


**SPECIAL ISSUE: TRANSPLANT  
INFECTIOUS DISEASES**

# Screening of donor and candidate prior to solid organ transplantation—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

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## Abstract

This updated section of the guideline from the Infectious Diseases Community of Practice of the American Society of Transplantation reviews the screening of donor and candidate prior to solid organ transplantation. Screening of donor and candidate is vital for optimizing post-transplant outcomes. Risk assessment based on detailed history and appropriate diagnostic evaluation is essential. Serologic screening for certain viral infections is important and aids in immunization counseling and risk mitigation of recipients. In addition to serology, nucleic acid testing for hepatitis B, hepatitis C and human immunodeficiency virus has been required for deceased and living donors. Certain endemic exposure may warrant additional evaluation beyond recommended standard testing. Diagnosed infection in the donor or recipient warrants treatment as well as additional testing and/or prophylaxis to mitigate risk for post-transplant complications. Certain infections in the immediate pre-transplant period may warrant delay of transplantation.

## KEYWORDS

donor evaluation, donor-derived infections, candidate evaluation, infection

## 1 | BACKGROUND

Pre-transplant screening of potential organ donors and recipients is essential to optimal outcome of solid organ transplantation.<sup>1-4</sup> The goals of pre-transplant infectious disease screening are to identify conditions which may disqualify either donor or recipient, to identify and treat active infection pre-transplant, to recognize and (if possible) define the risk of infection, and, lastly, to develop and implement strategies that prevent and mitigate post-transplant infections.<sup>5</sup> While there is general agreement on the major infections for which routine screening is performed, centers and national regulations may vary in the extent of infectious disease investigation and the actions taken as a result.

Candidates should be evaluated for risk of infection by obtaining a thorough medical history, including details of prior infections,

places of travel and residence, occupation and/or lifestyle, and exposures to animal and environmental pathogens. In addition to standard testing (Table 1), a detailed history can determine the need for additional testing to assess risk for reactivation of latent infection post-transplant. Transplant candidate screening also helps determine immunity to vaccine-preventable illnesses and may help with allocation of infected donor organs to recipients with known immunity to certain pathogens.<sup>6</sup> The pre-transplant period is an ideal time for comprehensive counseling of the candidate and his/her family about safe food handling and the risk of infection associated with pets, travel, lifestyle, and hobbies and infection prevention approaches including post-exposure prophylaxis and immunization.

A variety of pathogens may be transmitted by transplantation (Table 2).<sup>7-10</sup> Previous guidelines for pre-transplant screening have

**TABLE 1** Infectious disease screening for candidates and donors prior to transplantation<sup>a</sup>

Test	Candidate	Deceased donor	Living donor
<b>Viral</b>			
<b>HIV</b>			
Human immunodeficiency virus (HIV) antibody/antigen (fourth Generation HIV screening test)	x	x	x
HIV nucleic acid amplification testing (NAT)		x <sup>b</sup>	x <sup>b</sup>
Cytomegalovirus (CMV) IgG antibody	x	x	x
<b>Hepatitis B virus (HBV)</b>			
HBV surface antigen (HBsAg)	x	x	x
HBV core antibody (HBcAb-IgM and IgG, or total core antibody)	x	x	x
HBV surface antibody (HBsAb)	x		
HBV NAT		x <sup>b</sup>	x <sup>b</sup>
<b>Hepatitis C virus (HCV)</b>			
HCV antibody	x	x	x
HCV NAT	x <sup>c</sup>	x	x
Epstein-Barr virus (EBV) antibody (EBV VCA IgG, IgM)	x	x	x
West Nile virus serology or NAT (seasonal)			x
<b>Parasitic</b>			
<i>Toxoplasma</i> IgG antibody	x	x	x
<i>Strongyloides</i> IgG (if from endemic areas)	x	x	x
<i>Trypanosoma cruzi</i> serology (if from endemic areas)	x	x	x
<b>Fungal</b>			
<i>Coccidioides</i> serology (if from endemic areas)	x	x	x
<b>Bacterial</b>			
Syphilis (any of the following)	x	x	x
Fluorescent treponema antibody absorption (FTA-ABS)			
T. pallidum particle agglutination (TPPA)			
T. pallidum enzyme immunoassay (TP-EIA)			
Rapid plasma reagin (RPR)			
Venereal Disease Research Laboratory (VDRL)			
Tuberculosis (any of the following)	x		x
Purified protein derivative (PPD)			
Interferon gamma release assay (IGRA)			
Urine culture		x	
Blood culture		x	

<sup>a</sup>Donor required screening per the UNOS/OPTN policies.<sup>35</sup>
<sup>b</sup>PHS increased risk donors.

<sup>c</sup>Renal candidates on dialysis.

been developed by a number of national and international multidisciplinary transplant groups.<sup>6,10-15</sup> The Centers for Disease Control and Prevention (CDC) has published guidelines for the prevention of HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) transmission through organ transplantation.<sup>16</sup> In addition, the work of the United Network of Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) Ad Hoc Disease Transmission Advisory Committee (DTAC) has helped to define the risk of infection and disease transmission in organ donation in the United States and has shaped the discussion of screening and preventive measures.<sup>17,18</sup>

While conventional screening strategies are very effective in most cases, they are not a guarantee against donor-derived infections. There have been a number of high-profile incidents of donor-transmitted infection reported in recent years, including rabies,<sup>19</sup>

*Strongyloides*,<sup>20</sup> lymphocytic choriomeningitis virus,<sup>21</sup> West Nile virus,<sup>22</sup> HIV,<sup>23-25</sup> and HCV,<sup>24-26</sup> which have emphasized the importance and limitations of organ donor screening. In addition to DTAC, other transplant and public health community initiatives have helped guide practice to improve early detection and response to donor transmission events.<sup>21,27-30</sup> This guideline summarizes current recommendations on screening for bacterial, mycobacterial, fungal, parasitic, and viral infections in the donor and candidate (Table 1).<sup>5</sup> Donor-derived infections and post-transplant monitoring, prophylaxis, and treatment are discussed in other sections of this guideline.

