# TRANSMISSION OF HEPATITIS C VIRUS BY ORGAN TRANSPLANTATION

BRIAN J.G. PEREIRA, M.D., EDGAR L. MILFORD, M.D., ROBERT L. KIRKMAN, M.D., AND ANDREW S. LEVEY, M.D.

**Abstract** *Background.* Liver disease is a frequent and major complication after organ transplantation. We sought to determine whether hepatitis C virus (HCV) is transmitted by organ transplantation and whether it causes post-transplantation liver disease.

*Methods.* Serum samples from all cadaver organ donors to the New England Organ Bank between 1986 and 1990 were screened retrospectively for antibodies to HCV (anti-HCV) by enzyme-linked immunosorbent assay (ELISA). We reviewed the hospital records of all recipients of organs from anti-HCV–positive donors for evidence of liver disease. Serum samples from recipients obtained before transplantation and during follow-up were analyzed for anti-HCV.

*Results.* Of 716 organ donors, 13 (1.8 percent) were positive for anti-HCV. Their organs (19 kidneys, 6 hearts, and 4 livers) went to 29 recipients. Non-A, non-B hepatitis developed after transplantation in 14 of the 29 (48 percent), for a prevalence 7.4 times the 6.5 percent prevalence after transplantation from untested donors that was previously reported by two institutions in the organ bank ($P<0.0001$). The liver disease began a mean of 3.8 months after transplantation and became chronic in 12 patients; the other 2 had subfulminant hepatic failure. Liver disease was more frequent in the patients who had received antilymphocyte preparations ($P = 0.04$). HCV was the cause of the post-transplantation liver disease in 12 of the 13 recipients (92 percent) for whom serum samples were available. Anti-HCV was detected by ELISA in eight and enzyme immunoassay in one; in three others, HCV RNA was detected by polymerase chain reaction in serum samples obtained after transplantation.

*Conclusions.* Organ transplantation can transmit hepatitis C. This raises serious questions about the continued acceptance of organs from donors positive for anti-HCV. (N Engl J Med 1991; 325:454-60.)

LIVER disease is an important cause of morbidity and mortality in renal-transplant recipients, with abnormalities of liver function occurring in 7 to 24 percent of patients early in follow-up[1,2] and death due to liver failure in 8 to 28 percent of the long-term survivors.[1-10] Many factors have been implicated in the causation of post-transplantation liver disease, including drug toxicity and viral infections. Despite the exclusion of patients with hepatitis B surface antigen from organ and blood donation, the incidence of chronic liver disease after transplantation has remained high in renal-transplant recipients.[11,12] Moreover, extensive investigation with the use of available laboratory and serologic techniques has not identified the cause of liver disease in the majority of patients. This has led most authors to speculate that an unidentified non-A, non-B hepatitis virus plays an important part in the pathogenesis of post-transplantation liver disease.[1,2,4,8,9]

The development in 1989 of an assay to detect antibody against a recombinant viral antigen (c100-3) provided the first diagnostic test for hepatitis C virus (HCV) infection.[13,14] Since then, the role of this virus in acute and chronic liver disease and hepatocellular carcinoma has been better understood.[14-17] The transmission of the virus by the transfusion of blood products has been demonstrated unequivocally, and preliminary data suggest that sexual, vertical, and intrafamilial spread also occurs.[18-21] In this report, we examine evidence of the transmission of HCV by organ transplantation. We present the results of clinical and serologic testing of all 716 cadaver organ donors to the New England Organ Bank during the past five years and of all 29 recipients of organs from the 13 donors with antibody to HCV.

## METHODS

### Donors

Stored serum samples from 716 cadaver organ donors in the New England Organ Bank from 1986 through 1990 were screened for antibody to hepatitis C virus (anti-HCV) with a first-generation enzyme-linked immunosorbent assay (ELISA) (Ortho HCV ELISA Test System, Ortho Diagnostic Systems, Raritan, N.J.), which detects antibody to a recombinant antigen of HCV (c100-3). Initially reactive samples were tested twice more. Only samples that were reactive on repeated assay were considered to be confirmed as positive. The mean (±SD) optical density, expressed in arbitrary units, for the positive controls was 2.339±0.074 and for the negative controls, 0.084±0.004. The cutoff used for optical density in the final determination of reactivity was 0.484. In addition, the total amount of antibody (IgG and IgM) to hepatitis B core antigen was measured with a radioimmunoassay (CORAB, Abbott Laboratories, North Chicago). The case records of all anti-HCV–positive donors in the New England Organ Bank were reviewed.

### Recipients

The recipients of organs (kidneys, hearts, or livers) from the anti-HCV–positive donors were identified from the records of the New England Organ Bank. In accordance with the organ bank's responsibility to notify transplantation centers of information gathered after the release of donated organs, the directors of the centers were

From the New England Organ Bank, 138 Harvard St., Brookline, MA 02146, where reprint requests may be addressed to Dr. Levey.

Presented in part at the 10th annual meeting of the American Society of Transplant Physicians, Chicago, May 28 and 29, 1991.

Supported by a fellowship to Dr. Pereira from the International Society of Nephrology and by the Nephrology Clinical Research Fellowship Training Program of New England Medical Center and St. Elizabeth's Hospital, Boston.

