Title

Donor-derived Viral Infections in Liver Transplantation.

Journal

Transplantation, 102(11)

Authors

Nam, Hannah

Nilles, Kathy

Levitsky, Josh

et al.

Publication Date

2018-11-01

DOI

10.1097/TP.0000000000002326

Peer reviewed

Published in final edited form as:

Transplantation. 2018 November ; 102(11): 1824–1836. doi:10.1097/TP.0000000000002326.

Donor-derived Viral Infections in Liver Transplantation

Hannah Nam, MD[1], **Kathy M. Nilles, MD**[2], **Josh Levitsky, MD**[3,4], **Michael G. Ison, MD**[1,4]

[1]Division of Infectious Diseases, Northwestern University Feinberg School of Medicine, Chicago, IL.

[2]Division of Gastroenterology and Hepatology, University of Colorado School of Medicine, Aurora, CO.

[3]Gastroenterology and Hepatology, Northwestern University Feinberg School of Medicine, Chicago, IL.

[4]Organ Transplantation, Northwestern University Feinberg School of Medicine, Chicago, IL.

Abstract

Donor-derived infections are defined as any infection present in the donor that is transmitted to 1 or more recipients. Donor-derived infections can be categorized into 2 groups: “expected” and “unexpected” infections. Expected transmissions occur when the donor is known to have an infection, such as positive serology for cytomegalovirus, Epstein Barr virus, or hepatitis B core antibody, at the time of donation. Unexpected transmissions occur when a donor has no known infection before donation, but 1 or more transplant recipients develop an infection derived from the common donor. Unexpected infections are estimated to occur in far less than 1% of solid organ transplant recipients. We will review the epidemiology, risk factors, and approaches to prevention and management of donor-derived viral infectious disease transmission in liver transplantation.

Liver transplantation is the treatment of choice for end-stage liver disease and hepatocellular carcinoma. Currently, the demand for liver transplantation greatly outweighs the number of organs available; over 1000 patients die while awaiting liver transplantation annually (range 836–1914 deaths per year). Due to the imbalance in supply and demand, significant interest has resulted in implementing strategies to expand the donor pool. One such method is the use of organs from Public Health Service (PHS) defined increased risk donors.[1]

To better inform which donors with potential or known infection can safely be used, global organ vigilance systems, such as the Organ Procurement and Transplant Network (OPTN)/ UNOS ad hoc Disease Transmission Advisory Committee and the French Agence de la Biomedicine have been established. Given the growing pool of data, organ-specific details and risk of disease transmission can now be assessed. Donor-derived viral infections in liver transplantation will be reviewed below.

Correspondence: Michael G. Ison, MD, Divisions of Infectious Diseases and Organ Transplantation, Northwestern University Feinberg School of Medicine, 645N Michigan Avenue Suite 900, Chicago, IL 60611. (mgison@northwestern.edu).

Both have made substantial contributions in gathering information necessary in drafting the article, participated in writing the article, and revised it critically for important intellectual content. J.L. and M.G.I. have revised the article critically for important intellectual content and gave final approval of the version to be submitted, as well as any revised versions.

H.N. and K.M.N. are co-first authors.

DEFINITION OF DONOR-DERIVED INFECTIONS

Donor-derived infections are defined as any infection present in the donor that is transmitted to 1 or more of the recipients. A variety of pathogens can be transmitted by the transplanted organ (Table 1). Donor-derived infections can be categorized into 2 groups: “expected” and “unexpected” infections. Expected transmissions occur when the donor is known to have an infection, such as positive serology for cytomegalovirus (CMV), EBV, or hepatitis B core antibody (HBcAb), at the time of donation.[2] Unexpected transmissions occur when a donor is not known to be infected before donation, but 1 or more transplant recipients develop an infection derived from the common donor.[2] Unexpected infections are estimated to occur in less than 1% of solid organ transplant (SOT) recipients.[3] Donor-derived infections are suspected when clusters of infections sharing unusual clinical symptoms occur among recipients sharing a common donor.

The reporting of suspected or documented donor-derived infections is required in the United States by OPTN Policy 15.4.[1] Reporting of such transmissions generally remains voluntary in most other countries. Currently, the United States, Australia, France, Italy, and Eurotransplant have formal organ vigilance systems for collecting, organizing, and analyzing the reports of potential disease transmissions.

RISK MITIGATION THROUGH DONOR SCREENING

Donor screening usually identifies donors with exposure and often latent infection with a range of potentially transmissible viruses. Most organ procurement organizations (OPO) screen donors by serology for human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), CMV, and EBV; a minority of OPOs screen for other viral infections, including human T lymphotropic virus (HTLV), human herpesvirus (HHV)-8, West Nile virus (WNV), and Zika virus. Further, such screening may be accomplished by detection of antibodies (serology) or direct detection of the virus itself (antigen detection or nucleic acid testing [NAT]/polymerase chain reaction [PCR]).

Serologic testing detects the donor’s immune response to an infection, which may take several weeks to develop. As such, donors tested before their development of antibodies against the infection will have a false-negative test. This results in the “serologic window” (see Figure 1). Donors in the serologic window may transmit infection from the donor to recipient despite negative serologic testing. Further, hemodilution from blood transfusion or large volumes of intravenous fluids may also result in false-negative results and result in unexpected disease transmissions.[4] Finally, all tests have a low rate of false-negative testing that may also result in rare transmission of infection despite negative serologic testing.

Direct detection of the virus through antigen detection or NAT is often used to overcome many of these problems, particularly in donors with recognized risk factors for such transmittable infections. Although the interval between initial infection and detection of the virus in the blood via NAT is much shorter than for serology testing, the “eclipse period” is defined as the time when a donor may be infected, but the virus is not detectable in the blood (see Figure 1). For hepatotropic viruses, such as hepatitis B and C virus, liver transplantation

poses the most significant risk of transmission in patients in the eclipse period, as discussed below.

GENERALLY EXPECTED DONOR-DERIVED VIRAL INFECTIONS

The viruses described below are predictably associated with transmission to donors, although unexpected transmissions can occur. Standardized approaches exist to reduce transmission, and these measures generally result in excellent outcomes.[5]

Cytomegalovirus

Cytomegalovirus is the most common viral pathogen in transplant recipients despite effective antiviral therapies.[6] Cytomegalovirus is ubiquitous, with a seroprevalence of 60% in the United States,[7] and up to 100% in developing countries.[8–10] The risk is greatest in naïve recipients of organs from CMV-infected donors (D+/R− transplants); a more intermediate risk is recognized in seropositive recipients (D±/R+).[6,11,12] The lowest risk is in the D−/R− population, although CMV may occur in such settings due to false-negative serologic testing or de novo acquisition posttransplant, typically through blood transfusions or posttransplant exposures.[6,12]

In SOT recipients, CMV infection can present as asymptomatic viremia or progress to tissue invasive disease if left untreated.[13] Up to 70% of tissue-invasive CMV disease in liver transplant recipients manifest as gastrointestinal disease. CMV can also cause hepatitis and graft injury.[11]

Cytomegalovirus is most commonly diagnosed by NAT.[12] Definitive diagnosis of tissue-invasive disease relies on detection of CMV in the tissue specimen, except in CNS disease and retinitis, generally by using immunohistochemical staining of the biopsy material from all sites except CNS and retina. Patients with gastrointestinal disease may have undetectable or low viral load values in peripheral blood samples, and endoscopy with biopsies may be required to diagnose CMV disease.[14]

Approaches to prevention of CMV include universal prophylaxis, virological monitoring and preemptive treatment, and the hybrid approach.[12] All have been demonstrated to effectively reduce CMV disease.[12] Multiple antiviral agents are currently available for the treatment of CMV, whereas immunotherapy and novel antivirals are under investigation for SOT recipients.[15,16] Details of these options are reviewed elsewhere.[1,6,12,17–19]

Epstein-Barr Virus

Epstein-Barr virus is a herpesvirus that only affects humans. In developing nations, seroprevalence can be higher than 90% before the age of 5 years.[20] After transplantation, EBV seronegative individuals are at significant risk for primary acquisition of EBV, which in turn is associated with an increased risk of development of posttransplant lymphoproliferative disorder (PTLD). The EBV genome is found in over 90% of B-cell PTLD occurring within the first year of solid organ transplantation.[21]

Epstein-Barr virus can also present as hemolytic anemia, hemophagocytosis, and thrombocytopenia.[5] In liver transplant patients, EBV has been linked to hepatitis and subsequent liver failure as well.[22] Hepatic involvement of PTLD should be considered in the evaluation of early liver dysfunction after transplantation.[3]

Posttransplant lymphoproliferative disorder encompasses a diverse spectrum of disease states including polyclonal and monoclonal hyperplasia, B and T cell neoplasms, and classic Hodgkin lymphomas.[23,24] The risk of early-onset PTLD (<1 year after transplant) is associated with young age, an EBV seronegative recipient receiving an organ from a seropositive donor (D+/R−), persistent low-level EBV viremia, lymphocyte-depleting antibody therapy, and allograft involvement.

Typically, high-risk patients are screened at regular intervals (every 2–4 weeks for the first 3–6 months) although there are no guidelines for universal monitoring. Such practice is more common at pediatric than adult centers.[25] If viremia is persistent or rising, immunosuppression is typically reduced initially with additional interventions, including empiric use of rituximab for replication that persists despite reduction in immunosuppression.[25,26] There is no clear role for empiric antiviral use. Ultimately, the diagnosis and staging of PTLD require tissue histopathology and oncological consultation.[27]

Hepatitis B Virus

Hepatitis B virus is widely prevalent with approximately one third of the world population having current or previous infection,[28,29] and thus the proportion of donors with HBcAb positivity is substantial; up to 57% in Asia and 2% to 10% in the United States.[30] Management of HBV transmission risks is critical for safely expanding the donor pool. Vaccination, prior exposure, and active infection can be distinguished via DNA testing and serology, which provides insight into the risk of disease transmission (see Table 2).[31]

Patients with prior exposure to HBV (positive HbcAb) have lifelong hepatocyte infection due to covalently closed circular DNA (cccDNA) in the hepatocyte nucleus that cannot be cleared by the host immune response.[32] Even HbcAb-positive donors with negative serum HBV DNA can transmit HBV to the recipient.[31] In the United States, all organ donors are tested for surface antigen (HbsAg) and HbcAb.[33] Potential living kidney or liver donors are also tested for surface antibody (hepatitis B surface antibody [HbsAb]).[34] In deceased donation, additional testing (ie, HbsAb, HbcAb IgM, HBV DNA) can be performed at the discretion of the OPO. Nucleic acid testing for HBV DNA reduces the window period of acute infection from 44 to 22 days.[3] Negative NAT results are not fail-proof as the donor may have eclipse period infection or latent HBV (ie, HbcAb alone donor).[35–43]

