Deceased organ donors with a history of increased risk behaviour for the transmission of blood-borne viral infection: The UK experience

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Abbreviations:

BBV, Blood Borne Virus

IVDU, Intravenous drug user;

HIV, Human immunodeficiency virus;

HCV, Hepatitis C virus;

HBV, Hepatitis B virus;

HBsAg, Hepatitis B virus surface antigen

HTLV, Human T Lymphotropic Virus

IRB, Increased Risk Behaviour

MSM, Men who have had sex with men;

UK, United Kingdom;

NHS, National Health Service;

NHS BT, NHS Blood and Transplant;

HLA, Human leucocyte antigen;

DCD, Donation after circulatory death;

DBD, donation after brain-stem death;

Abstract

Background

Deceased organ donors are routinely screened for behaviours that increase the risk of transmissible blood borne viral (BBV) infection, but the impact of this information on organ donation and transplant outcome is not well documented. Our aim was to establish the impact of such behaviour on organ donation and utilization, as well transplant recipient outcomes.

Methods

We identified all UK deceased organ donors from 2003-2015 with a disclosed history of increased risk behaviour (IRB) including intravenous drug use (IVDU), imprisonment and increased risk sexual behaviour.

Results

Of 17,262 potential donors, 659 (3.8%) had IRB for BBV and 285 (1.7%) were seropositive for BBV, of whom half had a history of IRB (mostly IVDU (78.5%)). Of actual donors with IRB, 393 were seronegative for viral markers at time of donation. A history of recent IVDU was associated with fewer potential donors proceeding to become actual organ donors (64% vs. 75%, p=0.007). Donors with IRB provided 1,091 organs for transplantation (624 kidneys and 467 other organs). Transplant outcome was similar in recipients of organs from donors with and without IRB. There were three cases of unexpected HCV transmission, all from an active IVDU donor who was HCV seronegative at time of donation, but was found to be viraemic on retrospective testing

Conclusion

Donors with a history of IRB provide a valuable source of organs for transplantation with good transplant outcomes and there is scope for increasing the use of organs from such donors.

Introduction

Unintended transmission of Hepatitis C (HCV), Hepatitis B (HBV), Human Immunodeficiency Virus (HIV) and Human T-lymphotrophic virus (HTLV) from deceased organ donors is a rare but serious complication of organ transplantation (1). This risk is minimised by performing relevant laboratory screening investigations in deceased donors prior to implantation of their organs. Currently available screening strategies cannot completely discount the presence of a recently acquired viral infection, and considerable importance is attached to the identification of donors with a history of increased risk behaviour (IRB) associated with the acquisition of HCV, HIV, HBV and HTLV(1-4). While the discard of organs from those with a history of IRB would minimize disease transmission, it would markedly reduce the number of transplants performed. Consequently the risk of disease transmission from donors with IRB needs to be balanced against the potential benefits of organ transplantation. Solid organ donors who have a history of prior or current intravenous drug use (IVDU), or of recent or historical imprisonment, and those who have a history of high-risk sexual behaviour are viewed at greatest risk of transmission of BBV (2,3). In the United Kingdom (UK), current guidance from the Advisory Committee for the Safety of Blood, Tissues and Organs and the European Directive on Organ Donation requires that detailed information on 'behavioural history that could have put the donor at an increased risk of blood borne viruses' be obtained (5). The information needed includes 'questions about risk behaviours such as recreational drug use, men

who have sex with men (MSM), and risks such as accidental body fluid exposure' (5). UK guidance on donor assessment is consistent with that in the United States where the need to assess behavioural risk factors for a donor to be at increased risk of transmitting HIV, HBV and HCV is highlighted (2). The donor history with respect to such IRB also provides an important context for the interpretation of the results from microbiological screening for HIV, HCV, HBV and HTLV (3,5,6). Current screening tests for viral markers have limited sensitivity, and serological screening may result in an infective window period of up to 70 days following infection when antibodies to virus are undetectable (6).

We report the UK experience of deceased organ donors, both potential and actual, with a history of IRB, highlighting the overall prevalence and types of IRB. Our aim was to establish the impact of IRB on organ donation and utilization, as well as on their transplant recipient outcomes.

