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Hepatitis B and C virus infections transmitted through organ transplantation investigated by CDC, United States, 2014-2017

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Abstract

We evaluated clinical outcomes among organ recipients with donor-derived hepatitis B virus (HBV) or hepatitis C virus (HCV) infections investigated by CDC from 2014-2017 in the United States. We characterized new HBV infections in organ recipients if donors tested negative for total anti-HBc, HBsAg and HBV DNA, and new recipient HCV infections if donors tested negative for anti-HCV and HCV RNA. Donor risk behaviors were abstracted from next-of-kin interviews and medical records. During 2014-2017, seven new recipient HBV infections associated with seven donors were identified; six (86%) recipients survived. At last follow-up, all survivors had functioning grafts and five (83%) had started antiviral therapy. Twenty new recipient HCV infections associated with nine donors were identified; 19 (95%) recipients survived. At last follow-up, 18 (95%) survivors had functioning grafts and 14 (74%) had started antiviral treatment. Combining donor next-of kin interviews and medical records, 11/16 (69%) donors had evidence of injection drug use and all met Public Health Service increased risk donor (IRD) criteria. IRD designation led to early diagnosis of recipient infection, and prompt implementation of therapy, likely reducing the risk of graft failure, liver disease and death.

1. Introduction

Prior to the availability of current therapy, hepatitis B virus (HBV) infection was associated with high rates of cirrhosis, graft failure, and death in solid organ transplant recipients [1–3]. With new antiviral agents including tenofovir and entecavir, solid organ transplant recipients with HBV infection have similar outcomes to transplant patients without HBV infection [3]. For organ recipients acquiring hepatitis C virus (HCV) infection, some authors report decreased patient and graft survival [3–5] while others describe comparable survival

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in HCV-infected and uninfected patients after correcting for comorbidities [6, 7]. HCV infection in solid organ transplant recipients has been associated with accelerated rates of hepatic fibrosis [8, 9]. Fortunately, new direct acting antiviral agents (DAA) are effective in eliminating HCV when administered before or after transplantation and regimens are available for patients with kidney failure or hepatic decompensation [3, 10]. Patients with pre-existing chronic HCV infection have been successfully treated post-transplant with high rates of viral eradication 12 weeks after treatment and excellent clinical outcomes [11, 12]. In addition, limited data suggest that high cure rates are achievable with early initiation of DAA therapy in HCV RNA negative recipients receiving an organ from an HCV RNA positive donor [13–15]. In the United States, organ donations from people dying of drug overdose have increased from 66 in 2000 to 1263 in 2016, making up 1.1% and 12.7% of all deceased donors, respectively [16]. At the same time, the proportion of deceased donors who are HCV infected has increased along with the proportion of organ recipients receiving HCV positive organs [17]. Historically, United Network of Organ Sharing (UNOS) defined hepatitis C positivity as any donor testing positive for antibody to HCV (anti-HCV), indicative of either current or past infection, and many organs were discarded [17]. Since 2016, virtually all deceased donors have been tested for HCV RNA which indicates current infection, using Nucleic Acid Amplification technology (NAT) and 4.9% had HCV RNA positive results in 2017 [18].

Due to potential transmission of HBV and HCV infections through organ donation [19–24], the 2013 Public Health Service (PHS) guideline recommends testing all deceased donors for anti-HCV and HCV RNA and total antibody to hepatitis B core antigen (total anti-HBc) and hepatitis B surface antigen (HBsAg) [25]. The guideline also called for ascertainment of 11 donor behavioral risk factors for HBV, HCV and HIV infection, such as injection drug use, incarceration, and male-to-male sexual contact within the 12 months prior to death. Logistically, deceased donor behavioral screening is accomplished by interview of next-of-kin or review of medical and other records. Donors with one or more risk factors are designated as “increased risk donors” (IRD) [25]. Behavioral risk screening is intended to identify donors who might transmit viral bloodborne pathogen infection despite negative test results. The risk of undetected infection during the window period between bloodborne pathogen exposure and detectability of viral nucleic acid in serum has been estimated to occur at a frequency of 0.027 to 32.4 per 10,000 IRD for HCV [26], and 0.04 to 4.9 per 10,000 IRD for HIV [27]. Recipients of organs from IRD are recommended to have testing for HCV RNA, HBV DNA, and HBsAg at 1-3 months after transplantation and anti-HBs, total anti-HBc, and either HBV DNA or HBsAg at 12 months after transplantation [25].

Recent studies document that patient and graft survival are comparable among organ recipients who receive organs from IRD compared with recipients of organs from standard risk donors (SRD) [28, 29]. Survival has been reported to be higher in recipients who accept an IRD organ in comparison with those who decline and remain on the waiting list [30, 31]. Nonetheless, some reports suggest under-utilization of IRD organs [16, 29, 32] with no corresponding increased risk of HBV or HCV transmission from IRD versus SRD [32]. To examine whether increased risk designation assists in early diagnosis and prevention of HBV or HCV-associated morbidity and mortality among recipients, we describe cases of HBV or HCV transmission to organ recipients from NAT negative deceased donors

as investigated by CDC from 2014 to 2017. We also describe donor characteristics and recipient outcomes after transplantation and patterns of test conversions (i.e., conversion from NAT negative to NAT positive). HIV transmissions are not described in this paper as the most recent reported deceased donor-derived HIV transmission was in 2007 [33], and the most recent living donor-derived HIV transmission was in 2009 [34]; 0.1% of deceased donors were HIV antibody positive in 2017 [18].

2. Methods

In the United States, all suspected, unanticipated donor-derived disease transmissions are reported to the Organ Procurement and Transplantation Network (OPTN) for investigation by the ad hoc Disease Transmission Advisory Committee (DTAC), which includes CDC representation. Cases of public health importance (e.g. nationally notifiable infections, unknown syndromes, or multiple ill recipients) are referred to CDC for investigation to determine whether donor-derived disease transmission has occurred and to identify interventions to prevent further transmission.