Approach to the Isolated HbcAb-positive Donor—In donors who are HbsAg negative and HbcAb positive, transmission of HBVis expected, and preventative approaches with antiviral treatment and/or hepatitis B immune globulin (HBIG) can minimize the risk of disease transmission.[41,44–48] The risk of infection from these donors is significantly higher in liver rather than nonhepatic transplants.[31,49] Without prophylaxis, 1 study demonstrated that nonimmune liver recipients (HbsAb negative) have the highest rates (77%) of HBV infection from HbcAb-positive donors.[50] In vaccinated recipients (HbcAb negative, HbsAb

positive), HBV transmission can rarely occur. For recipients who had isolated HbcAb positivity, transmission occurred in 13%. No HBV transmission occurred in naturally immune (HbcAb positive, HBSAg negative, HbsAb positive) recipients. Another review of 140 liver recipients noted similar transmission rates, although 3 (4%) of 70 naturally immune recipients had viral transmission.[44]

Recent guidelines advocate for HBV vaccination in all organ transplant candidates, preferably in the pretransplant setting when the vaccine is most effective.[51–54] Until 2017, there were 3 available HBV vaccines: Energix-B, Recombivax HB, and the combined hepatitis A virus (HAV) and HBV vaccine, Twinrix. For such vaccines, higher doses of vaccine (40 μg) are required in patients who are immunosuppressed, posttransplant, or on hemodialysis.[31,51] Transplant recipients vaccinated with any of these vaccines should have HbsAb titers checked; decreasing titers may no longer be protective in the setting of immunosuppression.[55] Recently, HEPLISAV-B vaccine (Dynavax) was licensed as the only adjuvanted HBV vaccine.[56] It can be given in 2 doses separated by 1 month with improved vaccine responses compared to traditional, unadjuvanted vaccines. Accelerated vaccination for HBV, using high dose (40 μg) on days 0, 7, and 28, allows for 3 doses of traditional vaccine to be given, but has shown lower immunogenicity compared with traditional vaccine schedules.[51]

Current guidelines also recommend that recipients of organs from isolated HbcAb+ donors receive prophylaxis with antivirals. Hepatitis B immune globulin is no longer needed in the era of effective antivirals.[31,34,42,47] Vaccinated liver transplant recipients should receive antiviral prophylaxis for at least 1 year, and if the levels of HbsAb are greater than 10 IU/mL at 1 year, withdrawal of prophylaxis can be considered.[31] Prophylaxis is recommended indefinitely in patients who are HbsAb negative and HbcAb negative. For liver recipients who are naturally immune (HbcAb positive and HbsAb positive), prophylaxis is not generally required. In all liver recipients, HBV DNA and /or HBSAg should be monitored every 3 months for the first year and every 3 to 6 months indefinitely.[31] Prophylaxis is suggested if rituximab is given to recipients who do not have preexisting immunity.[57,58]

Approach to Use of HbsAg or HBV NAT-positive Donors—Donors who are HbsAg or HBV NAT positive are infrequently used out of safety concerns. Active HBV infection leads to unacceptably high rates of HBV transmission to the recipient. When used, these grafts are typically donated to recipients with active HBV infection themselves or after meticulous informed consent for urgent situations.[31,42] Any liver graft from a donor who is HbsAg positive should be evaluated for histological evidence of liver disease before transplantation. In liver transplant recipients, without prophylaxis, HBV infection occurs in nearly 100% of all recipients of HBSAg-positive donors.[59] Current guidelines recommend any organ recipients from HbsAg-positive donors receive indefinite prophylaxis with entecavir or tenofovir.[31] Additionally, if the recipient's HbsAb titer is low, HBIG can be administered as well. Hepatitis B virus DNA should be monitored every 3 months for at least the first year after transplant, and thereafter every 3 to 6 months indefinitely. Management of posttransplant HBV is typically with antivirals and HBIG per local center guidelines.[31]

Transmission of HBV through the use of HBV-positive donor vessels has occurred,[60] and thus, current OPTN policy precludes the storage of extra donor vessels that are HbsAg or HBV NAT positive.[61]

Hepatitis C Virus

Hepatitis C virus affects more than 130 million people globally and is the most common indication for liver transplantation in the United States. The newer direct-acting antiviral agents (DAAs) have revolutionized the treatment of HCV. The high efficacy (cure rates, >95%) and minimal side effect profile of DAAs make treatment of HCV simpler and more palatable than interferon-based regimens. In addition, SOT recipients with preexisting HCV can be successfully treated with DAAs before or after transplantation.

Testing of donors for HCV traditionally was limited to serology (anti-HCV antibody), the presence or absence of which labeled a donor HCV positive or negative.[62] However, window period transmissions (during which HCV antibody is negative) occurred. Antibody status does not account for either spontaneous viral clearance or cure after treatment. Therefore, in 2014, OPTN policy mandated that in addition to HCV antibody all donors must also undergo HCV NAT.[33,62] Use of NAT not only reduces the likelihood of missing a window period infection but also helps to discriminate between a viremic donor and ones who have either spontaneously cleared the virus or achieved cure after treatment. The most important exception to NAT is testing during the eclipse period when the virus is still undetectable. Donors with active infection (NAT positive and anti–HCV positive) clearly represent a risk of potential donor-to-recipient transmission. In contrast, patients who are NAT negative and anti–HCV positive have prior HCV exposure but no current infection (either treatment cure or spontaneous clearance), or possibly have a false-positive anti-HCV. Those who are NAT positive and anti–HCV negative may have acute infections in the window period, or possibly false-positive NAT. The term “HCV-viremic donor” has been proposed rather than “HCV-positive donor” to more precisely reflect the screening test results and to more accurately identify the donors with documented active infection.[62]

Hepatitis C virus transmission from donors can be either unexpected or expected. Unexpected transmission occurs in NAT-negative donors, and is most likely when donation occurs in the eclipse period. Two studies have looked at the residual risk of HCV; the risk of undetected infection is dependent on the interval between the last risk behavior and testing, as well as the specific behavior in question.[63,64] The donor with the highest residual risk, an active injection drug user, would have up to 3% residual risk of undiagnosed HCV if the NAT was done within the eclipse period (ie, 5–7 days after last risk behavior)[65] and 0.32% residual risk with negative NAT performed outside eclipse period[64] (see Table 3).

There have been a number of cases of unexpected donor-derived HCV transmission involving liver and nonliver transplants.[66–68] Donors in these cases were NAT negative and anti-HCV negative but increased-risk donors; in some cases, donor HCV was detected in splenocytes or lymphatic tissue.[68] Presumably, donation occurred during the eclipse period. These cases highlight the limitations of donor screening and the need for early screening of recipients of organs from PHS increased risk donors. Notably, all infected recipients were NAT positive, HCV antibody negative, which illustrates the need to use

PCR-based testing of recipients. Further, the data suggest that PCR will be positive relatively quickly posttransplant, highlighting the importance of early screening within the first month posttransplant.

In contrast to unexpected transmission, expected transmission of HCVoccurs when the donor has known active infection as documented by positive NAT testing, either with or without positive anti-HCV. Traditionally, HCV-“positive” organs (previously defined only by positive anti-HCV) were only transplanted into HCV-positive recipients.[62] Ample outcomes data support the safety of this practice in liver recipients, with no differences in graft or patient survival if the donor liver has no greater than stage 2 fibrosis.[69–77] Although virus may be transmitted, specific genotyping is often not repeated to confirm transmission, as cases of mismatched geno-types are not as relevant in the DAA era. Recent data suggest that only half of HCV seropositive organs have detectable viremia at donation.[73,78,79]

The newfound ease of treatment of HCV with DAAs pretransplant and posttransplant has generated a revival of interest in use of donors with either positive HCV NAT or positive anti-HCV antibodies. With broader use of DAAs in the general population, there will be significant growth in the number of donors who are anti-HCV positive, NAT negative. There may also be more donors who are HCV NAT positive due to the ongoing opioid epidemic.[62]

There is very limited long-term data on outcomes of HCV-negative recipients of liver and nonhepatic grafts that receive known HCV-positive (either anti-HCV or NAT positive) organs, as this practice had been previously avoided.[62] More centers are considering using anti–HCV-positive, NAT-negative donors for liver and nonliver transplants due to the presumed low risk of disease transmission, as well as the availability of highly effective DAAs. Limited evidence of safe donation from anti–HCV positive, NAT-negative donors has been demonstrated by 3 case reports, 2 in kidney recipients, and the third in a living liver donor who had achieved HCV cure years before donation.[80–82] No disease transmission to the recipients occurred in these cases. Further, there is a growing body of data among transplant recipients who have been successfully treated with DAAs posttransplant without relapse of infection. As such, donors who are NAT negative, anti–HCV positive are thought to represent an exceptionally low risk of donor-derived HCV transmission unless they have ongoing risk factors for acquisition of new HCVinfection.

Some have raised safety concerns of this practice in light of reports of “occult” HCV, in which RNA is still present in hepatocytes despite negative serum RNA.[83,84] These had previously been deemed of unclear clinical significance in the absence of known transmission of infection and a very large body of data that liver recipients treated both before and after transplant did not develop relapsed disease at a higher rate that patients without immunosuppression.[62] Four (16%) of 25 HCV-negative recipients of increased risk donors with active drug use who were HCV antibody positive, NAT negative developed HCV RNA-emia posttransplant.[85] While the authors questioned whether this transmission was the result of chronic, “occult” HCV infection in the liver despite negative NAT, window period infection is far more likely. Such donors with immediate injection drug use before donation were likely reinfected with HCV after previous clearance and result in an eclipse period transmission. As of now, this finding should not prevent other centers

from using anti–HCV-positive, NAT-negative donors, but data on these cases should be collected to confirm the safety of this approach. Further, this report highlights that donors with known risk factors represent a true risk, and when used, recipients should undergo early posttransplant PCR-based screening for transmission to allow early therapy.

At the other end of the spectrum is the intentional use of NAT-positive organ donors into NAT-negative recipients, which is not prohibited by OPTN policy. Although the experience with such HCV D+/R− transplant is limited, and mostly involving kidney and lungs, protocols exist to study this in all organs. The limited data suggest that HCV D+/R− can safely be performed with early use of DAA at the time of or early posttransplant.[62,86] Given the limited data on safety and questions about the ability to deliver DAAs posttransplant, as well as variation in insurer practices, a recent consensus conference on the topic recommended to obtain meticulous informed consent and proceed only under institutional review board-approved research protocols.[62] Data from ongoing trials will be helpful to mitigate the ethical, safety, and cost concerns of this practice.

Finally, as in HBV, transmission of HCV through the use of HCV-positive donor vessels has been described.[60] Current OPTN prohibits the storage of extra donor vessels that are HCV antibody or NAT positive.[61]

UNEXPECTED DONOR-DERIVED VIRAL INFECTIONS

Unexpected donor-derived viral infections reported include HAV, hepatitis D virus (HDV), hepatitis E virus (HEV), HIV, HTLV I/II, HHV-6,7, and 8, WNV, rabies, lymphocytic choriomeningitis virus (LCMV), and arboviruses.

Hepatitis A Virus

Hepatitis A virus is the most common etiology of viral hepatitis, with 1.5 million cases worldwide annually.[87] The infection is acute and no prolonged infectious carrier state exists.[88] Given the acute nature of the illness, organ donors are not tested for HAV.[3,89]

There was a case of a documented donor-derived HAV infection in 2015. The recipient was a child that received liver, pancreas, and intestine grafts and presented with transaminase elevation and increased stoma output 8 months posttransplant. HAV RNA was later identified in the recipient’s feces, serum, liver and intestinal biopsies and sequencing of RNA was identical in the donor and the recipient. Despite this case, pretransplant testing of donors was previously not considered practical.[90] However, since March 2017, recent reports exist of HAV in homeless and drug-using persons in California, Kentucky, Michigan, and Utah. Thus, OPOs should be diligent about the risk of acute HAV infection in donors with identified risk factors[91] and in these settings consider screening for HAV.

