Recognizing Seasonal and Geographically Endemic Infection in Organ Donors: Considerations for Deceased and Living Donation

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Background

Both deceased and living donors are at risk for transmitting endemic diseases that are either geographically or seasonally defined. Since 2014, Organ Procurement and Transplantation Network (OPTN) policy has required living donor hospitals to develop a written protocol for identification and testing potential donors at risk for these endemic infections as part of the medical evaluation process. More recently on June 26, 2023, the OPTN Board of Directors approved additional policies[1] to address screening of deceased donors for endemic diseases to further reduce the risk for potential donor-derived infectious events.

Summary and Goals

The OPTN Ad Hoc Disease Transmission Advisory Committee (DTAC) created this guidance document to assist programs in identification of potential living and deceased donors who may carry an increased risk of transmitting seasonal or geographically endemic disease to organ recipients. This document will also help programs manage recipients who receive organs from donors with endemic diseases. This resource is not OPTN policy, so it does not carry the monitoring or enforcement implications of policy. It is not an official guideline for clinical practice, nor is it intended to be clinically prescriptive or to define a standard of care. This is a resource tool intended to be of educational support for organ procurement organizations (OPOs) and transplant centers and is for voluntary use by members.

[1] Improve Deceased Donor Evaluation for Endemic Diseases," OPTN, Policy Notice, Accessed October 10, 2023, https://optn.transplant.hrsa.gov/media/lrxfreqj/dtac_endemics_policy-notice_june23bod.pdf.

Developing a Written Protocol for Identifying and Testing Donors

The DTAC reviews potential donor-derived disease transmission events (PDDTE) reported to the OPTN for both deceased and living donors. A number of the PDDTE reported are seasonally and geographically associated. Some of the reported events resulted in recipient illness or death. Recognition of disease in these donors can be especially challenging, as risk factors may not be recognized, and laboratory screening is not generally universally performed. This guidance document provides information the DTAC believes will help programs and OPOs identify and test donors at risk for transmissible seasonally or geographically defined disease. This information is meant to assist the transplant community in performing organ donor and recipient infectious disease screening procedures as part of the overall medical evaluation and recipient management process.

Recognizing Risk Factors

There are several factors to consider in determining a donor's risk of transmissible infection. OPOs and living donor recovery hospitals should consider the following when screening potential organ donors:

Geographic risks (including duration of time spent in a location)
- Birthplace of the potential donor
- Home country/region of the U.S., and prolonged residence outside home region, either recent or remote
- Close family members' countries of origin
- Donor hospital region
- Occupational or recreational travel to other countries and/or regions

- Occupational risks
  - Healthcare workers, veterinarian/animal care workers
  - Construction workers, landscapers, park rangers, and other outdoor workers
  - Peace Corps workers, international journalists
  - Current or previous military service, particularly outside the U.S.
  - Medical mission trips
  - Correctional workers
- Seasonal risks
  - Residence in/travel to warm weather climates with potential insect exposures
- Hobbies
  - Time living outdoors including camping, swimming in lakes, drinking stream water, insect exposures
  - Adventure sports
  - Gardening
- Significant animal exposure (wild and/or domestic)
  - Large numbers of cats or dogs or any unusual pets
  - Laboratory/research animals
  - Veterinarian/vet assistant
- Family members and close contacts with potential risk factors
  - Geographic or seasonal infections previously diagnosed in close family members or other contacts may predict risk for subclinical infection in the potential donor
- Personal history of seasonal or geographic infection in the potential donor, even if remote
- Deceased donor cause of death (if associated with signs/symptoms of infectious illness)

The organ donor population has become increasingly geographically diverse, reflecting the enhanced mobility and complex migration patterns of the general population. Therefore, it is not practical to list all the pathogens that have the potential for transmission through organ transplantation. Parasitic infections such as amebiasis, babesiosis, leishmaniasis, schistosomiasis, echinococcosis, and malaria, bacterial infections such as brucellosis and melioidosis, fungal infections such as paracoccidioidomycosis and talaromycosis, and viral infections such as Eastern Equine Encephalitis Virus have distinct areas of endemicity and may be transmitted through the organ allograft. In donors with a history of residence in developing countries or remote regions, unusual occupational exposure risks, or extensive travel, infectious disease (ID) consultation may be helpful as part of the pre-transplant evaluation for living donors or prior to organ acceptance for deceased donors. This guidance document does not replace consultation with ID.

Table 1 covers several common seasonal and geographically endemic infections that may be transmitted from organ donor to recipient.

Table 1: Common Seasonal and Geographically Endemic Infections in Organ Donors

Disease	Signs/Symptoms in Potential Donor	Known Risk Factors	Potential Testing for Deceased Donors	Potential Testing For Living Donors	Imaging that may be helpful
Histoplasmosis	Fever, night sweats, lymphadenopathy, cough, non-calcified pulmonary nodules or cavities	Residence in Midwestern or South-Central states along the Mississippi or Ohio River Valleys	-Urine and/or serum antigen enzyme immunoassay -Serology: complement fixation and/or immunodiffusion	-Urine and/or serum antigen enzyme immunoassay -Serology: complement fixation and/or immunodiffusion	Chest X-ray (CXR) or CT
Coccidioidomycosis	Fever, joint pains, cough, neck stiffness, headaches, pulmonary nodules or cavities, reticulonodular infiltrates	Residence in endemic areas of Washington state, the Southwestern United States, Northern Mexico, and parts of South & Central America	Serology: -enzyme immunoassay (preferred) -complement fixation -immunodiffusion -Urine or serum antigen testing	Serology: -enzyme immunoassay (preferred) -complement fixation -immunodiffusion -Urine or serum antigen testing	CXR or CT

Strongyloidiasis	Chronic abdominal pain, bloating, heartburn, intermittent diarrhea and constipation, dry cough, skin rashes, and/or eosinophilia, or could be entirely asymptomatic.	Soil exposure in tropical/warm climates. Walking barefoot or unprotected skin contact with human sewage or contaminated soil. Infection may persist for decades.	Serologic testing is required for all[2]	Donors could be tested by serology (preferred) and/or stool ova and parasite examination, specifically looking for *Strongyloides*.	None
Chagas disease	Most asymptomatic; symptomatic chronic infection may present with cardiomyopathy, cardiac conduction abnormalities, megaesophagus, megacolon	Born or resided in endemic areas of Mexico, South & Central America, child of woman who lived in endemic area, received blood transfusion in endemic area	Required by OPTN policy if donor is born in endemic country[3] Serology testing (See Chagas Guideline, Table 3)	Serology testing (See Chagas Guideline, Table 3)	None unless symptomatic with chronic Chagas disease
Tuberculosis	Fever, night sweats, weight loss, cough, recurrent pneumonia, exudative pleural effusion of unknown etiology, lymphadenopathy, non-calcified pulmonary nodules or cavities	Born outside U.S., prolonged residence outside U.S., homeless, alcohol or other substance abuse, jail/prison time, health care worker, known TB exposure	Positive tuberculin skin test (TST) or interferon gamma release assay (IGRA)**; Sputum/BAL AFB smear, culture, nucleic acid amplification, TB PCR; tissue AFB smear, culture, TB PCR **Deceased donors on high-dose steroids may have false-negative IGRA/TST	Positive tuberculin skin test (TST) or interferon gamma release assay (IGRA); sputum/BAL AFB smear, culture, nucleic acid amplification, TB PCR; tissue AFB smear, culture, TB PCR *refer to OPTN Policy 14	CXR, CT thorax, CT abdomen/ pelvis (renal TB)