2.1 Inclusion Criteria

Cases investigated by CDC during 2014-2017 were included if they met the following criteria:

Inclusion criteria for HBV: Deceased donors were included if they tested negative for total anti-HBc, HBsAg and HBV DNA at the time of organ procurement, and one or more recipients developed new HBV DNA positive results within 18 months after organ transplantation. All recipients who received an organ from an included donor were further classified according to HBV DNA results, positive or negative, at the time of investigation. Recipients were excluded if they were positive for total anti-HBc, HBsAg or HBV DNA prior to transplantation.

Inclusion criteria for HCV: Deceased donors were included if they were anti-HCV and HCV RNA negative at the time of organ procurement, and one or more recipients developed new evidence of HCV RNA positivity within 18 months after organ transplantation. All recipients who received a transplanted organ from an included donor were further classified according to HCV RNA results, positive or negative, at the time of investigation. Recipients were excluded if they had detectable HCV RNA prior to transplantation.

Sample of anti-HCV positive, HCV RNA negative donors: During most of 2014-2017, DTAC reports of recipients with new HCV infection after transplantation from anti-HCV positive, HCV RNA negative deceased donors were not investigated by CDC. A non-statistical sample of deceased donors who were anti-HCV positive and HCV RNA negative were referred to CDC by DTAC for investigation at the end of 2017 and these donors were included in this paper if one or more recipients developed new evidence of HCV RNA positivity within 18 months after organ transplantation. Recipients were excluded if they had detectable HCV RNA prior to transplantation.

Donor risk behaviors defined by the PHS IRD criteria [25] were not used as a basis for inclusion or exclusion from this study. HCV test results were not used for inclusion or exclusion of donors or recipients associated with donor-derived HBV; neither were HBV test results used for inclusion or exclusion of donors or recipients associated with donor-derived HCV. Donors were also not excluded for positive NAT results that became available only after a recipient was reported with possible donor-derived HBV or HCV. Among all organ recipients from the same donor, the index recipient is the first recipient identified with donor derived infection.

2.2 Epidemiological Investigation

Donor medical records were reviewed to identify demographic characteristics and cause of death. Responses to the organ procurement organization (OPO) donor history questionnaires by next-of-kin were reviewed to ascertain donor risk behaviors and to determine whether the donor met IRD criteria. Recipient records were abstracted to determine dates of test conversion, antiviral treatment, and clinical outcomes (survival and graft survival). Laboratory records were reviewed to identify date of specimen collection and results for HBV and HCV testing.

2.3 Laboratory Testing

Available donor specimens, which could include frozen serum, splenocytes and tissue blocks were tested for the presence of HBV DNA or HCV RNA by quantitative PCR using COBAS Ampliprep/COBAS TaqMan® CAP/CTM version 2.0 (Roche, Indianapolis, IN) according to the manufacturer's recommendations for serum/plasma samples. Splenocytes were extracted using the MagNa Pure Total Nucleic Acid Kit according to the manufacturer's instructions (Roche, Indianapolis, IN). Formalin fixed, paraffin embedded tissue blocks were deparaffinized in xylene, rinsed with two 100% ethanol washes, and air dried, followed by digestion with proteinase K at 45°C overnight. Following a seven minute incubation at 85°C, RNA was extracted using the phenol:chloroform method, or DNA was extracted using the Qiagen UCP Pathogen Mini Kit (Qiagen, Germantown, MD). Extracts were then tested for the presence of HBV DNA or HCV RNA using a quantitative laboratory developed PCR as described previously [35]. Genetic relatedness between matched donor-recipient pairs was identified using Next-generation Sequencing of the HCV hypervariable region (HVR1) [36]. Testing was done at CDC (Atlanta, Georgia).

2.4 Ethics

Because the primary intent of this project is disease control activity, CDC determined it was not human subjects research and did not require review by an institutional review board.

3. Results

3.1 HBsAg Negative, HBV DNA Negative, Total Anti-HBc Negative Donors Associated with Donor-derived Hepatitis B

During 2014-2017, potential donor-derived HBV infections from 14 HBV DNA negative deceased donors were investigated by CDC. Of those, seven were excluded (Figure 1), and seven deceased donors associated with new HBV infections in recipients were included

in this study. Table 1 shows selected donor demographic characteristics, cause of death, IRD status, laboratory results and hospital timeline. Mean (median) age of donors was 29 (29) years. Four (57%) died of anoxia due to drug intoxication. All met IRD criteria and four (57%) were anti-HCV positive, including one donor who was identified as HCV RNA positive prior to organ procurement. Donors were hospitalized for a mean (range) of three (one to seven) days prior to the date of cross-clamp (i.e., the date of organ procurement). All donors had documented HBV DNA negative results from the OPO one to three days prior to donation; in addition 4 donors tested negative in the CDC laboratory as part of the investigation. One recipient (related to donor number 5 in Table 1) had HBV DNA identified in a stored liver biopsy specimen obtained one week after transplantation. In summary, one (14%) of seven donor-derived transmission events was confirmed with laboratory evidence.

3.2 Recipients Associated with Donor-derived Hepatitis B

Twenty-one recipients received organs from included donors; six recipients were excluded from investigation because of HBV infection prior to transplantation, including 5 kidney recipients and 1 kidney and liver recipient. Of 15 remaining recipients, seven (47%) recipients became newly HBV DNA positive after transplantation of whom five (71%) were liver recipients (Table 1). All seven index recipients were tested because of PHS recommendations for recipients of organs from IRD [25].

Clinical outcomes for recipients are shown in Table 2. Six (86%) of seven recipients with HBV infection were alive at the time of investigation (approximately 6-18 months after transplantation). All six survivors had functioning grafts and five (83%) had started treatment for HBV.

3.3 Anti-HCV Negative, HCV RNA Negative Deceased Donors Associated with Donor-derived Hepatitis C

Thirty reports of possible donor-derived HCV transmission from anti-HCV negative, HCV RNA negative deceased donors were investigated by CDC, 21 were excluded (Figure 2), and nine donors associated with new HCV infection in recipients were included in this study. Table 3 shows data for CDC-led investigations of HCV donor-derived infections. Mean (median) age of these donors was 40 (39) years. Of the nine donors, six (67%) died of anoxia due to drug intoxication, eight (89%) were classified as IRD by the OPO, and one (11%) was not initially classified as IRD by the OPO but the transplant center followed the IRD protocol because of evidence for injection drug use in the medical record of the donor. Donors were hospitalized for a median (range) of five (two to nine) days prior to the date of cross-clamp.

