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Minireview

An Update on Donor-Derived Disease Transmission in Organ Transplantation

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Several recent donor-to-recipient disease transmissions have highlighted the importance of this rare complication of solid organ transplantation. The epidemiology of donor-derived disease transmissions in the United States has been described through reports to the Organ Procurement and Transplant Network (OPTN); these reports are reviewed and categorized by the *ad hoc* Disease Transmission Advisory Committee (DTAC); additional data comes through the published literature. From these reports, it is possible to estimate that donor-derived disease transmission complicates less than 1% of all transplant procedures but when a transmission occurs, significant morbidity and mortality can result. Only through continued presentation of the available data can continuous quality improvements be made. As the epidemiology of donor-derived disease transmission has become better understood, several groups have been working on methods to further mitigate this risk.

Key words: Donor-derived, donor screening, infection, malignancy, patient safety, transplantation

Abbreviations: CLL, Chronic Lymphocytic Leukemia; CMV, Cytomegalovirus; CNS, Central Nervous System; DSA, Donor Service Area; DTAC, *Ad Hoc* Disease Transmission Advisory Committee; GIST, Gastrointestinal Stromal Tumor; HBV, Hepatitis B; HCV, Hepatitis C; HIV, Human Immunodeficiency Virus; HTLV, Human T-Lymphotrophic Virus; IWDT, Intervention Without Documented Transmission; LCMV, Lymphocytic Choriomeningitis Virus; MOTT, Mycobacteria Other Than Tuberculosis; MRSA, Methicilin-resistant *Staphylococcus aureus*; NAT, Nucleic Acid Testing; OPO, Organ Procurement Organization; OPTN, Organ Procurement and Transplantation Network; TB, *Mycobacterium Tuberculosis*; UNOS, United Network for Organ Sharing; VRE, Vancomycin-Resistent Enterococuccus; WNV, West Nile Virus.

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Introduction

Organ transplantation uses fresh tissue from donors that have been screened for a finite number of pathogens; as such, the possibility of donor-derived disease transmission will always be a persistent risk associated with the procedure. Donor-derived disease transmissions are defined as any disease present in the organ donor that is transmitted to at least one of the recipients. Expected transmission, in which a disease, such as cytomegalovirus (CMV) and hepatitis B virus (HBV), is recognized in the donor and transmitted with the organ occur frequently; use of preemptive monitoring and universal prophylaxis minimize the impact of these disease transmissions (1,2). It is important to recognize that despite these interventions, clinically significant disease from these expected transmission does occur (3). Unfortunately, unexpected transmissions, such as Chagas, HIV, HCV, lymphocytic choriomeningitis virus (LCVM), *Mycobacterium tuberculosis*, rabies and West Nile Virus (WNV) (3–9), may occur despite current screening strategies. In some of these transmission events, clinical disease in the donor was not recognized at the time of donor death (3,8) while in other cases, screening, although available, was not performed for the pathogen of interest (10–12). Although most disease transmissions have involved deceased donors, a recent transmission of HCV has shown that recipients of living donors may be at risk as well.

The definitions of expected and unexpected donor derived disease transmission can be extended to encompass neoplasms. The overwhelming majority of such cases would fall into the unexpected category, since care is taken to avoid transplantation of tumor bearing organs. However, lifesaving transplants may on occasion require the use of organs from donors with a past history of neoplasia or with one of a small subset of active tumors whose possible transmission is felt to represent a reasonable and manageable risk. Such transplants would generate an expected risk of transmission and should similarly lead to specific monitoring with active intervention as necessary.

The transplant community has responded to the recognized threat of unexpected disease transmission through changes in policy and practice related to screening

Table 1: DTAC classification of donor-derived disease transmissions

Disease transmission	Category	Definition
Confirmed transmission	Proven	All of the following conditions must be met: • Suspected transmission event. • Laboratory evidence of the suspected organism or malignancy in a recipient. • Laboratory evidence of the same organism or malignancy in other recipients (if multiple recipients)[1]. • Laboratory evidence of the same organism or malignancy in the donor. • If there is pretransplant laboratory evidence, it must indicate that the same recipient was negative for this organism prior to transplantation.
	Probable	Both of the following two conditions must be met: • Suspected transmission event; and • Laboratory evidence of the suspected organism or malignancy in a recipient. And at least ONE of the following criteria must also be met: • Laboratory evidence of the same organism or malignancy in other recipients; • Laboratory evidence of the same organism or malignancy in the donor. If there is pretransplant laboratory evidence, it must indicate that the same recipient was negative for this organism prior to transplantation.
	Possible	• Suspected transmission event and • Laboratory evidence of the suspected organism or malignancy in a single recipient or • Data that strongly suggests but does not prove a transmission event.
No confirmed transmission	Intervention without disease transmission	• An intervention (i.e. antimicrobial agent) was given to all or most of the recipients with the intention to prevent disease transmission. • No disease transmission can be documented in recipients of the intervention.
	Excluded	• Suspected transmission event and at least one of the following conditions is met: ○ There is clear evidence for an alternative reason for the event. ○ Lack of infection with the same organism in any other recipients, from the same donor, given appropriate testing. Laboratory evidence that the recipient had infection with this organism or malignancy prior to transplantation.

