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CLINICAL GUIDELINE

Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C Virus Infection in Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2018 Clinical Practice Guideline

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Description: The Kidney Disease: Improving Global Outcomes (KDIGO) 2018 clinical practice guideline for the prevention, diagnosis, evaluation, and treatment of hepatitis C virus (HCV) infection in chronic kidney disease (CKD) is an extensive update of KDIGO's 2008 guideline on HCV infection in CKD. This update reflects the major advances since the introduction of direct-acting antivirals (DAAs) in the management of HCV infection in the CKD population.

Methods: The KDIGO work group tasked with developing the HCV and CKD guideline defined the scope of the guideline, gathered evidence, determined topics for systematic review, and graded the quality of evidence previously summarized by the evidence review team. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was used to appraise the quality of evidence and rate the strength of the recommendations. Searches of the English-language literature were conducted through May 2017 and were supplemented with targeted searches for studies of DAA treatment and with abstracts from nephrology, hepatology, and transplantation conferences. A review process involving many stakeholders, subject matter experts, and industry and national organizations informed the guideline's final modification.

Recommendation: The updated guideline comprises 66 recommendations. This synopsis focuses on 32 key recommendations pertinent to the prevention, diagnosis, treatment, and management of HCV infection in adult CKD populations.

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The first clinical practice guideline published by Kidney Disease: Improving Global Outcomes (KDIGO) was its 2008 guideline on the prevention, diagnosis, evaluation, and treatment of hepatitis C virus (HCV) infection in patients with chronic kidney disease (CKD) (1, 2). In the subsequent 10 years, the development of direct-acting antivirals (DAAs), which enabled a greater than 95% rate of viral eradication in CKD populations infected with HCV, prompted KDIGO to update its 2008 guideline (3, 4).

The guideline's overall objective is to inform the management of HCV infection, including the use of DAAs in adults with CKD. Its target audience includes nephrologists, transplant physicians, hepatologists, infectious disease specialists, primary care physicians, and other practitioners caring for adults with HCV infection and CKD worldwide. Like the original 2008 HCV and CKD guideline, recommendations are divided into 5 chapters addressing the detection and evaluation of HCV in CKD, treatment of HCV infection in patients with CKD, prevention of HCV transmission in hemodialysis units, management of HCV-infected patients before and after kidney transplantation, and diagnosis and management of kidney diseases associated with HCV infection.

Within the guideline, recommendations for clinical practice, implementation, and future research are highlighted. The guideline seeks to provide comprehensive guidance encompassing all aspects of managing HCV infection in CKD populations (**Appendix Figure**, available at Annals.org) and considers implementation across international settings where HCV and CKD are encountered. The complete version is available at www.kdigo.org and includes 66 recommendations. This synopsis focuses on 32 key recommendations relevant to clinical practice regarding HCV infection in patients with CKD. The major topics of the remaining 34 recommendations include the prevention of HCV transmission in hemodialysis units, CKD testing in HCV-infected patients, performance characteristics of noninvasive tests of hepatic fibrosis, and decisions regarding liver–kidney versus kidney-only transplantation.

Guideline Development Process, Evidence Grading, and Stakeholder Consultation

The work group consisted of an international body of clinicians and researchers, including nephrologists, hepatologists, virologists, a representative from the Centers for Disease Control and Prevention (CDC), and a professional evidence review team. The work group formulated the scope of the guideline and graded evidence on the basis of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system (5) in accordance with KDIGO's usual practice (**Appendix Tables 1** and **2**, available at www.Annals.org).

In brief, the process involved reviewing the 2008 KDIGO guideline on HCV and CKD, as well as other HCV guidelines (American Association for the Study of Liver Diseases and Infectious Diseases Society of America [AASLD/IDSA], European Association for the Study of the Liver,

and Japanese Society for Dialysis Therapy) that had sections related to CKD (6–8), and then developing research questions for each of the chapters. On the basis of specific research questions identified by the work group, the evidence review team conducted systematic reviews on 7 topics: HCV treatment in CKD populations (chapters 2, 4, and 5), pretransplant noninvasive testing for hepatic fibrosis (chapter 1), outcome of isolation of HCV-infected patients in hemodialysis units (chapter 3), outcomes with early versus late kidney transplantation for HCV-infected patients on the waitlist (chapter 4), transplantation of kidneys from HCV-infected donors to HCV-infected recipients (chapter 4), predictors of CKD progression associated with HCV (chapter 1), and relationships between HCV and graft loss and mortality in kidney transplant recipients (chapter 4). The search parameters are presented in **Appendix Table 3** (available at Annals.org). The formal literature search identified 125 eligible studies, which were summarized and assessed for quality by using the GRADE methodology (5). The work group then developed guideline statements rated as strong (level 1) or weak (level 2) on the basis of the strength of evidence from the systematic review as well as other evidence from non-CKD populations. In accordance with GRADE, the strength of the evidence supporting each guideline statement was rated from high (A) to very low (D). Guideline statements providing general guidance, and therefore not based on systematic evidence review, were labeled "nongraded."

The guideline statements and supporting text subsequently underwent external stakeholder review by individuals and organizations worldwide with expertise in the field. The final document incorporated comments and suggestions from the external review where appropriate.

