Healthcare-associated hepatitis C virus transmission among patients in an abdominal organ transplant center


Abstract: Background. De novo hepatitis C virus (HCV) infection among transplant patients is rarely recognized but can have severe consequences. We investigated the scope, source, and mode of HCV transmission within a transplant center after incident HCV infection was identified in 2 patients who had liver transplantation in late 2006. Methods. Patients were interviewed, and transplant logs, medical records, and staff practices were reviewed to identify opportunities for HCV transmission. Infection via receipt of blood or organs was evaluated. Molecular epidemiology was used to determine the relatedness between persons with incident and chronic HCV infection. Results. HCV from infected blood or organ donors was ruled out. Among the 308 patients who underwent transplant in 2006, no additional incident HCV infections were identified. Eighty-five (28%) had pre-transplant chronic HCV infection; 13 were considered possible HCV source patients based upon shared days on the inpatient unit, nursing assignment, or invasive procedures in common with incident HCV case-patients. Viral isolates from 1 HCV source patient and 1 incident case-patient were found to be highly related by quasispecies analysis, confirming patient-to-patient HCV transmission. Possible modes of transmission identified were the improper use of multidose vials, sharing of blood-contaminated glucometers, and touch contamination. Conclusion. Sporadic transmission or endemic levels of HCV transmission might be overlooked in a setting with high HCV prevalence, such as liver transplant units, where multiple, repeated opportunities for patient-to-patient HCV transmission can occur. Surveillance through pre- and post-transplant screening is necessary to identify incident HCV infection in this setting. Constant, meticulous attention must be paid to maintaining aseptic technique and good infection control practices to eliminate HCV transmission opportunities.

Chronic hepatitis C virus (HCV) infection is the leading indication for liver transplant in the United States (1–3). Virtually all HCV-infected liver transplant patients experience recurrence of HCV infection and may sustain accelerated progression to graft cirrhosis (2–4). Recurrent HCV is the leading cause of graft failure and, compared with uninfected patients, HCV-infected liver transplant patients have decreased survival (3, 5). De novo HCV infection after organ transplantation is rarely recognized. Such infections have previously been ascribed to the transfusion of infected blood or blood products (1, 6), the receipt of organs from infected donors (7, 8), and patient-to-patient spread following infection control lapses (9). While considerable efforts have been made to minimize HCV transmission risks from blood and organs, there has been less awareness of risks associated with breaks in infection control in the organ transplant setting.

In January 2007, incident HCV infection was diagnosed in 2 patients who had received liver transplants during
the latter half of 2006, at a medical center with one of the most active liver organ transplant programs in the United States. Pre-transplant HCV RNA screening tests had been negative in the 2 patients; their incident HCV infection was identified during routine post-transplant HCV RNA screening. We initiated an investigation to determine the scope, source, and mode of HCV transmission in this setting.

Materials and methods

Description of abdominal organ transplant program

Patients in the abdominal organ transplant programs (liver, kidney, and pancreas) shared the same surgical teams, operating rooms, and post-transplant inpatient unit. Since initiation of the transplant program in 1998, patients routinely received pre- and post-transplant HCV screening during evaluation of candidacy for transplantation, on the day of transplant, and at 4 and 12 months after transplant surgery.

Epidemiologic investigation

In-depth interviews were conducted by the State Health Department with patients who had incident HCV infection using the CDC Viral Hepatitis Case Report Form (10) to identify any HCV risk factors or other relevant exposures outside the hospital setting. The organ procurement organization and blood bank were contacted to evaluate the possibility of HCV transmission via the receipt of HCV-infected blood products or organs. Employee health needle-stick injury and blood exposure logs were reviewed and relevant surgical staff underwent HCV testing to evaluate the potential for transmission from an infected healthcare worker to a patient. To identify other transplant patients with incident HCV infection, transplant logs and patient medical records were reviewed to ascertain baseline (pre-transplant) and post-transplant HCV infection status.

A case of incident HCV infection was defined as a patient with no evidence of HCV infection at baseline and an HCV-positive test result during post-transplant follow-up. HCV uninfected patients had no evidence of HCV infection at baseline and during post-transplant follow-up. Patients with an HCV-positive test result before transplant were classified as having chronic HCV infection. Patients with HCV-negative results at baseline but without post-transplant HCV testing (e.g., deceased before follow-up, lost to follow-up) were classified as unknown HCV status.