[2] Pending policy implementation of *Improve Deceased Donor Evaluation for Endemic Diseases.*

[3] Pending policy implementation of *Improve Deceased Donor Evaluation for Endemic Diseases.*

West Nile Virus	Often asymptomatic; 20% develop acute febrile illness; <1% encephalitis, myelitis	Mosquito exposure, blood transfusion; risk varies by season & location	Nucleic acid test (NAT)	NAT	None

FUNGAL INFECTIONS

Histoplasmosis Guidance

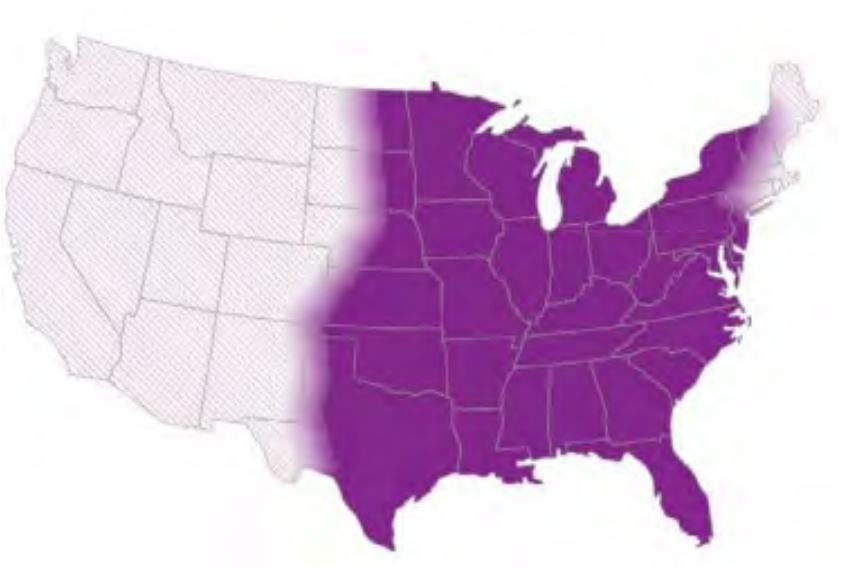
Background

Histoplasma capsulatum is a dimorphic fungus found throughout the world. It is endemic in the U.S. in the Ohio and Mississippi River Valleys and into the Midwest and South-Central states (Figure 1). In most cases, clinical signs of infection in immunocompetent patients are limited to the lungs, though many patients are asymptomatic. Immunocompromised patients may develop severe disseminated disease that is fatal without prompt diagnosis and treatment. Donor-derived histoplasmosis has only rarely been reported. In endemic areas, up to 75% of the population is infected with *Histoplasma capsulatum*; therefore, no further exposure risk factors need be elicited in residents of these areas.

Who Should be Screened

Living and Deceased Donors
Donors at higher risk of transmitting disease include those with recent infection or a prior history of known active histoplasmosis and should be screened. Potential donors with a history of pneumonia in the past three to six months where the clinical scenario was suspicious of histoplasmosis should also be considered for screening. Donors with signs, symptoms, or radiological findings consistent with active histoplasmosis (cough, fever, night sweats, weight loss, non-calcified pulmonary nodules/cavities, or lymphadenopathy) need a thorough medical evaluation including testing for histoplasmosis prior to organ donation. Even in endemic areas, universal screening of donors lacking any of the above characteristics is not likely to be productive. Potential donors with the sole finding of a calcified granuloma on chest imaging do not require further testing.

Figure 1: Centers for Disease Control and Prevention's (CDC) current estimate of *Histoplasma*endemicity in the United States[4]



[4] CDC. "More Information about the Estimated Areas with Blastomycosis ..." More information about the estimated areas with blastomycosis, coccidioidomycosis (Valley fever), and histoplasmosis in the United States. Accessed June 23, 2023.

Darker shading indicates areas where *Histoplasma* is more prevalent. Diagonal shading shows the potential geographic range of *Histoplasma*.

How to Screen

Living and Deceased Donors
In asymptomatic potential donors, screening should be conducted through urine and/or serum antigen enzyme immunoassays. Alternatively, serological testing can be used to screen those at risk for infection. Complement fixation and immunodiffusion testing are the most commonly performed tests. Complement fixation and immunodiffusion testing are the most commonly performed tests. Complement fixation titers of 1:8 and 1:16 may just indicate previous infection at low risk for transmission. Positive immunodiffusion testing is more concerning for the presence of viable organisms, particularly if a H band is present.

Management of Infected Living Donors

Potential living donors with clinical evidence of active histoplasmosis (fever, night sweats, lymphadenopathy, cough, non-calcified pulmonary nodules or cavities) or a serological pattern suggestive of active disease should receive treatment prior to organ donation. Living donors should be informed about the result and offered consultation with ID. For patients with histoplasmosis limited to the lungs, a reasonable approach would include six to 12 weeks of treatment, with resolution of clinical signs and symptoms of histoplasmosis. After treatment and resolution of antigenuria/antigenemia, the risk of donor-derived infection is likely low. Given that disseminated histoplasmosis is typically associated with other significant medical conditions, it is unlikely that a patient with a history of disseminated histoplasmosis would qualify for living organ donation.

Management of Recipients

Recipients of donors with a history of histoplasmosis may not require specific prophylaxis. Once transplant has occurred, consultation with ID is recommended. Clinical and laboratory monitoring for disease is a reasonable approach. Serial urine or serum antigen testing (every one to three months) for one year might identify donor-derived histoplasmosis prior to the development of clinical symptoms. Serological tests have low sensitivity after organ transplantation, and most solid organ transplant recipients with histoplasmosis have negative serological studies.

Infection Avoidance Between Testing and Transplant

In endemic areas, exposure to *H. capsulatum* may occur with many daily activities and is difficult to entirely avoid. Nonetheless, in the pre-donation period, certain activities (cave exploration, significant time in construction sites, exposure to bird droppings or bat guano, digging soil) should be avoided.

Coccidioidomycosis Guidance

Background

Coccidioides immitis and *Coccidioides posadasii* are dimorphic fungi endemic in arid and semi-arid climates in Washington State and the Southwestern part of the U.S. (Figure 2), Northern Mexico

https://www.cdc.gov/fungal/pdf/more-information-about-fungal-maps-508.pdf.

including areas along the U.S. border, and parts of Central and South America. The most common clinical syndrome is pneumonia often accompanied by joint pains, fatigue, and weight loss. Chronic fibrocavitary pulmonary disease may follow primary infection, and some infected persons have persistent symptomatic pulmonary nodules, reticulonodular disease, or cavitary disease. Immunosuppressed individuals may develop disseminated infection. Multiple cases of donor-derived coccidioidomycosis have been reported, often with poor outcomes.