CHAPTER 1: RECOMMENDATIONS RELATED TO THE DETECTION AND EVALUATION OF HCV IN CKD

1.1.1. We recommend screening all patients for HCV infection at the time of initial evaluation of CKD (1C).

1.1.1.1. We recommend using an immunoassay followed by nucleic acid testing (NAT) if immunoassay is positive (1A).

Hepatitis C virus infection is more prevalent among persons with CKD than it is in the general population. Approximately 5% of patients receiving incident dialysis have HCV-positive results on enzyme-linked immunosorbent assay (EIA) (9), compared with an estimated 1% of the general U.S. population (10). Recent studies implicated HCV infection as an independent risk factor for faster rates of CKD progression (11), related in part to the association of HCV with several glomerulonephritides but probably also independent of this connection. The AASLD/IDSA and CDC recommend 1-time HCV testing for the 1945 to 1965 birth cohort because of a higher prevalence of the virus in this group (6, 12). In addition, the AASLD/IDSA and CDC recommend HCV testing for high-risk patients, including those who have ever required long-term hemodialysis, have used injection or intranasal drugs, received a solid organ transplant before July 1992, have HIV infection, or were ever incarcerated (6) (**Table 1**). The recommendation to screen all patients for HCV at the time of initial CKD evaluation is based on these guideline recommendations, the higher prevalence of HCV infection among patients with CKD, and the more rapid CKD progression seen in patients with CKD and HCV infection compared with uninfected patients (13). Future studies should determine the degree of clinical benefit of this strategy of HCV testing in patients with CKD. Repeated HCV testing is prudent for patients who may be continuously exposed to HCV, such as through ongoing drug use or long-term hemodialysis. Decisions regarding the benefit of HCV screening in patients with CKD may be informed by a recent report describing a slower decrease in glomerular filtration rate (GFR) after versus before successful HCV treatment in patients with an estimated GFR less than 60 mL/min/1.73 m^2 (14).

Table 1. AASLD/IDSA Guidelines for 1-Time HCV Testing With a Focus on Recommendations Relevant to CKD Populations*

Patients should be tested if they:
Were born between 1945 and 1965, regardless of other risk factors
Ever required long-term hemodialysis
Received a solid organ transplant, particularly if before July 1992 or if they were informed that the donor had HCV
Ever used injection drugs
Ever used intranasal drugs
Were ever incarcerated
Have HIV infection
Have had any percutaneous/parenteral exposure to blood or other body fluids, including needlestick, sharp, or mucosal exposure (health care providers)

AASLD = American Association for the Study of Liver Diseases; CKD = chronic kidney disease; HCV = hepatitis C virus; IDSA = Infectious Diseases Society of America.
* The complete list is available at www.HCVguidelines.org.

Recommendations Related to HCV Testing in Patients With End-Stage Kidney Disease

1.1.2. We recommend screening all patients for HCV infection upon initiation of in-center hemodialysis or upon transfer from another dialysis facility or modality (1A).

1.1.2.1. We recommend using NAT alone or an immunoassay followed by NAT if immunoassay is positive (1A).

1.1.3. We suggest screening all patients for HCV infection upon initiation of peritoneal dialysis or home hemodialysis (2D).

1.1.4. We recommend screening all patients for HCV infection at the time of evaluation for kidney transplantation (1A).

The prevalence of HCV in the hemodialysis population exceeds that of the general population, with approximately 10% of patients in the recent DOPPS (Dialysis Outcomes and Practice Patterns Study) analyses having positive results on EIA, also known as anti-HCV or HCV antibody testing (9, 15). The high HCV preva-

lence occurs as a result of the high prevalence of HCV on initiation of dialysis (9) as well as nosocomial transmission within hemodialysis units. Testing for HCV before the start of in-center hemodialysis (including a transition from another dialysis method) and upon transfer between hemodialysis facilities provides the opportunity to identify patients potentially exposed to HCV at the previous facility. Acute HCV infection in hemodialysis units is identified by monitoring liver biochemical test results for increases above baseline, which may suggest acute HCV infection and prompt testing for HCV viremia several months before EIA testing shows positive results. The recommendation for HCV testing in patients receiving peritoneal dialysis or home hemodialysis is based on limited evidence; nevertheless, it is a prudent approach. Testing for HCV is recommended for kidney transplant candidates to determine who is at risk for progressive hepatic disease and might benefit from an HCV-infected donor kidney and to select the optimal HCV treatment strategies for transplant candidates.

Nucleic acid testing confirms active HCV infection (HCV RNA positivity or viremia); however, EIA followed by NAT for patients with positive EIA results, ideally via reflex testing, is a reasonable approach with adequate sensitivity and specificity in immunocompetent patients. Nonetheless, NAT is the most appropriate first-line test for immunocompromised kidney transplant recipients, and possibly for patients receiving hemodialysis, because of concerns regarding delayed seroconversion in acute HCV infection (the window period). The choice between EIA and NAT is informed by the prevalence and incidence of HCV in individual hemodialysis units, because the risk for false-negative EIA results rises with increasing HCV prevalence (closely associated with incidence) in the dialysis population (1).

