

Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2022 Clinical Practice Guideline

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Description: The Kidney Disease: Improving Global Outcomes (KDIGO) 2022 clinical practice guideline on prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease (CKD) is an update of the 2018 guideline from KDIGO.

Methods: The KDIGO Work Group (WG) updated the guideline, which included reviewing and grading new evidence that was identified and summarized. As in the previous guideline, the WG used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to appraise evidence and rate the strength of recommendations and used expert judgment to develop recommendations. New evidence led to updating of recommendations in the chapters on treatment of hepatitis C virus (HCV) infection in patients with CKD (Chapter 2), management of HCV infection before and after kidney transplant (Chapter 4), and diagnosis and management of kidney disease associated with HCV infection (Chapter 5). Recommendations in chapters on detection and evaluation of hepatitis C in CKD (Chapter 1) and prevention of HCV transmission in hemodialysis units (Chapter 3) were not updated because of an absence of significant new evidence.

Recommendations: The 2022 updated guideline includes 43 graded recommendations and 20 ungraded recommendations, 7 of which are new or modified on the basis of the most recent evidence and consensus among the WG members. The updated guidelines recommend expanding treatment of hepatitis C with sofosbuvir-based regimens to patients with CKD glomerular filtration rate categories G4 and G5, including those receiving dialysis; expanding the donor pool for kidney transplant recipients by accepting HCV-positive kidneys regardless of the recipient's HCV status; and initiating direct-acting antiviral treatment of HCV-infected patients with clinical evidence of glomerulonephritis without requiring kidney biopsy. The update also addresses the use of immunosuppressive regimens in such patients.

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The Kidney Disease: Improving Global Outcomes (KDIGO) 2022 clinical practice guideline on prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease (CKD) (<https://kdigo.org/wp-content/uploads/2022/11/KDIGO-2022-Hepatitis-C-in-CKD-Guideline.pdf>) (1) is a focused update of the prior 2018 guideline (2). The nature and scope of the KDIGO guideline, the guideline development process, details on evidence grading, and a summary of major recommendations from 2018 were published in the previous guideline synopsis (3). Our current synopsis includes the topic areas for which recommendations were updated, including Chapter 2 (Treatment of HCV [hepatitis C virus] infection in patients with CKD), Chapter 4 (Management of HCV infection before and after kidney transplantation), and Chapter 5 (Diagnosis and management of kidney disease associated with HCV infection). Chapters on the detection and evaluation of HCV infection in CKD (Chapter 1) and prevention of HCV transmission in hemodialysis units (Chapter 3) were deemed current by the Work Group (WG) and remained unchanged. These topics will not be

addressed further here as readers can refer to our previous synopsis (3).

The focused update was triggered by new data on antiviral treatment in patients with advanced stages of CKD (G4, G5, or G5D), transplant of HCV-infected kidneys into uninfected recipients, and evolution of the viewpoint on the role of kidney biopsy in managing kidney disease caused by HCV. This update is intended to assist clinicians in the care of patients with HCV infection and CKD, including patients receiving dialysis (CKD G5D) and patients with a kidney transplant (CKD G1T-G5T) (**Supplement Figure 1**, available at Annals.org). Treatment approaches and guideline recommendations are based on systematic review of relevant studies. Appraisal of the quality of the evidence and the strength of the recommendations followed the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. **Table 1** presents a summary of key messages from the KDIGO 2022 hepatitis C guideline (1). **Table 2** highlights recommendations that are new or have been updated since the previous version.

See also:

Web-Only
Supplement

METHODS

The methods for the guideline development process are described in the full guideline (1), which follows international standards for guideline development and has been reported in accordance with the AGREE II (Appraisal

of Guidelines for Research and Evaluation II) checklist (4) (see **Supplement Table 1**, available at [Annals.org](https://annals.org)). KDIGO (<https://kdigo.org>) funded and supported this guideline. KDIGO does not receive funding from commercial entities for the development of any specific guideline. The KDIGO HCV and CKD WG and the Evidence Review Team (ERT) were reconvened for this update. The WG comprised 6 nephrologists and 7 hepatologists from 9 countries. The ERT comprised 3 experts in systematic review and guideline development and included 1 nephrologist. The WG and the ERT convened via regularly scheduled teleconferences over the course of 18 months for discussion and deliberation. Relevant financial relationships were fully disclosed and published alongside the guideline; no conflicts of interests were identified for this guideline. The ERT conducted updated literature searches for Chapters 2, 4, and 5 from the 2018 guideline in February 2022. Details on the systematic review search criteria and literature search yields for this update are available in the Methods chapter of the guideline (**Supplement Table 2** and **Supplement Figure 2**, available at [Annals.org](https://annals.org)) (1). Newly identified evidence was presented to the WG, which reviewed ERT summaries to determine whether a full quantitative reassessment and reconsideration of recommendations was justified. For these topics, the ERT updated the evidence synthesis (both narrative and quantitative) and reassessed the grading for the quality of the evidence base using GRADE methods (5). Values