Methods

Identification of deceased organs donors with increased-risk behaviour

The UK Transplant Registry was examined to identify all deceased organ donors between 1st January 2003 and 31st December 2015, who had a history of any one of the following IRB: IVDU, current or previous imprisonment, MSM, sex in exchange for money or drugs, and high risk sexual partner (defined as a sexual relationship with any of the previously mentioned increased risk groups). For the purposes of this study, "potential donors" were defined as deceased donors for whom consent/ authorization for organ donation had been obtained, "actual organ donors" as deceased donors who had one or more solid organs removed for transplantation on the basis that recipient centres had provisionally agreed to use them for transplantation,

and “utilised organ donors” as actual organ donors whose organs where eventually transplanted. The decision as to whether or not a potential donor proceeds to organ donation is dependent on transplant clinicians at individual transplant centres indicating that they are willing to accept the organs for transplantation. There are no centralized clinical advisors involved in this decision.

In the UK, a donor transplant coordinator (designated in 2008 as a Specialist Nurse in Organ Donation) is required to enquire from the next of kin, medical notes and the potential donors family doctor, whether there is a history of IRB and record these findings. Additional UK guidance published in 2000 highlighted the requirement to screen potential organ donors for behavior associated with BBV.

Free text entries of all potential donors were searched using the terms ‘intravenous drug use’ ‘sex worker’ ‘Men who have sex with men’ and ‘prison’. All common abbreviations, misspellings, synonymous terms and colloquialisms of the above search terms were also searched. Donors with a history of IVDU and imprisonment were sub-categorised based on whether or not they had been an IVDU or imprisoned during the preceding 12 months. Donors with a history of high-risk sexual behaviour were sub-categorised according to the type behaviour into any one of ‘high risk partner’, ‘sex worker’, and ‘prior high risk partner’.

It is important to note that a number of patients did not fall into the category of potential donors because formal consent for donation was not sought for a variety of reasons that included a belief by the clinicians caring for the patient that the patient’s IRB would exclude organ and tissue donation. Information on the number of patients that did not progress to become potential donors for the entire study period (2003-2015) was not available but the potential donor audit (a prospective registry of all patients aged <80 years who died in critical care units of acute UK hospitals,

irrespective of their medical suitability to become organ donors) was interrogated to obtain information on patients excluded from the present analysis. Between January 2009 and 31st December 2015 there were 12,040 potential donors analysed in the present study, and during the same period the Potential Donor Audit showed that 1,022 patients with an identified IRB (89% IVDU) did not get consented for organ donation for a variety of reasons that included IRB. In 86 patients excluded from the present study, IVDU was stated explicitly as a reason why the patient's family was not approached for consent for organ donation.

Identification of recipients of organs from donors with increased-risk behavior

The UK transplant registry was examined to identify recipients of organs from donors with IRB and information on outcome (patient and graft survival) obtained. UK transplant centres are required to notify NHSBT of any potential donor-derived disease transmission and adverse events relating to the donation process. This reporting requirement became mandatory when the new European Union Organ Donation Directive guidelines came into effect (2010) and was written into UK law in the Quality and Safety of Organs for Transplantation Regulations (2012). Prior to 2010, recipient centres were expected, according to UK guidance, to report any adverse outcomes in recipients relating directly to the organ donation process to NHSBT. Details of any donor transmitted infections were collected from a designated transplant incident reporting registry held by NHSBT.

Statistical Analysis

Univariate analysis comparing clinical characteristics between IRB and non-IRB potential donors, who were seronegative for BBV, was carried out using Student's t-

test for approximately normal continuous data, and the Mann-Whitney U test for non-normal continuous data. Categorical comparisons were made using the χ^2–squared test.

Kaplan-Meier curves were used to show death-censored graft survival and patient survival and the univariate log-rank test was used to compare unadjusted survival rates.

