



## KDOQI US Commentary on the 2018 KDIGO Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C

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The first KDIGO (Kidney Disease: Improving Global Outcomes) guideline for the prevention, diagnosis, evaluation, and treatment of hepatitis C virus (HCV) infection was published in 2008. The ensuing decade bore witness to remarkable advances in the treatment of HCV infection following the approval of direct-acting antiviral (DAA) agents that deliver cure rates routinely >95%. In this context, the KDIGO organization correctly recognized the need for an updated HCV guideline that would be relevant to the treatment of HCV-infected patients with kidney disease in the DAA era. The current NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) commentary provides an in-depth review and perspective on the 2018 KDIGO guideline. Of note, the KDIGO work group made significant updates to guideline chapters 2 and 4 as a direct result of the availability of DAAs. The intent of this commentary is to provide useful interpretation for nephrologists and other practitioners caring for HCV-infected patients with chronic kidney disease, including dialysis patients and kidney transplant recipients. The availability of DAA agents that are safe and highly effective has created new opportunities, such as the transplantation of kidneys from HCV-infected kidney donors. The ability to treat HCV infection in patients with kidney disease will have a significant impact on the care of our patients and should favorably influence long-term outcomes as well.

Complete author and article information provided before references.

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### Introduction

In 2008, the first KDIGO (Kidney Disease: Improving Global Outcomes) guideline for the prevention, diagnosis, evaluation, and treatment of hepatitis C virus (HCV) infection in patients with kidney disease was published,<sup>1</sup> followed by a US-based commentary from NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative).<sup>2</sup> There have been significant advances in the diagnosis and management of patients infected with HCV in the decade following the release of this guideline, largely centered around the introduction of direct-acting antivirals (DAAs) that result in cure rates that are consistently >95%. Following publication of the large pivotal trials demonstrating the remarkable efficacy of the DAAs (trials that largely excluded patients with kidney disease),<sup>3,4</sup> several studies reported equally excellent outcomes in patients with chronic kidney disease (CKD), including recipients of kidney replacement therapy (dialysis or transplantation).<sup>5-8</sup> Before the approval of the

DAAs for patients with kidney disease, interferon-based regimens had been the standard of care. These protocols were generally poorly tolerated by patients with end-stage kidney disease and not recommended for kidney transplant recipients. Consequently, HCV-infected patients with kidney disease represented a population with a large unmet clinical need, especially in the context of the much higher prevalence of HCV infection in the CKD population than that of the general population. Having the option to treat HCV infection in the CKD population with DAAs that have excellent efficacy and limited adverse events has had a significant impact on the management of these patients. Moreover, being able to eradicate the virus has created a scenario in which clinicians must make important decisions surrounding the optimal timing of treatment. In this context, the KDIGO work group correctly recognized the importance of providing an updated version of the 2008 guideline.

A panel of international experts in HCV infection and nephrology, hepatology, and virology developed the 2018 KDIGO HCV guideline to provide evidence-based clinical practice guidelines that would be globally applicable.<sup>9</sup> The 2018 guideline resembles the earlier iteration in that it focuses on 5 aspects of the management of HCV-infected patients with CKD: diagnosis, treatment, preventing transmission in hemodialysis units, management of kidney transplantation patients before and after transplantation, and the management of kidney diseases associated with HCV infection. US Food and Drug Administration (FDA) approval of several DAAs over the last few years has dramatically changed the landscape for treatment of HCV infection in

patients with kidney disease. Therefore, the guideline recommendations concerning treatment, prevention of transmission, and management of kidney transplant patients required significant updating from their 2008 versions.

The purpose of the current article is to interpret the guidelines in the context of their applicability and implementation in the United States. This article lists guideline recommendations in each of the 5 topic areas, followed by a commentary that is designed to provide useful interpretation of the 2018 KDIGO HCV guideline for nephrologists and other practitioners caring for these patients in the United States. All guideline statements are reproduced with permission of KDIGO.

### KDOQI Commentary Process

The KDOQI Steering Committee selected the commentary chair, who then identified other members of the KDOQI commentary work group based on their clinical and research expertise, interest in the guideline process, and experience in taking care of adults with HCV infection and CKD. The KDOQI work group members reviewed recent literature and provided commentary on 5 major focus areas within the KDIGO guideline as previously outlined. The KDOQI work group discussed the KDIGO guideline and all work group members reviewed and approved the commentary after reaching consensus. The article was also reviewed and approved by the NKF Scientific Advisory Board and KDOQI leadership.

### Guideline Statements and Commentary

#### Screening Patients With CKD for HCV Infection

- 1.1 Screening patients with CKD for HCV infection
  - 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).
  - 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).
    - 1.1.1.2 We recommend using NAT alone or 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).

#### Commentary

The 2018 KDIGO guideline<sup>9</sup> is aligned with the 2008 recommendations<sup>1</sup> in advising that all patients with CKD be screened for HCV infection, although this is now a

recommendation (level 1) rather than a suggestion; however, the level of evidence is still graded as “low” (1C). Patients with CKD who are not receiving dialysis are not a group identified as a priority screening population for HCV infection by the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA),<sup>10</sup> US Centers for Disease Control and Prevention (CDC),<sup>11</sup> or US Preventive Services Task Force<sup>12</sup> guidelines. However, in light of the clear association between HCV and prevalent CKD,<sup>13-17</sup> as well as the fact that HCV infection can accelerate CKD progression, it is reasonable to propose that all patients presenting for CKD evaluation should be tested at least once for HCV infection. This is especially true in individuals with proteinuria, hematuria, or diabetes given that both glomerular disease and hyperglycemia have been associated with HCV. The updated guideline makes specific recommendations regarding which testing modality to use; the suggestion to screen using immunoassay is in line with similar recommendations from other groups<sup>10-12</sup> in which antibody-based testing is the preferred screening assay and nucleic acid testing (NAT) should be reserved to confirm viremia in those who are anti-HCV antibody positive.