Figure 2: CDC's current estimate of *Coccidioides* endemicity in the United States

[5]

Darker shading shows areas where *Coccidioides* is more likely to be present. Diagonal shading shows the potential geographic range of *Coccidioides*.

Who Should be Screened

Living and Deceased Donors

One study indicated that 2.1% of persons evaluated for living donation in an endemic region were seropositive, suggesting recent or active disease. Since many patients with transmissible coccidioidomycosis are asymptomatic and infection is widespread in endemic areas, some experts recommend screening as part of the routine evaluation of all potential donors who reside in endemic areas or who have recently resided or had prolonged stays in such areas. Persons with signs and symptoms consistent with coccidioidomycosis (fever, joint pains, cough, neck stiffness, headaches) or those with unexplained chest imaging findings (cavities, nodules, lymphadenopathy, reticulonodular infiltrates) warrant screening as well. Finally, it is reasonable to perform further screening on donors with a known history of coccidioidomycosis, as potential donors with persistently positive serologic studies are more likely to harbor viable organisms.

How to Screen

Living and Deceased Donors

[5] CDC. "More Information about the Estimated Areas with Blastomycosis ..." More information about the estimated areas with blastomycosis, coccidioidomycosis (Valley fever), and histoplasmosis in the United States. Accessed June 23, 2023. https://www.cdc.gov/fungal/pdf/more-information-about-fungal-maps-508.pdf.

In asymptomatic potential donors, serological tests (enzyme immunoassay, complement fixation, or immunodiffusion) may be combined with chest imaging. Patients with suggestive findings on imaging (non-calcified nodules, cavities, lymphadenopathy, reticulonodular infiltrates) may require sputum cultures or bronchoscopy with culture of lavage fluid, although sensitivity of cultures may be low. For prospective donors with normal imaging and negative serologies, the risk of donor-derived infection is likely low.

Management of Infected Living Donors

Potential living donors with evidence of active infection should be offered consultation with ID and require a thorough evaluation to determine the extent of the infection. Donation from actively infected donors should be deferred until treatment is complete and evidence of active infection (based on clinical, radiographic, and serological factors) has resolved.

Management of Recipients

Prophylaxis with antifungal medications active against *Coccidioides* species may be effective in preventing disease in recipients of infected donors. Fluconazole or itraconazole can be used as prophylaxis; fluconazole is more reliably absorbed and interactions with calcineurin inhibitors are less significant. Posaconazole and voriconazole are second-line options. Echinocandins or inhaled polyenes are not effective. Once transplant has occurred, consultation with ID is recommended. Whether additional prophylaxis is needed for recipients of donors who received adequate treatment for coccidioidomycosis in the past is unknown. While periodic post-transplant serological monitoring could be considered, the sensitivity of serological testing in immunosuppressed patients is likely low. Recipients should be closely monitored, when prophylaxis is discontinued, with periodic clinical, radiologic, and serologic assessments, especially in the first six to 12 months after cessation of prophylaxis.

Infection Avoidance between Testing and Transplant

For people living in endemic areas, completely avoiding exposure to *Coccidioides* is difficult to impossible. Highest risk activities include those that result in heavy inhalation of desert soil, particularly in the dry periods following the rainy season. Potential donors that develop pulmonary infection or illness characterized by fatigue, cough, and/or joint pain after initial screening may require repeat evaluation.

PARASITIC INFECTIONS

Strongyloidiasis Guidance

Background

Strongyloides stercoralis is a nematode (roundworm). Unlike other parasites, *Strongyloides* can replicate for decades within humans via an autoinfection cycle, resulting in chronic symptomatic or asymptomatic infections that can flourish in the setting of immunosuppression. There are an estimated 370 million infected people worldwide.

Strongyloides is most common in tropical, subtropical, or warm temperate climates, including the Caribbean, Mexico, South and Central America, Africa, Southeast Asia, Southern and Eastern Europe, and the Southeastern U.S. In the U.S., a prevalence of up to 6.1% has been reported in select populations, with a much higher prevalence of up to 46.1% in immigrant populations. Infection results primarily from exposed skin contact with soil that is contaminated with *Strongyloides* larvae. Activities that increase the risk of becoming infected include direct contact with contaminated soil (i.e., walking barefoot), unprotected skin contact with human waste or sewage, and occupations that increase contact with contaminated soil, such as farming and coal mining. Rural populations and those of a lower socioeconomic status are at higher risk.

Hyperinfection occurs in immunocompromised hosts and can lead to disseminated infection, with mortality as high as 85%. From 2009 to 2013, the CDC assisted in investigations of donor-derived strongyloidiasis in 11 recipients from seven organ donors and found 86% of the donors to originate from *Strongyloides* endemic areas. Prophylaxis with ivermectin was noted to be highly effective in preventing disease transmission in the CDC series and in another series reported by an OPO.

Who Should Be Screened

Living and Deceased Donors
Given the high mortality rate of donor-derived *Strongyloides* infection, and the efficacy, safety, simplicity and low cost of prophylactic therapy, universal screening for *Strongyloides* is recommended for all living donors and is required for deceased donors by OPTN Policy 2.9 pending implementation of *Improve Deceased Donor Evaluation for Endemic Diseases*[6]*,* and is recommended prior to implementation.

Donors with a personal history of previously treated *Strongyloides* infection should be at low risk for transmission, although repeat (new) infection after treatment can occur, and the autoinfection cycle could allow for subclinical persistence. Signs and symptoms include chronic abdominal pain, bloating, heartburn, intermittent diarrhea and constipation, dry cough, skin rashes, and/or eosinophilia, or persons can be entirely asymptomatic. Although transmission within families is unlikely, a family history should trigger screening given the likelihood of similar exposures.

How to Screen

Living and Deceased Donors
Screening is by serology or stool examination. Serology is required for deceased donors pending implementation of *Improve Deceased Donor Evaluation for Endemic Diseases*[7] and recommended for living donors. Serology is primarily an Immunoglobulin G (IgG) assay for antibodies to *Strongyloides*. The enzyme-linked immunosorbent assay (ELISA) is preferable because of its greater sensitivity (90%) and specificity (99%), compared with indirect fluorescent antibody (IFA) and indirect hemagglutination (IHA) tests. Antibody testing cannot differentiate between current and prior or treated infections; titers do not reliably decrease rapidly after treatment. The assays may produce false positive results in patients with filariasis and other nematode infections. Serology testing is commercially available, often with turnaround times of one to five days.

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[6] "Improve Deceased Donor Evaluation for Endemic Diseases," OPTN, Policy Notice, Accessed October 10, 2023, https://optn.transplant.hrsa.gov/media/lrxfreqj/dtac_endemics_policy-notice_june23bod.pdf.
[7] Ibid.