The following transplantation centers are participants in the New England Organ Bank: Yale–New Haven Hospital, New Haven, Conn.; Maine Medical Center, Portland; Beth Israel Hospital, Brigham and Women's Hospital, Children's Hospital, Massachusetts General Hospital, New England Deaconess Hospital, New England Medical Center, Veterans Affairs Medical Center, and University Hospital, Boston; Lahey Clinic Medical Center, Burlington, Mass.; Baystate Medical Center, Springfield, Mass.; University of Massachusetts Medical Center, Worcester; and the Medical Center Hospital of Vermont, Burlington.

informed of the names of the recipients from their centers who had received organs from anti-HCV–positive donors and were advised to notify these patients and assess them for liver disease and anti-HCV. At the request of the treating physicians at the transplantation centers, one of the study investigators visited each center to help review each recipient's record and gather data for the ongoing monitoring of transplantation outcomes by the New England Organ Bank.

#### *Clinical Information*

Recipients' pretransplantation records were reviewed for any history of liver disease or therapy with hepatotoxic drugs, for the results of liver-chemistry tests, and for the number of transfusions of blood products before transplantation. Information about transfusions was compiled from records at the hospital, the dialysis unit, and the blood bank.

The recipients' post-transplantation records were reviewed to determine the protocol used for immunosuppression, the number of episodes of rejection and the type of antirejection therapy used, the duration of the patients' survival and that of the grafts, the time of onset of clinical or laboratory evidence of liver disease, and any therapy with hepatotoxic drugs. Serial tests of liver function were reviewed to determine the onset and peak of any abnormality. The presence of liver disease was documented on the basis of hospital records in patients who underwent liver biopsy and of autopsy records in patients who died without a liver biopsy. The cause of each episode of abnormal liver function was assessed on the basis of all available investigations and with the help of the treating physicians. The surviving recipients were recalled by their treating physicians for an office visit, at which time an examination to detect evidence of liver disease was performed and blood was drawn for assessment of liver function and the presence of anti-HCV.

#### *Serologic Studies*

The results of tests for hepatitis B surface antigen and antibodies to cytomegalovirus before transplantation were obtained from the files of the New England Organ Bank. Serum samples stored at −70°C at the organ bank or other tissue-typing laboratories were used in the analysis of anti-HCV by the first-generation test (the Ortho ELISA). The results for hepatitis B surface antigen, antibody to hepatitis B core antigen, antibody to cytomegalovirus, hepatitis A virus, and Epstein–Barr virus after transplantation were obtained from hospital records. For the surviving recipients, the serum sample obtained at the follow-up visit was used to determine the current anti-HCV status. For patients who had died and for whom stored serum samples were available, the most recent sample was tested for anti-HCV.

Before and after transplantation, serum samples from recipients who had liver disease but were negative for anti-HCV according to the first-generation test were tested for anti-HCV with a second-generation enzyme immunoassay that detects antibody to a core antigen and a fusion of the c100-3 and 33c antigens of HCV (Abbott HCV 2.0 enzyme immunoassay, Abbott Laboratories).[22,23] In addition, these samples were analyzed for the presence of HCV RNA by a "nested" polymerase chain reaction,[24,25] using primers derived from the nonstructural domain (NS3) of the HCV genome (Pucci DL, Abbott Laboratories: personal communication). Second-generation tests for anti-HCV and polymerase-chain-reaction assays for HCV RNA were performed by Abbott Laboratories.

### Definitions

#### *Clinical*

The definitions used to classify post-transplantation liver disease were based on the presence of evolving abnormalities of liver function. An abnormality was defined as an increase in serum levels of alanine aminotransferase to more than 2.5 times the upper limit of normal (normal level, <0.58 μkat per liter [<35 U per liter]).[26] Acute liver disease was defined by an elevation in the serum alanine aminotransferase level on two or more occasions at least two weeks apart, but lasting less than six months. Chronic liver disease was defined by a persistent elevation of the serum alanine aminotransferase level for more than six months.[26] Subfulminant liver failure was defined by the onset of hepatic encephalopathy two weeks to three months after the onset of jaundice.[27]

#### *Pathological*

The diagnoses of acute hepatitis, chronic active hepatitis, or hepatic-allograft rejection were based on the pathologists' interpretations in the case records.

#### *Cause*

The absence of serologic markers of infection was used to exclude a diagnosis of infection with hepatitis B or hepatitis A. The absence of a temporal relation of liver disease to the introduction of a potentially hepatotoxic drug and the absence of a response to the withdrawal of the drug were used to exclude the diagnosis of drug-induced hepatitis. Either the absence of a fourfold rise in the titer of antibody to cytomegalovirus or a negative hybridization of liver tissue with a cytomegalovirus-specific complementary DNA probe was used to exclude cytomegalovirus hepatitis.[28] In liver-transplant recipients, the diagnosis of graft rejection was based on the clinical presentation and confirmed by histologic examination of the liver. The diagnosis of non-A, non-B hepatitis was considered by the treating physicians after all other causes had been excluded, and it was confirmed by our review of all clinical, pathological, and serologic records.

### Statistical Analysis

Values given for clinical indexes are means ±SD, unless otherwise specified. Actuarial survival of patients and grafts and survival without liver disease were calculated by life-table analysis.[29] The cumulative probability of liver disease was calculated as 1.00 minus the probability of survival without liver disease. Groups were compared with Student's t-test and the chi-square test (with Yates' correction, when appropriate). We considered differences between groups significant when the two-sided P value was 0.05 or less. Because the number of patients in each group was small for some analyses, the power to detect differences between groups could be low. Therefore, we also report the results of comparisons in which the P value was greater than 0.05.