[1]If there were only a single recipient of organs from the donor, there would have to be clear signatures tying the donor and recipient pathogen or malignancy to classify as proven (i.e. molecular fingerprinting of bacteria or mycobacteria). If this was not possible, a lower grade classification would be used.

of organ donors, consenting of transplant recipients, and identification of donor-derived disease transmissions (9,18,19). Many of these changes have not been entirely based on high level evidence; frequently changes were of necessity made based on consensus opinion. In this paper, we attempt to review available data on donor-derived infectious disease and malignancy transmission.

Epidemiology of Donor-Derived Disease Transmissions

Prior to the implementation of OPTN Policy 4.7, the only relevant data are derived from OPTN posttransplant malignancy forms, reports to the Centers for Disease Control and Prevention, and the medical literature (17). Since 2005, policy 4.7 has required that all donor-derived disease transmissions be reported to the OPTN, typically via the Patient Safety System (17). These reports are reviewed, in a blinded fashion, by the *ad hoc* Disease Transmission Advisory Committee (DTAC) which subsequently categorizes the event as a confirmed (further classified as proven, probable, possible), intervention without documented transmission (IWDT), or excluded transmission event (see Table 1) (3). Recently, policies 2 and 4 were amended to clarify reporting requirements and processes (16,17).

There are several limitations within the current system that impede the ability to classify all cases in a definitive fashion. There is significant variability in reporting of events across different donor service areas, suggesting that there is significant variability in either incidence or reporting; the latter is more likely (Figure 1). Not all confirmatory testing recommended by DTAC is performed. Often, an adequate

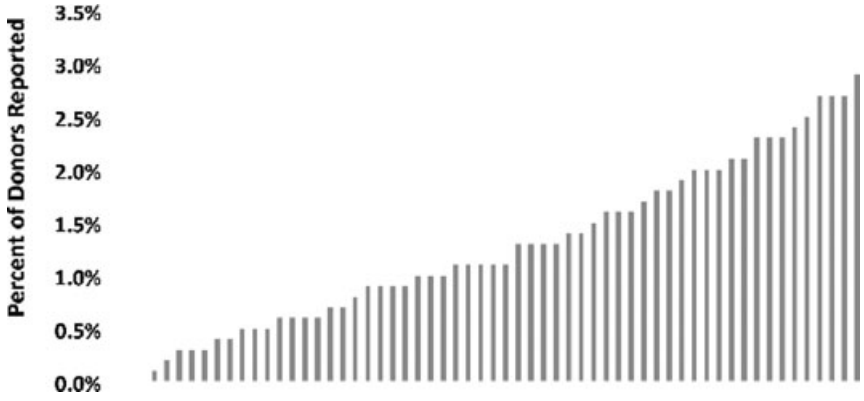

Figure 1: Potential disease transmission reports for deceased donors 3/2006–12/2009 by donor service area (DSA). Includes reported potential disease transmission cases March, 2006 through April 23, 2010, on deceased donors recovered March, 2006 through December, 2009. Each bar represents a single donor service area (DSA). Two DSA had zero reports during the time period represented.

specimen may not be available to conduct the testing: although sera on each donor are banked for 10 years by the OPO, pretransplant recipient blood or sera is rarely available for assessment of latent infection in the recipient. Further, not all cultures are maintained to allow sequencing to document similarity between isolated strains. In addition, the appropriate specimen or culture (i.e. fungal and mycobacterial cultures) are often not collected or set-up for the donor. The OPTN does not maintain its own reference laboratory and as a result testing may take place at a range of reference laboratories with variable sensitivity and quality. Finally, until the recent changes in policy 4, only 45 days of follow-up through the Patient Safety System specific to the reported case were required (17); since many potentially transmitted diseases (i.e. many malignancies) may require longer follow-up to assess if transmission has occurred, the policy was amended to allow the Patient Safety Staff to request additional information beyond 45 days.