Chapter 2: Recommendations Related to Treatment of HCV Infection in Patients With CKD

Treatment in Patients With CKD GFR Category G1 to G5 and G5D

2.1. We recommend that all CKD patients infected with HCV be evaluated for antiviral therapy (1A).

2.1.1. We recommend an interferon-free regimen (1A).

2.1.2. We recommend that the choice of specific regimen be based on HCV genotype (and subtype), viral load, prior treatment history, drug–drug interactions, glomerular filtration rate (GFR), stage of hepatic fibrosis, kidney and liver transplant candidacy, and comorbidities (1A).

2.2. We recommend that patients with GFR ≥30 mL/min/1.73 m^2 (CKD G1–G3b) be treated with any licensed direct-acting antiviral (DAA)-based regimen (1A).

2.3. Patients with GFR <30 mL/min/1.73 m^2 (CKD G4–G5D) should be treated with a ribavirin-free DAA-based regimen.

The development of DAAs has changed the approach to HCV treatment in patients with CKD since the 2008 guideline. Interferon treatment no longer is recommended because of high adverse event rates and modest sustained virologic response (SVR) rates of 37% to 41% (16, 17). Moreover, interferon is contraindicated in kidney transplant recipients because of a high risk for acute rejection and allograft loss (18). Treatment with DAAs achieves SVR rates of 90% to 100%, with few adverse events, even in patients with CKD G4 to G5, patients with end-stage kidney disease (ESKD), and kidney transplant recipients (19–22). All patients with CKD should be evaluated for DAA treatment, with the specific regimen determined by HCV genotype, viral load, treatment history, GFR, hepatic fibrosis stage, and kidney and liver transplant candidacy and after consideration of drug–drug interactions. Figure 1 presents a treatment algorithm based on CKD stage and HCV genotype.

The evidence base regarding DAA treatment in CKD populations is evolving rapidly, requiring professional organizations to frequently update recommendations regarding choice of antiviral regimens. Clinicians should refer to www.HCVguidelines.org, a useful resource that is updated frequently to reflect new evidence (6). Key studies in CKD populations include C-SURFER, a randomized controlled trial of immediate versus delayed treatment with a 12-week course of elbasvir and grazoprevir in 224 patients with HCV genotype 1 and CKD G4 to G5 (76% with ESKD) (22). The SVR rate was 94% in patients who received immediate treatment and 98% in those whose therapy was deferred (19). No patients discontinued treatment because of adverse events. Likewise, the pangenotypic regimen of glecaprevir and pibrentasvir for 12 weeks resulted in a 98% SVR rate in 104 patients with CKD G4 to G5 (82% with ESKD) (21). Four patients discontinued treatment, but 3 of them achieved an SVR. Although studies have reported the use of sofosbuvir-based regimens in CKD G4 to G5 and ESKD, sofosbuvir is excreted renally and is not approved by the U.S. Food and Drug Administration (FDA) for use in patients with a GFR below 30 mL/min/1.73 m^2.

Extrapolation of data from several studies in non-CKD populations (which probably included some patients with CKD G1 to G3b) (23, 24) has shown that patients with CKD who have a GFR of at least 30 mL/min/1.73 m^2 may receive treatment with any licensed DAA regimen. Patients with a GFR below 30 mL/min/1.73 m^2 should receive therapy with the specific regimens outlined earlier (Table 2).

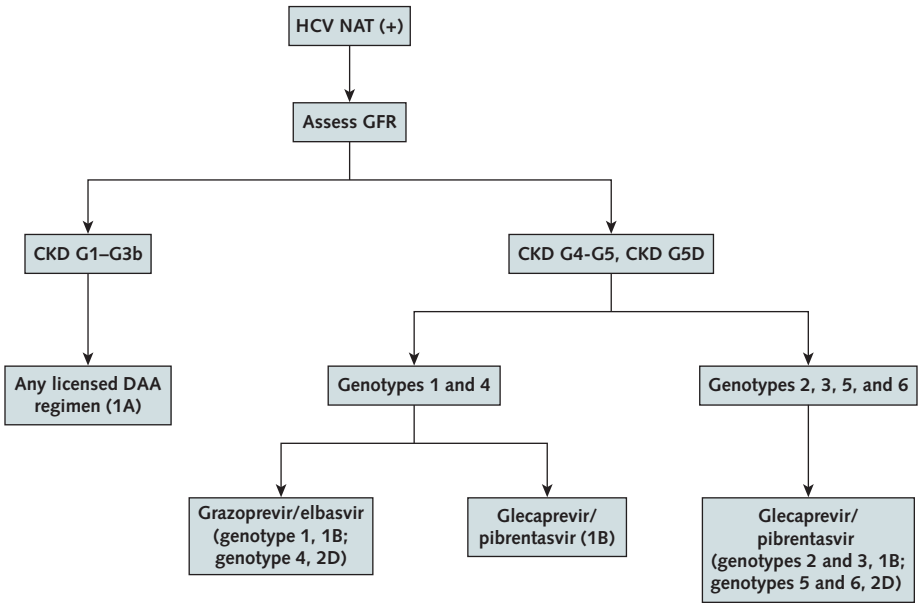
HCV Treatment for Kidney Transplant Recipients

2.4. We recommend that all kidney transplant recipients infected with HCV be evaluated for treatment (1A).

2.4.1. We recommend treatment with a DAA-based regimen (1A).

2.4.2. We recommend that the choice of regimen be based on HCV genotype (and subtype), viral load, prior treatment history, drug–drug interactions, GFR,

Figure 1. Treatment scheme for CKD GFR categories G1 to G5D.