Stool testing is less sensitive than serology, as stools are positive only during larval shedding which can be intermittent and would be indicated when serological testing is unavailable or when serological findings are negative but clinical suspicion of disease is high. A single stool specimen has a sensitivity of only 15%–30%, although sensitivity increases to nearly 100% if seven consecutive daily stool specimens are examined in an expert laboratory, which may not be practical in the transplant setting. Intestinal endoscopy with biopsies may also diagnose *Strongyloides* infection, although it would not be used for routine screening.

For living donors, screening should be done with initial testing to allow time for subsequent treatment if necessary.

Management of Infected Living Donors

Living donors who test positive should be informed about the result and offered consultation with ID. Donors infected with *Strongyloides* may still donate. Living donors can be treated with ivermectin, with no further delay in organ transplant. Additional serologic or stool testing after treatment is not likely to be helpful.

Management of Recipients

Once transplant has occurred, consultation with ID is recommended. Recipients who receive organs from infected and untreated donors may be treated with ivermectin or albendazole. Ivermectin is well tolerated and is preferred (when available) due to superior efficacy. Only oral ivermectin is available in the U.S. There may be a drug interaction between ivermectin and the calcineurin inhibitors (tacrolimus and cyclosporine), therefore monitoring of drug levels is recommended.

Transplant centers should follow up on such pre-transplant test results and give prophylaxis to recipients if their donors were not previously treated. Prophylaxis and treatment doses of anti-parasitic medications in this setting are probably the same, although they have not been studied. Most cases of donor-derived strongyloidiasis occur several weeks to months after transplant, so centers should have adequate time to treat recipients before infection occurs. In cases in which there is insufficient time for test results to return and treatment to be given to donors, centers should plan for post-transplant treatment of the recipient.

People dually infected with Human T-Cell Lymphotropic Virus-1 (HTLV-1) and *Strongyloides* are more likely to develop severe cases of strongyloidiasis and are at higher risk for recurrence. It may be worthwhile to screen patients with *Strongyloides* infection for HTLV-1, so the treating clinicians are aware of the risk of increased disease severity and recurrence.

Patients from areas of Africa endemic for loiasis (primarily central and western sub-Saharan Africa) should be screened for *L. loa* microfilaremia, as administration of ivermectin to those with microfilaremia can precipitate life-threatening encephalopathy, known as the Mazzotti reaction.

Infection Avoidance between Testing and Transplant

In the absence of exposure, acquisition of acute infection would generally be rare in the several months between testing and transplant for most living donors, unless they travel to endemic regions and have significant soil exposure. Shoes should be worn in endemic areas to avoid contact with infected soil.

Chagas Disease Guidance

Background

Chagas disease is caused by infection with the protozoan parasite *Trypanosoma cruzi (T. cruzi*). It is estimated that eight million people are infected in the Americas, with over 300,000 infected individuals currently living in the U.S. Most infections were acquired in endemic regions of Mexico, South and Central America, where infection is transmitted by the bite of an infected triatomine bug. Infection can also be transmitted from an infected mother during the second and third trimester of pregnancy or rarely during childbirth, as well as through infected food or drink, and through blood transfusion and organ transplantation.

Most infections are acquired in childhood during residence in an endemic area. The acute phase of infection may be associated with a mild febrile illness and is often unrecognized. Parasitemia clears within eight to 12 weeks without treatment, but individuals remain chronically infected. Infection persists for the individual's life, with chronic disease developing in 20-30%, usually manifesting as cardiac or gastrointestinal disease. Chronic infection can be diagnosed through serologic tests for antibody to *T. cruzi*.

Blood donor screening in the U.S. beginning in 2007 identified confirmed infections in donors from 37 states and Puerto Rico, with 57% of all positive tests from California and Florida, areas with significant Mexican, Central and South American immigrant populations. Latent infection with *T. cruzi* can persist for decades, therefore organ donor screening of high-risk individuals using serology testing is utilized at some centers. Transmission of Chagas disease has been studied in 32 organ transplant recipients from 14 seropositive donors in the United States. Two of 15 (13%) renal transplant recipients had donor-derived infection; none of these were living donor transplants. Living organ donor transmissions have been reported in Mexico and South America.

Who Should Be Screened

Living and Deceased Donors
Deceased donors who were born in a country currently classified as endemic for Chagas disease by the CDC must be screened according to OPTN Policy 2.9 pending implementation of *Improve Deceased Donor Evaluation for Endemic Diseases*[8] and is recommended until then. Screening is recommended for living donors born in a country currently classified as endemic for Chagas CDC by the CDC as well.

Screening should also be considered for living and deceased donors in the following circumstances:

- Children of women born in endemic regions if their birth mother's serology is positive or unknown
- Donors who have resided in an endemic region for more than three months
- Donors who received a blood transfusion in endemic regions and those who have a previous diagnosis of Chagas disease
- Symptomatic donors who have chronic infection and may present with cardiomyopathy, cardiac conduction abnormalities, megaesophagus, megacolon

[8] "Improve Deceased Donor Evaluation for Endemic Diseases," OPTN, Policy Notice, Accessed October 10, 2023, https://optn.transplant.hrsa.gov/media/lrxfreqj/dtac_endemics_policy-notice_june23bod.pdf.

Countries currently classified as endemic for Chagas disease by the CDC:
Argentina
Belize
Bolivia
Brazil
Chile
Colombia
Costa Rica
Ecuador
El Salvador
French Guiana
Guatemala
Guyana
Honduras
Mexico
Nicaragua
Panama
Paraguay
Peru
Suriname
Uruguay
Venezuela

How to Screen

Living and Deceased Donors
Serology testing using an FDA licensed, approved, or cleared assay (see Table 2) should be performed on donors with risk factors for Chagas disease. Turnaround time for serology tests ranges from one to 10 days. Tests for parasitemia are not sensitive enough to detect chronic *T. cruzi* infection. Detectable antibody is usually present within a month of infection and remains present throughout the individual's life.

Table 2: Serological Tests Available for *T. cruzi Infection*

Test name, Manufacturer	Target Antigen	Test Format	Sample Type	FDA-cleared/approved use
Abbott Prism Chagas (T. cruzi [E. coli, recombinant] antigen)[9], Abbott Laboratories, Abbott Park, IL	*T. cruzi* recombinant antigens (FP10, FP6, FP3, TcF)	ChLIA[10]	Serum/plasma	Donor screening
ORTHO T. cruzi ELISA Test System Ortho-Clinical Diagnostics, Inc. Raritan, NJ	Whole cell lysate	EIA[11]	Serum/plasma	Donor screening, individual diagnostics
Chagatest ELISA recombinant v.3.0 [12]Wiener Laboratories S.A.I.C., Rosario, Argentina	Recombinant epimastigote and trypomastigote Proteins	EIA	Serum/plasma	Diagnosis, NOT donor screening test
Hemagen Chagas' Kit, Hemagen Diagnostics, Inc., Columbia, MD	Purified antigens from cultured *T. cruzi*	EIA	Serum	Diagnosis, NOT donor screening test
Abbott ESA Chagas Assay, Abbott Laboratories, Abbott Park, IL	*T. cruzi* recombinant antigens (FP10, FP6, FP3, TcF)	Enzyme Strip Assay	Serum/plasma	Supplemental test in donors who test positive with first-line assays, not approved for individual diagnosis

*Serologic testing may also be available through the CDC

Management of Infected Living Donors

Living donors who test positive should be informed about the result and offered consultation with ID. Confirmatory testing through a submission to the CDC or performance of at least two different FDA licensed, approved, or cleared antibody diagnostic tests should be performed. Infected donors may

[9] This test may only be available through local blood bank.
[10] ChLIA, chemiluminescence immunoassay
[11] EIA, enzyme immunoassay
[12] Preferred tests for initial donor screening

require further evaluation for chronic Chagas disease and may ultimately require specific treatment. Evaluation and treatment of these individuals should proceed in accordance with local guidelines, as the availability of confirmatory diagnostics and anti-parasitic therapy varies.