While all donors were documented to be HCV RNA negative at the time of cross-clamp, two donors tested HCV RNA positive from stored specimens during investigation of donor-derived HCV infection; one of these (donor 4 in Table 3) had RNA sequences that were identical to sequences in all recipients. The remaining seven donors had negative testing for HCV RNA, including four donors who had testing performed in the CDC laboratory. For donor 2, three different recipients transplanted in two different centers subsequently tested positive for HCV RNA. For donor 5, both the heart and left kidney recipients had

HCV sequences identical to one another. For donor 6, both kidney recipients had identical HCV sequences. In summary, five (55%) of nine transmission events were confirmed with laboratory evidence; except for one transmission event (associated with Donor 6), recipients were transplanted at two or more transplant centers. Recipients of organs from Donor 6 underwent surgery in different operating suites with different equipment and only one recipient required dialysis postoperatively. Further details are found in Table 3.

3.4 Recipients with Donor-derived Hepatitis C Associated with Anti-HCV Negative, HCV RNA Negative Deceased Donors

A total of 35 recipients received organs from included donors; four organ recipients, including two liver recipients and two kidney recipients, were excluded from investigation because of evidence of HCV infection prior to transplantation. Of 31 remaining recipients, 20 (65%) became HCV RNA positive, including eight (40%) kidney and five (25%) liver recipients. Five (100%) of five liver recipients, four (100%) of four lung recipients, eight (50%) of 16 kidney recipients, two (67%) of three heart recipients and one (100%) of one kidney/pancreas recipient became HCV RNA positive (Table 3). Of nine index recipients, two (22%) were tested because of elevated liver function tests and the remainder were tested because of PHS recommendations for recipients of organs from IRD [25].

Nineteen (95%) of 20 recipients with HCV infection had survived at the time of investigation (approximately 3-6 months after transplantation); 18 (95%) survivors had functioning grafts (Table 4). Fourteen (74%) surviving recipients with HCV infection had started treatment at last follow-up, including all seven surviving HCV-infected recipients reported in 2017. None of the seven HCV-infected patients treated in 2017 had active HBV infection but one had laboratory evidence of prior HBV infection (total anti-HBc positive).

3.5 Donor Risk Behaviors

Regardless of HBV or HCV infection status, the most common risk factors reported from donor next-of-kin interviews were injection drug use and incarceration, both within 12 months prior to death (Table 5). Four (57%) of 7 donors associated with HBV recipient infection and 3 (33%) of 9 donors associated with HCV recipient infection were identified by next-of-kin as persons with a history of injection drug use. After including additional data derived from medical records, 6 (86%) of 7 donors associated with HBV recipient infection and 5 (55%) of 9 donors associated with HCV recipient infection had injection drug use as a risk factor. It was not possible to ascertain exact timing or duration of injection drug use behaviors from available donor records.

3.6 Timing of NAT Positivity After Transplantation for Donor-Derived HBV and HCV

The timeline for NAT positivity is shown in Figure 3a for seven recipients who developed HBV infection and in figure 3b for 20 recipients who developed HCV infection. Collection dates for HBV DNA positivity ranged from 119 to 459 days after transplantation with a mean (median) of 297 (358) days. By contrast, HCV RNA positivity collection dates were documented from 20 to 195 days after transplantation with mean (median) days to HCV RNA positivity of 62.9 (38.5).

3.7 Non-statistical Sample of Anti-HCV Positive, HCV RNA Negative Donors Associated with Donor-Derived HCV

Table 6 shows donor demographic characteristics, cause of death, IRD status, laboratory results and hospital timeline from the sample of 6 anti-HCV positive, HCV RNA negative donors associated with donor-derived HCV infection. All donors were initially HCV RNA negative at the time of cross-clamp, but repeat testing on donor splenocyte or serum samples for HCV RNA by the OPO or CDC was positive for four (67%) of six donors after investigation of recipient infection was initiated. The HCV RNA positive results were collected a mean (median) of 3.5 (3.5) days after admission from four donors; by comparison a total of eight HCV RNA negative results were collected a mean (median) of 2.4 (2.5) days after admission from all six donors. Table 6 shows the details of HCV RNA results by specimen type, date of collection and laboratory where the results were generated. Of 11 total recipients, 2 were excluded because of prior positive HCV RNA, six became HCV RNA positive after transplantation including all 5 liver recipients and three organ recipients remained HCV RNA negative.

4. Discussion:

Between 2014 and 2017, CDC investigated seven total anti-HBc, HBsAg and HBV DNA negative deceased organ donors associated with new HBV infections in seven (47%) of 15 recipients; nine anti-HCV and HCV RNA negative deceased organ donors associated with new HCV infections in 20 (65%) of 31 recipients were also identified. In one (14%) of seven investigations associated with HBV and 5 (55%) of nine investigations associated with HCV, there was laboratory confirmation of donor-derived infection. The remaining investigations are consistent with donor derived infection, but viremia was below detectable limits in available donor samples and only one infected recipient was associated with each donor. Most index recipients were identified because they were screened per the 2013 PHS guideline [25] for recipients of IRD organs, a substantial majority of recipients survived and most received antiviral therapy for HBV or HCV. These findings provide further evidence that early detection of HBV and HCV infections coupled with early initiation of antiviral therapy may be effective in preventing short-term morbidity and mortality among recipients with donor-derived HBV or HCV infection, as has been reported elsewhere [13–15, 37]. While HBV and HCV infection of transplant recipients has previously been associated with poor outcomes [1–5, 8, 9, 21], and underutilization of IRD organs has been plausibly linked to patient and provider concerns about HBV and HCV transmission [16, 29, 32], our findings suggest a continued important role for donor viral blood borne pathogen risk management: identification of recipients at risk for donor-derived HBV and HCV so these patients can be screened and offered antiviral treatment, which may prevent adverse outcomes [37].