and preferences were obtained from the literature when possible (for example, quality-of-life outcomes) or were assessed in the judgment of the WG when robust evidence was not identified. The WG members met virtually to discuss and finalize the guideline statements through consensus. The WG developed recommendations using the GRADE framework (**Supplement Tables 3 and 4**, available at [Annals.org](https://annals.org)) and considered the balance of benefits and potential harms, the quality of the evidence, values and preferences, resource use and costs, and considerations for implementation of each recommended statement (6). The draft guideline was made available for public review and commenting by all stakeholders, including patients. The updated guideline includes 43 graded recommendations and 20 ungraded recommendations, 7 of which are new or modified on the basis of the most recent evidence. A summary of all guideline recommendation statements is provided in **Supplement Table 5** (available at [Annals.org](https://annals.org)).

CHAPTER 2: TREATMENT OF HCV INFECTION IN PATIENTS WITH CKD

In the 2018 guideline, the polymerase inhibitor sofosbuvir was not recommended for patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m² because of concerns that its predominant circulating metabolite (GS-331007) is eliminated by the kidneys

Table 1. Summary of Key Messages From the KDIGO 2022 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation and Treatment of Hepatitis C in CKD

Key Messages, by Topic Area

Treatment of HCV infection in patients with CKD

- DAAs are highly effective and well-tolerated treatments for hepatitis C in patients across all stages of CKD, including those undergoing dialysis and kidney transplant recipients, with no need for dose adjustment.
- Pangenotypic DAA regimens, including glecaprevir-pibrentasvir and sofosbuvir-based regimens, are safe and effective for treatment of hepatitis C in patients with advanced CKD (G4 or G5 not on dialysis; or those receiving dialysis [G5D]).
- HCV genotype should be determined to guide treatment if a pangenotypic regimen is not available.
- Protease inhibitors (drugs ending in “-previr”) are contraindicated in patients with Child-Pugh B and C cirrhosis.
- Potential drug-drug interactions should be identified before DAA therapy in all candidates, especially in kidney transplant recipients using immunosuppressive medications (www.hep-druginteractions.org). *Protease inhibitors carry a significant risk for drug-drug interactions, particularly in patients who are treated with immunosuppressive agents, such as calcineurin inhibitors and mTOR inhibitors. Concurrent use of grazoprevir-elbasvir and cyclosporine is not recommended because it increases grazoprevir and elbasvir levels. Grazoprevir-elbasvir also increases tacrolimus levels.*
- HBV serologic markers should be measured before DAA therapy to identify patients at risk for HBV reactivation.

Management of HCV-infected patients before and after kidney transplantation

- Evaluation of kidney transplant candidates with hepatitis C should include establishing the severity of liver disease to determine whether simultaneous liver and kidney transplant is indicated.
- DAA therapy should be administered to all HCV-infected kidney transplant candidates, either before or after transplant. If transplant is imminent (<24 wk), treatment can begin afterward. If the expected time to transplant is >24 wk, treatment can be administered depending on the availability of treatment regimens.
- All living kidney donors should be screened for HCV infection with immunoassay, and nucleic acid testing should be done to confirm HCV infection if donors are seropositive.
- Transplant centers should extensively educate patients about the risks and benefits of transplant from HCV-positive donors to HCV-negative recipients and confirm availability of DAAs to be administered in the early post-transplant period.
- Kidneys from HCV-infected donors can be offered to all potential recipients, regardless of HCV status of the recipient.
- Kidney transplant from HCV-infected donors to uninfected recipients, with prompt DAA treatment, results in excellent allograft and recipient outcomes.

