Treatment of HCV in Persons with Renal Impairment

This is a PDF version of the following document:
Module 6: Treatment of Key Populations and Unique Situations
Lesson 3: Treatment of HCV in Persons with Renal Impairment

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Background

Epidemiology of Hepatitis C Infection and Renal Disease

Persons infected with hepatitis C virus (HCV) can develop kidney disease as a result of extrahepatic manifestation of HCV or as a disease process independent of the HCV infection. In addition, hemodialysis has been a risk factor for acquiring HCV infection, as shown by numerous outbreaks and HCV cross-infections that have occurred in hemodialysis units.\[1,2,3,4\] Earlier studies conducted in western countries have shown an HCV prevalence in hemodialysis patients that ranged from 2.6 to 23%, with higher prevalence correlating with longer duration of hemodialysis.\[5,6,7\] The risk of HCV transmission in hemodialysis units has declined due to improved testing and infection control practices.\[8,9\]

Interaction of Hepatitis C Infection and Renal Disease

Several studies have shown that patients on chronic hemodialysis have an increased overall mortality risk if they have chronic hepatitis C infection (when compared with those on dialysis who do not have hepatitis C infection).\[10,11\] There are also some data showing that chronic hepatitis C may be a risk factor for developing renal cell carcinoma.\[12\] Chronic hepatitis C infection has also been associated with an accelerated course of renal disease, including in persons with HIV coinfection.\[13,14\] Extrahepatic manifestations related to HCV, including immune complex-related renal disease, can require urgent HCV treatment to resolve or prevent further organ damage.

Definitions and Classification

As part of evaluating and treating patients with hepatitis C and renal disease, it is important to first determine the stage of the patient’s renal disease, a process that utilizes some of the following definitions.

- **Chronic Kidney Disease (CKD):** Chronic kidney disease is defined based on the presence of either kidney damage or decreased kidney function for three or more months, irrespective of cause.
- **Glomerular Filtration rate (GFR):** GFR is generally considered to be the best index of overall kidney function. The GFR varies in normal individuals by age and sex, dietary protein intake, and possibly by race-ethnicity. The normal value for GFR is approximately 130 and 120 mL/min/1.73 m$^2$ for men and women, respectively. The widely accepted threshold defining a decreased GFR is less than 60 mL/min per 1.73 m$^2$; kidney failure is defined as a GFR less than 15 mL/min/1.73 m$^2$ or treatment by dialysis (Figure 1). The GFR is equal to the sum of the filtration rates in all of the functioning nephrons, but since the GFR cannot be measured directly, it is usually estimated from serum markers. The gold standard for assessment of GFR is the renal inulin clearance test, but this method is highly...
complex and not practical for routine clinical purposes. Accordingly, several methods, including the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD), have been utilized in clinical practice to estimate GFR.[15,16,17]

- **Creatinine Clearance (CrCl):** The creatinine clearance is a widely used test to estimate the glomerular filtration rate (eGFR). The creatinine clearance, however, overestimates the GFR since creatinine is both filtered by the glomeruli and secreted in the renal tubules. The Cockcroft-Gault formula is commonly used in clinical practice to estimate the creatinine clearance based on the serum creatinine, patient age, body mass in kilograms, and sex (Figure 2).[18] Normal values are 95 to 145 mL/min in men and 75 to 115 mL/min in women. This formula is less accurate in weight extremes. A more accurate, but less practical, determination of creatinine clearance can be made with a 24-hour urine collection. The creatinine clearance is then calculated by dividing the 24-hour urine creatinine by the serum creatinine; the 24-hour urine creatinine is equal to the urine creatinine concentration multiplied by urine volume. There are several limitations to the 24-hour urine creatinine clearance that can cause inaccuracies, such as an incomplete urine collection.

- **Staging of Kidney Disease:** Guidelines such as the Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease state that among persons diagnosed using the criteria described above, staging of CKD should be done according to the cause of disease, category of eGFR and category of albuminuria.[19] The KDIGO classifies kidney disease based on the cause, patient’s GFR (Figure 3) and albuminuria categories (Figure 4), with an overall prognosis generated based on the both of these categories (Figure 5).[20,21]

**Evaluation of Persons with Chronic HCV and CKD**

Serum creatinine should be measured and creatinine clearance or GFR should be estimated as part of a pretreatment assessment for HCV patients. The CKD stage should be determined if renal function is abnormal. Complete blood count should be obtained as well, to assess for pre-treatment anemia.
HCV Treatment Studies in Persons with CKD

The availability of direct-acting antiviral agents (DAAs) has sparked major enthusiasm for treating persons with HCV who have chronic renal impairment, especially since many of these individuals historically have not been eligible for treatment given the toxicities associated with interferon and ribavirin-based therapies.[22] The following summarizes key studies involving use of new DAA-based therapy in persons with chronic renal insufficiency. Older studies that used peginterferon-based regimens or sofosbuvir plus ribavirin are not reviewed since these agents are no longer recommended for the treatment of HCV infection.

