

# The Natural History of Hepatitis C Virus Infection in Renal Transplantation

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Hepatitis C virus (HCV) infection is present in 20-50% of end stage renal disease patients worldwide and contributes significantly to morbidity and mortality following renal transplantation (1,2). Infection with HCV is the leading cause of liver dysfunction in the renal transplant recipient and advanced liver disease and failure either directly or indirectly contributes to a significant number of deaths in the second decade post transplant.

Although much has been learned about the impact of HCV infection in the ESRD population during the last ten years, most of this has come from single center experiences using data collected in a retrospective manner. Several studies have analyzed large data bases to better understand what effect HCV has in the renal transplant recipient, however these analyses are subject to the same criticisms, having analyzing retrospective data in patients that had not had a thorough baseline evaluation prior to transplant. Even such a fundamental and critical issue as the basis on which the diagnosis of HCV was made has been subject to great variability. Most studies have relied on the presence of a positive ELISA to make the diagnosis, whereas the 'gold standard' is considered to be the presence of viral RNA in the serum detected by polymerase chain reaction. Not only have the earlier generation ELISA assays been shown to have poor sensitivity in the general population, but the problem is further accentuated by the blunted humoral response to viral infection often seen in the uremic patient. Taken together, it is easy to understand that the interpretation of the data that is available is of limited value and must be taken in the context of the issues mentioned above.

**The course of HCV infection following renal transplantation:** Little is known about the natural history of HCV infection in the renal transplant recipient. This would require a thorough pre transplant evaluation to be performed in every patient, including liver biopsy, viral titers and genotyping. Furthermore, sequential liver biopsies in the years post transplant would be needed. Most studies that have been reported are lacking this critical data.

Published reports of pre transplant liver histology have demonstrated that 8- 22 % of patients have stage 3 or 4 (cirrhosis) disease, but precious little is available on the histologic progression, or lack thereof, post transplant. In a study by Huraib, et al., HCV-infected pre transplant candidates were randomized to receive either interferon or no therapy (3). The treated cohort had lower viral titers at one year post transplant, and importantly, follow-up liver biopsies at one year post transplant demonstrated worsened disease in the untreated group compared to stable liver disease in those who had received interferon. In a retrospective study from the Necker Hospital of 150 HCV infected renal transplant recipients, 28 had undergone at least 2 sequential liver biopsies in the post transplant period (4). This group was compared to 28 matched, immunocompetent HCV infected patients who also had sequential biopsies available. The interval between biopsies was between  $7.1 \pm 4$  and  $6.1 \pm 3$  years, respectively. In this study, it was determined that the yearly progression of activity and fibrosis was faster in the kidney recipients compared to the 'control' group of HCV-infected individuals.

The University of Miami. has an ongoing 10 year, prospective, observational study of patients who were identified as HCV infected during the pre trans- plant evaluation. All patients have had thorough virologic evaluation and baseline pre transplant liver biopsies. A significant number of patients are now between 5-10 years post transplant and have undergone follow-up liver biopsies.

The clinical course of HCV infection in the renal allograft recipient may be dependent on several factors. The baseline histologic status of the recipient's liver is certainly important. Patients with advanced chronic hepatitis or cirrhosis likely do not do well. The timing of the infection appears to be important, as it has been demonstrated that HCV infection acquired at the time of transplant from an infected donor has the potential for a much worse course than that of the patient who harbors chronic HCV infection. Studies looking at HCV genotypes have failed to find an association with patient or graft outcome. Finally, co-infection with hepatitis B and C virus has been clearly demonstrated to present a high risk situation for progressive liver disease post transplant.

**Clinical course of HCV-infected renal transplant recipients:** A large number of retrospective studies have looked at patient and graft survival in HCV- infected recipients compared to a non-infected cohort. In the last several years, several such studies have been published with 10 and 20 year outcomes. Hanafusa et al. did not find a significant difference at 10 years, but 20-year patient and graft survival were significantly worse in the HCV positive group (5). Mathurin et al. reported a poorer outcome in HCV positive recipients for both patient and graft survival at 10 years post transplant (6). In an analysis of the USRDS database, Batty et al. found an increased relative risk of death (RR, 1.23) associated with a positive HCV ELISA, with the greatest proportion of deaths in the HCV positive group being attributable to infection (7).

Other important clinical outcomes have been observed in HCV-infected renal allograft recipients. Bloom and colleagues have reported that HCV infected patients have a significantly greater risk of post transplant diabetes mellitus, with the greatest risk occurring in tacrolimus-treated patients (8). A significantly increased risk of proteinuria in HCV-infected recipients has also been reported, with a relative risk of 5.36 in the HCV positive patient compared to negative controls (9). This data is consistent with the reports of de novo immune complex glomerulonephritis occurring in the allograft.

**Conclusion:** Although much has been learned about the course of HCV infection in the immunosuppressed renal allograft recipient, the available data is of limited value due to the lack of carefully controlled studies that provide thorough pre transplant baseline data and sequential follow-up, including liver histology. It appears that HCV infection is associated with several clinical events in the post transplant period, including a greater incidence of infection, glucose intolerance and proteinuria, often in the context of immune-complex glomerular disease of the allograft.

### **References**

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