Management of Hepatitis C in Advanced Chronic Kidney Disease

Risk and Impact of HCV Infection in CKD

Introduction

Hepatitis C virus (HCV) remains a public health challenge. HCV is typically asymptomatic until major complications supervene. Detection had been based on screening patients with acknowledged risk factors, but more recently the focus has been on screening individuals born between 1945 - 1965 given the high prevalence of HCV infection in this age group. The advent of highly effective and well tolerated HCV therapies has made virological cure feasible for the vast majority of HCV infected patients, including those with chronic kidney disease (CKD).

Prevalence and Associations of HCV and CKD

HCV persists as the most common chronic blood-borne infection in the United States (U.S.). An estimated 2.7 - 3.9 million people in the United States have chronic HCV infection, which is associated with increased risk of liver fibrosis or cirrhosis, development of hepatocellular carcinoma, and is a common indication for liver transplant in the U.S.\(^1\text{-}^2\) The majority (75% - 85%) of newly infected individuals will develop chronic infection. The incidence of HCV infection is likely under-reported; most people infected are asymptomatic and it is estimated that only half of those infected have been tested and diagnosed.\(^3\)

HCV infection is a potentially life-threatening condition. The number of HCV-associated deaths increased 10.9% from 2011 through 2014 and decreased 0.2% in 2015.\(^4\) Approximately one-half of all deaths in 2015 occurred among persons aged 55 - 64 years.\(^4\) An observational cohort study of mortality data showed that 19% of decedents had HCV listed on the death certificate, despite 63% having medical record evidence of chronic liver disease, suggesting that HCV is under-reported even in people with liver disease.\(^5\)

In addition to hepatic complications (i.e., cirrhosis, hepatocellular carcinoma), HCV infection has been implicated in other extrahepatic manifestations, including cardiovascular disease, diabetes, neurocognitive dysfunction, systemic vasculitis, and B cell non-Hodgkin lymphoma (Figure 1).\(^6\text{-}^9,^{10,11}\) HCV infection has also been linked to higher incidence and faster progression of CKD as well as higher rates of end-stage renal disease (ESRD, also known as kidney failure).
HCV is more prevalent among patients with CKD than in the general population. HCV infection is a recognized cause of progression to kidney failure, and is associated with reduced survival in the CKD population. A study by Molnar et al found that HCV infection is associated with a higher mortality risk, incidence of decreased kidney function, and progressive loss of kidney function (Figure 2). Multivariate adjusted models showed HCV infection independently was associated with a 2.2-fold higher mortality (adjusted hazard ratio (aHR), 95% confidence interval (CI): 2.13; 2.21), and a 15% higher incidence of decreased kidney function (aHR, 95% CI: 1.12; 1.17).
Figure 2: Associations with HCV Infection, Mortality, and Decreased Kidney Function

A 6-year cohort study by Chen et al compared individuals newly diagnosed with HCV without traditional CKD risk factors to randomly selected matched controls without HCV infection. HCV-infected patients had a significantly higher rate of CKD compared with the control group (aHR 3.42 vs 2.48 per 1,000 person-years, P = 0.02) and had a significantly greater risk for CKD (aHR 1.75, 95% CI: 1.25; 2.43, P=0.0009). The authors concluded that this association between HCV and CKD may indicate a causative role for HCV in kidney injury.

