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**Hepatitis C and kidney diseas: An overview and approach to management**

Azmi AN *et al.* Hepatitis C and kidney disease

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**Abstract**

Hepatitis C infection and chronic kidney disease are major health burden worldwide. Hepatitis C infection is associated with a wide range of extra-hepatic manifestations in various organs including the kidneys. A strong association between hepatitis C and chronic kidney disease has come to light. Hemodialysis in supporting the end stage renal disease patients unfortunately carries a risk for hepatitis C infection. Despite much improvement in the care of this group of patients, the prevalence of hepatitis C infection in hemodialysis patients is still higher than the general population. Hepatitis C infection has a negative effect on the survival of hemodialysis and renal transplant patients. Treatment of hepatitis C in end stage renal disease patients using conventional or pegylated interferon with or without ribavirin remains a clinical challenge with low response rate, high dropout rate due to poor tolerability and many unmet needs. The approval of new direct acting antiviral agents for hepatitis C may dramatically change the treatment approach in hepatitis C infected patients with mild to moderate renal impairment. However it remains to be confirmed if the newer Hepatitis C therapies are safe in individuals with severe renal impairment. This review article discusses the relationship between hepatitis C and chronic kidney disease, describe the various types of renal diseases associated with hepatitis C and the newer as well as the existing treatments for hepatitis C in the context of this subpopulation of hepatitis C patients.

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**Key words:** Chronic hepatitis C; Kidney disease; Management

**Core tip:** There is a strong association between hepatitis C virus (HCV) infection and chronic kidney disease with negative impact on survival in hemodialysis and post renal transplant HCV infected patients. Recent data showed that treatment of HCV improves outcomes. In HCV infected diabetics, effective anti-HCV treatment reduces the incidence of end stage renal disease. There are now major advances in HCV treatment which may dramatically change the treatment approach in hepatitis C infected patients.

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**INTRODUCTION**

There are approximately 130-150 million people infected with hepatitis C virus (HCV) while the prevalence of chronic kidney disease (CKD) is between 10%-16% worldwide[1,2]. The prevalence of HCV positive among hemodialysis patients can vary from < 5% to as high as 60% from different region in the world[3,4]. The link between HCV infection and kidney disease is well recognized[5,6]. In a large population-based study in Taiwan, the prevalence of CKD among those who are seropositive for hepatitis C was 16.5% and chronic hepatitis C infection was found to be an independent risk factor for development of CKD[5,7]. In another study, the presence of anti-HCV antibody is associated with renal disease progression with a higher rate of positive anti-HCV in those with more severe stages of CKD[8].

The survival of HCV-infected CKD patients at stage 1 and 2 CKD is thought to be similar to the non-uremic HCV patients[9]. In contrast, a meta-analysis reported negative impact of anti-HCV positivity on survival in hemodialysis patients; the adjusted relative risks for all-cause mortality was 1.35 [95% confidence interval (CI) of 1.25-1.47] and for liver disease related mortality was 3.82 (95%CI: 1.92–7.61)[10].

The treatment for hepatitis C is rapidly evolving with many new agents in the pipeline either in late phases of development or awaiting approval. Direct acting anti-virals (DAAs) target various parts of the HCV lifecycle. In 2011, two new DAAs, the first generation of HCV-NS3/NS4A serine protease inhibitors (PI) telaprevir and boceprevir were approved for treatment of genotype 1 HCV. Two more DAAs were approved more recently; sofosbuvir, a nucleotide analog NS5B polymerase inhibitor which is effective against HCV genotypes 1, 2, 3 and 4 and simeprevir, the third NS3/NS4Aprotease inhibitor approved is effective against HCV genotype 1[11]. The newer generation of DAAs are associated with increased sustained viral response and good safety profiles.

This review describes the various types of clinical manifestations of HCV in patients with CKD and their management, which remains challenging with many unmet needs.

**HEPATITIS C RESULTING IN KIDNEY DISEASE**

HCV primarily affects the liver causing hepatitis; chronic hepatitis may progress to liver fibrosis and subsequently cirrhosis and hepatocellular carcinoma, which are the major burden of disease in people living with chronic hepatitis C. However, there are also extra-hepatic manifestations of HCV which include glomerulonephritis, thyroiditis, insulin resistance, diabetes mellitus, porphyria cutanea tarda, lichen planus, vitiligo, seronegative arthritis, cryoglobulinemia and lymphoproliferative disorders[6]. It has been reported that approximately 40% of the HCV infected patients have at least one extra-hepatic manifestation[12].

Large-scale community observational studies and others showed that HCV infection carries a risk for CKD and end stage renal disease (ESRD)[5,7,8,13]. Similarly in CKD patients, HCV infection increases the risk of developing ESRD with an estimated 5-year cumulative incidence rate of 52.6% compared to 38.4% in those without HCV infection[14]. This study also reported that HCV infection is an independent risk factor for developing ESRD[14]. The risk for CKD is higher in HCV patients with other co-morbidities such as diabetes, hyperlipidemia, cirrhosis, male gender, age < 50 years, and those on more than 6 years follow-up for HCV[7].

Several factors may contribute to the development of ESRD in HCV infected patients. HCV may trigger a cascade of immune reactions that subsequently attack the kidneys and result in glomerulonephritis. HCV was also found to be associated with insulin resistance and dyslipidemia[15], thus, indirectly increasing the risk of renal disease.

Kidney diseases associated with HCV may present clinically as nephritic, nephrotic syndrome or isolated proteinuria with or without impairment in renal function. The pathological changes on renal biopsy are membranoproliferative glomerulonephritis (MPGN), membranous glomerulopathy (MG), IgA nephropathy, focal segmental glomerulosclerosis, mesangial proliferative glomerular nephritis or tubulointerstitial nephritis[16]. In an Italian multi-centre study of 146 cryoglobulinemic glomerulonephritis, 87% was HCV infected[17]. Diffuse MPGN was the most common renal biopsy finding in 83% of patients and Type II cryoglobulin was detected in 74.4% of cases.

In a case-control study, it was also found that MPGN was significantly more prevalent than membranous glomerulopathy among HCV associated kidney disease patients (0.36% *vs* 0.05%; *P* < 0.0001), with the most common involvement being type I MPGN associated with type II mixed cryoglobulinemia[6].

Glomerulonephritis may occur many years or even decades after HCV infection. The mechanism for MPGN related to HCV is thought to be immune-complex mediated (antigen-antibody immune complexes formation from chronic infection) and these immune complexes activate the classical pathway of complements and cause deposition of immunoglobulins, complement factors and both kappa and lambda light chains in the mesangium and the capillary walls[18]. HCV-NS3 viral antigen deposits were detected in kidney tissues of patients with positive HCV RNA and MPGN[19,20]. Cryoglobulins are immunoglobulins which become insoluble at below body temperature and dissolve when rewarmed. In individuals with HCV infection, these cryoglobulins are immune complexes formed by monoclonal immunoglobulin M (usually IgM Rheumatoid factor), polyclonal immunoglobulin G and HCV RNA which are deposited in the small and medium-sized vessels of the skin, kidneys and peripheral nerves. The deposition of these immune complexes in the mesangium of the kidneys triggers glomerulonephritis. Although proteinuria below nephrotic range, microscopic hematuria, mild to moderate renal insufficiency and arterial hypertension are among the classical clinical features, 30% of chronic hepatitis C with cryoglobulinemia have non-specific features like purpura, asthenia and arthralgia. Less than 10% have vasculitis affecting the kidney, skin and nerves[21,22]. Alanine transaminases are raised in 70% of patients, complements like C4, C1q are very low while C3 is only slightly low and the majority are rheumatoid factor positive[21,23]. Patients with diffuse MPGN showed higher levels of proteinuria and lower C4 levels[17]. The clinical course of patients with MPGN and cryoglobulinemia is classically relapsing and remitting, the top three causes of death are cardiovascular, sepsis and liver failure[17]. ESRD requiring hemodialysis is infrequent due to early mortality during the course of CKD before approaching ESRD[17,23].

Interestingly, studies also found an association of occult HCV in immune-mediated glomerular nephropathies[24,25]. In these studies, occult HCV is defined as negative anti-HCV-antibodies and serum HCVRNA but presence of HCV RNA in mononuclear cells in peripheral blood or in serum after ultra-centrifugation or HCV antigen detection using immuno-histochemistry in frozen renal tissues. The clinical implication of this finding requires further studies.

In the management of HCV-infected individuals, it is imperative that clinicians actively screen for kidney disease and prevent or control the additional risk factors (diabetes, hyperlipidemia and cirrhosis) for CKD. The liver and renal clinical practice guidelines recommend annual surveillance for hematuria and proteinuria in HCV-infected patients for early detection of glomerulopathies[9,26].

**HEPATITIS C AND HEMODIALYSIS**

In 2004, the Dialysis Outcomes and Practice Patterns Study (DOPPS) reported that 13.5% of hemodialysis patients are infected with hepatitis C. The prevalence rates of hepatitis C among these patients exhibits regional variations with less than 5% in the United Kingdom and Germany and higher prevalence of more than 20% in Spain and Italy[27]. Among 10 countries studied within the Asia-Pacific region, the HCV seroprevalence among hemodialysis patients were between 0.7% and 18.1%[28]. In addition, the prevalence of HCV were higher in HD group compared to patients on peritoneal dialysis [(7.9% ± 5.5%) *vs* (3.0% ± 2.0%), *P* = 0.01]. More importantly, the prevalence of HCV patients with ESRD who underwent hemodialysis can be at least five times higher compared to the general population[3,9,29,30].

There are mainly two groups of HCV infected patients in the hemodialysis unit, either the patients already have HCV infection before entering into treatment with hemodialysis or the HCV infection was acquired during the maintenance hemodialysis. The mode of HCV transmission is parenteral through contaminations from surfaces, supplies, invasive procedures, direct contact among patients and from breach in infection control practices[9]. Before the era of screening blood donors for HCV and the use of erythropoetin, multiple blood transfusions to treat anemia in dialysis patients had contributed to the increased prevalence of HCV transmission[3]. In one prospective observational study conducted in three major continents, the prevalence of HCV in hemodialysis patients were higher among those who were on dialysis for longer duration, male gender, black ethnicity,, concurrent illness like diabetes or hepatitis B infection, prior kidney transplant and alcohol or substance abuse[27]. In its guideline to prevent HCV transmission in hemodialysis unit, Kidney Disease Improving Global Outcome (KDIGO) guidelines stressed the importance of compliance to strict infection-control procedures at all times[9].

A meta-analysis on patients receiving maintenance hemodialysis, found that HCV-positive patients have higher mortality compared to HCV-negative patients. This study showed that liver-related death was higher than cardiovascular-related death among these groups [adjusted relative risk 3.82 (95%CI: 1.92; 7.61) *vs* 1.26 (95%CI: 1.10; 1.45) respectively][10]. Deaths due to hepatocellular carcinoma and liver cirrhosis was higher in HCV-positive group[31]. There is no observed difference between hemodialysis and peritoneal dialysis on the survival rate of these HCV infected dialysis dependent patients[32,33].

**HEPATITIS C AND RENAL TRANSPLANT**

Hemodialysis is a risk factor for HCV infection. KDIGO guidelines recommend all renal transplant candidates should be screened for HCV and state that HCV infection is not a contraindication to renal transplant. A meta-analysis on 13 observational studies by Fabrizi *et al*[34] found that most studies showed an increase in all-cause mortality and all-cause renal graft loss among renal transplant recipients with HCV[34]. This is likely due to post-transplant immunosuppression and undiagnosed HCV infection prior to transplant. Hepatitis C infection in the setting of post renal transplant had been reported to cause specific diseases in the liver and the transplanted kidney.