#### Clinical Utility

The 2018 guideline provides more detailed recommendations for HCV testing in dialysis patient populations than the prior version. The recommendation to screen all patients at the initiation of in-center hemodialysis or unit transfer is unchanged and strongly supported by high-quality evidence. This is an appropriate recommendation because the prevalence of HCV infection remains greater among hemodialysis patients compared with the general US population.<sup>18-20</sup> Both immunoassay and NAT are proposed screening options, and a distinction is no longer made between high and low prevalence units as was proposed in the 2008 KDIGO guideline. The AASLD/IDSA guideline<sup>10</sup> identifies hemodialysis patients as an immunocompromised population in whom NAT is the preferred screening method. Given the limited cost differential between the 2 tests (\$22 for immunoassay vs \$65 for NAT in 2011 USD)<sup>21</sup> and the need for confirmatory NAT after HCV antibody detection, we believe that NAT may be more effective for screening patients receiving hemodialysis. However, this needs to be prospectively evaluated using contemporary data. One-time HCV screening is now specifically suggested for patients receiving peritoneal dialysis or home hemodialysis, but the level of evidence is weak for this recommendation. Ideally, these patients should have been screened as part of their CKD evaluation, and if they do not report high-risk behaviors, their likelihood of acquiring HCV on a home dialysis program is low. We believe that peritoneal dialysis and home hemodialysis patients who have been screened before dialysis start and tested negative do not require retesting in the absence of documented risk behaviors. The updated

guideline continues to recommend testing all kidney transplantation candidates and the evidence supporting this recommendation is high; we agree that testing this population is necessary. While the 2018 KDIGO guideline does not comment on a preferred testing method, we suggest that the NAT assay is preferred and reflects the practice at most US transplantation centers.

### Future Research Recommendations

There is a clear need for updated epidemiologic data regarding the prevalence of active HCV infection among populations receiving hemodialysis, peritoneal dialysis, and home hemodialysis. With the introduction of DAAs that can be administered independent of glomerular filtration rate (GFR), it is reasonable to expect that estimates from prior survey studies, such as the Dialysis Outcomes and Practice Patterns Study (DOPPS), may be outdated. A cost-effectiveness analysis would also provide much needed data in this arena to drive policy regarding population-level screening and frequency.

### Follow-up HCV Screening of Patients Receiving In-Center Hemodialysis

- 1.2 Follow-up HCV screening of in-center hemodialysis patients
  - 1.2.1 We recommend screening for HCV infection with immunoassay or NAT in in-center hemodialysis patients every 6 months (1B).
    - 1.2.1.1 Report any new HCV infection identified in a hemodialysis patient to the appropriate public health authority (Not Graded).
    - 1.2.1.2 In units with a new HCV infection, we recommend all patients be tested for HCV infection and the frequency of subsequent HCV testing be increased (1A).
    - 1.2.1.3 We recommend that hemodialysis patients with resolved HCV infection undergo repeat testing every 6 months using NAT to detect possible re-infection (1B).
  - 1.2.2 We suggest that patients have serum alanine aminotransferase (ALT) level checked upon initiation of in-center hemodialysis or upon transfer from another facility (2B).
    - 1.2.2.1 We suggest that hemodialysis patients have ALT levels checked monthly (2B).

### Commentary

The 2018 guideline provides specific recommendations regarding the frequency of follow-up testing for hemodialysis patients. The recommended interval for screening patients for HCV infection is now every 6 months, with either immunoassay or NAT. This aligns with CDC recommendations<sup>22</sup> and the clinical practice in at least 1 large dialysis corporation, but the evidence behind this recommendation is rated moderate. Interestingly, the AASLD/IDSA guideline<sup>10</sup> only recommends annual HCV testing for individuals with ongoing risk

factors, such as people who inject drugs or men who have sex with men. CDC guidelines for HCV screening in the general population<sup>11</sup> still recommend immunoassay testing as the first-line assay. The 2018 KDIGO guideline further elaborates that in dialysis units in which nosocomial HCV infection has been detected, universal and more frequent testing with NAT is advised, although a time frame for enhanced surveillance is not specified. This guidance is congruent with older versions of the AASLD guideline<sup>23</sup> in which immunoassay screening paired with NAT was recommended in patients with acute HCV infection. This approach takes into consideration the fact that NAT results would be positive even within the serologic window period before the immunoassay becoming positive. Nosocomial transmission of HCV in hemodialysis units is a well-documented but low-frequency occurrence (incidence < 1%)<sup>19,24</sup>; all cases of HCV infection acquired in the dialysis setting should be reported to the local health department.

### Implementation and Challenges

Given that the fundamental purpose of repeated screening among hemodialysis patients is to detect nosocomial infection, we would suggest NAT as the preferred screening assay. Patients who have either spontaneously cleared their HCV infection or been successfully treated are to be retested using NAT every 6 months indefinitely. The recommendation to only use NAT in this population has been advised in other guidelines<sup>10</sup> as well and seems reasonable because HCV antibodies persist indefinitely after the virus has been cleared. Increases in alanine aminotransferase (ALT) levels are no longer a prompt for HCV testing as they were in the 2008 guideline. However, the current recommendation is that ALT levels should be checked whenever patients change units and monthly in stable hemodialysis patients, although the evidence supporting this recommendation is low. Although following up ALT levels is certainly less expensive than performing HCV NAT, the result is also less specific because increases in ALT levels can be due to a variety of illnesses, medications, and other comorbid conditions.

### Future Research Recommendations

Concern for nosocomial transmission of HCV infection drives much of the policy surrounding patient testing and treatment algorithms, although contemporary data regarding the true risk are lacking. The CDC recently described 102 outbreak-associated cases reported from 2008 to 2017,<sup>25</sup> which is quite small considering the more than 1.3 million hemodialysis sessions performed in the United States per year. However, there continues to be significant concern about underreporting of cases. Understanding the true risk for HCV acquisition during dialysis is important to recommend and implement effective testing and treatment policies.