Management of Recipients

The risk of transmission of *T. cruzi* infection from an infected donor to an uninfected deceased kidney donor recipient has been reported to be between 13 and 18%. There are no data regarding living donor transmissions. It is reasonable to consider accepting donor organs from *T. cruzi* positive donors on an individual basis with informed consent and close monitoring of the recipient. Potential recipients of a *T. cruzi* positive donor organ should themselves be tested for the presence of *T. cruzi* antibody, particularly since they may share unrecognized risk factors with their potential living donor. If the recipient tests negative and the decision is made to proceed with the transplant, recipients must be counseled specifically about the transmission risk and the need for close monitoring post-transplant, with the potential need for anti-parasitic therapy that is FDA approved but may lead to side effects that may be difficult to tolerate.

Once transplant has occurred, consultation with ID is recommended to coordinate post-transplant testing. In the U.S., the CDC can assist with PCR and parasitemia testing. Incorporating a PCR testing platform into the post-transplant testing program is recommended, as molecular testing may be positive weeks before parasitemia is detected using standard screening.

PCR and parasitemia tests of peripheral blood should be performed using the following schedule:

- Weekly for the first three months post-transplant
- Every two weeks for the fourth post-transplant month
- Monthly thereafter until a minimum of six months post-transplant AND until net state of immunosuppression is at optimal post-transplant baseline with no evidence of infection or rejection
- More frequent monitoring is recommended any time the patient requires antirejection therapy

For access to testing of transplant recipients at risk for reactivation of Chagas, contact the CDC Division of Parasitic Diseases and Malaria at 404-718-4745 (business hours) or 770-488-7100 (nights and weekends) or via e-mail at parasites@CDC.gov.

Current therapy for Chagas disease is limited to benznidazole and nifurtimox (Lampit®, Bayer), both of which are partially metabolized via cytochrome P450 reductase and may increase tacrolimus and cyclosporine blood levels. Both drugs have potential adverse effects, but benznidazole is generally better tolerated and is given twice a day while nifurtimox is given three times a day.

Infection Avoidance between Testing and Transplant
Potential living donors should avoid prolonged travel to endemic regions, particularly rural areas with primitive housing or significant insect exposure. Consumption of uncooked food or drink from endemic regions should also be avoided.

BACTERIAL INFECTIONS

Mycobacterium Tuberculosis (MTB) Guidance

Background

Up to one-third of the world's population is infected with MTB; however, infection in the United States is much less common. Reported cases of MTB disease have been declining in the United States since 1992 with the majority of cases occurring in foreign-born persons. After initial infection with MTB, most people do not develop MTB disease; the infection disseminates throughout the body and remains dormant. This condition is called tuberculosis infection (TBI) (previously referred to as "latent tuberculosis infection"). In 2022, there were 8,300 reported TB cases[13] in the United States (a rate of 2.5 cases per 100,000 persons). Since initial infection does result in live MTB in many organs, tuberculosis can be transmitted via non-lung organs used for transplantation from donors who have never had clinical signs or symptoms of MTB disease.

Figure 3. World Health Organization Estimated Global TB Incidence Rates, 2021[14]

Who Should Be Screened

Living and Deceased Donors

Since TBI precedes the development of MTB disease, similar risk factors would be expected to be present. One difference is that since the rate of reactivation decreases with time from infection, donors with distant infection would still be at risk for transmission but at a lower risk for MTB disease. The most

[13] Provisional CDC data

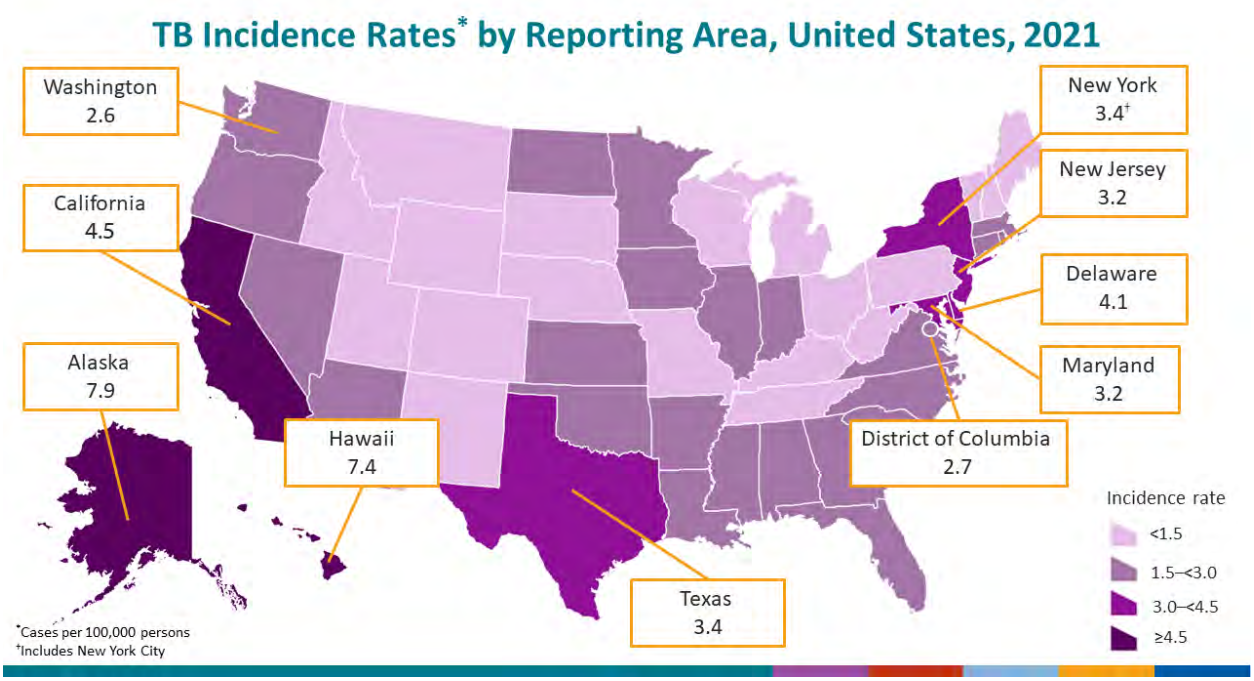
[14] WHO. "2.1 TB Incidence." World Health Organization, October 27, 2022. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022/tb-disease-burden/2-1-tb-incidence. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022/tb-disease-burden/2-1-tb-incidence.

powerful easily identifiable risk factor is place of birth with estimated risk of TBI of 18.7% among foreign-born persons in the U.S. as compared to 1.8% among U.S. born persons. Higher risk countries are identified by incidence per 100,000 population per year in Figure 3.

