 mo
People who have been on hemodialysis in the preceding 12 mo (HCV only)

HIV: Human immunodeficiency virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; MSM: Men who have sex with men.

select suitable organ donors. This has led to the usage of allografts taken from donors who have previously had HBV infection (anti-HB core antibody positive donors). The development of de novo hepatitis B infection in recipients of allografts from anti-HBc positive donors has been noted since 1992, but after initially excluding these donors, it has been found that allografts from these donors can be safely used[86-89]. Careful selection of the donor is essential when considering recipients coinfected with HBV and HDV as recurrence of disease is common in this setting and specific posttransplant treatments may need to be implemented to optimize outcomes[90]. HCV is a cause of chronic hepatitis in 3-4 million people in the United States and is the leading indication for liver transplantation[91]. As both HBV and HCV can be transmitted *via* organ donation, a thorough approach is needed for successful management of the recipient, and an emphasis on aggressive immunization and risk mitigation of transplant candidates prior to transplant should be pursued.

Decisions regarding donor suitability depend on whether living-related partial liver donation is planned and disease status of the donor and recipient at the time of allograft procurement. More stringent, evidence-based guidelines regarding the use of anti-HBc antibody donors are forthcoming, but currently it is felt that allografts from HBV infected donors should preferentially be given to recipients who are hepatitis B surface antigen positive, core antibody positive, or surface antibody positive[92]. In both hepatic and non-hepatic donors, an allograft from a donor with acute hepatitis B infection should not be accepted, regardless of the serologic status of the recipient. Hepatitis B surface antigen positive donors can donate to HB surface antigen positive recipients, but hepatitis B immunoglobulin (HBIG) and antiviral therapy should be given with advanced planning. Donors who are anti-HBc antibody positive and HBsAg negative are acceptable, but additional consent should be obtained from the recipient prior to transplant[65,93-95]. Antiviral treatment should be given at the time of transplant to recipients of liver allografts from donors with prior evidence of HBV infection. HBIG should be administered to liver allograft recipients who lack surface antibody to HBV[96-102]. Non-immune non-hepatic allograft recipients should also receive antiviral prophylaxis if the donor is anti-HBc positive and HBV DNA is detected. HCV infected donors should be precluded from donating an allograft to a HCV naïve recipient[103]. HCV infected hepatic and non-hepatic allografts can be donated to HCV infected recipients with the caveat that donors with HCV genotype 1 infection should preferentially be used for recipients with HCV genotype 1 infection if that donor information is known prior to donation[92,104-108].

Influenza and other respiratory viruses are another potential cause of DTI. Influenza, respiratory syncytial virus (RSV), parainfluenza virus, human metapneumovirus (hMPV), adenovirus, and coronavirus are usually self-limited illnesses in healthy adults but have the potential for significant morbidity and mortality in the SOT population. These viruses cause a wide range of disease, and transplant recipients often have atypical presentations and more severe symptoms[109]. The burden of illness of these viruses follows a seasonal pattern, mainly occurring during the fall and winter months[110]. DTI with these respiratory viruses can increase the risk of secondary bacterial or fungal pneumonia in the recipient, lead to a prolonged period of viral shedding, and potentially contribute to increased risk of allograft rejection in lung transplant recipients[109,111-114]. DTI of respiratory viruses is further complicated by limited treatment options. Influenza and adenovirus have both been reported as DTI with devastating consequences[115-117]. As such, high index of suspicion is needed when evaluating a donor, especially during the peak seasons of respiratory viral infections within the community. During peak seasonal epidemic activity or in the setting of an ongoing pandemic, donors and recipients should be screened for clinical symptoms of an influenza-like illness. Lung and intestinal potential donors who have been diagnosed with influenza within the previous two weeks should be disqualified from donation. Other types of allografts can be accepted if additional consent is obtained, the donor has received anti- influenza treatment, and the recipient is given neuraminidase inhibitor chemoprophylaxis after transplant. Donors of any allograft with influenza diagnosed greater

than 2 wk prior to donation, who are adequately treated and no longer symptomatic can be utilized. Oseltamivir resistant influenza diagnosed in any donor should preclude his/her use as a donor[118]. Lung allografts from donors infected with other respiratory viruses should be rejected with the exception of resolved RSV infection with no residual symptoms. Non-lung allografts infected with respiratory viruses other than influenza can be accepted. If lower respiratory tract sampling shows viral respiratory infection other than influenza or radiograph show an infiltrate and that lung allograft is accepted for use in a dire situation, oral ribavirin can be considered as chemoprophylaxis for the recipient[109]. All allografts from donors with adenovirus infection should be rejected as adenovirus infections in the recipient tend to recur in the transplanted organ[117,119].