Due to the organ donor shortage, it has become necessary to consider the use of organs from potentially infected donors and those with known HCV or HIV. HIV-positive donors for HIV-positive recipients are considered only under the setting of a clinical trial.<sup>31</sup> Due to the efficacy of direct-acting antivirals (DAAs), some centers have utilized hepatitis C viremic donors for non-infected kidney and heart transplant recipients in whom antiviral therapy can be guaranteed.<sup>32-34</sup> Long-term outcomes from the use of these donors remain unknown. The natural history and treatment options for donor infection, the urgency of transplantation of a vital organ into a recipient, and the likelihood (or lack thereof) of another organ offer for the patient on the transplant waiting list must all be weighed in determining the acceptability of the potentially infected donor.

**TABLE 2** Pathogens reported to be transmitted with solid organ transplantation

Bacteria	Mycobacteria
<i>Staphylococcus aureus</i>	<i>Mycobacterium tuberculosis</i>
<i>Klebsiella</i> species	Non-tuberculous mycobacteria
<i>Bacteroides fragilis</i>	
<i>Pseudomonas aeruginosa</i>	Parasites/Protozoa
<i>Escherichia coli</i>	<i>Toxoplasma gondii</i>
<i>Salmonella</i> species	<i>Strongyloides stercoralis</i>
<i>Yersinia enterocolitica</i>	<i>Plasmodium</i> species
<i>Treponema pallidum</i>	<i>Trypanosoma cruzi</i>
<i>Brucella</i> species	<i>Pneumocystis jirovecii</i>
<i>Enterobacter</i> species	
<i>Acinetobacter</i> species	Viruses
<i>Legionella</i> species	Cytomegalovirus
<i>Nocardia</i> species	Epstein-Barr virus
<i>Listeria monocytogenes</i>	Herpes simplex virus
	Varicella-zoster virus*
Fungi	Human herpesvirus-6
<i>Aspergillus</i> species	Human herpesvirus-7
<i>Candida</i> species	Human herpesvirus-8
<i>Coccidioides immitis</i>	Hepatitis B, D
<i>Cryptococcus neoformans</i>	Hepatitis C
<i>Histoplasma capsulatum</i>	Human immunodeficiency virus
<i>Scedosporium apiospermum</i>	Parvovirus B19
<i>Prototheca</i> species	Rabies
Zygomycetes	Lymphocytic choriomeningitis virus
	West Nile virus
	BK virus
	Human T-cell lymphotropic virus (HTLV)- 1/2

\*[Correction added on May 17, 2019, after first online publication: Varicella-zoster virus has been moved from the category of "Bacteria" to category of "Viruses".]

## 2 | DONOR SCREENING

The differences in screening of the living donor and the deceased donor are largely based on the different time constraints during which the donor evaluation must take place. The time frame of evaluation of deceased donors is typically hours, while living donors undergo a timely but non-urgent process. The screening of any prospective donor includes a thorough medical history, physical examination, laboratory studies [including serologic testing and molecular diagnostic studies (Table 1)] and radiographic evaluation as indicated by the donor's history and the procedure to be performed. The medical history should include an assessment of previous infections, vaccinations, travel, and occupational exposures, as well as the presence of behaviors posing risk for bloodborne or sexual pathogen exposure (e.g., drug use, sexual practices, incarceration). History obtained for deceased donors is limited by the historian's familiarity with the donor's lifestyle and exposure in contrast to living donors who can provide their own history. The OPTN/UNOS<sup>35</sup> mandates infectious disease testing of deceased donors for CMV, EBV, HIV, HBV, HCV, syphilis, and toxoplasmosis in addition to urine and blood cultures. Required screening of living donors includes CMV, EBV, HIV, HBV, tuberculosis, toxoplasmosis, and syphilis.

If the donor is determined an increased risk for HIV, HBV, HCV transmission per the U.S. Public Health Services (PHS) Guideline, informed consent from the recipient and post-transplant monitoring for HBV, HCV and HIV are required.<sup>16</sup> For living donors, testing for HBV, HCV, and HIV should be performed close as possible, but within 28 days prior to organ recovery.<sup>35</sup> Evaluation for

seasonal or geographically defined endemic infection such as WNV, *Strongyloides*, *Coccidioides*, and *Trypanosoma cruzi* should be considered in donors with the appropriate epidemiological risk factors.<sup>36</sup> Certain OPOs perform screening for these endemic infections in deceased donors with exposure history; however, results may not be available at time of organ procurement. Also, deceased donors with clinical features that may be associated with central nervous system (CNS) infection (e.g., cerebrovascular accident in a patient without risk factors and altered mental status/seizure at presentation of illness) warrant careful evaluation.<sup>37</sup> If there is relevant donor history, additional testing may be warranted. Consultation with a transplant infectious disease specialist may help with determining additional evaluation and management while awaiting transplantation.