## Results

### Prevalence of Anti-HCV among Organ Donors

Stored serum samples from 17 of the 716 cadaver donors screened for anti-HCV were reactive initially, but reactivity was confirmed in only 13 samples. The optical density of the 699 initially nonreactive samples was 0.029±0.041, that of the 4 initially reactive but unconfirmed samples was 0.597±0.076, and that of the 13 initially reactive and confirmed samples was 1.917±0.487. Thus, with a cutoff optical density of 0.484, the prevalence of anti-HCV in the cadaver donors was 1.8 percent (13 of 716). The prevalence of intermediate reactivity on initial testing that was not confirmed on repeated measurement was 0.56 percent (4 of 716). The predictive value of an initially reactive test was 76 percent (13 of 17).

None of the donors had evidence of hepatitis. All were negative for hepatitis B surface antigen, 5 of 11 (45 percent) were positive for antibody to hepatitis B core antigen, and 8 of 12 (67 percent) were positive for antibody to cytomegalovirus. Organs procured from

12 of the 13 anti-HCV–positive donors were used. Organs from one donor (Donor 3) were not used, because of diffuse atherosclerosis.

### Prevalence of Liver Disease and Anti-HCV before Transplantation

A total of 29 organs (19 kidneys, 6 hearts, and 4 livers) were transplanted into 29 recipients. As shown in Table 1, each recipient was designated by a letter (K, H, or L) representing the type of graft received and also by a number within the subgroup of recipients of the same type of organ. All the recipients were negative for hepatitis B surface antigen at the time of transplantation. One kidney recipient (Recipient K9) had a history of acute non-A, non-B hepatitis while receiving dialysis, but tests of liver function were normal at the time of transplantation. The causes of liver disease in the liver-transplant recipients were sclerosing cholangitis in two (recipients L2 and L3) and primary biliary cirrhosis in two (recipients L1 and L4). Seven of 26 recipients (27 percent) for whom serum samples obtained before transplantation were available for testing had anti-HCV (recipients K1, K2, K7, K8, K9, K12, and L1). Of the 18 kidney-transplant recipients in whom such serum samples were available, 6 (33 percent) had anti-HCV.

Table 1. Characteristics of 29 Recipients of Organs from Anti-HCV–Positive Donors.*

| Donor No. | Recipient† | Status before Transplantation | | Status after Transplantation | | Months of Follow-up | Survival Status | |
|---|---|---|---|---|---|---|---|---|
| | | Liver disease | Anti-HCV | Liver disease | Anti-HCV | | Patient | Graft‡ |
| 1 | K1 | N | + | N | + | 44 | Alive | Failed |
| | K2 | N | + | Y | NA | 36 | Dead | Failed |
| | L1 | N | + | N | − | 44 | Alive | Functional |
| | H1 | N | NA | Y | NA | 9 | Dead | Functional |
| 2 | K3 | N | − | Y | − | 39 | Alive | Functional |
| 4 | K4 | N | − | Y | + | 22 | Alive | Functional |
| | K5 | N | − | Y | + | 22 | Alive | Functional |
| | L2 | N | − | N | − | 22 | Alive | Functional |
| 5 | K6 | N | − | N | − | 32 | Alive | Functional |
| | K7 | N | + | N | NA | 32 | Alive | Functional |
| 6 | K8 | N | + | N | − | 30 | Alive | Functional |
| | K9 | Y§ | + | Y | + | 30 | Alive | Failed |
| 7 | H2 | N | NA | Y | − | 14 | Dead | Failed |
| 8 | K10 | N | − | N | − | 29 | Alive | Functional |
| | K11 | N | − | N | − | 29 | Alive | Functional |
| | H3 | N | − | N | NA | 2 | Dead | Failed |
| 9 | L3 | N | − | Y | + | 6 | Dead | Failed |
| 10 | K12 | N | + | Y | + | 15 | Alive | Functional |
| | K13 | N | − | N | − | 15 | Alive | Functional |
| 11 | K14 | N | − | Y | − | 16 | Dead | Functional |
| | K15 | N | NA | Y | + | 12 | Alive | Functional |
| | H4 | N | − | Y | − | 12 | Dead | Failed |
| 12 | K16 | N | − | N | − | 12 | Alive | Functional |
| | K17 | N | − | Y | − | 12 | Alive | Functional |
| | H5 | N | − | N | − | 12 | Alive | Functional |
| | L4 | N | − | Y | + | 12 | Alive | Failed |
| 13 | K18 | N | − | N | − | 3 | Alive | Functional |
| | K19 | N | − | N | − | 3 | Alive | Functional |
| | H6 | N | − | N | − | 3 | Alive | Functional |

*Organ recipients were screened for anti-HCV with a first-generation ELISA (Ortho). Liver disease denotes disease ascribed to non-A, non-B viral hepatitis. N denotes no, Y yes, and NA not available.

†Recipients are described numerically according to whether they received a kidney (K), heart (H), or liver (L).

‡Graft survival was assessed at the time of the last follow-up or just before death.

§This recipient had a history of acute non-A, non-B hepatitis before transplantation, but results of liver-function tests were normal at the time of transplantation.