Early diagnosis of HBV and HCV infection in organ recipients is important for patient outcomes. All patients with chronic HBV infection should undergo lifelong medical monitoring to evaluate for treatment indications or response to therapy, and to identify development of fibrosis and hepatocellular carcinoma [38]. All patients with HCV infection should be offered curative therapy unless they have a short life expectancy that cannot be

remediated by “HCV therapy, liver transplantation, or another directed therapy” [10]. In addition, past resolved infection with HBV or current coinfection may be present in these patients with HCV; for example, one 2017 recipient with HCV infection had positive total anti-HBc, evidence of prior HBV infection.–Reactivation of HBV infection during treatment for HCV has been documented, even among patients with past resolved infection; thus, close monitoring is recommended [38, 39]. HBV antiviral prophylaxis during HCV antiviral therapy is also recommended for some persons with current or resolved HBV infection who are receiving immunosuppressive therapy [38, 40].

Ideally, criteria for recognizing viral blood borne pathogen donor risk factors should have high sensitivity to identify a high proportion of donor-derived bloodborne pathogen infections through systematic recipient testing, and a high negative predictive value so that donors not meeting criteria are associated with very few or no bloodborne pathogen infections among recipients [41]. In our study all recipients with donor-derived HBV and HCV were associated with IRD or donor history of injection drug use. While it is not possible to estimate sensitivity and negative predictive value of IRD from these data, IRD criteria appear to be effective in stratifying donors by risk; 15.7% of IRD and 1.1% of SRD were HCV RNA positive in 2017 [18]. With the advent of near universal deceased donor NAT testing for bloodborne pathogens [18], the average window period between exposure and serum/plasma NAT detectability for HBV (20-22 days), HCV (3-5 days) and HIV (5-6 days) is considerably reduced [42] and risk of unrecognized donor-derived HBV, HCV and HIV is extremely low [26, 27]. Nonetheless, due to ongoing HBV [43], HCV [44] and HIV [45, 46] transmission in relation to the opioid crisis, recognition of viral blood borne pathogen risk factors among deceased organ donors and ongoing organ recipient monitoring will continue to be important to ensure that organ recipient infections are promptly diagnosed and treated. Provider and patient education will be critical to ensure full understanding of the purpose of risk stratification.

Our data suggest that liver recipients may be particularly susceptible to donor-derived HBV and HCV acquired during the window period. During early infection, these viruses replicate in liver cells before release into the bloodstream [47, 48], and thus liver recipients would be more likely than non-liver organ recipients to develop transplant-associated transmission from donors with window period infection, consistent with our observations. Following replication in hepatocytes, HCV antibodies develop within one to six months after infection [49]. While approximately 25% of acutely infected persons clear HCV viremia spontaneously, reinfection with HCV is particularly common in persons who inject drugs [50, 51]. Donor reinfection is the most likely explanation for our observation of window period transmission of HCV to recipients of organs from anti-HCV positive and HCV RNA negative donors: all six donors were IRD and five of six died of overdose, suggesting high risk activity continued up until the time of admission; and four of six donors had retrospective identification of HCV RNA positive specimens collected on average one hospital day later than the HCV RNA negative specimens, suggesting that exposure occurred close to the time of admission.

These findings are subject to the following limitations. First, causation cannot be inferred from a descriptive study and other risk factors such as healthcare-associated infection and

recipient risk behaviors cannot be fully excluded as causal factors for the recipient HBV and HCV cases where virus was not isolated from the donor or genetically identical virus was not documented among recipients. Second, risk factor information was reported by next-of-kin and therefore subject to information bias; data from medical records suggests that risk factors such as injection drug use may be underreported by next-of-kin. Third, this study included only those cases investigated by CDC and may not be generalizable to all donors or recipients. Because this study did not include data for all IRD recipients and all DTAC reports, risk estimates for HBV or HCV transmission from IRD donors cannot be generated from these data. Fourth, while HCV testing by NAT among IRD was recommended in 2013 [25] and prevalence of HCV RNA among IRD in 2014, 2015 and 2016-2017 was 4.6%, 86% and > 99%, respectively [18], recommended testing was not fully implemented during the early part of the study period. If testing of recipients of organs from IRD was also partially implemented during the 2014-2017 study period, then some cases of donor-derived HBV or HCV infection may have gone undetected. Fifth, identification of the date of NAT positivity for infected recipients is dependent on the date the test was ordered by the physician. Thus, the days from transplantation to NAT positivity were likely overestimated for recipients in this study. Sixth, prospective follow up to ascertain patient and graft survival was not conducted as part of this investigation and long-term outcomes are unknown. Finally, transplant-associated infections related to anti-HCV positive, HCV NAT negative increased risk donors were not investigated by CDC during most of the study period. It is not possible to estimate transmission risk from these donors based on our data and conclusions from our data are not generalizable to all anti-HCV positive, HCV NAT negative donors. Strengths of the paper include standardized prospective risk stratification conducted through next-of-kin interviews and other sources, ongoing protocol-driven NAT testing of donors and recipients of organs from IRD, and routine reporting of suspected cases of donor-derived HCV and HBV infections for investigation by DTAC and CDC.

Recipients of organs from IRD have comparable survival and graft survival relative to recipients of organs from standard risk donors [28, 29] and higher survival relative to those who decline an IRD organ [30,31]. The availability of effective antiviral treatment for HBV and HCV infection [3, 10–15, 38] offers an additional margin of safety to recipients who accept an organ from an IRD. The present study suggests that recognition of risk factors among organ donors likely contributed to the early diagnosis of donor-derived HBV and HCV infection and early treatment, which may reduce the risk of graft failure and recipient death. CDC will continue to work with governmental and other partners to evaluate current recommendations for donor risk factor criteria, designation, and nomenclature to enhance both safety and availability of organs.