Cox proportional hazards regression model and a logistic regression model were fitted in a stepwise selection method in order to control for potentially confounding factors. Donor related variables considered for inclusion in the multivariate model were donor age, donor type, ethnic group, sex, past medical history of diabetes and hypertension, liver disease, cardiac disease, smoking history and whether the donor had a history of IRB. Recipient factors included were age, ethnicity, sex, primary renal disease, Human Leukocyte Antigen (HLA) mismatch level and cold ischaemic time.

All analyses were performed using Statistical Analysis System (SAS) (version 9.3) and p-values less than 0.05 were deemed to be statistically significant (7).

HLA mismatch level (levels 1-4) was defined according to UK allocation policy for kidneys from brain-death donors and was based on the mismatch between donor and recipient (8).

The United Kingdom Model for End-Stage Liver Disease score was used when assessing differences in liver recipient characteristics. This score is calculated based on the patient's international normalized ratio, serum creatinine, serum bilirubin, and serum sodium (9,10).

Results

One or more IRB was identified in 659 (3.8%) of potential deceased donors, and 454 (3.6%) of actual organ donors. Of the potential donors with a history of IRB, 47% had a history of IVDU, 33% a history of imprisonment, 10% were MSM, and 9.9% a history of high risk sexual behaviour. For actual donors with a history of IRB, 41% had a history of IVDU, 37% had a history of imprisonment, and 21% had a history of high risk sexual behaviour, and these proportions did not differ significantly from the behaviours in potential donors (p=0.147).

Organ donors who were seropositive for HIV, HCV, HBV and HTLV

Overall, 285 (1.7%) of potential organ donors were found to be seropositive for BBVs markers.

104 (36.5%) seropositive potential donors proceeded to organ donation; in contrast to the 78% conversion rate observed in seronegative potential donors (p<0.001). Organs from 81 (77.8%) of the seropositive organ donors were subsequently transplanted, compared to 95.7% of seronegative organ donors (p<0.001).

Half (50.5%) of potential donors who were seropositive for viral infection had a history of IRB, and in most (78.5%) this included IVDU. A history of imprisonment, MSM and high risk sexual behavior was less common (16.7%, 2.7% and 2.1% respectively). The clinical characteristics of potential and actual seropositive donors are shown in table 1. Positive serology for HCV was more common in donors with a history of IRB. In contrast, markers of HIV, HBV and HTLV were all more common in seropositive donors with no history of IRB (table 1).

The types of organs from seropositive organ donors that were used for transplantation differed according to whether or not there was a history of IRB. The 62 organ donors

with a history of IRB provided 48 livers and 11 kidneys that were used for transplantation, whereas the 42 donors with no history of IRB donated 25 livers and 32 kidneys that were transplanted ($p<0.001$).

Increased-risk behaviour and organ donation in donors who were seronegative for viral infection

To examine the association between IRB and organ donation, all seropositive potential donors were excluded from subsequent analysis. After exclusion, there were 16,977 remaining potential donors of which 12,737 (75%) proceeded to organ donation (figure 1). A history of IRB was identified in 515 (3%) of potential and 392 (3%) of actual organ donors, suggesting that overall, a history of IRB did not adversely influence the decision to proceed to organ donation. 25% of potential donors with no history of IRB and 24% of those with a history of IRB did not proceed to donation (p=NS). Potential donors with a history of IRB were, when compared to those with no history of IRB, much younger, and significantly less likely to have hypertension, cardiac disease and diabetes (table 2). Potential donors with IRB were, however, more likely to be smokers and to have a history of alcohol abuse.

There were significant differences in the conversion rate from potential to actual donors according to the type of IRB (figure 2). Potential donors with a history of IVDU were less likely to proceed to organ donation than donors with no history of IRB and this effect was most marked in potential donors with a history of recent rather than historical IVDU Those with a history high risk sexual behaviour alone were as likely to proceed to donation as those with no history of high risk sexual behaviour (figure 2). History of imprisonment (previous or current) alone was associated with an increased rate of proceeding to donation compared to donors with

no history of IRB (figure 2). However, when a logistic regression model was fitted to adjust for the significant differences in age and co-morbidity between donors with or without a history of IRB, IRB was associated with significantly fewer potential organ donors becoming actual organ donors (odds ratio=1.580 (95% CI 1.273-1.962,p<0.001).When the logistic regression model was fitted for the different types of IRB, IVDU (both recent and historical) was associated with significantly fewer potential organ donors becoming actual organ donors (odds ratio=3.552 (95% CI (2.373-5.315), p<0.001 and odds ratio =1.984 (95% CI 1.205-3.268) p=0.007, respectively)(table 3).