Diagnosis and management of kidney diseases associated with HCV infection

- HCV-infected patients with a typical presentation of immune complex proliferative glomerulonephritis (e.g., hematuria, proteinuria, decreasing GFR) can be managed without a confirmatory kidney biopsy. Kidney biopsy should be considered if GFR decreases or proteinuria persists despite achievement of sustained virologic response or if immunosuppressive therapy is being considered.
- All patients with chronic hepatitis C and glomerulonephritis should be treated with DAAs, similar to those without glomerulonephritis.
- Patients with cryoglobulinemic flare or rapidly progressive glomerulonephritis can be treated simultaneously with both DAAs and immunosuppressive agents, with or without plasma exchange. Rituximab is the preferred first-line agent.

CKD = chronic kidney disease; DAA = direct-acting antiviral; GFR = glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; KDIGO = Kidney Disease: Improving Global Outcomes; mTOR = mammalian target of rapamycin.

Table 2. Key Changes in the KDIGO 2022 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation and Treatment of Hepatitis C in CKD

2018 Guideline	2022 Guideline
Sofosbuvir was not recommended in patients with CKD G4 and G5, including patients receiving dialysis. "We recommend that transplantation of kidneys from HCV NAT-positive donors be directed to recipients with positive NAT (1A)."	Sofosbuvir-based DAA regimens can be used in patients with GFR <30 mL/min/1.73 m ² , including those receiving dialysis (1A). "We recommend that kidneys from HCV infected donors be considered regardless of HCV status of potential kidney transplant recipients (1C)." "When transplanting kidneys from HCV infected donors into HCV-uninfected recipients, transplant centers must ensure that patients receive education and are engaged in discussion with sufficient information to provide informed consent. Patients should be informed of the risks and benefits of transplantation with an HCV-infected kidney, including the need for DAA treatment (Not Graded)." "When transplanting kidneys from HCV infected donors into HCV-uninfected recipients, transplant centers should confirm availability of DAAs for initiation in the early post-transplant period (Not Graded)."
"We recommend that a kidney biopsy be performed in HCV-infected patients with clinical evidence of glomerular disease (Not Graded)."	"HCV-infected patients with a typical presentation of immune-complex proliferative glomerulonephritis can be managed without a confirmatory kidney biopsy. However, a biopsy may be indicated in certain clinical circumstances (Not Graded)."
"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)."	"We recommend that patients with cryoglobulinemic flare or rapidly progressive glomerulonephritis be treated with both DAAs and immunosuppressive agents with or without plasma exchange (1C)." "The decision whether to use immunosuppressive agents in patients with nephrotic syndrome should be individualized (Not Graded)."

CKD = chronic kidney disease; DAA = direct-acting antiviral; GFR = glomerular filtration rate; HCV = hepatitis C virus; KDIGO = Kidney Disease: Improving Global Outcomes; NAT = nucleic acid testing.

and accumulates in patients with reduced GFR (7). However, there is now sufficient evidence that sofosbuvir, even at the full dose, is safe and effective in patients with CKD G4 and G5, including those receiving dialysis (G5D).

A systematic review conducted in preparation of the KDIGO guideline update included 106 studies of specified direct-acting antiviral (DAA) regimen use in patients with advanced CKD (22 studies of patients with CKD G4 or G5 who were not receiving dialysis, 69 studies of patients with CKD G5D, and 29 studies of kidney transplant recipients [KTRs]) through 1 February 2022 (8). The DAA regimens included sofosbuvir-based regimens (60 studies) and non-sofosbuvir-based regimens (such as glecaprevir-pibrentasvir, grazoprevir-elbasvir, or paritaprevir-ritonavir-ombitasvir and dasabuvir [PrOD]). In each population, DAAs achieved sustained virologic response in 12 weeks (SVR12) in more than 93% of participants. There was generally low quality of evidence of a low risk for serious adverse events (mostly 0%, up to 2.9%) and low risk for discontinuation because of adverse events (mostly 0% to 5%). Across 3 unadjusted observational studies in KTRs, the risk for death after DAA treatment was substantially lower than in those without treatment (summary odds ratio, 0.16 [95% CI, 0.04 to 0.61]). On the basis of these results, the WG concluded that DAA regimens are safe and highly effective in patients with advanced CKD, including patients receiving dialysis and KTRs.