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Abbreviations:

Anti-HCV	Antibody (IgG) to hepatitis C virus
Total anti-HBc	Total antibody to hepatitis B core antigen

Anti-HBs	Antibody to hepatitis B surface antigen
CDC	Centers for Disease Control and Prevention
DAA	Direct acting antiviral
DNA	Deoxyribonucleic acid
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
IRD	Increased risk donor
L	Left
NAT	Nucleic acid amplification technology
OPO	Organ Procurement Organization
OPTN	Organ Procurement Transplant Network
PHS	Public Health Service
R	Right
RNA	Ribonucleic acid
SRD	Standard risk donor
UNOS	United Network of Organ Sharing

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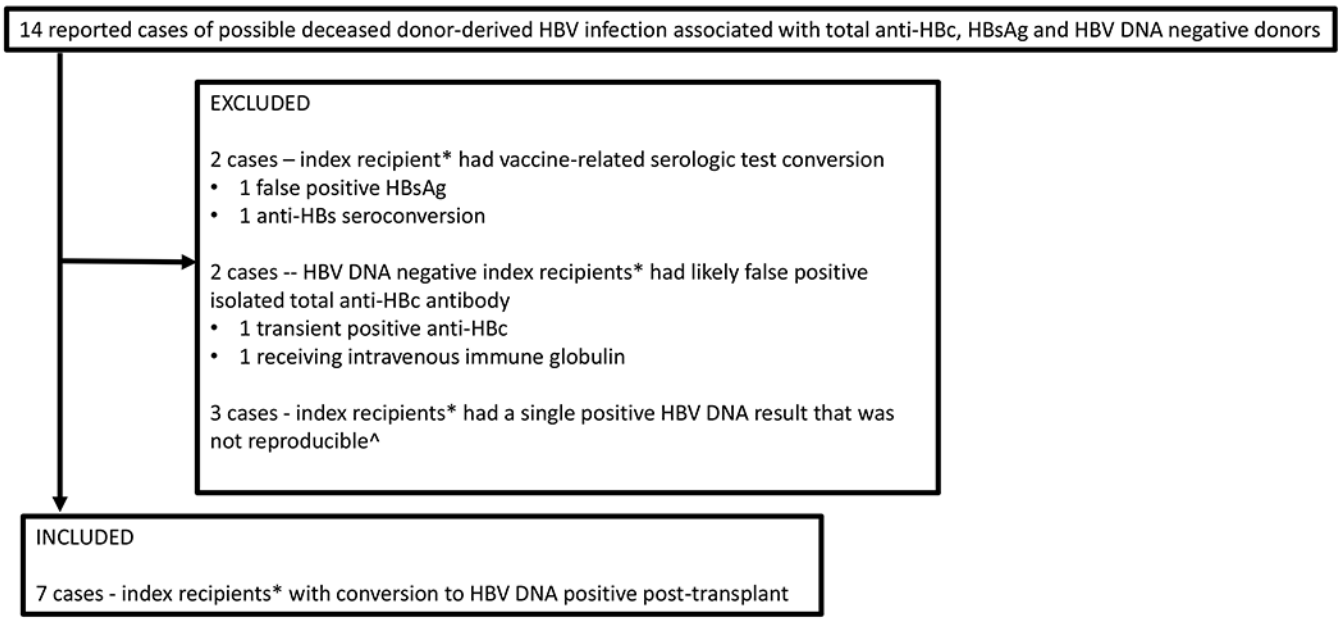


Figure 1. Inclusions and Exclusions for Donor-Derived HBV Infections in Organ Recipients Investigated by CDC, United States, 2014-2017

*Among recipients of organs from the same donor, the index recipient is defined as the first organ recipient to be reported with an HBV test conversion

^From 2014-2017 there were 8970 IRD [18].

Abbreviations: HBsAg, hepatitis B surface antigen; IRD, increased risk donor; DNA, deoxyribonucleic acid; HBV, hepatitis B virus; Total anti-HBc, total antibody to hepatitis B core antigen.