The number of potential donors with a history of IRB increased markedly over the 13-year study period and the percentage of donors proceeding to donation also rose in the latter part of the study period (figure 3).

Clinical characteristics of actual organ donors with history increased-risk behaviours

Potential donors with a history of IRB, that proceeded to become actual organ donors were younger (39.8 ± 12.6 years vs. 44.3 ± 11.6 years, p<0.001) and more likely to be DBD than DCD donors (36.2% DCD vs. 82.9% DCD, p<0.001) than those potential donors with IRB who did not proceed to organ donation.

The clinical characteristics of the 392 actual organ donors with a history of IRB, along with the clinical characteristics of all other deceased organ donors are shown in table 3. Actual organ donors with a history of IRB were younger, more often males and more likely to be of an ethnic minority other than white. Organ donors with a

history of IRB were more likely to have a history of smoking and of alcohol abuse (table 4).

Clinical characteristics of recipients receiving organs from donors with increased-risk behaviour

Over the 13-year study period, a total 1,091 transplants were carried out using organs from seronegative deceased donors with a history of IRB (624 kidney, 278 liver, 63 heart, 39 lung (including one lung pair), 2 heart and lung transplants, 84 pancreases, and 1 bowel transplant).

Recipients of kidneys from donors with a history of IRB were younger, more often of non-white ethnicity and less well matched for HLA than recipients of kidneys from donors with no IRB (table 5). Recipients of kidneys from donors with IRB spent a similar amount of time on the transplant waiting list and had a similar duration of dialysis pre-transplant when compared to those who received kidneys from donors without IRB. Recipients of kidneys from donors with IRB had similar graft and patient survival to those who received kidneys from all other deceased donors (figure 4a). When the recipients of the different types of IRB were compared to all other recipients, a donor history of recent IVDU did not adversely influence patient or graft survival (figure 4b).

Recipients of livers from donors with a history of IRB were older, more often male, had a lower UKELD score, and more often HCV positive than recipients of livers from donors with no IRB (Table 6). Similarly, patient and graft survival following liver transplantation was comparable for recipients of livers from donors with and without IRB (figure 5a and figure 5b).

Because of the differences in donor and recipient demographics between recipients that received organs from donors with a history of IRB compared to those that did not, a Cox proportional hazards regression model was fitted to adjust for donor and recipient age, donor history of hypertension, HLA mismatch, cold ischaemic time and primary recipient disease. This showed that patient survival after kidney transplantation was not adversely affected by a donor history of IRB (supplementary table 1). After assessing whether the different sub-types of IRB adversely impacted on transplant outcome the multivariate analysis indicated recipients of kidneys from donor's with high-risk sexual behaviour had significantly worse patient survival than those who received kidneys from donors with no history of high-risk sexual behaviour, even after adjusting for donor and recipient factors. Each of the high-risk sexual behaviours was assessed in turn, and this revealed that it was only those who received kidneys from donors with a high-risk sexual partner that had worse patient survival.

Disease transmission

From the 1,091 organ transplants from donors with IRB, one liver recipient and two renal recipients (all from the same organ donor) developed donor-derived HCV infection. The donor of the organs had a history of recent IVDU, and tested negative for HCV antibody at time of donation. Retrospective testing of the donor serum obtained at donation was positive for HCV Ribonucleic Acid. The liver recipient was known to be HCV positive at time of transplantation, but it was noted that the predominant HCV genotype changed from genotype 1 pre-transplant to donor genotype 3 after transplant. The two renal recipients were both HCV negative prior to transplantation.

There were no reported unexpected HIV, HBV or HTLV transmissions from these IRB donors.

Discussion

Routine screening of all potential organ donors for a history of IRB to determine risk of transmission of BBV infection is routinely undertaken in most countries to help inform the decision on organ usage. The present analysis provides insight on the impact of this policy on organ donation and utilization in the UK, where the prevalence of blood borne viral infection is slightly lower than that in the USA and broadly similar to Western Europe (11-14).

