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Chronic Viral Hepatitis and Renal Transplantation:

Challenges and Complexities of Management

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This is to acknowledge that Nilum Rajora, M.D. has disclosed that she does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Nilum Rajora will not be discussing off-label uses in her presentation.

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Biography:

Dr. Nilum Rajora earned her Master in microbiology and biochemistry and worked in laboratory doing research in basic sciences before she earned her M.D. from UT Southwestern medical Center. She also completed her internal medicine and nephrology training at UT Southwestern Medical Center. She has been actively involved with University Hospital Transplant Program and Parkland transplant Program. She is also Medical Director of acute dialysis unit at University Hospital and outpatient UTSW/Davita East dialysis unit. Her clinical interests include Chronic Kidney disease, dialysis and Renal transplant.

Purpose and Overview: The purpose of this presentation is to familiarize the audience with the effect of chronic viral hepatitis on renal patient and review current literature on the management. In past, chronic hepatitis B and hepatitis C infections were considered to be contraindication for renal transplant. This has changed in last few years and these patients are getting renal transplant alone or combined liver kidney transplant now. Patients with chronic HBV and HCV infections require multidisciplinary approach, with nephrologist, hepatologist and surgeons, to manage pre and post transplant. It is important to understand the concept of renal injury, effect of immunosuppression and management of renal transplant patients with chronic HBV and HCV.

Learning Objectives:

1. Understand the renal manifestations and impact of chronic Hepatitis B and C on renal patients.
2. To gain the understanding of special issues in management of renal patients with Hepatitis B and C.
3. Highlight the evaluation and management of renal transplant candidates
4. To establish a concrete basis for addressing our patient's questions regarding their outcome with renal transplant and immunosuppression

Introduction:

Hepatitis C, B and chronic renal disease are serious medical problems throughout the world. There are five known hepatitis viruses, three of these can cause chronic hepatitis: Hepatitis C virus (HCV), Hepatitis B virus (HBV) and Hepatitis delta virus (HDV). Two more viruses have been identified, Hepatitis G virus and hepatitis GB virus but their role in chronic hepatitis is not clear yet (2) (3). Most common causes of chronic viral hepatitis are Hepatitis C and hepatitis B. Even in chronic kidney disease (CKD) patients the most common cause of liver disease is infection from HCV and/or HBV. Both hepatitis C and hepatitis B can lead to chronic viral hepatitis (CVH), cirrhosis, and hepatocellular carcinoma (4). It places patients at higher risk of death as compared to the patients without HBV or HCV infection.

Although the primary burden of chronic HBV and HCV infection is liver related these viruses are also responsible for systemic manifestations including cryoglobulinemia, lymphoproliferative disorder and renal disease (5). The extra-renal complications of HBV and HCV also affect the survival in End Stage Renal Disease (ESRD) patients and even in renal transplant recipients. In the past, renal transplant in an HCV or HBV positive patient was contraindicated but now with the availability of new anti virals and better outcomes it is no longer a contraindication. This review is focused on the management and outcome of patients with HCV and HBV infection and renal disease with special focus on the renal transplant related issues.

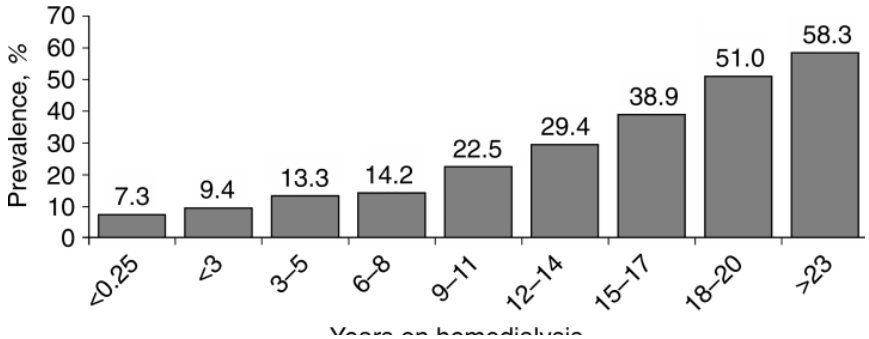
Hepatitis C Infection

Epidemiology and Prevalence:

There are about 180 million people who are affected with Hepatitis C virus (HCV) infection worldwide. With an estimated 3.2 million chronically infected persons nationwide, HCV infection is the most common blood-borne infection in the United States (6). According to National Health and Nutrition Examination Survey (NHANES) prevalence of HCV in the general population is about 1.6% (6). The strongest risk factor for acquiring HCV infection is intravenous drug use or blood transfusion (6). The prevalence of HCV infection among dialysis patients varies in different countries and different facilities. In one study, mean HCV prevalence

in dialysis patients was 15.3% and varied from 2.6 to 22.9% depending on the country (1). In US, prevalence of HCV positive antibodies among dialysis patients is reported to be 7.8% (1,7). The rate of seroconversion of a dialysis patient to HCV positivity has been shown to increase with the patient's time on dialysis and other infections like HIV, cellulitis or HBV (Figure 1) (1).

FIGURE 1: Patterns of hepatitis C prevalence and seroconversion in hemodialysis units. Variation in hepatitis C virus (HCV) prevalence by patient's time with end-stage renal disease (ESRD) From: (1).



Natural History of HCV:

After the exposure to HCV the host's immune response, primarily, determines the possibility of complete eradication of the virus or developing chronic infection. The natural course of HCV is variable. About 15-30% of patients with exposure to HCV develop chronic HCV infection(8). As significant number of patients with chronic HCV infection will develop liver related complications primary mortality in chronically HCV infected CKD patients still comes from cirrhosis and related complications. Duration of infection is the most consistent factor which is significantly associated with progression of liver fibrosis with chronic HCV infection (8). Most of the patients with chronic HCV infection are asymptomatic because natural history of liver or renal disease requires patients to have chronic infection for decades (8). Some of the patients with chronic HCV infection and renal insufficiency will progress to ESRD and will require dialysis and transplant (9).

