

Hepatitis C Virus Infection and Kidney Transplantation

A Review for Clinicians

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Hepatitis C virus (HCV) infection is frequent among kidney transplant recipients, and it is currently the major cause of chronic liver disease following kidney transplantation. The presence of HCV infection has been found to negatively affect the morbidity and mortality rates in patients on dialysis, as well; it seems that kidney transplantation is a reasonable treatment option after a careful pretransplant evaluation. Nevertheless, there are several questions about the indications of kidney transplantation, pretransplant evaluation, transplantation from HCV-infected donors, patient and graft survival rates, and kidney diseases associated with hepatitis C virus after kidney transplantation. This review deals with the most current information on pretransplant and posttransplant evaluations, complications, treatment, and prognosis of HCV-infected kidney transplant recipients.

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INTRODUCTION

Kidney transplantation is the treatment of choice for end-stage renal disease (ESRD); however, complications thereafter are a major source of concern, one of which is liver disease, a frequent complication that represents as one of the leading causes of death in long-term.¹ Chronic hepatitis, cirrhosis, and hepatocellular carcinoma are well-known liver complications of hepatitis C virus (HCV), especially after kidney transplantation.^{2,3} Previously, hepatitis B virus (HBV) was the major cause of viral hepatitis in patients with ESRD⁴; however, HCV infection is currently frequent among patients with ESRD receiving a kidney transplant.⁵ Today, HCV infection is the major cause of chronic liver disease after kidney transplantation.⁶⁻⁸

Importantly, liver dysfunction is an important cause of morbidity and mortality following kidney transplantation, and liver failure has been reported as a cause of death in 8% to 28% of long-term survivors after kidney transplantation.⁶⁻¹¹ There has been a noticeable decrease in HCV infection among patients on hemodialysis; after the introduction

of regular screening for HCV and the use of erythropoietin, its incidence varied from 5% to 25% in the United States, and it was about 6.8% in Europe.^{4,12} However, nosocomial spread of HCV within dialysis units continues to occur and dialysis is the main source of acquired infection, and most kidney transplant recipients would have acquired HCV infection prior to transplantation.¹³⁻¹⁶

The prevalence of anti-HCV antibodies, however, among kidney recipients living in different countries varies between 2.6% and 66%, and it is also different between centers, countries, and geographic areas.¹⁷⁻¹⁹ Hepatitis C virus infection in immunocompetent hosts causes a slowly progressive liver dysfunction and has an indolent course.²⁰ For example, full impact of posttransfusion HCV infection may not be observable until the second decade after the infection.¹¹ However, data on natural history of HCV infection in kidney transplant recipients are conflicting.²⁰ Furthermore, the viral load increases during immunosuppressive therapy.¹⁴ However, little is known about the natural history of HCV infection in the setting of long-term treatment

by immunosuppressive drugs, and the effect of HCV infection on patient and graft survival is controversial.¹¹ Nevertheless, the presence of HCV infection has been found to negatively affect the morbidity and mortality rates in the patients on dialysis,^{11,21,22} and it seems that kidney transplantation is a reasonable treatment option after a careful pretransplant evaluation.²³

There has been controversial data about the prognosis of HCV-infected patients who received kidney transplantation.^{11,22-24} Moreover, HCV infection is an important consideration among kidney transplantation candidates and kidney transplant recipients following a dramatic increase in the number of kidney transplantations, using potent immunosuppressive agents and longer survival for transplant recipients.¹² Consequently, chronic liver disease related to HCV infection is an important cause of late morbidity and mortality in these patients, and hepatic cirrhosis and clinically active hepatitis as a result of HBV or HCV infection clearly contraindicate kidney transplantation.¹⁷ Nevertheless, some studies have shown better survival in HCV-positive kidney transplant recipients than in HCV-positive patients with ESRD who are on dialysis. The optimal immunosuppressive regimen in this group of patients remains uncertain.⁵

This review deals with the most current information on pretransplant and posttransplant evaluation, complications, treatment, and prognosis of HCV-infected kidney transplant recipients.