In a cohort study of 614 renal transplant recipients, 2.45% (15 recipients) were diagnosed with membranous glomerulopathy (MG) post transplant. In eleven of them were de novo MG and 6 out of the 11 de novo MG cases were associated with HCV infection. All but one of the HCV infected recipients were not treated before the transplant[35]. Other studies also found that HCV is a strong aetiologic factor for development of MG post transplant[36,37].

Fibrosing cholestatic hepatitis had been reported in HCV-infected renal transplant recipients. It is a complication of immunosuppression resulting in extremely high serum HCV RNA levels causing rapid progression to liver failure, sepsis and associated with high mortality rates. Biochemical profiles showed progressive cholestatic jaundice with liver biopsy showing characteristic features of cholestasis and fibrosis. Withdrawal or reductions of immunosuppression tend to have significant impact on preventing the progression of liver failure[38,39] but at the expense of possible renal graft loss.

In a study by de Olivuera Uehara *et al*[40], 22 renal transplant recipients who were HCV-positive and have pre and post transplant liver biopsies, were followed up to 7 years post transplant. Fifty percent of the patients showed progression in liver fibrosis and 32% had worsening of liver necro-inflammatory activity. Post transplant worsening of liver fibrosis was also detected in patients with no histological changes prior to the transplant[40]. In another study by Roth *et al*[41], 44 patients with HCV-positive recipients were followed for slightly shorter interval showed no significant liver disease progression, 16% of the studied recipients showed histologic improvement, and 23% showed progression of liver disease[41]. It is likely that HCV infection post renal transplant will gradually cause worsening of liver disease in the majority of cases.

A prospective study showed that despite significant decrease in patient and renal graft survival post renal transplant in HCV positive recipients compared to their HCV negative counterparts, the survival of HCV positive ESRD is still better with renal transplant rather than remaining on maintenance hemodialysis[42]. Kidneys from anti-HCV positive donors have been used to transplant HCV infected renal recipients[43]. This approach will help to shorten the waiting time for HCV RNA positive renal transplant candidates[44,45]. In addition to the benefit of shorter waiting time, the use of kidneys from HCV positive donors had also been shown to improve the overall survival compared to staying on the waiting list (adjusted hazard ratio for death 0.76, 95% CI 0.60, 0.96)[46]. However, transmission from infected donor may produce super-infection from a different HCV genotype[47].

**ASSESSMENT OF HEPATITIS C AND LIVER DISEASE STATUS IN RENAL PATIENTS**

The clinical tools used in assessing HCV and the liver disease in non-uremic patients are generally applicable to renal patients apart from a few notable differences. HCV infected patient on hemodialysis tend to have normal ALT possibly due to high lactate level, which cause rapid consumption of NADH co-enzyme or enzyme during dialysis[48].

All anti-HCV-positive CKD patients should be assessed for HCV RNA viral load, HCV genotyping as well as liver fibrosis. HCV genotype is a strong predictor of response to anti-HCV treatment. KDIGO recommended special steps in drawing blood sample for HCV RNA tests in hemodialysis patients because heparin is an inhibitor of polymerase chain reaction(PCR)[49]. In order to avoid contamination with heparin which is used in hemodialysis session, the blood sample for HCV RNA should be taken from a peripheral vein before the dialysis session[9].

Assessment of severity of liver disease is recommended prior to anti-HCV therapy. KDIGO recommend that HCV-infected potential kidney transplant candidates to undergo liver biopsy as part of the pre-transplant assessment. In a study which had 284 HCV infected hemodialysis patients undergoing liver biopsies, the complications reported were local pain in 18.3%, shoulder soreness in 11.7%, oozing at puncture site in 11.3%, liver hematoma in 1.1% and only one patient suffered from hemoperitoneum[50]. Another study on percutaneous liver biopsy in chronic hepatitis C patient with or without renal failure also found the procedure to be safe without any increased risk in hepatitis C infected ESRD[51].

We look into several studies that analysed liver biopsy findings in this group of patients. These studies revealed that about 22%-81% of HCV positive ESRD patients had histological evidence of liver fibrosis on biopsy while a smaller percentage of approximately 13%-25% had biopsy proven cirrhosis[52-54].

Although serious complications of liver biopsy are uncommon, the procedure is not well accepted by patients, and is open to sampling as well as interpretation errors. Non-invasive methods to evaluate the severity of liver disease in management of hepatitis C patients have been recommended[26,55]. A combination of non-invasive tests improves the diagnostic accuracy. An easily available method for assessing liver fibrosis in HCV patients is by using amino transaminase-to-platelet ratio index (APRI). APRI is calculated by [(amino-transaminase/upper limit normal)/platelet count (109/L)] × 100. A study in HCV infected ESRD patients found that APRI >0.4 and <0.95 can correctly predict 50% patients with F3-F4 fibrosis, 33% of F3-F4 fibrosis patients may have been mislabeled and consequently did not have a liver biopsy as part of the renal transplant assessment. The authors concluded that APRI was not a good predictor of hepatic fibrosis in transplant evaluation of HCV-positive ESRD patients[56]. An earlier study showed that APRI is a precise and reproducible test in predicting hepatic fibrosis in hemodialysis patients[57]. The different findings in these two studies were probably due to the different cut-off values used in predicting fibrosis.

Transient elastography (TE) has been found to be superior to APRI in assessing the severity of liver fibrosis especially in hemodialysis HCV infected patients with significant liver fibrosis (≥ F2 and ≥ F3)[50]. Overnight fasting before TE measurement is recommended to minimize the effect of raised portal and central venous pressure. The optimal cut off values were 5.3 kPa, 8.3kPa and 9.2 kPa for fibrosis stage ≥ F2, ≥ F3 and F4, respectively. It is noteworthy that a systematic review of 12 studies showed that TE is an excellent tool to identify HCV-related cirrhosis but not accurate for early stages of liver damage[58].

Patients with clinical or histological evidence of cirrhosis should have further assessments to look for the complications of cirrhosis such as upper endoscopy for varices and liver ultrasound for hepatocellular carcinoma surveillance.

**TREATING HEPATITIS C INFECTION IN CKD PATIENTS**

KDIGO recommends that all CKD patients with HCV infection to be assessed for anti-HCV therapy. As there are risks of IFN therapy and benefits of avoiding the complications related to HCV infection in post renal transplant setting, KDIGO and other liver guidelines state that HCV infected renal transplant candidates should be treated for hepatitis C before renal transplant[9,26]. In clinical practice, the decision to treat HCV infection in a patient with CKD must be individualized after discussion of the potential risks and benefits of therapy. Factors such as life expectancy, renal transplant candidacy, other co-morbidities and the available expertise should be taken into consideration[9,26,55]. CKD patients in Stages 1 and 2 have normal survival as in the general population but CKD stage 3 and 4 have lower 5 years survival at 76 % and 54% respectively. However the survival of CKD Stage 5 patients is markedly diminished compared to the general population without renal impairment[9]. The liver-related complications of HCV, namely cirrhosis and hepatocellular carcinoma, have been implicated in the lower survival of HCV infected CKD Stage 5D or hemodialysis patients[31].

The widely accepted standard of care (SoC) for HCV therapy is pegylated interferon (PegIFN) in combination with ribavirin[26]. Using this SoC in renal impaired patients has several limitations mainly due to aggravated side effects resulting in premature discontinuation of therapy, higher dropout rates and treatment related mortality. Consequently, only few HCV-infected kidney disease requiring hemodialysis patients are treated. Dialysis Outcomes and Practice Patterns Study (DOPPS) reported that 4735 out of 49762 patients on hemodialysis were HCV-positive (9.5%) but only 48 out of 4589 (1%) patients with prescription data receive anti-viral treatment[59]. In the same study, among 617 HCV-positive renal transplant candidates, only 3.7% receive anti-viral treatment. Nevertheless, HCV-positive dialysis patients who received treatment were found to have better survival than untreated group.

CKD patients mostly suffer from multiple co-morbidities. Diabetes mellitus, hypertension and cardiovascular disease are among the co-morbidities that reduce the survival rate among CKD patients but also render them poor candidates for the current SoC anti-HCV therapy. Management of HCV-infection in kidney disease patients with multiple co-morbidities remains a challenge.

Renal transplant candidates with HCV-infection are recommended to receive HCV treatment due to benefits in slowing the development of liver disease and reduce the risk of HCV-related post-transplant complications[41] such as new-onset diabetes mellitus[60] and chronic allograft nephropathy[61]. In a controlled clinical trial by Cruzado *et al*[62], renal transplant recipients who received pre-transplant IFN therapy were shown to have a significantly lower rate of de novo glomerulonephritis compared to recipients who were untreated[62].

The objective of anti-HCV treatment is to achieve sustained virological response (SVR), which is classically defined as undetectable HCV RNA by polymerase chain reaction at 6 mo after interferon-based treatment. Achieving SVR in advanced fibrosis patients is associated with a decrease in all cause mortality, reduce risk of liver transplantation as well as liver related deaths like liver failure and hepatocellular[63]. However the benefits span beyond the liver. A Taiwan population based cohort study stratified diabetes mellitus patients into 3 groups; HCV-infected patients who were treated with Peg-IFN and ribavirin, HCV-infected patients who were never treated and an uninfected group. The 8-year cumulative incidence of ESRD and acute coronary syndrome were significantly lower in those who received anti-HCV therapy[64]. The authors concluded that treatment of HCV-infected patients with Peg-IFN and ribavirin was associated with improvements in cardiovascular and renal outcomes in diabetes mellitus patients.

Moreover, a meta-analysis on the durability of SVR in successfully treated HCV showed 86% durability in those who remained on maintenance hemodialysis while in those who received renal transplant it was 95% durable after a follow-up of 48 months[65].

**Approved anti-HCV therapies and their use in renal impairment**

Interferon (IFN) is broken down mainly in the kidneys therefore IFN therapy in patients with kidney disease may result in a significant amount of IFN accumulation in the body. Peg-IFN was introduced where the polyethylene glycol is attached to the IFN molecule making it more stable and longer half-life in the plasma. Instead of thrice weekly IFN injection, Peg-IFN requires only weekly injection. The two formulations of pegylated interferon are Peg-IFN-α2a and Peg-IFN-α2b. The latter is weight based at 1.5 mcg/kg while Peg-IFN-α2a dose is 180 mcg regardless of body weight. Peg-IFN-α2a is metabolized in both the kidneys and liver while Peg-IFN-α2b only by the kidneys. Plasma concentration of Peg-IFN is significantly elevated in hemodialysis patients, thus, Peg-IFN dose has to be reduced. For patients with creatinine clearance (CrCl) of < 30mL/min and on hemodialysis, Peg-IFN-α2a dose should be reduced from 180 mcg to 135 mcg weekly[66]. Peg-IFN-α2b dose should be reduced by 25% in patients with CrCl of 30-50 mL/min, and by 50% in patients with CrCl of < 30 mL/min or on hemodialysis[67].

Ribavirin is a nucleoside analogue that when combined with Peg-IFN increases the rates of SVR. Ribavirin can accumulate in the red blood cells and may lead to hemolytic anemia due to the lack of phosphatase. Toxicity increases significantly with impaired CrCl as its plasma concentration increase when the CrCl is < 50 mL/min. Measuring plasma levels of ribavirin is not a widely available clinical tool. Studies have shown that ribavirin 200 mg or 400 mg on alternate days to be reasonably well tolerated by patients with moderate renal impairment, while in patients with severe renal impairment or on dialysis ribavirin 200 mg daily can be used[68]. Using low-dose ribavirin in CKD patients need more frequent monitoring of hemoglobin[69,70].

Boceprevir selectively inhibits NS3 serine protease, which is vital for HCV RNA replication into virions inside the host cells[71]. In phase 3 clinical trials, boceprevir combined with Peg-IFN and ribavirin in HCV genotype 1 achieved SVR of 60% for treatment naïve HCV patients, and 63% SVR for relapsers and previous partial responders[72,73]. A study by Treitel *et al*[74] showed no significant pharmacokinetic changes in patients with liver and renal impairments. The authors suggest that boceprevir dose modification is not necessary in patients on dialysis[74].