Additional viral infections that are potentially donor transmitted include HTLV-1/2 and the etiologic agents of viral encephalitis. Although no longer required as a screening test in deceased donors, concerns remain regarding donor-transmission of HTLV-1/2[120,121]. Rapid progression from infection to disease has been noted in transplant recipients, with the development of myelopathic spastic paraparesis and adult T-cell leukemia/lymphoma[122]. Donors who test positive for these viruses should be precluded from allograft donation unless required for an emergent life-threatening situation. If allograft is accepted, additional consent should be obtained, and the recipient should have virus-specific serology and polymerase chain reaction (PCR) testing at the time of transplant and 1, 3, and 12 mo[123]. Allografts from patients with suspected viral encephalitis should not be accepted given the risk of transmission of WNV, rabies, LCM and herpes simplex virus infections[124-126]. This recommendation may also extend to cerebrospinal fluid pleocytosis where bacterial meningitis has not been proven by either culture or antigen testing indicating a specific bacterial pathogen as the cause of infection.

FUNGAL INFECTIONS

Fungal infections often affect the critically ill potential organ donor and, as such, have the potential to be donor-transmitted. Recipient DTIs with *Candida* species, cryptococcosis, endemic fungal infections, aspergillosis, and non-*Aspergillus* mold infections have all been documented and, when they occur, are important causes of recipient morbidity and mortality[127].

Outcomes of fungal DTI depend on the type of fungal infection identified, the specific allograft donated, and antifungal susceptibilities of recovered isolates. Infections associated with *Candida* species may occur in the setting of positive preservation fluid cultures, possibly due to contamination at the time of organ procurement[61,63,128]. Bowel perforation in the donor is another common source of *Candida* contamination of the allograft[61]. In general, patients with untreated invasive fungal infections should not be used as organ donors. *Aspergillus* and other invasive mold infections result in significant morbidity and mortality from graft site abscesses and anastomotic infections, despite treatment of both donor and recipient[127]. Renal allografts from donors with candiduria and lung allografts from donors with bronchial cultures positive for *Candida* species can be used with appropriate treatment. Recipients of lung allograft from a donor with documented *Candida* colonization of the airways have been shown to benefit from universal prophylaxis with an echinocandin for the prevention of early posttransplant infections; including empyema[127,129]. Treatment of renal allograft recipients from donors with candiduria should consist of a tailored antifungal agent for urinary tract involvement. Urinary levels of fluconazole exceed minimum inhibitory concentration values for most *Candida* species and can be used in most cases. Therapy should be continued for up to 6 wk depending on whether there is vascular involvement of the urinary tract[62,127,130]. After lung transplant, treatment should be continued until bronchoscopic evaluation confirms the integrity of the bronchial anastomosis[127].

Cryptococcosis can occur in up to 5% of SOT recipients[131]. Most infections after transplant represent reactivation of recipient latent infection, but DTIs do occur in a subset of patients[132,133]. The potential for cryptococcal DTI should be considered when a donor presents with undiagnosed neurological illness, unrecognized meningoencephalitis, or pulmonary nodules in the setting of risk factors for cryptococcosis, such as prior hematologic malignancy, steroid treatment, sarcoidosis, or other cell-mediated immune dysfunction[134]. Cerebrospinal fluid cryptococcal antigen and serum cryptococcal antigen should be obtained from donors who meet these clinical risk factors. Donors with active cryptococcal disease should be excluded from donation. Recovery of *Cryptococcus* in the recipient should not be treated as contamination or colonization, but should prompt initiation of therapeutic antifungal treatment[135].

Endemic fungal infection should be considered as a potential DTI when donors reside in endemic areas or travel frequently to areas with high incidence of histoplasmosis, blastomycosis, or coccidioidomycosis. These areas include the Ohio and Mississippi river valleys, the Great Lakes region, and Southwestern United States, respectively. Since histoplasmosis occurs in only 0.5% of SOT recipients residing in endemic regions, routine laboratory screening of all donors is not warranted[136]. Donors should be evaluated for a prior history or signs and symptoms compatible with active histoplasmosis. If current concerns or prior history exist, an assessment consisting of agar gel immunodiffusion, complement fixation antibody titers, and urine *Histoplasma* antigen should be undertaken. The presence of antigenuria, H precipitin bands, or complement fixation antibody titers $\geqslant$ 1:32 should lead to rejection of the donor allograft. Coccidioidomycosis is a dimorphic fungus that is endemic in the Southwestern United States, Mexico, Central and South America. Approximately 150000 infections occur annually in the US, with an estimated 1.4%-6.9% of transplant recipients becoming infected[137]. Reactivation of latent infection is the most common mode of

posttransplant infection, but multiple cases of DTI have been documented in patients from both endemic and non-endemic areas[138,139]. Patients with active coccidioidomycosis should not be permitted to donate an organ for transplantation. In donors with prior history of coccidioidomycosis, an evaluation should be undertaken to document clearance of infection; including history documenting the resolution of symptoms, resolution of radiographic abnormalities, and at least a 4-fold decrease in antibody titer[140]. Fluconazole or itraconazole can be used for the prevention of DTI in the event that a recipient receives an organ from a donor who in retrospect had evidence of remote infection[141]. Lifelong prophylaxis is indicated following treatment doses for at least one year. Fluconazole at an average daily dose of 200-400 mg can be used depending on whether prophylaxis is primary or secondary[137].

