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Viral Transmission in Organ Transplantation: The Importance of Risk Assessment

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Additional information is available at the end of the chapter

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Abstract

Organ transplantation presents a low but extant risk of allograft transmission of blood-borne viruses (BBV) including human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Other infections temporarily present in blood are also transmissible from donor to recipient, such as cytomegalovirus (CMV), polyomavirus (BK), Epstein-Barr virus (EBV), and others, where the donor has acute infection at the time of donation. Decisions about accepting organs for transplantation involve a trade-off between the acquisition of good-quality organs, which can confer longer survival time for the recipient, but at the risk of dying from waiting too long from the underlying condition, versus accepting an organ of less quality, but at the risk of potentially acquiring a donor-derived infection (DDI), unless such infection can be ruled out in the donated organ. In this chapter, we describe the different factors contributing to the overall risk of acquiring a BBV infection through the allograft, mechanisms for assessing risk of the donor and the different strategies available to minimize or mitigate the risk. The process is one of risk assessments and risk ameliorations through optimum laboratory and clinical assessment processes, so that transplantation professionals can balance the overall risk against the life-saving and life-enhancing benefits of organ transplantation.

Keywords: blood-borne virus infection through transplantation, donor-derived infections, risk assessment, risk management, risk mitigation

1. Introduction

Organ transplantation currently provides definitive therapy for individuals with end-organ failure. Despite the enormous therapeutic advances in this area, donor-derived infections (DDI)

in the recipient from the donated organ, although rare, have been associated with significant morbidity and mortality [1,2]. These unexpected DDI are often with blood-borne viruses (BBV), including hepatitis B virus (HBV), hepatitis C virus (HCV), and less frequently human immunodeficiency virus (HIV) [3–5]. There are few data available to ascertain the risk of infection in organ transplantation for known and emerging pathogens, as most information comes from events of transmission, which are rare and not always well characterized, with few countries having well-established post-transplant surveillance systems with universal recipient assessment [6].

Due to the scarcity of donor organs, the safety paradigm in solid organ transplantation (SOT) should be based on a risk-benefit trade-off and the decision-making strategy for organ allocation be based on risk management. In this context, it is important to consider that most often the benefits of transplanting the organ outweigh the risk of DDI. Therefore, care should be taken to find the appropriate balance between minimizing the risk of transmission and organ wastage or recipient illness progression [7].

This chapter describes the different factors contributing to the overall risk of acquiring a BBV infection through the allograft, the risk assessment of the donor, and the different strategies available to minimize or mitigate the risk.

2. Donor assessment

Donor assessment often uses a questionnaire based on review of medical and social history to identify donor risks, including those associated with infection with blood-borne pathogens. In Australia, a standard questionnaire is available nationwide to streamline the assessment criteria [8]. The organ donor coordinator must review all potential donor's available medical records to identify evidence of an infectious disease or documentation of established risk behaviors associated with BBV infection. The information should be obtained from a next of kin and/or other person who has an established relationship with the donor (e.g. the donor's general practitioner). Attention to travel history is critical to identify donors at risk of endemic infections [9,10].

-
- Men who have had sex with another man in the preceding 5 years.
 - Intravenous, intramuscular, or subcutaneous injection of drugs in the preceding 5 years.
 - Incarceration in the previous 12 months.
 - Persons who have had sex in the preceding 12 months with any of the above persons or a person known or suspected to have HIV, HCV, or HBV infection.
 - Persons who have engaged in sex in exchange for money or drugs in the preceding 5 years.
 - Exposure in preceding 12 months through percutaneous inoculation or open wound.
 - Nonsterile tattooing, piercings in the past 12 months.
 - Unexplained fever/weight loss/LAD/cough.
 - Cocaine snorting.
 - Physical concern.
-

Table 1. Donors with identified risk factors.

Careful physical assessment of the donor’s body is conducted by both the organ procurement team and the procuring surgeon. The examination also searches for evidence of underlying disease, such as cirrhosis or other surface manifestations of infections, malignancies or of recent drug use [11]. In the acute donation situation, the appropriate person is not always available to question regarding the donor’s risk, and manifestations of BBV can be minimal or non-existent. Thus, optimal donor screening testing is of paramount importance.

3. Prevalence of infection

The prevalence of BBV infection on a given population is particularly important as donor history may fail to uncover donor risk factors and, especially in the case of HBV or HCV, the rate of prevalent disease remains relatively high in 2016 in many countries, even in donors without identified risks. BBV potentially transmitted from donor organ to recipient are prevalent at 2% of the Australian population (**Table 2**) [12], whereas cytomegalovirus (CMV), Epstein–Barr virus (EBV), and polyomavirus (BK) virus are far more common, with prevalence rates of 50–70%, 95% [13], and ~60% [14], respectively.

Virus estimated	Infected population	Prevalence rate (%)	Prevalence rate in high-risk population (%)
HIV	25,700	0.10	2.8
HBV	218,000	0.87	50
HCV	233,525	0.93	50
Total	468,525	1.9	80*

* Some individuals are infected with both HCV and HBV.

Table 2. Prevalence of BBV (HIV-1, HBV, and HCV) in the Australian population.