Across 16 studies that evaluated sofosbuvir-based regimens in patients receiving dialysis (12 studies using the full dose of sofosbuvir), no drug-related serious adverse events were reported in 803 patients receiving hemodialysis. In a phase 2, single-group study, sofosbuvir-velpatasvir at a dose of 400 mg/100 mg was used to treat hepatitis C (genotypes 1 to 6) in 59 patients receiving hemodialysis or peritoneal dialysis (9), and SVR12 was 95%. The most common adverse events were headache (17%), fatigue

(14%), and nausea and vomiting (14%). Serious adverse events were reported in 11 patients (19%), but all were deemed by the authors to be unrelated to the study drug.

Similarly, across 5 studies of patients with CKD G4 or G5 who were not receiving dialysis and were treated with sofosbuvir-based regimens, no serious adverse events were reported in 210 patients (162 receiving the full dose of sofosbuvir), and only 4 of 183 patients (all from 1 study [10]) discontinued treatment because of adverse events.

The 2022 guideline (1) recommends that no dose adjustment is necessary for sofosbuvir in patients with CKD G4 or G5, including those receiving dialysis. In Europe and the United States, labeling for sofosbuvir has been expanded to include these patients. Our systematic review found no evidence to select any specific DAA regimen in patients receiving peritoneal dialysis, but it is reasonable to follow guidance as for patients receiving hemodialysis.

Clinical Practice Recommendations

Given the significant benefits to morbidity and mortality of hepatitis C cure (11–13), all patients with hepatitis C should be treated with the goal of achieving SVR. **Supplement Figure 3** (available at [Annals.org](https://annals.org)) shows currently available DAA treatment targets. The advent of pangenotypic DAA regimens that can be used regardless of GFR has simplified treatment of hepatitis C in patients with CKD. Rates of SVR12 range from 92% to 100% across a variety of DAA regimens in all stages of CKD (14). Thus, in patients with CKD, several pangenotypic regimens can be used (**Figure 1**).

Viral genotype needs to be tested only if a pangenotypic treatment regimen is not locally available. Genotype-specific DAA regimens can be used across the entire spectrum of CKD stages, including G4 and G5. Combination regimens, such as grazoprevir-elbasvir and PrOD, have

been studied in advanced CKD and are recommended for use in infection with HCV genotypes 1 and 4. Duration of treatment ranges from 8 to 12 weeks, based on the regimen used and the previous treatment history.

Direct-acting antiviral regimens similar to the ones used in the general population with CKD (Figure 1) can be used in KTRs. Drug-drug interactions are a key consideration in KTRs, as DAAs can lead to altered levels of calcineurin inhibitors and mammalian target of rapamycin (mTOR) inhibitors, potentially leading to toxicity or graft rejection. Protease inhibitors (drugs ending in “-previr”) interact with calcineurin inhibitors or mTOR inhibitors, whereas NS5A replication complex inhibitors (drugs ending in “-asvir”) and NS5B polymerase inhibitors (drugs ending in “-buvir”) are associated with lower risk for interaction with immunosuppressive medications.

CHAPTER 4: MANAGEMENT OF HCV INFECTED-PATIENTS BEFORE AND AFTER KIDNEY TRANSPLANTATION

The 2018 guideline recommended that transplant of kidneys from donors who were shown to be HCV-positive

on nucleic acid testing be restricted to recipients with positive nucleic acid test results. At that time, only the THINKER (Transplanting Hepatitis C kidneys Into Negative Kidney Recipients) (15) and EXPANDER (Exploring transplants using hepatitis-C infected kidneys for HCV-negative recipients) (16) studies had demonstrated that transplanting kidneys from HCV-infected donors to uninfected recipients with DAA treatment after transplant resulted in excellent allograft and patient survival with SVR12 in all recipients. Although the results were compelling, this experience was considered preliminary. A follow-up of THINKER-1 participants plus an additional 10 participants showed eGFR and quality-of-life measures similar to those in matched recipients of HCV-negative kidneys at 12-month follow-up (17). An additional 16 studies (with ≥10 participants) have now been published in which a total of 525 HCV-uninfected patients received a kidney from an HCV-infected donor followed by DAA treatment. The overall SVR12 rate was 97.7% (CI, 96.3% to 98.8%), with patient and graft survival of 98% at 1 year (18). In 12 studies with reporting of liver injury ($n = 457$), there were 3 reported cases of fibrosing cholestatic hepatitis, all of which occurred in patients who had received DAA treatment that was

Figure 1. Direct-acting antiviral (DAA) regimens with evidence of effectiveness for various chronic kidney disease (CKD) populations.