## 2.1 | Donor screening: bacterial infections

Donors may harbor known or unsuspected bacterial infections.<sup>6,38-42</sup> Identifying the presence of active infection should include review of history, medical records, vital signs, physical examination, radiographic studies, and any available microbiologic studies. In general, bacterial infections of the respiratory tract, urinary tract, bloodstream infection, or the organ to be transplanted should have documented appropriate treatment of infection and evidence of control prior to donation. For living donors, identified active infection should be treated and transplantation should be delayed until infection resolves. Clinical reassessment of the prospective living donor is indicated if clinical signs or symptoms of possible infection occur, particularly any unexplained febrile illness between the time of initial screening and the planned date of transplantation. In contrast, deceased donors may not have sufficient time to complete treatment prior to donation. The use of these organs should be carefully considered.

Blood cultures should be obtained to rule out occult bacteremia in deceased donors. Bacteremia with virulent organisms such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* may result in early post-transplant sepsis or mycotic aneurysm formation at the site of allograft vascular anastomoses.<sup>39-46</sup> A review of 95 bacteremic deceased donors found no evidence of transmission when recipients were treated with appropriate antimicrobial therapy for a mean of 3.8 days post-transplant.<sup>43</sup> However, the standard of care is to administer longer courses of therapy in the recipient (eg, two weeks) if the donor is known to have been bacteremic with a virulent organism.<sup>47-52</sup> In general, there is no reason to treat the recipient of an allograft from a deceased donor with non-bacteremic, localized infection not involving the transplanted organ, with the exception of meningitis, in which occult bacteremia frequently occurs.<sup>53-58</sup> Organs have been safely transplanted from donors with bacterial meningitis due to pathogens such as *Streptococcus pneumoniae* when appropriate antimicrobial therapy was administered to both the donor and the recipients.<sup>53,57,58</sup>

Lung transplantation from deceased donors deserves special attention.<sup>59</sup> Donor bacterial colonization is common, as the lungs are in contact with the external environment, and the airways are colonized with multiple organisms, with increasing resistance noted

in the hospitalized, critically ill potential organ donor. Donor bronchoscopy with cultures performed at the time of evaluation and/or procurement allows for the administration of antibiotics directed at these colonizing organisms and can prevent invasive infection in the recipient.<sup>7,8,59</sup>

*Syphilis* may be latent and asymptomatic in the donor and requires therapy if time permits. Syphilis has rarely been transmitted by transplantation, but it is not a contraindication to deceased organ donation if the recipient is treated post-transplant with an appropriate course of penicillin.<sup>38,60</sup>

*Mycobacterium tuberculosis* (TB) has been transmitted by transplantation; in the largest study to date (511 recipients), donor transmission accounted for approximately 4% of reported post-transplant TB cases.<sup>61</sup> Donors in whom active tuberculosis is a clinical possibility should not be utilized. If there are symptoms of infection or radiographic findings suggestive of active disease, sputum and/or appropriate specimens should be collected for acid fast bacilli (AFB) culture nucleic acid amplification testing.<sup>62,63</sup> In the potential kidney donor with evidence of latent TB infection (LTBI), this could include urine AFB cultures and abdominal computed tomography (CT) scanning. If there are no signs or symptoms of active disease and the chest radiograph is normal, sputum AFB cultures are not indicated due to their low yield.

Potential living donors should have PPD testing performed (a two-stage tuberculin skin test if from an endemic area) or interferon gamma release assay (IGRA) testing<sup>61,64,65</sup>; if either test is positive, chest radiograph should be obtained to look for evidence of active pulmonary infection. In deceased donors, time does not allow for tuberculin skin testing. Also, IGRA is not logistically practical in most cases and evidence is lacking to support its routine use in deceased donors. In cases where a potential deceased donor is known to have recent PPD skin test conversion, suggesting recent acquisition of infection with the potential for a high organism burden, transplantation should be approached with caution due to the risk of dissemination in the recipient. Deceased donors with a history of an untreated LTBI but without evidence of active disease are acceptable but warrant consideration of treatment of the recipient(s) with isoniazid.<sup>61,65-67</sup> Guidelines for the prevention and management of *Mycobacterium tuberculosis* in organ transplantation have been published in the American Journal of Transplantation<sup>67</sup> and the TB section of this updated guideline.

### 2.1.1 | Key recommendations

- Bacterial infections of the respiratory tract, urinary tract, bloodstream infection, or the organ to be transplanted should have documented appropriate treatment with evidence of infection control prior to donation (strong, low).
- If a deceased donor is determined to have active bacterial infection based on cultures obtained at the time of procurement, antibiotics should be administered to each recipient for at least 14 days for infections with Gram-negative bacilli or *Staphylococcus aureus* (strong, low).

- A shorter course of therapy may be considered for less virulent organisms (weak, low).
- Recipient of an allograft from a deceased donor with non-bacteremic, localized infection not involving the transplanted organ does not require treatment, with the *exception of meningitis*, in which occult bacteremia frequently occurs (strong, moderate).
- For potential lung donors, bronchoscopy with cultures should be performed and appropriate antibiotics initiated in the recipient to cover recovered bacteria (strong, low).
- Syphilis has rarely been transmitted by transplantation, but it is not a contraindication to deceased organ donation if the recipient is treated post-transplant with an appropriate course of penicillin (strong, low).
- Donors in whom active tuberculosis is a clinical possibility should not be utilized (strong, moderate).
- Potential living donors should have PPD testing performed (a two-stage tuberculin skin test if from an endemic area) or IGRA testing; if either test is positive, chest radiograph should be obtained to look for evidence of active pulmonary infection (strong, low).
- Deceased donors with a history of an untreated LTBI but without evidence of active disease are acceptable but warrant consideration of treatment of the recipient(s) with isoniazid (strong, low).