Medical records of patients with incident HCV infection were reviewed to identify percutaneous exposures where healthcare-associated HCV transmission could have occurred. Transplant surgery, inpatient stays, and invasive procedures with a risk of blood exposure (e.g., endoscopy, interventional radiology, and dermatology) were considered. Opportunities for HCV transmission were further evaluated when inpatient stays, invasive procedure times or rooms, healthcare personnel, or re-usable equipment, medical devices, and vials, coincided with other patients known to have HCV infection. These patients with known HCV infection were considered potential HCV source patients, unless infected with a different HCV genotype than the patient with incident HCV infection.

Hospital infection control policies were reviewed. Healthcare personnel were observed and interviewed about their practices in the operating rooms, post-anesthesia care unit, medication preparation rooms, drug dispensing systems, inpatient units, and invasive procedures areas at the hospital.

Analysis of HCV sequences from patient isolates

Serum was obtained from patients with incident HCV infection and from those identified as potential HCV source patients. Serum was tested for HCV RNA with polymerase chain reaction (PCR) (AMPLICOR HCV Test, version 2.0; Roche Molecular Systems, Branchburg, New Jersey, USA), with a lower limit of detection of ~50 copies/mL. Genotype was determined from a 300-nucleotide NS5b coding region of the HCV genome. The genetic relatedness among patient isolates was determined by quasispecies analysis. Quasispecies is a closely related viral population that shares a common origin, and occurs within HCV-infected individuals due to HCV replication errors. Quasispecies distribution was examined by sequencing HCV hypervariable 1 region PCR products from the different isolates, using methods previously described (8, 11). The hypervariable 1 region quasispecies sequences from the patient’s specimens were compared with each other and with sequences from randomly selected HCV-infected individuals from the Third National Health and Nutrition Examination Survey (NHANES III) (12), a representative sample of the noninstitutionalized civilian population of the United States.

Results

Baseline and post-transplant HCV test results were reviewed for all 212 patients undergoing liver and 96 patients undergoing kidney/pancreas transplantation at the hospital during 2006 (Table 1). For liver transplant patients HCV RNA testing was used. Post-transplant follow-up testing
for this group was conducted a median 125 days after transplant (range 89–481 days). Among the kidney/pancreas transplant patients, HCV testing was usually (77% of patients) performed using antibody to HCV (anti-HCV) test, otherwise an HCV RNA test was used. Post-transplant follow-up testing was conducted a median 128 days after transplant (range 17–294 days).

No cases of post-transplant incident HCV infection had been diagnosed previously among transplant recipients at the hospital. A review of state viral hepatitis surveillance data for 2006 by the county and state health departments identified no additional persons with a diagnosis of HCV infection and a history of transplantation at this hospital.

**Description of patients with incident HCV infection**

Both liver transplant patients were diagnosed with incident HCV infection in January 2007 and had HCV genotype 1a infection. Aside from unexplained elevations in hepatocellular enzymes, neither had any signs or symptoms of acute hepatitis. Case-patient 1 was transplanted in late July 2006 for end-stage liver disease from alcohol and had a negative HCV RNA result from serum drawn on the day of transplant. This patient denied any behavioral risk factors for HCV infection upon interview, and had not received healthcare at any other facility during the 6-month period before HCV infection diagnosis. Subsequent to liver transplantation, Case-patient 2 had 23 inpatient days, 8 invasive procedures, and 3 emergency room visits. HCV RNA testing of serum, performed approximately 5 weeks after transplant because of a slight elevation of hepatocellular enzymes, was negative. Therefore, the period of likely transmission was 5 weeks after the date of transplant to January 2007, when incident HCV infection was diagnosed (~11 weeks). During this period Case-patient 2 had 14 inpatient days, 5 invasive procedures, and had 3 emergency room visits.

**Organ and blood product donors**

Stored blood from the 2 deceased organ donors for Case-patients 1 and 2, respectively, were confirmed to be HCV negative by nucleic acid testing, a standard test used to detect RNA. No other organ or tissue specimens were recovered from the donor for Case-patient 1. The donor for Case-patient 2 provided a kidney for another recipient, who remained HCV RNA negative at 6 months after transplantation.