Telaprevir in combination with Peg-IFN and ribavirin achieved up to 75% SVR in treatment naïve HCV Genotype 1 patients, while in previous relapsers, partial responders and null responders the SVR were up to 88%, 59% and 33% respectively, *vs* 24%, 15% and 5% in the Peg-IFN/ribavirin arm[75]. Telaprevir plasma concentration increase by 21% in patients with renal impairment compared to normal renal functions[76]. According to the package insert, telaprevir does not require any dose adjustment in patients with mild, moderate or severe renal impairment[77].

A recent study by Mauss *et al*[78], reported that 4.7% patients on boceprevir and 6.6% patients on telaprevir experienced reduction in estimated glomerular filtration rate (eGFR) to < 60 mL/min compared to 0.9% in the Peg-IFN and ribavirin only group (*P* < 0.05). Several factors contributing to the reduction in glomerular filtration rate (GFR) were older age (*P* < 0.001), hypertension (*P* < 0.05), higher serum baseline creatinine (*P* < 0.001) and being on triple therapy Peg-IFN/ribavirin with boceprevir or telaprevir (*P* < 0.01)[78]. Similar findings were also reported in other studies[79,80].

Simeprevir together with Peg-IFN plus ribavirin in phase III studies achieved SVR rates of 80% and in treatment naïve HCV genotype 1 patients and previous relapsers to Peg-IFN/ribavirin compared to 36.1% in Peg-IFN/ribavirin group[81]. No dose adjustment is needed in mild, moderate or severe renal impairment but the data on simeprevir in ESRD or dialysis patients is lacking[82].

In treatment naïve HCV genotype 1, sofosbuvir with Peg-IFN plus ribavirin therapy for 12 wk achieved SVR up to 89%[83]. With the approval of sofosbuvir and ribavirin, interferon free regimen is now available for genotype 2 and 3 patients. For genotype 2 HCV patients, sofosbuvir with ribavirin for 12 wk yielded 95%-97% SVR in treatment naïve patients and 82%-90% SVR rate in previously treated patients. In HCV genotype 3 patients, sofosbuvir with ribavirin for 24 wk produced SVR rate of 93% in treatment naïve and 77% in previously treated patients[83,84]. No dose adjustment is required in renal impaired patients. However, sofosbuvir package insert does not recommend the use of this drug in those with severe renal impairment or ESRD due to higher exposures of the predominant sofosbuvir metabolite[85]. EASL and AASLD/IDSA/IAS–USA2014 guidelines on HCV treatment do not recommend sofosbuvir in patients with estimated glomerular filtration rate (eGFR) of < 30 mL/min per 1.73 m2 or with ESRD until more data are available[55,86].

Apart from the above, there are also specific restrictions on co-administration of certain drug categories with each of DAAs mentioned above which may affect the plasma levels of these DAAs. For instance, sofosbuvir co-administration with drugs which induce P-glycoprotein like rifampin, carbamazepine, phenytoin or St. John’s wort are not allowed[85]. In the case of simeprevir, dose adjustments are needed with some medications that are commonly prescribed in CKD patients like anti-arrhythmics, warfarin, calcium channel blockers, antibiotics, antifungals and HMG Co-A reductase inhibitors[82]. As CKD patients are likely to be prescribed various medications for their co-morbidities, taking a good medication history and checking for drug-drug interactions are important steps before initiating treatment with DAAs.

Table 1 shows a summary of recommendations on HCV therapy in various stages of renal impairment according to the various guidelines. A summary of systematic reviews on the treatment of HCV in patients with renal disease is shown in Table 2.

**TREATMENT FOR HEPATITIS C RELATED GLOMERULONEPHRITIS**

In the current understanding of HCV related glomerulonephritis (GN), HCV is the infectious agent which cause GN. The renal disease shows injury from immune complex deposition and cryoglobulins. According to the recent AASLD/IDSA/IAS-USA hepatitis C guideline, HCV patients with type 2 or 3 essential mixed cryoglobulinemia and end-organ manifestations (*e.g.*, vasculitis), proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis are included in the highest priority for anti-HCV treatment due to the high risk for severe complications[87]. Progressive renal disease, proteinuria to the extent of nephrotic syndrome and hypertension are the main manifestations of GN. Therefore a multi-prong approach to the management of HCV related GN involves controlling the clinical manifestations and protecting the kidneys, eradicating HCV, and also reducing the formation and deposition of HCV containing immune complexes in the glomeruli. Anti-hypertensive and anti-proteinuric medications are reno-protective agents, which will delay progression of renal disease while anti-hyperlipidemic therapy may also be required. Diuretics administered together with angiotensin converting enzymes inhibitors and/or angiotensin receptor blockers were proven to be effective[88,89].

Data on specific treatment in HCV related GN was generally limited. Anti-viral therapies like IFN with or without ribavirin were studied in small number of clinical trials or pilot studies and the results were heterogenous. A systematic review on anti-viral therapy in symptomatic HCV-associated mixed cryoglobulinemia showed that combination therapy of PegIFN and ribavirin achieved SVR of 0.52 (95%CI: 0.40; 0.63) while conventional IFN plus ribavirin achieved SVR of 0.32 (95%CI: 0.15; 0.49)[90]. Other than anti-HCV treatment, immunosuppressive agents (cytotoxics and corticosteroids) and plasma exchange are also among the approach in treating HCV related GN. HCV related cryoglobulinemic GN is currently using a more targeted approach, which are anti-virals, B-cell depletion therapy and non-specific immunosuppressive therapy[91]. Fabrizi *et al*[92] in a recent review article on HCV-mixed cryoglobulinemia have divided treatment strategies based on clinical-biological presentation. The presentations were divided to mild to moderate disease, severe disease and life threatening[92]. Mild to moderate disease was defined as no worsening nephritis, polyneuropathy or other complications. Severe disease was defined as progressive motor neuropathy, worsening nephritis and extensive skin involvement. Life-threatening disease was defined as rapidly progressing GN, central nervous system (CNS), gastrointestinal with or without respiratory involvement.

Studies on anti-viral agents used in HCV related GN were mainly explored in small observational studies. Most of these studies showed positive effects of anti-viral therapy in terms of achieving SVR and clinical improvement[93-97]. In HCV-mixed cryoglobulinemia, the use of standard IFN alpha monotherapy showed high frequency of viral and clinical relapse[98,99]. Combination of IFN alpha with ribavirin has shown improvement in HCV-mixed cryoglobulinemia patients with cutaneous, kidney and neurologic manifestation[100] together with better rate of clinical and viral response[95]. In HCV-related GN, IFN alpha monotherapy was shown to improve proteinuria and HCV RNA clearance compared to immunosuppressive therapy with corticosteroids, but no significant improvement of kidney function by either treatment was observed[101]. The authors suggested that further well-designed study is needed. In a recent meta-analysis of 11 controlled and uncontrolled clinical studies on IFN-based anti-HCV therapy in CKD patients showed significantly decrease in proteinuria and stabilization of serum creatinine. Improvement in proteinuria is related to SVR but there was no association between serum creatinine and HCV RNA clearance[102].

Rituximab is an anti-CD20 monoclonal antibody which cause rapid depletions of B-cells and therefore interferes with cryoglobulins and monoclonal IgM production. In HCV-mixed cryoglobulinemia, the use of rituximab was shown to reduce proteinuria significantly[103] and achieve complete clinical response in up to 60%-70% of patients[104]. A prospective cohort study by Saadoun *et al*[97] showed that rituximab plus Peg-IFN and ribavirin produced better renal response rate (normalization of serum creatinine and resolution of proteinuria and/or hematuria), shorter time to clinical remission and higher rate of cryoglobulin clearance compared to Peg-IFN and ribavirin only therapy in HCV-mixed cryoglobulinemia patients[97]. Hence rituximab may be considered in severe or life-threatening disease.

Corticosteroids and other immunosuppressive agents like cyclophosphamide or azathioprine may be considered in life threatening HCV-mixed cryoglobulinemic vasculitis. High dose corticosteroids may induce remission during the acute stage. However, several studies that evaluated the use of immunosuppressive agents gave variable results with small success rates[23,105,106].

A problem with the use of steroids or immunosuppressive agents is the increase in HCV replications and consequent detrimental effects on the liver. Acute exacerbation with increase in serum transaminases and HCV RNA viral load had been reported in cancer patients with chronic hepatitis C who received treatment with chemotherapy and the use of rituximab is an associated risk factor[107]. The KDIGO guideline on GN noted that cyclical corticosteroids or alkylating agents is contraindicated in idiopathic membranous nephropathy when there is untreated infection including hepatitis C.

Plasmapheresis theoretically removes immune complexes and cryoglobulins[108]. It is usually performed during acute phase or life-threatening disease and is effective in rapidly progressive GN[109]. It may be useful in patients with poor response to anti-viral therapy or immunosuppressant.

The recent KDIGO clinical practice guideline for GN recommended the use of Peg-IFN alpha plus ribavirin in patients with moderate proteinuria, stable renal functions (CKD stages 1 and 2) and mild to moderate histological changes[110]. In nephrotic range proteinuria and/or rapid progressive GN and acute flare of cryoglobulinemia, rituximab or plasmapheresis, cyclophosphamide and intravenous corticosteroids should be given[9]. Once the acute phase has resolved, IFN-alpha therapy may be initiated to prevent exacerbation of cryoglobulinemic vasculitis[111]. It is unclear how soon the anti-HCV therapy should be initiated after starting the immunosuppressive agents; further research in the optimal treatment of this group of patients is required[104].

**TREATMENT FOR ACUTE HEPATITIS C IN CKD PATIENTS**

Acute hepatitis C occur among CKD populations mainly due to past blood transfusions, horizontal transmissions or even from nosocomial infections in dialysis unit. This is a concern as 85%-90% of untreated acute hepatitis C progress to chronic hepatitis C[112]. Data on treatment in acute HCV infection among CKD patients is limited, partly due to the silent nature of an acute HCV infection causing difficulty in the diagnosis. Spontaneous clearance of HCV RNA in acute hepatitis C occur in 5%-30% of patients[112-114], hence, KDIGO 2008 recommended waiting for a minimum 12 wk before initiating HCV treatment in CKD patients[9]. Treatment of acute hepatitis C in hemodialysis patients with conventional IFN achieved higher rate of HCV RNA clearance compared to those not treated. Patients given high dose IFN (6-10 million units three times per week) therapy are more likely to stop therapy compared to those on low dose IFN (3 million units three times per week) due to adverse events[113]. A study on acute hepatitis C hemodialysis patients, showed high SVR rate at 88.6% in those receiving Peg-IFN 135 mcg once per week *vs* 16.7% spontaneous viral clearance rate in the control group[115]. A meta-analysis on treatment of acute HCV in patients on dialysis with conventional or Peg-IFN showed SVR rates of 58% (95%CI: 38:77) and dropout rates of 9% (95%CI: 4:14)[116]. The higher SVR rate achieved in dialysis patients with acute HCV compared to chronic HCV underscore the need to treat acute HCV infection in hemodialysis patients to reduce the risk of chronicity.