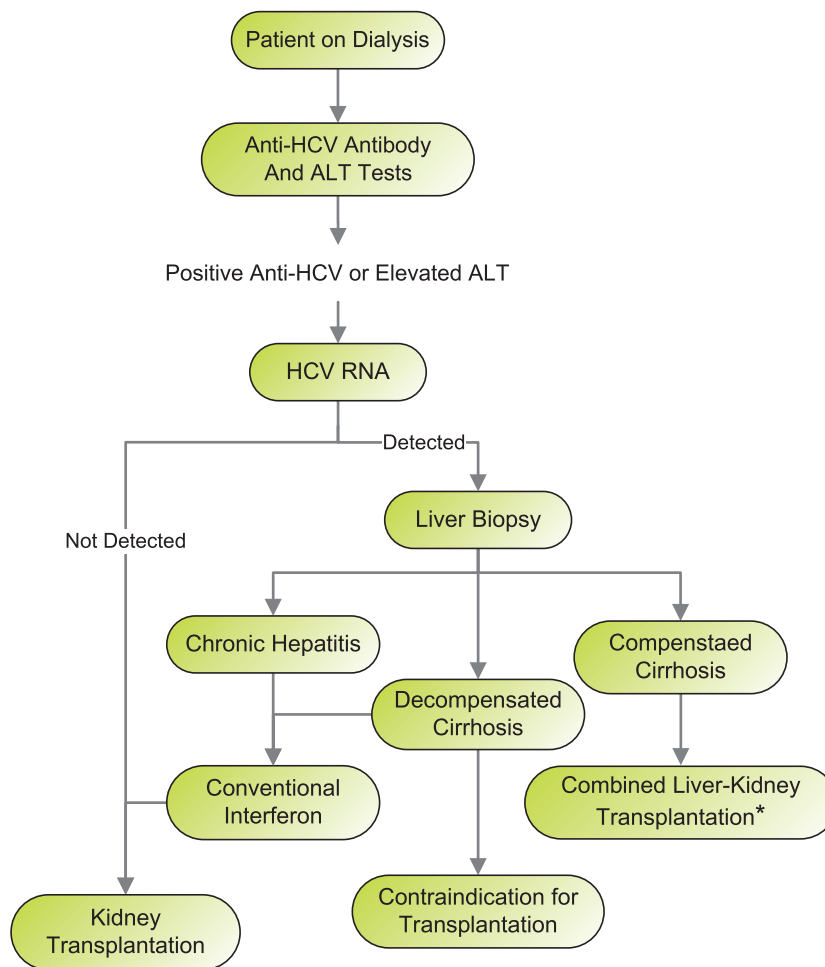
HEPATITIS C VIRUS IN CANDIDATES Evaluation of Kidney Transplant Candidates for Infection

There is a consensus that all kidney transplant candidates should be tested for HCV infection, and HCV must be screened in all kidney allograft donors.²⁵ However, the prevalence of HCV infection may be underestimated according to an antibody assay alone, and HCV RNA testing, to confirm infection in anti-HCV-positive patients, is performed inconsistently.¹² The rate of false-negative results is significantly lower with a third generation immunoassay in comparison with the earlier assays,²⁶⁻²⁸ which were less sensitive to the diminished antibody response to HCV antigens that is present in individuals undergoing dialysis.^{12,29} On the other hand, all HCV-infected

patients should undergo a liver biopsy prior to kidney transplantation for exclusion of HCV-related liver complications, particularly silent cirrhosis.²⁵ Furthermore, serum aminotransferase levels are not reliable in determining the activity of the liver disease and severity of fibrosis in patients with chronic HCV infection before kidney transplantation^{30,31}; hence, level of the liver enzymes within the reference ranges does not exclude the presence of liver disease.¹² Although, liver biopsy remains the gold standard for assessment of severity of the disease, it is a controversial issue in the general population, and at present, a liver biopsy is commonly only suggested to the individuals infected by type 1 and type 4 genotypes in order to guide therapy.^{32,33}