- **Elbasvir-Grazoprevir (C-SURFER):** In this phase 3, randomized study, investigators enrolled 224 adults with HCV genotype 1 and chronic renal disease, including individuals on hemodialysis, to receive immediate treatment with 12 weeks of therapy with elbasvir plus grazoprevir, or deferred therapy.[23] Subjects in the deferred group received placebo during the first 12 weeks; use of placebo was considered important as a comparator for safety purposes, particularly due to safety concerns in this population with advanced renal disease.[23] Overall, 80% of the participants enrolled in the trial were treatment naïve and 76% were receiving hemodialysis. Among all the participants who completed therapy, 99% (115 of 116) achieved an SVR12. Six individuals were excluded from the modified full analysis, but all 6 had HCV RNA levels less than 15 IU/mL at that time of study discontinuation.[23] The safety profile observed in participants who received elbasvir plus grazoprevir was comparable to that seen in the placebo group.

- **Glecaprevir-Pibrentasvir (EXPEDITION-4):** This phase 3 single-arm open-label trial evaluated the safety and efficacy of 12 weeks of glecaprevir-pibrentasvir in 104 adults with HCV genotype 1, 2, 3, 4, 5, or 6 infection and advanced renal insufficiency (estimated glomerular filtration rate less than 30 mL/min/1.73m$^2$); 88% had chronic kidney disease stage 5 and 82% were on hemodialysis.[24] Fifty-two percent of participants had HCV genotype 1 infection, 19% had compensated cirrhosis, and 42% were treatment-experienced (all but two with prior interferon-based therapy). The overall SVR rate was 98% by intent-to-treat analysis.[24] The rate of adverse events (pruritus 20%, fatigue 14%, nausea 12%) attributable to glecaprevir-pibrentasvir were comparable to those observed in other glecaprevir-pibrentasvir trials.[24]

- **Glecaprevir-Pibrentasvir (EXPEDITION-5):** In this open-label, single arm, phase 3 trial, investigators evaluated the safety and efficacy of the fixed-dose combination of glecaprevir-pibrentasvir for 8, 12, or 16 weeks in treatment-naïve and treatment-experienced participants with chronic HCV genotypes 1, 2, 3, 4, 5, or 6 and advanced renal insufficiency.[25] The renal insufficiency was defined as eGFR less than 45 mL/min/1.73 m$^2$ (stage 3b, 4, or 5 chronic kidney disease). Most of the participants enrolled received glecaprevir-pibrentasvir for 8 weeks.[25] Overall, 97% (97 of 101) of the participants treated with glecaprevir-pibrentasvir achieved an SRV12.[25]

- **Ledipasvir-Sofosbuvir (ERCHIVES-Renal):** In an observational cohort study conducted in the Veterans Administration system, investigators used the Electronically Retrieved Cohort of HCV-Infected Persons (ERCHIVES) to analyze HCV treatment responses for 13,663 persons who received ledipasvir-sofosbuvir, with or without ribavirin.[26] This cohort included a total of 1,607 with CKD stage 3, 4, or 5 who completed HCV treatment.[26] The SVR12 rates for individuals with stage 3 CDK who completed treatment was 97.0% (1080 of 1113) in those who received ledipasvir-sofosbuvir and 97.1% (375 of 386) with ledipasvir-sofosbuvir plus ribavirin.[26] For those with stage 4 or 5 CKD, the SVR12 rates were 94.0% (78 of 83) with ledipasvir-sofosbuvir and 100% (25 of 25) with ledipasvir-sofosbuvir plus ribavirin.

- **Sofosbuvir-Velpatasvir (Sofosbuvir-Velpatasvir in Patients with ESRD on Dialysis):** In this phase 2, single-arm study, 59 adults with HCV genotype 1, 2, 3, 4, 5, or 6 and ESRD undergoing hemodialysis or peritoneal dialysis received open-label sofosbuvir-velpatasvir (400 mg/100 mg) once daily for 12 weeks.[27] The participants included treatment-naïve or experienced (not NSSA-experienced) individuals, with and without compensated cirrhosis.[27] Overall, 95% (56 of 59) of the participants...
achieved an SVR12.[27] Serious adverse events occurred in 11 persons, but the adverse effects were thought to be unrelated to the HCV treatment medications.[27]