Serologies :

For screening of HCV infection, anti HCV antibody is the initial screening test. In immunosuppressed patients false negative anti HCV is common and it needs to be confirmed with HCV recombinant immunoblot assay (RIBA) and HCV RNA quantification (10). Unlike Hepatitis B surface or core antibodies, HCV antibodies do not provide protective immunity (11). HCV RNA quantitative test can distinguish between active or past infection. It can also be used for monitoring of response to treatment. For active HCV infection, viral genotyping is usually done as there are 6 major HCV genotypes and the treatment duration and response varies among these (12).

HCV Related Renal Diseases:

HCV associated renal manifestations are mixed cryoglobulinemia, membranoproliferative glomerulonephritis (MPGN), membranous nephropathy, Focal segmental sclerosis, fibrillary and immunotactoid glomerulopathies (13-15). Most common GN associated with HCV is MPGN. Usually, GN develops after decades of chronic HCV infection. It is still not clear why some patients develop renal manifestations and others do not. HCV RNA and related proteins have been found in mesangial cells, tubular epithelial cells and endothelial cells (16,17). Patients with presence of HCV proteins in the mesangium have more proteinuria (17).

Several studies have shown striking association between HCV infection and MPGN or mixed cryoglobulinemia (MC). HCV proteins as the antigenic constituent of the glomerular immune deposits have been proposed and it has been shown that the deposits of HCV containing immune complexes were found in patients with HCV associated MPGN and MC (18). In an Italian study HCV immunoreactive deposits displayed the following two major patterns: 1) a linear, homogeneous deposition along glomerular capillary walls, including endothelial cells and sub-endothelial spaces; and 2) a granular bead-like appearance with distinct deposits in mesangial and paramesangial cells. Immunoglobulin G (IgG) and M (IgM) and C3 fraction deposition in adjacent kidney sections displayed features comparable with those found for HCV deposits (17). Patients with granular deposits showed more pronounced renal impairment and severe proteinuria. It has been shown that these findings indicate that in MC patients with HCV-

associated MPGN, kidney deposits consist of HCV-containing immune complexes that are likely to play a direct pathogenic role in the renal damage.

Chronic HCV infection also elicits systemic immune response and causes HCV- Ab complexes, cryoglobulinemia and amyloid deposition. With persistent overstimulation of B lymphocytes, from chronic inflammatory state in setting of chronic HCV infection, mixed cryoglobulinemia production occurs. These cryoglobulins get deposited in the mesangium and glomerular capillaries and cause the histological picture of fibrinoid necrosis (18). Cryoglobulins usually involve small vessels and is observed in less than 10% of the patients (19).

Majority of the patients with HCV associated renal manifestations present with difficult to control hypertension, proteinuria and hematuria (20,21). Patients with HCV associated cryoglulinemia present with cryoglobulinemic vasculitis and vasculitic picture(22) which involves: rash, fever, hematuria and renal insufficiency.

Renal Outcome with Chronic HCV:

Renal outcomes among HCV positive CKD patients have been compared with HCV negative CKD patients. HCV seropositivity is independently associated with approximately 5% decline in GFR per year as compared to HCV seronegative HIV infected women. (23). Long term outcome was studied in a cohort study of 474,369 patients using medicare and VA data (9). This retrospective cohort study of 474,369 adult veterans had serum creatinine and HCV antibody measured. Patients with HCV had more than two fold risk of developing End Stage Renal Disease (ESRD) than non infected CKD patients even if their estimated glomerular filtration rate was more than 30mL/minute per 1.73m2 (9). Patient with CKD who are also HCV positive have increased risk of progression of CKD regardless of underlying renal pathology (24). If the patients have coinfection with HCV and HIV, the decline in GFR is significantly higher over time (23).

Outcome of Patients on Dialysis with Chronic HCV:

Evaluation of the seriousness of chronic viral hepatitis in chronic kidney disease (CKD) patients is slightly difficult as most of these patients are asymptomatic and compared to the general population the serum levels of aminotransferases are lower in CKD patients (25). Chronic HCV

infection tends to run a different clinical course in dialysis patients and have less pronounced hepatic inflammation (26). One of the reasons for the different clinical course may be that uremia itself causes various immune defects. Uremia leads to hypercytokinemia from increased production and decreased clearance of pro-inflammatory cytokines which should cause more inflammation but uremia also causes decrease in T-Cell proliferation and B-Cell lymphopenia due to increased rate of apoptosis (27,28). Overall, it leads to less hepatic inflammation.

Outcome data has been compared between HCV negative and HCV positive dialysis patients. Dialysis patients with presence of anti-HCV antibodies were found to have higher all cause mortality from cardiovascular disease as compared to HCV-negative subjects (29). Duration of infection is found to be the most consistent factor significantly associated with progression of liver fibrosis (8). It is still hard to predict the degree of fibrosis without a liver biopsy in dialysis patients.

Renal Transplant with Chronic HCV:

Renal transplant is the best option for treatment of End stage renal disease for most of the ESRD patients. As transplant provides a better quality of life and on average has a lower cost than dialysis it is an important task for a nephrologist to evaluate and refer a patient for transplant (30). The majority of these patients may not develop cirrhosis while they remain on dialysis but with the need of immunosuppression, after renal transplant, the viral load may increase. It is important to consider the burden of HCV related issues during the screening of HCV positive ESRD patients for their eligibility for renal transplant.