## Liver Testing in Patients With CKD and HCV Infection

- 1.3 Liver testing in patients with CKD and HCV infection
  - 1.3.1 We recommend assessing HCV-infected patients with CKD for liver fibrosis (1A).
  - 1.3.2 We recommend an initial noninvasive evaluation of liver fibrosis (1B).
  - 1.3.3 When the cause of liver disease is uncertain or noninvasive testing results are discordant, consider liver biopsy (*Not Graded*).
  - 1.3.4 We recommend assessment for portal hypertension in CKD patients with suspected advanced fibrosis (F3–4) (1A).

### Commentary

Early detection of HCV infection in patients with CKD is clinically important because the presence of HCV infection can contribute to the development and progression of CKD, as well as to other adverse outcomes in patients with CKD.<sup>26,27</sup> Subsequent to the publication of the 2008 guideline, there are now very effective treatment options available for HCV infection, and HCV treatment may slow CKD progression when HCV is detected early.<sup>28,29</sup>

### Clinical Utility

In a significant change from the 2008 recommendations, the 2018 guideline introduces the recommendation that patients with CKD who are HCV-infected should be screened for liver fibrosis. Importantly, liver biopsy is no longer suggested in all cases for evaluation of liver disease. In this context, there are 2 types of noninvasive tests available to assess liver fibrosis: biochemical markers (FibroTest/FibroMeter, aspartate aminotransferase–platelet ratio index, Forns, or FIB-4 index) and morphologic tests such as transient elastography. All these tests have comparable accuracy in estimating liver fibrosis in patients with advanced CKD as in the general population.<sup>30</sup> Nevertheless, the noninvasive biochemical markers are less accurate (receiver operating characteristic range of 0.70–0.85)<sup>31–36</sup> than transient elastography, which has excellent discrimination statistics: 0.96, 0.98, and 0.99 for scores of  $\geq$ F2,  $\geq$ F3, and F4, respectively, for severity of hepatic fibrosis staged by METAVIR score.<sup>30</sup>

### Implementation and Challenges

Most insurance carriers will approve transient elastography and the test is readily available in the hospital setting. However, some payers still require other noninvasive testing before approval of antiviral therapy. The only caveat when using this assay is that an increased volume status could lead to falsely elevated results, suggesting the presence of more advanced fibrosis than is actually the case. The updated guideline suggests performing liver biopsy only if the cause of liver disease is uncertain or noninvasive testing results are discordant. Liver biopsy, while associated with a

nontrivial risk for bleeding and complications, can provide an exact pathologic diagnosis and measurements of portal vein pressures when done through the transjugular approach. Similar to the general population, an elevated hepatic vein wedge pressure gradient ( $\geq$ 10 mm Hg) is used to diagnose portal hypertension.<sup>37</sup> Transient elastography of  $<$ 20 kPa and a platelet count  $>$  150,000/ $\mu$ L makes a finding of portal hypertension unlikely.<sup>38</sup>

### Future Research Recommendations

There is a need for direct comparison of methods to determine the degree of liver fibrosis regarding discrimination ability as well as cost-effectiveness to determine which noninvasive method should be used in the routine clinical setting for screening patients with CKD. We also require better data to assess the ability of noninvasive testing to predict the severity of portal hypertension in patients with compensated cirrhosis with CKD more accurately and determine whether they are candidates for kidney-alone transplantation or should be referred for simultaneous liver-kidney transplantation.

## Other Testing of Patients With HCV Infection

- 1.4 Other testing of patients with HCV infection
  - 1.4.1 We recommend assessing all patients for kidney disease at the time of HCV infection diagnosis (1A).
    - 1.4.1.1 Screen for kidney disease with urinalysis and estimated glomerular filtration rate (eGFR) (*Not Graded*).
  - 1.4.2 If there is no evidence of kidney disease at initial evaluation, patients who remain NAT-positive should undergo repeat screening for kidney disease (*Not Graded*).
  - 1.4.3 We recommend that all CKD patients with a history of HCV infection, whether NAT-positive or not, be followed up regularly to assess progression of kidney disease (1A).
  - 1.4.4 We recommend that all CKD patients with a history of HCV infection, whether NAT-positive or not, be screened and, if appropriate, vaccinated against hepatitis A virus (HAV) and hepatitis B virus (HBV), and screened for human immunodeficiency virus (HIV) (1A).

### Commentary

The 2008 guideline suggested that all patients with CKD should be tested for HCV (a weak recommendation) and it was strongly recommended that all dialysis and transplant patients be screened for HCV as well. However, there was no reciprocal recommendation regarding CKD screening in patients with established HCV infection. The 2018 guideline suggests screening for CKD using urinalysis and assessment of estimated GFR (eGFR) at the time of diagnosis of HCV infection. Ongoing screening for CKD is a new recommendation that was added to the guideline in case the initial screening was negative in HCV-infected patients.

### Clinical Utility

The recommendation to screen for CKD in patients infected with HCV is supported by several observational studies, which found an association between the presence of HCV and CKD.<sup>14,16,26,27,39-41</sup> The recommendation to screen with urinalysis and by estimating GFR is reasonable in routine primary care settings. Further screening using urinary protein- or albumin-creatinine ratio should also be considered.

New to the 2018 guideline is a suggestion that all patients with CKD with a history of HCV infection, whether currently NAT-positive or not, be followed up regularly to assess for progression of kidney disease. This recommendation corresponds with the KDIGO CKD guideline.<sup>42</sup> Epidemiologic data indicate that successful antiviral therapy has a beneficial effect on the progression in CKD, but most of these data are coming from the pre-DAA era.<sup>43-48</sup> There are a limited number of studies demonstrating that effective treatment of HCV infection with DAAs slows the decline in kidney function in patients infected with HCV.<sup>28,29,49</sup> An important new recommendation in the 2018 document (recommendation 1.4.4) states that all patients with CKD with a history of HCV infection, whether NAT positive or not, should be screened and, if appropriate, vaccinated against hepatitis A virus and hepatitis B virus (HBV). Screening for human immunodeficiency virus (HIV) is also suggested. This recommendation corresponds to guidelines from both the CDC and AASLD/IDSA.<sup>10,11</sup>

### Implementation and Challenges

Given the limited cost differential between the immunoassay and NAT (\$22 vs \$65 in 2011 USD)<sup>21</sup> and the need for confirmatory NAT after HCV antibody detection, we believe that NAT-based testing may be more effective for screening hemodialysis patients. However, cost-effectiveness studies are needed in this area. The final decision of which assay is best suited to monitor maintenance dialysis patients for HCV infection and how often the test should be repeated is often decided at the corporate level by the large dialysis providers that manage the care of many patients with kidney failure in the United States. Their policy may or may not be aligned with the 2018 KDIGO guidelines or what practicing nephrologists decide is most appropriate for their patients.