The prevalence of HCV infection is higher among CKD patients of all stages compared with rates in the general population, but is particularly high among patients receiving hemodialysis. A study by Goodkin et al evaluated data from the Dialysis Outcomes and Practice Patterns Study (DOPPS). The study reviewed the HCV status of 76,689 adults enrolled between 1996 – 2015 and found that 7.5% of patients were HCV-positive at enrollment. HCV infection among patients receiving hemodialysis was associated with higher risk of death, hospitalization, and worse quality-of-life scores. Cardiovascular and infectious hospitalizations are also greater among patients infected with Hepatitis C. A meta-analysis of 14 observational studies by Fabrizi et al observed an independent and significant relationship between anti-HCV seropositivity in patients receiving hemodialysis and mortality risk (relative risk (RR) 1.35; 95% CI, 1.25; 1.47).
Mortality in HCV-infected patients receiving hemodialysis is most often related to progression of liver disease (RR 3.82; 95% CI, 1.92; 7.61), with the cause of death attributed to cirrhosis and hepatocellular carcinoma in most cases.\textsuperscript{21} HCV was also associated with increased risk for cardiovascular mortality in patients receiving hemodialysis (RR 1.26; 95% CI, 1.10; 1.45).\textsuperscript{21} The role of HCV in cardiovascular risk is believed to be related to inflammation of chronic disease and atherogenesis mediated by the metabolic syndrome and dyslipidemia.\textsuperscript{9}

Patients with CKD can be at increased risk for acquiring HCV infection due to factors directly related to the treatment of their renal disease. For example, patients receiving hemodialysis are at elevated risk for acquiring HCV due to their increased exposure to factors implicated in viral transmission. Risk factors that relate to HCV risk among patients receiving hemodialysis include duration and mode of dialysis, and prevalence of HCV in the hemodialysis unit.\textsuperscript{22} In 2016 a report by the Centers for Disease Control and Prevention (CDC), highlighted an increased number of reports of newly acquired HCV infection in patients on maintenance hemodialysis.\textsuperscript{23} Additional risks factors include intravenous drug use and a history of kidney transplantation.\textsuperscript{24}

HCV infection is a concern in kidney transplantation, as it has been implicated in diminished patient and graft survival. A meta-analysis by Fabrizi et al showed that HCV-positive patients after kidney transplantation have an increased risk of mortality and graft loss.\textsuperscript{25} The study identified 18 observational studies (n=133,530) of kidney transplant recipients. The summary estimate for adjusted relative risk (aRR) of all-cause mortality was 1.85 (95% CI, 1.49; 2.31, $P < 0.0001$) and; for all-cause graft loss was 1.76 (95% CI, 1.46; 2.11, $P < 0.0001$).\textsuperscript{25} HCV infection also increases the likelihood of posttransplant diabetes in kidney transplant recipients.\textsuperscript{26}

There is an association between chronic HCV infection and glomerular diseases, including mixed cryoglobulinemia, membranoproliferative glomerulonephritis (MPGN), membranous nephropathy, and polyarteritis nodosa (PAN).\textsuperscript{27,28,29} Among patients with HCV-related glomerulonephritis, rapid deterioration in kidney function has been observed in 20% - 25% of patients, moderate renal insufficiency in 50% of patients, and hypertension in 80% of patients.\textsuperscript{29} When biopsied, patients most often are found to have a MPGN pattern of injury on light microscopy with immunofluorescence microscopy demonstrating granular staining for IgG, IgM, C3 and C1q. Electron microscopy shows electron dense deposits in subendothelial locations.\textsuperscript{30}
**Pathogenesis of HCV**

The HCV genome is a single-stranded, RNA virus (Figure 3). The virus is transmitted predominantly through blood and infects hepatocytes by interacting with co-receptors that results in its endocytosis, followed by fusion of the viral genome with the endosome and uncoating of its RNA, which is then cleaved into 10 viral proteins (3 structural and 7 nonstructural). The nonstructural HCV proteins (P7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B) are processed by both viral and host proteases, and are essential in the HCV life cycle. There are at least six HCV genotypes (GT 1 - 6). Of the six genotypes, HCV GT 1 is the most prevalent in the U.S. Viral treatment responses to interferon-based therapies have varied based on genotype.