The clinical outcomes of hepatitis C infection after kidney transplantation, as compared to remaining on maintenance dialysis, have been controversial. The outcome of the dialysis patients with chronic hepatitis C infection is worse than non infected patients (8). This has raised the concern about worsening liver fibrosis and risk of HCV related glomerulonephritis in renal allograft. As dialysis patients with chronic HCV have a higher mortality than HCV negative patients it has been of concern weather these patients will do any better after transplant (29). Renal transplant recipients with HCV can develop *de novo* immune-mediated glomerulonephritis (MPGN or membranous glomerulonephritis) can have accelerated loss of the renal allograft (31). The rate of progression to cirrhosis is highly variable and is influenced by several factors. A

systematic review and meta-analysis was published this year which compared 5-year mortality rates between waiting list and kidney transplantation patients with hepatitis C infections (32). Ingsathit et. al. looked at the outcome of 1734 HCV + dialysis patients with average follow up of 5 years. The pooled numbers were 666 and 1068 patients in kidney transplant and waiting list, respectively. Dialysis patients had 55% lower risk of death after transplant than wait listed patients suggesting survival advantage from kidney transplantation over dialysis. Survival benefit after kidney transplant may be from better clearance of uremic toxins and lower inflammatory and oxidative stress and decreased mortality from coronary heart disease (33).

HCV Positive Kidney Donors:

There is a severe shortage of deceased donors and mortality is high on dialysis (8). Outcome of dialysis patients is better after transplant than remaining on dialysis even with chronic HCV infection (32). Consideration has been given to the use of HCV positive donors in HCV positive or HCV negative recipients. Transplant recipients can also acquire denovo HCV infection, from different genotype after transplant, and concern has been about worsening of existing liver disease. An observational cohort data from John Hopkins was published in 2012 on HCV positive recipients who received HCV positive kidney and compared to HCV positive recipients who received HCV negative kidney (34). Outcome of 6,250 HCV positive patients, from United Network for Organ Sharing (UNOS) database who had a kidney transplant from 1995-2008, was reviewed. Among HCV+ kidney recipients, during the 13-year study period, only 1% eventually joined the liver transplant waitlist. Those who received HCV+ kidneys had a 2.6-fold higher hazard of joining the liver list. However, the absolute difference in rate of listing for liver transplant between recipients of HCV- and HCV+ kidneys was <2%. This is consistent with findings of only 2% lower patient survival at 3 years in HCV+ patients receiving HCV+ versus HCV- kidneys. As the recipients of HCV positive kidneys have slightly decreased patient and allograft survival the decision should include consideration of decreased time on dialysis. Longer time on dialysis itself has been shown to be associated with worse outcomes (32). The benefit of the use of HCV positive kidneys among HCV positive recipients outweighs the risk of a slight increased need for liver transplant in this population and most of the transplant centers are accepting HCV positive donors for HCV positive recipients if the potential recipient agrees to it.

Treatment Options:

For chronic HCV infection, currently recommended treatment is pegylated interferon alfa and ribavirin. The choice of this regimen was based upon the results of three pivotal, randomized, clinical trials that demonstrated the superiority of this combination treatment over standard interferon alfa and ribavirin (35-37). Treatment of HCV is challenging as the response rate depends on the HCV genotype. Goal of treatment is to reduce HCV RNA levels to undetectable levels in most treated persons. Peg-IFN and ribavirin treatment given for 48 weeks cures approximately 50% of patients with chronic hepatitis C genotype 1 (38). Treatment response among HCV genotypes 2 and 3 infected patients has been shown to be even better (80%) than genotypes 1 and 4 (50%) (39).

Based on KDIGO recommendations, patients who meet the criteria for treatment with antivirals should be treated for chronic HCV even if they have chronic kidney disease (CKD) (40). For dialysis patients with chronic HCV infection treatment can be challenging as some of the antivirals can cause more side effects and may be poorly tolerated by these patients. Chronic HCV in the general population is usually treated with combination of IFN and ribavarin. As interferon alfa is metabolized by renal tubules and in dialysis patients half-life is greatly increased, concern has been that prolonged treatment can cause accumulation of the drug. Pegylated interferon alfa has longer half life but is not better tolerated and causes similar adverse effects of nausea, diarrhea, fatigue, leucopenia, thrombocytopenia, thyroid dysfunction, alopecia, and depression which leads to withdrawal of the drug in up to 50% of the patients (41). Interferon also causes exacerbation of anemia, neutropenia, and protein malnutrition leading to withdrawal in up to 50% of the patients (42). A recent metanalysis by Fabrizi et al reviewed available clinical studies on safety and efficacy of IFN alpha in dialysis population (43). Viral response after antiviral therapy was found to be more common than the spontaneous viral clearance in dialysis patients with acute hepatitis C. Pooled analysis also demonstrated that IFN-based therapy of acute hepatitis C in dialysis populations gives a sustained viral response (SVR) in around one half of the patients. This supports IFN-based therapy for acute hepatitis C in dialysis patients.

As ribavarin (RBV) is also metabolized in kidney and not efficiently removed by dialysis it was considered to be contraindicated in patients with creatinine clearance <50ml/minute. Recent data

has suggested that low dose of ribavarin with IFN increases SVR rates upto 56% but these patients also had higher drop out rate (44). Poor tolerance to RBV in dialysis patients, particularly the ribavarin induced hemolytic anemia, makes this treatment difficult before renal transplant (45). As hepatitis C virus is associated with direct and indirect injury to kidney (16-18) there is concern of post transplant glomerulonephritis in renal allograft leading to graft failure. A recent retrospective study (46) was published to look at the association of Hepatitis C virus replication and the evolution of renal allograft and patient. It compared the evolution of patients with and without pre-renal transplant antiviral treatment. HCV positive patients and patients with reactivation of HCV have higher incidence of liver disease and worse renal function. The Indication of antiviral treatment in HCV-positive patients on dialysis should be individualized and should be considered prior to renal transplant.

There are several antivirals available now for treatment of HCV infection. Protease inhibitors have emerged as a third feature of combination therapy for HCV infection. In May 2011, protease inhibitors Telaprevir and Boceprevir were approved by FDA for treatment of HCV infection for the general population. Treatment response, in general, depends on variables such as prior treatment experience, severity of fibrosis, race and early response to the new therapy. Based on these expected cure rate has increased to up to over 80% (47).