Case-patients 1 and 2 received blood products from 57 and 32 different donors, respectively. They had no common blood product donors. Consistent with US blood screening policies, all blood products had been screened at the time of donation and were found to be anti-HCV and HCV RNA negative. A blood bank look-back found that 50 of 57 (88%) and 27 of 32 (84%) of the blood product donors for Case-patient 1 and 2, respectively, had been re-screened using anti-HCV and HCV RNA; all were negative.

**Identification of potential HCV sources**

No healthcare worker was identified to have sustained a needle-stick injury or blood exposure while providing healthcare to Case-patients 1 and 2. Four surgical team members were asked to submit blood for HCV testing; all 4 were HCV RNA negative. During their likely periods of
transmission, Case-patients 1 and 2 were exposed to 7 and 8 potential chronic HCV genotype 1a source patients, respectively. Only 1 potential HCV source patient was common to both incident case-patients.

Analysis of HCV sequences from patient isolates

HVR1 quasispecies analysis indicated an 18% minimum nucleotide difference between the 2 incident case-patient viral isolates, confirming that the viruses were not genetically related to one another (Fig. 1). These patients did not have a common HCV source and direct HCV transmission between them did not occur.

All 14 transplant patients identified as potential HCV sources had serum submitted for molecular analysis. Thirteen were HCV RNA positive and confirmed to be genotype 1a infections; 1 was HCV RNA negative. Analysis of the NS5b region indicated one of these isolates was clustered with the isolate from incident Case-patient 1 (≥ 98.3% nucleotide identity). HVR1 quasispecies analysis confirmed these specimens share quasispecies sequences (Fig. 1), indicating that this patient was the likely source of HCV infection for Case-patient 1. This HCV source patient received a kidney transplant 1 day before Case-patient 1’s liver transplant. They had stayed on the same inpatient unit immediately after transplantation for 6 days, and received nursing care from the same nursing teams on 4 of those days. None of the isolates from potential HCV source patients were closely related to the virus isolated from Case-patient 2.

Review of staff and infection control practices

No deficiencies were identified in standard operating procedures or infection control polices, and no opportunities for HCV transmission were identified during observations of staff practices. During interview, healthcare personnel denied administration of medication from a multidose vial to more than 1 patient occurred, as this was against hospital policy; however, 1 exception was noted. A healthcare worker revealed, on rare occasions on the inpatient units, multidose insulin vials dedicated for use on 1 patient were accessed to obtain insulin for a second patient, when supplies for the second patient were temporarily exhausted. Additionally, both Case-patients 1 and 2 had glucose levels checked multiple times daily during their post-transplant inpatient stays. Healthcare personnel reported that while shared finger-stick devices were not in use, glucose test meters (Abbott Precision Point-of-Care System) were shared among patients and these were typically cleaned only when blood contamination was visible.

Fig. 1. Unrooted phylogenetic tree based on unique 138-bp E1-hypervariable region 1 quasispecies sequences obtained by end-point limiting-dilution real-time polymerase chain reaction assay from the sera of 2 hepatitis C virus (HCV) incident case-patients, the likely HCV source-patient for Case-patient 1, and selected National Health and Nutrition Examination Survey (NHANES III) participants – United States, 1988–1994.
Discussion

Through a system of routine pre- and post-transplant screening, 2 cases of incident HCV infection were identified among a cohort of 308 patients who had received abdominal organ transplants at a single facility in 2006. This investigation provided a unique opportunity to assess the risk of incident HCV infection after organ transplantation at one of the busiest transplant hospitals in the United States. The overall incidence of HCV infection in 2006 was 0.99% (2 of 202 HCV susceptible liver and kidney/pancreas transplant patients). This is similar to the incidence of 0.46% (6 of 1301 susceptible patients) reported by Forns et al. (9) in a study of patients admitted to liver medical, transplant, and surgical care units.

Our investigation ruled out HCV exposures outside the hospital setting, and infection via receipt of infected donor organs. The estimated risk of HCV infection via transfusion is remote at 1 in 2,000,000 units transfused (6); in addition, nearly all of the blood donors were retested and found to be HCV negative. Transmission from HCV-infected healthcare workers to patients is very rare in the United States (13), and has primarily been associated with exposure-prone surgical procedures. As relevant surgical team members were found to be free of HCV infection, this mode of transmission was ruled out. Molecular analyses indicated the 2 incident HCV infections each originated from a separate source, and also indicated that the likely HCV source for 1 case-patient was a kidney transplant recipient with chronic HCV infection. These 2 patients shared multiple days on the same inpatient unit and had the same nursing team providing post-transplant care. Likewise, Forns et al. (9) reported sharing a nursing team with a patient with chronic HCV infection was an independent risk factor for incident HCV infection.