Universal vaccination (including all donors) is the most feasible way to prevent donor-derived HAV infections.

Hepatitis D Virus

Hepatitis D virus is a “defective” virus that uses the envelope protein of HBV to cause chronic hepatitis.[92] Of approximately 240 million people with active HBV infection, 15 to 20 million have HDV coinfection.[92] Hepatitis D virus is most prevalent in Asia, whereas the prevalence in the United States is only 70 000.[93] Because HDV is present in only 3% of HBV-infected patients, it is considered unlikely to cause an unexpected donor-derived infection.[93] However, it is likely that in HBV-infected donors with concurrent or superinfection with HDV transmission of both viruses could occur. Currently, there are no reports of known donor-derived unexpected HDV infection. In the United States, donor HDV testing is not required by the current OPTN policy,[33] although testing for HDV in all HBsAg-positive donors is recommended by the European guidelines.[94]

Hepatitis E Virus

Hepatitis E virus is most commonly encountered in under-developed countries where transmission is largely fecal-oral.[95] Hepatitis E virus is traditionally characterized as causing acute hepatitis only, but chronic infections (persistence of HEV RNA for >6 months) in immunosuppressed patients have been described.[96–98] Because of the acute self-limited course of HEV infection, HEV is not routinely tested for in organ donors.[33]

Most cases of posttransplant HEV infection develop from reactivation of prior infection or a new acquisition. To date, there have been few cases of donor-derived HEV infection in SOT recipients. A review of 17 SOT recipients who developed early posttransplant HEVinfection found that 1 donor had positive anti–HEV IgM, but undetectable serum HEV RNA.[99] Another case of donor-derived HEV infection occurred in a liver recipient who developed severe HEV infection 37 days posttransplant.[100] While the donor retrospectively had negative serum HEV RNA, the donor liver contained high concentrations of HEV RNA, and sequencing of HEV RNA confirmed donor-to-recipient transmission.[100] The case represents either eclipse period infection, or a low-level carrier state in which virus persists in hepatic tissue but serum antibody response is minimal.[101] Two other cases of donor-derived HEV in nonhepatic recipients are reported.[102,103]

The various clinically available HEV IgM and IgG serologic assays have significant variability in their sensitivity, making these assays challenging to interpret in the transplant setting. As a result, RNA testing, which is less widely available than serology, is preferred when possible[95]; serum and stool HEV RNA are detectable during the incubation and early phase of infection. HEV RNA usually becomes undetectable in the serum approximately 3 weeks after the onset of symptoms, but can persist in stool for 2 additional weeks in immunocompetent patients[104] and for prolonged periods in the immunocompromised patient.[96]

In patients who develop HEV posttransplant, antivirals, such as ribavirin, are typically needed, because the course is not self-limited as it is in immunocompetent patients. In fact, those who develop chronic HEV can progress to cirrhosis and liver failure. Treatment algorithms for chronic HEVexist and are described elsewhere.[95]

Human Immunodeficiency Virus

With the advent of routine screening, transmission of HIV from donor to recipient is now an exceptionally rare event. Nonetheless, rare transmissions do occur. Of the 4 documented HIV transmission events, 2 involved errors in communication of positive results,[105,106] 1 involved an HIV-HCV cotransmission from a likely window period infection without NAT of the increased risk donor,[66] and 1 involved a living kidney donor with likely acquisition of infection between initial donor screening and the transplant event without interval testing.[2] A liver recipient was involved in all of the transmission events except the isolated living kidney transplant case.

In 2007, HIV-positive organs were transplanted from a common donor to 3 separate recipients in Tuscany, Italy, due to an error in communication. The donor HIV testing results had been erroneously transcribed as negative despite being positive. Although systems failure leading to the communication error was identified, an eerily similar case occurred in Taiwan involving the transmission of HIV to 5 separate recipients, including a liver recipient.[106]

The case involving the living kidney donor occurred in 2009 after the living donor had identified as men who have sex with other men. He had negative HIV serology 79 days before the transplant but did not have additional testing before donation. The donor eventually tested HIV positive about a year postdonation which resulted in the discovery of transmission. Retrospective white blood cell NAT testing of residual donor blood obtained 11 days before transplant confirmed donor infection. This case highlights the need for repeat HIV screening by both serology and NAT in all living donors as close to the time of organ donation as possible.[2] It is recommended that HIV, HBV, and HCV are tested within 30 days (but optimally within 14 days) from the organ donation procedure.[3] Although the donor was a kidney donor, the key lessons and screening recommendations are true for living liver donors as well.

Finally, in 2011, there was a high-profile HIV-HCV cotransmission case involving an OPTN-defined increased-risk deceased donor to 4 separate recipients (2 kidneys, 1 liver, and 1 heart recipient) despite negative predonation serologies. The donor was NAT positive by retrospective testing, suggesting a window period transmission.[66] In response to the HIV-HCV cotransmission event, OPTN clarified language for a requirement of special informed consent to accept organs from increased risk donors. More recently, the policy was modified to also require centers to develop and follow policies to offer appropriate follow-up testing to recipients of increased risk donors.

To prevent transmissions, OPTN policy was revised requiring HIV, HBV, and HCV screening to include NAT for PHS-identified increased risk donors.[1] It is currently estimated that about 0.2% of HIV seronegative donors would be captured during their “window period” with NAT. The estimated window period for HIV serological testing is approximately 22 days.[107] NAT can be positive 5.6 to 10.2 days after infectious exposure, which reduces the window period by 12 days.[108] In addition, NAT screening may provide the benefit of capturing false seropositive donors (estimated <1%) if the patient is not a known HIV patient on antiretroviral therapy with viral suppression.[109]

Because of the concerns for donor-derived HIV transmission, HIV-positive patients are excluded from organ donation in most countries. This leads to the loss of an estimated 356 potential organ donors per year in the United States, with a potential loss of 247 HIV-infected livers annually.[110] To use organs from HIV-positive donors in HIV-positive recipients, the HIV Organ Policy Equity Act was signed into law. Initially, this will be done under tight research restrictions in the United States.[111] To date, 9 HIV-positive livers have been transplanted into HIV-positive recipients (Personal Communication, Christine Durand & Dorry Segev, HIV Organ Policy Equity in Action Study). There has also recently been a report of successful HIV-to-HIV liver transplantation in Switzerland from a virologically suppressed donor to virologically suppressed recipient.[112] From these ongoing studies, the safety and challenges of using HIV-infected donors will be better understood.

Human T Lymphotropic Virus

Human T lymphotropic virus screening in deceased donors was standard of practice in the United States until 2009. Human T lymphotropic virus-1 is transmitted by transfusion of blood products, sexual activity, IV drug injection, breastfeeding, and SOT[113] and is endemic in the Caribbean, South America (Brazil, Peru, Ecuador, and Venezuela), and Asia. Nearly 15 to 20 million individuals are infected with HTLV-1, which amounts up to 10% in endemic areas such as Japan.[114] In contrast, the United States is considered a low seroprevalence region with only 0.0006% of healthy blood donors positive for HTLV-1. Human T lymphotropic virus-2 is more widespread in intravenous drug users and is endemic in North, South, and Central America as well as West and Central Africa.

Human T lymphotropic virus-1 establishes as a latent infection in lymphocytes, and the infection persists for life. Most patients remain asymptomatic, but 2% to 5% of patients can develop adult T-cell leukemia/lymphoma (ATL).[114] In addition to ATL, patients can also develop severe neurological disease known as HTLV-1 associated myelopathy/tropical spastic paraparesis. Unfortunately, no reliably effective treatment is currently available.[115,116] Disease association with HTLV-2 is unclear and HTLV-2–positive donors are generally not considered to present a risk of donor-derived disease.

All reported cases of donor-derived HTLV-1 are from endemic regions. There are currently only a few reported cases of HTLV-1 related disease after liver transplantation. Although most posttransplant cases represent reactivation of latent infection, donor-transmitted HTLV-1 is associated with HAM and ATL.[116–120] Available data from Japan suggest that HTLV-1 has a negative impact on 5-year survival rate after living donor liver transplantation for HCV.[121] In low-prevalence populations, HTLV-1/2 reactive organs do not show a significant risk of graft failure or decreased survival.[115,122]

Routine screening for HTLV-1 is no longer recommended in low-seroprevalence regions, such as the United States.[114,115,123] In addition, most commercially available assays currently are not able to reliably distinguish between HTLV-1 and HTLV-2.

Human Herpesvirus 6, 7, and 8

There is increased interest and awareness of the possible roles of HHV-6 and HHV-7 as cofactors for CMV effects, fungal infections, and possible allograft dysfunction.[124]

However, given that almost all adults are seropositive, screening for these viruses is not recommended.[125]

Human herpesvirus-8 is thought to be transmitted by direct contact with saliva, semen, blood (transfusions) or other bodily fluids,[126] but can reactivate during transplantation, as well as be transmitted through transplantation.[127–131] Human herpesvirus-8 is the causative agent of Kaposi sarcoma (KS), Castleman disease, hemophagocytic syndrome and primary effusion lymphoma. The risk of KS is about 400 to 1000 times in transplant recipients when compared to the general population.[131,132] The seroprevalence of HHV-8 is less than 5% in the United States, Asia, and Northern Europe but increases to more than 50% in sub-Saharan Africa, with intermediate risk of 10–30% in the Mediterranean area.[127,133,134] The mean time from transplantation to development of KS is 6.2 to 10.4 months,[135,136] while the risk of KS is thought to be highest within 30 days posttransplantation.[137]

Posttransplant immunosuppression-associated KS tends to have an aggressive clinical course involving lymph nodes, mucosa, and visceral organs, sometimes in the absence of skin lesions.[138] Kaposi sarcoma has been described primarily in renal transplant recipients of Mediterranean descent,[139] but also has been reported in some liver transplant recipients.[131,135,140–142] Presentations similar to that of PTLD have also been reported with diagnoses of visceral KS.[132,140] Screening for HHV-8 DNA may miss many latent infections so antilytic and antilatent antibodies are usually used to identify patients at risk for posttransplant HHV-8 related disease.[127] Treatment consists of either reduction of immunosuppression, switching from calcineurin inhibitors to mammalian target of rapamycin inhibitors, using anti-herpesvirus agents and/or chemotherapy.[143]

West Nile Virus

West Nile virus was first detected in the United States in 1999 and has become endemic nationally with areas of enhanced infection locally.[144] Although most WNV infections are asymptomatic, less than 1% of infected persons within the general population can develop neuroinvasive disease.[145] West Nile virus has been transmitted directly through the allograft and through the use of infected blood products.[146–153] Clinical symptoms, including encephalomyelitis, develop after an incubation period of 3 to 17 days.[148] Death occurs in 40% to 64% with severe neurologic consequences in many of the survivors.[148,154] To date, there have been 6 WNV transmissions involving liver recipients.[152] There are no effective therapies for WNV, although immunoglobulins have been tried with variable success, along with reduction of immunosuppression.[150,155,156]

Unfortunately, current methods of screening for WNV are imperfect. West Nile virus serological testing with IgM and IgG antibodies of both the serum and CSF are unreliable and may lead to a significant number of false positives. These antibodies may cross-react to other Flaviviridae, and IgM can persist up to 500 days after exposure and is therefore not always indicative of acute infection.[157,158] As a result of these limitations, serology is not recommended for donor screening and could lead to a loss of 272.6 life years annually in liver transplant patients.[159,160] There are no regulatory requirements that recommend NAT-based screening for WNV in the United States, but OPTN recommends deferring organs from all potential donors with encephalitis, meningitis, or flaccid paralysis of undetermined

etiology residing in areas of known WNV activity. Screening can be considered for deceased donors in areas of WNV activity. Further, the OPTN policy requires following a written protocol for screening for geographically defined endemic disease for all living donors; as such, areas with active WNV transmission should likely include WNV NAT as part of their screening protocols. This screening is often triggered based on a predefined WNV season, local WNV activity or positive testing in local blood banks. Current OPTN guidance advocates for deferral of live donors who test positive for 120 days with negative serum NAT.