Recommendation grades (1 or 2) and strength of evidence (A to D) are provided for each recommended treatment regimen and HCV genotype. Sofosbuvir/velpatasvir-based regimens are not shown here because they were not formally reviewed by the evidence review team at the time of guideline publication. However, these regimens may be considered in patients with CKD G1 to G3b given their availability in certain jurisdictions. + = positive results; CKD = chronic kidney disease; DAA = direct-acting antiviral; GFR = glomerular filtration rate; HCV = hepatitis C virus; NAT = nucleic acid testing.

stage of hepatic fibrosis, liver transplant candidacy, and comorbidities (1A).

2.4.3. We recommend avoiding treatment with interferon (1A).

2.4.4. We recommend pre-treatment assessment for drug–drug interactions between the DAA-based regimen and other concomitant medications including immunosuppressive drugs in kidney transplant recipients (1A).

2.4.4.1. We recommend that calcineurin inhibitor levels be monitored during and after DAA treatment (1B).

Studies of DAA treatment in kidney transplant recipients generally have enrolled patients with a GFR of 30 mL/min/1.73 m^2 or higher and therefore have included sofosbuvir-based regimens. Treatment with DAAs in kidney transplant recipients has resulted in SVR rates exceeding 95%. Colombo and colleagues (20) reported an SVR of 100% after 114 kidney transplant recipients received treatment with sofosbuvir and ledipasvir, with only 1% discontinuing treatment because of adverse events. A study combining kidney and liver transplant recipients demonstrated an overall SVR of 98% after treatment with glecaprevir and pibrentasvir, with all 20 kidney transplant recipients achieving an SVR (25).

For kidney transplant recipients, the selection of DAA regimen should reflect HCV genotype, viral load, treatment history, GFR, and hepatic fibrosis stage, and particularly should consider drug–drug interactions between the DAA and other medications, notably calcineurin inhibitors. Information on drug–drug interactions is available at www.hep-druginteractions.org, which is updated frequently on the basis of new data. Clinicians providing care for HCV-infected kidney transplant recipients should have a heightened awareness of changes in allograft function, particularly in those receiving calcineurin inhibitors, because increased or decreased plasma levels have been described as a result of drug–drug interactions with DAAs. Treatment of HCV infection in kidney transplant recipients should follow the algorithm in Figure 2 and the specific regimens outlined in Table 2. Although early evidence suggests that most DAAs may be used safely in patients receiving transplant immunosuppressive agents, and most DAAs are FDA-approved for patients with a GFR above 30 mL/min/1.73 m^2, the clinical experience with DAAs in organ transplant recipients remains relatively sparse; therefore, careful attention to treatment in this population is prudent.

Timing of Treatment in Kidney Transplant Candidates

2.1.3. Treat kidney transplant candidates in collaboration with the transplant center to optimize timing of therapy (not graded).

As a result of the universally high SVR rates in all CKD populations, decisions regarding optimal timing of treatment for transplant candidates should include the transplant center (26). Kidney transplant candidates with HCV who are willing to accept a kidney from an HCV-infected donor may benefit from a shorter waitlist time if they forgo treatment until after receiving the HCV-positive donor organ, a graft that might otherwise be discarded (27). However, kidney transplant candi-

dates with compensated cirrhosis from HCV should be considered for pretransplant treatment to induce fibrosis regression after achieving SVR to allow kidney-only transplantation.

2.5. All treatment candidates should undergo testing for HBV infection prior to therapy (not graded).

Assessment for unrecognized hepatitis B virus (HBV) infection before DAA treatment is recommended because of recent reports of fulminant HBV reactivation during DAA therapy (28). The prevalence of HBV in the hemodialysis facilities sampled in DOPPS was 3.0% (29), suggesting that the prevalence in patients with CKD probably exceeds that of the general population. Testing should include hepatitis B surface antigen, surface antibody, and core antibody and, if required by test results, HBV DNA.

Chapter 4: Recommendations Related to the Management of HCV-Infected Patients Before and After Kidney Transplantation

4.1.1. We recommend kidney transplantation as the best therapeutic option for patients with CKD G5, irrespective of presence of HCV infection (1A).

4.1.3. Timing of HCV treatment in relation to kidney transplantation (before vs. after) should be based on donor type (living vs. deceased donor), wait-list times by donor type, center-specific policies governing the use of kidneys from HCV-infected deceased donors, HCV genotype, and severity of liver fibrosis (not graded).

4.1.3.1. We recommend that all HCV-infected patients who are candidates for kidney transplantation be considered for DAA therapy, either before or after transplantation (1A).

4.1.3.2. We suggest that HCV-infected kidney transplant candidates with a living kidney donor can be considered for treatment before or after transplantation according to HCV genotype and anticipated timing of transplantation (2B).

