Background

Interaction 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] 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 m² for men and women, respectively. The widely accepted threshold defining a decreased GFR is less than 60 mL/min per 1.73 m²; kidney failure is defined as a GFR less than 15 mL/min/1.73 m² 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 pre-treatment 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 therapy.[22] The following summarizes key studies involving use of new DAA-based therapy in persons with chronic renal insufficiency. Older studies that used interferon- or peginterferon-based regimens 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 the 116 subjects who completed therapy, 115 (99%) achieved a sustained virologic response 12 weeks after completing treatment (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 1-6 infection and advanced renal insufficiency (estimated glomerular filtration rate less than 30 mL/min/1.73m²); 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]

- **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.[25] This cohort included a total of 1,607 with CKD stage 3, 4, or 5 who completed HCV treatment.[25] 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.[25] 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. The ERCHIVES-Renal also included analysis of persons with CKD and HCV treatment responses to ombitasvir-paritaprevir-ribavirin and dasabuvir, with or without ribavirin.

- **Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir (ERCHIVES-Renal: OPRD)**: In an observational ERCHIVES cohort study based in the Veterans Administration, investigators analyzed treatment responses to ombitasvir-paritaprevir-ritonavir and dasabuvir, with or without ribavirin in 3,961 persons with chronic HCV infection.[25] The SVR12 rates ranged from 94 to 100% among those treated with ombitasvir-paritaprevir-ribavirin and dasabuvir.[25] The SVR12 rates for individuals with stage 3 CDK who completed treatment was 96.0% (95 of 99) in the group without ribavirin and 95.3% (203 of 213) with ribavirin. With individuals who had stage 4 or 5 CKD, the SVR12 rates were 100% (42 of 42) in the group without ribavirin and 89.1% (41 of 46) with ribavirin.[25] The ERCHIVES-Renal also included analysis of persons with CKD and treatment responses to ledipasvir-sofosbuvir, with or without ribavirin.

- **Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir (RUBY-I)**: In the RUBY-1 trial, investigators treated adults with chronic HCV infection and stage 4 or 5 CKD, including individuals on hemodialysis, with a 12-week regimen of ombitasvir-paritaprevir-ribavirin and dasabuvir, with or without ribavirin.[26] All participants had HCV genotype 1, were treatment-naïve, and had noncirrhotic liver...
disease. Ninety percent (18 of 20) participants achieved an SVR12. Nine of the 13 individuals with HCV genotype 1a had ribavirin therapy interrupted due to anemia and 4 received erythropoietin.[26]

- **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.[27] 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/1.73m$^2$ had lower SVR12 rates.[27] 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. The only DAA for which there has been some concern regarding reduced renal clearance and high drug levels has been sofosbuvir; available data on the safety of sofosbuvir for patients with advanced renal disease (i.e. GFR less than 30 mL/min/1.73m$^2$) have been mixed, but more recently several observational reports suggested sofosbuvir is safe in this setting.[27, 28, 29, 30] The AASLD-IDSA HCV Guidance does not recommend using sofosbuvir-containing regimens in persons with advanced (stage 4-5) CKD or on dialysis.[31]

- **Daclatasvir**: No dosage adjustment of daclatasvir is needed for patients who have mild, moderate, or severe renal impairment. There are no recommendations regarding the use of daclatasvir in patients requiring dialysis (see Daclatasvir Prescribing Information).
- **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 or moderate renal impairment. There are insufficient data regarding the safety and efficacy of ledipasvir-sofosbuvir in patients with severe renal impairment (eGFR less than 30 mL/min/1.73m$^2$) or end-stage renal disease requiring dialysis (see Ledipasvir-Sofosbuvir Prescribing Information).
- **Ombitasvir-Paritaprevir-Ritonavir**: No dosage adjustment of ombitasvir-paritaprevir-ritonavir is needed for patients who have mild, moderate, or severe renal impairment. There are insufficient data regarding the safety and efficacy of ombitasvir-paritaprevir-ritonavir in patients requiring dialysis (see Ombitasvir-Paritaprevir-Ritonavir Prescribing Information).
- **Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir**: No dosage adjustment of ombitasvir-paritaprevir-ritonavir and dasabuvir is needed for patients who have mild, moderate, or severe renal impairment, including individuals requiring dialysis (see Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir Prescribing Information).
- **Simeprevir**: No dosage adjustment of simeprevir is needed for patients who have mild, moderate, or severe renal impairment. There are insufficient data regarding the safety and efficacy of simeprevir in patients requiring dialysis (see Simeprevir Prescribing Information).
- **Sofosbuvir**: No dosage adjustment of sofosbuvir is needed for patients who have mild or moderate renal impairment. There are insufficient data regarding the safety and efficacy of sofosbuvir in patients with severe renal impairment (eGFR less than 30 mL/min/1.73m$^2$) or end-stage renal disease requiring dialysis (see Sofosbuvir Prescribing Information).
- **Sofosbuvir-Velpatasvir**: No dosage adjustment of sofosbuvir-velpatasvir is needed for patients who have mild or moderate renal impairment. There are insufficient data regarding the safety and efficacy of sofosbuvir-velpatasvir in patients with severe renal impairment (eGFR less than 30 mL/min/1.73m$^2$) or end-stage renal disease requiring dialysis (see Sofosbuvir-Velpatasvir Prescribing Information).
- **Sofosbuvir-Velpatasvir-Voxilaprevir**: No dosage adjustment of sofosbuvir-velpatasvir-voxilaprevir is needed for patients who have mild or moderate renal impairment. There are insufficient data regarding the safety and efficacy of sofosbuvir-velpatasvir-voxilaprevir in patients with severe renal impairment (eGFR less than 30 mL/min/1.73m$^2$) or end-stage renal disease (see Sofosbuvir-Velpatasvir-Voxilaprevir Prescribing Information).