Despite these limitations, information collected by the OPTN currently represents the most robust published data on donor-derived disease transmission via organ transplantation globally (3). Since data collection began in 2005, the number of cases has increased significantly, from 7 reports in 2005 to 152 reports in 2009; this large increase likely suggests early under-reporting of cases rather than a true increased incidence of disease transmissions.

Malignancies

A high level summary of potential donor-derived malignancy transmissions reported between 2005 and 2009 is presented in Table 2. Of 146 submitted reports, 20 represent confirmed donor derived malignancy transmissions with 9 attributable deaths [lung cancer (3), lymphoma (2), neuroendocrine carcinoma (2), melanoma (1) and glioblastoma multiforme (1)]. An additional patient with metastatic renal cell carcinoma detected 7 months posttransplant expired following a fall and is provisionally included in this category, for an overall 50% (10/20) mortality. In addition, there have been several reports of 'donor-derived' but not 'donor-transmitted' malignancies. For this purpose, we define a 'donor transmitted' malignancy as one that was present, or presumed present, as a tumorous growth in the donor prior to transplant. 'Donor derived' implies that the tumor was technically derived from donor cells, but would not reasonably be expected to exist as a clinical neoplasm at or before the time of transplant. It is not currently possible to assign these categories on the basis of a single time point. However, for practical purposes, tumors arising after extended posttransplant intervals (e.g. 12.5 and 17 years), were considered to represent donor derived and not donor transmitted conditions. Although the overwhelming majority of the remaining 113 patients did not show any evidence of tumor, the short follow-up period did not allow adequate assessment of the frequency with which donor derived tumors might arise.

Despite these limitations, the pattern of reports allows for several preliminary generalizations that may be clinically useful. The highest number of reports involves donor-associated renal cell adenocarcinoma, with 64 such cases (43.8% of all malignancy reports) through 2009. The usual scenario of the 'possible' donor transmission events consisted of detection of a small, usually well differentiated renal cell carcinoma, restricted to the kidney, at time of recovery. The kidney was almost always discarded and the contralateral kidney was discarded 39% of the time, but other organs were used without tumor transmission recognized to date (75 patients total, primarily contralateral kidney, liver). In this regard, several reports have suggested that small solitary and well differentiated renal cell carcinomas may be resected at the time of organ procurement and the kidney used for transplant (20,21), a concept with which we agree. Seven recipients were considered to have confirmed renal tumor transmission. In all cases, diagnosis was first suspected and made on posttransplant imaging or biopsy at times up to 17 months posttransplant, without retrospective evidence of donor-associated malignancy or posttransplant malignancy in eight other recipients of organs from these donors.

Five examples of donor associated prostate adenocarcinoma were reported. In each case the diagnosis was made at donor autopsy and consisted of small moderately differentiated adenocarcinoma restricted to the prostate gland in so far as could be determined, without documented

Table 2: Potential donor-derived malignancy transmissions reported to the OPTN, 2005–2009

Malignancy	# of donor reports[1]	# of recipients with confirmed transmission[2]	# of DDD-attributable recipient deaths[3]
Renal cell carcinoma	64	7	1[4]
Lung cancer	12	4	3
Lymphoma	8	6	2
Thyroid carcinoma	7	0	0
Glioblastoma multiforme	7	1	1
Prostate	5	0	0
Liver cancer	3	1	0
Melanoma	5	2	1
Pancreas	2	3	0
Neuroendocrine	4	2	2
Ovarian carcinoma	2	2	0
Other[5]	26	0	0
Total malignancies	146	20	10

[1]Each report reflects a single donor but may involve multiple recipients.
[2]Number of recipients with a confirmed malignancy transmission–transmission classified by DTAC as either proven, probable, or possible.
[3]Number of recipients with a confirmed malignancy transmission that died directly as the result of the transmitted malignancy.
[4]One patient with probable/proven disease expired; final tumor assessment pending.
[5]Other reported malignancies without confirmed transmission: astrocytoma, breast (3), colon carcinoma (2), dermatofibrosarcoma protuberans, Kaposi's sarcoma, leukemia (CLL), medulloblastoma, myeloid sarcoma, pinealoblastoma, liposarcoma, gastrointestinal stromal tumor (GIST) spindle cell CNS carcinoma, carcinoma not otherwise specified (4), urothelial carcinoma.

transmission to date. In a recent autopsy study of organ donors, prostatic adenocarcinoma was documented in 23%, 35% and 45% in donors aged 50–59, 60–69 and 70–81, respectively (22). No case of donor associated prostate adenocarcinoma has been reported to the DTAC since its inception, despite the increased use of older donors in the recent past. This suggests that many presumably small and early prostate cancers may have limited potential for transmission via organ transplantation.