The prevalence of BBV among potential increased-risk organ donors in our laboratory in the Serology and Virology Division (SAVID), providing testing services to the NSW Organ and Tissue Donation Service was 50% for HBV, 10% for HCV, and 0.1% for HIV-1 [15]. In the United States, the prevalence of HIV and HCV in average-risk donors was reported to be 0.10 and 3.45%, respectively, whereas the prevalence of HIV and HCV among increased risk donors (IRDs) was 0.50 and 18.20%, respectively [16]. Viruses endemic to certain geographical areas or population groups including human T-cell lymphotropic virus 1 (HTLV-1) in the Australian Aboriginal population and HBV in Mediterranean and Asian Countries may be one reason for unexpected positive screening results of average-risk donors or donors without apparent risk factors [17]. The WHO publishes updated prevalence figures of BBV worldwide, which could assist in ascertaining the probability of BBV latent infections [18] and hence background risk of donor infection.

4. Serology/nucleic acid testing results

Donors are routinely screened to identify viral or bacterial infection using serology and nucleic acid testing (NAT) assays. NAT assays detect the presence of specific viral or bacterial RNA/DNA in a patient's blood. The latter is a marker of infectivity of the organ donor when compared with antibody tests, which show previous infection without distinguishing current infection. All BBV serological tests have a 'window period' (WP), which is a time after infection during which the antibody response cannot be detected by the usual testing methods (**Figure 1**). The serological WP varies with the sensitivity of the assay, but generally are 17–22 days for HIV, 38–60 days for HBV, and 70 days for HCV.

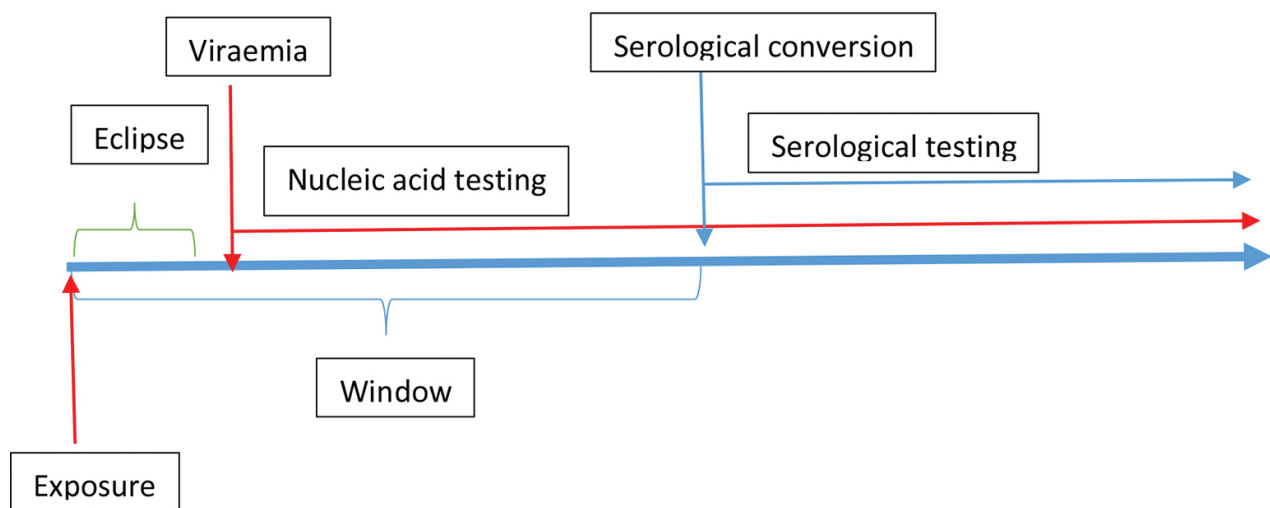


Figure 1. Events taking place after viral exposure.

NAT assays significantly reduce the WP between infection and detection compared with serological testing (6–7 days for HIV, 30–40 days for HBV, and 4–6 days for HCV) (**Figure 2**). Thus, NAT assays also have WP when they are negative following acute infection, therefore a negative NAT assay result does not completely eliminate the possibility of recent infection. In practice, the risk of infection from screened donors has been extremely low, but no screening test that is performed on a donor is entirely capable of reducing risk of transmission to nil, although all efforts are taken to reduce risk of BBV transmission and effectively resulting in extremely low risk.

All potential organ donors (living or deceased) should be tested for antibodies to HIV (anti-HIV 1/2 antigen/antibody combo assay), HCV and HBV. Donors should also be tested for HIV, HCV, and HBV RNA/DNA, whereas increased-risk organ donors should be tested by NAT for HIV, HCV, and HBV prospectively (**Table 3**).