CKD populations	Direct-acting antiviral (DAA) regimens*	HCV genotypes	Quality of evidence (total N)†
G1–G3b,‡ not KTR	Any licensed DAA regimen	All	Not evaluated
G4–G5ND,§ including KTR ,¶	Sofosbuvir / Daclatasvir, 12 or 24 wk Glecaprevir / Pibrentasvir, 8 wk Grazoprevir / Elbasvir, 12 wk Sofosbuvir / Velpatasvir, 12 wk Sofosbuvir / Ledipasvir, 12 wk	All All 1a, 1b, 4 All All	High (571) High (132) High (857) Low (99) Very low (43)
G5D**	Sofosbuvir / Velpatasvir, 12 wk Glecaprevir / Pibrentasvir, 8 wk Sofosbuvir / Daclatasvir, 12 or 24 wk Sofosbuvir / Ledipasvir, 12 wk Grazoprevir / Elbasvir, 12 wk PrO ± D, 12 wk Daclatasvir / Asunaprevir, 24 wk	All All All All 1a, 1b, 4 1a, 1b, 4 1b	High (405) Moderate (529) Moderate (278) Moderate (220) Moderate (962) Moderate (582) Low (341)
KTR, G1–G3b‡	Sofosbuvir / Ledipasvir, 12 or 24 wk Sofosbuvir / Daclatasvir, 12 or 24 wk PrO ± D, 12 wk Grazoprevir / Elbasvir, 12 wk	All All 1a, 1b, 4 1a, 1b, 4	High (300) High (290) Very low (33) Very low (21)

“G” refers to the GFR category, with the suffix “D” denoting patients on dialysis and “ND” denoting patients not on dialysis. PrO ± D = ritonavir-boosted paritaprevir and ombitasvir with or without dasabuvir. (From KDIGO; available under Public License at [www.kidney-international.org/article/S0085-2538\(22\)00595-6/fulltext](http://www.kidney-international.org/article/S0085-2538(22)00595-6/fulltext).)

* Readers are encouraged to consult the Association for the Study of Liver Diseases (AASLD) or European Association for the Study of the Liver (EASL) guidelines for the latest information on various regimens. The figure includes only regimens that were evaluated by *at least 2 studies* in the specific CKD population and for which summary sustained virologic response at 12 weeks (SVR12) was >92%. Sofosbuvir monotherapy is excluded because current DAA regimens incorporate at least 2 agents. The suggested durations of treatment are those most commonly employed by the relevant studies. Studies commonly extended treatment for patients with cirrhosis, prior DAA failure, or for some genotypes. Readers should consult the AASLD or EASL guidelines, as needed, to determine optimal treatment duration.

† The order of hepatitis C virus (HCV) regimens does not indicate a ranking or preferential order of selection. The regimens are presented in order of the quality of evidence, then by HCV genotype, then alphabetically. The differences in quality of evidence primarily relate to the numbers of evaluated patients and small differences in methodological quality of the underlying studies (see Supplementary Tables S5–S7 in the full guideline).

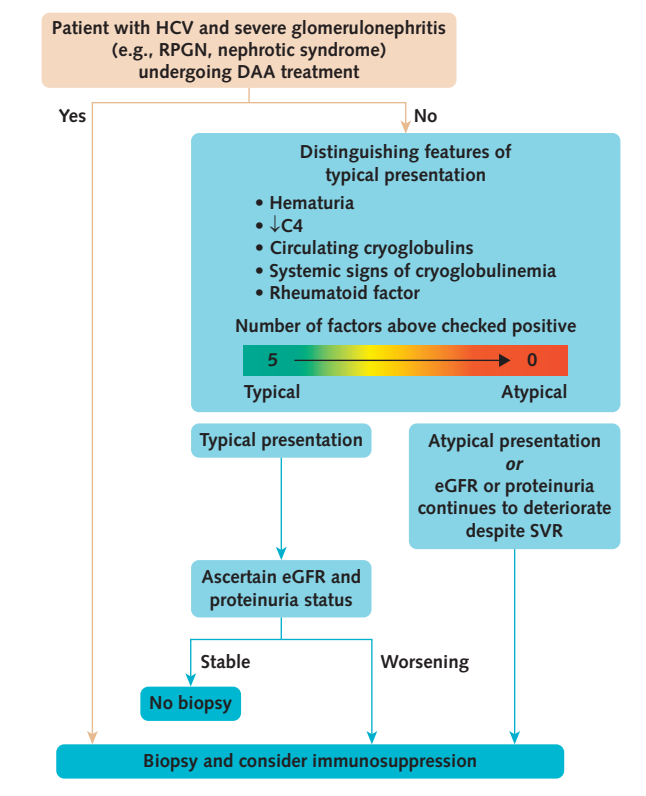
‡ Estimated glomerular filtration rate (eGFR) ≥30 mL/min per 1.73 m².