The guideline provides evidence that transient elastography is replacing liver biopsy in many patients as a means to assess the degree of liver fibrosis in HCV-infected patients with CKD. The nephrologist must take into consideration the volume status at the time the test was performed, especially if the result suggests advanced stages of fibrosis because this could lead to false-positive outcomes and a change in clinical recommendations. Furthermore, transient elastography is not yet widely available across the country and may not be an option for nephrologists practicing in more rural locations. In that

circumstance, liver biopsy would remain the only reliable choice to accurately determine the extent of liver fibrosis in an HCV-infected patient being considered for kidney transplantation.

The guideline strongly recommends that just as patients with CKD should be screened for HCV infection, the reciprocal also holds true in that HCV-infected patients should be screened for CKD. The limitation on full implementation of this recommendation is ensuring that this message is disseminated to the hepatologists and primary care physicians who are caring for these patients before a nephrologist becoming involved.

### Future Research Recommendations

Although emerging data suggest that effective antiviral treatment slows kidney function decline in patients with HCV infection,<sup>28,29,49</sup> further data are necessary to determine whether HCV treatment can actually prevent the development of CKD.

### Treatment of HCV Infection in CKD: General Considerations

- 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).
  - 2.1.3 Treat kidney transplant candidates in collaboration with the transplant center to optimize timing of therapy (Not Graded).

### Commentary

Patients with CKD and HCV infection, especially those with cirrhosis, have higher mortality than those without HCV, providing a strong rationale for offering curative therapy.<sup>50,51</sup> SVR<sub>12</sub> (sustained virologic response 12 weeks after the completion of therapy—defined by an undetectable HCV RNA level at that time point) is used to define treatment success. Because there is very small risk for late virologic relapse beyond SVR<sub>12</sub>, experts recommend confirmation of viral clearance by repeat testing 24 weeks or beyond.<sup>52</sup> Longitudinal studies evaluating outcomes in different patient populations with SVR<sub>12</sub> (general population and those with cirrhosis or HIV co-infected) show reduced rates of cirrhosis and liver cancer. Among patients with CKD, survival was higher among those treated with DAAs compared with untreated patients, supporting a survival benefit in this population as well.<sup>53</sup>

### Clinical Utility

In this context, recommendation 2.1 states that all patients with CKD should be evaluated for HCV treatment.

However, decisions regarding the optimal timing for treatment of patients on the waiting list for a kidney transplant are complex and affected by dialysis vintage, local transplantation program policies concerning the use of kidneys from HCV-infected donors, the extent of liver injury, and patient preference. In some cases, deferral of treatment until after transplantation may be prudent. Coordination of HCV treatment with the kidney transplantation center is critical because patients with untreated HCV infection may be candidates for kidneys from HCV-viremic donors, translating into shorter waiting times in many instances.<sup>54</sup> However, this advantage might diminish as more centers accommodate the practice of transplanting HCV-infected kidneys into uninfected recipients.

### Implementation and Challenges

Given the availability of safe and effective oral DAAs, there is no longer any justification for the use of interferon-based regimens. Increasingly, DAA treatment guidance focuses on simplification—favoring pan-genotypic and ribavirin-free DAA regimens.<sup>52,55</sup> Previously, the patient's baseline eGFR was a key variable when considering DAA options for patients with CKD, as sofosbuvir was not approved for use in patients with GFR < 30 mL/min/1.73 m<sup>2</sup>. Other relevant considerations in choosing the optimal DAA regimen include the presence or absence of cirrhosis, drug-drug interactions, severity of liver dysfunction (if cirrhotic), prior HCV treatment history, and insurance preferences. An FDA warning highlighted the risk for hepatotoxicity in patients with cirrhosis who were treated with protease inhibitor-inclusive DAAs.<sup>56</sup> Regimens that include protease inhibitors (all “previr” DAAs) are not recommended if the patient's Child-Pugh score is ≥7.

### Treatment of HCV Infection in CKD: Patients With CKD G1-G3b

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

#### Commentary

There are currently 2 pan-genotypic regimens that are FDA approved for treatment-naïve patients: sofosbuvir-velpatasvir and glecaprevir-pibrentasvir (Fig 1). Both offer once-daily dosing, with no need for resistance testing or use of ribavirin. These are the preferred regimens with lower cost and greater ease of approval as of 2019 in the United States. Regimens that require approval of 2 different drugs, such as sofosbuvir plus daclatasvir, are nonpreferred in the United States due to higher cost and complexity of insurer approval. Data for optimal use of DAAs in patients with CKD continues to be enriched by

clinical trials and real-world data and thus clinicians should consult with up-to-date guidelines, such as those from the AASLD-IDS (https://www.hcvguidelines.org/unique-populations/renal-impairment).

### Treatment of HCV Infection in CKD: Patients With CKD G4-G5D

2.3 Patients with GFR < 30 ml/min per 1.73 m<sup>2</sup> (CKD G4–G5D) should be treated with a ribavirin-free DAA-based regimen as outlined in Figure 1.