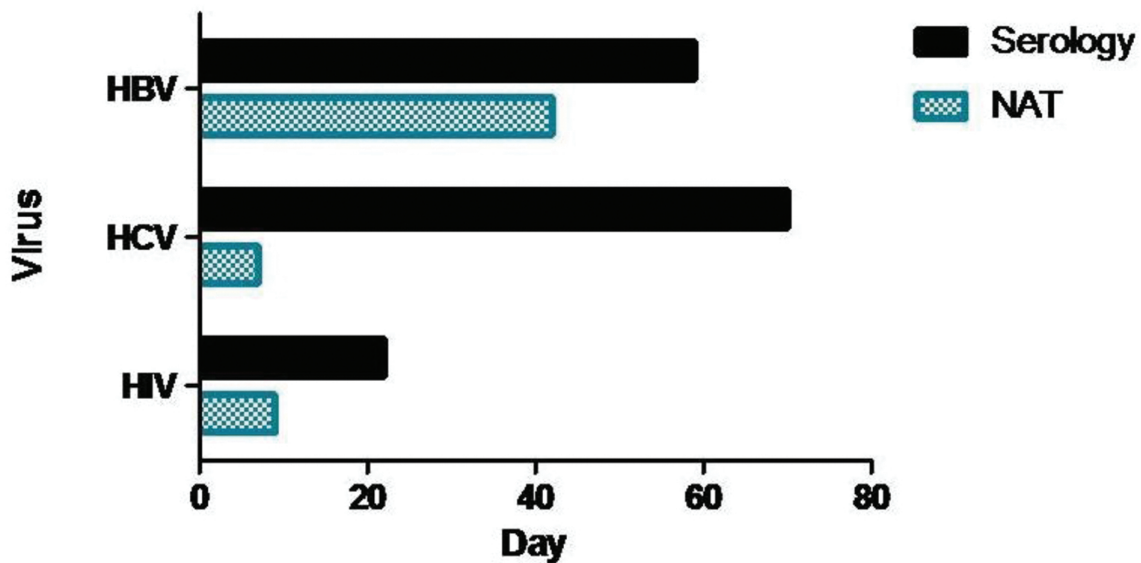


Figure 2. Differences in window periods for serology and NAT for HIV, HCV, and HBV (Data from SAVID).

Serology:	NAT:
• Anti-HIV-1/2	• HIV-1 RNA
• Anti-HCV	• HCV RNA
• Anti-HTLV-I/II	• HBV DNA
• HBsAg	• Prospective in increased risk donors
• Anti-HBc	• Retrospective in average-risk donors
• Anti-HBs	
• Anti-EBV	
• Anti-CMV	
• Syphilis antibody (TPHA)	

Table 3. Mandatory testing for prospective organ donors in Australia.

The WP of an assay has important implications for the risk assessment of a particular donor. The definition of IRD as per the Transplantation Society of Australia and New Zealand guidelines [11] is “where there is concern regarding the donor’s risk behavior and it cannot be reliably determined or the behavior may have occurred within the last 2 months”. These 2 months cover the NAT WPs for HIV, HCV, and HBV (**Figure 2**).

The arrival of fully automated platforms for triple viral NAT currently in 2016 in Australia by at least two manufacturers opens the possibility of 24-hour access to HBV, HCV, and HIV NAT testing. New technologies, such as the Cobas 6800 system [19] from Roche Molecular Systems

and the Panther system [20] from Hologic, are now available with shorter turnaround time (TAT = 3.5 hours), and the possibility of confirmatory testing of initially positive results.

5. Conduct of donor testing

If the specimen sample used for testing has unusual characteristics, such as where donors have had massive blood and/or blood product transfusion, it is essential to indicate to the testing laboratory and the transplanting team the underlying condition of the donor. If the donor has received greater than 50% of blood volume in blood product transfusion, the sample is unsuitable for serology and NAT testing due to dilution of native antibodies by transfused fluids [21]. A pre-transfusion sample should be provided to the laboratory. If this is not possible, NAT-enhanced sensitivity may reduce the frequency of false-negative test results when donor specimens are haemodiluted.

There are significant concerns that the use of assays with higher sensitivity for pathogen detection—such as NAT assays—will result in net organ loss. This is because the majority of positive tests in low-prevalence populations will be false positives [22], and time constraints do not allow confirmatory testing with certain testing platforms. The NAT laboratory at SAVID, Prince of Wales Hospital in Sydney, Australia, has developed screening algorithms using three NAT assays run in parallel for prospective screening of IRD to maximize organ availability by effectively eliminating false-positive results (FPR) [15]. The availability of a 24-hour NAT screening service for organ donors provided diagnosis within 8 hours and enabled the use of organs from donors with positive serology but negative NAT results or donors with false-positive serology results. This algorithm allowed us to perform real-time discrimination of initially reactive results and the use of 35 IRD, which resulted in transplantation of 102 additional organs with safer expansion of the donor pool.

Positive serology or NAT results should be interpreted consistent with current guidelines [10,16] by the accepting teams in consultation with an Infectious Disease Physician.

6. Risk of transmission

The risk of acquisition of a BBV through organ transplantation is related to the efficiency of virus transmission and replication after contact with blood and tissues. Not all BBV are transmitted in the same way, and the result may be related to the type and size of the inoculum, the titre of virus and the immunization status of the recipient. Most of the well-documented transmissions are from blood transfusions but this may correlate with similar level of infectivity from donated organs. In humans, HBV transmission has been reported to be from blood donors in the WP or from donors with occult hepatitis B (OBI) with HBV viral loads of >20 IU/ml [23], whereas donors with an anti-HBs titre of >100 seem to have a protective role to prevent de novo HBV infection [24]. In terms of HIV, a pre-seroconversion donation with a viral load of ≤150 copies of RNA/ml went undetected and resulted in an HIV transmission [25]. Finally, HCV-infected recipients have been reported from donors with a viral load of as low as 182 cp/

ml and even from a donor with undetectable levels of RNA in the transcription-mediated amplification (TMA) assay (limit of detection (LOD) = 9.6 IU/ml)) [26].

In a report by the Canadian Society for Transplantation and Canadian National Transplant Research Program [27], the residual risk to acquire a HIV or HCV infection from transplanted organs of IRD after screening with serology and NAT was calculated (**Table 4**). The group concluded that these donors should be screened by serological testing in conjunction with NAT testing for HCV and HIV and hepatitis B surface antigen (HBsAg) or NAT for HBV.