**TREATMENT FOR CHRONIC HEPATITIS C IN HEMODIALYSIS PATIENTS**

The higher prevalence of HCV infection in hemodialysis patients compared to the general population, as well as robust data showing increased mortality in HCV positive hemodialysis patients and renal transplants patients and the higher risk of all cause renal graft loss are some of the reasons why HCV positive hemodialysis patients need to be treated[3,9,29,30,34]. Two meta-analyses by Fabrizi *et al*[117] found that SVR rate for HCV infected hemodialysis patients treated with conventional IFN monotherapy resulted in SVR of 39% and a drop-out rate of 19%[117], while for Peg-IFN monotherapy the SVR was 33% and drop-out rate was 23%[118]. The adverse effects were mainly anemia and gastrointestinal symptoms. However, late side effects such as neurological and cardiovascular adverse effects were the main reasons for discontinuation of therapy. The reason for the high occurrence of side effects was probably due to altered pharmacokinetics of IFN in ESRD patients; doubling of the plasma IFN concentration-time curve was observed in ESRD patients compared to normal kidney function patients[119]. Gradual increase in the IFN-alpha is an option to improve tolerability and achieve adequate dose of treatment and consequently better SVR. Treatment with Peg-IFN-α2b monotherapy beginning with a dose of 0.5 μg/kg per week, and gradually increasing every 4 wk to a maximum of 1 μg/kg per week resulted in an overall SVR rate of 50% while in genotype 3 patients the SVR rate was 80%[120].

Ribavirin is mainly removed by the kidneys and there is very little elimination by hemodialysis. The use of ribavirin in patients with ESRD, therefore, carries a significant risk of hemolytic anemia. A recent randomized trial compared Peg-IFN monotherapy *vs* the combination of Peg-IFN and ribavirin 200mg daily in treatment naïve HCV genotype 1 hemodialysis patients[121]. The combination therapy group had a significantly lower hemoglobin level (less than 8.5 g/dL) compared to monotherapy group (72% *vs* 6%, *P* < 0.001) but a significantly higher SVR rate (64% *vs* 33%, *P* < 0.001). The drop out rate was slightly higher in combination therapy group compared to monotherapy group (7% *vs* 4%). A systemic review revealed that combination therapy of Peg-IFN plus ribavirin in hemodialysis patients with HCV infection resulted in SVR rate of 56% and dropout rate of 25%[122]. Heart failure and anemia were recognized as the main reasons for the high dropout rate[102]. Patients for combination therapy with IFN and ribavirin are recommended to receive a lower dose of Ribavirin of 200-400 mg three times weekly with closer monitoring for anemia at weekly intervals. Other strategies to prevent worsening of anemia is to optimize the use of erythropoietin and intravenous iron supplement[9].

The role of triple therapy consisting of first generation PI with the backbone of Peg-IFN and ribavirin in long-term hemodialysis HCV-genotype 1 patients remains unclear. A pilot study on the use of telaprevir-based triple therapy reported efficacy with good tolerability in ESRD patients who previously failed to achieve SVR with Peg-IFN/ribavirin therapy. Three out of 4 patients achieved undetectable HCV RNA at 12 wk with telaprevir-based triple therapy[123]. In another study, therapy with telaprevir, Peg-IFN plus ribavirin was evaluated in 7 HCV-infected ESRD patients on hemodialysis; six out of 7 patients achieved SVR with the majority (5/7 patients) developing anemia < 10 g/dL[124]. Newer direct-acting antiviral agents are in the horizon, however as most studies or clinical trials did not include patients with abnormal renal function, the use of these newer anti-HCV treatments in patients with renal impairment requires further evaluation.

**TREATMENT FOR CHRONIC HEPATITIS C IN POST-KIDNEY TRANSPLANT PATIENTS**

In organ transplant setting, hepatitis C viral replications have been shown to increase significantly with chronic immunosuppression use and after corticosteroids treatment for acute rejection[125,126]. Treatment of HCV with IFN alpha after renal transplant showed variable graft rejections rates of 15%-100% and a 20% chance for permanent renal allograft failure[127]. A recent meta-analysis in HCV infected renal transplant patients who received anti-HCV therapy with conventional IFN or Peg-IFN with or without ribavirin found that the SVR rate was 26.6 % (95%CI: 15.0%–38.1%), dropout rate of 21.1% (95%CI: 10.9%–31.2%) and the graft rejection rate was 4% (95%CI: 0.8%-7.1%). In the Peg-IFN-based therapy the SVR was up to 40.6% and graft rejection rate was 4% while in conventional IFN-based therapy group, the SVR was only 20.9%, and graft dysfunction was 19.2%. Combination therapy of conventional IFN or Peg-IFN with ribavirin led to a better SVR rate compared to monotherapy, with the best results achieved with Peg-IFN and ribavirin combination[128]. In another study, it was shown that the risk of renal allograft rejection is higher in the first year post transplantation therefore delaying interferon treatment after the first anniversary of transplant is preferred[129]. However most guidelines do not recommend IFN treatment for HCV in kidney transplant recipients[9,26,55]. Initiating IFN therapy with the possibility of renal graft loss and return to the need for hemodialysis is probably justifiable and unavoidable in cases of severe rapidly progressive liver failure from fibrosing cholestatic hepatitis and life-threatening vasculitis[9]. Comprehensive discussion on the risks and benefits of such therapy must be made with the individual patient. As IFN treatment has a limited role in patients post renal transplant, studies on the use of IFN-free therapy in this group of patients is urgently required. The newer generation DAAs like sofosbuvir and daclatasvir have been reported to salvage liver transplant patients with HCV related fibrosing cholestasis[130].

There are limited data on the use of the new DAAs together with the calcineurin inhibitors like cyclosporins and tacrolimus in HCV-infected post renal transplant recipients. Prescribing information from boceprevir and telaprevir showed significant increase in plasma concentration of cyclosporin, sirolimus or tacrolimus, thus the plasma concentration level of these drugs should be monitored closely[77,131]. The AASLD/IDSA guideline does not recommend the co-administration of simeprevir and cyclosporine[132] based on a pharmacokinetic study of simeprevir, daclatasvir and ribavirin in recurrent hepatitis C patients after orthotopic liver transplant, where the simeprevir plasma concentration was found to be raised by 6-fold in the presence of cyclosporin[133]. According to the AASLD/IDSA guidelines, no dose adjustment is required for combination therapy of sofosbuvir and simeprevir when co-administered with tacrolimus based on studies in liver transplant patients.

**CONCLUSION**

HCV infection is strongly associated with CKD, as both the cause and the consequence. Furthermore, HCV imparts a major medical burden in renal patients and increases the mortality of ESRD patients whether maintained on hemodialysis or after renal transplant. Successful anti-HCV therapy in this setting ameliorates these poor outcomes. It is vital for clinicians involved in the care of HCV patients to recognize, diagnose and manage the kidney component of this viral infection. Annual testing for proteinuria and hematuria should be part of the screening tests in chronic hepatitis C patients. The management of HCV patients should also include prevention of modifiable risk factors for HCV related CKD like diabetes and hyperlipidemia. However without large-scale clinical trials in this subpopulation of HCV patients with associated kidney disease, the current recommendations and common day-to-day practice are based on extrapolation from the non-CKD population and incorporating necessary dose adjustments based on the pharmacology of these drugs. The poor tolerability and efficacy from current Peg-IFN and low dose ribavirin in HCV patients with ESRD, call for an urgent need for interferon-free anti-HCV regimens. Clinical studies on pharmacokinetics, safety and efficacy of the newer anti-HCV agents in this group of patients are ongoing[134]. With the rapid pace of development of the newer DAAs that we have been observing, interferon-free regimen may soon become a reality and will offer a new hope for everyone living with HCV.

**REFERENCES**

1 Chapter 1: Definition and classification of CKD. *Kidney Int Suppl (2011)* 2013; **3**: 19-62 [PMID: 25018975 DOI: 10.1038/kisup.2012.64]

2 **WHO.** Hepatitis C Factsheets. [accessed on 2014 August 1]. Available from: http: //www.who.int/mediacentre/factsheets/fs164/en/

3 **Wreghitt TG**. Blood-borne virus infections in dialysis units--a review. *Rev Med Virol* 1999; **9**: 101-109 [PMID: 10386337]

4 **Chan TM**, Lok AS, Cheng IK, Chan RT. Prevalence of hepatitis C virus infection in hemodialysis patients: a longitudinal study comparing the results of RNA and antibody assays. *Hepatology* 1993; **17**: 5-8 [PMID: 7678575]

5 **Li WC**, Lee YY, Chen IC, Wang SH, Hsiao CT, Loke SS. Age and gender differences in the relationship between hepatitis C infection and all stages of Chronic kidney disease. *J Viral Hepat* 2014; **21**: 706-715 [PMID: 24304473 DOI: 10.1111/jvh.12199]

6 **El-Serag HB**, Hampel H, Yeh C, Rabeneck L. Extrahepatic manifestations of hepatitis C among United States male veterans. *Hepatology* 2002; **36**: 1439-1445 [PMID: 12447870 DOI: 10.1053/jhep.2002.37191]

7 **Chen YC**, Lin HY, Li CY, Lee MS, Su YC. A nationwide cohort study suggests that hepatitis C virus infection is associated with increased risk of chronic kidney disease. *Kidney Int* 2014; **85**: 1200-1207 [PMID: 24257691 DOI: 10.1038/ki.2013.455]

8 **Lee JJ**, Lin MY, Yang YH, Lu SN, Chen HC, Hwang SJ. Association of hepatitis C and B virus infection with CKD in an endemic area in Taiwan: a cross-sectional study. *Am J Kidney Dis* 2010; **56**: 23-31 [PMID: 20400217 DOI: 10.1053/j.ajkd.2010.01.015]

9 KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int Suppl* 2008; **(109)**: S1-99 [PMID: 18382440 DOI: 10.1038/ki.2008.81]

10 **Fabrizi F**, Dixit V, Messa P. Impact of hepatitis C on survival in dialysis patients: a link with cardiovascular mortality? *J Viral Hepat* 2012; **19**: 601-607 [PMID: 22863263 DOI: 10.1111/j.1365-2893.2012.01633.x]

11 **Pawlotsky JM**. New hepatitis C virus (HCV) drugs and the hope for a cure: concepts in anti-HCV drug development. *Semin Liver Dis* 2014; **34**: 22-29 [PMID: 24782255 DOI: 10.1055/s-0034-1371007]

12 **Cacoub P**, Renou C, Rosenthal E, Cohen P, Loury I, Loustaud-Ratti V, Yamamoto AM, Camproux AC, Hausfater P, Musset L, Veyssier P, Raguin G, Piette JC. Extrahepatic manifestations associated with hepatitis C virus infection. A prospective multicenter study of 321 patients. The GERMIVIC. Groupe d'Etude et de Recherche en Medecine Interne et Maladies Infectieuses sur le Virus de l'Hepatite C. *Medicine (Baltimore)* 2000; **79**: 47-56 [PMID: 10670409]

13 **Tsui JI**, Vittinghoff E, Shlipak MG, Bertenthal D, Inadomi J, Rodriguez RA, O'Hare AM. Association of hepatitis C seropositivity with increased risk for developing end-stage renal disease. *Arch Intern Med* 2007; **167**: 1271-1276 [PMID: 17592100 DOI: 10.1001/archinte.167.12.1271]

14 **Lee JJ**, Lin MY, Chang JS, Hung CC, Chang JM, Chen HC, Yu ML, Hwang SJ. Hepatitis C virus infection increases risk of developing end-stage renal disease using competing risk analysis. *PLoS One* 2014; **9**: e100790 [PMID: 24971499 DOI: 10.1371/journal.pone.0100790]

15 **Dai CY**, Yeh ML, Huang CF, Hou CH, Hsieh MY, Huang JF, Lin IL, Lin ZY, Chen SC, Wang LY, Chuang WL, Yu ML, Tung HD. Chronic hepatitis C infection is associated with insulin resistance and lipid profiles. *J Gastroenterol Hepatol* 2013 [PMID: 23808794 DOI: 10.1111/jgh.12313]

16 **Ozkok A**, Yildiz A. Hepatitis C virus associated glomerulopathies. *World J Gastroenterol* 2014; **20**: 7544-7554 [PMID: 24976695 DOI: 10.3748/wjg.v20.i24.7544]