Other situations may also arise during the organ procurement process. The presence of dense hematolymphoid infiltrates within donor organs may lead to difficulties in distinguishing between inflammation and lymphoma on frozen section. In several cases this diagnosis was made retrospectively following additional studies on permanent tissue sections. Difficulty in distinguishing between these two conditions should be recognized by the transplant surgeon, and particular attention should be given to sampling enlarged lymph nodes, when present. However, lymphoid neoplasia may be confined to the donor organ itself and the pathologist must remain alert to this possibility.

On occasion there has been a prolonged interval of time between procurement and final diagnosis in the donor. While autopsy and biopsy results from nondonor deceased patients are typically not time-sensitive, pathologists should remain cognizant of the need for timely completion of pathology reports when dealing with both biopsy and autopsy specimens from organ donors. The OPO should emphasize to the pathologist the importance of rapid communication of unexpected results, and should implement systems to rapidly acquire pathology reports completed postprocurement on all donors. Organ Procurement Organizations (OPOs) should also facilitate sharing of these results with all accepting transplant centers.

The DTAC is currently preparing a resource document designed to provide aid in the assessment of potential organ donors with evidence of active or historical malignancy.

Infectious diseases

A wide range of infections have been recognized to be transmitted from donor to recipient through organ transplantation (Table 3); the available literature also provides additional information about some of the cases reported to the OPTN and older cases before reporting was required (23). From this growing data, it is possible to make a few conclusions. A potential donor-derived transmission event is reported in less than 1% of donors, although many of these reports are found not to be a confirmed disease transmission. When an infection is transmitted, it is typically associated with significant morbidity and mortality; there is likely under-recognition and therefore underreporting of cases that are associated with less severe disease (i.e. transient bacteremia that responds quickly to therapy but was likely of donor-origin). Further, there are variable rates of transmission likely related to inoculum of pathogen, organ transplanted and type of immune suppression used (i.e. lymphocyte depletion).

Many of the reports associated with viral infections (notably HIV, HBV, HCV and HTLV) represent nonreproducible molecular diagnostic testing results and suggest a higher false positive rate when performed under the conditions required for organ donation than is described in the blood donation community. Further, in evaluating the three cases

Table 3: Potential donor-derived infectious diseases transmissions reported to the OPTN, 2005–2009

Disease	# of donor reports[1]	# of recipients with confirmed transmission[2]	# of DDD-attributable recipient deaths[3]
Virus[4]	86	31	8
Bacteria[5]	38	26	7
Fungus[6]	30	26	8
Mycobacteria[7]	26	10	2
Parasitic[8]	21	13	4
Total infections	201	106	29

[1]Each report reflects a single donor but may involve multiple recipients.
[2]Number of recipients with a confirmed infectious disease transmission–transmission classified by DTAC as either proven, probable or possible.
[3]Number of recipients with a confirmed infectious diseases transmission that died directly as the result of the transmitted infection.
[4]Reported viruses: Adenovirus (2), Hepatitis B virus (13), Hepatitis C virus (25), herpes simplex, human immunodeficiency virus (HIV, 15), human T-lyphotrophic virus (HTLV, 3), influenza (3), LCMV, parainfluenza (PIV)-3, parvovirus B19 (3), rabies, West Nile virus (14). Confirmed viral transmissions: HCV, HIV, LCMV, parvovirus B19 and West Nile virus (there are previous reports of documented influenza and rabies transmissions not included in this report).
Note: Several viral transmission reports (esp HBV, HCV, HIV and HTLV) represent false positive testing (mostly NAT) that was subsequently documented to be nonreproducible and not associated with documented disease transmission. See text for further discussion.
[5]Reported bacteria: *Acinetobacter* (2), Brucella *Enterococcus* (including VRE), *Ehrlichia* spp (2), *E. coli*, Gram Positive Bacteria, *Klebsiella* (2), legionella, listeria, Lyme disease, nocardia, *Pseudomonas* (4), Rocky Mountain Spotted Fever, *Serratia* (2), *S. aureus* (MRSA 2), *Streptococcus* spp, Syphilis (5) *Veillonella*; bacterial meningitis and bacterial emboli.
[6]Reported fungi: *Aspergillus* spp (4), *Candida* spp (5), *Coccidioides imitis* (6), *Cryptococcus neoformans* (5), *Histoplasma capsulatum* (6), zygomyces (5). Although not all cases were associated with confirmed transmission, each of the listed pathogen has been confirmed to have been transmitted through organ donation.
[7]Reported mycobacteria: Tuberculosis (22), Non-TB mycobacteria (4): All confirmed mycobacterial transmissions have involved *M. tuberculosis*; no mycobacteria other than tuberculosis (MOTT) have been associated with a confirmed transmission to date.
[8]Reported parasites: Babesia (2), *Balmuthia mandrillaris*, Chagas (*Trypanosoma cruzi*, 9), *Naegleria fowleri*, schistosomiasis (3), strongyloides (5). Confirmed parastic transmissions: Babesia, *Balmuthia*, Chagas, schistosomiasis and strongyloides.