Virus	Risk of WP infection for NAT and ELISA per 10,000	Risk of WP infection for NAT and ELISA expressed as ratio
HIV	0.71	1:14,923
HCV	3.79	1:2,637

Table 4. Risk per 10,000 donors of an HIV or HCV infection occurring during the WP, by enzyme-linked immunosorbent assay (ELISA) and NAT. Assumes a WP of 21 days for ELISA and 7 days for NAT.

7. Organ-specific risks

HBV- and HCV-infected livers produce universally infected HBV- or HCV-naïve recipients, with outcomes determined by factors, such as the viral genotype, the presence or absence of previous immunity and the response to antiviral therapy. On the other hand, a HCV- or HBV-infected donor may be able to donate other organs rather than the liver. As both HBV and HCV can be transmitted via organ donation, especially through liver grafts, a thorough approach is needed for successful management of the recipient, and an emphasis on aggressive immunization and risk mitigation of transplant candidates prior to transplant should be pursued.

Allografts from HBV-infected donors should preferentially be given to recipients who are HBsAg positive, hepatitis B core antibody (anti-HBc) positive, or hepatitis B surface antibody (HBsAb) positive [28]. Transmission of de novo HBV infection to liver graft recipients from anti-HBc-positive donors has been detected since 1992; however, further studies demonstrated that non-liver allografts from these donors can be safely used [29,30]. Several studies have clearly shown that non-liver organs and tissues from donors who are anti-HBc positive and HBsAg negative can be used with negligible risk, especially if the recipient is protected through vaccination or prior exposure to HBV [31,32].

A different scenario is that of donors with OBI, characterized by persistence of HBV DNA in the liver tissue (and in some cases also in serum) of HBsAg-negative individuals [33], therefore exhibiting undetectable HBsAg in serum and low-level HBV DNA (<200 IU/ml). In HBV, low-prevalence countries, the prevalence of OBI is low (0.1–2.4%) [34], whereas in HBV, high-prevalence countries, the prevalence can range from 7.5 to 16% [35,36].

The molecular bases of OBI appear to be related to the long-lasting persistence in the nuclei of the hepatocytes of the HBV cccDNA, an intermediate form of the virus life cycle that serves as a template for gene transcription [37,38]. The risk of OBI being associated with anti-HBc seropositivity has been demonstrated [39,40], and one of the best sentinel markers for OBI is a positive anti-HBc serology result [41]. Long-standing abnormal results of liver function tests of unknown aetiology in the absence of HBV serological markers and serum HBV DNA may also indicate the presence of HBV DNA in the liver and peripheral blood mononuclear cells [42]. Donors with OBI may transmit HBV infection, especially in orthotopic liver transplantation (OLT), because the hepatocytes are the reservoir of the viral cccDNA. These recipients may develop de novo hepatitis B, particularly when they are HBV naïve [43,44]. Prevention measures include anti-HBV prophylaxis, based on anti-HBs immunoglobulin alone or in combination with lamivudine. These measures, however, cannot completely eliminate HBV transmission because there have been documented reports on the development of OBI in recipients who received an organ from an OBI carrier [44], exhibiting the same viral genomes (including HBV cccDNA) in the transplanted liver.

As already mentioned, HBV-infected donors can be safely used for potential HBV-infected recipients [28] with the use of post-transplantation prophylaxis (hepatitis B immune globulin (HBIG) and nucleoside/nucleotide polymerase inhibitors, such as lamivudine in combination with adefovir, entecavir, or tenofovir) [45–47]. It has also been reported that a titre of HBsAb greater than 100 in the donor has a protective effect [48]. Recipient sero-protection through prior exposure or vaccination is a highly effective way to prevent transmission of HBV through organ transplantation [49]. As some potential organ recipients do not respond well to vaccination and remain unprotected, a priority area is to devise new ways to enhance vaccination responses.

HCV-positive donor organs can also be used in HCV-positive recipients with minimal impact on clinical outcomes [50,51]. Clinical studies have shown that there is no significant difference in survival in HCV-positive recipients who receive either HCV-positive or HCV-negative livers or kidneys [51–55]. Therefore, there needs to be education to enhance uptake of HCV-positive organs in HCV-positive recipients. As first-generation direct acting antivirals (DAAs) offer a significant therapeutic improvement when compared with previous therapies, particularly for patients with HCV genotype-1 infection, this may lead to the use of more HCV-infected organ donors for HCV-infected recipients treated with this highly effective post-transplant prophylaxis [56,57].

8. Use of IRDs

In the United States alone, almost 10,000 individuals die annually while awaiting organ transplantation [58], whereas in Australia, there are almost 3000 individuals in the waiting list. Due to organ scarcity, attempts at expanding the pool of potential donors are necessary, and the criteria for donation are under continuous scrutiny. Recent campaigns globally from organ procurement agencies to expand the donor pool have resulted in use of organs from IRD, who

are at greater risk of infection with BBV, including HBV, HCV, and HIV. The use of NAT to screen such IRD has been associated with increased utilization of these organs [10,11,16,27].