4.1.3.3. We suggest that if receiving a kidney from an HCV-positive donor improves the chances for transplantation, the HCV NAT-positive patient can undergo transplantation with an HCV-positive kidney and be treated for HCV infection after transplantation (2B).

Use of Kidneys From HCV-Infected Donors

4.2.1. We recommend that all kidney donors be screened for HCV infection with both immunoassay and NAT (if NAT is available) (1A).

Table 2. HCV Treatment Regimens for Patients With CKD and for Kidney Transplant Recipients*

Patients (GFR)†	Recommended Regimens (Strength of Evidence)	Alternate Regimens (Strength of Evidence)
Persons with CKD G4–G5 (<30 mL/min/1.73 m²), including kidney transplant recipients‡		
HCV genotype		
1a	Grazoprevir/elbasvir (1B)	Ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir§ with ribavirin (2D)
	Glecaprevir/pibrentasvir (1B)	Daclatasvir/asunaprevir (2C)
1b	Grazoprevir/elbasvir (1B)	Ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir§ (2D)
	Glecaprevir/pibrentasvir (1B)	Daclatasvir/asunaprevir (2C)
2, 3	Glecaprevir/pibrentasvir (1B)	–
4	Grazoprevir/elbasvir (2D)	–
	Glecaprevir/pibrentasvir (1B)	–
5, 6	Glecaprevir/pibrentasvir (2D)	–
Kidney transplant recipients (≥30 mL/min/1.73 m²)		
HCV genotype		
1a	Sofosbuvir with ledipasvir, daclatasvir, or simeprevir (1B)	Sofosbuvir/ribavirin (2D)
	Glecaprevir/pibrentasvir (1C)‖	–
1b	Sofosbuvir with ledipasvir, daclatasvir, or simeprevir (1B)	–
	Glecaprevir/pibrentasvir (1C)‖	–
2, 3, 5, 6	Glecaprevir/pibrentasvir (1D)‖	Sofosbuvir/daclatasvir/ribavirin (2D)¶
4	Sofosbuvir with ledipasvir, daclatasvir, or simeprevir (1D)	–
	Glecaprevir/pibrentasvir (1D)‖	–

AASLD = American Association for the Study of Liver Diseases; CKD = chronic kidney disease; GFR = glomerular filtration rate; HCV = hepatitis C virus; IDSA = Infectious Diseases Society of America.

* Therapy duration for all regimens is usually 12 wk, but readers should consult guidelines from the AASLD/IDSA or European Association for the Study of the Liver for latest guidance. We recommend that patients with CKD and a GFR ≥30 mL/min/1.73 m² (CKD G1–G3b) receive treatment with any licensed direct-acting antiviral regimen. Sofosbuvir/velpatasvir-based regimens are not listed here because they were not formally reviewed by the evidence review team at the time of guideline publication. However, these regimens may be considered in patients with a GFR ≥30 mL/min/1.73 m² given their availability in certain jurisdictions.

† For patients with CKD G5 who are receiving peritoneal dialysis, no evidence or data are available; therefore, following the proposed regimens for patients receiving hemodialysis is reasonable.

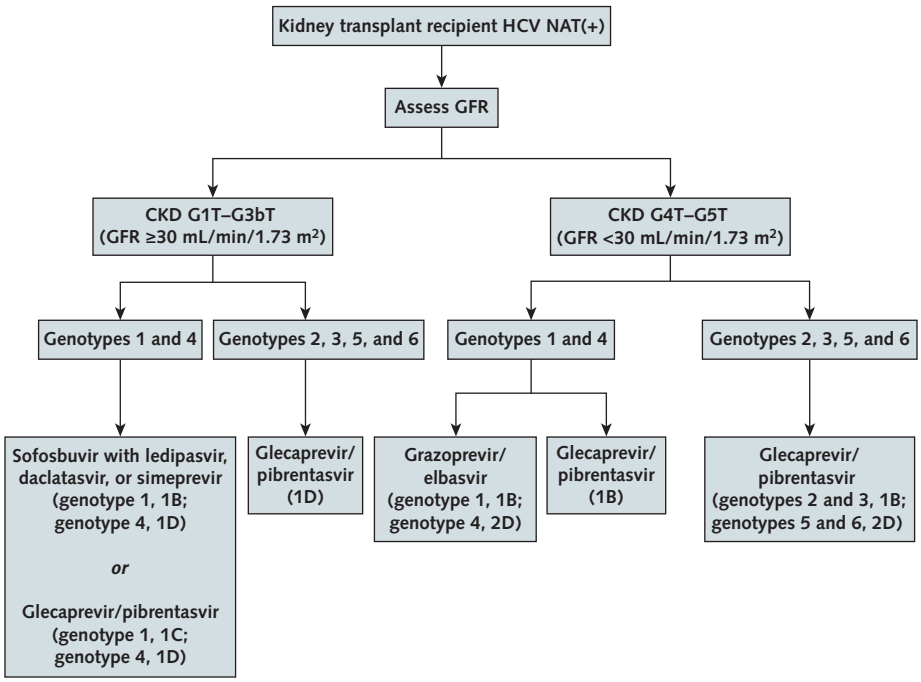
‡ Little published evidence exists to guide treatment regimens in kidney transplant recipients with a GFR <30 mL/min/1.73 m² (CKD G4T–G5T). For these patients, regimens should be selected to avoid drug–drug interactions, particularly with calcineurin inhibitors.