Dosing of Ribavirin in Persons with CKD

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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.
- 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 *Ribosphere* 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 provides the following specific recommendations for treatment of HCV in persons with renal impairment, with the guidance stratified based on the degree of renal impairment.[31]

Mild-to-Moderate Renal Impairment: Any DAA Regimen

For persons with chronic HCV infection and mild-to-moderate renal impairment (CKD stage 1, 2, or 3), any of the DAA regimens recommended in the AASLD-IDSA HCV Guidance can be used without the need for dose adjustment. Interactions between DAA medications and other medications may require dose adjustment.

Severe Renal Impairment: Glecaprevir-Pibrentasvir or Elbasvir-Grazoprevir

For persons with severe renal impairment (CKD stage 4 or 5, with eGFR less than 30 mL/min or end-stage renal disease), the AASLD-IDSA HCV Guidance recommends using standard doses of a 12-week course of elbasvir-grazoprevir (for HCV genotypes 1a, 1b, or 4) and an 8 to 16 week course of glecaprevir-pibrentasvir (for HCV genotypes 1-6); the duration of glecaprevir-pibrentasvir is based on prior treatment history and presence of cirrhosis. Interactions between DAA medications and other medications may require dose adjustment.
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.[32, 33] 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 post-transplant and the improved clinical outcomes in those who underwent HCV clearance prior to transplantation.[34, 35, 36] 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 DAA regimens are the same as those recommended to treat persons with chronic severe renal impairment.[31]

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 involved a small number of participants, typically 25 or less.[37, 38, 39, 40] In these studies, DAA therapy was safe and highly effective. Several larger studies also support the efficacy of HCV treatment in renal transplant recipients.[41, 42] 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.[41] All 114 (100%) of study participants achieved an SVR12.[41] 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.[42] Overall, 94.5% (52 of 55) renal transplant recipients achieved an SVR12 with DAA therapy for chronic HCV infection.[42]

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 genotype.[43] Note that consideration for drug interactions is extremely important in the post-transplantation period, particularly with regard to immunosuppressant calcineurin inhibitors, particularly cyclosporine and tacrolimus.

- **Genotypes 1 and 4, with or without Compensated Cirrhosis**: The recommended regimens are a 12-week course of glecaprevir-pibrentasvir or a 12-week course of ledipasvir-sofosbuvir.
- **Genotypes 2, 3, 5 or 6, with or without Compensated Cirrhosis**: The recommended regimen is a 12-week course of glecaprevir-pibrentasvir. The alternative regimen is a 12-week course of daclatasvir plus sofosbuvir plus low initial dose of ribavirin (starting at 600 mg per day and increasing to standard dosing as tolerated). 

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 mild-moderate renal impairment (CKD stage 1, 2, or 3) no dose adjustments are needed for DAA medications.
- For persons with severe renal impairment (CKD stage 4 or 5, including those with end-stage renal disease), the AASLD-IDSA HCV Guidance recommends using standard doses of a 12-week course of elbasvir-grazoprevir (for HCV genotypes 1a, 1b, or 4) or an 8- to 16-week course of glecaprevir-pibrentasvir (for HCV genotypes 1-6); the duration of glecaprevir-pibrentasvir is based on prior treatment history and presence of cirrhosis.
- 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


31. AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. Unique populations: patients with renal impairment. [AASLD-IDSA Hepatitis C Guidance] -


33. Kidney Disease Improving Global Outcomes (KDIGO) Guideline for the Prevention, Diagnosis, Evaluation and Treatment of Hepatitis C in Chronic Kidney Disease. [KDIGO] -


38. Kamar N, Marion O, Rostaing L, et al. Efficacy and Safety of Sofosbuvir-Based Antiviral Therapy to


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References


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