#### Commentary

For patients with CKD GFR categories 4 to 5 (including 5D), corresponding to eGFRs < 30 mL/min/1.73 m<sup>2</sup> or receiving dialysis, recommendation 2.3 (which includes a reference to a figure in the guideline<sup>9</sup>) suggests that treatment options are more restricted. However, additional safety studies using sofosbuvir-based therapies in patients with CKD GFR categories 4-5 has resulted in the FDA amending the label for sofosbuvir-inclusive regimens. Consequently, treatment of patients with CKD GFR categories 4-5 is now the same as that of those with categories 1-3 (Fig 1). The phase 3 studies conducted in patients with CKD GFR categories 4-5 used grazoprevir-elbasvir and glecaprevir-pibrentasvir. The randomized multicenter C-SURFER trial treated 116 patients with genotype 1 HCV with CKD G4-G5/5D (76% receiving hemodialysis) with grazoprevir-elbasvir for 12 weeks.<sup>5</sup> An SVR<sub>12</sub> was achieved in 99% of the cohort. The multicenter EXPEDITION-4 trial treated 104 patients with CKD G4-G5 and HCV genotypes 1 to 6 (82% receiving hemodialysis) with glecaprevir-pibrentasvir for 12 weeks; 98% achieved SVR<sub>12</sub>.<sup>6</sup> Real-world and clinical trials from US and non-US centers report SVR<sub>12</sub> rates ≥95% with ritonavir-boosted paritaprevir-ombitasvir-dasabuvir<sup>57,58</sup> and daclatasvir-asunaprevir<sup>59</sup> in patients with decreased GFRs. However these regimens are not available or are nonpreferred in the United States.

Sofosbuvir undergoes extensive hepatic metabolism and the predominant inactive metabolite GS-331007 (SOF-007) is mainly eliminated renally.<sup>60</sup> Compared with persons with normal GFRs, the AUC<sub>0-∞</sub> of the 400-mg dose of sofosbuvir and SOF-007 are increased in patients with kidney failure (by 81% and 71%, respectively).<sup>61</sup> For this reason, sofosbuvir-based DAA combinations were not initially FDA approved for use in patients with eGFRs < 30 mL/min/1.73 m<sup>2</sup> pending additional safety studies. Additionally, concerns that sofosbuvir might accelerate progression of CKD based on off-label use of sofosbuvir-based therapies<sup>62</sup> led to recommendations for continued vigilance for unexpected safety events with broader use of DAAs in patients with CKD.



**Figure 1.** Treatment options for hepatitis C virus (HCV)-infected patient with chronic kidney disease (CKD). \*Not to be used if Child-Pugh score > 7.

However, recent results from phase 2 studies provide more clarity regarding the safety and efficacy of sofosbuvir in patients with CKD. In a phase 2 study of 59 dialysis patients with HCV genotypes 1 to 6 treated with full-dose sofosbuvir-velpatasvir for 12 weeks, the SVR<sub>12</sub> rate was 95%.<sup>61</sup> There were no early discontinuations and no serious adverse events; 12% had grade 3 or higher adverse events, mostly elevation of creatinine levels and/or hyperkalemia. In a smaller phase 2 study of 18 patients with genotype 1 with CKD G4-G5 not requiring kidney replacement therapy who were treated with full-dose ledipasvir-sofosbuvir for 12 weeks, the SVR<sub>12</sub> was 100%.<sup>63</sup> In a real-world cohort of 95 patients receiving dialysis treated for 8, 12, or 24 weeks, SVR<sub>12</sub> was 92% with no virologic failures.<sup>64</sup> In a systematic review of 717 patients with CKD G4-G5/5D (421 receiving dialysis) treated with sofosbuvir-inclusive

regimens (a mixture of full- and reduced-dose sofosbuvir) across 21 studies, the overall serious adverse event rate was 4.8%.<sup>65</sup> Given these data, the label restrictions for sofosbuvir-based DAA combinations in patients with CKD G4-G5/5D changed in the United States in November 2019. Clinicians are advised to consult with up-to-date guidelines, such as those from the AASLD-IDSA (<https://www.hcvguidelines.org/unique-populations/renal-impairment>) to review the latest recommendations.

### Treatment of HCV Infection in CKD: 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 as outlined in Figure 1 (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, 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).

### Commentary

We affirm that all kidney transplant recipients with HCV viremia should be evaluated and treated with DAAs to prevent the many potential complications of HCV infection in the setting of immunosuppression, as outlined in recommendation 2.4. Although no specific evidence basis can support the exact timing of DAA treatment, we recommend that treatment should be initiated as early as possible posttransplantation (eg, weeks to months posttransplantation). The THINKER and EXPANDER trials of transplanting HCV-viremic kidneys into uninfected recipients provide relevant clinical evidence that treatment in the first week posttransplantation can be safely integrated into usual posttransplantation care.<sup>66,67</sup> The 2018 KDIGO guideline appropriately draws attention to the need for consideration of HCV genotype, eGFR, liver disease, and concomitant medications and the possibility for drug–drug interactions. The guideline also appropriately draws attention to the need to carefully monitor and adjust calcineurin trough levels because calcineurin inhibitor metabolism may be affected by some DAAs.

## Treatment of HCV Infection in CKD: Testing for HBV Infection

- 2.5 All treatment candidates should undergo testing for HBV infection prior to therapy (*Not Graded*).
- 2.5.1 If hepatitis B surface antigen [HBsAg] is present, the patient should undergo assessment for HBV therapy (*Not Graded*).
- 2.5.2 If HBsAg is absent but markers of prior HBV infection (HBcAb-positive with or without HBsAb) are detected, monitor for HBV reactivation with serial HBV DNA and liver function tests during DAA therapy (*Not Graded*).

### Commentary

DAA therapy and achievement of HCV clearance can lead to HBV reactivation.<sup>68</sup> The risk period is greatest during DAA therapy and for up to 12 weeks posttreatment. This observation generated an FDA warning to monitor for this potential complication. The overall likelihood of HBV reactivation is low (<5%) but is highest among patients who are positive for HBV surface antigen (HBsAg).<sup>69</sup> Thus, guideline 2.5 emphasizes that testing of all patients for HBV markers before HCV treatment is recommended.<sup>4</sup> Those who are HBsAg positive may be considered for HBV therapy or close monitoring with preemptive therapy if HBV DNA increases. Because the risk is very low in those with markers of prior HBV infection (but HBsAg negative), testing for HBV DNA should be considered in patients with elevated ALT levels.