of confirmed HCV transmission [one case from a OPTN-defined high risk donor to four recipients (coinfection with HIV), one case from a donor who did not meet OPTN criteria for high risk to three recipients and one case in which HCV+ donor vessels were inadvertently used for a HCV— living-donor recipient), all recipients remained serologically negative while on immune suppression despite having documented viremia by nucleic acid testing (NAT). As such, screening of recipients for viral infections posttransplant requires the use of both serology and direct studies to detect the virus (i.e. NAT). In the first two cases, donor serology was negative but subsequent NAT done after recognition of recipient infection documented the infection in the donors. From the available data, it is unclear if these transmissions resulted from window period infection in the donor or hemodilution. The role of NAT has been discussed elsewhere and decisions to use NAT as part of donor screening need to balance reduction of disease transmission against organ loss through false positive test results (24). Similarly, it is important to recognize that HBV and HCV can be transmitted to all organ recipients, not just recipients of the liver. Parvovirus B19 has now been clearly documented to be transmissible through both blood and organs and should be considered in recipients with severe anemia.

Bacterial contamination of organs or bacterial infections and colonization in the donor occurs frequently but rarely results in transmission of infection (6). There is likely under-recognition of bacterial transmissions as transient fevers without a documented cause and bacterial infections caused by common infections (such as *Staphylococcus aureus*) may not be recognized as donor-derived. As such, all early bacterial infections in the recipient should prompt a careful review of donor cultures and consideration of the donor as a potential source of the infections. From the cases proven bacterial transmission, resistant bacteria (i.e. MRSA, VRE and multidrug resistant gram-negative rods) are frequently involved; typical antimicrobial prophylaxis given to recipients usually was not active against the transmitted bacteria. In addition, challenges to data sharing have been recognized as potential contributors to some of the transmission events: each donor hospital has its own medical informatics system—the systems may limit the access to the procurement coordinators and some results may be missed; further, susceptibility data may become available after initial culture results, requiring diligent review of outstanding results which may be challenging for an OPO to do with a large number of hospitals that may not have mechanisms in place to automatically share the results with the OPOs; labs have different policies with regard to the handling of cultures for deceased patients which may affect availability of results (some do not complete testing when a patient dies); finally, there is no well established system to ensure that clinically pertinent results (i.e. susceptibility data) is rapidly transmitted to the appropriate clinical decision maker for all recipients (often it is sent to a member of the pretransplant team who may not be caring for the patient posttransplant). Policy was recently amended to require each OPO and transplant program to have an identified 'patient safety contact'

to facilitate data sharing. Further, in the transition from clinical care of the patient to donor management by the procurement team, standard follow-up cultures (i.e. daily blood cultures for bacteremic patients) may not get done; as a result, failure to clear the infection, a potential marker for resistance, may be missed.

Fungal disease transmissions are associated with significant morbidity when disease is transmitted. Several transmissions of endemic mycoses, particularly coccidiomycosis, have been recognized suggesting that clearer guidance on optimal screening of donors from endemic regions should be considered; such guidance is currently under development (25). In addition, the transmission of cryptococcus suggests that unrecognized colonization with this fungus in the donor may cause transmitted disease in the recipient; cryptococcal disease that develops early posttransplant should prompt evaluation of the donor as the potential source (26).