Around 4% of all potential organ donors, for whom consent for donation was obtained, had a history of IRB and 22% of these (2% of all potential donors) were seropositive for blood borne viral infection (mostly HCV), at the time organ donation was being considered and over half had a history of IRB. Positive serology for blood borne viruses may indicate a very high risk of disease transmission during transplantation, and enables an informed decision on whether to proceed with organ donation, and if so, to allocate organs to appropriate potential recipients; in the majority of cases the recipients are likely to be selected on the basis that they already have infection corresponding to that identified in the donor.

In the present study, we were particularly interested in the extent to which IRB in seronegative potential donors impacted on organ donation and transplantation

Overall, around three quarters of all potential organ donors in the UK proceeded to become actual organ donors, on the basis that transplant implanting centres had provisionally accepted them for transplantation. A history of IRB (all types) was not associated with a reduction in the proportion of potential donors that proceeded to

become organ donors. However, a history of IVDU accounted for nearly half of all IRB and was associated with a relatively small but significant reduction in the proportion of potential donors proceeding to donation, especially when the drug use may have been recent.

Potential donors with IRB were significantly younger and had less additional comorbidity than those with no IRB, and when these variables were taken into account by logistic regression analysis, IVDU (both recent and historical) were associated with donors not proceeding to become actual organ donors. Our analysis of the potential donor audit (a prospective registry of all patients aged <80 years who died in critical care units of acute UK hospitals, irrespective of their medical suitability to become organ donors) indicated that a large number of these identified registry patients did not get consented for organ donation because of their history of IRB (in particular IVDU).

The number of potential donors with IRB in the present study increased markedly over the 13-year study period. This likely reflects, for the most part, a true increase in the number of such donors over time, in line with the general trend towards increased consideration of organs from other types of high-risk donor (15). However, it is also likely that some of the increase in potential donors with IRB over time may be attributable to a bias in data capture, as clinical practice in organ donor screening by transplant coordinators and documentation became more standardised.

While the risk of disease transmission in seronegative donors with IRB is very low, not all transplant centres routinely assess recipients for graft-derived acquisition of blood borne viral disease and consequently the present study may provide and underestimate of disease transmission from donors with IRB. Although seronegative donors with a history of IRB represent a small proportion of the total donor

population they made a significant contribution to organ transplantation in the UK over the 13-year study period, providing organs for over a thousand transplants. There were three confirmed transmissions of HCV to two renal transplant recipients and one liver transplant recipient. All three episodes of disease transmission originated from the same donor, who was known to be an active IVDU at time of donation. Using standard serological testing the window period from infection with HCV to detection by antibody assays is around 70 days (6,16-18) and with Nucleic Acid Technology (NAT) is 3-5 days (6,16,18). However, both serological testing and NAT testing carries the risk of false positive results and hence the unnecessary discard of potentially infection free organs from potential donors. NAT testing is only currently available in selected UK centres and recent evidence suggests that NAT testing would improve utilization of organs from IRB donors, but not from donors with no history of IRB (6). Hence even when NAT testing is available a thorough history regarding IRB is still important to aide interpretation of positive results.

As might be expected, recipients of organs from seronegative donors with IRB had transplant outcomes (patient and graft survival) comparable to recipients of organs from deceased donors with no history of IRB, even after adjustment for differences in donor and recipient demographics. However, those who received kidneys from donors with a high-risk sexual partners had worse patient survival than all other deceased donors. The exact cause of this remains unclear. When the causes of renal recipient death in this cohort were examined, no deaths (n=8) were on inspection attributable to disease transmission from the donor (n=1 Gastro-intestinal haemorrhage, n=1 haemorrhage from graft site, n=1 septicaemia, n=1 liver viral hepatitis, n= 2 post-transplant lymphoproliferative disorder, n= 1 non-lymphoid malignant disease, n=1 ischaemic heart disease). The case of viral hepatitis was fulminant liver failure

secondary to HCV genotype 1b, which was already present in the recipient prior to transplantation. There was no significant difference in graft or patient survival in recipients of livers from donors with high-risk sexual behavior and all other deceased donors.