### Implementation and Challenges

Following the release of the 2008 guideline, the development and subsequent FDA approval of a class of drugs referred to as the DAAs has revolutionized the treatment of HCV infection and had an enormous impact on the care of HCV-viremic patients with CKD. The pre-DAA-era treatment for HCV infection relied almost entirely on interferon-based protocols that were ineffective (~40% SVR), very poorly tolerated in patients with kidney failure, and relatively contraindicated in kidney transplant recipients. As a consequence, HCV infection in patients with kidney disease went largely untreated for decades, and to some extent, a “therapeutic nihilism” developed among nephrologists when it came to treating HCV infection. The results from clinical trials of DAAs in patients with CKD have unequivocally demonstrated the safety and effectiveness of the DAAs in patients with kidney disease and challenged nephrologists and others caring for these patients to: (1) identify the infected patients and (2) refer for treatment when appropriate.<sup>5,6</sup> Education of nephrologists about the importance of diagnosing HCV infection in their patients and then participating in the decision process about who and when to treat

has been part of the challenge of the last few years. This is of special importance in 2 clinical scenarios in particular; one relates to the data suggesting that HCV infection contributes to the progression of CKD<sup>26,27</sup> and that treatment might slow this process,<sup>28,29</sup> and second, the rapidly evolving data contributing to our understanding of the use of kidneys from HCV-infected donors and how best to make use of these organs. It is imperative that nephrologists participate in the discussion with their patients with CKD G4-G5/5D about the optimal timing to treat existing HCV infection, and for those without HCV infection, whether they might be good candidates to accept a kidney from an HCV-infected donor and receive DAA therapy post-transplantation. The latter approach may shorten waiting times in some transplantation centers but also introduces the challenge of obtaining insurance approval for DAA therapy in a recent transplant recipient who has a newly acquired HCV infection from the donor. It is anticipated that data from both additional clinical trials and real-world experience from noninfected patients who receive a kidney from an HCV-viremic donor will continue to become available and provide guidance on the best approach for our patients.

## Preventing HCV Transmission in Hemodialysis Units: Infection Control Procedures

- 3.1 We recommend that hemodialysis facilities adhere to standard infection control procedures including hygienic precautions that effectively prevent transfer of blood and blood-contaminated fluids between patients to prevent transmission of blood-borne pathogens (see Table 1) (1A).
- 3.1.1 We recommend regular observational audits of infection control procedures in hemodialysis units (1C).
- 3.1.2 We recommend *not* using dedicated dialysis machines for HCV-infected patients (1D).
- 3.1.3 We suggest *not* isolating HCV-infected hemodialysis patients (2C).
- 3.1.4 We suggest that the dialyzers of HCV-infected patients can be reused if there is adherence to standard infection control procedures (2D).

### Commentary

The prevalence of HCV infection in hemodialysis patients continues to exceed that of the general population.<sup>70</sup> DOPPS data from 2012 report an anti-HCV antibody prevalence of 7.3% in the US dialysis population.<sup>71</sup> The 2008 guideline stressed both the importance and effectiveness of adherence to standard infection control procedures on limiting patient-to-patient transmission of HCV in the dialysis setting; the



2018 guideline strongly reiterates this position (note that Table 1 mentioned in the guideline statement is not reproduced in this article). Evidence that implementation of infection control practices as recommended in the guideline results in a meaningful decline in infection rates has been clearly demonstrated.<sup>72,73</sup> Nevertheless, data collected by the CDC between 2008 and 2015 documents that >50% of all health care–associated HCV outbreaks occurred in the in-center hemodialysis setting.<sup>25</sup> Using epidemiologic and phylogenetic data obtained by viral sequencing,<sup>1,74–78</sup> nosocomial transmission of HCV within dialysis clinics has been confirmed and continues to be an ongoing issue of significant clinical importance more than 10 years after publication of the first guideline. Consequent to and in response to these important observations, the CDC has provided further guidance focused on improving infection control practices in hemodialysis clinics.<sup>79</sup>

### Clinical Utility

Recommendation 3.1 recommends adherence to standard infection control procedures as a primary strategy to limit transmission of disease between patients. Virtual elimination of HCV transmission in dialysis clinics is achievable through adherence to already published and recommended infection control practices. This is essentially identical to the 2008 guideline, and the message for practitioners and dialysis staff is straightforward and remains unchanged.

The work group emphasized several infection control practices that are critical to limiting outbreaks of HCV infection in the dialysis setting. Proper hand hygiene and glove changes—particularly before invasive procedures, after contact with blood or contaminated surfaces, and between patient contacts—are especially important.<sup>25</sup> It should be noted that HCV can remain in an infectious state for at least 16 hours on a room temperature surface so that contact with contaminated surfaces, even in the absence of visible blood, can become a cause of nosocomial transmission. HCV RNA has been detected on the surface of dialysis machines, waste carts, and dialysis connectors,<sup>80–86</sup> emphasizing the need for proper hand hygiene. Another vulnerable spot in the point of care that can translate into an increased risk for transmission is the mishandling of parenteral medications. Accessing vials with previously used needles or the use of multidose heparin vials, especially those stored or prepared in close proximity to an item contaminated with HCV-infected blood, substantially increases the risk for transmission within the dialysis clinic. To help manage this risk, the CDC has put forth a One and Only Campaign (<https://www.cdc.gov/injectionsafety/one-and-only.html>) that promotes single-use syringes.

### Implementation and Challenges

Recommendation 3.1.2 reiterates the statement from the 2008 guideline recommending against the use of dedicated machines for HCV-infected patients, emphasizing that this may foster a false impression among the staff that the risk for transmission within the clinic has been attenuated. This could translate into a decrease in staff attentiveness to standard infection control procedures, with a subsequent increased risk for transmission. The basis for this recommendation is an absence of evidence for transmission of HCV through the internal circuits of current single-pass dialysis equipment.