The key to using these IRD is to maximize the measures to identify risk factors; particularly ensuring that infectious diseases are not transmitted from donor to recipient in the allograft. A successful strategy to mitigate the overall risk has been to match the allograft to the most appropriate recipient by improved selection and monitoring. In such scenarios, additional consent and recipient screening at regular intervals during the first year after transplant should be performed [10,11,16,27].

We documented in one study that with the use of prospective NAT, 102 additional organs from IRD were used in Australia. These organs would otherwise have been discarded or used with restrictions [15]. This represents 18.8% of all organs transplanted during the study period. Furthermore, the utilization of parallel NAT assays combined with mathematical modeling enabled us to estimate the probability that the combination of results were predictive of true-positive results. Thus, we piloted a methodology for effectively minimizing FPR. This resulted in higher confidence in the NAT results and minimizing the loss of organs secondary to FPR to negligible.

In a Canadian study of 3746 transplants using deceased liver donors [59], it was concluded that over the last decade, there was an increase in the use of older donors and donation after cardiac death (DCD) organs, but recipient survival was not compromised. In Australia, IRDs are routinely used, and this strategy has substantially contributed to an increased use of organs [15]. Furthermore, the acceptance of these organs by the transplantation community has been increased over the years, and from 2013 onwards, the same number of organs was retrieved from IRD and from average-risk donors (**Figure 3**).

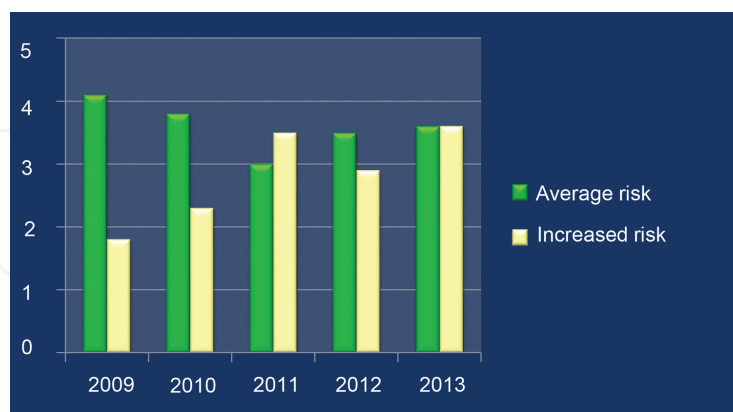


Figure 3. Number of organs retrieved from increased-risk donors vs average-risk donors over the years (data from SA-VID).

Final decisions in individual cases about using organs of IRD must acknowledge the recommendations from national and international guidelines, the risk-benefit trade-off in the context of the gravity of recipient's prognosis without transplantation, consideration of all clinical and

laboratory assessment parameters and a fully informed consent and risk acceptance by the recipient.

9. Scoring the risk

Decision aids are increasingly being developed to support transplantation teams in making difficult treatment decisions involving trade-offs between provision of a good quality organ with longer survival but longer wait pre-transplant versus accepting an organ of less quality with earlier transplantation but higher risk of shorter survival post-transplantation or post-transplant infections. Furthermore, transplant providers who are helping patients to make treatment decisions may find it difficult to communicate the risks associated with each option in a clear, understandable fashion, particularly for IRD organs, given the complexities of risk assessment.

Scoring systems to indicate recipient's gravity include the Model for End-Stage Liver Disease (MELD) score, which is a scoring system for assessing the severity of chronic liver disease. It was found to be useful in determining prognosis and prioritizing for receipt of a liver transplant [60]. The score was developed by the Organ Procurement and Transplantation network (OPTN)/United Network for Organ Sharing (UNOS) and implemented in February 2002. MELD uses the patient's values for serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time (INR) to predict survival. It is calculated according to formula [61]. On the other hand, the donor risk index (DRI) by Feng et al. [62] using Organ Procurement and Transplantation Network (OPTN) data was developed as a continuous scoring system that includes donor and transplant parameters that significantly influence outcomes after liver transplantation (LTx). The author undertook a multivariate analysis of a large cohort (20,023 transplants) from the Scientific Registry of Transplant Recipients database. The parameters used were the donor's age, race, height, and cause of death (COD); the split liver donation status; the donation after cardiac death (DCD) status; the type of allocation (local, regional, or national); and the cold ischaemia time.

The DRI was validated in a study conducted by the Eurotransplant region, which aimed to identify its potential use [63]. The study was a database analysis of all 5939 liver transplants involving deceased donors and adult recipients from January 1, 2003, to December 31, 2007, in the Eurotransplant region. Follow-up data were available for 5723 patients with a median follow-up of 2.5 years. The mean DRI was remarkably higher in the Eurotransplant region versus OPTN (1.71 versus 1.45). The results demonstrated that Kaplan-Meier curves per DRI category showed a significant correlation between the DRI and outcomes ($p < 0.001$). A multivariate analysis demonstrated that the DRI was the most significant factor influencing outcomes ($p < 0.001$). Among all donor, transplant, and recipient variables, the DRI was the strongest predictor of outcomes.