Several donor-derived tuberculosis cases have been confirmed. Clinical disease in recipients may not be associated with a primary respiratory infection, which contributes to the delay in diagnosis seen in some of the transmitted cases (12). There are currently no approved methods to screen potential donors for TB and culture results obtained from the donor as part of routine care may take up to 6 weeks to become positive; often the patient is not recognized as a donor and results are not shared with the OPO even when the local health department is involved. The CDC and others are currently working to educate the health departments about the importance of recognizing if a transmissible disease involves an organ donor and rapidly communicate such data to the OPO.

Parasitic infections have emerged as a significant cause of morbidity and mortality when transmitted from donor-to-recipient in the United States. Screening of high risk donors for Chagas disease could allow the selective use of these organs with careful monitoring for disease activation and early antiparasitic therapy; a guidance document will be published in the near future (27). Recognition that strongyloidiasis was transmitted through organ transplantation was initially a somewhat surprising finding since these parasites are typically limited to the gastrointestinal tract. Many donors receive high doses of steroids as part of donor management, which could allows parasitemia and risk of disease transmission. Transmission of Balmuthia through organ donation serves as a significant reminder that patients with unexplained neurologic conditions may pose a significant risk of disease transmission and should be excluded from donation (28).

Donors at Increased Risk of Disease Transmission

In response to the transmission of HIV and HCV from one donor to four recipients, the OPTN implemented policy that used 'exclusionary criteria' from the 1994 US Public Health Service Guideline for Preventing the Transmission of HIV through Transplantation of Human Tissue and Organs to define 'high risk' donors which has been renamed 'donors at increased risk of disease transmission' in current policy (15,17). Policy further required OPOs to obtain a history to determine if the donor met any of these criteria. If the donor did, they are labeled 'increased risk of disease transmission' and the OPO has to inform each accepting transplant center who, in turn, has to obtain special consent from each recipient before using such organs. Many in the transplant community have interpreted 'high risk' in a variety of ways and in regard to many pathogens, including HIV, HBV and HCV. Available evidence suggests that risk of transmitting HIV from a high risk donor screened by serology ranges from 0.05 (for hemophiliac donors) to 12.9 (for injection drug using donors) transmissions per 10 000 donors while the risk for HCV ranges from 0.46 (for hemophiliac donors) to 350 (for injection drug using donors) per 10 000 donors (29). Prospective studies with use of posttransplant NAT screening of transplant recipients have not confirmed this data. Further, how this information is shared with patients as part of the informed consent process has neither been studied to determine if the patients understand the information so that they can make an informed decision nor has the impact on organ acceptance by recipients been assessed. The dichotomous labeling system also does not recognize when incomplete data is collected and does not take into account the wide range of risk of undiagnosed infection across risk groups. Further, donors who have risk factors that are not disclosed by or known to the interviewed historian go unrecognized and the donor may be erroneously not labeled 'increased risk'. The guidelines are currently being updated to reflect changes in the epidemiology of HIV, HBV and HCV in the United States.

Identification of Donor-Derived Disease Transmissions

Although donor-derived disease transmissions are rare, it is critical to consider the donor as the source of any posttransplant infection or malignancy and report that concern to the local OPO immediately. All transplant centers should have an established plan for investigating potential disease transmissions and reporting them to the OPTN and appropriate public health authorities. Unfortunately, recipients may be cared for by different teams within the same hospital or in a number of different hospitals, which may hamper recognition of the transmission. In addition, as has been the case in several recent transmissions (5,8,9,30), the patients present with clinical symptoms at different times posttransplant; mechanisms to flag all recipients of a single donor with concern about a potential transmission should be in place but typically are not available. The OPO should have a mechanism in place to rapidly assess the status of all other recipients of organs, tissues or vessels

from the same donor and report the concern to the OPTN and appropriate public health authorities. Similarly, all transplant centers should have a plan to ensure that information about the potential disease transmission is communicated to the appropriate physician in their program so that the recipients can be assessed and that appropriate tests and/or therapies can be ordered. Further, transplant centers and OPOs need to develop mechanisms to flag recipients with findings of donor disease or concern disease transmission in other recipients. Without such a system, it may be challenging for centers to recognize that the same pathogen is present in both a donor and recipient.