Dumortier et al from France has reported 4 cases of HCV infection who did not respond to pegylated interferon (Peg-IFN) and ribavirin (RBV) and who were listed for kidney transplantation (KTx) (47). These 4 patients received a second-line antiviral treatment with Peg-IFN, RBV and telaprevir. After 12 weeks of triple therapy, HCV RNA was undetectable in 3/4 of the patients. Authors concluded that "triple therapy with a first generation protease inhibitor could be the new standard for the treatment of HCV patients with ESRD." These new agents, however,must be used in combination with RBV. Therefore, patients who can not tolerate RBV, will not be candidates for these drugs. We still need large investigation in larger series. Pharmacokinetics of telaprevir and Boceprevir in ESRD patients is still not available so need to be cautious about using these new antivirals in dialysis patients.

Recently, another target to treat chronic HCV has been micro RNA-122. It is abundantly expressed in liver and provides stability and reproduction of HCV RNA(48). Miravirse is a

locked nucleic acid-modified DNA phosphorothioate antisense oligonucleotide that sequesters mature miR-122 in a highly stable heteroduplex, thereby inhibiting its function. A phase 2a study was published recently for Miravirse and was shown to have prolonged dose dependent reductions in HCV RNA with chronic HCV genotype 1(49). No data is available yet for safety in renal patients. Hopefully new drugs with more safety profile and better response rate will be available to treat even HCV positive dialysis or transplant patients.

As the HCV positive patients have increased risk of progression of liver disease with immunosuppressive therapy and have poor tolerance to IFN therapy after renal transplantation(46) all HCV-positive candidates who are considered for kidney transplantation should be assessed for the possibility to receive antiviral treatment before transplantation. In addition to liver disease, HCV infection in renal transplant recipients is also implicated in new-onset diabetes after transplantation (NODAT), de novo allograft nephropathy, and sepsis which can compromise the patient and allograft outcomes and provides with strong argument for treatment prior to transplant (31,50).

Treatment after Renal Transplant

There are several antivirals available now for treatment of HCV infection. As current interferon-based therapy for hepatitis C has poor tolerance and safety before renal transplant,the question has been should these patients be even treated with antivirals after renal transplant. Among the available antivirals, interferon treatment is shown to cause high incidence of renal allograft failure and provides only low sustained viralogic response (SVR) and should be avoided if renal allograft is not affected from HCV associated glomerulonephritis (51). According to KDIGO guidelines(52) from 2010; monotherapy with standard IFN alfa should only be considered in kidney transplant recipients with HCV infection resulting in fibrosing cholestatic hepatitis or life-threatening vasculitis and the patients with HCV-associated glomerulopathy.

As the combined use of pegylated interferon alpha and ribavarin has greater rate of SVR it has been considered for HCV positive renal transplant patients. Use of this combination is missing randomized trials for renal transplant patients. A recent study has shown safety and efficacy of Pegylated interferon alpha and ribavarin in HCV positive renal transplant patients. Sanai et al treated 32 HCV (Genotype 1 and 4) positive renal transplant patients with combination of

Pegylated interferon alpha and ribavarin for 48 weeks and none of the patients had acute allograft rejection (53) . The dosages of both antivirals had to be reduced during this study due to poor tolerability. Authors suggest PegIFNα-2a dose of 135 μg/week and Ribavarin (RBV) dose of 400 mg/day as a starting dose to improve treatment tolerance without necessarily compromising sustained virological response(SVR) rates (53). As IFN-based therapy may cause reductions in Calcinuerin inhibitors (CNI) levels due to an improvement in hepatic microsomal function after viral clearance, close monitoring of CNI levels is recommended during treatment of HCV infection to avoid subtherapeutic levels of CNI and allograft rejection (54). There are case reports of treatment of combined liver kidney recipients with combination of Pegylated IFN alpha and RBV without liver or kidney rejection (55,56). Another study from France has also reported safety of pegylated IFN alpha and RBV in combined liver and kidney transplant recipients (57). Of the 12 patients, four (25%) had a SVR, two (16.7%) had an initial viral response, but then relapsed under treatment, and six patients (50%) had no viral response.

Guidelines from KDIGO suggest: (a) HCV-infected kidney transplant recipients (KTR) be treated only when the benefits of treatment clearly outweigh the risk of allograft rejection due to interferon-based therapy (e.g., fibrosing cholestatic hepatitis, life-threatening vasculitis). (b) monotherapy with standard interferon for HCV-infected KTRs in whom the benefits of antiviral treatment clearly outweigh the risks. It may be better to treat potential renal transplant candidates prior to transplant and if needed, after transplant, treatment with combination of pegylated IFN and ribavarin can be considered. Management of HCV positive renal transplant patient is outlined in Figure 2.