In another study [64], it was investigated the impact of the DRI on the outcome of HCV-infected patients undergoing LTx, where the median DRI was 1.3 (range, 0.77–4.27). Increasing DRI was associated with a statistically significant increase in the relative risk (RR) of graft failure

and patient death for both HCV (+) and HCV (-) recipients. Finally, Rosemberg et al. [65] using a prospectively collected infection data set, matched liver transplant recipients (and the respective allograft DRI scores) with their specific post-transplant infectious complications. All transplant recipients were organized by DRI score and divided into groups with low-DRI and high-DRI scores. Three hundred and seventy-eight liver transplants were identified, with 189 recipients each in the low-DRI and high-DRI groups. The mean MELD scores were 26.25–0.53 and 24.76–0.55, respectively ($p = 0.052$), and the mean number of infectious complications per patient were 1.60–0.19 and 1.94–0.24, respectively ($p = 0.26$). Logistic regression showed only length of hospital stay and a history of vascular disease as being associated independently with infection, with a trend toward significance for MELD score ($p = 0.13$). The study concluded that although DRI score predicts liver graft survival, infectious complications depended more heavily on recipient factors.

Even though organs from donors with high DRI score correlate with poorer post-transplant survival, the overall contribution of high-DRI grafts to the donor pool and the resultant reduction in wait list mortality make them cost-effective [66].

10. Clinical guidelines

Deciding how to allocate organs for transplantation is a very complex process and raises a number of clinical and ethical issues. Up-to-date guidelines provide an overarching framework to facilitate the decision-making process in clinical robust ways based on previous evidence. In general, transplantation guidelines follow many of the recommendations in place for the selection and microbiological testing of blood donors. However, as in organ donation and transplantation, the logistics are greatly influenced by the need to retain organ viability, the testing of potential donors will be conducted under severe time constraints. In these situations, the testing that needs to be carried out, and the general principles for balancing the risks and benefits are unique to this field.

Some of the most important transplantation guidelines published recently are as follows:

- *PHS Guideline for Reducing Human Immunodeficiency Virus, Hepatitis B Virus, and Hepatitis C Virus Transmission Through Organ Transplantation* was published in the United States in August 2013 [16]. The aim of the guide was to improve organ transplant recipient outcomes by reducing the risk of HIV, HBV, and HCV transmission. The guide is truly comprehensive and based on systematic reviews. It is extremely detailed and specialized and not very practical for the daily use of transplantation professionals.
- Advisory Committee on the Safety of Blood Tissues and Organs (SaBTO) published the *Guidance on the Microbiological Safety of Human Organs, Tissues and Cells Used for Transplantation* in February 2011 in the United Kingdom [67]. The guidance was written by a working group after extensive consultation and is extremely clear, accurate, and user friendly. However, as professionals involved in transplantation need to take real-time decisions that could be life saving for patients, most of the information given in the guidance could have been summarized and presented on tables to facilitate the information to readers.

- The Council of Europe in 2013 published the 5th edition of *the Guide to the Quality and Safety of Organs for Transplantation* [68]. This guideline collates updated information to provide professionals in transplantation with a useful overview of the most recent advancements in the field. The guide has a very comprehensive section on risk of transmission of infectious diseases. However, as pointed out before, the information is too comprehensive and should have been summarized.
- Transplantation Society of Australia and New Zealand (TSANZ) published version 1.4 of the guideline *Organ Transplantation from Deceased Donors: Consensus Statement on Eligibility Criteria and Allocation Protocols* in April 2015 [11]. The guide has only one section related to transmission of infectious agents from donor to recipient with data from HCV and HBV infection risks alone. The information is insufficient as many other real-life situations are not contemplated. Within Australia, the NSW Ministry of Health published the guide *Organ Donation and Transplantation—Managing Risks of Transmission of HIV, HCV and HBV* in 2013 [10]. This is a very useful guide for transplantation professionals.

Ideally, guidelines for transplantation should be comprehensive but presented in a concise manner to facilitate its use to readers, as shown in **Table 5** [69].

Donor status	Advice	References
Antibody to HIV (+)	Exclude from organ donation	[11,67]
Antibody to HCV (+)	Exclude from organ donation for HCV (-) recipients If used, usually reserve organ for recipient HCV (+) or severely ill recipient. HCV RNA testing should be done and allocated to a donor with a higher HCV viral load	[11,67]
Hepatitis B surface antigen HBsAg (+)	Exclude from organ donation. Use in life-threatening situations with recipient antiviral prophylaxis against HBV	[11,67]
Hepatitis B core antibody IgG (anti-HBc) (+)	Indicates past HBV infection. Organs from anti-HBc (+) of anti-HBs (-) may still be infectious. High risk for transmission with liver donation—generally used with intensive prophylaxis. Non-hepatic organs—small risk of transmission of HBV, and generally used for immunized HBsAb (+) recipients	[11,67,70,71]
Hepatitis B surface antibody Anti-HBs (+)	Anti-HBs >100 IU/l and anti-HBc (+) donations unlikely to be infectious and donation is permitted with the potential exception of livers (see above). HBV DNA NAT should be done and available prior to organ donation HBV DNA (-) indicates suitability for donation, though does not exclude risk of infection from liver. Use in vaccinated recipients and with negative NAT testing if donor vaccination unknown	[11,67,70,71]
Antibody to CMV (+)	Donation permitted. Post-transplant CMV monitoring and preventive strategy based on risk to the recipient	[67]
Antibody to EBV (+)	PCR monitoring of the seronegative or paediatric recipient	[67]