17 **Roccatello D**, Fornasieri A, Giachino O, Rossi D, Beltrame A, Banfi G, Confalonieri R, Tarantino A, Pasquali S, Amoroso A, Savoldi S, Colombo V, Manno C, Ponzetto A, Moriconi L, Pani A, Rustichelli R, Di Belgiojoso GB, Comotti C, Quarenghi MI. Multicenter study on hepatitis C virus-related cryoglobulinemic glomerulonephritis. *Am J Kidney Dis* 2007; **49**: 69-82 [PMID: 17185147 DOI: 10.1053/j.ajkd.2006.09.015]

18 **Sethi S**, Fervenza FC. Membranoproliferative glomerulonephritis--a new look at an old entity. *N Engl J Med* 2012; **366**: 1119-1131 [PMID: 22435371 DOI: 10.1056/NEJMra1108178]

19 **Bataille S**, Kaplanski G, Boucraut J, Halfon P, Camus C, Daniel L, Burtey S, Berland Y, Dussol B. Membranoproliferative glomerulonephritis and mixed cryoglobulinemia after hepatitis C virus infection secondary to glomerular NS3 viral antigen deposits. *Am J Nephrol* 2012; **35**: 134-140 [PMID: 22248563 DOI: 10.1159/000335375]

20 **Cao Y**, Zhang Y, Wang S, Zou W. Detection of the hepatitis C virus antigen in kidney tissue from infected patients with various glomerulonephritis. *Nephrol Dial Transplant* 2009; **24**: 2745-2751 [PMID: 19377056 DOI: 10.1093/ndt/gfp167]

21 **Fabrizi F**, Lunghi G, Messa P, Martin P. Therapy of hepatitis C virus-associated glomerulonephritis: current approaches. *J Nephrol* **21**; **21**: 813-825 [PMID: 19034865]

22 **Monti G**, Galli M, Invernizzi F, Pioltelli P, Saccardo F, Monteverde A, Pietrogrande M, Renoldi P, Bombardieri S, Bordin G. Cryoglobulinaemias: a multi-centre study of the early clinical and laboratory manifestations of primary and secondary disease. GISC. Italian Group for the Study of Cryoglobulinaemias. *QJM* 1995; **88**: 115-126 [PMID: 7704562]

23 **Tarantino A**, Campise M, Banfi G, Confalonieri R, Bucci A, Montoli A, Colasanti G, Damilano I, D'Amico G, Minetti L. Long-term predictors of survival in essential mixed cryoglobulinemic glomerulonephritis. *Kidney Int* 1995; **47**: 618-623 [PMID: 7723249]

24 **Castillo I**, Martinez-Ara J, Olea T, Bartolomé J, Madero R, Hernández E, Bernis C, Aguilar A, Quiroga JA, Carreño V, Selgas R. High prevalence of occult hepatitis C virus infection in patients with primary and secondary glomerular nephropathies. *Kidney Int* 2014; **86**: 619-624 [PMID: 24646855 DOI: 10.1038/ki.2014.68]

25 **Kong D**, Wu D, Wang T, Li T, Xu S, Chen F, Jin X, Lou G. Detection of viral antigens in renal tissue of glomerulonephritis patients without serological evidence of hepatitis B virus and hepatitis C virus infection. *Int J Infect Dis* 2013; **17**: e535-e538 [PMID: 23474175 DOI: 10.1016/j.ijid.2013.01.017]

26 **Omata M,** Kanda T, Yu M-L, Yokosuka O, Lim S-G, Jafri W, Tateishi R, Hamid SS, Chuang W-L, Chutaputti A. APASL consensus statements and management algorithms for hepatitis C virus infection. *Hepa Inter* 2012; **6**: 409-435 [DOI: 10.1007/s12072-012-9342-y]

27 **Fissell RB**, Bragg-Gresham JL, Woods JD, Jadoul M, Gillespie B, Hedderwick SA, Rayner HC, Greenwood RN, Akiba T, Young EW. Patterns of hepatitis C prevalence and seroconversion in hemodialysis units from three continents: the DOPPS. *Kidney Int* 2004; **65**: 2335-2342 [PMID: 15149347 DOI: 10.1111/j.1523-1755.2004.00649.x]

28 **Johnson DW**, Dent H, Yao Q, Tranaeus A, Huang CC, Han DS, Jha V, Wang T, Kawaguchi Y, Qian J. Frequencies of hepatitis B and C infections among haemodialysis and peritoneal dialysis patients in Asia-Pacific countries: analysis of registry data. *Nephrol Dial Transplant* 2009; **24**: 1598-1603 [PMID: 19096083 DOI: 10.1093/ndt/gfn684]

29 **Finelli L**, Miller JT, Tokars JI, Alter MJ, Arduino MJ. National surveillance of dialysis-associated diseases in the United States, 2002. *Semin Dial* 2005; **18**: 52-61 [PMID: 15663766 DOI: 10.1111/j.1525-139X.2005.18108.x]

30 **Di Napoli A**, Pezzotti P, Di Lallo D, Petrosillo N, Trivelloni C, Di Giulio S. Epidemiology of hepatitis C virus among long-term dialysis patients: a 9-year study in an Italian region. *Am J Kidney Dis* 2006; **48**: 629-637 [PMID: 16997059 DOI: 10.1053/j.ajkd.2006.07.004]

31 **Fabrizi F**, Martin P, Dixit V, Bunnapradist S, Dulai G. Meta-analysis: Effect of hepatitis C virus infection on mortality in dialysis. *Aliment Pharmacol Ther* 2004; **20**: 1271-1277 [PMID: 15606388 DOI: 10.1111/j.1365-2036.2004.02290.x]

32 **Chou CY**, Wang IK, Liu JH, Lin HH, Wang SM, Huang CC. Comparing survival between peritoneal dialysis and hemodialysis treatment in ESRD patients with chronic hepatitis C infection. *Perit Dial Int* 2010; **30**: 86-90 [PMID: 20056985]

33 **Bose B**, McDonald SP, Hawley CM, Brown FG, Badve SV, Wiggins KJ, Bannister KM, Boudville N, Clayton P, Johnson DW. Effect of dialysis modality on survival of hepatitis C-infected ESRF patients. *Clin J Am Soc Nephrol* 2011; **6**: 2657-2661 [PMID: 21903989 DOI: 10.2215/CJN.02200311]

34 **Fabrizi F**, Martin P, Dixit V, Messa P. Meta-analysis of observational studies: hepatitis C and survival after renal transplant. *J Viral Hepat* 2014; **21**: 314-324 [PMID: 24716634 DOI: 10.1111/jvh.12148]

35 **Aline-Fardin A**, Rifle G, Martin L, Justrabo E, Bour JB, D'Athis P, Tanter Y, Mousson C. Recurent and de novo membranous glomerulopathy after kidney transplantation. *Transplant Proc* 2009; **41**: 669-671 [PMID: 19328952 DOI: 10.1016/j.transproceed.2009.01.042]

36 **Morales JM**. Hepatitis C virus infection and renal disease after renal transplantation. *Transplant Proc* 2004; **36**: 760-762 [PMID: 15110654 DOI: 10.1016/j.transproceed.2004.03.041]

37 **Cruzado JM**, Carrera M, Torras J, Grinyó JM. Hepatitis C virus infection and de novo glomerular lesions in renal allografts. *Am J Transplant* 2001; **1**: 171-178 [PMID: 12099366]

38 **Delladetsima JK**, Boletis JN, Makris F, Psichogiou M, Kostakis A, Hatzakis A. Fibrosing cholestatic hepatitis in renal transplant recipients with hepatitis C virus infection. *Liver Transpl Surg* 1999; **5**: 294-300 [PMID: 10388502 DOI: 10.1002/lt.500050417]

39 **Delladetsima JK**, Makris F, Psichogiou M, Kostakis A, Hatzakis A, Boletis JN. Cholestatic syndrome with bile duct damage and loss in renal transplant recipients with HCV infection. *Liver* 2001; **21**: 81-88 [PMID: 11318976]

40 **de Oliveira Uehara SN**, Emori CT, da Silva Fucuta Pereira P, Perez RM, Pestana JO, Lanzoni VP, e Silva IS, Silva AE, Ferraz ML. Histological evolution of hepatitis C virus infection after renal transplantation. *Clin Transplant* 2012; **26**: 842-848 [PMID: 22594774 DOI: 10.1111/j.1399-0012.2012.01635.x]

41 **Roth D**, Gaynor JJ, Reddy KR, Ciancio G, Sageshima J, Kupin W, Guerra G, Chen L, Burke GW. Effect of kidney transplantation on outcomes among patients with hepatitis C. *J Am Soc Nephrol* 2011; **22**: 1152-1160 [PMID: 21546575 DOI: 10.1681/ASN.2010060668]

42 **Maluf DG**, Fisher RA, King AL, Gibney EM, Mas VR, Cotterell AH, Shiffman ML, Sterling RK, Behnke M, Posner MP. Hepatitis C virus infection and kidney transplantation: predictors of patient and graft survival. *Transplantation* 2007; **83**: 853-857 [PMID: 17460555 DOI: 10.1097/01.tp.0000259725.96694.0a]

43 **Pereira BJ**, Natov SN, Bouthot BA, Murthy BV, Ruthazer R, Schmid CH, Levey AS. Effects of hepatitis C infection and renal transplantation on survival in end-stage renal disease. The New England Organ Bank Hepatitis C Study Group. *Kidney Int* 1998; **53**: 1374-1381 [PMID: 9573555 DOI: 10.1046/j.1523-1755.1998.00883.x]

44 **Pereira BJ**, Wright TL, Schmid CH, Bryan CF, Cheung RC, Cooper ES, Hsu H, Heyn-Lamb R, Light JA, Norman DJ. Screening and confirmatory testing of cadaver organ donors for hepatitis C virus infection: a U.S. National Collaborative Study. *Kidney Int* 1994; **46**: 886-892 [PMID: 7527878]

45 **Kucirka LM**, Peters TG, Segev DL. Impact of donor hepatitis C virus infection status on death and need for liver transplant in hepatitis C virus-positive kidney transplant recipients. *Am J Kidney Dis* 2012; **60**: 112-120 [PMID: 22560841 DOI: 10.1053/j.ajkd.2012.03.015]

46 **Abbott KC**, Lentine KL, Bucci JR, Agodoa LY, Peters TG, Schnitzler MA. The impact of transplantation with deceased donor hepatitis c-positive kidneys on survival in wait-listed long-term dialysis patients. *Am J Transplant* 2004; **4**: 2032-2037 [PMID: 15575906 DOI: 10.1046/j.1600-6143.2004.00606.x]

47 **Widell A**, Månsson S, Persson NH, Thysell H, Hermodsson S, Blohme I. Hepatitis C superinfection in hepatitis C virus (HCV)-infected patients transplanted with an HCV-infected kidney. *Transplantation* 1995; **60**: 642-647 [PMID: 7570969]

48 **Wolf PL**, Williams D, Coplon N, Coulson AS. Low aspartate transaminase activity in serum of patients undergoing chronic hemodialysis. *Clin Chem* 1972; **18**: 567-568 [PMID: 5026769]

49 **Schrader C**, Schielke A, Ellerbroek L, Johne R. PCR inhibitors - occurrence, properties and removal. *J Appl Microbiol* 2012; **113**: 1014-1026 [PMID: 22747964 DOI: 10.1111/j.1365-2672.2012.05384.x]

50 **Liu CH**, Liang CC, Huang KW, Liu CJ, Chen SI, Lin JW, Hung PH, Tsai HB, Lai MY, Chen PJ, Chen JH, Chen DS, Kao JH. Transient elastography to assess hepatic fibrosis in hemodialysis chronic hepatitis C patients. *Clin J Am Soc Nephrol* 2011; **6**: 1057-1065 [PMID: 21393486 DOI: 10.2215/CJN.04320510]