Rabies

Rabies is an acute fatal encephalitis caused by neurotropic viruses in the genus *Lyssavirus,* family *Rhabdoviridae*.[161] Although prevalent globally, human rabies is rare in the United States.[162] Rabies virus has been transmitted by corneal transplants[163] as well as solid organ and vascular tissue transplant.

The first US reported case in a liver transplant recipient occurred in 2004 from a common donor whose liver, 2 kidneys, and iliac artery segment were transplanted to 4 separate recipients.[164,165] All transplant recipients developed rapid encephalitis resulting in death at an average of 13 days. It was determined in retrospect that the donor had been bitten by a bat. This history was initially obscured as the donor had presented with subarachnoid hemorrhage in the setting of a positive toxicology screen for cocaine.

A more recent case involved delayed development of rabies in a kidney transplant recipient 18 months posttransplant. The 3 other recipients (1 each kidney, heart and liver) were given rabies immune globulin and 5 doses of rabies vaccine, and remained asymptomatic.[166] Retrospective sequencing of the virus from the donor and the recipient was consistent with raccoon rabies. Additional cases have been reported from Germany[167,168] and, most recently, China.[169,170] The US raccoon rabies and German experience demonstrated the efficacy of the postexposure prophylaxis in transplant recipients.[166,168] These cases also demonstrate that while index cases typically develop symptoms early posttransplant, usually within 6 weeks of the procedure[163;] delayed onset of symptoms can occur.

Lymphocytic Choriomeningitis Virus

Lymphocytic choriomeningitis virus is a rodent-borne virus that causes aseptic meningitis in immunocompetent humans. Most recover without complication.[171–173] Infection is presumed to occur through aerosols or other contamination from rodents such as wild mice or pet mice and hamsters with 5% of the US population demonstrating LCMV seropositivity.[174]

There have been several clusters of donor-derived LCMV transmissions in the United States resulting in a 70.5% mortality rate (5 total clusters, 17 LCMV-infected organ recipients, 12 deaths).[173,175–178] There is an additional case of a related Arenavirus from Australia that resulted in the death of 2 kidney and 1 liver recipient.[179] Affected patients typically present with fever, altered mental status, renal and liver dysfunction early posttransplant (2–23 days).[175,176] Early recognition and use of antiviral therapy and reduction of immunosuppression has been associated with improved outcomes.[177,178]

Arbovirus Infections

Arboviruses are of a global concern given that more than 30% of the world's population is living in risk areas. The risk of donor-derived transmission of arboviruses, such as Dengue, Chikungunya, or Zika is not well delineated.

Chikungunya—Chikungunya infection is rarely fatal in the immunocompetent host but is known to cause debilitating arthritis.[180] Death from Chikungunya virus (CHIKV) is rare but can occur in neonates, elderly, and immunocompromised patients. Severe clinical syndromes include encephalitis, myocarditis, hepatitis, and multiorgan failure. To date, there have been no documented cases of CHIKV transmission by SOT, although infection posttransplant has occurred with no graft dysfunction.[181–183] Screening by CHIKV NAT has identified a single living donor candidate, who was able to safely donate 4 months later to an HIV-positive recipient without transmission.[183] Routine screening of donors is not currently recommended in the United States.

Dengue Virus—Dengue virus (DENV) is the most common vector-borne disease worldwide and classically presents with high fevers, debilitating arthralgias, severe headache, nausea/vomiting, and rash. Hemorrhagic fever, hepatitis, and thrombocytopenia can also be observed.[184] Dengue virus has been well described in transplant recipients, but there are only a few case reports of donor-derived transmission of DENV in liver transplant recipients.[185–187] Dengue virus appears to cause a similar clinical presentation (fever and exanthema) in transplant recipients. Donor screening is not routinely performed but could be considered in areas of DENVendemicity, particularly among symptomatic donors.

Zika—Although no donor-derived cases have been reported, it is thought that transmission via transplantation is possible. There is a case of Zika virus (ZIKV)-related fatal meningoencephalitis in a heart transplant patient.[188] While there is no formal OPTN policy on donor ZIKV screening, Disease Transmission Advisory Committee has provided guidance recommending caution when using deceased or living donors with exposure to ZIKV and compatible symptoms. Living donors with symptoms could be tested for ZIKV with the assistance of state health departments. Testing for DENV and CHIKV would be appropriate as well. Potential living donors with documented ZIKV should defer donation a period longer than 4 weeks up to 6 months.[189]

CONCLUSIONS

Although organ transplantation is considered a lifesaving event, it is not without risk. The risk of unexpected donor-derived infections is exceptionally low, likely around 0.1% to 0.2%.[3] Donor screening can mitigate the risk of disease transmission. Limitations to current screening will not fully remove the risk of disease transmission. Clinicians managing transplant recipients must maintain a high index of suspicion for donor-derived infections to ensure early recognition and optimal management (see Figure 2). Understanding the risk through collaboration with organ vigilance systems and Transplant Infectious Diseases experts can facilitate the safe use of organ for individuals with risk factors. Ultimately,

discarding organs due to fear of disease transmission may result in more adverse outcomes, including deaths, than the rare transmitted infection.

Acknowledgments

H.N. and K.M.N. declare no conflicts of interest. J.L. is a paid speaker for Gilead and Novartis. M.G.I. has received support for research, paid to Northwestern University from Beckman Coulter, Cephied, Chimerix, Emergent BioScience, Gilead, Janssen, and Shire; compensated consultation from Chimerix, Celltrion, Genentech/Roche, MediVector, Seqirus, Shionogi, and VirBio; and paid membership of DSMB from GlaxoSmithKlein, Shionogi.

REFERENCES

1. Guidance on explaining risk related to use of U.S. PHS increased risk donor organs when considering organ offers. Organ Procurement and Transplantation Network (OPTN). https://optn.transplant.hrsa.gov/media/2171/dtac_boardreport_201706.pdf.Published June 2017. AccessedMarch 2, 2018.
2. Garzoni C, Ison MG. Uniform definitions for donor-derived infectious disease transmissions in solid organ transplantation. Transplantation. 2011; 92:1297–1300. [PubMed: 21996654]
3. Echenique IA, Ison MG. Update on donor-derived infections in liver transplantation. Liver Transpl. 2013;19:575–585. [PubMed: 23526639]
4. Rogers MF, Simonds RJ, Lawton KE, et al.Guidelines for preventing transmission of human immunodeficiency virus through transplantation of human tissue and organs. MMWR Recomm Rep. 1994;43:1–17.
5. Fishman JA. Infection in Organ Transplantation. Am J Transplant. 2017; 17:856–879. [PubMed: 28117944]
6. Razonable RR, Humar A; AST Infectious Diseases Community of Practice. Cytomegalovirus in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):93–106. [PubMed: 23465003]
7. Staras SA, Dollard SC, Radford KW, et al.Seroprevalence of cytomegalovirus infection in the United States, 1988–1994. Clin Infect Dis. 2006; 43:1143–1151. [PubMed: 17029132]
8. Bate SL, Dollard SC, Cannon MJ. Cytomegalovirus seroprevalence in the United States: the national health and nutrition examination surveys, 1988–2004. Clin Infect Dis. 2010;50:1439–1447. [PubMed: 20426575]
9. Cannon MJ, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. Rev Med Virol. 2010;20:202–213. [PubMed: 20564615]
10. Zhang S, Hu L, Chen J, et al.Cytomegalovirus seroprevalence in pregnant women and association with adverse pregnancy/neonatal outcomes in Jiangsu Province, China. PLoS One. 2014;9:e107645. [PubMed: 25211647]
11. Bruminhent J, Razonable RR. Management of cytomegalovirus infection and disease in liver transplant recipients. World J Hepatol. 2014;6:370–383. [PubMed: 25018848]
12. Kotton CN, Kumar D, Caliendo AM, et al.Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation. 2013;96:333–360. [PubMed: 23896556]
13. Manuel O, Husain S, Kumar D, et al.Assessment of cytomegalovirus-specific cell-mediated immunity for the prediction of cytomegalovirus disease in high-risk solid-organ transplant recipients: a multicenter cohort study. Clin Infect Dis. 2013;56:817–824. [PubMed: 23196955]
14. Eid AJ, Arthurs SK, Deziel PJ, et al.Clinical predictors of relapse after treatment of primary gastrointestinal cytomegalovirus disease in solid organ transplant recipients. Am J Transplant. 2010;10:157–161. [PubMed: 19889123]
15. Marcelin JR, Beam E, Razonable RR. Cytomegalovirus infection in liver transplant recipients: updates on clinical management. World J Gastroenterol. 2014;20:10658–10667. [PubMed: 25152570]
16. Stoelben S, Arns W, Renders L, et al.Preemptive treatment of Cytomegalovirus infection in kidney transplant recipients with letermovir: results of a phase 2a study. Transpl Int. 2014;27:77–86. [PubMed: 24164420]