According to our policy, patients with liver disease should be treated by pegylated or nonpegylated (ie, standard) interferon before transplantation; if they respond to the therapy, they will be referred to the surgeon for kidney transplantation. Nearly 60% to 70% of the patients on hemodialysis cannot achieve sustained viral response after interferon therapy, and nonresponders are still candidates for kidney transplantation. In a metaanalysis we carried out, the conventional interferon had comparable results with pegylated interferon in eradication of HCV (unpublished study). Although combination therapy by interferon plus ribavirin is the standard of treatment for chronic HCV infection, interferon alone is recommended in patients on dialysis, because ribavirin is contraindicated in the presence of kidney failure due to the risk of hemolysis.¹² In addition, using interferon after transplantation should be avoided because of increasing the rate of rejection episodes, unless in special cases.¹² The Figure demonstrates our policy for evaluation of anti-HCV-positive patients who are candidates for kidney transplantation. Although HCV-infected patients with cirrhosis confirmed by liver biopsy should be rejected for kidney transplantation, in an investigational setting for patients with clinically compensated cirrhosis, it has been suggested.²⁵

It is better to mention that every kidney transplant recipient with HCV infection should be followed closely for liver function, and it is rational to reduce the immunosuppressive drugs to the lowest dose in order to decrease the rate of progression of liver damage. Evaluation of liver function tests (alanine transaminase and prothrombin time) every



Algorithm for evaluation and management of chronic hepatitis C infection in patients who are under consideration for kidney transplantation. HCV indicates hepatitis C virus and ALT, alanine transaminase.

*Currently combined liver-kidney transplantation is not available in Iran.

2 to 3 months, HCV RNA testing by quantitative polymerase chain reaction assay every 6 to 12 months, and performing liver biopsy every 3 to 5 years are recommended.³⁴

Transplantation From Infected Donors

The use of kidneys from donors with a positive anti-HCV antibody has been restricted to positive anti-HCV transplant candidates.^{20,25} This approach is consistent with the recommendations of the 2008 guidelines of Kidney Disease Improving Global Outcomes (KDIGO).³⁵ In addition, some authors declared that using kidneys of -positive anti-HCV donors for -positive anti-HCV recipients has been found to be safe.^{20,36} Furthermore, Mandal and colleagues showed that such practice reduced the waiting time for anti-HCV-positive individuals

without rising the rate of acute rejection and infection complications, as well as worsening the patient and graft survival.³⁷

Patient and Graft Survival

Chronic liver disease has a significant impact on the survival of kidney transplant recipients with a mortality rate of 4% to 38%,¹⁷ and represents one of the leading causes of death in longterm period.³⁸ Roughly, 8% to 28% of the kidney recipients die due to chronic liver disease.^{17,38} Hepatitis C virus seems to be the most important cause of chronic liver disease in kidney transplant recipients.¹⁷ Furthermore, it has been reported that HCV positive recipients are at increased risk of liver disease when compared to those with other infections.¹¹ Also, early mortality due to HCV-related liver failure

is infrequent in these individuals.^{20,39} On the other hand, the long-term immunosuppressive therapy in kidney recipients might have harmful effects on liver function as reported in individuals with diseases other than kidney disease.¹¹ Moreover, an HCV RNA-positive carrier was reported with normal biochemical parameters who had a relatively benign course during the first decade after kidney transplant.¹¹ Some authors believe that HCV infection does not influence on the patient or graft survival, and it has been suggested that fewer than 10% of the patients develop advanced fibrosis even 10 years after infection.^{18,20} We have previously reported that pretransplant HCV infection did not adversely affect the patient and graft medium-term survival rates.³⁸ Although graft survival was not significantly different between HCV-positive and HCV-negative recipients, the survival rate of HCV-positive recipients appeared to decrease gradually in long-term period, especially in the second decade following transplantation.¹¹ Our results also showed that HCV infection had adverse effects on the graft and patient survival rates in the long-term period.⁴⁰