Recommendation 3.1.3 restates the statement from the 2008 guideline that isolation of HCV-infected patients is not recommended in hemodialysis clinics. Literature supporting the practice of isolation of HCV-infected patients is of very poor quality, with many methodological challenges.<sup>87–90</sup> In contrast, data from the DOPPS cohort concluded that a policy of isolation did not translate into protection against transmission of HCV in hemodialysis units. Last, the CDC has clearly stated that isolation of HCV-infected dialysis patients is not warranted based on available evidence.<sup>91</sup>

The 2008 HCV KDIGO guideline stated, “When dialyzer reuse is unavoidable, it is suggested that the dialyzers of HCV-infected patients can be reused”<sup>1(p 246)</sup> provided that strict infection control procedures are in place and are adhered to. The 2018 guideline has somewhat stepped back from that position; recommendation 3.1.4 states that dialyzers of HCV-infected patients can be reused, removing the stipulation that this would only be when dialyzer reuse was unavoidable. Of course, adherence to standard infection control procedures must be in place if reuse of dialyzers from HCV-infected patients is the standard of care.

### Preventing HCV Transmission in Hemodialysis Units: Identifying New Cases

3.2 We recommend that hemodialysis centers examine and track all HCV test results to identify new cases of HCV infections in their patients (1B).

3.2.1 We recommend that aggressive measures be taken to improve hand hygiene (and proper glove use), injection safety, and environmental cleaning and disinfection when a new case of HCV is identified that is likely to be dialysis-related (1A).

### Commentary

Recommendation 3.2 is new to the 2018 guideline. It emphasizes the importance of monitoring the dialysis clinic for new cases of HCV infection. The work group makes a strong recommendation that there be a reemphasis and retraining of the staff on the importance of strict adherence to infection control practices when a new case has been identified.

## Preventing HCV Transmission in Hemodialysis Units: Prioritization of Strategies

3.3 Strategies to prevent HCV transmission within hemodialysis units should prioritize adherence to standard infection control practices and should not primarily rely upon the treatment of HCV-infected patients (*Not Graded*).

### Commentary

Recommendation 3.3 is also new in 2018 and emphasizes the importance of adherence to strict infection control practices as the primary method to control HCV infection in the dialysis clinic, rather than relying on the availability of effective DAA agents (see guideline chapter 2). The relative safety and high response rates to the DAA agents has the potential to influence staff and care givers to incorrectly rely on antiviral treatment as a means of infection control in the clinic. The work group emphasizes that this is not the proper approach and may place other patients at increased risk.

### Implementation and Challenges

Recommendation 3.3 is largely intact from the 2008 guideline and continues to emphasize the importance of developing and maintaining the highest standards of infection control practices in the dialysis clinic as the primary prevention of HCV transmission between patients. The challenge is to have staff properly trained and then retrained at regular intervals so that the day-to-day operation of a busy clinic does not compromise these high standards. Prompt reporting of any new HCV infection in the dialysis clinic must also be reported to the local public health authority, something that is not always completed.

### Future Research Recommendations

Continued close surveillance for possible transmission in the dialysis setting coupled with thorough reporting of suspicious cases will be important to determine whether current recommendations are effective and are being followed to prevent transmission of HCV in the dialysis clinic.

## Evaluation and Management of HCV Infection in Kidney Transplant Candidates

4.1 Evaluation and management of kidney transplant candidates regarding HCV infection

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

4.1.2 We suggest that all HCV-infected kidney transplant candidates be evaluated for severity of liver disease and presence of portal hypertension (if indicated) prior to acceptance for kidney transplantation (*2D*).

4.1.2.1 We recommend that HCV-infected patients with compensated cirrhosis (without portal hypertension) undergo isolated kidney transplantation (*1B*).

4.1.2.2 We recommend referring HCV-infected patients with decompensated cirrhosis for combined liver-kidney transplantation (*1B*) and deferring HCV treatment until after transplantation (*1D*).

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*).

### Commentary

We agree with recommendation 4.1 that the treatment of choice for eligible patients infected with HCV who have kidney failure is kidney transplantation, with several studies in the United States demonstrating a significant life expectancy advantage with this approach compared to remaining on dialysis.<sup>92–94</sup> Similarly, preemptive kidney transplantation is the preferred modality for the eligible CKD G4–G5 population infected with HCV, although there are less supporting observational data. Assessment of liver disease severity before transplantation is important for purposes of gauging surgical risk, DAA treatment, and liver cancer surveillance. Although no studies have established definitively that histologic stage on pre-kidney transplantation liver biopsy predicts posttransplantation outcomes in HCV-infected kidney recipients, we agree that candidates should be evaluated for the presence of cirrhosis. Noninvasive testing for liver disease is largely replacing liver biopsy in the general HCV population and has been investigated, although not validated, in kidney transplant candidates.<sup>30,95</sup> Because liver stiffness is influenced by central venous pressure and, by extension, volume status, it is possible that elastography will overestimate fibrosis severity in hypervolemic dialysis patients.<sup>95,96</sup> A recent proposal has put forth that the finding of mild fibrosis with noninvasive testing is a powerful argument

against more invasive testing, whereas more severe fibrosis on noninvasive testing dictates that a liver biopsy be performed to assess for cirrhosis.<sup>97</sup> Absent supportive data, this seems to be an intuitively reasonable approach. Patients with cirrhosis should be further assessed for portal hypertension because this would factor into considerations of surgical risk and possible need for simultaneous liver-kidney evaluation. We agree that patients infected with HCV who have decompensated cirrhosis and CKD G4-G5 should be considered for simultaneous liver-kidney transplantation.

Regarding the timing of HCV treatment relative to transplantation, we agree that the decision should be based around donor type, liver disease severity, and anticipated time frame for transplantation. The epidemic of HCV infection among drug overdose death victims in the United States during the past decade has been accompanied by both high rates of discard for these organs and shorter wait times for candidates willing to accept an HCV-infected kidney.<sup>98</sup> To improve chances of transplantation within a shorter time frame, common practice in the United States (that we endorse) has been to use HCV-infected kidneys in HCV-infected candidates and to delay DAA therapy until after transplantation. We agree with the guideline that when anticipated wait times to transplantation are likely to be short (eg, if there is a medically suitable live donor), it is reasonable to proceed with treating HCV infection before transplantation.