51 **Pawa S**, Ehrinpreis M, Mutchnick M, Janisse J, Dhar R, Siddiqui FA. Percutaneous liver biopsy is safe in chronic hepatitis C patients with end-stage renal disease. *Clin Gastroenterol Hepatol* 2007; **5**: 1316-1320 [PMID: 17904916 DOI: 10.1016/j.cgh.2007.07.010]

52 **Fabrizi F**, Messa P, Martin P. Current status of renal transplantation from HCV-positive donors. *Int J Artif Organs* 2009; **32**: 251-261 [PMID: 19569034]

53 **Sterling RK**, Sanyal AJ, Luketic VA, Stravitz RT, King AL, Post AB, Mills AS, Contos MJ, Shiffman ML. Chronic hepatitis C infection in patients with end stage renal disease: characterization of liver histology and viral load in patients awaiting renal transplantation. *Am J Gastroenterol* 1999; **94**: 3576-3582 [PMID: 10606322 DOI: 10.1111/j.1572-0241.1999.01649.x]

54 **Martin P**, Carter D, Fabrizi F, Dixit V, Conrad AJ, Artinian L, Peacock V, Han S, Wilkinson A, Lassman CR, Danovitch G. Histopathological features of hepatitis C in renal transplant candidates [see comment]. *Transplantation* 2000; **69**: 1479-1484 [PMID: 10798774]

55 . EASL recommendations on treatment of hepatitis C 2014. *J Hepatol* 2014; **61**: 373-395 [PMID: 24818984 DOI: 10.1016/j.jhep.2014.05.001]

56 **Jiang Y**, Huang E, Mehrnia A, Kamgar M, Pham PT, Ogunorunyinka O, Brown I, Danovitch GM, Bunnapradist S. Can aminotransferase-to-platelet ratio index and other non-invasive markers effectively reduce liver biopsies for renal transplant evaluation of hepatitis C virus-positive patients? *Nephrol Dial Transplant* 2014; **29**: 1247-1252 [PMID: 24353319 DOI: 10.1093/ndt/gft485]

57 **Liu CH**, Liang CC, Liu CJ, Hsu SJ, Lin JW, Chen SI, Hung PH, Tsai HB, Lai MY, Chen PJ, Chen JH, Chen DS, Kao JH. The ratio of aminotransferase to platelets is a useful index for predicting hepatic fibrosis in hemodialysis patients with chronic hepatitis C. *Kidney Int* 2010; **78**: 103-109 [PMID: 20357753 DOI: 10.1038/ki.2010.74]

58 **Shaheen AA**, Wan AF, Myers RP. FibroTest and FibroScan for the prediction of hepatitis C-related fibrosis: a systematic review of diagnostic test accuracy. *Am J Gastroenterol* 2007; **102**: 2589-2600 [PMID: 17850410 DOI: 10.1111/j.1572-0241.2007.01466.x]

59 **Goodkin DA**, Bieber B, Gillespie B, Robinson BM, Jadoul M. Hepatitis C infection is very rarely treated among hemodialysis patients. *Am J Nephrol* 2013; **38**: 405-412 [PMID: 24192505 DOI: 10.1159/000355615]

60 **Gürsoy M**, Güvener N, Köksal R, Karavelioğlu D, Baysal C, Ozdemir N, Boyacioğlu S, Bilgin N, Erdal R. Impact of HCV infection on development of posttransplantation diabetes mellitus in renal allograft recipients. *Transplant Proc* 2000; **32**: 561-562 [PMID: 10812113]

61 **Mahmoud IM**, Sobh MA, El-Habashi AF, Sally ST, El-Baz M, El-Sawy E, Ghoneim MA. Interferon therapy in hemodialysis patients with chronic hepatitis C: study of tolerance, efficacy and post-transplantation course. *Nephron Clin Pract* 2005; **100**: c133-c139 [PMID: 15855796 DOI: 10.1159/000085442]

62 **Cruzado JM**, Casanovas-Taltavull T, Torras J, Baliellas C, Gil-Vernet S, Grinyó JM. Pretransplant interferon prevents hepatitis C virus-associated glomerulonephritis in renal allografts by HCV-RNA clearance. *Am J Transplant* 2003; **3**: 357-360 [PMID: 12614294]

63 **van der Meer AJ**, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, Heathcote EJ, Manns MP, Kuske L, Zeuzem S, Hofmann WP, de Knegt RJ, Hansen BE, Janssen HL. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012; **308**: 2584-2593 [PMID: 23268517 DOI: 10.1001/jama.2012.144878]

64 **Hsu YC**, Lin JT, Ho HJ, Kao YH, Huang YT, Hsiao NW, Wu MS, Liu YY, Wu CY. Antiviral treatment for hepatitis C virus infection is associated with improved renal and cardiovascular outcomes in diabetic patients. *Hepatology* 2014; **59**: 1293-1302 [PMID: 24122848 DOI: 10.1002/hep.26892]

65 **Gordon CE**, Uhlig K, Schmid CH, Levey AS, Wong JB. Long-term viral negativity after interferon for chronic hepatitis C virus infection in hemodialysis. *Clin J Am Soc Nephrol* 2011; **6**: 2226-2234 [PMID: 21784816 DOI: 10.2215/CJN.00410111]

66 **Pegasys Prescribing Information.** [Accessed on 15 July 2014] Available from: URL: http: //www.gene.com/download/pdf/pegasys\_prescribing.pdf

67 **Gupta SK**, Pittenger AL, Swan SK, Marbury TC, Tobillo E, Batra V, Sack M, Glue P, Jacobs S, Affrime M. Single-dose pharmacokinetics and safety of pegylated interferon-alpha2b in patients with chronic renal dysfunction. *J Clin Pharmacol* 2002; **42**: 1109-1115 [PMID: 12362925]

68 **Brennan BJ**, Wang K, Blotner S, Magnusson MO, Wilkins JJ, Martin P, Solsky J, Nieforth K, Wat C, Grippo JF. Safety, tolerability, and pharmacokinetics of ribavirin in hepatitis C virus-infected patients with various degrees of renal impairment. *Antimicrob Agents Chemother* 2013; **57**: 6097-6105 [PMID: 24080649 DOI: 10.1128/AAC.00608-13]

69 **Alavian SM**, Tabatabaei SV. Meta-analysis of factors associated with sustained viral response in patients on hemodialysis treated with standard or pegylated interferon for hepatitis C infection. *Iran J Kidney Dis* 2010; **4**: 181-194 [PMID: 20622305]

70 **Yu YC**, Wang Y, He CL, Wang MR, Wang YM. Management of hepatitis C virus infection in hemodialysis patients. *World J Hepatol* 2014; **6**: 419-425 [PMID: 25018852 DOI: 10.4254/wjh.v6.i6.419]

71 **Njoroge FG**, Chen KX, Shih NY, Piwinski JJ. Challenges in modern drug discovery: a case study of boceprevir, an HCV protease inhibitor for the treatment of hepatitis C virus infection. *Acc Chem Res* 2008; **41**: 50-59 [PMID: 18193821 DOI: 10.1021/ar700109k]

72 **Poordad F**, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, Jacobson IM, Reddy KR, Goodman ZD, Boparai N, DiNubile MJ, Sniukiene V, Brass CA, Albrecht JK, Bronowicki JP. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1195-1206 [PMID: 21449783 DOI: 10.1056/NEJMoa1010494]

73 **Bacon BR**, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, Poordad F, Goodman ZD, Sings HL, Boparai N, Burroughs M, Brass CA, Albrecht JK, Esteban R. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1207-1217 [PMID: 21449784 DOI: 10.1056/NEJMoa1009482]

74 **Treitel M**, Marbury T, Preston RA, Triantafyllou I, Feely W, O'Mara E, Kasserra C, Gupta S, Hughes EA. Single-dose pharmacokinetics of boceprevir in subjects with impaired hepatic or renal function. *Clin Pharmacokinet* 2012; **51**: 619-628 [PMID: 22799589 DOI: 10.2165/11633440-000000000-00000]

75 **Zeuzem S**, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, Focaccia R, Younossi Z, Foster GR, Horban A, Ferenci P, Nevens F, Müllhaupt B, Pockros P, Terg R, Shouval D, van Hoek B, Weiland O, Van Heeswijk R, De Meyer S, Luo D, Boogaerts G, Polo R, Picchio G, Beumont M. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011; **364**: 2417-2428 [PMID: 21696308 DOI: 10.1056/NEJMoa1013086]

76 **Matthews SJ**, Lancaster JW. Telaprevir: a hepatitis C NS3/4A protease inhibitor. *Clin Ther* 2012; **34**: 1857-1882 [PMID: 22951253 DOI: 10.1016/j.clinthera.2012.07.011]

77 **Vertex.** Incivek (Telaprevir) Prescribing Information. [Accessed on 27th August 2014] Available from: URL: http: //pi.vrtx.com/files/uspi\_telaprevir.pdf

78 **Mauss S**, Hueppe D, Alshuth U. Renal impairment is frequent in chronic hepatitis C patients under triple therapy with telaprevir or boceprevir. *Hepatology* 2014; **59**: 46-48 [PMID: 23813604 DOI: 10.1002/hep.26602]

79 **Virlogeux V**, Pradat P, Bailly F, Funingana G, Gonçalves F, Maynard M, Hartig-Lavie K, Amiri M, Zoulim F. Boceprevir and telaprevir-based triple therapy for chronic hepatitis C: virological efficacy and impact on kidney function and model for end-stage liver disease score. *J Viral Hepat* 2014; **21**: e98-e107 [PMID: 24612466 DOI: 10.1111/jvh.12237]

80 **Loustaud-Ratti V**, Rousseau A, Carrier P, Vong C, Chambaraud T, Jacques J, Debette-Gratien M, Sautereau D, Essig M. eGFR decrease during antiviral C therapy with first generation protease inhibitors: a clinical significance? *Liver Int* 2014 [PMID: 25039814 DOI: 10.1111/liv.12631]

81 **Forns X**, Lawitz E, Zeuzem S, Gane E, Bronowicki JP, Andreone P, Horban A, Brown A, Peeters M, Lenz O, Ouwerkerk-Mahadevan S, Scott J, De La Rosa G, Kalmeijer R, Sinha R, Beumont-Mauviel M. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: a phase 3 trial. *Gastroenterology* 2014; **146**: 1669-79.e3 [PMID: 24602923 DOI: 10.1053/j.gastro.2014.02.051]

82 Janssen. Olysio (Simeprevir) Prescribing Information. [Accessed 3rd August 2014] Available from: URL: http: //www.olysio.com/shared/product/olysio/prescribing-information.pdf

83 **Lawitz E**, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, Schultz M, Davis MN, Kayali Z, Reddy KR, Jacobson IM, Kowdley KV, Nyberg L, Subramanian GM, Hyland RH, Arterburn S, Jiang D, McNally J, Brainard D, Symonds WT, McHutchison JG, Sheikh AM, Younossi Z, Gane EJ. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013; **368**: 1878-1887 [PMID: 23607594 DOI: 10.1056/NEJMoa1214853]

84 **Jacobson IM**, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, Shiffman ML, Lawitz E, Everson G, Bennett M, Schiff E, Al-Assi MT, Subramanian GM, An D, Lin M, McNally J, Brainard D, Symonds WT, McHutchison JG, Patel K, Feld J, Pianko S, Nelson DR. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013; **368**: 1867-1877 [PMID: 23607593 DOI: 10.1056/NEJMoa1214854]

85 Gilead. Sovaldi (Sofosbuvir) Prescribing Information. [Accessed on 2nd August 2014] Available from: URL: http: //www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi\_pi.pdf

86 **AASLD/IDSA/IAS-USA.** Unique Patient Populations: Renal Impairment Box. Summary of recommendations for Patients with Renal Impairment Including Severe Renal Impairment (CrCl <30 ML/min) or ESRD Requiring Hemodialysis or Peritoneal Dialysis. [Accessed 26th August 2014] Available from: URL: http: //hcvguidelines.org/full-report/unique-patient-populations-renal-impairment-box-summary-recommendations-patients-renal