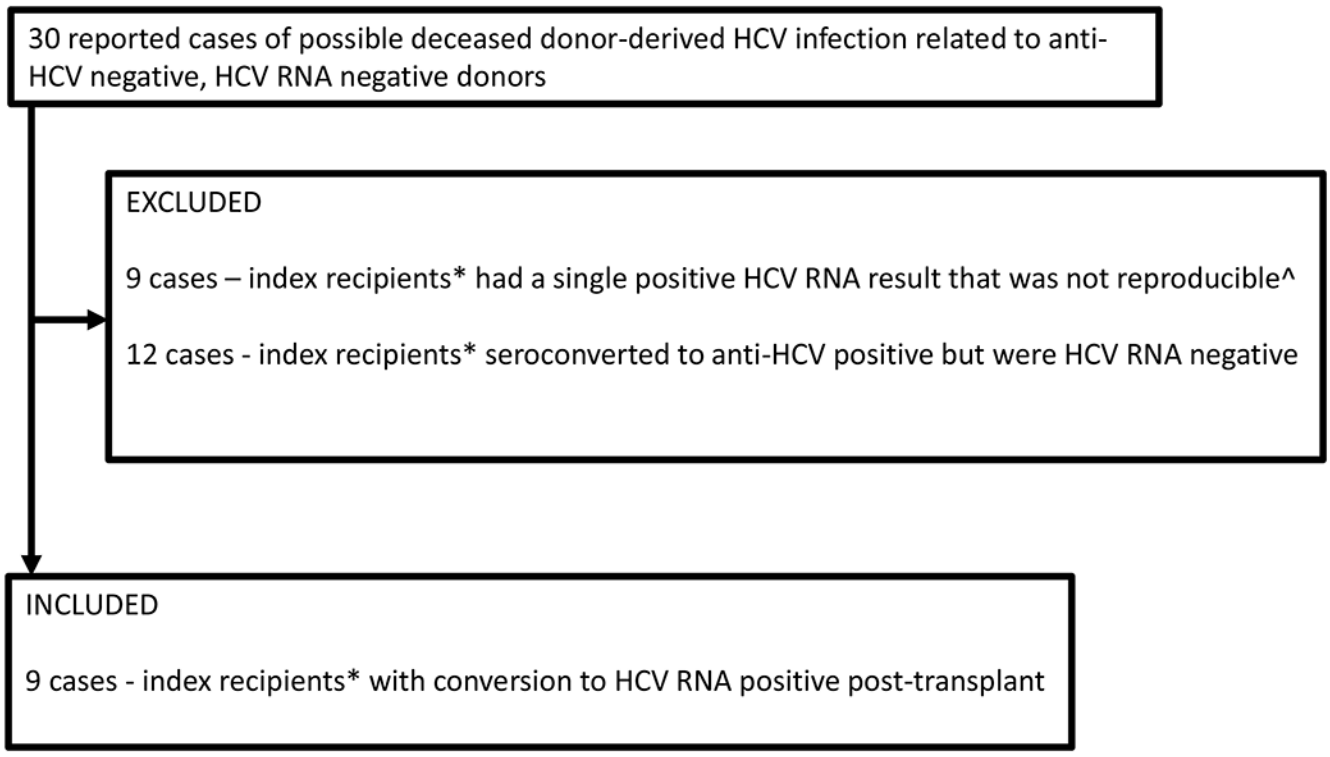
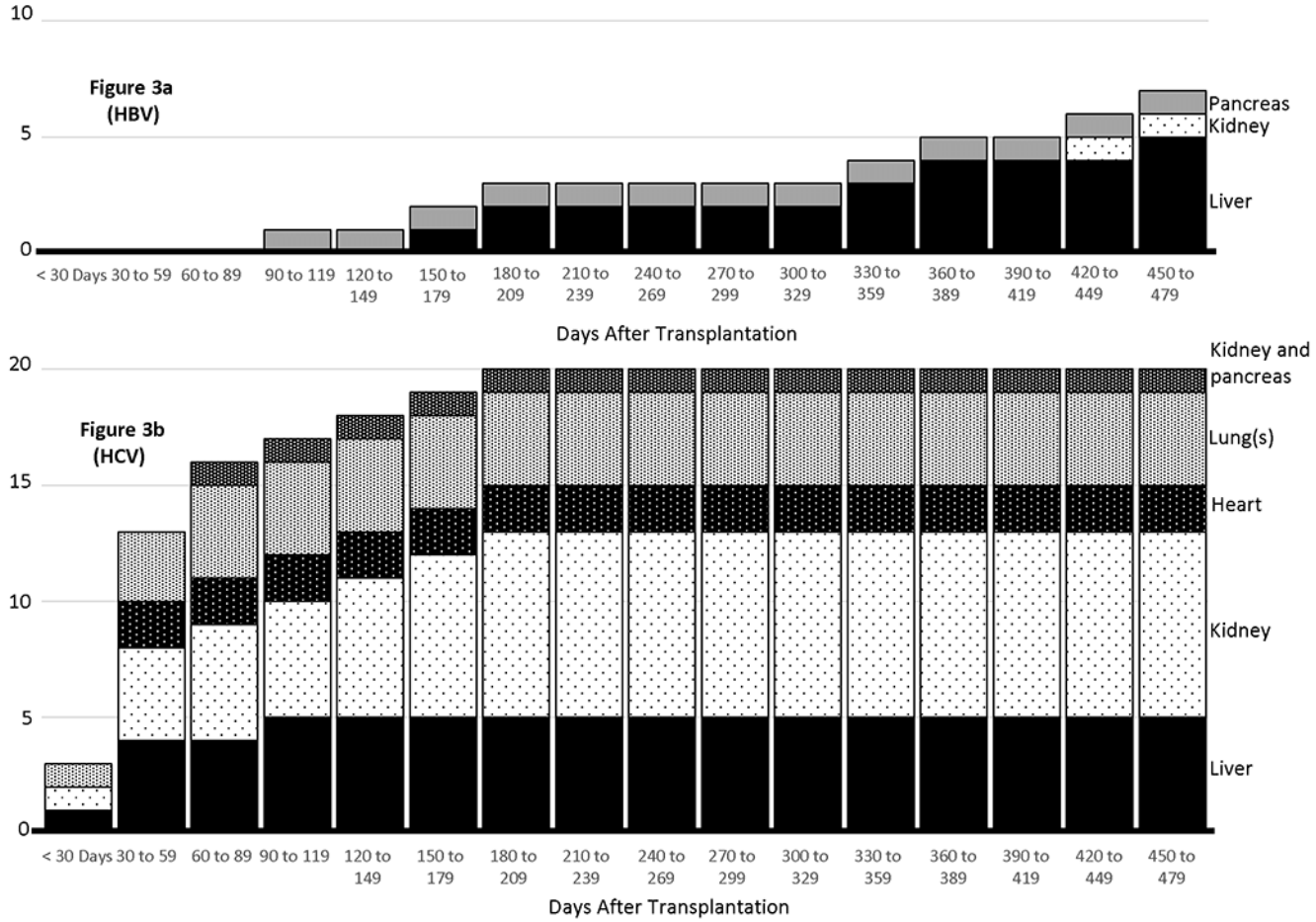


Figure 2. Inclusions and Exclusions for Donor-Derived HCV Infections in Organ Recipients Investigated by CDC, United States, 2014-2017

*Among recipients of organs from the same donor, the index recipient is defined as the first organ recipient to be reported with HCV test conversion.

^From 2014-2017 there were 8970 IRD [18]. Frequency of HCV window period infection is estimated at 0.027 to 32.4 per 10,000 IRD [26]. Estimated specificity of HCV RNA in transplant centers is calculated at > 99%.

Abbreviations: anti-HCV, antibody (IgG) to hepatitis C virus; HCV, hepatitis C virus; RNA, ribonucleic acid.



Cumulative NAT Conversions for Donor-Derived HBV (Figure 3a) and Donor-Derived HCV (Figure 3b), by Organ Type and Days After Transplantation, United States, 2014 - 2017
Abbreviations. DNA, deoxyribonucleic acid; HBV, hepatitis B virus; HCV, hepatitis C virus; RNA, ribonucleic acid.