Hepatitis C virus infection remains a risk factor of mortality and morbidity in kidney transplant recipients.⁴¹ The mortality rate in HCV-positive recipients was approximately 3 times more than those not infected (12.1% versus 3.7%).¹¹ Causes of death in the HCV-positive recipients included sepsis and liver failure. However, there was no difference in the incidence of mortality due to any cause other than liver failure and infection.¹¹ The high rate of mortality has been suggested to be the consequence of altered immunity due to liver disease or the progression of liver disease secondary to immunosuppression in kidney transplant recipients. Although HCV infection has been reported to be characterized by a significant increase in viral titers and histological deterioration after transplantation, early kidney transplantation has favorable effects on the patient survival.²³ The HCV-infected patients easily tolerated the immunosuppressive treatment with a less morbidity and mortality than the HCV-infected patients with ESRD who were on dialysis. It was shown that the relative risk of mortality was 0.36 for kidney transplant recipients, a 64% lower risk of death than individuals on the waiting list.¹¹ Although HCV-positive kidney transplant recipients had a better survival than HCV-positive

patients on dialysis, there was a selection bias and HCV-infected patients would be more desirable for kidney transplantation as well as they might have less clinical impact.¹¹

POSTTRANSPLANT COMPLICATIONS Kidney Diseases Associated With Hepatitis C Virus

Hepatitis C virus-associated posttransplant glomerulopathies, both recurrent and de novo, can occur in kidney transplant recipients with HCV infection. Higher HCV viral loads may result in more immune complexes, leading to reduced clearance and increased deposition of viral complexes in the kidney.¹² The prevalence of proteinuria was greater among HCV-positive kidney transplant recipients.¹⁴ Membranoproliferative glomerulonephritis type I, focal and segmental glomerulosclerosis, minimal change disease, membranous nephropathy, renal thrombotic microangiopathy, and mixed essential cryoglobulinemia in kidney transplant recipients have been associated with HCV infection.^{14,42-44}

Hepatitis C virus infection has been associated with a greater incidence of diabetes mellitus, both in the general population and among transplant patients.^{14,45-49} The underlying mechanism has yet to be elucidated; it is possible that the HCV virus exerts a harmful effect on beta cells of the pancreas.⁵⁰ However, it seems that there is a defect in insulin secretion, increased hepatic glucose production, and resistance to the action of insulin, all of which contribute to the development of overt hyperglycemia.⁵¹ On the other hand, a reduction in carbohydrate tolerance due to steroids or toxic effects of tacrolimus on beta-pancreatic cells may exert synergistic effects to trigger diabetes mellitus after kidney transplantation.^{49,50,52} Finally, posttransplant diabetes mellitus is associated with poorer short-term and long-term outcomes.⁵³

Torres and coworkers recently performed a retrospective case-control study to investigate the importance of HCV infection in the development of tuberculosis in a cohort of kidney transplant recipients by univariate and multivariate logistic regression analysis. The percentage of HCV-positive patients was significantly higher in cases than in controls (56.3% versus 18.8%). Multivariate analysis revealed that HCV infection was an important risk factor of tuberculosis in kidney transplant recipients.⁵⁴

TREATMENT OF POSTTRANSPLANT HEPATITIS C INFECTION

Posttransplant treatment of HCV infection is not routinely recommended due to the potential increased risk of acute rejection.⁵⁵⁻⁵⁹ Several reports indicated that acute rejection rate in HCV-infected kidney transplant recipients varied from 15% to 100%.^{55,56,60-65} Furthermore, interferon has immunomodulatory effects that induce cytokine gene expression, enhance antigen expression on the cell surface which can lead to production of donor-specific alloantibodies, and increase the probability of humoral rejection.⁶⁰ Consequently, these immunostimulant effects can lead to increased allograft rejection. Another potential limitation of interferon in kidney transplant recipients is decreased response to antiviral therapy due to the effects of immunosuppressive agents.¹² On the other hand, successful treatment of HCV-infected patients undergoing dialysis may result in maintained HCV eradication after transplantation.¹² Attainment of sustained virologic response, defined as an undetectable HCV RNA (< 50 IU/mL) in serum at least 6 months after withdrawal of the treatment in patients on dialysis, would be expected to reduce the risk of long-term complications after kidney transplantation.¹² Moreover, several studies showed that sustained viral eradication in kidney transplant candidates was durable after kidney transplantation and might result in possible improvement in posttransplant diabetes mellitus and reduce posttransplant recurrence of HCV-associated glomerulonephritis, as well as chronic allograft nephropathy.^{16,66-68} Thus, eradication of HCV infection before kidney transplantation is rational and treatment with interferon should be considered in HCV-infected patients undergoing dialysis who are on the waiting list for transplantation.