§ Also known as the PrOD or 3D regimen.

‖ Based on reference 25.

¶ As suggested by AASLD/IDSA guidelines (www.HCVguidelines.org).

Figure 2. Treatment scheme for kidney transplant recipients.



Recommendation grade (1 or 2) and strength of evidence (A to D) are provided for each recommended treatment regimen and HCV genotype. Sofosbuvir/velpatasvir-based regimens are not shown here because they were not formally reviewed by the evidence review team at the time of guideline publication. However, these regimens may be considered in kidney transplant recipients with a GFR ≥30 mL/min/1.73 m^2 given their availability in certain jurisdictions. + = positive results; CKD = chronic kidney disease (*T* suffix in GFR categories [e.g., G1T] denotes transplant recipient); GFR = glomerular filtration rate; HCV = hepatitis C virus; NAT = nucleic acid testing.

4.2.2. We recommend that transplantation of kidneys from HCV NAT-positive donors be directed to recipients with positive NAT (1A).

4.2.3. After the assessment of liver fibrosis, HCV-positive potential living kidney donors who do not have cirrhosis should undergo HCV treatment before donation; they can be accepted for donation if they achieve sustained virologic response (SVR) and remain otherwise eligible to be a donor (not graded).

Hepatitis C virus infection is not a contraindication to kidney transplantation. The mortality rates are much lower in HCV-infected kidney transplant recipients than in HCV-infected patients on the transplant waitlist (30–32). Nevertheless, HCV-infected kidney transplant recipients have had increased mortality (33, 34), allograft loss (35, 36), posttransplant diabetes (37–39), and glomerulonephritis (40, 41) compared with noninfected patients; therefore, DAA treatment is critical, and the decision regarding pre- versus posttransplant treatment must be individualized to maximize the benefit for each patient (26). Incorporating the judgment of the transplant center and other specialists in these complex decisions is critical. Specific details regarding evidence-based DAA treatment regimens, timing of treatment, and the importance of monitoring GFR and calcineurin inhibitor levels during and after treatment are discussed elsewhere (chapter 2, section 2.4).

HCV-Infected Kidney Donors

Potential deceased donors require HCV testing with both EIA and NAT to determine whether viremia is present. Kidneys from HCV-infected deceased donors should be directed to recipients with positive NAT results. This practice has been modified by the development of research protocols describing transplantation of kidneys from NAT-positive donors to non–HCV-infected recipients who received immediate DAA treatment; these studies have reported a 100% SVR rate with good short-term allograft outcomes (42, 43). This practice may become more widespread in the future but for now should be restricted to investigational settings, although this statement may require revision as new evidence accrues. Potential living kidney donors with HCV infection should receive DAA treatment and, upon achieving an SVR, be re-evaluated to ensure that they are still appropriate kidney donors.

CHAPTER 5: RECOMMENDATIONS RELATED TO THE DIAGNOSIS AND MANAGEMENT OF KIDNEY DISEASES ASSOCIATED WITH HCV INFECTION

5.2. We recommend that patients with HCV-associated glomerular disease be treated for HCV (1A).

5.2.1. We recommend that patients with HCV-related glomerular disease showing stable kidney func-

tion and/or non-nephrotic proteinuria be treated initially with DAA (1C).

5.2.2. We recommend that patients with cryoglobulinemic flare, nephrotic syndrome, or rapidly progressive kidney failure be treated, in addition to DAA treatment, with immunosuppressive agents with or without plasma-exchange (1C).

5.2.3. We recommend immunosuppressive therapy in patients with histologically active HCV-associated glomerular disease who do not respond to antiviral therapy, particularly those with cryoglobulinemic kidney disease (1B).

5.2.3.1. We recommend rituximab as the first-line immunosuppressive treatment (1C).

The role of DAAs in managing HCV-associated glomerulonephritis, including HCV-associated mixed cryoglobulinemia and membranoproliferative glomerulonephritis, has become clearer in recent years. Rates of SVR have ranged from 74% to 83% in studies of DAAs for HCV-associated glomerulonephritis, with low adverse event rates (44–46). It is important to note that DAA treatment leads to diminished proteinuria and increased GFR and quality of life, but studies have been limited to patients with stable GFR and without rapidly progressive glomerulonephritis, cryoglobulinemic vasculitis, or nephrotic-range proteinuria. In these more urgent scenarios, immunosuppressive therapy should be administered concomitantly with DAAs, and plasma exchange should be considered. Among immunosuppressive agents, rituximab is the best-studied agent for HCV-related glomerulonephritis (47, 48). Before initiating rituximab therapy, patients should be assessed for HBV infection to avoid fulminant hepatitis resulting from HBV reactivation.