17. Paya C, Humar A, Dominguez E, et al.Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. Am J Transplant. 2004;4:611–620. [PubMed: 15023154]
18. Kumar D, Chernenko S, Moussa G, et al.Cell-mediated immunity to predict cytomegalovirus disease in high-risk solid organ transplant recipients. Am J Transplant. 2009;9:1214–1222. [PubMed: 19422346]
19. Humar A, Snydman D. Cytomegalovirus in solid organ transplant recipients. Am J Transplant. 2009;9(Suppl 4):S78–S86. [PubMed: 20070700]
20. Allen UD. The ABC of Epstein-Barr virus infections. Adv Exp Med Biol. 2005;568:25–39. [PubMed: 16107064]
21. Preiksaitis JK. New developments in the diagnosis and management of posttransplantation lymphoproliferative disorders in solid organ transplant recipients. Clin Infect Dis. 2004;39:1016–1023. [PubMed: 15472855]
22. Feranchak AP, Tyson RW, Narkewicz MR, et al.Fulminant Epstein-Barr viral hepatitis: orthotopic liver transplantation and review of the literature. Liver Transpl Surg. 1998;4:469–476. [PubMed: 9791157]
23. Kinch A, Baecklund E, Backlin C, et al.A population-based study of 135 lymphomas after solid organ transplantation: The role of Epstein-Barr virus, hepatitis C and diffuse large B-cell lymphoma subtype in clinical presentation and survival. Acta Oncol. 2014;53:669–679. [PubMed: 24164103]
24. Strouse PJ, Platt JF, Francis IR, et al.Tumorous intrahepatic lymphoproliferative disorder in transplanted livers. AJR Am J Roentgenol. 1996;167: 1159–1162. [PubMed: 8911173]
25. Allen UD, Preiksaitis JK. Epstein-Barr virus and posttransplant lymphoproliferative disorder in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):107–120. [PubMed: 23465004]
26. Kamdar KY, Rooney CM, Heslop HE. Posttransplant lymphoproliferative disease following liver transplantation. Curr Opin Organ Transplant. 2011;16:274–280. [PubMed: 21467936]
27. Swerdlow SH, Campo E, Pileri SA, et al.The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016; 127:2375–2390. [PubMed: 26980727]
28. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. J Hepatol. 2012;57:167–185. [PubMed: 22436845]
29. Liaw YF, Chu CM. Hepatitis B virus infection. Lancet. 2009;373:582–592. [PubMed: 19217993]
30. Cholongitas E, Papatheodoridis GV, Burroughs AK. Liver grafts from anti-hepatitis B core positive donors: a systematic review. J Hepatol. 2010;52:272–279. [PubMed: 20034693]
31. Huprikar S, Danziger-Isakov L, Ahn J, et al.Solid organ transplantation from hepatitis B virus-positive donors: consensus guidelines for recipient management. Am J Transplant. 2015;15:1162–1172. [PubMed: 25707744]
32. Ji M, Hu K. Recent advances in the study of hepatitis B virus covalently closed circular DNA. Virol Sin. 2017;32:454–464. [PubMed: 29280054]
33. OPTN. Policy 2.0 Deceased Donor Organ Procurement (Policy 2.9). Organ Procurement and Transplant Network (OPTN). https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf.Effective Date March 1, 2018.Dated Accessed:March 22, 2018.
34. Lucey MR, Terrault N, Ojo L, et al.Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transpl. 2013;19:3–26. [PubMed: 23281277]
35. Chazouillères O, Mamish D, Kim M, et al."Occult" hepatitis B virus as source of infection in liver transplant recipients. Lancet. 1994;343:142–146. [PubMed: 7904004]
36. Zollner B, Feucht HH, Sterneck M, et al.Clinical reactivation after liver transplantation with an unusual minor strain of hepatitis B virus in an occult carrier. Liver Transpl. 2006;12:1283–1289. [PubMed: 16868945]
37. Kim HY, Choi JY, Park CH, et al.Adult living donor liver transplantation using hepatitis B core antibody-positive grafts in Korea, a Hepatitis B-endemic region. Gut Liver. 2011;5:363–366. [PubMed: 21927667]

38. Pan JJ, Oh SH, Soldevila-Pico C, et al.Low prevalence of HBV DNA in the liver allograft from anti–HBc-positive donors: a single-center experience. Clin Transplant. 2011;25:164–170. [PubMed: 20156222]
39. Rokuhara A, Tanaka E, Yagi S, et al.De novo infection of hepatitis B virus in patients with orthotopic liver transplantation: analysis by determining complete sequence of the genome. J Med Virol. 2000;62:471–478. [PubMed: 11074476]
40. Ghisetti V, Marzano A, Zamboni F, et al.Occult hepatitis B virus infection in HBsAg negative patients undergoing liver transplantation: clinical significance. Liver Transpl. 2004;10:356–362. [PubMed: 15004761]
41. Humar A, Morris M, Blumberg E, et al.Nucleic acid testing (NAT) of organ donors: is the 'best' test the right test? A consensus conference report. Am J Transplant. 2010;10:889–899. [PubMed: 20121734]
42. Levitsky J, Doucette K; AST Infectious Diseases Community of Practice. Viral hepatitis in solid organ transplantation. Am J Transplant. 2013;13 (Suppl 4):147–168. [PubMed: 23465008]
43. Ouseph R, Eng M, Ravindra K, et al.Review of the use of hepatitis B core antibody-positive kidney donors. Transplant Rev. 2010;24:167–171.
44. Skagen CL, Jou JH, Said A. Risk of de novo hepatitis in liver recipients from hepatitis-B core antibody-positive grafts—a systematic analysis. Clin Transplant. 2011;25:E243–E249. [PubMed: 21323735]
45. Chang MS, Olsen SK, Pichardo EM, et al.Prevention of de novo hepatitis B in recipients of core antibody-positive livers with lamivudine and other nucleos(t)ides: a 12-year experience. Transplantation. 2013;95:960–965. [PubMed: 23545507]
46. MacConmara MP, Vachharajani N, Wellen JR, et al.Utilization of hepatitis B core antibody-positive donor liver grafts. HPB (Oxford). 2012;14:42–48. [PubMed: 22151450]
47. Saab S, Waterman B, Chi AC, et al.Comparison of different immunoprophylaxis regimens after liver transplantation with hepatitis B core antibody-positive donors: a systematic review. Liver Transpl. 2010;16:300–307. [PubMed: 20209589]
48. Vizzini G, Gruttadauria S, Volpes R, et al.Lamivudine monoprophylaxis for de novo HBV infection in HBsAg-negative recipients with HBcAb-positive liver grafts. Clin Transplant. 2011;25:E77–E81. [PubMed: 21039887]
49. Roque-Afonso AM, Feray C, Samuel D, et al.Antibodies to hepatitis B surface antigen prevent viral reactivation in recipients of liver grafts from anti-HBC positive donors. Gut. 2002;50:95–99. [PubMed: 11772974]
50. Yen RD, Bonatti H, Mendez J, et al.Case report of lamivudine-resistant hepatitis B virus infection post liver transplantation from a hepatitis B core antibody donor. Am J Transplant. 2006;6:1077–1083. [PubMed: 16611347]
51. Danziger-Isakov L, Kumar D, AST Infectious Diseases Community of Practice. Vaccination in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):311–317. [PubMed: 23465023]
52. Lefebure AF, Verpooten GA, Couttenye MM, et al.Immunogenicity of a recombinant DNA hepatitis B vaccine in renal transplant patients. Vaccine. 1993;11:397–399. [PubMed: 8470423]
53. Carey W, Pimentel R, Westveer MK, et al.Failure of hepatitis B immunization in liver transplant recipients: results of a prospective trial. Am J Gastroenterol. 1990;85:1590–1592. [PubMed: 2252022]
54. Feuerhake A, Muller R, Lauchart W, et al.HBV-vaccination in recipients of kidney allografts. Vaccine. 1984;2:255–256. [PubMed: 6241770]
55. Stevens CE, Alter HJ, Taylor PE, et al.Hepatitis B vaccine in patients receiving hemodialysis. Immunogenicity and efficacy. N Engl J Med. 1984; 311:496–501. [PubMed: 6235453]
56. HEPLISAV-B, 2018. Food and Drug Administration (FDA). https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm584752.htm.Updated January 4, 2018. AccessedMarch 22, 2018.
57. Hwang JP, Lok AS. Management of patients with hepatitis B who require immunosuppressive therapy. Nat Rev Gastroenterol Hepatol. 2014;11: 209–219. [PubMed: 24247262]

58. FDA Hepatitis Update - Hepatitis B reactivation with certain immune-suppressing and anti-cancer drugs. Infectious Diseases Society of America (IDSA). http://www.idsociety.org/FDA_20131029.aspx.Updated October 29, 2013. AccessedMarch 22, 2018.
59. Saidi RF, Jabbour N, Shah SA, et al.Liver transplantation from hepatitis B surface antigen-positive donors. Transplant Proc. 2013;45:279–280. [PubMed: 23267801]
60. Centers for Disease Control and Prevention (CDC). Potential transmission of viral hepatitis through use of stored blood vessels as conduits in organ transplantation—Pennsylvania, 2009. MMWR Morb Mortal Wkly Rep. 2011;60:172–174. [PubMed: 21330966]
61. OPTN. Policy 16.6 Vessel Recovery, Transplant, and Storage (Policy 16. 6B). Organ Procurement and Transplant Network (OPTN). https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf.Effective Date March 1, 2018. AccessedMarch 22, 2018.
62. Levitsky J, Formica RN, Bloom RD, et al.The American Society of Transplantation Consensus Conference on the Use of Hepatitis C Viremic Donors in Solid Organ Transplantation. Am J Transplant. 2017;17:2790–2802. [PubMed: 28556422]
63. Annambhotla PD, Gurbaxani BM, Kuehnert MJ, et al.A model to estimate the probability of human immunodeficiency virus and hepatitis C infection despite negative nucleic acid testing among increased-risk organ donors. Transpl Infect Dis. 2017;19.
64. Kucirka LM, Sarathy H, Govindan P, et al.Risk of window period hepatitis-C infection in high infectious risk donors: systematic review and meta-analysis. Am J Transplant. 2011;11:1188–1200. [PubMed: 21401874]
65. Understanding the risk of transmission of HIV, Hepatitis B, and Hepatitis C from U.S. PHS increased risk donors. Organ Procurement and Transplantation Network (OPTN). https://optn.transplant.hrsa.gov/resources/guidance/understanding-hiv-hbv-hcv-risks-from-increased-risk-donors/.Published June 2017. AccessedMarch 2, 2018.
66. Ison MG, Llata E, Conover CS, et al.Transmission of human immunodeficiency virus and hepatitis C virus from an organ donor to four transplant recipients. Am J Transplant. 2011;11:1218–1225. [PubMed: 21645254]
67. Shah AP, Cameron A, Singh P, et al.Successful treatment of donor-derived hepatitis C viral infection in three transplant recipients from a donor at increased risk for bloodborne pathogens. Transpl Infect Dis. 2017;19.
68. Suryaprasad A, Basavaraju SV, Hocevar SN, et al.Transmission of hepatitis C virus from organ donors despite nucleic acid test screening. Am J Transplant. 2015;15:1827–1835. [PubMed: 25943299]
69. Saab S, Chang AJ, Comulada S, et al.Outcomes of hepatitis C- and hepatitis B core antibody-positive grafts in orthotopic liver transplantation. Liver Transpl. 2003;9:1053–1061. [PubMed: 14526400]
70. Burr AT, Li Y, Tseng JF, et al.Survival after liver transplantation using hepatitis C virus-positive donor allografts: case-controlled analysis of the UNOS database. World J Surg. 2011;35:1590–1595. [PubMed: 21384242]
71. Northup PG, Argo CK, Nguyen DT, et al.Liver allografts from hepatitis C positive donors can offer good outcomes in hepatitis C positive recipients: a US National Transplant Registry analysis. Transpl Int. 2010;23:1038–1044. [PubMed: 20444239]
72. Alvaro E, Abradelo M, Fuertes A, et al.Liver transplantation from anti-hepatitis C virus-positive donors: our experience. Transplant Proc. 2012; 44:1475–1478. [PubMed: 22841188]
73. Ballarin R, Cucchetti A, Spaggiari M, et al.Long-term follow-up and outcome of liver transplantation from anti-hepatitis C virus-positive donors: a European multicentric case-control study. Transplantation. 2011;91:1265–1272. [PubMed: 21478815]
74. Saab S, Ghobrial RM, Ibrahim AB, et al.Hepatitis C positive grafts may be used in orthotopic liver transplantation: a matched analysis. Am J Transplant. 2003;3:1167–1172. [PubMed: 12919097]
75. Marroquin CE, Marino G, Kuo PC, et al.Transplantation of hepatitis C-positive livers in hepatitis C-positive patients is equivalent to transplanting hepatitis C-negative livers. Liver Transpl. 2001;7:762–768. [PubMed: 11552208]