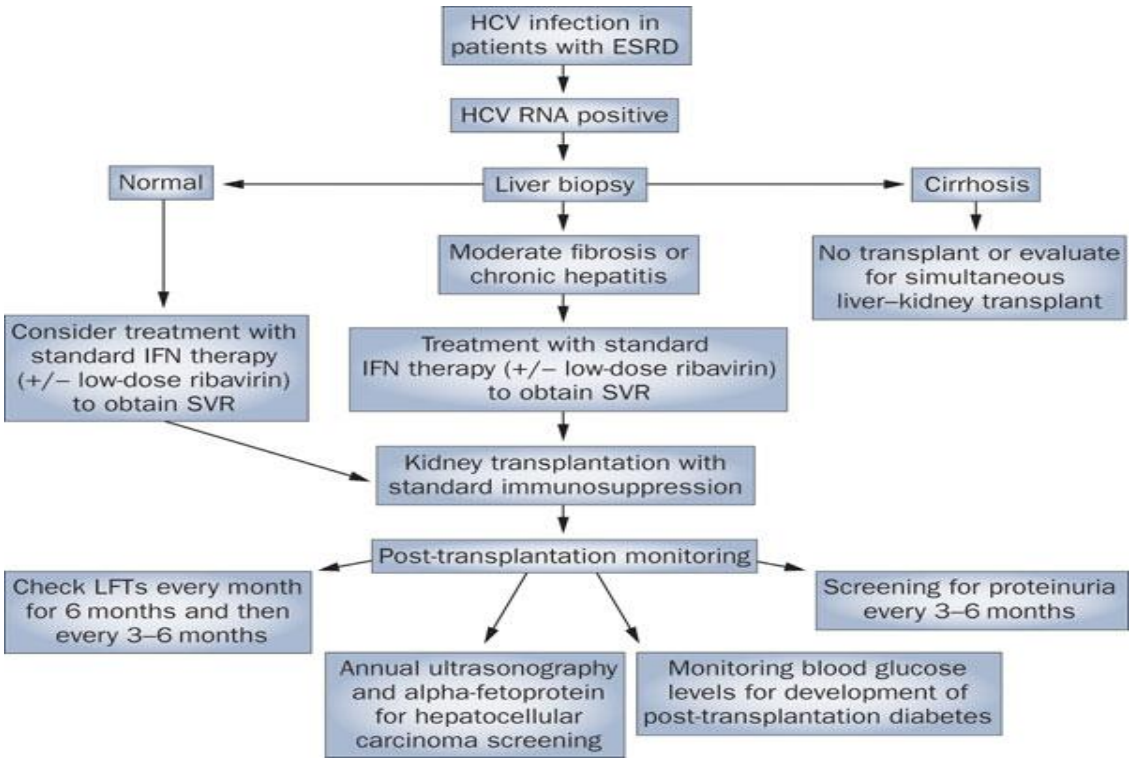


Figure 2 : **Proposed algorithm for pretransplantation and post-transplantation management of HCV-infected kidney transplant patients.** From : Huskey & Wiseman. Nature Reviews Nephrology 7, 156-165 (March 2011)

Hepatitis B Infection

Epidemiology and Prevalence:

There are about 400 million people who are infected with hepatitis B virus (HBV) globally. In the United States, 804,000-1.4 million persons are estimated to be infected with this virus, most of whom are unaware of their infection status(58). According to NHANES survey prevalence of chronic HBV in US is 0.28 % (59) is higher in non-Hispanic black, Mexican American people, low family income and those who had more than twenty sexual partners in their lifetime (6) (59). The prevalence of HBV infection among dialysis patients varies in different countries and different facilities and it has been reported to range from 0-75% (60,61). In US, prevalence of HBV in dialysis population is reported to be 1% (7) and has declined in renal transplant patients

due to availability and education about Hepatitis B vaccine and standard isolation precautions for HBV+ dialysis patients(7).

Natural History of HBV:

Transmission of HBV is via intravenous drug abuse (IVDA), needle sharing, perinatally, contaminated blood products and sexual contact (58,62). After exposure to HBV, the clinical course is variable and about 3-5% of HBV infected patients (63) develop chronic infection. Presenting symptoms of acute HBV hepatitis include jaundice, abdominal pain and fatigue (64).

Most of the patients with chronic HBV infection are asymptomatic because the natural history of liver or renal disease requires patients to have chronic infection for decades.

Serologies:

Serological testing for hepatitis B infection involves measurement of several different antibodies against different antigens. This is important to understand as all the kidney donors and recipients are screened for HBV infection by serological testing. Any patient who has positive hepatitis B surface Ag Hepatitis B early antigen (HBeAg) or HBV DNA has active HBV infection and is infectious. During different phases of HBV infection antibodies against different antigens are present (65). Serological testing can help to identify the patients with response to HBV vaccine vs active HBV infection. Interpetation of different antibodies is summarized in Table 1.

Table 1. Interpretation of hepatitis B serologies

Serology	Result	Interpretation
HBsAg Anti-HBc Anti-HBS	Negative Negative Negative	Susceptible
HBsAg Anti-HBc Anti-HBS	Negative Positive Positive	Possibly Immune due to natural infection
HBsAg Anti-HBc Anti-HBS	Negative Negative Positive	Possibly Immune due to Hepatitis B vaccination
HBsAg Anti-HBc IgM anti-HBc Anti-HBS	Positive Positive Positive Negative	Acutely infected
HBsAg Anti-HBc Anti-HBc Anti-HBS	Positive Positive Negative Negative	Chronically Infected.
HBsAg Anti-HBc Anti-HBS	Negative Positive Negative	Four possibilities: -Resolved Infection (Most common) -False positive anti-HBc, so susceptible - Low level chronic infection -Resolving acute inefction

Antibodies against Hepatitis B core antigen indicate previous or current infection. Presence of IgM antibody to hepatitis B core antigen indicates most recent infection (<6 months). Hepatitis B surface Antigen is a protein on the surface of HBV and can be detected in active infection. It is the same antigen, which is used to make vaccines, and presence of antibodies against Hepatitis B surface antigen indicates a good response and some immunity to HBV infection.

HBV Related Renal Diseases

Besides liver pathology several kind of renal manifestations have been identified with chronic HBV infection. Most of the renal diseases associated with HBV are encountered in endemic areas where HBV was acquired at an early age (66,67). Chronic Hepatitis B carriers can develop glomerulonephritis (GN) which includes membranous GN, Membranoproliferative GN (MPGN), polyarteritis nodosa (PAN), IgA nephropathy or amyloidosis (66-68). Most of the patients present with proteinuria (Membranous GN), hematuria (MPGN), decreased GFR or hypertension (PAN). Membranous nephropathy is more common in pediatric patients with chronic HBV infection while IgA nephropathy is more common in adult patients(69).

Both HCV and HBV have been shown to cause direct injury to renal parenchyma (16,17,70). Various HBV antigens including Hepatitis B surface Ag (HBsAg), Hepatitis early antigen (HBeAg), Hepatitis B Core Ag (HBcAg) or covalently closed circular Hep B DNA have been demonstrated in glomeruli of patients with HBV related glomerulopathy(70). Due to smaller size of HBeAg, it is able to traverse glomerular basement membrane and it has been shown that proteinuria decreases with clearance of HBeAg (71). Besides evidence of direct toxicity of HBV viral proteins to renal parenchyma, there is clear evidence of immune complex mediated renal injury(18,72). Immune complexes consist of viral antigens and the antibodies to those antigens. Immune complex of HBV virus antigen and antibodies directed to various HBV antigens deposits mostly in subepithelial region but can also deposit in mesangium and, rarely, in subendothelial regions(73).