### Prevalence and Course of Liver Disease after Transplantation

Follow-up information was available for all 29 recipients, with a mean duration of 20±12 months (Table 1). Data on the survival of patients and grafts are shown in Figure 1. Actuarial survival rates for patients and grafts were 93 and 85 percent, respectively, after six months and 56 and 42 percent, respectively, after three years.

#### *Prevalence of Liver Disease*

Non-A, non-B hepatitis developed in 14 of the 29 organ recipients (48 percent) after transplantation. Using actuarial methods, we calculated the risk as a function of time after transplantation. The cumulative probability of liver disease was 52 percent after six months (Fig. 1). The prevalence of liver disease was similar among the recipients of different types of organs — 47 percent for the 19 kidney recipients, 50 percent for the 6 heart recipients, and 50 percent for the 4 liver recipients. Serologic markers of hepatitis A, hepatitis B, and cytomegalovirus infection and evidence of drug-induced toxicity were absent in all cases. These 14 recipients had received organs from 9 donors. Thus, non-A, non-B hepatitis was observed after transplantation in the recipients of organs from 75 percent of the 12 anti-HCV–positive donors.

#### *Clinical and Pathologic Features of Liver Disease*

The mean time from transplantation to the onset of liver disease was 3.8±1.5 months (range, 1 to 6) (Table 2). The median peak serum levels of bilirubin and alanine aminotransferase were 74 μmol per liter (4.3 mg per deciliter) and 3.84 μkat per liter (230 U per liter), respectively. Of the 14 recipients in whom non-A, non-B hepatitis developed, 12 (86 percent) had chronic liver disease, and 2 (14 percent) had subfulminant liver failure. The results of pathological studies of the liver were available for eight patients, revealing chronic active hepatitis in six and cirrhosis in two. None of the liver-biopsy studies showed evidence of hepatitis B infection. Liver disease resulted in liver failure in 4 patients (29 percent) and caused or contributed to death in 2 of the 14 patients (14 percent) within 10 months.

The clinical characteristics of the patients in whom liver disease developed are compared in Table 3 with those in whom it did not. Ten of the 14 recipients (71

percent) in whom liver disease developed received an antilymphocytic preparation (antilymphocytic globulin, antithymocyte globulin, or muromonab-CD3 after transplantation, as compared with only 5 of the 15 recipients (33 percent) in whom no liver disease developed (P = 0.04). Among the patients who had hepatitis, there were more men than women (P = 0.07). Data on transfusions of blood products were available before transplantation for 28 of the 29 recipients and did not reveal a significant difference in the number of transfusions between those in whom liver disease developed after transplantation and those in whom it did not.

### Relation of Post-transplantation Liver Disease to HCV

#### *First-Generation Test for Anti-HCV*

For 25 patients, serum samples obtained after transplantation were available to be tested for anti-HCV. Table 4 shows data on the prevalence of anti-HCV both before and after transplantation in the recipients, according to whether liver disease did or did not develop after transplantation. The prevalence of anti-HCV before transplantation was the same among the recipients in whom liver disease did develop (3 of 11, or 27 percent) and those in whom it did not (4 of 15, or 27 percent). After transplantation, the prevalence of anti-HCV increased to 58 percent (7 of 12) among recipients with liver disease. Only recipients with liver disease had seroconversion. In contrast, the prevalence of anti-HCV after transplantation decreased to 8 percent (1 of 13) among the recipients without liver disease. Loss of antibody occurred only in the recipients in whom liver disease did not develop. Consequently, anti-HCV was significantly more common after transplantation in the patients with liver disease (P = 0.03).

#### *Second-Generation Anti-HCV Test and Nested Polymerase Chain Reaction*

As shown in Table 1, 13 of 14 organ recipients with post-transplantation liver disease had either pretransplantation or post-transplantation serum samples available for testing. The results of the first-generation anti-HCV test were positive in eight recipients. To assess the role of HCV further in the remaining five recipients, we analyzed serum samples obtained before and after transplantation for anti-HCV, using a second-generation anti-HCV test, and for HCV RNA using a nested polymerase chain reaction. In these five patients all the pretransplantation serum samples were negative for anti-HCV and HCV RNA. The samples obtained after transplantation were positive for anti-HCV in one recipient (recipient K17) and positive for HCV RNA in three others (recipients K3, H2, and H4). Thus, 12 of the 13 recipients (92 percent) had markers of HCV in their serum.

As shown in Table 1, the one recipient with post-transplantation liver disease who tested negative for all serum HCV markers (recipient K14) received an organ from donor 11, as did recipients K15 and H4, in whom post-transplantation liver disease also developed. Evidence of HCV infection was present in both recipients K15 and H4, indirectly implicating HCV as the cause of the liver disease in recipient K14 as well. Thus, HCV was implicated as the cause of post-transplantation liver disease in all the patients.

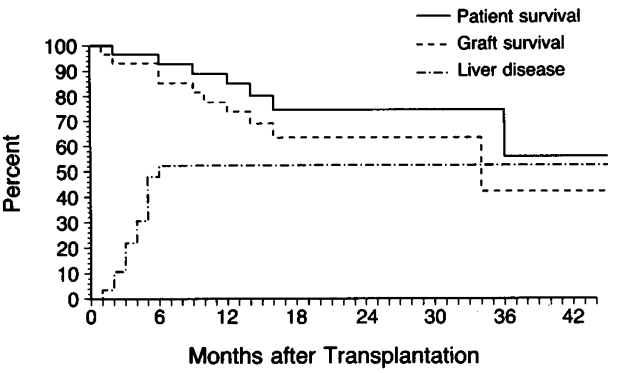


Figure 1. Actuarial Survival Rates of Grafts and Patients and Cumulative Probability of Liver Disease in the 29 Recipients of Organs from 12 Anti-HCV–Positive Donors.