**Structure of HCV**

Several mechanisms have been implicated in the pathogenesis of kidney disease in patients with HCV infection. HCV may have direct cytopathic effects on renal parenchyma associated with HCV binding on the cell surface and undergoing endocytosis. Research has identified a role for immune-mediated responses to HCV infection in the development of glomerulonephritis, including an innate immune response mediated by increased expression of toll-like receptors (TLRs) in glomeruli and a systemic immune response via cryoglobulins and the formation of HCV-antibody immune complexes.
Patients infected with HCV and with renal disease often have additional comorbidities that are recognized risk factors for CKD, including diabetes mellitus, hypertension, hyperlipidemia, cardiovascular disease, and liver cirrhosis. Several of these can be directly mediated by HCV and not just comorbid conditions. For example, HCV may directly inhibit insulin signaling and increase oxidative stress, thereby leading to endothelial dysfunction in CKD and progression of kidney disease.40,41

**Evaluation and Prevention Strategies for HCV Infection in Advanced CKD**

*Recognition of Risk Factors*

Blood transfusions and the sharing of used needles and syringes had been the commonest route of HCV spread in the U.S.42 Following introduction of routine blood screening for HCV during 1991 - 1992, transfusion-related HCV infection has virtually disappeared. Injection drug use is now the most common risk factor for HCV transmission. A needle-stick accident in the healthcare setting is another significant risk factor.42 People with high-risk sexual behavior, multiple partners, and sexually transmitted diseases are also at increased risk.42

Society guidelines recommend screening patients at increased risk for HCV.1,45,43 The American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) guidelines on testing, managing, and treating HCV provide recommendations on HCV risk factors that should prompt at least one-time testing for HCV in the general population (Figure 4).43 These include birth between 1945 and 1965, current or previous injection or intranasal illicit drug use, receiving a tattoo in an unregulated setting, incarceration, healthcare-related exposure to HCV-infected blood, being a recipient of an organ transplantation or blood transfusion prior to 1992, and undergoing long-term hemodialysis, among others (Figures 4 and 5).
HCV Screening

- One-time HCV testing is recommended for persons born between 1945 and 1965,* without prior ascertainment of risk.

- Other persons should be screened for risk factors for HCV infection, and one-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection.‡

*Regardless of country of birth.
‡See Figure 5 for behaviors, exposures, and conditions.
Adapted from AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C.

Figure 4: HCV Screening

HCV Screening Continued

Risk Exposures
- Long-term hemodialysis (ever)
- Percutaneous/parenteral exposures in an unregulated setting
- Getting a tattoo in an unregulated setting
- Healthcare, emergency medical, and public safety workers after needlesticks, sharps, or mucosal exposures to HCV-infected blood
- Children born to HCV-infected women
- Prior recipients of transfusions or organ transplants, including persons who:
  - Were notified that they received blood from a donor who later tested positive for HCV infection
  - Received a transfusion of blood or blood components, or underwent an organ transplant before July 1992
  - Received clotting factor concentrates produced before 1987
- Persons who were ever incarcerated

Risk Behaviors
- Injection-drug use (current or ever, including those who injected once)
- Intranasal illicit drug use

Other
- HIV infection
- Sexually active persons about to start pre-exposure prophylaxis (PrEP) for HIV
- Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase levels
- Solid organ donors (deceased and living)


Figure 5: HCV Screening Continued
Screening and Testing

Screening for HCV in CKD patients is justified for a number of reasons, including the high prevalence of HCV infection in CKD patients. In addition, regular monitoring of kidney function in HCV-infected patients is also important, including evaluation of proteinuria, hematuria and serum creatinine. As a result of decreased muscle mass, serum creatinine values may be low in patients with severe liver disease, so estimates of glomerular filtration rate (eGFR) should be interpreted with this in mind.

HCV infection can be asymptomatic, or may cause abdominal pain, gastrointestinal bleeding, bloating, nausea, fatigue, fever, loss of appetite, weight loss, or jaundice. Because HCV is asymptomatic in many cases, detection usually requires screening patients with risk factors and confirming viremia in seropositive patients.

Diagnostic tests consist of two broad categories: (1) serologic assays that detect antibodies to HCV and (2) molecular assays that detect or quantify HCV RNA. Other diagnostic modalities (e.g., genotype testing, serum fibrosis panels, and liver biopsy) can help predict prognosis and help select the optimal treatment regimen. The CDC and 2008 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on Hepatitis C and CKD recommend a testing sequence for identifying current HCV infection, consisting of initial HCV antibody testing (either rapid or laboratory-conducted assay) followed by an HCV RNA assay for all positive antibody tests.