76. Vargas HE, Laskus T, Wang LF, et al.Outcome of liver transplantation in hepatitis C virus-infected patients who received hepatitis C virus-infected grafts. Gastroenterology. 1999;117:149–153. [PubMed: 10381921]
77. Testa G, Goldstein RM, Netto G, et al.Long-term outcome of patients transplanted with livers from hepatitis C-positive donors. Transplantation. 1998;65:925–929. [PubMed: 9565096]
78. O'Leary JG, Neri MA, Trotter JF, et al.Utilization of hepatitis C antibody-positive livers: genotype dominance is virally determined. Transpl Int. 2012;25:825–829. [PubMed: 22643162]
79. Denniston MM, Jiles RB, Drobeniuc J, et al.Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. Ann Intern Med. 2014;160:293–300. [PubMed: 24737271]
80. Tokumoto T, Tanabe K, Simizu T, et al.Kidney transplantation from a donor who is HCV antibody positive and HCV-RNA negative. Transplant Proc. 2000;32:1597–1599. [PubMed: 11119853]
81. Cruzado JM, Gil-Vernet S, Castellote J, et al.Successful treatment of chronic HCV infection should not preclude kidney donation to an HCV negative recipient. Am J Transplant. 2013;13:2773–2774. [PubMed: 23919533]
82. Takeichi T, Asonuma K, Yamamoto H, et al.Liver transplant from an ABO-incompatible and hepatitis C antibody-positive but an HCV-RNA negative living donor in a familial amyloid polyneuropathy patient. Exp Clin Transplant. 2013;11:182–185. [PubMed: 23194392]
83. Elmasry S, Wadhwa S, Bang BR, et al.Detection of occult hepatitis c virus infection in patients who achieved a sustained virologic response to direct-acting antiviral agents for recurrent infection after liver transplantation. Gastroenterology. 2017;152:550–553.e8. [PubMed: 27838287]
84. Koutsoudakis G, Perez-Del-Pulgar S, Forns X. Occult hepatitis C virus infection: are we digging too deep?Gastroenterology. 2017;152:472–474. [PubMed: 28038930]
85. Bari K, Luckett K, Kaiser T, et al.Hepatitis C transmission from seropositive, non-viremic donors to non-hepatitis C liver transplant recipients. Hepatology. 2018;67:1673–1682. [PubMed: 29205441]
86. Goldberg DS, Abt PL, Blumberg EA, et al.Trial of transplantation of HCV-infected kidneys into uninfected recipients. N Engl J Med. 2017;376:2394–2395. [PubMed: 28459186]
87. Franco E, Meleleo C, Serino L, et al.Hepatitis A: Epidemiology and prevention in developing countries. World J Hepatol. 2012;4:68–73. [PubMed: 22489258]
88. Tjon GM, Coutinho RA, van den Hoek A, et al.High and persistent excretion of hepatitis A virus in immunocompetent patients. J Med Virol. 2006; 78:1398–1405. [PubMed: 16998883]
89. Hughes JA, Fontaine MJ, Gonzalez CL, et al.Case report of a transfusion-associated hepatitis A infection. Transfusion. 2014;54:2202–2206. [PubMed: 24689888]
90. Foster MA, Weil LM, Jin S, et al.Transmission of hepatitis A virus through combined liver-small intestine-pancreas transplantation. Emerg Infect Dis. 2017;23:590–596. [PubMed: 28322704]
91. 2017 - Outbreaks of hepatitis A in multiple states among people who are homeless and people who use drugs. Center for Disease Control (CDC). https://www.cdc.gov/hepatitis/outbreaks/2017March-HepatitisA.htm.Published March 5, 2018. AccessedMarch 7, 2018.
92. Abbas Z, Abbas M. Management of hepatitis delta: Need for novel therapeutic options. World J Gastroenterol. 2015;21:9461–9465. [PubMed: 26327754]
93. Alter MJ, Hadler SC. Delta hepatitis and infection in North America. Prog Clin Biol Res. 1993;382:243–250. [PubMed: 8502688]
94. Lampertico P, Agarwal K, Berg T, et al.EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370–398. [PubMed: 28427875]
95. Kamar N, Legrand-Abravanel F, Izopet J, et al.Hepatitis E virus: what transplant physicians should know. Am J Transplant. 2012;12:2281–2287. [PubMed: 22549004]
96. Kamar N, Selves J, Mansuy JM, et al.Hepatitis E virus and chronic hepatitis in organ-transplant recipients. N Engl J Med. 2008;358:811–817. [PubMed: 18287603]
97. Dalton HR, Bendall RP, Keane FE, et al.Persistent carriage of hepatitis E virus in patients with HIV infection. N Engl J Med. 2009;361:1025–1027. [PubMed: 19726781]
98. Ollier L, Tieulie N, Sanderson F, et al.Chronic hepatitis after hepatitis E virus infection in a patient with non-Hodgkin lymphoma taking rituximab. Ann Intern Med. 2009;150:430–431.

99. Legrand-Abravanel F, Kamar N, Sandres-Saune K, et al.Hepatitis E virus infection without reactivation in solid-organ transplant recipients, France. Emerg Infect Dis. 2011;17:30–37. [PubMed: 21192851]
100. Schlosser B, Stein A, Neuhaus R, et al.Liver transplant from a donor with occult HEV infection induced chronic hepatitis and cirrhosis in the recipient. J Hepatol. 2012;56:500–502. [PubMed: 21798217]
101. Kamar N, Garrouste C, Haagsma EB, et al.Factors associated with chronic hepatitis in patients with hepatitis E virus infection who have received solid organ transplants. Gastroenterology. 2011;140:1481–1489. [PubMed: 21354150]
102. Pourbaix A, Ouali N, Soussan P, et al.Evidence of hepatitis E virus transmission by renal graft. Transpl Infect Dis. 2017;19.
103. Murkey JA, Chew KW, Carlson M, et al.Hepatitis E virus-associated meningoencephalitis in a lung transplant recipient diagnosed by clinical metagenomic sequencing. Open Forum Infect Dis. 2017; 4:ofx121.
104. Dalton HR, Bendall R, Ijaz S, et al.Hepatitis E: an emerging infection in developed countries. Lancet Infect Dis. 2008;8:698–709. [PubMed: 18992406]
105. Bellandi T, Albolino S, Tartaglia R, et al.Unintended transplantation of three organs from an HIV-positive donor: report of the analysis of an adverse event in a regional health care service in Italy. Transplant Proc. 2010;42:2187–2189. [PubMed: 20692439]
106. Ison MG, Holl JL, Ladner D. Preventable errors in organ transplantation: an emerging patient safety issue?Am J Transplant. 2012;12:2307–2312. [PubMed: 22703471]
107. Kucirka LM, Sarathy H, Govindan P, et al.Risk of window period HIV infection in high infectious risk donors: systematic review and meta-analysis. Am J Transplant. 2011;11:1176–1187. [PubMed: 21366859]
108. Fishman JA, Grossi PA. Donor-derived infection—the challenge for transplant safety. Nat Rev Nephrol. 2014;10:663–672. [PubMed: 25178971]
109. Theodoropoulos N, Nowicki MJ, Chinchilla-Reyes C, et al.Deceased organ donor screening for human immunodeficiency virus, hepatitis B, and hepatitis C viruses: discordant serology and nucleic acid testing results. Transpl Infect Dis. 2017.
110. Richterman A, Sawinski D, Reese PP, et al.An assessment of HIV-infected patients dying in care for deceased organ donation in a United States urban center. Am J Transplant. 2015;15:2105–2116. [PubMed: 25976241]
111. Organ procurement and transplantation: implementation of the HIV Organ Policy Equity Act. Final rule. Fed Regist. 2015;80: 26464–26467. [PubMed: 25985481]
112. Calmy A, van Delden C, Giostra E, et al.HIV-positive-to-HIV-positive liver transplantation. Am J Transplant. 2016;16:2473–2478. [PubMed: 27109874]
113. Gonzalez-Perez MP, Munoz-Juarez L, Cardenas FC, et al.Human T-cell leukemia virus type I infection in various recipients of transplants from the same donor. Transplantation. 2003;75:1006–1011. [PubMed: 12698089]
114. Kaul DR, Davis JA; AST Infectious Diseases Community of Practice. Human T cell lymphotrophic virus 1/2 in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):355–360. [PubMed: 23465028]
115. Armstrong MJ, Corbett C, Rowe IA, et al.HTLV-1 in solid-organ transplantation: current challenges and future management strategies. Transplantation. 2012;94:1075–1084. [PubMed: 23060278]
116. Yoshizumi T, Shirabe K, Ikegami T, et al.Impact of human Tcell leukemia virus type 1 in living donor liver transplantation. Am J Transplant. 2012; 12:1479–1485. [PubMed: 22486853]
117. Kawano N, Shimoda K, Ishikawa F, et al.Adult T-cell leukemia development from a human T-cell leukemia virus type I carrier after a living-donor liver transplantation. Transplantation. 2006;82:840–843. [PubMed: 17006333]
118. Soyama A, Eguchi S, Takatsuki M, et al.Human T-cell leukemia virus type I-associated myelopathy following living-donor liver transplantation. Liver Transpl. 2008;14:647–650. [PubMed: 18433046]