In the calculations of graft survival, the patient's death was included as a cause of graft loss. In the calculation of the probability of liver disease, Recipient K9 (who had a history of liver disease before transplantation) was not included.

## Discussion

Advances in immunosuppression have led to increasingly successful organ transplantations, necessitating a concurrent increase in the supply of organs, especially from cadaver donors. Ironically, advances

Table 2. Characteristics of Patients with Liver Disease after Transplantation.*

| Recipient | Months to Onset of Disease | Peak Laboratory Abnormality | | | | Classification | |
|---|---|---|---|---|---|---|---|
| | | Bilirubin | | ALT | | Clinical | Pathological |
| | | *μmol/liter* | *mg/dl* | *μkat/liter* | *U/liter* | | |
| K2 | 1 | 30 | 1.7 | 2.42 | 145 | CLD | NA |
| K3 | 5 | 94 | 5.5 | 4.54 | 273 | CLD | CAH |
| K4 | 3 | 56 | 3.3 | 12.42 | 745 | CLD | NA |
| K5 | 5 | 36 | 2.1 | 3.68 | 221 | CLD | NA |
| K9 | 0† | 6 | 0.4 | 3.04 | 183 | CLD | NA |
| K12 | 2 | 18 | 1.0 | 2.50 | 150 | CLD | NA |
| K14 | 4 | 74 | 4.3 | 3.66 | 220 | CLD | Cirrhosis |
| K15 | 5 | 24 | 1.4 | 4.00 | 240 | CLD | NA |
| K17 | 3 | 90 | 5.3 | 3.38 | 203 | CLD | CAH |
| H1 | 5 | 502 | 29.3 | 2.74 | 165 | SFLF | CAH |
| H2 | 5 | 54 | 3.2 | 5.16 | 310 | CLD | CAH |
| H4 | 2 | 198 | 11.6 | 4.12 | 247 | CLD | CAH |
| L3 | 4 | 140 | 8.2 | 7.48 | 449 | SFLF | CAH |
| L4 | 6 | 530 | 31.0 | 11.68 | 701 | CLD | Cirrhosis |

*ALT denotes alanine aminotransferase, CLD chronic liver disease, CAH chronic active hepatitis, SFLF subfulminant liver failure, and NA not available.

†This recipient had a history of non-A, non-B hepatitis before transplantation.

in serologic testing for transmittable diseases have resulted in the exclusion of an increasing number of cadaver donors. Using a recently developed ELISA to detect serum antibody to a recombinant antigen of HCV (c100-3),[13,14] we sought to determine whether hepatitis C is transmitted by organ transplantation. Our results show a 1.8 percent prevalence of anti-HCV among cadaver donors and a 27 percent prevalence before transplantation among recipients. Of the 29 recipients of organs from anti-HCV–positive donors, 14 (48 percent) had non-A, non-B hepatitis after transplantation. Of the 13 recipients with non-A, non-B hepatitis in whom serum samples were available, 12 (92 percent) had markers of HCV infection. The remaining recipient received an organ from a donor who appeared to have transmitted HCV to two other recipients, indirectly implicating HCV as the cause of liver disease in this recipient as well.

The 1.8 percent prevalence of HCV antibodies among the cadaver donors in our study is higher than the 0.6 percent prevalence among healthy blood donors in the United States,[30] perhaps because of a higher prevalence of social behavior, such as intravenous drug use or sexual promiscuity, that is associated with the spread of viral infections. The fact that 45 percent of the donors with anti-HCV in our study also had antibody to hepatitis B core antigen supports this suggestion. This observation raises the possibility that the donors in our study may also have transmitted other non-A, non-B hepatitis viruses. The 33 percent prevalence of anti-HCV among kidney recipients before transplantation is similar to the prevalence reported by others among patients undergoing dialysis,[11,15,30-39] and it presumably reflects the transmission of HCV by blood transfusion before the exclusion of blood donors with anti-HCV.

The 48 percent prevalence of non-A, non-B hepatitis after transplantation among recipients of organs from anti-HCV–positive donors far exceeds the prevalence expected among transplant recipients in general. It is possible that we may even have underestimated the true prevalence of liver disease in these recipients of organs from anti-HCV–positive donors. Patients with non-A, non-B hepatitis characteristically have variable elevations in aminotransferase levels,[40] and immunosuppressed patients with liver disease tend to have lower aminotransferase levels.[9] Thus, the cutoff value for alanine aminotransferase that we used to define liver disease (>2.5 times the upper limit of normal) may have excluded some patients with non-A, non-B hepatitis. Previous studies from two transplantation centers associated with the New England Organ Bank document post-transplantation liver disease in 26 of 184 recipients (14 percent) and 42 of 405 recipients (10 percent) of kidneys from donors who were not tested for anti-HCV.[1,4] The respective causes could be identified in 14 of the 26 patients (54 percent) and 16 of the 42 patients (32 percent), with hepatitis B virus, cytomegalovirus, and toxicity from drugs and alcohol being the main causes. The remaining cases were ascribed to non-A, non-B hepatitis. Thus, non-A, non-B hepatitis was observed in 38 of the 589 recipients in these two studies combined (6.5 percent). Hepatitis C probably accounted for a large proportion of the cases of liver disease in these patients receiving frequent transfusions. More recently, the abandon-