Alanine aminotransferase (ALT) is a nonspecific marker of liver damage. HCV infection results in an increase in serum ALT. However, spuriously “normal” ALT levels have been often reported in HCV infected patients with advanced CKD, including patients receiving hemodialysis. Liver biopsy, increasingly replaced by non-invasive transient elastography, can provide prognostic information on extent of fibrosis in HCV-associated hepatic disease, but requires caution in advanced CKD because of the low, but still potential, risk of bleeding complications.

HCV testing of patients with CKD should be performed in patients with unexplained proteinuria, microscopic hematuria, increased ALT levels, or other known risk factors for HCV acquisition. All transplant candidates are also tested. Serologic testing to detect HCV antibodies is suggested for non-dialysis CKD and hemodialysis in units with low prevalence of HCV. A positive result should be followed by molecular testing to detect HCV RNA in the blood—qualitative testing to detect the presence of HCV RNA, and quantitative testing to detect the viral load.
Prevention

In general, primary prevention strategies for HCV include screening and testing blood donors, inactivating HCV in plasma-derived products, testing and risk-reduction counseling for at-risk patients, and vigilant infection control in health-care settings.

Effective infection control programs are an important part of providing high-quality health care in multiple clinical settings, particularly in hemodialysis facilities. Certain components are important parts of a successful program, including HCV surveillance through periodic testing of ALT and HCV enzyme immunoassay (EIA), engaging of hemodialysis personnel into preventing transmission of blood-borne pathogens, and implementation of clinical practice guidelines related to HCV transmission.\textsuperscript{15,49} Surveillance of staff practices related to blood-borne pathogens allows hemodialysis units the opportunity to understand specific problems with hygienic precautions, monitor changes and outcomes over time, and assess the effects of interventions or changes in protocols. Hemodialysis staff should be allowed sufficient opportunity and time to perform the required responsibilities without compromising standard hygienic precautions. These functions should be performed separate from other clinical duties, in order to maintain focus on infection control measures. Staff should also undergo appropriate, structured, and ongoing training on infection control policies and practices. Infection control requirements and procedures within hemodialysis facilities should include all standard precautions adopted in multiple healthcare settings, to prevent transmission of blood-borne pathogens, such as HCV.\textsuperscript{49}

Infection control techniques to prevent HCV transmission in dialysis facilities have mainly included safe injection and hygiene practices.\textsuperscript{49} Activities to help reduce the risk of infection include preparing single-use medications for patients in a clean area separate from dialysis stations, avoidance of using common medication carts to deliver medications to patients, cleaning and disinfecting stations between patients, and appropriate use of hand hygiene before and after patient contact.\textsuperscript{49,50} Items taken into a dialysis station for individual patients (e.g., supplies, medications, equipment) should be either cleaned or disinfected between patients, or disposed of if they cannot be cleaned or disinfected.
Management of HCV and CKD: A Clinical Update

Interferon-Based Therapy

The goal of treatment is to achieve sustained virologic response (SVR) (defined as undetectable HCV RNA 12 weeks post-treatment). Optimal treatment for HCV-infected CKD patients should consider the HCV genotype, extent of liver damage, CKD stage, transplant candidacy, prior HCV treatment, patient comorbidities, and the benefits and risks of antiviral treatment itself.\textsuperscript{15}

Historically, identifying the specific HCV genotype and determining the viral load through nucleic acid testing (NAT) allowed stratification about the likelihood of achieving sustained virologic response (SVR) following treatment and determined treatment duration with IFN-based regimens.