For individuals from lower risk regions, including the United States, the following factors should help OPOs and transplant programs make screening decisions:

- Close contacts of persons with infectious TB disease
- Those who spend significant time (greater than 3 months) in areas of the world with high rates of TB or those born in these regions (all but the lightest shaded area of Figure 4) including relief work in a country with high TB risk.
- History of non-medical injection drug use
- Persons who reside (or ever resided) or worked in institutional settings which resulted in increased risk of exposure to TB (hospitals, nursing homes, correctional facilities, other health care settings, homeless shelters)
- Radiographic evidence of prior tuberculosis on chest radiograph
- Symptoms such as fever, night sweats, weight loss, cough, recurrent pneumonia, exudative pleural effusion of unknown etiology, lymphadenopathy, non-calcified pulmonary nodules or cavities

Figure 4: TB Incidence Rates by Reporting Area, United States, 2021[15]



How to Screen

Living and Deceased Donors

While MTB disease can involve almost any organ and cause many syndromes (e.g., meningitis), a careful medical history and examination will likely identify most patients with MTB disease. TBI, by definition, is asymptomatic, and specific testing is required to identify patients with TBI. The current FDA-approved screening methods for TBI in the US include the tuberculin skin test (TST) and the interferon gamma release assays (IGRAs): QuantiFERON-TB gold in tube (QFT), and T-SPOT.TB. These tests do not differentiate TBI from MTB disease and may be negative during times of MTB disease. The TST test requires injection into the skin and a return visit in 48-72 hours to interpret the test. The IGRAs are blood tests and may show positive, negative, or indeterminate results.

Indeterminate results indicate that the controls did not work in that patient, and this result is more common in immunosuppressed patients. One advantage of the IGRAs is that patients who received a childhood BCG vaccine (very common outside of North America and Western Europe) are less likely to have a false-positive test with IGRAs than with the TST test, due to enhanced specificity of the *Mycobacterium tuberculosis* antigens used in the IGRA assays.

[15] CDC. "Health Disparities." Centers for Disease Control and Prevention, November 10, 2022. https://www.cdc.gov/tb/topic/populations/healthdisparities/default.htm.

Management of Infected Living Donors and Recipients

Table 3 outlines management of living donors with a history of active TBI and treatment of recipients of these organs. In all clinical scenarios, consultation with ID is recommended.

TABLE 3: Management of latent or history of active TB in living donors and recipients of these organs

Clinical Scenario: Living Donor	Risk for Transmission	Recommendation
History of TBI-treated appropriately	Lower	Monitor recipient clinically
History of TBI-treated insufficiently or not treated or treatment details not clear OR new diagnosis of TBI-positive TST or Interferon gamma release assay found during pre-transplant evaluation; evaluation finds no evidence of active TB	Moderate	Consider deferring transplant if possible until donor has taken some/all of chemoprophylaxis and consider chemoprophylaxis of recipient; monitor clinically.
Unexplained pulmonary apical fibrosis in donor without cavitation and without additional testing	Variable	Defer donation pending further evaluation.
History of MTB disease treated appropriately over two years ago	Lower to moderate	Monitor recipient clinically; consider cultures of previous TB sites if possible. Consider TB prophylaxis of recipient.
History of MTB disease-site remote from transplant (organ not being transplanted) treated appropriately within two years.	Lower to moderate	Monitor recipient clinically; consider cultures of previous TB sites if possible. Suggest chemoprophylaxis of recipient.
History of MTB disease-site remote from transplant (organ not being transplanted) treated insufficiently and/or with other than standard regimen Excluding disseminated or CNS TB.	Higher Increased risk if less than two years since active TB diagnosis.	Defer live donors until adequately treated; recommend cultures of previous TB sites prior to transplant if possible
History of renal MTB disease treated appropriately. (If not treated appropriately donation should be deferred until after appropriate treatment)	Moderate	Verify treatment; monitor clinically; recommend chemoprophylaxis for recipient; recommend cultures of previous TB site(s).

Management of Recipients of Deceased Donors

For recipients of an organ from a donor who is TST or IGRA-positive, had recent exposure to active TB, or had radiographic evidence of untreated TB should be considered for TBI therapy, following CDC guidance for anti-tuberculosis agents and durations. Once transplant has occurred, consultation with ID is recommended. Specific attention should be given to potential drug-drug interactions of TBI agents and immunosuppressive medications with careful monitoring of calcineurin inhibitors.

Infection Avoidance between Testing and Transplant

Potential living donors should avoid prolonged travel to endemic regions and behavioral exposures that increase risk if possible, including institutional settings which may result in increased risk of exposure to TB (hospitals, nursing homes, correctional facilities, other health care settings, and homeless shelters).