DISCUSSION

The 2018 KDIGO clinical practice guideline on HCV and CKD represents a major update to the original 2008 guideline. Because of the efficacy of DAAs in populations with CKD, including CKD G4, G5, and G5D, as well as in kidney transplant recipients, the approach to HCV management has evolved dramatically in the past 10 years. The ability to eradicate HCV with DAA treatment influenced all chapters of the 2018 update. Medium-sized prospective cohort studies and randomized controlled trials in CKD G4 and G5, as well as in patients receiving hemodialysis and in kidney transplant recipients, have consistently revealed SVR rates of 90% to 100%. The results add to the evidence base supporting efficacy of DAA treatment in patients without CKD and directly translate to the recommendation to evaluate treatment candidacy for all HCV-infected patients with CKD. Direct-acting antiviral–based treatment of HCV-associated glomerular disease is another area of rapid change, with a shift in focus from immunosuppression to HCV eradication as the first-line management approach for most patients.

The potential to cure HCV infection also affects the recommendations on HCV testing. The CDC and AASLD/IDSA already recommend 1-time HCV testing for the 1945 to 1965 birth cohort and for patients with a high risk for HCV infection, which includes several risk factors common to patients with CKD. Nephrologists generally recommend HCV testing for patients under evaluation for glomerular disease; in addition, the yield of HCV testing in patients with CKD is higher because of the increased prevalence of HCV in the CKD population. The growing evidence base supporting an association between HCV infection and faster progression of CKD to ESKD also supports the recommendation to test all patients at initial CKD evaluation. If future investigation replicates the early finding that DAA treatment may slow CKD progression (49), the imperative for HCV testing of all patients with CKD would gain strength because it would offer a novel avenue to slow CKD progression (50).

Finally, the efficacy of DAA therapy in patients with advanced kidney disease, including those receiving dialysis and kidney transplant recipients, has greatly affected the approach to HCV infection in kidney transplant candidates. Careful attention to strategies for timing HCV treatment that maximize benefit to individual patients as well as those that improve the use of HCV-infected deceased donor kidneys are becoming increasingly important (27). The new development in which HCV-infected organs are transplanted to HCV-uninfected persons who receive immediate posttransplant DAA treatment may represent a major advance (42, 43, 51), but it is a new field that warrants further investigation. Clinicians treating HCV-infected kidney transplant recipients should have heightened awareness for changes in allograft function, particularly in patients receiving calcineurin inhibitors. Until more extensive experience is available to ensure the safety of DAAs, with the transplanted kidney functioning in the common GFR range of 30 to 60 mL/min/1.73 m^2, kidney allograft function should be monitored closely while these patients are receiving DAA therapy.

Future research in HCV and CKD will probably shift to implementation science, as well as to cost-effectiveness and decision analysis. What are the best approaches to identify HCV-infected patients with CKD? How do we ensure equitable access to DAA treatment? Does HCV treatment actually slow CKD progression? What is the optimal timing of HCV treatment in patients whose kidney disease may progress to ESKD? What are the cost implications of strategies designed to test all patients with CKD and to provide treatment to all HCV-infected persons? The answers to these and other questions will probably guide the future of HCV management in patients with CKD.

We are optimistic that the current KDIGO guideline will increase attention on the intersection between HCV and CKD and spur future investigation into new directions to improve the care of this patient population.

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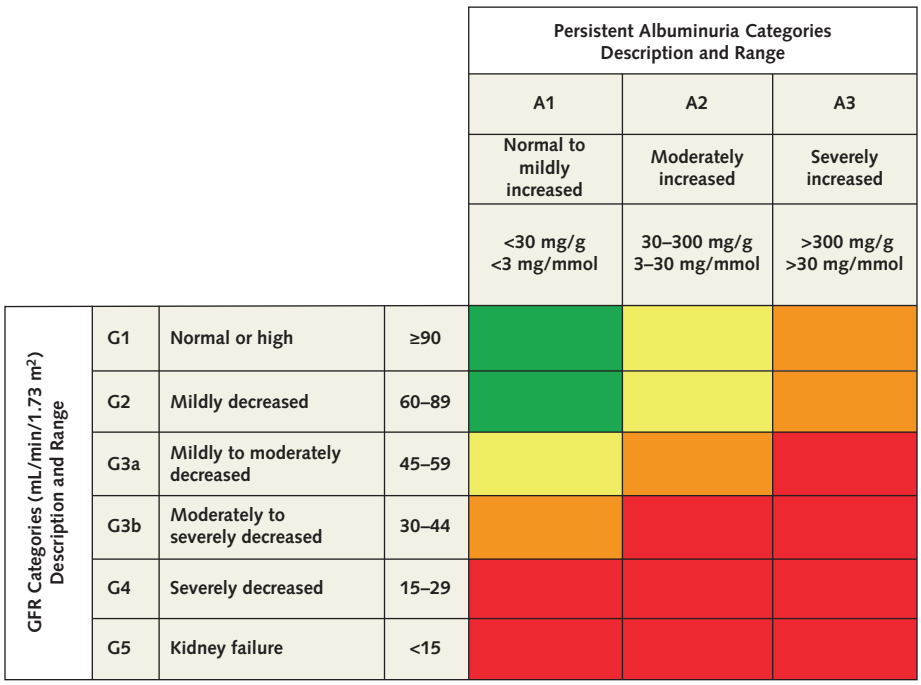
Appendix Figure. Prognosis of CKD, by categories of GFR and albuminuria.