Majority of the patients with GN related to chronic HBV present with proteinuria, hematuria or hypertension. HBV related membranous nephropathy patients develop heavy proteinuria and one third of these patients can develop decreased GFR (74,75).

Renal Outcome with Chronic HBV:

As compared to pediatric patients, adults with chronic HBV infection tend to have more progressive renal disease. HBV related membranous nephropathy has progressive course in up to one third of the patients (67). A small number of the patients with chronic HBV infection will develop CKD and ESRD (76) requiring dialysis and kidney transplant.

Outcome of Chronic HBV patients on Dialysis:

The natural history of HBV in dialysis patients and after renal transplant is poorly studied. Chronic liver disease is still one of the causes of mortality in HBV infected CKD patients. As the patients with CKD have higher mortality as compared to general population it is difficult to assess long term outcomes from chronic HBV infections. Besides chronic HBV infection there are other associated factors, like alcohol abuse, co-infection with HCV or HIV, which can accelerate progression of liver disease in CKD patients (77).

Survival data from US did not show any difference between HBSAg positive or negative dialysis patients (78,79). More often these patients may have slight elevation of liver enzymes and persistent viral antigenemia, however, risk of death from liver disease is low.

Renal Transplant with Chronic HBV Infection:

In the past, renal transplant in an HBV positive patient was contraindicated due to poor patient and allograft outcomes reported in 1970s and 1980s (80,81). According to a survey of Transplant Centers in 1994, twenty two percent of centers excluded HBsAg positive patients for renal transplantation and 45% of the centers required liver biopsy (82). The concern was that dialysis patients being immunosuppressed from ESRD or from immunosuppressants after renal transplant, may have an accelerated course of HBV and treatment response may be less effective leading to a detrimental effect of HBsAg on patient and graft survival. In pre-lamivudine era, HBsAg positive renal transplant patients had excessive early mortality within the first 2 years and the deaths were mostly from liver complications (83,84). A meta-analysis of observational studies was published by Fabrizi et al in 2005 (85) and it looked at six non-US (Europe and Asia) cohort, restrospective studies and reported increased risk of death and graft failure among

HBsAg positive renal transplant recipients as compared to HBsAg seronegative patients. Liver related mortality was still the important cause of death after transplant.

Lamivudine was licensed for treatement of HBV in 1996 and subsequently the availability of several additional anti-viral agents have contributed to better outcomes in HBV-infected recipients. Non inferior outcomes, after renal transplant, has been reported among HBV positive kidney recipients as compared to HBV negative recipients (86,87). Recently, a retrospective cohort study was published which compared the outcome of pre-existing HBV positive patients in the USA after renal transplant (88). In previous era (1987 to 1994), graft and recipient survival in HBsAg positive was found to be inferior to HBsAg negative recipient. When UNOS data from 1995-2007 was analyzed in this study, HBV infected renal transplant recipients were found to have no difference in rate of graft failure or death. The risk of liver disease was found to be 5.5 fold higher in HBV+ recipients but, interestingly, patient survival was not inferior to HBV negative recipients. There was also no increased incidence of glomerulonephritis noticed in HBV+ recipients. Use of current anti-viral drugs may reduced the incidence of renal allograft nephropathy related to HBV infection.

Although there is slightly increased risk of liver failure among HBV positive kidney recipients as compared with uninfected patients, chronic HBV infection is no longer considered to be a contraindication for renal transplant and an excellent renal allograft and patient survival in HBV-infected recipients can be expected.

HBV Positive Donors:

Based on United Network for Organ Sharing (UNOS) data from April 18, 2013 there are 96,063 patients who are currently listed on kidney transplant waitlist and this number is projected to grow(89) . It is important to increase the number of available organs to decrease the waiting time on dialysis. Renal transplant from hepatitis B core Ab positive donors have been done safely and the risk of acquiring HBV infection is low. An electronic data review recently published (90) reviewed nine studies and 1385 kidney recipients who had received HBcAb positive donor kidney. Seroconversion of HBV markers was found to be HBsAg (n = 4) (0.28%) HBcAb (n = 32), HBsAb (n = 5), and either HBcAb or HBsAb (n = 4). The total rate of seroconversion after renal transplantation was 3.24%. Currently most of the centers are using HBcAb positive

donors in immunized patients with post transplant prophylaxis. Donor HBV DNA is checked and duration of prophylaxis is decided based on donor's HBV DNA results. As the incidence of acquiring HBV infection from HBcAb positive donors is low, kidneys from HBsAg-negative/anti-HBc-positive donors can be safely transplanted to immunized ESRD patients. An absolute protective threshold of HBsAb titer in transplant recipients is still undefined but titer of >10 IU/ml is considered to be protective(91). These recipients need monitoring of sustained immunity with regular quantitative serologic follow-up and should receive booster dose of Hepatitis vaccine if anti-HBsAb titer decrease to <10 IU/ml (91).

Another donor pool is from HBsAg positive donors. Traditionally, transplant centers in US have been skeptical about using HBsAg positive donors but in the countries with endemic HBV these donors have been used for kidney donation (92,93) with good outcomes. All of these recipients had natural or vaccine-induced immunity against HBV as documented with positive anti-HBsAb titers. A recent case (94) from US has been reported about successful transplant from a living unrelated HBsAg positive donor and recipient was given hepatitis B immunoglobulin. As about one million people have HBV infection in US(58) and these can be potential organ donors, use of kidneys from HBsAg positive donors can increase the donor pool and decrease the time of dialysis for immunized HBsAg-negative recipients and can be considered in certain dialysis patients.