Donor status	Advice	References
RPR (+)	Not a contraindication to donation. Recipients receive standard prophylaxis (benzathine penicillin or ceftriaxone). Ensure administration of adequate antimicrobial therapy and the patient should be monitored for serological evidence of syphilis infection	[11,67,70,71]
Antibody to HTLV I/II (+)	High rate of false-positive results and consistent strategy not available. Some centers exclude from organ donation or use for life-threatening situations, with informed consent	[11,67,71]
Antibody to Toxoplasma IgG (+)	Not a contraindication to donation. Seronegative recipients with a seropositive donor should receive prophylaxis. Cardiac recipients particularly prone to transplant-associated toxoplasmosis	[11,67,71]
Viral encephalitis	Unknown etiology in donor is a contraindication to transplantation (risk of rabies, West Nile Virus or other exotic neurotropic infections). HSV or VZV CNS infection is a contraindication as it may cause systemic infection. HSV encephalitis without evidence of systemic infection treated with antivirals may be used, and antiviral prophylaxis should be used for the recipient. Local HSV/VZV infection treated with adequate antiviral therapy for >7 days organs can be used; if treated <7 days, recipient should receive antiviral prophylaxis (the serological status of the recipient must be known)	[67]

Anti-HBs, hepatitis B surface antibody; IgG, immunoglobulin G; RPR, rapid plasma reagin; VZV, Varicella Zoster virus.

Table 5. Recommendations for organ allocation based on screening data as at 2015 – subject to change with changes in policy.

This kind of format is how the Scandinavian guidelines have been presented and this could be a very useful resource for professionals identifying organ donors, transplant co-ordinators managing the donation process, and transplant physicians responsible for organ allocation [72].

11. Risk stratification and management

Currently, there are two ways in which organ donors are risk stratified in Australia: donors are dichotomized as being either at increased risk (IRD) or without identified risk factors for transmission of infectious diseases. **Figure 4** shows the flowchart for BBV testing and risk stratification in New South Wales (NSW), Australia [10].

In principle, any reactivity in one or more of the mandatory marker assays used for screening donors renders the donor ineligible. However, in life-preserving situations, it is possible to waive this exclusion. The risk-benefit trade-off means that using an IRD should only be considered when the donation is life-preserving. In this situation, the transplant surgeon with

the informed consent of the potential recipient should balance the risk of infection against the risk of dying while waiting for another graft. Heart, lung, and liver transplants will almost always fit within this definition because the clinical situation of the recipient is likely to be terminal. However, short-term or intermediate support measures can be employed to avoid the immediate need for transplantation with an organ from an IRD.

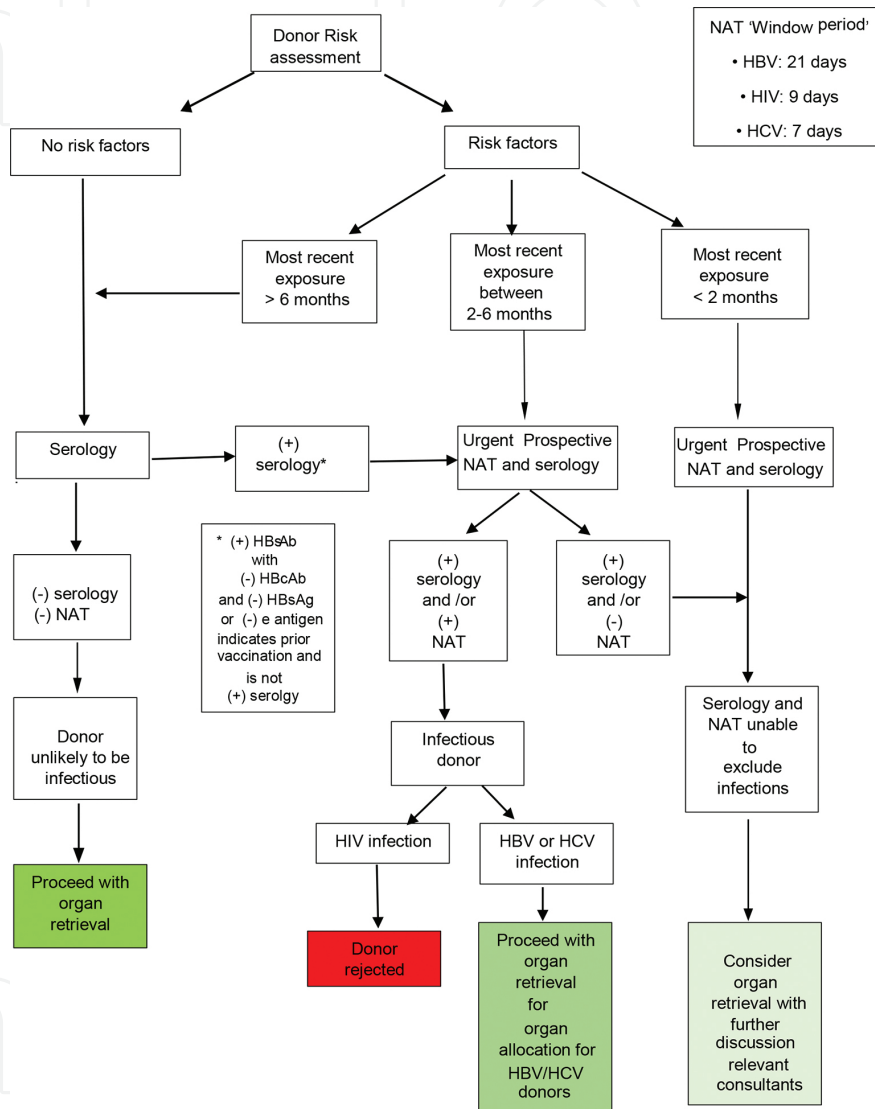


Figure 4. Blood-borne virus testing and risk stratification flowchart (from Organ Donation and Transplantation – Managing Risks of Transmission of HIV, HCV, and HBV). Reproduced with permission from NSW Ministry of Health, 2015.