Table 1

Timeline, Laboratory Test Results and Outcomes for Total Anti-HBc, HBsAg and HBV DNA Negative Deceased Donors with Donor-Derived HBV Infection in Organ Recipients Investigated by CDC, United States 2014-2017; N=7

Donor #	Cause of Death	Mechanism of Injury	Increased Risk Donor	Anti-HCV Result	Hospital Course, by Day of Hospitalization									HBV NAT (+) Recipients	HBV NAT (−) Recipients	Total recipients
					Admission, Day 0	1	2	3	4	5	6	7	8	9			
1	Head trauma	Blunt injury	Yes	Negative		Ω * * [a]		χ							Liver	Bilateral lungs, L kidney, R kidney	4
2	Anoxia	Drug intoxication	Yes	Positive		*	Ω	χ							Liver	L kidney	2
3	Cerebrovascular/ stroke	Intracranial hemorrhage/ stroke	Yes	Positive	Ω * * [a]	χ									R kidney		1
4	Anoxia	Asphyxiation	Yes	Positive			Ω *		χ						Liver	R kidney	2
5	Anoxia	Drug intoxication	Yes	Positive					*		Ω	χ			Liver [1a]		1
6	Anoxia	Drug intoxication	Yes	Negative		Ω * * [a]		χ							Liver	L kidney	2
7	Anoxia	Drug intoxication	Yes	Negative			Ω * * [a]		χ						Pancreas	Liver, R kidney	3

Key, Table 1

*	Collection date for negative HBV DNA test
Ω	Date of death
χ	Date of cross-clamp

Results are for serum and for antemortem testing by the OPO laboratory unless otherwise indicated, as below:

[1] Liver biopsy of recipient was HBV DNA positive 1 week after transplant

[a] Testing in CDC Laboratory after donor-derived infection was reported

Organ recipients positive for HBV prior to transplantation are excluded

Abbreviations: Anti-HCV, antibody (IgG) to hepatitis C virus; DNA, deoxyribonucleic acid; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; L, left; R, right; Total anti-Hbc, total antibody to hepatitis B core antigen..

Table 2

Outcomes Within 3-18 Months After Transplantation Among All Organ Recipients from Donors with Donor-Derived HBV Investigated by CDC, United States, 2014-2017

Organ Transplanted	Total Recipients[1]	HBV DNA Positive Recipients[2]	HBV DNA Positive Recipients Who Survived	Outcomes Among Survivors		
				Graft Functioning	Discharged from Hospital	Started on Treatment for HBV
Bilateral Lungs	1	0				
Kidney	7	1	1	1	1	1
Liver	6	5	5	5	5	4
Pancreas	1	1	0			
TOTAL (%)	15	7 (46.7)	6 (85.7) [3,4]	6 (100)[5]	6 (100)[5]	5 (83.3)[5]

[1] Total organ recipients, including recipients with and without donor-derived HBV infection

[2] Total organ recipients with donor-derived HBV infection

[3] Denominator is organ recipients with donor-derived HBV infection

[4] The single death was not attributed to HBV infection

[5] Denominator is survivors with donor-derived HBV infection

Abbreviations. DNA, deoxyribonucleic acid; HBV, hepatitis B virus.

Table 3

Timeline, Laboratory Test Results and Outcomes for Anti-HCV Negative, HCV RNA Negative Deceased Donors with Donor-Derived HCV Infection in Organ Recipients Investigated by CDC, United States 2014-2017; N=9

Donor #	Age (years)	Sex	Cause of Death	Mechanism of Injury	Increased Risk	Anti-HCV Result	Hospital Course, by Day of Hospitalization; Admission on Day 0									HCV NAT (+) Recipients	HCV NAT (−) Recipients	Total recipients
							Day 0	1	2	3	4	5	6	7	8	9			
1	38	Male	Head trauma	Blunt injury	Yes	negative		Ω * (+) *a*		χ (+) *1 a*							pancreas, L lung, R lung[*i*]	Heart, R kidney	5
2	39	Female	Anoxia	Cardiovascular	Yes	negative					*			Ω		χ * *1 a*	L kidney, liver, R kidney[*ii*]		3
3	43	Male	Head trauma	Blunt injury	Yes	negative				Ω *		χ					R kidney	Heart, L kidney	3
4	22	Female	Anoxia	Drug intoxication	Yes	negative					χ *			χ * (+) *b §*			lung[§], liver[§], R lung[§*iii*]	R kidney	6
5	36	Female	Anoxia	Drug intoxication	Yes	negative				*		χ *		χ			Heart[₸], L kidney[₸], liver[*iv*]	R kidney	4
6	41	Male	Anoxia	Drug intoxication	Yes	negative		* *[*b*] *[*2a*]					Ω χ				L kidney[≠], R kidney[≠*v*]		2
7	53	Female	Anoxia	Drug intoxication	No[^]	negative			*	Ω	χ * *a*						R kidney		1
8	47	Male	Anoxia	Drug intoxication	Yes	negative	Ω *		χ								Liver	Heart, L kidney, R kidney	4

Donor #	Age (years)	Sex	Cause of Death	Mechanism of Injury	Increased Risk	Anti-HCV Result	Hospital Course, by Day of Hospitalization; Admission on Day 0									HCV NAT (+) Recipients	HCV NAT (−) Recipients	Total recipients
							Day 0	1	2	3	4	5	6	7	8	9			
9	39	Male	Anoxia	Drug intoxication	Yes	negative		Ω * * [a]		χ							Liver	L kidney, R kidney	3

Key, Table 3

(+)	Collection date for positive donor NAT test
*	Collection date for negative donor NAT test
Ω	Date of death
χ	Date of cross-clamp

Results are for serum and for antemortem testing by the OPO laboratory unless otherwise indicated, as below:

[1] Splenocytes

[2] Lymphocytes

[a] Testing in CDC laboratory after HCV RNA positive recipient was reported.

[b] Follow-up testing in OPO laboratory after HCV RNA positive recipient was reported

Organ recipients positive for HCV prior to transplantation are excluded.

[§] Phylogenetic sequencing of matched donor and all recipient sequences in the CDC laboratory indicated genetic relatedness.

[ǂ] Phylogenetic sequencing of heart and L kidney recipient HCV RNA indicated genetic relatedness.

[ǂ] Phylogenetic sequencing of L kidney and R kidney indicated genetic relatedness.

[^] Donor was classified as standard risk by OPO, but transplant center evaluated recipients according to IRD protocol because of a donor history of injection drug use

[i] Left kidney and pancreas, and right lung were transplanted at the same center. The right lung was transplanted at a second transplant center.

[ii] Right and left kidney were transplanted at the same center. The liver was transplanted at a second transplant center.

[iii] Heart, left lung and right lung were transplanted at the same center. Liver was transplanted at a second transplant center. Left kidney was transplanted at a third transplant center.