Treatment Options for HBV:

In the general population, treatment of chronic HBV is usually decided by hepatologists. The European Association for the Study of the Liver (EASL) has published the guidelines for the treatment of chronic HBV infection (95). The indications of treatment are: Persistent elevations in aminotransferases, compensated liver disease, and detectable active viral activtivities which includes HBSAg, HBeAg and HBV DNA for HBV, and detectable HCV RNA among chronic HCV patients. There should not be any contraindications to antiviral therapy which include active psychiatric disorder and non adherence. Currently, there are seven therapeutic agents approved by the Food and Drug Administration (FDA) for the treatment of chronic hepatitis B. These include two formulations of interferon (interferon alpha and pegylated interferon) and five nucleoside or nucleotide analogs (lamuvidine, telbivudine, adefovir, entecavir, and tenofovir).

Among the approved analogs, both entecavir and tenofovir have potent antiviral activity as well as very low rates of drug resistance(65). Goal of the treatment with these agents is to suppress HBV DNA and virtually all treated patients can expect to achieve a reduction of HBV DNA viral loads to very low levels within weeks or months of initiating therapy (84,96). The risk of developing lamivudine resistance has been identified and adefovir and entecavir has been used safely for lamivudine resistant HBV strains (97,98) in the general population.

HBV Treatment on Dialysis

The treatment of HBV in allograft recipients and dialysis is based on nucleos(t)idic analogues as in the general population with the same advantages and indications. The best approach to manage dialysis patients is vaccination against HBV along with isolation of infected patients during hemodialysis sessions to prevent the exposure of other patients. For treatment of HBV infection Lamivudine, adefovir, entecavir or tenofovir can be used. Lamivudine given prior to renal transplant has been shown to improve both 10-year patient and graft survivals compared to Ag positive renal recipients who did not take lamivudine(99). As lamivudine resistance is very common Adefovir seems to function better as an add-on therapy in patients who have developed lamivudine resistance(98). Adefovir has not been well examined in dialysis patients and although, tenofovir and entecavir are likely to be more effective and safer in dialysis patients, long-term empirical data are very limited on these drugs.

HBV Treatment after Renal Transplant

The suppression of the immune status after renal transplant may result in reactivation or accelerated viral replication. Management of chronic or denovo HBV infection is different from HCV infection, after renal transplant, as nucleos(t)ide analogues are well tolerated by renal transplant recipients. Any HBs Ag carrier exposed to immune suppression should be evaluated for viral replication and underlying liver disease and should be treated by a so-called pre-emptive treatment.

Survival of HBsAg positive renal transplant treated with lamivudine is similar to HBsAg negative renal transplant recipients (84). Lamivudine is no longer regarded as the first-line treatment for chronic hepatitis B due to high rates of drug resistance. Adefovir has also been

found to be safe and efficacious in treatment of lamivudine resistant HBV infection(98). However, with high dose of adefovir (30 mg) nephrotoxicity and Fanconi-like syndrome with phosphaturia and proteinuria has been reported (100) and lower dose (10 mg) should be used. As Adefovir has been reported to cause renal dysfunction close monitoring of renal function after transplant is needed. Even with renal dysfunction, reduction of the dose to even 10 mg every other day leads to renal improvement without compromising treatment efficacy (101).

Entecavir (0.5-1mg/day) has been used safely in one study (97) without any significant changes in creatinine or microalbuminuria after median follow up of 16.5 months. For now, entecavir is the preferred antiviral agent for lamivudine resistant HBV infection after renal transplant. Tenofovir is another antiviral agent available for treatment of chronic HBV infection but have also been reported to cause nephrotoxicity and renal transplant patients being at higher risk (102) require close monitoring and dose adjustments if needed. Routinely, only HBsAg positive patients are treated with lamivudine or adefovir pre-emptively but risk of reactivation of HBV has been identified among occult HBV carriers (HBsAg negative, Hep Bcore Ab positive) . Reactivation rate ranges from 4-6% (103,104) and lamivudine could protect occult HBV carriers and should be considered in these patients.

Pre-Transplant Screening

United Network of Organ Sharing has guidelines to screen all the transplant candidates and organ donors for blood born pathogens(105). Relatively high prevalence of HCV and HBV carriage in the general population means that HCV or HBV infection will be found in organ donors and organ recipients. All kidney transplant candidates should be screened for HCV infection with anti HCV enzyme-linked immunoassays (EIA) and if positive it should be confirmed with polymerase chain reaction(PCR). As HCV Ab can be negative in ESRD patients, being immunosuppressed, they should also be screened with PCR to avoid false negatives as they can have low HCV Ab titers. As the dialysis patients are at higher risk for hepatitis B, all the dialysis patients should be vaccinated with Hepatitis B vaccine and after completion of vaccination, the immunity should be verified with Hepatitis B Surface antibody screening(52). Prior to transplant, candidate should be screened for HBsAg and HBV DNA.

Organ donors are also screened for active hepatitis B infection with hepatitis B serologies including HBsAg and anti Hepatitis B core Ab.

If potential kidney transplant is found to have chronic HBV or HCV infection patient should be referred to hepatologist for further evaluation. Evaluation of extent of HCV and HBV associated liver disease is difficult among dialysis patients as the aminotransferases are lower in this population (25). All the patients with active HBV or HCV infection should have a liver biopsy done to assess the extent of liver damage. Cirrhosis is contraindication for renal transplantation alone given its poor short-term prognosis and a combined liver-kidney transplantation has to be discussed. Thus, it is necessary to evaluate the liver severity of the liver disease. Current recommendations for evaluation for chronic HVC or HBV dialysis patients are shown in Figure 1 (51).