119. Toro C, Rodés B, Poveda E, et al.Rapid development of subacute myelopathy in three organ transplant recipients after transmission of human T-cell lymphotropic virus type I from a single donor. Transplantation. 2003;75:102–104. [PubMed: 12544880]
120. Zarranz JJ, Rouco I, Gomez-Esteban JC, et al.Human T lymphotropic virus type I (HTLV-1) associated myelopathy acquired through a liver transplant. J Neurol Neurosurg Psychiatry. 2001;71:818.
121. Ichikawa T, Taura N, Miyaaki H, et al.Human T-cell leukemia virus type 1 infection worsens prognosis of hepatitis C virus-related living donor liver transplantation. Transpl Int. 2012;25:433–438. [PubMed: 22417010]
122. Marvin MR, Brock GN, Kwarteng K, et al.Increasing utilization of human T-cell lymphotropic virus (+) donors in liver transplantation: is it safe?Transplantation. 2009;87:1180–1190. [PubMed: 19384165]
123. Gallo RC, Willems L, Hasegawa H. Screening transplant donors for HTLV-1 and −2. Blood. 2016;128:3029–3031. [PubMed: 28034870]
124. Le J, Gantt S; AST Infectious Diseases Community of Practice. Human herpesvirus 6, 7 and 8 in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):128–137. [PubMed: 23465006]
125. Fischer SA, Lu K; AST Infectious Diseases Community of Practice. Screening of donor and recipient in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):9–21.
126. Jenkins FJ, Hoffman LJ, Liegey-Dougall A. Reactivation of and primary infection with human herpesvirus 8 among solid-organ transplant recipients. J Infect Dis. 2002;185:1238–1243. [PubMed: 12001040]
127. Chiereghin A, Barozzi P, Petrisli E, et al.Multicenter prospective study for laboratory diagnosis of HHV8 infection in solid organ donors and transplant recipients and evaluation of the clinical impact after transplantation. Transplantation. 2017;101:1935–1944. [PubMed: 28333859]
128. Regamey N, Tamm M, Wernli M, et al.Transmission of human herpesvirus 8 infection from renal-transplant donors to recipients. N Engl J Med. 1998;339:1358–1363. [PubMed: 9801396]
129. Vijgen S, Wyss C, Meylan P, et al.Fatal outcome of multiple clinical presentations of human herpesvirus 8–related disease after solid organ transplantation. Transplantation. 2016;100:134–140. [PubMed: 26120765]
130. Ariza-Heredia EJ, Razonable RR. Human herpes virus 8 in solid organ transplantation. Transplantation. 2011;92:837–844. [PubMed: 21946171]
131. Marcelin AG, Roque-Afonso AM, Hurtova M, et al.Fatal disseminated Kaposi's sarcoma following human herpesvirus 8 primary infections in liver-transplant recipients. Liver Transpl. 2004;10:295–300. [PubMed: 14762870]
132. Benhammane H, Mentha G, Tschanz E, et al.Visceral Kaposi's sarcoma related to human herpesvirus-8 in liver transplant recipient: case report and literature review. Case Rep Oncol Med. 2012;2012:137291. [PubMed: 23320218]
133. Bonatti H, Sawyer R, Dickson RC, et al.Transmission of viral disease to the recipient through the donor liver. Curr Opin Organ Transplant. 2007; 12:231–241. [PubMed: 27711010]
134. Plancoulaine S, Gessain A. Epidemiological aspects of human herpesvirus 8 infection and of Kaposi's sarcoma. Med Mal Infect. 2005; 35:314–321. [PubMed: 15907610]
135. Di Benedetto F, Di Sandro S, De Ruvo N, et al.Kaposi's sarcoma after liver transplantation. J Cancer Res Clin Oncol. 2008;134:653–658. [PubMed: 17922290]
136. García-Astudillo LA, Leyva-Cobián F. Human herpesvirus-8 infection and Kaposi's sarcoma after liver and kidney transplantation in different geographical areas of Spain. Transpl Immunol. 2006;17:65–69. [PubMed: 17157220]
137. Piselli P, Busnach G, Citterio F, et al.Risk of Kaposi sarcoma after solid-organ transplantation: multicenter study in 4767 recipients in Italy, 1970–2006. Transplant Proc. 2009;41:1227–1230. [PubMed: 19460525]
138. Antman K, Chang Y. Kaposi's Sarcoma. N Engl J Med. 2000;342: 1027–1038. [PubMed: 10749966]
139. Barozzi P, Luppi M, Facchetti F, et al.Post-transplant Kaposi sarcoma originates from the seeding of donor-derived progenitors. Nat Med. 2003;9:554–561. [PubMed: 12692543]

140. Pozo F, Tenorio A, de la Mata M, et al.Persistent human herpesvirus 8 viremia before Kaposi's sarcoma development in a liver transplant recipient. Transplantation. 2000;70:395–397. [PubMed: 10933172]
141. Kadry Z, Bronsther O, Fung JJ. Kaposi's sarcoma in liver transplant recipients on FK506. Transplantation. 1998;65:1140. [PubMed: 9583882]
142. Dollard SC, Douglas D, Basavaraju SV, et al.Donor-derived Kaposi's sarcoma in a liver-kidney transplant recipient. Am J Transplant. 2018;18: 510–513. [PubMed: 28941319]
143. Riva G, Luppi M, Barozzi P, et al.How I treat HHV8/KSHV-related diseases in posttransplant patients. Blood. 2012;120:4150–4159. [PubMed: 22968461]
144. Centers for Disease Control and Prevention (CDC). Outbreak of West Nile-like viral encephalitis–New York, 1999. MMWR Morb Mortal Wkly Rep. 1999;48:845–849. [PubMed: 10563521]
145. Mostashari F, Bunning ML, Kitsutani PT, et al.Epidemic West Nile encephalitis, New York, 1999: results of a household-based seroepidemiological survey. Lancet. 2001;358:261–264. [PubMed: 11498211]
146. Centers for Disease Control and Prevention (CDC). West Nile virus infections in organ transplant recipients—New York and Pennsylvania, August-September, 2005. MMWR Morb Mortal Wkly Rep. 2005;54: 1021–1023. [PubMed: 16224451]
147. Rabe IB, Schwartz BS, Farnon EC, et al.Fatal transplant-associated west nile virus encephalitis and public health investigation—California, 2010. Transplantation. 2013;96:463–468. [PubMed: 23823653]
148. Rhee C, Eaton EF, Concepcion W, et al.West Nile virus encephalitis acquired via liver transplantation and clinical response to intravenous immunoglobulin: case report and review of the literature. Transpl Infect Dis. 2011;13:312–317. [PubMed: 21235711]
149. Iwamoto M, Jernigan DB, Guasch A, et al.Transmission of West Nile virus from an organ donor to four transplant recipients. N Engl J Med. 2003;348:2196–2203. [PubMed: 12773646]
150. Morelli MC, Sambri V, Grazi GL, et al.Absence of neuroinvasive disease in a liver transplant recipient who acquired West Nile virus (WNV) infection from the organ donor and who received WNVantibodies prophylactically. Clin Infect Dis. 2010;51:e34–e37. [PubMed: 20597692]
151. Kusne S, Smilack J. Transmission of West Nile virus by organ transplantation. Liver Transpl. 2005;11:239–241. [PubMed: 15666374]
152. Winston DJ, Vikram HR, Rabe IB, et al.Donor-derived West Nile virus infection in solid organ transplant recipients: report of four additional cases and review of clinical, diagnostic, and therapeutic features. Transplantation. 2014;97:881–889. [PubMed: 24827763]
153. Centers for Disease Control and Prevention (CDC). Update: Investigations of West Nile virus infections in recipients of organ transplantation and blood transfusion—Michigan, 2002. MMWR Morb Mortal Wkly Rep. 2002;51:879. [PubMed: 12375688]
154. Kleinschmidt-DeMasters BK, Marder BA, Levi ME, et al.Naturally acquired West Nile virus encephalomyelitis in transplant recipients: clinical, laboratory, diagnostic, and neuropathological features. Arch Neurol. 2004;61:1210–1220. [PubMed: 15313837]
155. Hazell SL. Serological diagnosis of West Nile virus. MLO Med Lab Obs. 2004;36:10–12, 16; quiz 18–19.
156. Zak IT, Altinok D, Merline JR, et al.West Nile virus infection. AJR Am J Roentgenol. 2005;184:957–961. [PubMed: 15728624]
157. Singh N, Levi ME. Arenavirus and West Nile virus in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):361–371. [PubMed: 23465029]
158. Guidance for Industry: Assessing donor suitability and blood product safety in cases of known or suspected West Nile Virus infection. Food and Drug Administration (FDA). https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm080286.pdf.Published June 2015. AccessedMarch 22, 2018.
159. Ison MG, Grossi P. AST Infectious Diseases Community of Practice. Donor-derived infections in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):22–30. [PubMed: 23464995]
160. Kiberd BA, Forward K. Screening for West Nile virus in organ transplantation: a medical decision analysis. Am J Transplant. 2004;4:1296–1301. [PubMed: 15268731]

161. Warrell MJ, Warrell DA. Rabies and other lyssavirus diseases. The Lancet. 2004;363:959–969.
162. World Health Organization (WHO). WHO Expert Consultation on Rabies. World Health Organ Tech Rep Ser. Vol 9312005.
163. Bronnert J, Wilde H, Tepsumethanon V, et al.Organ transplantations and rabies transmission. J Travel Med. 2007;14:177–180. [PubMed: 17437474]
164. Centers for Disease Control and Prevention (CDC). Investigation of rabies infections in organ donor and transplant recipients–Alabama, Arkansas, Oklahoma, and Texas, 2004. MMWR Morb Mortal Wkly Rep. 2004;53: 586–589.
165. Centers for Disease Control and Prevention (CDC). Update: Investigation of rabies infections in organ donor and transplant recipients—Alabama, Arkansas, Oklahoma, and Texas, 2004. MMWR Morb Mortal Wkly Rep. 2004;53:615–616.
166. Vora NM, Basavaraju SV, Feldman KA, et al.Raccoon rabies virus variant transmission through solid organ transplantation. JAMA. 2013;310:398–407. [PubMed: 23917290]
167. Johnson N, Brookes SM, Fooks AR, et al.Review of human rabies cases in the UK and in Germany. Vet Rec. 2005;157:715. [PubMed: 16311386]
168. Hellenbrand W, Meyer C, Rasch G, et al.Cases of rabies in Germany following organ transplantation. Euro Surveill. 2005;10:E050224.6.
169. Zhou H, Zhu W, Zeng J, et al.Probable rabies virus transmission through organ transplantation, China, 2015. Emerg Infect Dis. 2016;22:1348–1352. [PubMed: 27331337]
170. Chen S, Zhang H, Luo M, et al.Rabies virus transmission in solid organ transplantation, China, 2015–2016. Emerg Infect Dis. 2017;23:1600–1602. [PubMed: 28820377]
171. Baum SG, Lewis AM Jr, Rowe WP, et al.Epidemic nonmeningitic lymphocytic-choriomeningitis-virus infection. an outbreak in a population of laboratory personnel. N Engl J Med. 1966;274:934–936. [PubMed: 5948615]
172. Fischer SA. Emerging viruses in transplantation: there is more to infection after transplant than CMV and EBV. Transplantation. 2008;86:1327. [PubMed: 19033999]
173. Centers for Disease Control and Prevention (CDC). Brief report: Lymphocytic choriomeningitis virus transmitted through solid organ transplantation—Massachusetts, 2008. MMWR Morb Mortal Wkly Rep. 2008;57:799–801. [PubMed: 18650788]
174. Peters CJ. Lymphocytic choriomeningitis virus–an old enemy up to new tricks. N Engl J Med. 2006;354:2208–2211. [PubMed: 16723613]
175. Fischer SA, Graham M, Kuehnert MJ, et al.Transmission of lymphocytic choriomeningitis virus by organ transplantation. N Engl J Med. 2006; 354:2235–2249. [PubMed: 16723615]
176. Centers for Disease Control and Prevention (CDC). Lymphocytic choriomeningitis virus infection in organ transplant recipients—Massachusetts, Rhode Island, 2005. MMWR Morb Mortal Wkly Rep. 2005;54:537–539. [PubMed: 15931158]
177. Schafer IJ, Miller R, Ströher U, et al.Notes from the field: a cluster of lymphocytic choriomeningitis virus infections transmitted through organ transplantation—Iowa, 2013. MMWR Morb Mortal Wkly Rep. 2014;63:249. [PubMed: 24647402]
178. Mathur G, Yadav K, Ford B, et al.High clinical suspicion of donor-derived disease leads to timely recognition and early intervention to treat solid organ transplant-transmitted lymphocytic choriomeningitis virus. Transpl Infect Dis. 2017;19.
179. Palacios G, Druce J, Du L, et al.A new arenavirus in a cluster of fatal transplant-associated diseases. N Engl J Med. 2008;358:991–998. [PubMed: 18256387]
180. Burt FJ, Chen W, Miner JJ, et al.Chikungunya virus: an update on the biology and pathogenesis of this emerging pathogen. Lancet Infect Dis. 2017;17:e107–e117. [PubMed: 28159534]
181. Kee AC, Yang S, Tambyah P. Atypical chikungunya virus infections in immunocompromised patients. Emerg Infect Dis. 2010;16:1038–1040. [PubMed: 20507772]
182. Dalla Gasperina D, Balsamo ML, Garavaglia SD, et al.Chikungunya infection in a human immunodeficiency virus-infected kidney transplant recipient returning to Italy from the Dominican Republic. Transpl Infect Dis. 2015;17:876–879. [PubMed: 26771689]
183. Moura-Neto JA, de Souza Moura AF, Souza E, et al.Successful live kidney transplantation after chikungunya disease in the donor. Kidney Int Rep. 2017;2:1250–1253. [PubMed: 29270535]