**Table 3. Characteristics of the Organ Recipients According to Whether They Had Post-transplantation Liver Disease.***

| Characteristic | Recipients with Disease | Recipients without Disease | P Value† |
|---|---|---|---|
| No. of recipients | 14 | 15 | |
| Age (yr) | 35±14 | 42±12 | 0.16 |
| Male:female ratio | 12:2 | 7:8 | 0.07 |
| Pretransplantation status | | | |
| Previous transplant — no. (%) | 2 (14) | 5 (33) | 0.45 |
| Dialysis (mo)‡ | 52±58 | 49±26 | 0.86 |
| Transfusions of blood products (no.)§ | 22±35 | 22±31 | 0.59 |
| Donor's serologic status | | | |
| Anti-HCV (OD) | 1.903±0.463 | 2.000±0.402 | 0.55 |
| Anti-HBc — no. (%) | 5/11 (45) | 6/13 (46) | 0.84 |
| Anti-CMV — no. (%) | 7 (50) | 13 (87) | 0.08 |
| Organ received — no. (%) | | | |
| Kidney | 9 (47) | 10 (53) | 0.91 |
| Liver | 2 (50) | 2 (50) | |
| Heart | 3 (50) | 3 (50) | |
| Type of immunosuppression used — no. (%) | | | |
| Steroids | 14 (100) | 15 (100) | 0.98 |
| Azathioprine | 11 (79) | 12 (80) | 0.72 |
| Cyclosporine | 14 (100) | 15 (100) | 0.98 |
| ALG, ATG, or OKT3 | 10 (71) | 5 (33) | 0.04 |
| Anti-HCV — no. (%) | | | |
| Before transplantation | 3/11 (27) | 4/15 (27) | 0.73 |
| After transplantation | 7/12 (58) | 1/13 (8) | 0.03 |
| Months of follow-up | 18±9 | 19±10 | 0.84 |
| No. of rejection episodes | 0.93±0.88 | 0.66±0.88 | 0.43 |
| Survival — no. (%) | | | |
| Graft¶ | 6 (43) | 13 (87) | 0.04 |
| Patient | 8 (57) | 14 (93) | 0.07 |

*Plus–minus values are means ±SD. Values in parentheses are percentages. OD denotes optical density, anti-HBc antibody to hepatitis B core antigen, anti-CMV antibody to cytomegalovirus, ALG antilymphocytic globulin, ATG antithymocyte globulin, and OKT3 muromonab-CD3.

†Either the chi-square test with Yates' correction or an unpaired t-test was used to test the significance of the data.

‡Kidney recipients only.

§Data on transfusions were available for all patients with liver disease and for 14 of the 15 patients without liver disease.

¶In the calculations of graft survival, the patient's death was included as a cause of graft loss.

**Table 4. Prevalence of Anti-HCV Seropositivity in Organ Recipients According to Whether They Had Post-transplantation Liver Disease.***

| Type of Graft | Recipients with Disease | | Recipients without Disease | |
|---|---|---|---|---|
| | Before Transplant | After Transplant | Before Transplant | After Transplant |
| | *no. with anti-HCV/no. studied* | | | |
| Kidney | 3/8 | 5/8 | 3/10 | 1/9 |
| Heart | 0/1 | 0/2 | 0/3 | 0/2 |
| Liver | 0/2 | 2/2 | 1/2 | 0/2 |
| All | 3/11 | 7/12‡ | 4/15 | 1/13 |

*The Ortho HCV ELISA was used to detect anti-HCV.

†P = 0.03 for the comparison with the prevalence of anti-HCV after transplantation among recipients without liver disease.

ment of policies requiring blood transfusions before transplantation and the exclusion of blood donors with hepatitis B surface antigen and elevated alanine aminotransferase levels would be expected to lower the risk of post-transfusion hepatitis and therefore to lower the prevalence of post-transplantation non-A, non-B hepatitis. The 7.4-fold higher prevalence (48 percent) of non-A, non-B hepatitis in this study ($P<0.0001$) strongly suggests the transmission of infection by the transplantation of organs from donors with anti-HCV.

It is important to note that liver disease developed in recipients of organs from only 9 of 12 donors (75 percent), an indication that a positive test for anti-HCV does not necessarily imply infectivity. In addition, only 14 of 21 recipients (67 percent) of organs from these 9 donors had post-transplantation non-A, non-B hepatitis, indicating that not all recipients may be equally susceptible. The absence of anti-HCV in some recipients with post-transplantation non-A, non-B hepatitis probably reflects the limitations of test sensitivity, especially in immunosuppressed patients.[25,40] The absence of anti-HCV and HCV RNA in the serum of one of our recipients with liver disease does not exclude HCV as the cause of non-A, non-B hepatitis. Examination of liver tissue for HCV RNA may answer this question. Alternatively, the liver disease could be due to the transmission of another non-A, non-B hepatitis virus by this donor.