- **Sofosbuvir-Based Therapy (HCV Target: Renal Disease):** In the HCV TARGET Renal Disease trial, investigators reported findings from a longitudinal cohort study of 1,893 adults with chronic HCV using one of four sofosbuvir-containing regimens: (1) sofosbuvir plus peginterferon plus ribavirin, (2) sofosbuvir plus ribavirin, (3) sofosbuvir plus simeprevir, and (4) sofosbuvir plus simeprevir plus ribavirin.[28] Overall, the SVR12 rates were high (81 to 89%) across different levels of baseline renal insufficiency, with one exception: individuals with cirrhosis who had an estimated GFR less than 30 mL/min/1.73m² had lower SVR12 rates.[28] Rates of treatment-related anemia were higher in persons with more advanced renal disease.
HCV Medication Dosing in Persons with CKD

Dosing of DAA Medications in Persons with CKD

The following (in alphabetical order) summarizes recommended dosing information for oral DAA medications (and ribavirin) used to treat HCV in persons with renal impairment. The information provided is based on specific drug prescribing information for persons with renal impairment. In November 2019, the FDA approved the use of sofosbuvir-based regimens in persons with advanced kidney disease, including those on dialysis, without the need for dose adjustment.

- **Elbasvir-Grazoprevir**: No dosage adjustment of elbasvir-grazoprevir is needed for patients who have mild, moderate, or severe renal impairment, including individuals requiring dialysis (see [Elbasvir-Grazoprevir Prescribing Information](#)).

- **Glecaprevir-Pibrentasvir**: No dosage adjustment of glecaprevir-pibrentasvir is needed for patients who have mild, moderate, or severe renal impairment, including individuals requiring dialysis (see [Glecaprevir-Pibrentasvir Prescribing Information](#)).

- **Ledipasvir-Sofosbuvir**: No dosage adjustment of ledipasvir-sofosbuvir is needed for patients who have mild, moderate, or severe renal impairment, including individuals requiring dialysis (see [Ledipasvir-Sofosbuvir Prescribing Information](#)).

- **Sofosbuvir-Velpatasvir**: No dosage adjustment of sofosbuvir-velpatasvir is needed for patients who have mild, moderate, or severe renal impairment, including individuals requiring dialysis (see [Sofosbuvir-Velpatasvir Prescribing Information](#)).

- **Sofosbuvir-Velpatasvir-Voxilaprevir**: No dosage adjustment of sofosbuvir-velpatasvir-voxilaprevir is needed for patients who have mild, moderate, or severe renal impairment, including individuals requiring dialysis (see [Sofosbuvir-Velpatasvir-Voxilaprevir Prescribing Information](#)).

Dosing of Ribavirin in Persons with CKD

Ribavirin is not a DAA and dosing of ribavirin in persons with CKD requires special consideration independent of recommendations for DAA medication in CKD. In the current era of HCV treatment, ribavirin is recommended for use only in select situations:

- In combination with ledipasvir-sofosbuvir in persons who have decompensated cirrhosis, or
- In persons with HCV genotype 1a who are receiving treatment with elbasvir-grazoprevir and who have baseline NS5A resistance-associated substitutions (RASs) for elbasvir.

Ribavirin is manufactured by multiple companies and is available as a generic preparation. In general, concern exists with the use of ribavirin in patients with renal impairment since ribavirin levels will increase as renal function decreases. Several ribavirin company package inserts, including Rebetol and Ribasphere recommend not using ribavirin in patients with an estimated glomerular filtration rate less than 50 mL/min. The package insert for Copegus permits the use of ribavirin in patients with an estimated glomerular filtration rate less than 50 mL/min if the dose is reduced and careful monitoring occurs. The AASLD-IDSA HCV Guidance recommends adults with a creatinine clearance of 30 to 50 mL/min should have the ribavirin dose reduced to alternating doses of 200 and 400 mg every other day (for example, 200 mg on Monday, 400 mg on Tuesday, 200 mg on Wednesday, etc.). In addition, these guidelines recommend reducing the dose of ribavirin to 200 mg once daily in adults who have severe renal disease (creatinine clearance less than 30 mL/min), end-stage renal disease, or hemodialysis.
AASLD-IDSA Recommended HCV Treatment in Persons with CKD

The AASLD-IDSA HCV Guidance now recommends that no dose adjustment is required for HCV treatment in persons with renal impairment when the treatment regimen is a recommended regimen.[29] The one exception is that if ribavirin is added to a regimen, dose adjustment of the ribavirin is required, as noted in the prior section.[29]
Treatment of HCV in Setting of Renal Transplantation

Hepatitis C Treatment Prior to Renal Transplantation

Most experts recommend that persons with chronic HCV infection who are renal transplantation candidates receive treatment of HCV prior to renal transplantation, if possible.\(^\text{[30, 31]}\) In some circumstances, however, it may not be possible to treat HCV prior to renal transplantation. Historically, HCV treatment was recommended pretransplant, given the potential for graft dysfunction in patients who received interferon-based therapy posttransplant and the improved clinical outcomes in those who underwent HCV clearance prior to transplantation.\(^\text{[32, 33, 34]}\) Pretransplant treatment of HCV has also been shown to prevent some HCV-related renal complications, such as glomerulonephritis in the kidney transplant population. When treating HCV in a person waiting for renal transplant, the recommended DAA regimens are the same as those for persons with chronic severe renal impairment.\(^\text{[29]}\)