184. Gibbons RV, Vaughn DW. Dengue: an escalating problem. BMJ. 2002; 324:1563–1566. [PubMed: 12089096]

185. Gupta RK, Gupta G, Chorasiya VK, et al.Dengue virus transmission from living donor to recipient in liver transplantation: a case report. J Clin Exp Hepatol. 2016;6:59–61. [PubMed: 27194898]

186. Chen LH, Wilson ME. Update on non-vector transmission of dengue: relevant studies with Zika and other flaviviruses. Trop Dis Travel Med Vaccines. 2016;2:15. [PubMed: 28883959]

187. Weerakkody RM, Palangasinghe DR, Dalpatadu KP, et al.Dengue fever in a liver-transplanted patient: a case report. J Med Case Rep. 2014;8:378. [PubMed: 25412699]

188. Schwartzmann PV, Ramalho LN, Neder L, et al.Zika virus meningoencephalitis in an immunocompromised patient. Mayo Clin Proc. 2017; 92:460–466. [PubMed: 28259231]

189. Recorded Zika Virus Webinar is Available. Organ Procurement and Transplant Network (OPTN). https://optn.transplant.hrsa.gov/news/recorded-zika-virus-webinar-is-available/#ref.Published July 27, 2016. AccessedFebruary 25, 2018.

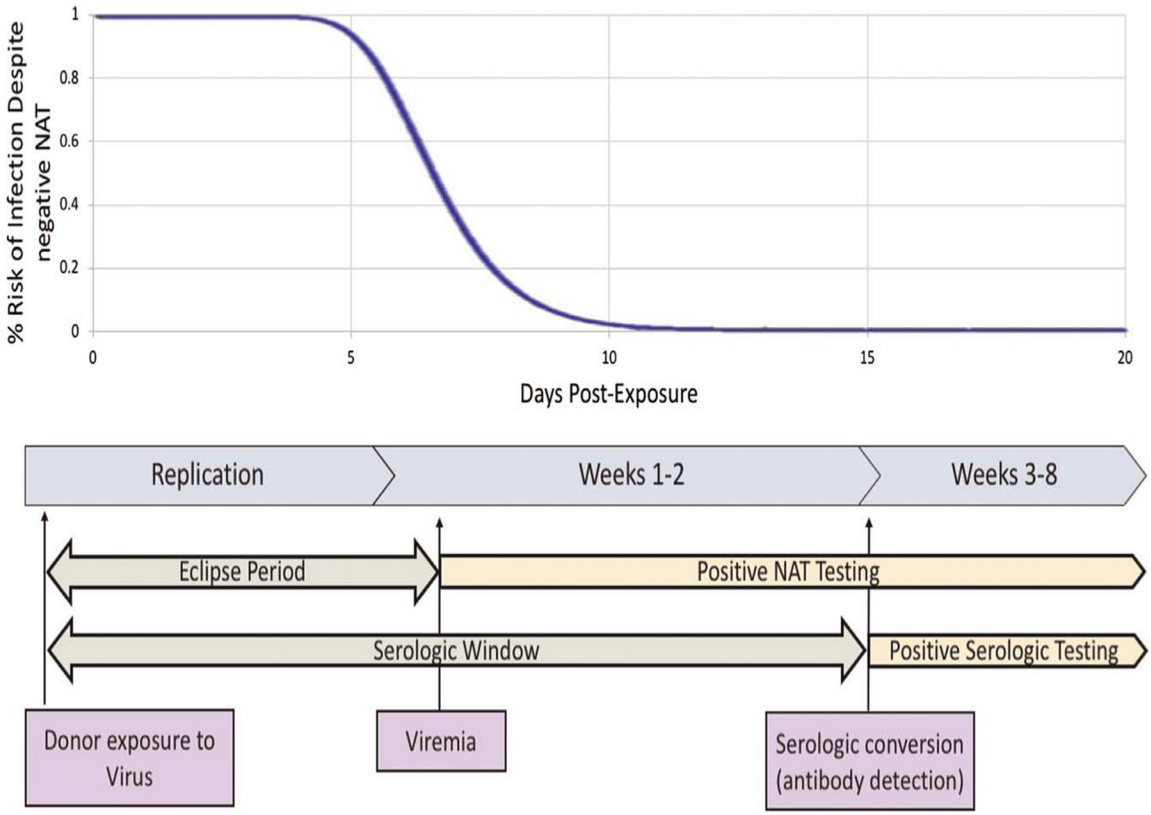

FIGURE 1.
Timing of positive screening testing after infection of the donor.

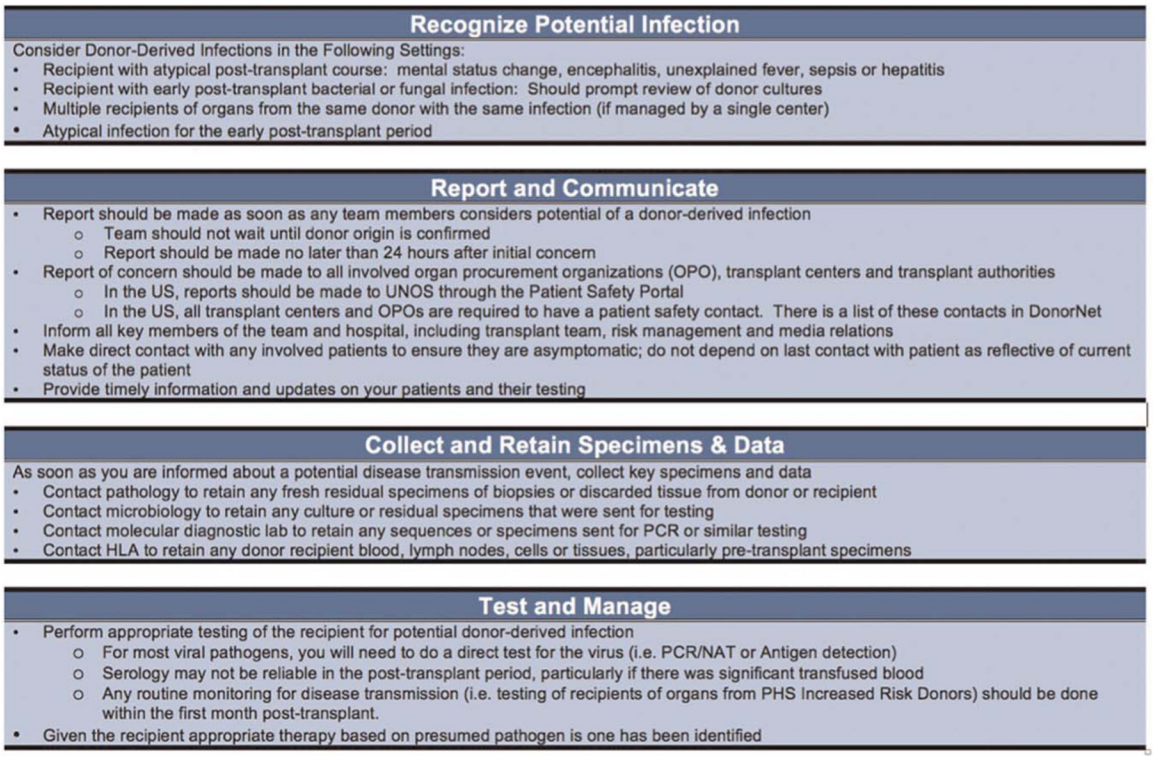

FIGURE 2.

Approach to a potential donor-derived infection.

TABLE 1.

Potential donor-derived disease transmission as reported to the OPTN: 2005–2016

	Reports (donors)	Recipients potentially involved	Recipients with proven/ probable transmission	Donor-derived disease attributable deaths (recipients)	Liver recipients with proven/ probable transmission[a]	Liver recipients donor-derived disease attributable deaths[a]
Malignancy	513	1111	156	42	49	16
Viruses	421	1243	192	25	48	4
Bacteria	455	1452	209	18	55	5
Fungi	258	847	166	24	39	4
Mycobacteria	123	394	30	7	7	1
Parasites	108	300	99	16	24	3
Other disease	102	341	56	3	17	1
Total	1980	5688	908 (15.1%)	135 (14.9%)	239	34 (14.2%)

[a]Liver Specific numbers are only reflective of 2012–2016 data; organ-specific data were not effectively collected before this time point.

Transplantation. Author manuscript; available in PMC 2021 September 10.

TABLE 2.

Hepatitis B serologic markers and interpretation

HBsAg	HBV NAT	HBcAb	HBsAb[a]	Interpretation	Risk of donor-derived transmission
+	+	+	+/−	Active HBV Infection	High
+	−	+	+/−	Active HBV Infection	High/medium
−	−	+	+	Recovered with cccDNA in hepatocytes	Organ dependent[b]
−	−	+	−	Recovered with cccDNA in hepatocytes[c]	Organ dependent[b]
−	−	−	+	HBV Vaccinated	No risk
−	−	−	−	No infection, no immunity	No risk

[a] Not usually available for deceased organ donors.

[b] High for liver transplants and typically requires antivirals posttransplant; nonliver patients represents low risk, especially if recipient is vaccinated with detectable HBsAb.

[c] In most cases, this represents recovered with cccDNA in hepatocytes; rarely may reflect false-positive HBcAb, occult chronic infection, resolving acute infection.

TABLE 3.

Residual risk of HIV and HCV by risk behavior

Risk factor	HIV serology only	HIV serology + NAT°	HCV serology only	HCV serology + NAT[a]
Men who have sex with men	0.10%	0.04%	0.33%	0.04%
IV drug users	0.12%	0.05%	3.00%	0.32%
Commercial sex workers	0.07%	0.03%	1.20%	0.12%
Sex with partner in the above categories	0.007%	0.003%	1.20%	0.12%
Exposed to blood products	0.015%	0.006%	0.04%	0.004%
Incarceration	0.02%	0.009%	0.07%	0.008%

[a]The residual risk of infection with serology and NAT infection is only true if testing is done outside the NAT window period which is 5–6 days for HIV and 3–5 days for HCV. The NAT window period is the time from last risk behavior to testing. If a donor is tested within the NAT window period, the serology only residual risk should be utilized for discussions with potential recipients. For detailed guidance, see: https://optn.transplant.hrsa.gov/media/2270/dtac_guidance_risks_201706.pdf.