One strategy when using IRD is matching infection status of donor and recipient. Previous infection, current infection, or immunization may decrease or remove the risk of infection following the use of a transplant from a donor who is known to be infected. Thus, it is appropriate to consider the use of an organ from a donor who is known to be infected, or who is potentially infected with HCV or HBV or a recipient who is also infected with HCV or HBV

(i.e. infection match). Another approach involves matching of the immune status of the recipient to the infection status of the donor. For example, a recipient shown to be immune to hepatitis B, naturally or by immunization, is unlikely to suffer re-infection from an HBV-infected donor. In this type of matching, it is essential that the status of the recipient is known with certainty.

Matching the status will also include an assessment of the likelihood of transmitting viral genotypes, which may pose an additional hazard to the already infected recipient, such as using an organ infected with HCV genotype 1 for a non-1 genotype-infected recipient; drug-resistant variants, and immune escape variants. Infectious Disease specialist support should be sought to ensure that appropriate testing has been undertaken to inform the risk assessment and to confirm the recipient's status.

Risk mitigation measures include the use of prophylaxis with antiviral drugs or antibiotics; counseling and discussing with the recipient the potential infection risk and the possibility of disease arising from infection. In addition, a full informed consent and post-transplant surveillance for infection of the recipient with planned interventions should they become necessary in the case of infection transmission should be undertaken.

12. Post-transplant surveillance

The final verification of risk estimates for DDI is carried out using post-transplant surveillance aiming to identify possible donor-derived events and clusters of transmissions. These procedures require careful post-transplant follow-up, diligent clinicians to suspect and report cases and reporting systems to accept and inform investigation of potential transmission reports in a proactive manner. These systems, if universally instituted, could improve investigation of potential clusters of infection, with enhanced rapid detection and improved advice to clinicians. Furthermore, they can be valuable resources for examination of clinical data to establish evidence-based guidelines.

Recent biovigilance initiatives in the United States and Europe have occurred with the aim of developing national surveillance systems for cells, tissues, and organs. In Europe, the Eustite project [73] initiated in 2008 focused especially on inspection, training, and vigilance for tissue banks. The project developed special tools and a system for the classification and reporting of adverse events to all European countries that could be used internationally for biovigilance and surveillance. Subsequently, the tools developed by the Eustite project were streamlined by the WHO, resulting in an educational program designed for organs and tissues through the NOTIFY Project. The vigilance information database collected by the Notify Project is available on the WHO/CNT Global NOTIFY Library website [74]. The library aims to be a comprehensive reference of different types of adverse events and reactions identifying their underlying root causes. The library is regularly maintained and updated and serves as a communication hub for transplantation institutions with international vigilance and surveillance data to enhance donor and recipient safety and for greater public transparency in

transplantation. The project also aims to be a reference of internationally terminology for biovigilance of organs, tissues, and cells.

The US program monitoring DDI (the UNOS and the Disease Transmission Advisory Committee (DTAC)) [75] undertakes data collection and dissemination on pre-transplant and post-transplant events and examines and classifies potential donor-derived transmission through transplantation of infection or malignancy. These aim to educate the transplant community and help change policy and improve processes. The membership includes CDC, FDA, transplant centers, transplant infectious disease professionals, laboratory testing personnel, and organ procurement organizations. The OPTN currently requires reporting of donor-derived events. All potential donor-derived transmission events (PDDTE) reported to OPTN/UNOS are reviewed by the DTAC, and real-time reports are available for transplantation professionals.

The ANZDATA [76] registry in Australia and New Zealand is a retrospective reporting system to evaluate data from donors and recipients. Attempts are recently made for timely data collection of key events and the creation of a real-time Web-based system utilization, including historical data for all years and real-time data for the current year grouped by country and state with interactive reports that can be generated at any point of time.

Most of the established surveillance systems are passive, that is laboratories notify positive test results to public health regulators. Thus, only recipients tested are notified. This system is far from ideal as most infections with a BBV do not have symptoms at the time of infection and an infected recipient may not be tested for some time post-transplant. Furthermore, not all notifications are followed up, so a recently infected organ recipient may not be detected even if tested and notified.

Despite the efforts in many countries to gather transplantation data, the main difficulty seems to lie in the absence of dedicated organ donation and transplantation surveillance registries, as usually the transplant team reports back to the organ donation agency and the data are not shared. The transplantation community requires a real-time worldwide surveillance system to identify possible clusters of infections worldwide. This could be achieved through data linkage from already established biovigilance programs. An important aspect of biovigilance systems is to develop data linkages with public health regulators and healthcare providers, so that the integration of databases can be conducted to strengthen responses to potential BBV threats worldwide.

13. Conclusions

The development of national policies for risk assessment and definition of acceptable levels of risk for BBV infection—including specific risk-benefit assessments—is increasing safety, equity and transparency in organ allocation. All decisions related to virological risk assessment need to be supported by up-to-date guidelines, optimal diagnostic testing and ongoing surveillance for DDI post-transplantation. This will continue to result in additional use of organs and continuous improvement of transplantation outcomes.

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