87 **AASLD/IDSA/IAS-USA.** When and in Whom to Initiate HCV Therapy. [Accessed 26th August 2014] Available from: URL: http: //hcvguidelines.org/full-report/when-and-whom-initiate-hcv-therapy

88 **Klahr S**, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, Striker G. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med* 1994; **330**: 877-884 [PMID: 8114857 DOI: 10.1056/NEJM199403313301301]

89 **GISEN.** Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia) *Lancet* 1997; **349**: 1857-1863 [PMID: 9217756]

90 **Fabrizi F**, Dixit V, Messa P. Antiviral therapy of symptomatic HCV-associated mixed cryoglobulinemia: meta-analysis of clinical studies. *J Med Virol* 2013; **85**: 1019-1027 [PMID: 23588727 DOI: 10.1002/jmv.23562]

91 **Fabrizi F**, Donato F, Messa P. Hepatitis C virus infection and glomerular disease. *Minerva Urol Nefrol* 2014; **66**: 139-149 [PMID: 24988205]

92 **Fabrizi F**, Plaisier E, Saadoun D, Martin P, Messa P, Cacoub P. Hepatitis C virus infection, mixed cryoglobulinemia, and kidney disease. *Am J Kidney Dis* 2013; **61**: 623-637 [PMID: 23102733 DOI: 10.1053/j.ajkd.2012.08.040]

93 **Bruchfeld A**, Lindahl K, Ståhle L, Söderberg M, Schvarcz R. Interferon and ribavirin treatment in patients with hepatitis C-associated renal disease and renal insufficiency. *Nephrol Dial Transplant* 2003; **18**: 1573-1580 [PMID: 12897097]

94 **Alric L**, Plaisier E, Thébault S, Péron JM, Rostaing L, Pourrat J, Ronco P, Piette JC, Cacoub P. Influence of antiviral therapy in hepatitis C virus-associated cryoglobulinemic MPGN. *Am J Kidney Dis* 2004; **43**: 617-623 [PMID: 15042538]

95 **Saadoun D**, Resche-Rigon M, Thibault V, Piette JC, Cacoub P. Antiviral therapy for hepatitis C virus--associated mixed cryoglobulinemia vasculitis: a long-term followup study. *Arthritis Rheum* 2006; **54**: 3696-3706 [PMID: 17075881 DOI: 10.1002/art.22168]

96 **Garini G**, Allegri L, Lannuzzella F, Vaglio A, Buzio C. HCV-related cryoglobulinemic glomerulonephritis: implications of antiviral and immunosuppressive therapies. *Acta Biomed* 2007; **78**: 51-59 [PMID: 17687818]

97 **Saadoun D**, Resche Rigon M, Sene D, Terrier B, Karras A, Perard L, Schoindre Y, Coppéré B, Blanc F, Musset L, Piette JC, Rosenzwajg M, Cacoub P. Rituximab plus Peg-interferon-alpha/ribavirin compared with Peg-interferon-alpha/ribavirin in hepatitis C-related mixed cryoglobulinemia. *Blood* 2010; **116**: 326-34; quiz 504-5 [PMID: 20439619 DOI: 10.1182/blood-2009-10-248518]

98 **Naarendorp M**, Kallemuchikkal U, Nuovo GJ, Gorevic PD. Longterm efficacy of interferon-alpha for extrahepatic disease associated with hepatitis C virus infection. *J Rheumatol* 2001; **28**: 2466-2473 [PMID: 11708420]

99 **Casato M**, Agnello V, Pucillo LP, Knight GB, Leoni M, Del Vecchio S, Mazzilli C, Antonelli G, Bonomo L. Predictors of long-term response to high-dose interferon therapy in type II cryoglobulinemia associated with hepatitis C virus infection. *Blood* 1997; **90**: 3865-3873 [PMID: 9354653]

100 **Zuckerman E**, Keren D, Slobodin G, Rosner I, Rozenbaum M, Toubi E, Sabo E, Tsykounov I, Naschitz JE, Yeshurun D. Treatment of refractory, symptomatic, hepatitis C virus related mixed cryoglobulinemia with ribavirin and interferon-alpha. *J Rheumatol* 2000; **27**: 2172-2178 [PMID: 10990230]

101 **Fabrizi F**, Bruchfeld A, Mangano S, Dixit V, Messa P, Martin P. Interferon therapy for HCV-associated glomerulonephritis: meta-analysis of controlled trials. *Int J Artif Organs* 2007; **30**: 212-219 [PMID: 17417760]

102 **Feng B**, Eknoyan G, Guo ZS, Jadoul M, Rao HY, Zhang W, Wei L. Effect of interferon-alpha-based antiviral therapy on hepatitis C virus-associated glomerulonephritis: a meta-analysis. *Nephrol Dial Transplant* 2012; **27**: 640-646 [PMID: 21558431 DOI: 10.1093/ndt/gfr236]

103 **Quartuccio L**, Soardo G, Romano G, Zaja F, Scott CA, De Marchi G, Fabris M, Ferraccioli G, De Vita S. Rituximab treatment for glomerulonephritis in HCV-associated mixed cryoglobulinaemia: efficacy and safety in the absence of steroids. *Rheumatology (Oxford)* 2006; **45**: 842-846 [PMID: 16418196 DOI: 10.1093/rheumatology/kel004]

104 **Cacoub P**, Delluc A, Saadoun D, Landau DA, Sene D. Anti-CD20 monoclonal antibody (rituximab) treatment for cryoglobulinemic vasculitis: where do we stand? *Ann Rheum Dis* 2008; **67**: 283-287 [PMID: 17644544 DOI: 10.1136/ard.2006.065565]

105 **Misiani R**, Bellavita P, Fenili D, Vicari O, Marchesi D, Sironi PL, Zilio P, Vernocchi A, Massazza M, Vendramin G. Interferon alfa-2a therapy in cryoglobulinemia associated with hepatitis C virus. *N Engl J Med* 1994; **330**: 751-756 [PMID: 8107741 DOI: 10.1056/NEJM199403173301104]

106 **Dammacco F**, Sansonno D, Han JH, Shyamala V, Cornacchiulo V, Iacobelli AR, Lauletta G, Rizzi R. Natural interferon-alpha versus its combination with 6-methyl-prednisolone in the therapy of type II mixed cryoglobulinemia: a long-term, randomized, controlled study. *Blood* 1994; **84**: 3336-3343 [PMID: 7524736]

107 **Mahale P**, Kontoyiannis DP, Chemaly RF, Jiang Y, Hwang JP, Davila M, Torres HA. Acute exacerbation and reactivation of chronic hepatitis C virus infection in cancer patients. *J Hepatol* 2012; **57**: 1177-1185 [PMID: 22871500 DOI: 10.1016/j.jhep.2012.07.031]

108 **Koziolek MJ**, Scheel A, Bramlage C, Groene HJ, Mueller GA, Strutz F. Effective treatment of hepatitis C-associated immune-complex nephritis with cryoprecipitate apheresis and antiviral therapy. *Clin Nephrol* 2007; **67**: 245-249 [PMID: 17474561]

109 **Saadoun D**, Delluc A, Piette JC, Cacoub P. Treatment of hepatitis C-associated mixed cryoglobulinemia vasculitis. *Curr Opin Rheumatol* 2008; **20**: 23-28 [PMID: 18281853 DOI: 10.1097/BOR.0b013e3282f1330c]

110 **KDIGO.** Chapter 9: Infection-related glomerulonephritis. *Kidney Int Suppl (2011)* 2012; **2**: 200-208 [PMID: 25018934 DOI: 10.1038/kisup.2012.22]

111 **Cid MC**, Hernández-Rodríguez J, Robert J, del Río A, Casademont J, Coll-Vinent B, Grau JM, Kleinman HK, Urbano-Márquez A, Cardellach F. Interferon-alpha may exacerbate cryoblobulinemia-related ischemic manifestations: an adverse effect potentially related to its anti-angiogenic activity. *Arthritis Rheum* 1999; **42**: 1051-1055 [PMID: 10323463 DOI: 10.1002/1529-0131(199905)42: 5<1051: : AID-ANR26>3.0.CO; 2-Q]

112 **Espinosa M**, Martin-Malo A, Alvarez de Lara MA, Gonzalez R, Rodriguez M, Aljama P. Natural history of acute HCV infection in hemodialysis patients. *Clin Nephrol* 2002; **58**: 143-150 [PMID: 12227687]

113 **Gürsoy M**, Gür G, Arslan H, Ozdemir N, Boyacioglu S. Interferon therapy in haemodialysis patients with acute hepatitis C virus infection and factors that predict response to treatment. *J Viral Hepat* 2001; **8**: 70-77 [PMID: 11155154]

114 **Furusyo N**, Hayashi J, Kakuda K, Ariyama I, Kanamoto-Tanaka Y, Shimizu C, Etoh Y, Shigematsu M, Kashiwagi S. Acute hepatitis C among Japanese hemodialysis patients: a prospective 9-year study. *Am J Gastroenterol* 2001; **96**: 1592-1600 [PMID: 11374705 DOI: 10.1111/j.1572-0241.2001.03701.x]

115 **Liu CH**, Liang CC, Liu CJ, Lin JW, Chen SI, Hung PH, Tsai HB, Lai MY, Chen PJ, Chen DS, Kao JH. Pegylated interferon alfa-2a monotherapy for hemodialysis patients with acute hepatitis C. *Clin Infect Dis* 2010; **51**: 541-549 [PMID: 20645865 DOI: 10.1086/655682]

116 **Fabrizi F**, Dixit V, Messa P, Martin P. Interferon therapy of acute hepatitis C in dialysis patients: meta-analysis. *J Viral Hepat* 2012; **19**: 784-791 [PMID: 23043385 DOI: 10.1111/j.1365-2893.2012.01607.x]

117 **Fabrizi F**, Dixit V, Messa P, Martin P. Interferon monotherapy of chronic hepatitis C in dialysis patients: meta-analysis of clinical trials. *J Viral Hepat* 2008; **15**: 79-88 [PMID: 18184190 DOI: 10.1111/j.1365-2893.2007.00907.x]

118 **Fabrizi F**, Dixit V, Messa P, Martin P. Pegylated interferon monotherapy of chronic hepatitis C in dialysis patients: Meta-analysis of clinical trials. *J Med Virol* 2010; **82**: 768-775 [PMID: 20336712 DOI: 10.1002/jmv.21542]

119 **Rostaing L**, Chatelut E, Payen JL, Izopet J, Thalamas C, Ton-That H, Pascal JP, Durand D, Canal P. Pharmacokinetics of alphaIFN-2b in chronic hepatitis C virus patients undergoing chronic hemodialysis or with normal renal function: clinical implications. *J Am Soc Nephrol* 1998; **9**: 2344-2348 [PMID: 9848789]

120 **Tan SS**, Abu Hassan MR, Abdullah A, Ooi BP, Korompis T, Merican MI. Safety and efficacy of an escalating dose regimen of pegylated interferon alpha-2b in the treatment of haemodialysis patients with chronic hepatitis C. *J Viral Hepat* 2010; **17**: 410-418 [PMID: 19758272 DOI: 10.1111/j.1365-2893.2009.01191.x]

121 **Liu CH**, Huang CF, Liu CJ, Dai CY, Liang CC, Huang JF, Hung PH, Tsai HB, Tsai MK, Chen SI, Lin JW, Yang SS, Su TH, Yang HC, Chen PJ, Chen DS, Chuang WL, Yu ML, Kao JH. Pegylated interferon-α2a with or without low-dose ribavirin for treatment-naive patients with hepatitis C virus genotype 1 receiving hemodialysis: a randomized trial. *Ann Intern Med* 2013; **159**: 729-738 [PMID: 24297189 DOI: 10.7326/0003-4819-159-11-201312030-00005]