IFN is a naturally occurring nonglycosylated serum protein produced by immune cells in response to foreign antigen exposure; pegylated IFN (pegIFN) is a long acting polymer formulation of IFN. Ribavirin (RBV) is a nucleoside analog. These therapies can be effective, but have also have been associated with suboptimal SVR rates, multiple side effects, and poor tolerability. Infections with HCV can be less responsive to IFN therapy and may require up to 48 weeks of treatment. A meta-analysis of 10 clinical studies by Fabrizi et al studying IFN/RBV in HCV-infected patients receiving hemodialysis showed a summary SVR rate of 56\% and discontinuation rate of 25\%.\textsuperscript{51} Antiviral therapy for HCV infection had been difficult in patients with CKD due to the generally poor tolerance of IFN and RBV based regimens in patients that often have with multiple comorbidities including anemia.\textsuperscript{52} The possible hemolytic anemia induced by ribavirin can be hazardous in patients with CKD in whom baseline anemia is typical. Importantly, RBV is not efficiently dialyzed and thus the associated anemia can be long lasting.\textsuperscript{53} IFN-based HCV therapy post-kidney transplant generally has not been advised due to concerns about risk of precipitating graft rejection.\textsuperscript{54}

The advent of direct-acting antivirals (DAAs) has dramatically changed the approach to HCV genotype and viral load. For example, SVR rates generally exceed 90\% in most subpopulations with DAAs. Determining HCV genotype is still a part of defining the Hepatitis C treatment regimen for a patient, as the efficacy of several DAAs can vary by genotype. With the recent arrival of several pan-genotypic DAAs, it is possible that determining genotype may have a lesser role in planning HCV treatment in the future.
**Direct-Acting Antivirals**

A greater understanding of the HCV genome and proteins has led to the discovery of multiple therapeutic targets and the development of a host of DAAs, which target non-structural parts of the HCV genome (Figure 6). These therapies include NS3/4A protease inhibitors, nucleotide analog NS5B polymerase inhibitors, NS5A inhibitors, and multi-class combination antiviral medications. Examples include simeprevir, sofosbuvir, and daclatasvir. Simeprevir is a macrocyclic noncovalent NS3/NS4A protease inhibitor for use in combination with IFN/RBV in HCV GT 1 infection. Sofosbuvir is a nucleotide analog NS5B polymerase inhibitor, for the treatment of HCV infection subtypes GT 1-4. Daclatasvir is a NS5A inhibitor, for use with sofosbuvir (with or without RBV) for the treatment of patients with chronic HCV GT 1 or 3 infection. The advent of DAAs has dramatically changed the field of Hepatitis C. These newer therapies have been the focus of clinical research in recent years for their improved efficacy.

**Figure 6: HCV Life Cycle and Potential Targets for Direct-Acting Antivirals**

Typically, multiple DAAs are used in combination, NS5A or NS5B inhibitor with a protease inhibitor, to target the different aspects of the HCV genome. Multi-class combination antiviral medications for HCV infection are summarized in Figure 7.
Elbasvir-grazoprevir is a once-daily tablet, which consists of a NS3/4A protease inhibitor (grazoprevir) and a NS5A replication complex inhibitor (elbasvir), approved for the treatment of chronic HCV GT 1 or 4 infections with or without RBV in adult patients. No dosage adjustment of elbasvir-grazoprevir is required in patients with any degree of renal impairment including patients on hemodialysis.\textsuperscript{57}

The Phase II/III C-SURFER trial evaluated elbasvir-grazoprevir in patients with HCV GT 1 infection and advanced CKD (stages 4 and 5 (eGFR <30 mL/min/1.73m\textsuperscript{2})), including patients on hemodialysis) with or without liver cirrhosis. The study compared 12 weeks of the daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) versus placebo.\textsuperscript{58} Of the 224 patients in the study, 179 were hemodialysis-dependent. The SVR12 rates (primary intention-to-treat [ITT] and modified intention-to-treat [mITT] analysis) were 94\% and 99\%, respectively, supporting the use of elbasvir-grazoprevir in patients with severely compromised kidney function.\textsuperscript{43,58,59}

Paritaprevir-ritonavir-dasabuvir-ombitasvir is a multi-class DAA for the treatment of HCV GT1. Ombitasvir is a NS5A inhibitor, paritaprevir is a NS3/4A protease inhibitor, and ritonavir is a CYP3A inhibitor. These three therapies are combined as a fixed-dose tablet and dasabuvir (NS5B inhibitor) is a separate tablet. Ombitasvir-paritaprevir-ritonavir is indicated in combination with RBV for the treatment of patients with HCV GT 4 infection without cirrhosis or with compensated cirrhosis.
Due to ritonavir boosting this combination has significant drug-drug interactions with calcineurin inhibitors, requiring dose adjustments and careful monitoring in transplant recipients.