## 2.2 | Donor screening: fungal infections

Potentially transmissible fungal infection in the donor is a contraindication to transplantation. The endemic mycoses may be difficult to diagnose, as infection may be dormant. Transmission of histoplasmosis by transplantation has been described,<sup>68,69</sup> but most cases appear to be the result of reactivation of past infection in the recipient.<sup>70-72</sup> In many individuals from the Midwestern United States, calcified pulmonary, hilar, and splenic granulomata are the radiographic residua of old *Histoplasma* infection, but such signs have not traditionally been considered a contraindication to donation. Routine donor screening of all donors for histoplasmosis from an endemic area is not warranted; however, explanted organs that may have granuloma should undergo prompt fungal culture and testing for antigen and antibodies to *Histoplasma*.<sup>73</sup> Transmission of coccidioidomycosis by transplantation has been reported<sup>74-80</sup>; however, reactivation of coccidioidomycosis in the previously infected recipient appears to be far more common.<sup>81</sup> Screening for *Coccidioides* should be considered in living donors from endemic areas; however, universal screening is not recommended for those outside the endemic area. Screening of cryptococcosis should be considered in donors who have meningoencephalitis of unknown etiology,<sup>37</sup> pulmonary nodules of unknown etiology, or fever of unknown origin if they have underlying medical conditions that predispose to this pathogen (eg, end stage liver/renal disease, rheumatologic disorder, sarcoidosis, or receipt of corticosteroid/immunosuppressant).<sup>73</sup> Guidelines for donor evaluation for fungal infection and suggested prophylaxes for recipients are further discussed in a separate section in this updated guideline.

### 2.2.1 | Key recommendations

- Routine donor screening of all donors for histoplasmosis from an endemic area is not warranted; however, explanted organs that may have granuloma should prompt fungal culture and testing for antigen and antibodies to *Histoplasma* (strong, low)
- Calcified pulmonary, hilar, and splenic granulomata that are suggestive of old *Histoplasma* infection are not a contraindication to donation (weak, low).
- Screening for *Coccidioides* should be considered in living donors from endemic areas; however, universal screening is not recommended for those outside the endemic area (strong, moderate).
- Screening of cryptococcosis should be considered in donors who have meningoencephalitis of unknown etiology, pulmonary nodules of unknown etiology, or fever of unknown origin if they have underlying medical conditions that predispose to this infection (eg, end stage liver/renal disease, rheumatologic disorder, sarcoidosis, or receipt of corticosteroid/immunosuppressant) (strong, moderate).

### 2.3 | Donor screening: parasitic infections

Toxoplasmosis is a significant issue in heart transplantation, where the *Toxoplasma*-seronegative recipient of a *Toxoplasma*-seropositive heart is at highest risk for developing active toxoplasmosis post-transplant.<sup>82-84</sup> Toxoplasmosis has also rarely been transmitted to liver and kidney recipients.<sup>83-85</sup> As of April 2017, toxoplasma screening with *Toxoplasma* IgG is performed universally for donors by OPOs per OPTN/UNOS policy. Donor seropositivity is not a contraindication to organ donation but allows for appropriate prophylaxis to be administered to the recipient; routine trimethoprim-sulfamethoxazole against *Pneumocystis jirovecii* prophylaxis<sup>84</sup> or, if with sulfa allergy, atovaquone with or without pyrimethamine/leucovorin is effective in preventing toxoplasmosis transmission for mismatched heart and other organ recipients.

Transmission of Chagas' disease (*Trypanosoma cruzi*) by transplantation is a significant problem in endemic areas (Mexico, Central America, and South America) but has increasingly been reported in the United States.<sup>86-88</sup> A recent consensus conference resulted in recommendations including avoidance of transplantation of the hearts from infected donors; liver and kidney can be considered with informed consent from recipients and preemptive monitoring by PCR and microscopy of buffy coat to detect early infection and initiate therapy.<sup>89</sup>

Transmission of *Strongyloides* by transplantation has been described and had significant mortality and morbidity.<sup>20,90-94</sup> Hyperinfection syndrome and disseminated disease can occur. The common use of pre-conditioning high-dose corticosteroid in deceased donors can intensify the rates of transmission.<sup>92</sup> Screening of living donors and, if feasible, deceased donors with epidemiological risk factors should be strongly considered.<sup>36,95</sup> Serology is the preferred screening for *Strongyloides* infection due to limited sensitivity of stool testing. Recipients of untreated infected donors should

receive treatment with ivermectin post-transplant with close monitoring for infection.<sup>95</sup>

### 2.3.1 | Key recommendations

- OPTN/UNOS mandates *Toxoplasma* screening by serology in all donors (strong, moderate).
- Donor seropositivity for *Toxoplasma* is not a contraindication to organ donation but allows for appropriate prophylaxis to be administered to the recipient; routine trimethoprim-sulfamethoxazole against *Pneumocystis jirovecii* prophylaxis or, if with sulfa allergy, atovaquone with or without pyrimethamine/leucovorin is effective in preventing toxoplasmosis transmission for mismatched heart and other organ recipients (strong, moderate).
- Screening for endemic infection including *T cruzi* and *Strongyloides* should be performed based on epidemiologic risk factors (strong, moderate).
- Transplantation of the hearts from donors with positive *T cruzi* serology should be avoided (strong, high)

## 2.4 | Donor screening: viral infections

Screening for viral infections with serologies and/or nucleic acid testing is detailed in Table 1. The donor's serostatus result is interpreted in tandem with the recipient's serostatus to predict the infection risk in the potential recipient (Table 3). Caution should be used in interpreting antibody status in infants, due to the role of maternal antibody. More detailed information on the clinical presentation and treatment of these infections is found elsewhere in this guideline.