Post Transplant Monitoring and Management

HCV and HBV viral loads increase after renal transplant from immunosuppression and can lead to worsening liver disease (84,106). HCV or HBV related liver complications can be denovo or from acute flare of chronic infection from use of immunosuppression. These patients need close monitoring after renal transplant to assess the progression of associated complications. Kidney Disease: Improving Global Outcomes guidelines (KDIGO) (52) suggest that all renal transplant patients with chronic HCV or HBV infection should have : (a) Liver function tests checked every month for first 6 months and then every 3-6 months (b) Surveillance for hepatocellular carcinoma with annual ultransonography of the liver and alpha-feto protein measurement and (c) Monitoring for proteinuria every 3-6 months. All conventional current induction and maintenance immunosuppressive regimens can be used in HCV or HBV infected patients (52) but if they are treated with IFN based regimen their CNI levels and renal function should be monitored closely due to higher risk of rejection and increased metabolism of CNI (54).

Simultaneous Liver-Kidney Transplantation (SLKT)

Advanced liver disease is a contraindication for kidney transplant due to poor short term outcomes and these patients should be considered for SLKT. Currently, allocation of liver is

decided by Model of End Stage Liver Disease (MELD) score. Calculation of MELD score is largely influenced by creatinine as below:

MELD = 3.8[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.6[Ln serum creatinine (mg/dL)] + 6.4.

Even if all other liver parameters are normal, a patient on dialysis automatically receives a score of 21 as calculated MELD score is increased by renal insufficiency. This provides the higher MELD score for dialysis patients and increases the availability of both organs. Since the adoption of MELD score in 2002, death rate on liver transplant wait list has decreased and number of combined liver-kidney transplant has increased by 300% (107). The degree of fibrosis alone is not correlated with the outcome of the patient or allograft after kidney transplant (108). Appropriately assessing the extent of portal hypertension is important in dialysis patients with cirrhosis, prior to considering SLKT as some of the patients may not require SLKT and may do well with kidney transplant alone (109). As hepatic portal vein gradient of >10 mm Hg predicts clinical decompensation, it is considered a good reference point for SLKT (110). Also the liver biopsy can be performed at the same time to evaluate the extent of fibrosis.

As renal function worsens with use of calcineurin inhibitors in liver transplant patients with chronic kidney disease (CKD) they may need a kidney transplant in future. When outcome of cirrhotic patients with renal insufficiency, but not requiting dialysis, was compared with SLKT or liver transplant alone survival was not improved with SLKT (111). But patient with cirrhosis and End stage renal disease have better liver allograft and patient survival with SLK transplant as compared to liver transplant alone (112). Combined liver-kidney transplant has now become a common practice for patients with combined end stage liver and kidney disease and SLKT is recommended for cirrhosis patients with ESRD. But patients with acute kidney injury, who require dialysis for less than 8 weeks, should be considered for liver transplant only as the role of SLKT in cirrhotic patients with acute kidney injury of short duration remains highly controversial (107).

Not much data is available in the utility of kidney biopsy in cirrhosis patients as very few patients will undergo biopsy due to higher risk of bleeding with coagulopathy associated with cirrhosis. According to Combined Kidney-Liver Transplantation Consensus Conference

Statement (107) SLKT should be considered for (a) cirrhotic patients with symptomatic portal hypertension and end-stage renal disease, (b) liver failure and Chronic kidney disease (duration more than 90 days) with glomerular filtration rate (GFR) of 30 mL/min or less, (c) acute kidney injury or hepato-renal syndrome with creatinine level of >2.0 mg/dL and need of dialysis for 8 weeks or more, (d) liver failure and CKD and biopsy demonstrating greater than 30% glomerulosclerosis or 30% fibrosis. Algorithm for evaluation of ESRD and liver disease patient for transplant are outlined in Figure 3.

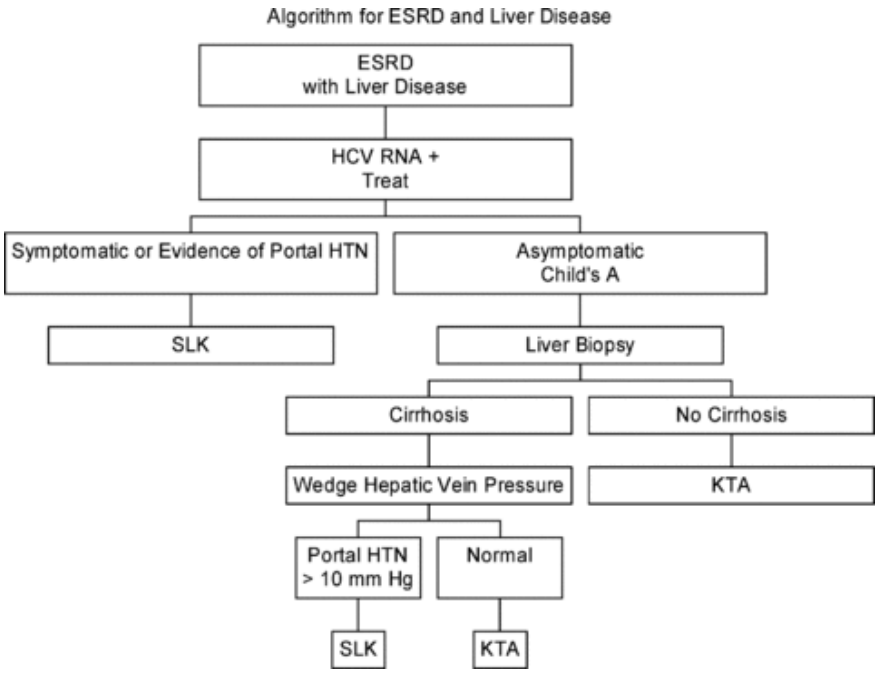


Figure 3: Algorithm for ESRD and Liver Disease. (107) From: Eason et. al. *American Journal of Transplantation 2008; 8: 2243–2251*

Summary:

With the availability of new anti-viral agents the survival of chronic HBV and HCV patients has significantly improved in last decades and it is not a contraindication for renal transplant. These patient require multidisciplinary approach of management of immunosuppression and viral hepatitis. All potential renal transplant candidates with chronic HBV and HCV should undergo

evaluation of portal hypertension and liver biopsy to assess the extent of liver disease prior to consideration of renal transplant alone as some of these patients may require SLKT.

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