A single-arm, multicenter study by Pockros et al examined the use of paritaprevir-ritonavir-dasabuvir-ombitasvir (with or without RBV) in the treatment-naïve adult patients (n=25) with HCV GT 1 infection, without cirrhosis and with CKD stage 4 or 5 (including hemodialysis).

Patients with HCV GT 1a also received RBV, while those with HCV GT1b did not receive RBV. The study showed an SVR12 of 90% in patients treated with paritaprevir-ritonavir- dasabuvir-ombitasvir. Overall, the treatments were well-tolerated, although use of RBV may require a reduction or interruption to manage anemia.

**Glecaprevir-pibrentasvir** is a multi-class DAA for the treatment of HCV GT 1 - 6 without cirrhosis or with compensated cirrhosis. Glecaprevir is an NS3/4A protease inhibitor and pibrentasvir is an NS5A inhibitor. No dosage adjustment of glecaprevir-pibrentasvir is required in patients with mild, moderate or severe renal impairment, including those on dialysis.

The EXPEDITION-4 study evaluated treatment of glecaprevir-pibrentasvir in patients infected with HCV GT 1 - 6. The study included treatment-naïve and -experienced patients (previous IFN or pegIFN ± RBV, or sofosbuvir and ribavirin ± pegIFN) with CKD stage 4 or 5 (including hemodialysis). The daily fixed-dose combination of glecaprevir (300 mg)-pibrentasvir (120mg) was administered as three 100 mg-40 mg fixed-dose combination pills. The study showed that glecaprevir-pibrentasvir achieved an SVR12 of 98% (primary ITT) in HCV-infected patients with advanced CKD and on dialysis, across all major HCV genotypes. A modified ITT (excluding subjects who did not achieve SVR for reasons other than virologic failure), showed an SVR 12 of 100%. The study supports the efficacy and safety of glecaprevir-pibrentasvir in patients with CKD and ESRD. The recommended duration of therapy is similar for patients without CKD.

MAGELLAN-2 was a phase III, open-label, single arm study that evaluated treatment of glecaprevir-pibrentasvir in liver (n=80) or kidney (n=20) transplant recipients with HCV GT 1-6 infection (≥3 months posttransplant). The study included patients without cirrhosis who were HCV treatment naïve, or treatment experienced with IFN, pegIFN ± RBV or sofosbuvir with RBV ± pegIFN (except for HCV GT 3 patients). Glecaprevir-pibrentasvir (300mg – 120 mg) was administered for 12 weeks. The study showed an SVR12 achieved in 99% of patients receiving glecaprevir-pibrentasvir.
Ledipasvir-sofosbuvir is a multi-class DAA for the treatment of HCV GT 1, 4, 5, or 6, without cirrhosis or with compensated cirrhosis, or in combination with RBV in patients with decompensated cirrhosis. Ledipasvir is a NS5A inhibitor. Sofosbuvir-velpatasvir is another DAA combination for the treatment of adult patients with chronic HCV GT 1-6 infection, without cirrhosis or with compensated cirrhosis, or in combination with RBV in patients with decompensated cirrhosis. Velpatasvir is a NS5A inhibitor. No dosage recommendation can be given for patients with severe renal impairment (eGFR <30 mL/min/1.73m²) or with ESRD due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite. In general, this consideration applies to multi-class combination therapies that contain sofosbuvir.