The usual onset of post-transfusion hepatitis C is 8 weeks (range, 2 to 26) after exposure, with progression to chronic active hepatitis or cirrhosis in 10 percent of patients over a period of several years.[40-42] The mean onset of liver disease of 3.8 months after transplantation in our patients supports the contention that they acquired hepatitis C from the allograft. The more severe course and more rapid progression of post-transplantation liver disease that we observed may be due to the impairment of host defenses by immunosuppression. This is analogous to infection with the human immunodeficiency virus, in which the acquired immunodeficiency syndrome develops 1½ to 2 years after infection in immunosuppressed transplant recipients, as compared with 7 to 8 years in normal hosts.[43] The role of immunosuppression is clearly seen in the association of the use of antilymphocyte preparations with the occurrence of liver disease. A similar association is observed with cytomegalovirus and Epstein–Barr virus infections in recipients treated with antilymphocyte preparations.[44,45]

The high prevalence of chronic liver disease in recipients of organs from donors with evidence of HCV infection, the rapidity of the onset, and the relentless progression are worrisome and raise two questions. First, should otherwise acceptable donors who test positive for anti-HCV be excluded from organ donation? The effect of such a policy would be to reduce the incidence of post-transplantation liver disease. However, it would also reduce the supply of organs from cadaver donors, in inverse relation to the prevalence of positive tests in the pool of potential donors. Current estimates based on first-generation antibody tests suggest that the prevalence is 1 to 2 percent. For potential recipients of kidney or pancreas transplants, who can survive with dialysis or insulin therapy, respectively, while they await more suitable donors, the effect of this policy would be to increase marginally the waiting time for transplantation. For potential heart, liver, or lung recipients, however, who may not survive the wait for more suitable donors, this policy is likely to increase the number of deaths from organ failure. At our organ bank, all donors are now tested for anti-HCV. Life-saving transplantation (of a heart, liver, or lung) from a donor with a positive test is permitted only with the informed consent of the recipient. Transplantation of other organs (kidneys or pancreases) from such donors is not permitted.

Second, should patients with kidney failure and positive tests for anti-HCV be excluded from kidney transplantation to avoid a potentially detrimental effect on the course of liver disease? This question can be answered only by comparing the outcomes of transplantation and dialysis in patients who test positive for anti-HCV. We have not presented data that bear on this comparison. Moreover, it will be necessary to reexamine both questions when more sensitive and specific tests for HCV have been developed.

We are indebted to the surgeons, physicians, nurses, transplantation coordinators, technicians, and secretaries of the member institutions of the New England Organ Bank, of the University of Michigan Hospital, Ann Arbor, and of Humana Hospital, San Antonio, Texas, for their assistance; to the staff of the Immunology Laboratory of Brigham and Women's Hospital, Boston, for kindly performing the Ortho HCV ELISA and assay for anti-HBc; and to Abbott Laboratories, North Chicago, for performing the Abbott 2.0 enzyme immunoassay and polymerase chain reaction for HCV RNA.

## References

1. LaQuaglia MP, Tolkoff-Rubin NE, Dienstag JL, et al. Impact of hepatitis on renal transplantation. Transplantation 1981; 32:504-7.
2. Boyce NW, Holdsworth SR, Hooke D, Thomson NM, Atkins RC. Nonhepatitis B-associated liver disease in a renal transplant population. Am J Kidney Dis 1988; 11:307-12.
3. Mahony JF. Long term results and complications of transplantation: the kidney. Transplant Proc 1989; 21:1433-4.
4. Weir MR, Kirkman RL, Strom TB, Tilney NL. Liver disease in recipients of long-functioning renal allografts. Kidney Int 1985; 28:839-44.
5. Parfrey PS, Forbes RDC, Hutchinson TA, et al. The impact of renal transplantation on the course of hepatitis B liver disease. Transplantation 1985; 39:610-5.
6. Harnett JD, Zeldis JB, Parfrey PS, et al. Hepatitis B in dialysis and transplant patients. Transplantation 1987; 44:369-76.
7. Sopko J, Anuras S. Liver disease in renal transplant recipients. Am J Med 1978; 64:139-46.
8. Ware AJ, Luby JP, Hollinger B, et al. Etiology of liver disease in renal-transplant recipients. Ann Intern Med 1979; 91:364-71.
9. Debure A, Degos F, Pol S, et al. Liver disease and hepatic complications in renal transplant patients. Adv Nephrol 1988; 17:375-400.
10. Braun WE. Long-term complications of renal transplantation. Kidney Int 1990; 37:1363-78.
11. Fernandez JA, Roth D, Burke G, Esquenazi V, Miller J. Detection of antibody to hepatitis C virus (HCV) in renal transplant recipients. J Am Soc Nephrol 1990; 1:757. abstract.
12. Andres A, Morales JM, Campo C, et al. Clinical implications of the presence of antibody to hepatitis C after renal transplantation. J Am Soc Nephrol 1990; 1:754. abstract.

13. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989; 244:359-62.
14. Kuo G, Choo QL, Alter HJ, et al. An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. Science 1989; 244:362-4.
15. Estaban JI, Estaban R, Viladomiu L, et al. Hepatitis C virus antibodies in risk groups in Spain. Lancet 1989; 2:294-7.
16. Bruix J, Barrera JM, Calvet X, et al. Prevalence of antibodies to hepatitis C virus in Spanish patients with hepatocellular carcinoma and hepatic cirrhosis. Lancet 1989; 2:1004-6.
17. Colombo M, Kuo G, Choo QL, et al. Prevalence of antibodies to hepatitis C virus in Italian patients with hepatocellular carcinoma. Lancet 1989; 2:1006-8.
18. Hess G, Massing A, Rossol S, Schütt H, Clemens R, Meyer zum Büschenfelde K-H. Hepatitis C virus and sexual transmission. Lancet 1989; 2: 987.
19. Giovannini M, Tagger A, Ribero ML, et al. Maternal-infant transmission of hepatitis C virus and HIV infections: a possible interaction. Lancet 1990; 335:1166.
20. Perez-Romero M, Sanchez-Quijano A, Lissen E. Transmission of hepatitis C virus. Ann Intern Med 1990; 113:411.
21. Riestra S, Suarez A, Rodrigo L. Transmission of hepatitis C virus. Ann Intern Med 1990; 113:411-2.
22. Trepo C, Pichoud C, Saint Pol E, Smilovici W, Stewart J, Troonen H. Earlier detection of HCV-seroconversion in chimpanzees, post-transfusion hepatitis and implicated donors by Abbott HCV-EIA. Presented at the 8th International Congress of Virology, Berlin, Germany, August 26–31, 1990. abstract.
23. Kidd S, Gilbert A, Heyermann H, et al. Specificity performance of Abbott HCV 2nd generation EIA. Presented at the 8th International Congress of Virology, Berlin, Germany, August 26–31, 1990. abstract.
24. Kubo Y, Takeuchi K, Boonmar S, et al. A cDNA fragment of hepatitis C virus from an implicated donor of post-transfusion non-A, non-B hepatitis in Japan. Nucleic Acids Res 1989; 17:10367-72.
25. Weiner AJ, Kuo G, Bradley DW, et al. Detection of hepatitis C viral sequences in non-A, non-B hepatitis. Lancet 1990; 335:1-3.
26. Sherlock S. Diseases of the liver and biliary system. 8th ed. Oxford, England: Blackwell Scientific, 1989:32-4, 339.
27. Bernuau J, Rueff B, Benhamou JP. Fulminant and subfulminant liver failure: definitions and causes. Semin Liver Dis 1986; 6:97-106.
28. Masih AS, Linder J, Shaw BW Jr, et al. Rapid identification of cytomegalovirus in liver allograft biopsies by in situ hybridization. Am J Surg Pathol 1988; 12:362-7.
29. Parker RL, Dry TJ, Willius FA, Gage RP. Life expectancy in angina pectoris. JAMA 1946; 131:95-100.
30. Williams AE, Dodd RY. The serology of hepatitis C virus in relation to post-transfusion hepatitis. Ann Clin Lab Sci 1990; 20:192-9.
31. Jeffers LJ, Perez GO, de Medina MD, et al. Hepatitis C infection in two urban hemodialysis units. Kidney Int 1990; 38:320-2.
32. Mortimer PP, Cohen BJ, Litton PA, et al. Hepatitis C antibody. Lancet 1989; 2:798.
33. Roggendorf M, Deinhardt F, Rasshofer R, et al. Antibodies to hepatitis C virus. Lancet 1989; 2:324-5.
34. Zeldis JB, Depner TA, Kuramoto IK, Gish RG, Holland PV. The prevalence of hepatitis C virus antibodies among hemodialysis patients. Ann Intern Med 1990; 112:958-60.
35. Gilli P, Moretti M, Soffritti S, Menini C. Anti-HCV positive patients in dialysis units? Lancet 1990; 336:243-4.
36. Par A. Antibodies to hepatitis C virus in Hungary. Lancet 1990; 336:123.
37. Mondelli MU, Cristina G, Filice G, Rondanelli EG, Piazza V, Barbieri C. Anti-HCV positive patients in dialysis units? Lancet 1990; 336:244.
38. Schlipköter U, Roggendorf M, Ernst G, et al. Hepatitis C virus antibodies in haemodialysis patients. Lancet 1990; 335:1409.
39. Yamaguchi K, Nishimura Y, Fukoka N, et al. Hepatitis C virus antibodies in haemodialysis patients. Lancet 1990; 335:1409-10.
40. Dienstag JL. Non-A, non-B hepatitis. I. Recognition, epidemiology, and clinical features. Gastroenterology 1983; 85:439-62.
41. *Idem*. Non-A, non-B hepatitis. II. Experimental transmission, putative agents and markers, and prevention. Gastroenterology 1983; 85:743-68.
42. Alter MJ, Mares A, Hadler SC, Maynard JE. The effect of underreporting on the apparent incidence and epidemiology of acute viral hepatitis. Am J Epidemiol 1987; 125:133-9.
43. Rubin RH, Tolkoff-Rubin NE. Infection: the new problems. Transplant Proc 1989; 21:1440-5.
44. Cheeseman SH, Rubin RH, Stewart JH, et al. Controlled clinical trial of prophylactic human-leucocyte interferon in renal transplantation: effects on cytomegalovirus and herpes simplex virus infections. N Engl J Med 1979; 300:1345-9.
45. Cheeseman SH, Henle W, Rubin RH, et al. Epstein-Barr virus infection in renal transplant recipients: effects of antithymocyte globulin and interferon. Ann Intern Med 1980; 93:39-42.