### 2.4.1 | Cytomegalovirus

The cytomegalovirus (CMV) serologic status of donor is important in risk stratification for CMV infection in the potential transplant recipient.<sup>96-98</sup> All donors are required by the UNOS/OPTN policy to be screened by CMV serology. While not a contraindication to transplantation, a seropositive donor matched with a seronegative recipient (D+/R-) will require more intensive monitoring and prevention strategies post-transplant than in donor/recipient pairs with a lower risk of CMV infection. There are many different protocols in use; a full discussion of CMV prevention and treatment is found elsewhere in the guideline.

### 2.4.2 | Epstein-Barr Virus

While primary Epstein-Barr Virus (EBV) infection can be severe and disseminated in the post-transplant setting, the development of post-transplant lymphoproliferative disease (PTLD) is the EBV-associated complication of greatest concern. The highest PTLD risk is in the EBV-seronegative recipient of an EBV-seropositive graft, which most commonly occurs in pediatric recipients.<sup>99-101</sup> PTLD may occur in the seropositive recipient, especially under the influence of

potent immunosuppressants such as antithymocyte globulin (ATG) and belatacept. Awareness of pre-transplant serologies helps target the highest risk group for close monitoring by EBV-PCR and preemptive interventions such as decreasing immunosuppression.<sup>99-101</sup> EBV serology should be performed on all donors and recipients in order to define the risk of post-transplant lymphoma. The British Transplantation Society and British Committee for Standards in Haematology published extensive guidelines on the pre-transplant screening and diagnosis of PTLD in organ transplant recipients.<sup>102</sup> Additional information is available in the EBV section of this guideline.

### 2.4.3 | Hepatitis B

All donors should be tested for hepatitis B (HBV). Donor screening should include at least hepatitis B surface antigen (HBsAg) and HBV core antibody (HBcAb, which should be performed as separate IgG and IgM to be most useful). HBV DNA is performed in screening of PHS increased donors; however, many OPOs include this in routine screening of all deceased donors. Living donors should be evaluated for HBV as close as possible, but within 28 days prior to the organ donation.<sup>35</sup>

Hepatitis B serologies require careful interpretation. Donor HBsAg positivity or HBcAb-IgM positivity indicates active HBV infection. HBsAg-negative, HBcAb-IgM-positive persons may be in the "window period"; such donors have generally not been utilized, although some centers have used these donors in recipients with evidence of immunity to hepatitis B (those with a positive hepatitis B surface antibody, HBsAb) and/or with intensive post-transplant prophylaxis and monitoring. Isolated HBsAb positivity usually indicates prior vaccination or resolved infection and is not generally considered a risk for HBV transmission. The most complex question is the use of the HBsAg-negative, HBcAb-IgG-positive donor ("core-positive donor").<sup>103-105</sup> This may represent either a false-positive test (if isolated HBcAb positive) or the presence of chronic HBV infection. If the latter, there is a significant risk of transmission of HBV to a liver transplant recipient, and therefore, these livers were often not utilized in the past; however, it has now become more common to transplant livers from HBcAb-positive donors utilizing intensive post-transplant prophylaxis.<sup>105</sup> The risk of transmission to extrahepatic recipients appears to be low but has occurred.<sup>104,106-108</sup> The complex issues surrounding HBV and transplantation are discussed in more detail in the hepatitis section of this guideline including information on prophylactic strategies and post-transplant monitoring (Table 3).

### 2.4.4 | Hepatitis C

Hepatitis C (HCV) infection is frequently chronic, and donors should be tested for the presence of HCV via standard serologic techniques. Hepatitis C antibody positivity may be interpreted as either active infection, spontaneously cleared infection, or treated infection. Since 2015, HCV NAT testing has been required for all



**TABLE 3** Interventions related to donor and recipient screening results

Pathogen	Donor antibody status	Recipient antibody status	Recommendations regarding transplantation	Comment
HIV	Positive	Negative	Reject donor	
		Positive	HIV + deceased donors can be only utilized for HIV-positive recipients in the setting of a clinical trial.	
	Negative	Positive	Proceed if HIV well controlled; be cautious about major drug interactions between antiretrovirals and CNIs	
CMV	+ or -	Positive	Proceed	D/R status used to determine prevention strategy (preemptive therapy versus prophylaxis)
	Positive	Negative	Accept; high risk for CMV infection	See CMV guideline for approach to management of the CMV D + R- recipient
	+ or -	Positive	Proceed	
	Positive	Negative	Accept; higher risk for primary EBV infection and PTLD	
<i>Toxoplasma gondii</i>	+ or -	Positive	Proceed	Consider post-transplant NAT monitoring to guide immunosuppression
	Positive	Negative	Accept	TMP/SMX prophylaxis is effective in prevention. If intolerant or allergic to TMP/SMX, use atovaquone with or without pyrimethamine/leucovorin.
HCV	Positive	Positive	If donor is HCV NAT negative, proceed	For recipients of PHS increased risk donor, post-transplant monitoring is needed
			May consider HCV NAT positive	HCV NAT-positive donors can be utilized with appropriate informed consent of the recipient and plan for antiviral treatment of the recipient
	Positive	Negative	If donor is HCV NAT negative, proceed	For recipients of PHS increased risk donor, post-transplant monitoring is needed
			May consider HCV NAT positive	HCV NAT-positive donors can be utilized with appropriate informed consent of the recipient and plan for antiviral treatment
HBV	HBsAb+	+ or -	Accept	
	HBsAg+	- HBsAb	Reject	Some centers use in life-saving situations with preemptive antiviral treatment of the recipient
		+ HBsAb	Reject	
	HBcAb-IgM+	- HBsAb	Reject	
		+HBsAb	Reject	Some centers use in life-saving situations with preemptive antiviral treatment of the recipient
	HBcAb-IgG+	-HBsAb	Accept after individualized risk and benefit assessment and appropriate informed consent	Prophylaxis with HBIG ± antivirals
	(with concurrent negative HBsAg and negative HBcAb-IgM)	+HBsAb	Accept	Immune extrahepatic recipients may not require prophylaxis. Hepatic recipients who acquired natural immunity to HBV (HBcAb+/HBsAb+) will not require prophylaxis while those who acquired immunity by vaccine (HBcAb-/HBsAb+) will require antiviral prophylaxis <sup>1,29</sup>
RPR (syphilis)	Positive	+ or -	Accept	Recipients should be treated for presumed transmission with penicillin
CNS viral pathogens (eg, LCMV, rabies, WNV)	Clinical suspicion of infection		Reject	