VIRAL INFECTIONS

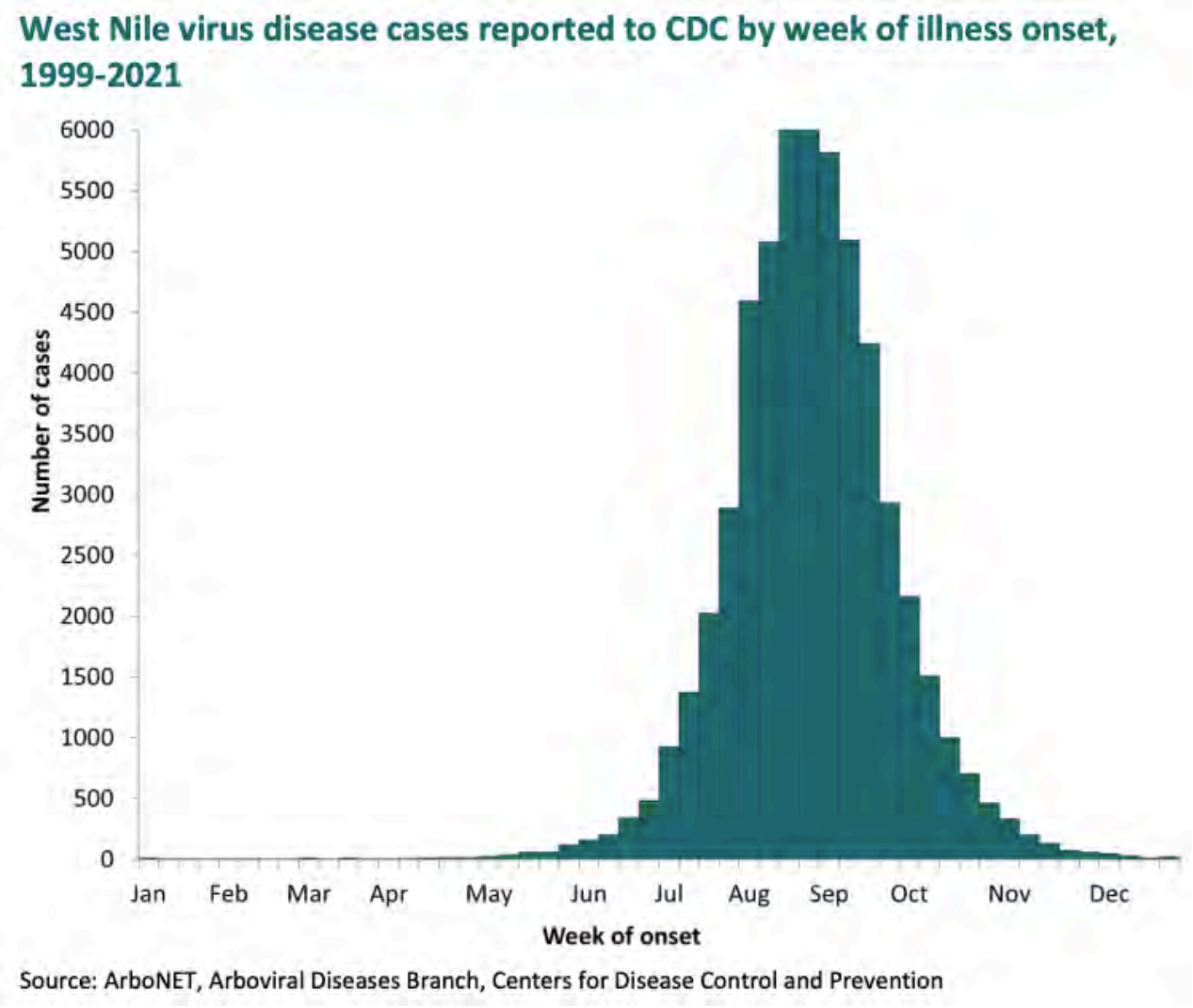
West Nile Virus (WNV) Guidance

Background

Epidemiology and pathophysiology

WNV is an RNA virus that spreads to humans primarily by the bite of infected mosquitoes, although multiple non-vector modes of transmission have been described, including blood transfusion, organ transplantation, breastfeeding, intrauterine, and laboratory exposure. Birds serve as a reservoir for WNV, and humans are a dead-end host for the virus. The virus was first detected in North America in 1999, and since then, has spread to all 48 contiguous U.S. states. The number of human infections varies significantly based on the region and year, with most transmission (as shown in Figure 5) occurring during the warmer months (July to October) when mosquitoes are most active, although warmer regions can have a longer season. While the majority of WNV infections are asymptomatic, about 20% of those infected may develop fever, and less than one percent develop neurological complications such as encephalitis or acute flaccid myelitis (involving the spinal cord). This means that even donors who do not display symptoms could still transmit the virus to recipients. While several treatments have been explored, there is currently no established treatment for WNV.

Figure 5: Months of typical WNV activity in the United States[16]



Who Should Be Screened

Living and Deceased Donors

Since the transmission of WNV is limited by geography and season, OPOs and transplant programs should consider certain factors when determining whether to perform laboratory testing on a potential donor. A positive test result obtained during a period of WNV inactivity is more likely to represent a false positive than when the test was performed during periods of higher activity. Any false positive result could result in unnecessary delays to transplant.

[16] CDC. "West Nile Virus Disease Cases Reported to CDC by Week of Illness Onset ..." West Nile virus cases reported to CDC by week of illness onset, 1999-2021. Accessed June 23, 2023. https://www.cdc.gov/westnile/resources/pdfs/data/WNV-Week-Onset-1999-2021-P.pdf.

Factors to consider in evaluating donors for possible WNV infection:

- Has human infection with WNV virus been recognized locally this WNV season?
- Has the donor travelled to an area with human WNV activity this WNV season?
- Has the donor ever been diagnosed with WNV fever or WNV neuroinvasive disease?
- Has the donor had an undifferentiated febrile illness within the current WNV season?
- Has the donor had significant mosquito exposure this WNV season?

Geographic and seasonal factors to consider.

Screening strategies for WNV in donors include universal year-round testing of all donors versus targeted testing during periods of human WNV activity. As the yield of testing during the winter months is likely low and given the potential for IgM to remain positive after resolution of the illness, year-round testing is discouraged unless programs are unable to manage the complexity of more targeted testing strategies. Targeted testing strategies could include testing during a pre-determined timeframe, or testing donors only during times of human WNV activity in the area where the donor lives or has traveled (i.e., triggered strategy).

Triggering strategies can involve communicating with local blood collection organizations and determining whether they have shifted from minipool to individual donation (ID)-NAT screening, indicating that a WNV-reactive donor has been identified within a 50-mile radius of the triggering zip code. Another method involves using WNV human and non-human surveillance data collected by state and local health departments. Alternatively, testing could begin each year during the local WNV transmission season as determined by historical data (typically July through October, or longer intervals in warmer regions).

Given that human WNV disease incidence varies greatly from year to year and even county to county, targeted testing based on real-time measurement of local WNV activity at local blood banks might be the most cost-effective strategy and will reduce the number of false positives. This strategy is, however, more complex and time-consuming than a fixed seasonal strategy. Some institutions may already be using a local or regional blood bank testing lab to test other material (e.g., peripheral stem cells used in stem cell transplantation). In contrast, the strategy of testing during a defined time period regardless of local WNV activity would be simpler to implement, but both costs and false positive rates would be expected to be higher. **Table 4** describes the advantages and disadvantages of different testing strategies.

Table 4: Advantages and Disadvantages of Different Testing Strategies

	Year-round testing (1)	Seasonal testing (2)	Triggered testing (3)
Ease of implementation	Easy	Intermediate	Difficult
Positive predictive value	Lower during periods of human WNV inactivity	Intermediate depending on level of human WNV activity	High
Cost effectiveness	Least	Intermediate	Most

1. This strategy is not recommended.
2. Typically July through October, but time period should be guided by local historical WNV data, in consultation with state and local health departments
3. Testing triggered by switch from minipool to individual blood donation-NAT testing in zip codes of residence of donors. Testing stops when WNV activity no longer noted and blood banks switch back to minipools. Routine communication with local blood banks is required.

How to Screen

Living and Deceased Donors

To screen for WNV, healthcare professionals use NAT and IgM serologic tests. Currently, there are two FDA-licensed NAT donor screening assays; these are routinely performed at blood banks or some reference labs but are not commonly available in hospital laboratories. Serologic tests which rely on the response of the immune system to infection with WNV, particularly the IgM assay performed on serum and cerebrospinal fluid, are commonly used to diagnose neuroinvasive WNV. IgM is detectable for a median of about five months after infection but may persist longer, even years after infection, and is not used in blood donors to screen for WNV, although it may be performed for use in donor counseling. IgG typically remains positive for life and would not be useful to routinely screen for WNV. Table 5 describes the characteristics of NAT and IgM testing.