PARASITIC INFECTIONS

With increase in international travel and immigration, potential organ donors have greater risk for parasitic infections not endemic to the United States. Transmission of Chagas disease, schistosomiasis, and *Strongyloides* has been reported[142-144].

The optimal screening procedure for schistosomiasis in donors from endemic areas has not yet been established. Screening of living donors from endemic areas with fecal parasitological analysis paired with blood *Schistosoma* antibody detection assay is a reasonable starting point. This can be followed with a stepwise approach including rectal biopsy, liver biopsy, or both depending on the results of the initial screening tests. If stool analysis shows *Schistosoma* eggs, liver biopsy should be performed regardless of the result of *Schistosoma* serology. In the situation where *Schistosoma* eggs are not detected in the stools but the donor is noted to be seropositive for *Schistosoma*, further investigation with a rectal biopsy is indicated. If rectal biopsy demonstrates *Schistosoma* eggs, all allografts from this donor should be rejected. If eggs are found on initial screening, living donor treatment with praziquantel should be initiated followed by repeat testing of stools for *Schistosoma* eggs. Only if repeat stool testing is negative, should the patient be accepted to donate[145].

Screening of both donors and recipients for strongyloidiasis in the pretransplant period is recommended for those at epidemiologic risk and should include both serology and stool studies[146]. A donor with documented strongyloidiasis should not be precluded from donation, but additional consent from the recipient should be obtained. Recipients of organs from such donor should be prophylactically treated with ivermectin.

Chagas disease is an infection caused by the parasite *Trypanosoma cruzi*. It is endemic to Mexico, Central, and South America but has the potential to cause DTI in the setting of transplantation from a donor from an endemic region to a recipient in a non-endemic country[147]. Most posttransplant infections occurring in recipients from endemic regions occur due to reactivation of latent infection as a result of iatrogenic immunosuppression. Transmission rates from seropositive donors to seronegative recipients are approximately 20% for kidney transplant recipients and 30% for liver transplant recipients. Screening for Chagas disease should be performed on donors who were born or spent significant time living in an endemic country[148]. Donors who have a history of treated Chagas disease should also be screened using the Ortho enzyme immunoassay test (Ortho-Clinical Diagnostics, Inc.; Raritan, New Jersey) and the Abbot Prism Chagas test (Abbott Laboratories; Abbott Park, Illinois). If the initial screening of a living donor is positive, a second confirmatory test should be sent to the CDC; using the radioimmune precipitation assay. Deceased donor testing should also be performed but this information may not be available at the time of transplantation[149]. No allograft should be accepted from a donor who died from acute Chagas disease. When a donor has positive serology for Chagas disease or has a history of treated Chagas disease, organs other than the heart or intestine may be suitable for transplantation with additional consent and posttransplant screening of the recipient. Testing should include *T. cruzi* PCR and microscopy of blood peripheral smears at predetermined time intervals, or in the event of fever, and when rejection is present. Treatment is only indicated if surveillance testing of the recipient is consistent with *T. cruzi* infection. Heart or intestinal transplantation from a donor with a positive history or serology for *T. cruzi* is thought to represent too high of a potential risk for DTI to be acceptable[146,150-152].

CONCLUSION

The demand for allografts for the treatment of end-stage disease processes continues to grow. The need for a thoughtful and thorough approach to donor selection has never been more important in balancing unnecessarily discarding potentially lifesaving organs with reducing infectious complications for the recipient after transplant. Decisions regarding donor acceptability should be made in conjunction with a clinician who has special training and experience in dealing with infections related to transplantation. Donor history and physical examination should be meticulous with an emphasis on documenting current or latent infections that can be transmitted to the recipient. Screening using molecular and microbiological testing should be attempted, as time permits, prior to organ procurement in order to allow for rejection of an unacceptable allograft, or to allow for monitoring and treatment in the recipient. As the need for organs continues to rise, special attention will be focused on ways to expand the donor pool.

Multiple HIV-infected patients die each year awaiting organs that could be provided from living or deceased HIV-infected donors. Approximately 500 HIV positive deceased donors are not currently being utilized to donate organs to HIV-positive recipients[153]. Improvements in antiretroviral therapy and report of successful kidney transplantation from a donor with HIV infection in

South Africa make this an interesting, albeit complicated, area for future evaluation and research. A key advancement has recently occurred with the passage of the HIV Organ Policy Equity Act (HOPE Act) on 11/21/2013.

Improved development of NAAT in conjunction with defined and validated algorithms of application may allow for faster and more accurate testing of donor specimens enabling previously excluded donors to be accepted for donation. Focused efforts to reassess the risk of using high-risk donors should be undertaken, and methods for decreasing recipient risk of DTI are imperative. Finally, it is important to continue to build on the substantial contributions to quality and safety made by the DTAC in recent years. Providers should be strongly encouraged to report any possible donor-transmitted event in real time. Critical infrastructure is now in place to investigate potential DTI, to take appropriate action in the treatment of potential recipients at risk, and to analyze indispensable data in the pursuit of evidence-based decision making essential to improving outcomes in this unique patient population.

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