CNIs, calcineurin inhibitors; CNS, central nervous system; D+/R-, donor seropositive, recipient seronegative; PTLD, post-transplant lymphoproliferative disease; RPR, rapid plasma reagin; TMP-SMX, trimethoprim-sulfamethoxazole.

deceased donors by the OPTN/UNOS. The use of HCV NAT testing is able to distinguish active infection from cleared or treated infection. For living donors, HCV antibody and NAT should be done as close as possible, but within 28 days of the organ procurement.<sup>35</sup> The risk of transmission from those who have cleared or treated infection (HCV Ab+/HCV NAT-) is not well defined. A recent consensus from the American Society of Transplantation has stated that HCV Ab+/HCV NAT- donors should be viewed no differently from HCV Ab- donors.<sup>109</sup> Recent data from a single center observed HCV seroconversion among 32 HCV-negative kidney transplant recipients of HCV Ab+/HCV NAT- donor without development of viremia.<sup>110</sup> In the era of DAAs, some centers have expanded their donor pool by utilizing hepatitis C viremic donors for non-infected kidney and heart transplant recipients.<sup>32-34</sup> Further details are discussed in the HCV section of this guideline.

#### 2.4.5 | Human immunodeficiency virus

All donors should be screened for human immunodeficiency virus (HIV). HIV-1 and HIV-2 serologies are required for all potential donors; because HIV-2 is rare in the United States and HIV-2 screening serologies are frequently falsely positive, specific testing for this virus should be performed on those donors or recipients from western Africa, where HIV-2 is endemic. Current fourth-generation HIV tests can detect both HIV antibody and HIV p24 antigen<sup>111,112</sup> and has improved sensitivity and specificity approaching 100% for patients with chronic HIV infection and up to 80% of patients with acute/early infection. HIV NAT is currently required for PHS increased risk donors in addition to serology, unless the donor has been screened with HIV antigen/antibody combination test.<sup>35</sup> Living donors should have HIV screen performed as close as possible to, but within 28 days prior to donation.<sup>35</sup> Utilization of HIV-positive donors is only possible under clinical trial and will be discussed further in the HIV section of this guideline.

#### 2.4.6 | Human T-lymphotropic virus (HTLV-1/2)

HTLV-1 is endemic in certain parts of the world including the Caribbean, Japan, and parts of Africa, and is often asymptomatic. HTLV-1 is associated with the development of acute T-cell leukemia/lymphoma in 2%-5% of infected individuals and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) can occur infrequently.<sup>113,114</sup> HTLV-2 is a virus which is likely more widespread geographically and is serologically difficult to distinguish from HTLV-1; it has not been convincingly associated with human disease. Screening for HTLV-1/2 in deceased donors was standard in US practice until 2009, when UNOS/OPTN discontinued the requirement to perform prospective deceased donor screening due to false-positive results of screening tests resulting in organ wastage, the lack of a serologic assay that distinguishes HTLV-1 from HTLV-2, and the unavailability of an FDA licensed HTLV-1 screening test in OPO laboratories.<sup>115</sup> Despite the removed requirement for donor screening of HTLV-1, some OPOs may elect to perform either routine screening

or targeted screening of deceased donors at higher risk for HTLV-1. Issues that arise with use of HTLV-1/2-positive donors will be addressed in HTLV section of these guidelines.

#### 2.4.7 | West Nile Virus

West Nile Virus (WNV) is a flavivirus which can cause meningoencephalitis and has been transmitted via blood transfusion and solid organ transplantation.<sup>22,116-118</sup> It is unclear as yet what the magnitude of the risk of such transmission is, and any risk assessment is complicated by the fluctuating levels and geographic distribution of WNV infection in mosquitoes and humans each year. Serology and PCR for WNV are available but time-consuming. Since July 2002, all US blood bank products have been tested for WNV using a NAT assay. In the fall of 2003, the US Health Resources and Service Administration (HRSA) issued a Guidance statement regarding organ donors and West Nile virus, which recommended testing all prospective live donors with NAT close to the time of transplant; avoiding donors with any form of unexplained or confirmed WNV encephalitis; and heightened clinical suspicion on the part of the treating clinician for any febrile illness occurring shortly after transplant. NAT poses logistical challenges in some UNOS regions and is not currently mandated for deceased donor screening. There is also concern that false-positive NAT results may lead to a loss of non-infected organs and net loss of life, particularly for liver and heart candidates on the waiting list.<sup>119</sup>

#### 2.4.8 | Key recommendations

- All donors should be screened for CMV, EBV, HBV, HCV, and HIV (strong, high).
- NAT is used in addition to serology for HCV screening of deceased donors (strong, moderate).
- HBV, HCV, and HIV screening of living donors should be close as possible to but no longer than 28 days prior to organ procurement (strong, moderate).
- Due to the low seroprevalence of HTLV-1 in the United States and the poor positive predictive value of screening HTLV-1/2 assays in this population, routine screening of all deceased donors is not recommended (strong, moderate).
- Living donors should have WNV NAT close to time of transplant (strong, low).
- Avoid donors with any form of unexplained or confirmed WNV encephalitis (strong, high).