HCV Treatment Studies in Renal Transplant Recipients

In recent years, multiple HCV treatment studies have been conducted using DAAs in renal transplant recipients. Most of these studies have typically involved 25 or fewer participants.\(^\text{[35, 36, 37, 38]}\) In these studies, DAA therapy was safe and highly effective. Several larger studies also support the efficacy of HCV treatment in renal transplant recipients.\(^\text{[39, 40]}\) In a phase 2, open-label trial, investigators in Europe enrolled 114 treatment-naïve or treatment-experienced kidney transplant recipients with chronic HCV genotype 1 or 4 infection to receive either a 12- or 24-week course of ledipasvir-sofosbuvir.\(^\text{[39]}\) All 114 (100%) of study participants achieved an SVR12.\(^\text{[39]}\) In the observational HCV-TARGET study, 55 renal transplant recipients had treatment of HCV with DAA therapy, most often ledipasvir-sofosbuvir, with or without ribavirin.\(^\text{[40]}\) Overall, 94.5% (52 of 55) renal transplant recipients achieved an SVR12 with DAA therapy for chronic HCV infection.\(^\text{[40]}\)

AASLD-IDSA Guidance for HCV Treatment after Renal Transplant

The following summarizes the AASLD-IDSA HCV Guidance for the treatment of renal transplant recipients, which are stratified based on HCV treatment experience.\(^\text{[41]}\) Note that consideration for drug interactions is extremely important in the posttransplantation period, particularly with regard to immunosuppressant calcineurin inhibitors, particularly cyclosporine and tacrolimus.

- **Treatment-Naïve and Non-DAA Experienced; All Genotypes (1, 2, 3, 4, 5, or 6) with or without Compensated Cirrhosis:** The recommended regimens are a 12-week course of glecaprevir-pibrentasvir, ledipasvir-sofosbuvir, or sofosbuvir-velpatasvir.\(^\text{[41]}\) For persons with HCV genotype 1 or 4, elbasvir-grazoprevir is an option if they do not have any baseline NS5A resistance-associated substitutions for elbasvir.\(^\text{[41]}\)
- **DAA-Experienced; All Genotypes (1, 2, 3, 4, 5, or 6) with or without Compensated Cirrhosis:** The recommended regimen is a 12-week course of sofosbuvir-velpatasvir-voxilaprevir, with or without ribavirin.\(^\text{[41]}\)
Summary Points

- Chronic kidney disease is a major potential comorbidity in people living with chronic HCV infection.
- Renal function, including an estimation of CrCl or GFR, must be assessed before initiating any hepatitis C treatment. Based on the estimated CrCl or GFR value, individuals with renal impairment are classified as having mild (50 to 80 mL/min), moderate (30 to 50 mL/min), or severe (less than 30 mL/min) disease.
- For persons with any stage of renal impairment, from mild to severe (CKD stages 1, 2, 3, 4, or 5) no dose adjustments are needed for DAA medications.
- Ribavirin is required in limited situations in persons with chronic renal failure; these include in combination with ledipasvir-sofosbuvir with extended duration of 24 weeks for persons with decompensated cirrhosis and in combination with elbasvir-grazoprevir in those with HCV genotype 1a who have presence of NS5A resistance-associated substitutions prior to treatment.
- For individuals with severe renal impairment who require ribavirin, the recommended ribavirin dose is 200 mg/day (typically starting at 200 mg three times weekly and titrating up to 200 mg/day as tolerated). Caution should be exerted when using ribavirin in persons with renal failure because of the risk of severe hemolysis.
- Persons with chronic HCV infection who require renal transplantation should undergo prompt evaluation for HCV treatment; the treatment of hepatitis C prior to renal transplantation is strongly preferred over treatment of hepatitis C post renal transplantation.
Citations


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**Figures**

**Figure 1 Glomerular Filtration Rate Categories in Chronic Renal Disease and Definition of Renal Failure**

Figure 2 Cockcroft-Gault Formula for Estimating Creatinine Clearance

Note: this is the original Cockcroft-Gault formula for estimating creatinine clearance. This formula should be used only in patients with stable renal function. In addition, the formula performs better when adjusted for body surface area, particularly in patients with diminished renal function.

Figure 3 Glomerular Filtration Rate Categories in Chronic Renal Disease

Figure 4 Albumin Categories in Chronic Renal Disease

Figure 5 Prognosis of Chronic Kidney Disease Based on GFR and Albumin Categories