Chronic kidney disease is defined as abnormalities of kidney structure or function that are present for >3 months and have health implications. It is classified on the basis of cause, GFR category (G1 to G5), and albuminuria category (A1 to A3 [presented as albumin–creatinine ratios]). Green means low risk (no CKD if no other markers of kidney disease), yellow means moderately increased risk, orange means high risk, and red means very high risk. The suffix *D* denotes dialysis (for example, CKD G5D refers to a patient with CKD stage G5 who is receiving dialysis). CKD = chronic kidney disease; GFR = glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes. (Reproduced with permission of KDIGO.).

Appendix Table 1. GRADE Criteria Used for Grading the Strength of a Recommendation*

	Implications		
Grade	**Patients**	**Clinicians**	**Policy**
Level 1 ("We recommend")	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 ("We suggest")	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require debate and involvement of stakeholders before policy can be determined.

GRADE = Grading of Recommendations Assessment, Development and Evaluation.
* The additional category "not graded" is used, typically, to provide guidance on the basis of common sense or if the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements but are not meant to be interpreted as being stronger than level 1 or 2 recommendations.

Appendix Table 2. GRADE Criteria Used for Grading the Overall Quality of Evidence

Grade	Quality of Evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

GRADE = Grading of Recommendations Assessment, Development and Evaluation.

Appendix Table 3. Research Questions Addressing the Systematic Update of Selected Recommendations

Parameters	Values
Predictor analyses*	
Population	Predictors of CKD progression: any (including general population) *except* CKD G5D (dialysis) HCV as predictor: kidney transplant recipients
Predictor	HCV infection (untreated), other predictors of CKD progression (if HCV infected)
Outcome	CKD progression (change in GFR, SCr doubling, ESKD), proteinuria, patient mortality, graft loss, delayed graft function, kidney pathology (HCV-associated GN)
Design	Longitudinal, multivariable analyses HCV-associated GN: any (except autopsy studies)
Minimum follow-up	Any
Patients, *n*	≥100
Publication dates	Predictors of CKD progression: any HCV as predictor: 2008 or later (plus studies in 2008 KDIGO CPG)
HCV treatment†	
Population	CKD G3a–5 (including dialysis and transplant recipients) or equivalent; HCV infection
Intervention	DAAs (except first generation: telaprevir, boceprevir), pegylated interferon ± ribavirin, immunosuppression including induction (in combination with DAA or as treatment for HCV-associated GN)
Comparator	Active or control or none (single-group studies)
Outcome	Categorical: all-cause mortality, SVR (preferably 24 wk), hepatocellular carcinoma, graft loss, NODAT, QoL, adverse events (including treatment discontinuation), pharmacokinetics/dynamics Continuous (HCV-associated GN only): kidney function, proteinuria
Study design	RCT, nonrandomized comparative, single-group, prospective (all topics), or retrospective (immunosuppression or GN topics only) Interferon in dialysis: RCT only
Minimum follow-up	HCV treatment studies: 12 wk after treatment Other topics: no minimum
Patients, *n*	≥10 Immunosuppression topic: any, including case reports
Publication dates	All: 2008 or later (plus studies in 2008 KDIGO CPG) Interferon and dialysis topic: Cochrane Review and studies published in 2012 or later
Liver testing‡	
Population	Tests for cirrhosis: CKD (all stages) Pretransplant biopsy: CKD G4–G5 pretransplant (or equivalent)
Intervention/comparator	Noninvasive liver testing, including upper endoscopy (for varices), and liver biopsy
Outcome	Noninvasive test performance characteristics, change in management strategy, patient mortality, graft loss
Design	Any
Patients, *n*	Noninvasive testing: ≥10 Pretransplant biopsy: ≥5
Publication dates	Any
Early vs. late transplantation‡	
Population	HCV-infected transplant candidates
Intervention	Transplantation ("now")
Comparator	Remaining on waitlist or awaiting HCV-negative status
Outcome	Patient mortality, graft loss
Design	Any, multivariable analysis
Minimum follow-up	None
Patients, *n*	≥100
Publication dates	2008 or later (plus studies in 2008 KDIGO CPG)
HCV-infected donors‡	
Population	HCV-infected kidney transplant recipients
Intervention	HCV-infected donors
Comparator	HCV-negative donors
Outcome	Patient mortality, graft loss
Design	Longitudinal comparative, multivariable analysis
Minimum follow-up	None
Patients, *n*	≥100
Publication dates	Any

CKD = chronic kidney disease; CPG = clinical practice guideline; DAA = direct-acting antiviral; ESKD = end-stage kidney disease; GFR = glomerular filtration rate; GN = glomerulonephritis; HCV = hepatitis C virus; KDIGO = Kidney Disease: Improving Global Outcomes; NODAT = new-onset diabetes after transplantation; QoL = quality of life; RCT = randomized controlled trial; SCr = serum creatinine; SVR = sustained virologic response.
* Chapter 1: Recommendations Related to the Detection and Evaluation of HCV in CKD.
† Chapter 2: Recommendations Related to Treatment of HCV Infection in Patients With CKD, and Chapter 5: Recommendations Related to the Diagnosis and Management of Kidney Diseases Associated With HCV Infection.
‡ Chapter 4: Recommendations Related to the Management of HCV-Infected Patients Before and After Kidney Transplantation.