However, some reports proposed that certain kidney transplant recipients might benefit from treatment of HCV infection, interferon monotherapy, or combination therapy with interferon plus ribavirin.^{69,70} For instance, recurrence of HCV-associated glomerulonephritis can be observed after kidney transplantation and may lead to deterioration of kidney allograft function, and therefore, antiviral therapy may be required to prevent graft loss.^{71,72} In addition, the KDIGO 2008 guidelines for HCV infection in patients with chronic kidney disease recommend that kidney transplant recipients with

advanced liver disease such as cirrhosis or fibrosing cholestatic hepatitis, need to receive antiviral therapy to prevent liver-related mortality.²⁵ Thus, antiviral therapy in kidney transplant recipients with HCV infection should be individualized and the patient should be clearly informed about the risks prior to initiating the therapy. On the other hand, the risk of acute rejection may be increased during the first year of transplantation after treatment.⁶⁰ Therefore, antiviral therapy may be safer in kidney transplant recipients with stable kidney function and no history of rejection after 1 year of transplantation.⁷³

The combination of interferon and ribavirin has the superior efficacy in nontransplanted patients with chronic hepatitis C; hence, this regimen may be used in kidney transplant recipients without kidney allograft dysfunction,¹² but the risk of acute rejection with interferon remains to be a concern. On the other hand, the use of ribavirin, a drug with immunomodulatory effect, may result in a reduction in the risk of acute rejection.⁷⁴ However, there is no advantage for ribavirin monotherapy in the management of HCV infection in kidney transplant recipients.¹² Additionally, ribavirin is cleared by the kidneys, and therefore, it should be avoided, as monotherapy or in combination with interferon, in kidney transplant recipients with impaired kidney allograft function due to the hemolytic complication. A modified combination of very low dosage of interferon (1 MU thrice weekly) plus ribavirin (600 mg/d) for 48 weeks is suggested, and it is assumed to improve the compliance with the regimen, and is argued against the risk of interferon-associated rejection.⁷⁰

All current conventional maintenance immunosuppressive regimens can be considered for use in HCV-infected kidney transplant recipients.²⁵ In a recent report, the use of mycophenolate mofetil as a part of maintenance immunosuppression in kidney transplant recipients with HCV-positive serology was associated with better patient survival.⁵

Recurrent and de novo HCV-associated glomerulopathy occurs in kidney transplant recipients. However, there are no clear practice guidelines available for management of HCV-associated glomerulopathy. Overall, treatment depends on the type of renal histological lesion and the severity of clinical symptoms.

Antiviral therapy with interferon and ribavirin is commonly considered as the first-line treatment in individuals with mild to moderate HCV-related glomerulopathy.⁷⁵⁻⁷⁷ Although the rate of relapse after interferon discontinuation was high, it might be decreased after using ribavirin in combination with interferon.⁷⁵⁻⁷⁷ Nonetheless, benefits of interferon therapy in kidney transplant recipients with HCV-induced kidney disease require to be weighed against the risks of acute rejection and return to dialysis. On the other hand, the KDIGO 2008 guidelines for HCV infection in the patients with chronic kidney disease recommend that kidney transplant recipients with HCV-associated glomerulopathy do not receive interferon-based therapy due to the risk of rejection, unless it is determined that the benefits of therapy outweigh the risks of treatment.²⁵

Finally, the optimal treatment of hepatitis C infection after kidney transplant is unclear and requires additional agents or alternative therapeutic approaches^{12,78} and further studies in this regard are needed.

CONFLICT OF INTEREST

None declared.

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