§ eGFR <30 mL/min per 1.73 m², not on dialysis therapy.

|| Regimens in kidney transplant recipients (KTRs) should be selected to avoid drug-drug interactions, particularly with calcineurin inhibitors.

¶ Strength of evidence for CKD G4T–G5T is very low for all regimens.

** Evidence primarily for patients on hemodialysis. Very few patients were on peritoneal dialysis.

Figure 2. Indications for biopsy in patients with hepatitis C virus (HCV) and severe glomerulonephritis.

Algorithm above assumes that patient with HCV and with HCV and chronic kidney disease (CKD) is already receiving direct-acting antiviral (DAA) treatment. Systemic signs of cryoglobulinemia include skin lesions such as purpura, arthralgias, and weakness. eGFR = estimated glomerular filtration rate; RPGN = rapidly progressive glomerulonephritis; SVR = sustained virologic response. (From KDIGO; available under Public License at [www.kidney-international.org/article/S0085-2538\(22\)00595-6/fulltext](http://www.kidney-international.org/article/S0085-2538(22)00595-6/fulltext).)

delayed until 30 days after the transplant. Therefore, the current guideline recommends that HCV-infected donors be considered regardless of the HCV status of the potential kidney transplant recipients (1C) after informed consent is obtained from the recipients, including on the need for DAA treatment. The guideline further stresses that DAA therapy must be administered promptly after the transplant.

Clinical Practice Recommendations

HCV-Infected Recipients

Hepatitis C virus infection in the recipient is not a contraindication for kidney transplant. Untreated HCV infection reduces patient and allograft survival after kidney transplant; consequently, DAA treatment should be initiated either before or after the transplant. Before the transplant, the extent of liver disease and the degree of fibrosis should be ascertained. Kidney transplant candidates with decompensated liver disease (characterized by esophageal varices, hepatic encephalopathy, and portal hypertension, among other conditions) should be evaluated for simultaneous liver and kidney transplant; patients without cirrhosis or with compensated cirrhosis can receive a kidney transplant only. The timing of antiviral treatment is

determined by the anticipated wait time until the transplant. If a donor organ is not anticipated to be available within 24 weeks, DAA therapy can be administered before the transplant to allow 8 to 12 weeks of treatment, with confirmation of SVR at 12 weeks after treatment.

HCV-Infected Donors

Use of kidneys from HCV-infected donors (living or deceased) expands the donor pool and reduces the transplant wait time (19). Kidneys from HCV-infected donors have been transplanted to HCV-uninfected recipients with use of DAA therapy before or shortly after the transplant. This strategy leads to viral clearance (SVR12) with excellent patient and graft survival rates at 1-year post-transplant follow-up. A recent study reported that 5-year mean allograft survival did not differ statistically between donors who were positive for HCV RNA versus those who were not (18, 20). However, DAA therapy may not always be readily available because of insurance delays or denials due to a risk for HCV-associated liver or kidney injury (21–23). Transplant centers should discuss this possibility with potential transplant recipients and ensure availability of DAAs before proceeding with transplant from an HCV-positive donor to an HCV-negative recipient. Reports have differed on the specific DAA regimens used and the timing of initiation of DAA treatment for recipients, but it is hoped that future studies can help clarify the optimal duration and timing of treatment as well as longer-term patient and allograft clinical outcomes. Although DAA treatment for 4 to 8 weeks has been reported, a full 12-week treatment is often required to prevent viral relapse. Therapy should be started promptly after the transplant to prevent hepatic complications of untreated acute HCV infection.

CHAPTER 5: DIAGNOSIS AND MANAGEMENT OF KIDNEY DISEASES ASSOCIATED WITH HCV INFECTION

In contrast to the 2018 guideline, the 2022 update does not suggest performing a kidney biopsy in all HCV-positive patients with clinically suspected glomerulonephritis before initiation of DAA therapy. In patients with a typical presentation of immune complex glomerulonephritis (for example, with hematuria, proteinuria, or deteriorating GFR), DAA therapy can be initiated without a confirmatory kidney biopsy.