Posttransplant screening of recipients for potential infectious disease transmission is variably performed in the United States and results of such testing are not currently being collected in a centralized manner (31). Without this data, it is impossible to assess the true rate of donor-derived disease transmission. Although it is unlikely that transmission of HIV, HBV or HCV may go unrecognized clinically, there is evidence that it may be missed in a small number of cases (9). Current policy requires recipients of organs from donors at increased risk for blood borne pathogens to have additional posttransplant testing for HIV, HCV and/or HBV, if not already infected pretransplant, since there is an ethical imperative to identify and treat any transmitted disease. Currently, experts recommend that HIV, HBV and HCV serology and NAT be sent at 1 and 3, and HBV testing at 12 months after receipt of an OPTN-defined increased risk donor organ (15,24). The use of direct detection of the pathogen, by antigen detection or NAT, is essential since transplant recipients may not seroconvert after donor-derived disease transmission. This is particularly true of HCV in which all recipients with proven donor-derived HCV transmission reported to DTAC have been seronegative but NAT positive posttransplant. Donors who are not classified as 'increased risk' may still transmit blood-borne pathogens; at least one of the HCV transmissions involved a donor that did not have identified risk factors—the yield of screening such recipients warrants further study.

Outstanding Issues and Future Directions

Donor-derived disease transmissions are a rare but clinically significant complication of solid organ transplantation. Prospective studies of donors and recipients are needed to define the true incidence of organ-associated transmission similar to what has been accomplished by the blood industry (32,33). A number of new and emerging infections have been recognized as transmissible or potentially transmissible through organ transplantation. Since additional testing will very likely result in the loss of donors through false positive testing, the transplant community will need to define a risk threshold which will inform which pathogens are clinically important enough to screen for despite the impact on organ availability. Further, resources need to facilitate the development of screening assays that can be performed by the OPO community; the requirements and characteristics of such tests are typically different from what is needed for blood donor screening.

Communication is a key to recognizing and managing donor-derived infectious and neoplastic disease transmissions. A biovigilance system, such as piloted with the Transplant Transmission Sentinel Network (34) may facilitate such communication and recognition of disease transmission (35). Until then, each OPO and transplant center needs to establish policies that identify a key contact for patient safety concerns and facilitate sharing of data whenever contacted about a potential disease transmission as currently required by OPTN policy. Further, OPOs should implement systems to understand what tests are outstanding on each donor at the time of procurement and have a plan for acquiring the results as soon as they are available. To accomplish this, OPOs should work with donor hospitals to create systems that clearly identify a deceased patient as a donor so that results are handled in a timely fashion and universally shared with the OPO. Further, OPOs should transmit any clinical information about donors that becomes available postprocurement in a timely fashion to all accepting transplant centers. These centers can then determine if the results are clinically meaningful to their recipient and if additional testing or treatment is warranted.

Most importantly, clinicians should consider any early posttransplant disease as potentially of donor origin; by doing so, more cases of donor-derived disease transmission may be recognized. Such early recognition and resultant reporting of such cases is critical as it may allow interventions to prevent morbidity or mortality in other recipients. In a similar light, routine screening of recipients at increased risk of disease transmission, particularly those who have received organs from an OPTN-defined 'increased risk' donor or with recognized disease in the donor, will help to document disease transmission early and as a result improved patient care and outcomes of transplant recipients. Further, this data will allow improved clarification of the risk of using such donors and potentially inform future policy. Finally, it is critical that the transplant community and key members of the federal government are continually updated with the current data about donor-derived disease transmission. Without such detailed reports, it is challenging for the transplant community to continually improve on transplant safety. This communication requires finally integrating the processes that are currently conducted in parallel without coordination between OPTN and the Centers for Disease Control.