Although we did not conclusively identify a mode of HCV transmission, 1 possible mechanism was the infrequent practice of dispensing insulin from a multidose medication vial to more than 1 patient. This practice may have been sufficient for patient-to-patient HCV transmission if entry into the vial with a used needle or syringe occurred or if the septum of the vial had been contaminated during use. Both case-patients and the identified HCV source patient received insulin during their post-transplant inpatient stay. Unsafe injection practices, including failure to use aseptic technique when preparing and administering medications from multidose vials, have been implicated as a cause of patient-to-patient HCV transmission in healthcare settings (13–19).

A second practice possibly responsible for HCV transmission was the sharing of portable point-of-care glucose test meters without cleaning between each patient use. Post-transplant hyperglycemia is a common complication of solid organ transplantation (20, 21), and the organ recipients we evaluated underwent frequent blood glucose screenings, creating repeated opportunities for patient-to-patient transmission of blood-borne pathogens via shared and potentially blood-contaminated glucose monitoring equipment. Patient-to-patient transmission of hepatitis B virus through unsafe glucose monitoring practices, including sharing of glucometers without cleaning, has been well documented (22, 23). HCV transmission is less common, but has also been reported (24), and in a setting with HCV prevalence, the risk of HCV via shared blood-contaminated equipment increases.

Patient-to-patient HCV transmission via touch contamination during the course of routine patient care should also be considered. Patients on the inpatient abdominal transplant unit frequently had blood-soaked dressings on surgical wounds, surgical drains, and central venous catheters, in addition to collections of bloody ascitic fluid in ostomy receptacles placed over the sites of surgical drains after liver transplantation. HCV can survive on environmental surfaces at room temperature for at least 16 h (25). Therefore, opportunities for cross-contamination and HCV transmission via inadequately disinfected surfaces, or by lapses in hand hygiene or glove use by healthcare personnel may occur. This is not unlike the mechanism of transmission proposed in chronic hemodialysis units (26–29).

Despite the useful information provided by this study, there are limitations. Ascertainment of post-transplant HCV infection status was incomplete due to losses to follow-up and deaths; therefore, additional patients with incident HCV infection may have been missed. Moreover, with the use of anti-HCV testing for screening among the kidney and pancreas transplant cohort, it is not entirely possible to rule out additional patients with incident HCV infection given that false-negative anti-HCV results may occur among immunosuppressed persons (1). For this reason, HCV RNA testing should be strongly considered when screening transplant populations that include subpopulations with increased prevalence of HCV infection. Another limitation was that no HCV source was found for Case-patient 2. Absent an infected donor and given that other risk factors for HCV infection were not identified during extensive patient interview and medical history review for this patient, it is highly likely that healthcare transmission also occurred. The HCV source for Case-patient 2 could have been one of several patients with chronic HCV infection, but who could not be genotyped or assessed using molecular techniques (i.e., undetectable viral load at the time of investigation) or others whose HCV infection status was unknown. This limitation highlights the challenge of investigating healthcare-related viral hepatitis transmission events, despite labor- and resource-intensive efforts.
In January 2007 active surveillance of all solid organ transplant recipients with HCV RNA testing was implemented at the transplant center, and infection control practices with respect to the use of insulin vials, disinfection of glucose test meters, and touch contamination were augmented.

Multiple opportunities for patient-to-patient HCV transmission can occur on a daily basis in healthcare settings with a high prevalence of HCV infection, such as transplant units. For this reason, constant and meticulous attention must be paid to maintaining good infection control practices and aseptic technique. Standard precautions include recommendations for safe injection practices (30); all healthcare facilities should review these guidelines to ensure that current policies and practices for delivering injections are sufficient to prevent the transmission of blood-borne pathogens. In addition, implementation and adherence to all safe blood glucose monitoring recommendations (23, 30) is warranted, and staff training should emphasize the risk of blood-borne pathogen transmission via shared equipment and touch contamination.

Finally, pre- and post-transplant HCV testing and surveillance was fundamental to the detection of HCV transmission within this setting. Abdominal organ transplant programs should review their HCV screening protocols and post-transplant surveillance procedures to facilitate swift detection and investigation of incident HCV infections should they occur.

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**References**