Because almost all patients with chronic hepatitis C (with or without glomerulonephritis) should be treated with DAAs, a kidney biopsy is unlikely to change management in most patients with hepatitis C and clinical glomerulonephritis. In a recent study by Pérez de José and colleagues (24), more than 50% of patients with hepatitis C and kidney involvement due to mixed cryoglobulinemia were treated with DAAs without a kidney biopsy. Regardless, DAA treatment reduced overall mortality and improved kidney survival at a median follow-up of 138 months. Therefore, the WG concluded that treatment with DAAs should not be delayed while the patient is awaiting a kidney biopsy. However, if kidney disease does not improve or stabilize despite achievement of SVR or if there is evidence of rapidly progressive glomerulonephritis, a kidney biopsy may be warranted to confirm the

diagnosis before initiation of immunosuppressive therapy. **Figure 2** presents one clinical approach to decision making while kidney biopsy is being contemplated.

Although the previous guideline suggested using immunosuppressive therapy in all patients with nephrotic syndrome, the 2022 update recommends that the decision to use such therapy in patients with nephrotic syndrome should be individualized (not graded). Nephrotic-range proteinuria (>3.5 g/d) alone does not warrant use of immunosuppressive treatment because such patients can achieve remission of proteinuria after treatment with DAAs (24). However, if patients have other associated complications, such as thromboembolic disease, severe hypoalbuminemia, or anasarca, immunosuppressive treatment in addition to DAAs should be considered. Rituximab remains the first-line immunosuppressive treatment in these patients.

Clinical Practice Recommendations

The most frequent form of kidney involvement in chronic hepatitis C is membranoproliferative glomerulonephritis, often caused by cryoglobulinemic vasculitis, although tubulointerstitial injury is also possible (25). Membranoproliferative glomerulonephritis can present in the absence of cryoglobulinemia. Although kidney biopsy can establish a precise diagnosis and exclude other possible causes, such as diabetic nephropathy, it does not change management in most patients with hepatitis C, as DAA therapy will need to be instituted regardless of biopsy results. Therefore, DAA therapy can be initiated without biopsy, followed by monitoring of GFR, proteinuria, and hematuria to see whether these parameters improve with HCV treatment. In addition to DAA therapy, use of rituximab as the first-line immunosuppressive agent should be considered, with or without plasma exchange, in patients with rapidly progressive glomerulonephritis, acute cryoglobulinemic vasculitis flare, or nephrotic syndrome with associated complications (26, 27). When rituximab is being considered, clinicians should be mindful that it can lead to reactivation of hepatitis B virus, as reflected in a black box warning from the U.S. Food and Drug Administration.

It is hoped that future randomized controlled trials will be able to better identify patients who would benefit from plasma exchange and/or immunosuppressant therapy with DAAs. Markers of hepatitis B virus infection should be measured, as noted by guidelines from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver (28, 29).

COMPARISON WITH OTHER GUIDELINES

This KDIGO guideline update is overall concordant with guidelines from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (www.hcvguidelines.org) and from the European Association for the Study of the Liver (<https://easl.eu/publications/clinical-practice-guidelines>). Clinicians should consult these resources for the most up-to-date information on specific DAA regimens. Interaction of DAAs

with other drugs can be checked at www.hep-druginteractions.org.

CONCLUSION

Treatment of HCV infection in patients with kidney disease has evolved over the past decade due to the availability of pangenotypic DAAs that can be safely administered across all stages of CKD. The 2022 update to the 2018 KDIGO guideline incorporates newer evidence confirming the safety and efficacy of sofosbuvir in patients with CKD G4 or G5 who are or are not receiving dialysis, the feasibility of transplanting kidneys from HCV-infected donors to HCV-uninfected recipients, and a WG consensus that a kidney biopsy is no longer mandatory before initiation of DAA therapy in HCV-infected patients with kidney disease. Future studies of kidney donations from HCV-positive donors to HCV-negative recipients are needed to refine and clarify the timing of initiation and duration of DAA therapy and to assess long-term outcomes associated with this practice. Also, randomized controlled trials are needed to determine which patients with HCV-associated kidney disease can be treated with DAA therapy alone versus in combination with immunosuppression and plasma exchange. KDIGO will assess the currency of its recommendations and the need to update them in the next 3 years.

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