Studies have evaluated the use of sofosbuvir-containing regimens in hemodialysis. A study of 15 HCV GT 1-infected patients with advanced CKD (eGFR <30 mL/min/1.73m²), 11 of which received hemodialysis, showed that SVR at week four and 12 were documented to be 93% and 87%, respectively, in patients treated with half-dose sofosbuvir plus full-dose simeprevir. Data from HCV-TARGET, a multicenter, longitudinal treatment cohort, showed that SVR12 rates of 82% - 83% were similar across eGFR groups (<30 mL/min; 31-45 mL/min; 46-60 mL/min; and >60 mL/min) in patients receiving a sofosbuvir-containing regimen. However, patients with eGFR ≤45 mL/min/1.73m² more frequently experienced anemia, worsening renal function and serious adverse events.

Studies have indicated successful use of sofosbuvir-containing regimens in kidney transplant recipients, with dose reductions in some cases. A study by Sawinski et al evaluated 20 kidney transplant recipients, 88% of which were infected with HCV GT 1. The study showed use of sofosbuvir-containing regimens achieved 100% SVR without major toxicity and with adjustment of immunosuppression necessary in less than half of patients. The most commonly used regimen was sofosbuvir 400 mg daily in combination with simeprevir 150 mg daily. A study by Columbo et al evaluated the use of 90 mg ledipasvir with 400 mg sofosbuvir in kidney transplant recipients (n=114) with chronic HCV GT 1 or 4 infection (with or without compensated cirrhosis), and an eGFR ≥40 mL/min/1.73m². The study showed 100% of patients achieved SVR12. Most studies in kidney transplant recipients have enrolled patients with eGFR >30 mL/min/1.73m², allowing the use of sofosbuvir-based regimens.

Overview of AASLD-IDSA Recommendations for DAAs in CKD

The most recent AASLD-IDSA guidelines issued recommendations for use of DAAs, as it relates to patients with Hepatitis C and CKD. In HCV-infected patients with CKD Stage 1, 2, or 3, no dose adjustment is required when using the following.
Daclatasvir (60 mg, usually used in combination)

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)
- Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)
- Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)
- Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)
- Simeprevir (150 mg, usually used in combination)
- Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)
- Sofosbuvir (400 mg, usually used in combination)

Recommended regimens for patients with CKD Stage 4 or 5 (eGFR <30 mL/min/1.73m² or ESRD) include 12 weeks of daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for HCV GT 1 or GT 4. Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) is recommended in CKD 4/5 for HCV GT 1-6 for 8-16 weeks. Duration of glecaprevir-pibrentasvir should be based on presence of cirrhosis and prior treatment experience, and patients in this group should be treated as would patients without CKD.43

In treatment-naive and -experienced kidney transplant patients with HCV GT 1 or 4 (with or without compensated cirrhosis), daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for 12 weeks is recommended. Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is also recommended for this patient population.43

In treatment-naive and -experienced kidney transplant patients with HCV GT 2, 3, 5, or 6 (with or without compensated cirrhosis), daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for 12 weeks is recommended. Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) plus low initial dose of ribavirin (600 mg; increase as tolerated) for 12 weeks is an alternative regimen for this patient population.43

Additional Considerations for DAAs

Studies have shown that DAAs can be more effective compared to IFN-based regimens. However, issues regarding their use need to be considered. For example, testing for HBV prior to starting therapy is generally recommended for DAAs, and protease inhibitors generally should be avoided in patients with decompensated cirrhosis.43,73,74 The presence of resistance-associated variants of HCV can attenuate the efficacy of DAAs.76 NS5A resistance variants can alter the length of therapy and necessitate the addition of RBV.
Drug interactions are also an important consideration for DAAs, thus, the Package Insert should be reviewed for specific interactions, contraindications, and dose adjustments. Online resources, such as https://www.hep-druginteractions.org/, are also available.\textsuperscript{77} Generally, drugs/supplements to consider for potential interactions with certain DAAs can include statins, proton pump inhibitors, St John’s wort, and other antiretroviral agents.\textsuperscript{43,55} Drug interactions are also an important consideration in kidney transplant recipients. A summary of drug interactions between calcineurin inhibitors and DAAs, along with AASLD-IDSA recommendations in the setting of post liver transplantation, is provided in Figure 8.