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References

1. Fischer SA, Avery RK, Practice tAIDCo. Screening of donor and recipient prior to solid organ transplantation. Am J Transplant 2009; 9(Suppl 4): s7–s18.
2. Levitsky J, Doucette K, Practice tAIDCo. Viral hepatitis in solid organ transplant recipients. Am J Transplant 2009; 9(Suppl 4): s116–s130.
3. Ison MG, Hager J, Blumberg E et al. Donor-derived disease transmission events in the united states: Data reviewed by the OPTN/UNOS disease transmission advisory committee. Am J Transplant 2009; 9: 1929–1935.
4. Fischer SA, Graham MB, Kuehnert MJ et al. Transmission of lymphocytic choriomeningitis virus by organ transplantation. N Engl J Med 2006; 354: 2235–2249.
5. 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.
6. Lumbreras C, Sanz F, Gonzalez A et al. Clinical significance of donor-unrecognized bacteremia in the outcome of solid-organ transplant recipients. Clin Infect Dis 2001; 33: 722–726.
7. 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.
8. Srinivasan A, Burton EC, Kuehnert MJ et al. Transmission of Rabies virus from an organ donor to four transplant recipients. N Engl J Med 2005; 352: 1103–1111.
9. Ison MG, Friedewald JJ. Transmission of human immunodeficiency virus and hepatitis C virus through liver transplantation. Liver Transpl 2009; 15: 561; author reply 562.
10. Chagas disease after organ transplantation–United States, 2001. MMWR Morb Mortal Wkly Rep 2002; 51: 210–212.
11. Chagas disease after organ transplantation–Los Angeles, California, 2006. MMWR Morb Mortal Wkly Rep 2006; 55: 798–800.
12. Transplantation-transmitted tuberculosis–Oklahoma and Texas, 2007. MMWR Morb Mortal Wkly Rep 2008; 57: 333–336.
13. The National Organ Transplant Act. In. 42 U.S.C. §273 et seq. (1987).
14. The OPTN Final Rule. In. 42 CFR, part 121 et seq.
15. Guidelines for preventing transmission of human immunodeficiency virus through transplantation of human tissue and organs. MMWR Morb Mortal Wkly Rep 1994; 43(RR-8): 1–17.
16. OPTN Policy 2. Available at: http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_2.pdf. Accessed on February 6, 2011.
17. OPTN Policy 4. Available at: http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_16.pdf. Accessed on February 6, 2011.
18. Kaye S, Baddon A, Jones M, Armitage WJ, Fehily D, Warwick RM. A UK scheme for reporting serious adverse events and reactions associated with ocular tissue transplantation. Cell Tissue Bank 2010; 11: 39–46.
19. European Directorate for the Quality of Medicines and Healthcare. Guide to safety and quality assurance for the transplantation of organs tissues and cells, 3rd Ed. Strasbourg, France: Council of Europe Publishing, 2009.
20. Buell JF, Hanaway MJ, Thomas M et al. Donor kidneys with small renal cell cancers: Can they be transplanted? Transplant Proc 2005; 37: 581–582.
21. Nicol DL, Preston JM, Wall DR et al. Kidneys from patients with small renal tumours: A novel source of kidneys for transplantation. BJU Int 2008; 102: 188–192; discussion 192–193.
22. Yin M, Bastacky S, Chandran U, Becich MJ, Dhir R. Prevalence of incidental prostate cancer in the general population: A study of healthy organ donors. J Urol 2008;179(3):892–895; discussion 895.
23. Ison MG. The epidemiology and prevention of donor-derived infections. Adv Chronic Kidney Dis 2009; 16: 234–241.
24. 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.
25. Proia L, Miller R. Endemic fungal infections in solid organ transplant recipients. Am J Transplant 2009; 9(Suppl 4): S199–S207.
26. Singh N, Forrest G. Cryptococcosis in solid organ transplant recipients. Am J Transplant 2009; 9(Suppl 4): S192–S198.
27. Kotton CN, Lattes R. Parasitic infections in solid organ transplant recipients. Am J Transplant 2009; 9(Suppl 4): S234–S251.
28. Grossi PA, Fishman JA. Donor-derived infections in solid organ transplant recipients. Am J Transplant 2009; 9(Suppl 4): S19–S26.
29. Kucirka LM, Wolfe J, Sarathy H, Govindan P, Montgomery R, Segev DL. The risk of window period HIV and HCV infection in high risk donors: A meta-analysis. San Diego, California: American transplant congress, 2010: Abstract LB 22.
30. West Nile virus infections in organ transplant recipients–New York and Pennsylvania, August-September, 2005. MMWR Morb Mortal Wkly Rep 2005; 54: 1021–1023.
31. Ison MG, Stosor V. Transplantation of high-risk donor organs: A survey of US solid organ transplant center practices as reported by transplant infectious diseases physicians. Clin Transplant 2009; 23: 866–873.
32. Glynn SA, Kleinman SH, Schreiber GB et al. Trends in incidence and prevalence of major transfusion-transmissible viral infections in US blood donors, 1991 to 1996. Retrovirus epidemiology donor study (REDS). JAMA 2000; 284: 229–235.
33. Murphy EL, Bryzman SM, Glynn SA et al. Risk factors for hepatitis C virus infection in United States blood donors. NHLBI retrovirus epidemiology donor study (REDS). Hepatology 2000; 31: 756–762.
34. Fishman JA, Strong DM, Kuehnert MJ. Organ and tissue safety workshop 2007: Advances and challenges. Cell Tissue Bank 2008; 10: 271–280.
35. Tugwell BD, Patel PR, Williams IT et al. Transmission of hepatitis C virus to several organ and tissue recipients from an antibody-negative donor. Ann Intern Med 2005; 143: 648–654.