122 **Fabrizi F**, Dixit V, Martin P, Messa P. Combined antiviral therapy of hepatitis C virus in dialysis patients: meta-analysis of clinical trials. *J Viral Hepat* 2011; **18**: e263-e269 [PMID: 21108701 DOI: 10.1111/j.1365-2893.2010.01405.x]

123 **Dumortier J**, Guillaud O, Gagnieu MC, Janbon B, Juillard L, Morelon E, Leroy V. Anti-viral triple therapy with telaprevir in haemodialysed HCV patients: is it feasible? *J Clin Virol* 2013; **56**: 146-149 [PMID: 23149155 DOI: 10.1016/j.jcv.2012.10.009]

124 **Wiegand J**, Maasoumy B, Buggisch P, Buslau A, Schiefke I, Berg T, Wedemeyer H, Sarrazin C, Hinrichsen H. Letter: Telaprevir triple therapy in chronic hepatitis C genotype 1 patients receiving haemodialysis. *Aliment Pharmacol Ther* 2014; **39**: 1342-1344 [PMID: 24803258 DOI: 10.1111/apt.12748]

125 **Rostaing L**, Izopet J, Sandres K, Cisterne JM, Puel J, Durand D. Changes in hepatitis C virus RNA viremia concentrations in long-term renal transplant patients after introduction of mycophenolate mofetil. *Transplantation* 2000; **69**: 991-994 [PMID: 10755563]

126 **Gane EJ**, Naoumov NV, Qian KP, Mondelli MU, Maertens G, Portmann BC, Lau JY, Williams R. A longitudinal analysis of hepatitis C virus replication following liver transplantation. *Gastroenterology* 1996; **110**: 167-177 [PMID: 8536853]

127 **Okoh EJ**, Bucci JR, Simon JF, Harrison SA. HCV in patients with end-stage renal disease. *Am J Gastroenterol* 2008; **103**: 2123-2134 [PMID: 18796105 DOI: 10.1111/j.1572-0241.2008.01981.x]

128 **Wei F**, Liu J, Liu F, Hu H, Ren H, Hu P. Interferon-based anti-viral therapy for hepatitis C virus infection after renal transplantation: an updated meta-analysis. *PLoS One* 2014; **9**: e90611 [PMID: 24699257 DOI: 10.1371/journal.pone.0090611]

129 **Baid S**, Tolkoff-Rubin N, Saidman S, Chung R, Williams WW, Auchincloss H, Colvin RB, Delmonico FL, Cosimi AB, Pascual M. Acute humoral rejection in hepatitis C-infected renal transplant recipients receiving antiviral therapy. *Am J Transplant* 2003; **3**: 74-78 [PMID: 12492714]

130 **Fontana RJ**, Hughes EA, Bifano M, Appelman H, Dimitrova D, Hindes R, Symonds WT. Sofosbuvir and daclatasvir combination therapy in a liver transplant recipient with severe recurrent cholestatic hepatitis C. *Am J Transplant* 2013; **13**: 1601-1605 [PMID: 23593993 DOI: 10.1111/ajt.12209]

131 Merck. Victrelis Prescribing Information. [Accessed 5th October 2014] Available from: URL: http: //www.merck.com/product/usa/pi\_circulars/v/victrelis/victrelis\_pi.pdf

132 **AASLD/IDSA/IAS-USA.** Recommendations for Testing, Managing, and Treating Hepatitis C. [accessed on 26th August 2014] Available from: URL: http: //hcvguidelines.org/full-report-view

133 **JanssenR&D.** A study of pharmacokinetics, efficacy, safety, tolerability, of the combination of simeprevir (TMC435), daclatasvir (BMS-790052), and ribavirin (RBV) in patients with recurrent chronic hepatitis C genotype 1b infection after orthotopic liver transplantation (posted 2013b). [Accessed on 2 October 2014] Available from: URL: http: //www.clinicaltrials.gov/ct2/show/NCT01938625

134 **ClinicalTrials.gov.** Clinical Trials on Chronic Hepatitis C. [Accessed 26th August 2014] Available from: URL: http: //clinicaltrials.gov/

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**Table 1 Summary of recommendations on hepatitis C virus therapy in various stages of renal impairment according to guidelines**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **CKD stage** | **KDIGO 2008** | **APASL 2012** | **EASL 2014** | **AASLD/IDSA/IAS–USA2014** |
| **Stage 1 and 2**Stage 1 = GFR ≥ 90 mL/min per 1.73 m2Stage 2 = GFR 60- 89 mL/min per 1.73 m2 | Peg-IFN and ribavirinDose of ribavirin to be titrated to patient’s tolerance | Peg-IFN and ribavirin |  | Peg-IFN and ribavirin/sofosbuvir/simeprevirDose of:(1) Peg-IFN 2a is 180 ug/wk(2) Peg-IFN 2b is 1.5 ug/kg per week 1. Ribavirin is 1000 mg or 1200 mg if body weight < 75 kg or ≥ 75 kg

(4) Sofosbuvir is 400 mg daily(5) Simeprevir is 150 mg daily |
| **Stage 3, 4 and 5**Stage 3 = GFR 30-59 mL/min per 1.73 m2Stage 4 = GFR 15-29 mL/min per 1.73 m2Stage 5 = GFR < 15 mL/min per 1.73 m2 | Peg-IFNDose of Peg-IFN to be adjusted to renal function | Peg-IFN and ribavirinDose of:(1) Peg-IFN 2a is 135 ug/wk(2) Peg-IFN 2b is 1 ug/kg per week(3) Ribavirin is 200-800 mg/d |  | **For GFR = 30-50 mL/min per 1.73 m2**Peg-IFN and ribavirin/sofosbuvir/simeprevirDose of:(1) Peg-IFN 2a is 180 ug/wk(2) Peg-IFN 2b is 1 ug/kg per week or 25% reduction.(3) Ribavirin is alternating doses200 and 400 mg every other day.(4) Sofosbuvir is 400 mg daily(5) Simeprevir is 150 mg daily**For GFR < 30 mL/min per 1.73 m2**Peg-IFN and ribavirin/simeprevirDose of:(1) Peg-IFN 2a is 135 ug/wk(2) Peg-IFN 2b is 1 ug/kg per week or 50% reduction.(3) Ribavirin is 200 mg daily(4) Simeprevir is 150 mg daily |
| **Stage 5D** GFR < 15 mL/min per 1.73 m2 on maintenance hemodialysis | Conventional IFNDose to be adjusted to a GFR < 15 mL/min per 1.73 m2 | Conventional IFN or Peg-IFN and markedly reduced dose of ribavirin.Dose of:(1) Peg-IFN 2a is 135 ug/wk(2) Peg-IFN 2b is 1 ug/kg per week | IFN free and if possible ribavirin free but no safety and efficacy data | Peg-IFN or conventional IFN and ribavirinDose of:(1) Peg-IFN 2a is 135 ug/wk(2) Peg-IFN 2b is 1 ug/kg per week (3) Conventional IFN is 3 mU 3x/wk(4) Ribavirin is 200 mg/d |

CKD: Chronic kidney disease; KDIGO: Kidney Disease Improving Global Outcome; APASL: Asian Pacific Association for the Study of the Liver; EASL: European Association for the Study of the Liver; AASLD: American Association for the Study of Liver Disease; IDSA: Infectious Disease Society of America; IAS-USA: International Antiviral Society-United States of America; Peg-IFN: pegylated interferon; IFN: interferon. KDIGO 2008: Patients with genotypes 1 or 4 is for 48 wk of therapy if an early virological response (EVR) is obtained at 12 wk (> 2 log fall in viral titer). Genotype 2 or 3 is for 24 wk[9]. APASL 2012: Patients with genotypes 1 is for 48 weeks treatment if achieve a complete EVR at week12, if achieved rapid virological response (HCVRNA undetectable) at week 4 and HCV RNA at baseline is < 400000 IU/mL for shorten treatment to 24 wk and if not achieve an EVR at week 12, but show a significant reduction in HCV RNA levels (partial EVR) and negativity of HCV RNA at week 24 (late virological response, LVR), treatment may be continued up to 72 wk. For Genotype 2 or 3 is 24 wk treatment[26]. EASL 2014: Regimens for patients with genotype 1 are 12 wk of sofosbuvir/ribavirin/Peg-IFN or 12 wk of sofosbuvir/simeprevir/ribavirin or 24 wk of sofosbuvir/ribavirin. For genotype 2 is 12 wk of sofosbuvir/ribavirin. For genotype 3 are 24 wk of sofosbuvir/ribavirin or 12 wk of sofosbuvir/ribavirin/Peg-IFN. For genotype 4 are 12 wk of sofosbuvir/ribavirin/Peg-IFN or 24 wk of sofosbuvir/ribavirin or 24 wk Peg-IFN/ribavirin/simeprevir for first 12 wk. For genotype 5 or 6 are 12 wk of sofosbuvir/ribavirin/Peg-IFN or 24 wk of sofosbuvir/ribavirin[55]. AASLD/IDSA/IAS–USA 2014: Regimens for patients with genotype 1 are 12 weeks of sofosbuvir/ribavirin/Peg-IFN or 12 weeks of sofosbuvir/ribavirin/simeprevir or 24 wk of Peg-IFN/ ribavirin/simeprevir for first 12 wk or 24 wk of sofosbuvir/ribavirin or 24 wk of sofosbuvir/simeprevir. For genotype 2 is 12 wk of sofosbuvir/ribavirin. For genotype 3 are 24 wk of sofosbuvir/ribavirin or 12 wk of sofosbuvir/ribavirin/Peg-IFN. For genotype 4 are 12 wk of sofosbuvir/ribavirin/Peg-IFN or 24 weeks of sofosbuvir/ribavirin or 24-48 wk of Peg-IFN/ ribavirin/sofosbuvir for first 12 weeks. For genotype 5 or 6 are 12 wk of sofosbuvir/ribavirin/Peg-IFN or 48 wk of Peg-IFN/ribavirin[132].

**Table 2 Summary of systematic reviews on** hepatitis C virus **treatment in patients with renal disease**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **HCV and renal condition/ Reference and year** | **No. of trials/patients** | **Types and duration of treatment** | **SVR** | **Notes** |
| **Glomerulonephritis** |
| Reference *et al*[90](2013) | Trials = 10Patients = 300 | Combination of PegIFN plus ribavirin (P/R)6 mo to more than 12 moConventional IFN plus ribavirin6 mo to more than 12 mo | 52% 32% | Dropout rate = 15% |
| **Acute Hepatitis C** |
| Reference *et al*[116](2012) | Trials = 8Patients = 173 | Conventional or PegIFN3 mo to 12 mo | 58% | Dropout rate = 9%Genotype 1 = 49 % |
| **Hemodialysis** |
| Reference *et al*[117] (2008)Reference *et al*[118](2010)Reference *et al*[122](2011) | Trials = 28Patients = 645Trials = 16Patients = 254Trials = 10Patients = 151 | Conventional IFN or PegIFNPegIFN24-48 wkConventional interferon + ribavirin or Peg-IFN + ribavirin24-48 wk | 31%-39%33%-38%56% | Dropout rate = 19%-27%Dropout rate = 23%Dropout rate = 25%Genotype 1 = 58.3% |
| **Renal transplant** |
| Reference *et al*[128] (2014) | Trials = 12Patients = 140 | Conventional IFN monotherapy or Conventional IFN plus ribavirin or PegIFN + ribavirin3.5 to 33 mo | 26.6%PegIFN base = 40.6%Conventional IFN base = 20.9% | Dropout rate = 21.1%Graft rejection rates = 4% |

HCV: Hepatitis C virus; SVR: Sustained viral response; IFN: Interferon; Peg-IFN: Pegylated interferon.