[iv] Heart, left kidney and liver were transplanted at three different transplant centers.

[v] Left kidney and right kidney were transplanted at the same transplant center by the same surgical team in two different operating rooms using different equipment 45 minutes apart. Only 1 of the 2 patients received hemodialysis at the facility post-transplant. Both patients converted to HCV RNA positive within a month after transplantation.

Abbreviations: anti-HCV, antibody (IgG) to hepatitis C virus; HBV, hepatiis B virus; HCV, hepatitis C virus; L, left; R, right; RNA, ribonucleic acid.

Table 4

Outcomes Within 3-18 Months After Transplantation Among All Organ Recipients from Donors with Donor-Derived HCV Investigated by CDC, United States, 2014-2017

Organ Transplanted	Total Recipients[1]	HCV RNA Positive Recipients[2]	HCV RNA Positive Recipients Who Survived	Outcomes Among Survivors		
				Graft functioning	Discharged from Hospital	Started on Treatment for HCV
Heart	5	2	2	2	2	1
Kidney	16	8	8	8	8	7
L kidney and pancreas	1	1	1	1	1	1
liver	5	5	5	5	4	4
lung	4	4	3	2	1	1
TOTAL (%)	31	20 (64.5)	19 (95.0)[3,4]	18 (94.7)[5]	16 (84.2)[5,6]	14 (73.7)[5]

[1]Total organ recipients, including recipients with and without donor-derived HCV infection

[2]Total organ recipients with donor-derived HCV infection

[3]Denominator is organ recipients with donor-derived HCV infection

[4]The single death was unrelated to HCV infection

[5]Denominator is survivors with donor-derived HCV infection

[6]Hospitalizations were unrelated to HCV infection

Abbreviations. HCV hepatitis C virus; RNA, ribonucleic acid.

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Table 5

Risk Factors for Donors * with Donor-Derived Organ Recipient HBV or HCV Infections Investigated by CDC, Based on Next-of-Kin Interviews, United States, 2014-2017

Characteristic	HBV	HCV
Total Donors	7	9
Risk factors (%)		
People who have injected drugs by intravenous, intramuscular, or subcutaneous route for nonmedical reasons in the preceding 12 months	4^ (57.1)	3^ (33.3)
People who have been in lockup, jail, prison, or a juvenile correctional facility for more than 72 hours in the preceding 12 months	5 (71.4)	2 (22.2)
People who have had sex with a person who injected drugs by intravenous, intramuscular, or subcutaneous route for nonmedical reasons in the preceding 12 months	4 (57.1)	1 (11.1)
People who have had sex with a person who had sex in exchange for money or drugs in the preceding 12 months	3 (42.9)	1 (11.1)
People who have been newly diagnosed with or have been treated for syphilis, gonorrhea, Chlamydia, or genital ulcers in the preceding 12 months	2 (28.6)	1 (11.1)
Sex with a person known or suspected to have HIV, HBV or HCV in the preceding 12 months	1 (14.3)	1 (11.1)
People who have had sex in exchange for money or drugs in the preceding 12 months	1 (14.3)	1 (11.1)
Donors who meet the following criterion should be identified as being at increased risk for recent HCV infection only: People who have been on hemodialysis in the preceding 12 months	--	0 (0)
Men who have had sex with men in the preceding 12 months (% of males)	0 (0)	0 (0)
Women who have had sex with a man with a history of MSM behavior in the preceding 12 months (% of females)	0 (0)	0 (0)
Unknown risk history	0 (0)	2 (22.2)
Hemodilution	0 (0)	0 (0)

* Donors associated with HBV in recipients were anti-HBc, HBsAg and HBV DNA negative. Donors associated with HCV in recipients were anti-HCV and HCV RNA negative. Risk behaviors were recorded from next-of-kin interviews.

^ In addition to next-of-kin interviews, history of injection drug use was also ascertained through medical records and/or identification of drug paraphernalia at the scene. When all sources of information were considered, six (86%) of seven donors associated with donor-derived HBV and five (55%) of nine donors associated with HCV had a history of injection drug use.

Abbreviations. Anti-HBc, total antibody to hepatitis B core antigen; anti-HCV, antibody (IgG) to hepatitis C virus; DNA, deoxyribonucleic acid; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; RNA, ribonucleic acid.

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Table 6

Timeline, Laboratory Test Results and Outcomes for Anti-HCV Positive HCV NAT Negative Deceased Donors with Donor-Derived HCV Infection in Organ Recipients Investigated by CDC, United States 2014-2017; N=6

Donor #	Cause of Death	Mechanism of Injury	Increased Risk Donor	Anti-HCV Result	Hospital Course, by Day of Hospitalization; Admission on Day 0										HCV RNA Positive Recipients	HCV RNA Negative Recipients	Total recipients
					Day 0	1	2	3	4	5	6	7	8	9			
1	Anoxia	Drug intoxication	Yes	positive					Ω * (+) *a*	χ					Liver		1
2	Anoxia	Cardiovascular	Yes	positive		Ω *		χ (+) *1 a*							Liver		1
3	Anoxia	Drug intoxication	Yes	positive		Ω * * *a*	χ								Liver		1
4	Anoxia	Drug intoxication	Yes	positive				Ω * (+) *a*	χ						Liver	Bilateral lungs	2
5	Anoxia	Drug intoxication	Yes	positive	*			Ω *		χ * *1 a*					Liver	Bilateral lungs, R kidney	3
6	Anoxia	Drug intoxication	Yes	positive			*		Ω χ (+) *b*						L kidney		1

Key, Table 6

(+)	Collection date for positive HCV RNA
*	Collection date for negative HCV RNA
Ω	Date of death
χ	Date of cross-clamp

Results are for serum and for antemortem testing by the OPO laboratory unless otherwise indicated, as below:

1 Splenocytes

a Testing in CDC laboratory after HCV RNA positive recipient was reported

[b] Follow up testing in OPO laboratory after HCV RNA positive recipient was reported

Organ recipients positive for HCV prior to transplantation are excluded

Abbreviations: anti-HCV, antibody (IgG) to hepatitis C virus; HCV, hepatitis C virus; RNA, ribonucleic acid.