### 3 | CANDIDATE SCREENING

#### 3.1 | Candidate screening: pre-transplant detection of active bacterial infection in the recipient

Transplant recipients are at risk for infections related to complications of end-organ failure. Patients awaiting kidney transplantation



may have infected hemodialysis or peritoneal dialysis access sites or catheters, or complicated upper- and/or lower-tract urinary infections. Candidates awaiting liver transplants are at risk for aspiration pneumonia, spontaneous bacterial peritonitis, urinary tract infection, and infections associated with intravenous catheters. Liver transplant candidates with biliary tree disease due to fibrosis/stricture (eg, biliary atresia in pediatric patients, primary sclerosing cholangitis) are predisposed to recurrent cholangitis. Pancreas transplant candidates can develop diabetic foot infections and associated osteomyelitis. Those awaiting heart transplants may have infections related either to indwelling intravenous catheters, or to ventricular assist devices (VADs) utilized as a bridge to transplantation.<sup>120,121</sup> In addition, heart candidates are also at risk for pneumonia in the setting of congestive heart failure and debilitation. VAD-associated infections that are controlled (ie, resolution of bacteremia and eradication of metastatic foci of infection) do not constitute a contraindication to transplantation, as complete removal of the VAD at the time of transplant, combined with appropriate post-transplant antibiotic therapy, is often curative.<sup>120,121</sup>

Knowledge of the pre-transplant colonizing flora can assist in developing an individualized peri-transplant prophylactic antimicrobial regimen. Screening of lung transplant candidates includes an assessment of colonizing airway flora and careful review of their previous pulmonary infections.<sup>122</sup> Cystic fibrosis patients may be colonized with multi-drug resistant strains of *Pseudomonas* and/or *Burkholderia cepacia* as well as other organisms such as *Staphylococcus aureus*, *Alcaligenes*, *Klebsiella*, *Acinetobacter*, *Stenotrophomonas*, *Aspergillus*, and *Scedosporium*. There is controversy as to whether patients colonized with *Burkholderia* should be excluded from receiving lung transplants; molecular typing of *Burkholderia* isolates may be used to define risk, as genomovar III (*B. cenocepacia*) is associated with the highest risk of poor outcomes after transplantation.<sup>123-125</sup> For lung and non-lung transplant recipients, screening practices for MRSA, vancomycin-resistant *Enterococcus*, and carbapenem-resistant *Enterobacteriaceae* (CRE) may vary across transplant centers. For individuals colonized or infected with CRE prior to transplant, a risk-benefit evaluation is important. A recent multi-center study demonstrated an acceptable one-year graft survival close to 80% in 57 SOT recipients colonized or infected with CRE before transplant.<sup>126</sup> This finding suggests that prior CRE colonization or infection should not be an absolute contraindication to transplant.

### 3.1.1 | Key recommendations

- In general, active or uncontrolled infection in the potential recipient should delay transplant until infection resolves or is controlled (eg, controlled VAD-related infections) (strong, moderate)
- Knowledge of the pre-transplant colonizing flora can assist in developing an individualized peri-transplant prophylactic antimicrobial regimen (strong, low)

## 3.2 | Candidate screening: mycobacterial infections

All candidates should have a PPD or IGRA performed prior to transplant, and those who have a positive skin test or IGRA, or a history of active tuberculosis, should undergo additional screening to rule out active disease.<sup>61</sup> IGRAs may be particularly useful in assessing patients who received Bacillus Calmette-Guerin (BCG) vaccination, as the IGRA assay has the potential to distinguish PPD positivity related to BCG from that related to latent TB infection in those above the age of 5.<sup>64,127</sup> Patients with LTBI should be given prophylaxis to prevent reactivation of disease in the setting of immunosuppression.<sup>61,66</sup> Details on the treatment of LTBI are found in TB section of this guideline.

In transplant candidates with a clinical history, radiographs, and/or cultures suggesting infection with TB or non-tuberculous mycobacteria, a thorough evaluation for active disease should be performed, which may include CT scans, bronchoscopy, or other tests as deemed clinically necessary. Any mycobacterial infection should optimally be treated with documented microbiologic and radiographic resolution before transplantation is considered.

### 3.2.1 | Key recommendations

- All candidates should have a PPD or IGRA performed prior to transplant, and those who have a positive skin test or IGRA, or a history of active tuberculosis, should undergo additional screening to rule out active disease (strong, moderate).
- Candidates with LTBI should be given prophylaxis to prevent reactivation of disease in the setting of immunosuppression (strong, moderate)

## 3.3 | Candidate screening: fungal infections

Pre-transplant colonization with fungi such as *Aspergillus* spp, is common in lung transplant candidates, particularly in cystic fibrosis patients. Such colonization should prompt a rigorous evaluation to exclude active infection. Although post-transplant aspergillosis is a feared complication, transplant clinicians have generally relied more on post-transplant preemptive and prophylactic strategies rather than pre-transplant antifungal therapy for colonized patients. A pre-transplant candidate with invasive fungal infection (rather than colonization) should be treated at least until there is radiographic, clinical, and microbiologic resolution in order to minimize the risk of this high-mortality infection post-transplant. Additional information on the diagnosis, prevention, and treatment of infection with *Aspergillus* spp is found in other parts of these guidelines.