### DAA Interactions with Calcineurin Inhibitors

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<thead>
<tr>
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<th>Cyclosporine</th>
<th>Tacrolimus</th>
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<tbody>
<tr>
<td>Sofosbuvir</td>
<td>4.5-fold ↑ in SOF AUC; but GS-331007 metabolite unchanged; no a priori dose adjustment</td>
<td>No interaction observed; no a priori dose adjustment</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>No data; no a priori dose adjustment</td>
<td>No data; no a priori dose adjustment</td>
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<tr>
<td>Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir</td>
<td>5.8-fold ↑ in CSA AUC; modeling suggest using 1/5 of CSA dose during PrOD treatment, monitor CSA levels and titrate CSA dose as needed</td>
<td>57-fold ↑ in TAC AUC; modeling suggests TAC 0.5 mg every 7 days during PrOD treatment, monitor TAC levels and titrate TAC dose as needed</td>
</tr>
<tr>
<td>Elbasvir-Grazoprevir</td>
<td>15-fold ↑ in GZR AUC and 2-fold ↑ in EBR AUC; combination is not recommended</td>
<td>43% ↑ in TAC; no a priori dose adjustment</td>
</tr>
<tr>
<td>Velpatasvir</td>
<td>No interaction observed; no a priori dose adjustment</td>
<td>No data; no a priori dose adjustment</td>
</tr>
<tr>
<td>Glecaprevir-Pibrentasvir</td>
<td>5-fold ↑ in GLE AUC with higher doses (400 mg) of CSA; not recommended in patients requiring stable CSA doses &gt;100 mg/day</td>
<td>1.45-fold ↑ in TAC AUC; no a priori dose adjustment, monitor TAC levels and titrate TAC dose as needed</td>
</tr>
<tr>
<td>Sofosbuvir-Velpatasvir-Voxilaprevir</td>
<td>9.4-fold ↑ in VOX AUC; combination is not recommended</td>
<td>No data; no a priori dose adjustment</td>
</tr>
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AUC, area under the curve; CSA, cyclosporine; DAC, daclatasvir; EBR, GZR; elbasvir/grazoprevir; GLE/PR, glecaprevir/pibrentasvir; LED, ledipasvir; SMV, simeprevir; SOF, sofosbuvir; TAC, tacrolimus; VEL, velpatasvir. Adapted from AASLD-IDSA. Recommendations for testing, managing, and treating Hepatitis C. http://www.hcguidelines.org. Accessed 10/20/2017.

**Figure 8: DAA Interactions with Calcineurin Inhibitors**
Summary

HCV infection has been associated with multiple adverse outcomes, increased risk in CKD, and unmet medical needs. Effective prevention strategies, along with timely diagnosis and treatment, are important components of Hepatitis C management. There are multiple areas of research aimed at improving outcomes and addressing unmet medical needs, such as the utility and safety of HCV positive donor organs, which have the potential to help broaden supply, and thus, shorten wait times. Research has also focused on newer treatment options, including pan-genotypic, multi-class combination DAAs. These newer therapies offer the opportunity to manage HCV infection more effectively (Figure 9). Areas that require further study include the optimal timing of therapy and impact on long-term outcomes (e.g., morbidity, mortality, quality-of-life) within the CKD population. However, recent data on newer therapeutic options suggests a greater opportunity to treat CKD patients with an HCV infection more effectively.

Hepatitis C Treatment in CKD: The KDIGO Perspective

- In patients with an eGFR >30 mL/min, all licensed DAAs regimens can be used.
- Cure of HCV appears at hand in CKD stages 4–5, including dialysis patients, and in kidney transplant recipients.
- The choice of DAA regimen in CKD should be based on HCV genotype, viral load, eGFR, concomitant medications, transplant candidacy and comorbidities.
- The timing of treatment in potential kidney transplantation candidates (before versus after transplantation) should be decided in collaboration with the transplant center.

Figure 9: Hepatitis C Treatment in CKD: The KDIGO Perspective
References


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