The comparison of recipient characteristics according to whether or not they received a kidney from a donor with a history of IRB revealed that recipients of kidneys from donors with IRB were significantly younger and significantly more likely to be of non-white ethnicity. Donors with a history of IRB were also significantly younger and of non-white ethnicity than all other deceased donors, and kidney allocation and acceptance policies in terms of age, blood group and HLA matching would likely explain the differences observed in recipient demographics. In support, it was notable that for liver transplant recipients, where HLA-matching is not undertaken there was no significant difference in the ethnicity of recipients according to whether or not they received a liver from a donor with IRB. Because kidney donors with IRB were significantly younger than other deceased kidney donors, and recipients of kidneys from younger donors have improved transplant outcomes, it might have been expected that transplant outcomes would have been better in recipients of kidneys from donors with IRB (15, 19). The number of recipients of kidneys from donors with IRB in the present study may not have been sufficient to demonstrate the advantage of younger donor age on transplant outcome.

The present study is the first to report in detail on different categories of IRB in a national cohort of deceased organ donors, and provides important information on which to base future transplant policy for managing the risk of disease transmission. The numbers presented likely represent an underestimate of potential donors with IRB in the donor population, because of underreporting. This is evidenced by the small

number of reported MSM in the registry (0.44%), whilst estimates from a recent US census analysis and meta-analysis estimated that around 3.9% of the US adult male populations are MSM, and in the UK it is estimated that 2.0-2.5% of the adult male population are MSM (20,21).

Research suggests that a patient would be willing to accept a kidney from a donor with IRB if the organ was deemed otherwise healthy (22): individuals are more concerned about the perceived poor quality of the organ and the risk of disease transmission rather than having a prejudice or concern about a particular type of increased risk behaviour per se (22).

While the present study indicates that a history of IRB, particularly IVDU, in seronegative potential donors is associated with a reduction in organs being accepted for transplantation, such donors represent a valuable source of organs for transplantation and the risk of disease transmission in the context of UK blood borne virus epidemiology is relatively small. Moreover, recent advances in the management of transmissible viruses particularly HCV, means that even if viral disease transmission occurs it can in many cases be successfully managed (23). It has also been suggested that kidneys from seronegative donors with a history of IRB may be a valuable source of organs for potential recipients with an increased likelihood of death whilst on the waiting list (24-26). When organs from donors with a history of IRB are used for transplantation it would be prudent for all centres to test recipients within an appropriate time period following transplantation in order to exclude donor derived infection.

Conclusions

Around 4% of UK deceased donors have an identifiable history of behaviour associated with an increased risk of blood borne transmissible viral infection, but are seronegative at time of donation. Three quarters of such donors provide organs for transplantation with good transplant outcomes, and apparently low risk of disease transmission. Recent advances in the treatment of viral disease, particularly HCV, further reduce the risks associated with disease transmission. Donors with a history of IRB provide a valuable source of organs for transplantation with good transplant outcomes and there is scope for increasing the use of organs from donors with IRB, in particular for donors with a history of IVDU.

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Figure Legend.

Figure 1. Flow diagram for seronegative organ donors identified with increased-risk behaviour

Figure 2. Proceeding and non-proceeding seronegatiove consented organ donors according to whether or not they had history increased-risk behaviour.
IVDU=Intravenous drug use; IRB= Increased Risk Behaviour
* All p values refer to category of increased risk behaviour compared to all donors with no history of increased risk behaviour.

Figure 3. Number of seronagtive potential donors with increased-risk behaviour whose organs were used for transplantation and those whose were not used for transplantation.
Proportion of potential organ donors with a history of high-risk behaviour who did not proceed to organ donation is shown above each colum.

Figure 4a and Figure 4b. Patient and Graft survival of kidney transplant recipients from organ donors with a history of increased risk behaviour and from all other deceased organ donors

Figure 5a and Figure 5b. Patient and Graft survival of liver transplant recipients from organ donors with increased-risk behaviour and all other deceased organ donors