Table 5: Tests that could be used to screen for WNV infection

	Nucleic Acid Tests (NAT)(1)	IgM (serology)(2)
Available Tests	Procleix West Nile Virus Assay COBAS TaqScreen West Nile Virus Test	Various
FDA licensed for organ screening	Yes	No
Availability	Blood bank testing labs Reference labs	Reference labs Commercial labs State public health labs
False positive rate	Low	Likely higher than NAT, but not evaluated for donor screening
Indicates active infection	Yes	Remains positive for median of five months (up to seven years documented); active infection may have cleared
Required for blood donor screening	Yes	No

1. Should be used as part of any testing strategy
2. Consider in combination with NAT testing but will increase false positive rate

Deceased donors

It is advisable to screen deceased donors during months of regional WNV activity. WNV NAT testing is a viable option, but the results may not be available before transplantation. It is important to note that WNV transmission has occurred in donors who tested negative on NAT, and that there is potential for false positive NAT test results if protocols are not in place to improve specificity, as are used by blood collection organizations, or if testing is performed outside of the WNV transmission season, decreasing the pretest probability.

In cases involving deceased donors, the feasibility of conducting WNV testing within a required timeframe is uncertain. As such, the Committee advises against proceeding with donors who satisfy any of the following criteria: (1) a confirmed WNV infection, (2) a positive WNV NAT test result, ideally meeting a threshold signal-to-cutoff ratio or verified by repeat testing as recommended by the manufacturer, or (3) clinical manifestations of meningitis, encephalitis, or flaccid paralysis of indeterminate origin, particularly if they originate from regions with documented WNV activity.

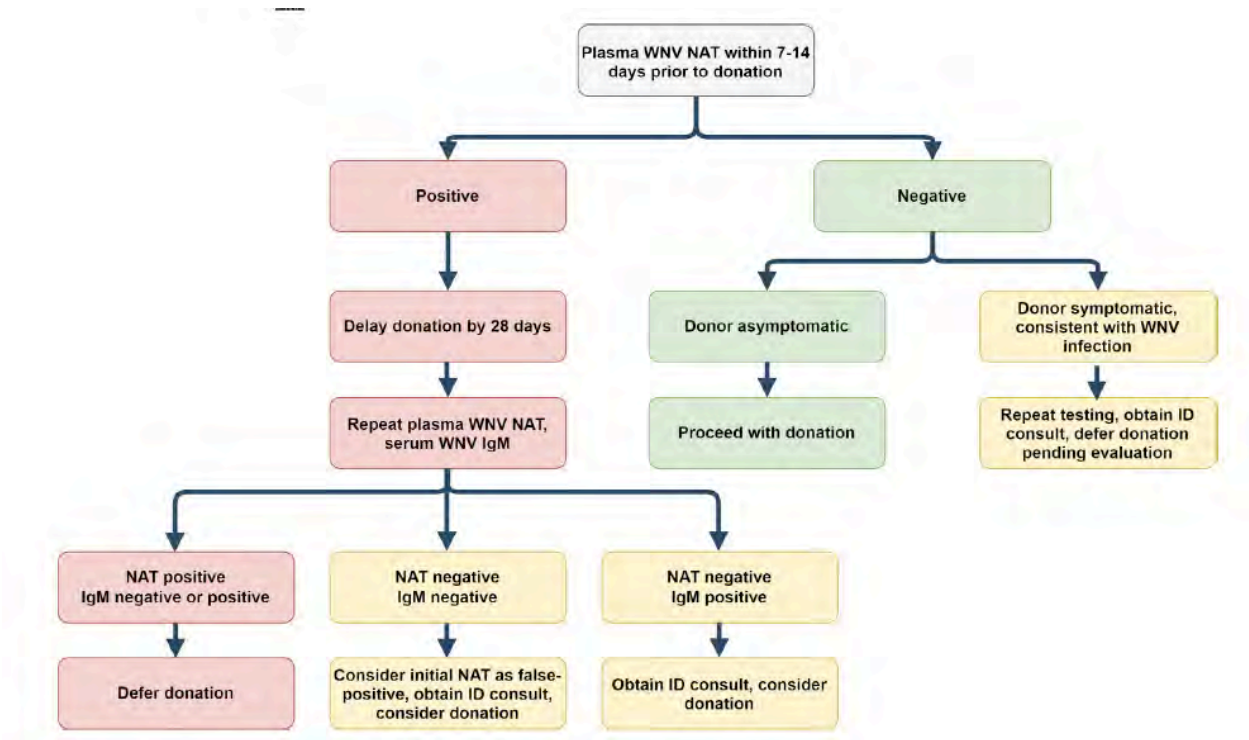
Living donors

Living donors should be screened with WNV NAT within seven to 14 days of donation.

Management of Infected Living Donors

Living donors who test positive should be informed about the result and offered consultation with ID. Although no studies have examined organ donation after WNV infection, we suggest postponing donation for a minimum of 28 days in living donors, after which NAT and IgM testing should be performed. If negative, it is likely that the initial NAT test was a false positive, and organ donation can be considered. If the NAT is negative but IgM is positive, this likely reflects viral clearance and organ donation can be considered. However, if the NAT remains positive, organ donation should be postponed. (Refer to Figure 6 for additional information).

Figure 6: Living donor screening recommendations for WNV[17]



Management of Recipients

Development of symptoms compatible with WNV disease within the first several weeks of transplant (and up to six weeks, since transplant recipients can have prolonged incubation periods with WNV infection) should prompt testing in the recipient. There are currently no specific medications available for the treatment of WNV infection. Once transplant has occurred, consultation with ID is recommended.

Infection Avoidance Between Screening and Transplant

We advise potential living donors to take measures to prevent mosquito exposure during periods of mosquito activity, such as wearing loose-fitting, long sleeve shirts and pants, using EPA-registered insect repellent, and avoiding outdoor activities during dawn and dusk when mosquitoes are most active. Further, a potential living donor should report febrile illnesses to his or her transplant center. WNV diagnostic testing should be performed if clinical evaluation suggests the possibility of WNV infection in the potential living donor.

[17] Anesi, JA, Silveira, FP; the AST Infectious Diseases Community of Practice. Arenaviruses and West Nile Virus in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019; 33:e13576. https://doi.org/10.1111/ctr.13576

SHARING INFORMATION

Recommendations for Sites Participating in Paired Organ Exchanges

Transplant hospitals participating in organ exchanges should consider sharing their protocols for screening donors for seasonal and geographically endemic infections in addition to related test results. This will provide recipient centers more information about the donor screening process at the donor organ center.

When to Report a Potential Donor-Derived Transmission Event

If the recipient is suspected to be at risk for disease transmission either by the OPO or a transplant center, a potential donor-derived disease transmission event should be reported to the OPTN Improving Patient Safety Portal per OPTN Policies *15.4 Host OPO Requirements for Reporting Post-Procurement Test Results and Discovery of Potential Disease Transmissions* and *15.5 Transplant Program Requirements for Communicating Post Transplant Discovery of Disease or Malignancy.* This promotes prompt intervention for other recipients of the same donor's organs.

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