Pre-transplant screening for endemic mycoses is most useful in areas endemic for coccidioidomycosis, where a pre-transplant history of active disease and/or seropositivity may prompt lifelong azole prophylaxis.<sup>81</sup> Pre-transplant screening for histoplasmosis is of limited value since latent histoplasmosis may be present with

negative serology; instead, heightened awareness of the possibility of histoplasmosis is important when investigating a post-transplant febrile illness in a transplant recipient from an endemic area.

### 3.3.1 | Key recommendations

- A pre-transplant candidate with invasive fungal infection (rather than colonization) should be treated at least until there is radiographic, clinical, and microbiologic resolution in order to minimize the risk of this high-mortality infection post-transplant (strong, low).
- Pre-transplant screening for endemic mycoses is most useful in areas endemic for *Coccidioides* spp, where a pre-transplant history of active disease and/or seropositivity may prompt lifelong azole prophylaxis (strong, moderate).
- Pre-transplant screening for histoplasmosis is not recommended (weak, very low)

### 3.4 | Candidate screening: parasitic infections

Patients from (or with prolonged travel history to) endemic areas for strongyloidiasis, including most tropical countries and parts of the southeastern United States, are at risk for development of disseminated strongyloidiasis after transplant. Screening with serology for *Strongyloides* is much more sensitive than stool exams and is recommended for those with epidemiologic risk. For seropositive patients and/or those from endemic areas, a short course of ivermectin or thiabendazole is indicated pre-transplant, although randomized data are not available. As discussed above, *Toxoplasma* serology should be performed in all organ transplant recipients, in particular heart transplant candidates; seronegative recipients with seropositive donors and seropositive recipients should receive prophylaxis.<sup>82-84</sup> Chagas' disease and other parasitic infections are more fully discussed elsewhere in this guideline.

#### 3.4.1 | Key recommendations

- Candidates with known endemic exposure to *Strongyloides* and *T. cruzi* should be screened (strong, moderate).
- Serologic screening for *Strongyloides* is preferred over stool examinations (weak, low).
- *Toxoplasma* serology should be performed in all patients undergoing organ transplantation, in particular heart transplant candidates; seronegative recipients with seropositive donors and seropositive recipients should receive prophylaxis (strong, low).

### 3.5 | Candidate screening: viral infections

Active primary infection with viruses such as CMV, EBV, or HBV at the time of transplant is uncommon. Nonetheless, if active viral infection is detected in a potential recipient, transplantation should be delayed, if possible, until the infection resolves in order to allow for development of natural immunity prior to transplant

immunosuppression. This recommendation also extends to candidates who present for transplantation with clinical symptoms suggestive of an acute community-acquired viral infection. The International Pediatric Transplant Association Infectious Diseases Clinical Care, Advocacy, Research and Education (IPTA ID-CARE) Committee published recommendations on how to approach transplant candidates who developed viral central nervous system, gastrointestinal, upper and lower respiratory tract infections based on urgency of transplantation.<sup>128</sup> Risk-benefit evaluation should be performed depending on urgency of transplant, nature of infection, and available treatment options. If there is any chance of exposure to HIV pre-transplant, the candidate should have an HIV NAT and HIV antibody/antigen test performed.

Other herpesviruses of clinical importance in the transplant candidate include herpes simplex virus (HSV-1 and HSV-2), varicella-zoster virus (VZV), human herpesvirus-6 and 7 (HHV-6 and -7), and HHV-8. HSV screening is performed by some centers, whereas other centers administer universal antiviral prophylaxis for at least the first month post-transplant. As primary varicella infection post-transplant can be fatal, VZV screening of the candidate is important, with vaccination of the seronegative candidate pre-transplant if at all possible. Candidate screening for measles (rubeola), mumps, and rubella immunity by serology is important to determine the need for live vaccine administration that can only be given before transplant due to its contraindication after transplant. Hepatitis A and B serologies screen for both active disease and presence of immunity. Those without evidence of immunity can benefit from immunization preferably given prior to transplantation.

#### 3.5.1 | Key recommendations

- Screening for CMV, EBV, HBV, HCV, and HIV should be performed in all transplant candidates (strong, high)
- Active viral infection in a potential recipient transplantation should be delayed if possible until the infection resolves (strong, low)
- VZV and MMR screening of the recipient is important, with vaccination of the seronegative recipient pre-transplant if at all possible (strong, very low).

### 3.6 | Pre-transplant counseling of candidates

Preventive strategies for infection should not be confined to medications and vaccinations. Extensive education of the transplant recipient and his or her family is a very important preventive tool. Pre-transplant classes and printed materials are helpful and should include information on handwashing/hand hygiene, environmental exposures, activities to avoid, food safety and handling, foodborne pathogens, pets, and travel. This is discussed further in the strategies for safe living section of this updated guideline. It is also helpful for patients to have a general idea of the infections to which transplant patients are susceptible and the preventive strategies in use at their particular center. It is fundamental that

patients know what to expect, what can go wrong, and what is expected of them.

#### 4 | CONCLUSION/FUTURE DIRECTIONS

Pre-transplant screening of the potential organ donor and recipient affords an opportunity to assess the feasibility and safety of transplantation, to determine the prophylaxis and preventive strategies utilized post-transplant, to detect and fully treat active infection in the potential recipient prior to transplant, to update the vaccination status of the potential recipient, and to sufficiently educate the patient and family about preventive measures. Future advances will incorporate the increasing use of rapid molecular diagnostic testing, and possibly ancillary testing for emerging pathogens in clinical practice.

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#### CONFLICT OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose.

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