### Clinical Utility

The landscape in the United States is rapidly evolving because of 2 major recent practice initiatives. First, programs put in place by the large dialysis organizations to treat patients receiving dialysis who are HCV-infected in an effort to reduce hemodialysis-related transmission of the virus has led to eradication of infection in many waitlisted candidates before transplantation. Until now, these patients have been rendered ineligible for HCV-infected donor kidneys because of risk for reinfection. Second, shorter waiting times for HCV-infected kidneys has spawned successful initial trials of transplanting kidneys from HCV-infected donors into uninfected patients, followed by post-transplantation DAA therapy.<sup>67,99</sup> This has resulted in increasingly widespread use of this approach around the country as a strategy to increase the use of kidneys that may otherwise be discarded.<sup>100</sup> The consequences of these 2 initiatives are that: (1) kidneys from HCV-infected donors are now more commonly transplanted into uninfected than HCV-infected candidates,<sup>100</sup> and (2) as use of HCV-infected kidneys in uninfected candidates becomes standard practice, the wait time advantage for transplantation with these kidneys will be eliminated, and moreover, candidates whose HCV was previously eradicated could remain eligible for these kidneys under this approach.

## Use of Kidneys From HCV-Infected Donors

### 4.2 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).
- 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).

### Commentary

Section 4.2 of the 2018 KDIGO guideline addresses the use of kidneys donated by persons or deceased donors with HCV infection. The recommendations carry implications for the kidney donor as well as the recipient of the donated allograft. We structure our comments about this section based on the concept that the set of considerations for the donor ought to relate primarily to long-term donor health, whereas the set of considerations for the recipient relate primarily to allograft and recipient outcomes.

We agree that all kidney donors should be screened with both an immunoassay for HCV and HCV NAT. In the US context, this recommendation conforms with both United Network for Organ Sharing (UNOS) regulations and national US transplantation practice. Analysis of national registry data provided by UNOS shows that HCV antibody and NAT were essentially ubiquitous for all deceased donors after April, 2015.<sup>99</sup> Particularly for deceased donors, the practice of requiring NAT should have the effect of improving the sensitivity of identifying HCV among donors, many of whom in the United States die of an opiate overdose, having recently used injection drugs.

We strongly disagree with recommendation 4.2.2 that HCV-viremic kidneys “be directed to recipients with positive NAT.” In our view, multiple studies and associated publications have become available subsequent to the preparation and publication of the 2018 KDIGO guideline that provide useful information about outcomes for transplanting HCV-viremic organs into uninfected recipients.<sup>67,99,101–105</sup> These studies provide preliminary evidence that transplantation of a viremic kidney into an HCV-negative recipient with subsequent eradication of transmitted virus with DAA therapy is an option for some patients on the waiting list.

The leading principles that guide organ allocation ethics are equity and utility, with additional consideration of respect for autonomy for the wait-listed patient considering the organ.<sup>106</sup> An assertion that the organ allocation system should preferentially direct HCV-viremic kidneys to

wait-listed candidates with HCV infection would require that this practice is either more equitable or more efficient (eg, better allograft survival or better patient survival) than allocating HCV-viremic kidneys according to the usual rules of allocation. Little or no evidence supports that directing HCV-viremic kidneys to recipients with HCV infection versus uninfected recipients would improve the outcomes for those organs. Notably, however, a recent study reveals that as transplantation of HCV-viremic kidneys into uninfected recipients has become more common in the United States, rates of discard of kidneys from HCV-viremic deceased donors have declined, consistent with improved utility.<sup>100</sup>

In the United States and some other nations, the kidney allocation system, motivated by principles of equity, gives preference to patients with the most priority time based on dialysis vintage or placement on the waiting list and to children and sensitized patients. The US system also preferentially allocates the kidneys predicted to survive the longest to patients predicted to live the longest, which is intended to maximize utility. To focus on specific cases, HCV-infected candidates do not deserve a transplant more than patients with many years of dialysis time, or children, or sensitized patients. No such prioritization takes place for cytomegalovirus infection, which causes severe illness, is costly to treat, and cannot be cured.<sup>98</sup> The 2018 KDIGO guideline does not address why directing an HCV-viremic kidney to a recipient with HCV infection would improve equity.

Current data also do not suggest that the allocation of kidneys from HCV-viremic donors to candidates with HCV infection would be more efficient, except perhaps in terms of cost to society. Existing trials and cohort studies report 100% HCV cure rates with the practice of transplanting HCV-viremic kidneys, hearts, and lungs into uninfected recipients followed by DAA treatment.<sup>67,99,101–105</sup> A recent publication by Potluri et al<sup>100</sup> using national US registry data showed no meaningful difference in 1-year eGFRs between kidneys from HCV-viremic donors allocated to HCV-seropositive versus matched HCV-seronegative recipients.

To support autonomy, we strongly endorse that transplant candidates be well informed about the potential risks accompanying transplanting HCV-viremic versus HCV-negative kidneys. These risks are not yet fully defined and require further study; however, these risks must also be compared with the reference data indicating that patients on the kidney transplant waiting list face substantial risk for death (4%–6% per year) or health deterioration while awaiting a transplant. In the US context, we contend that transplantation centers should only transplant HCV-viremic organs when DAA treatment can definitely be implemented posttransplantation, through mechanisms including clinical trials, insurance approval, hospital support, or the patient's private means. Notably, the current US kidney allocation system requires that centers use an

“opt-in” mechanism to indicate with certainty that a wait-listed patient can receive offers of HCV-viremic kidneys.

The guideline affirms that “HCV-positive” potential living donors “can be accepted for donation if they achieve SVR<sub>12</sub> and remain otherwise eligible to be a donor.” We support that living kidney donors should be cured of HCV (defined as SVR<sub>12</sub>) before donation to prevent viral transmission to the recipient. We affirm that a donor cured of HCV infection should not pose risk for HCV transmission to the recipient.

The transplantation center otherwise has ethical duties to allow kidney donation when long-term risks to donor health are reasonably low (in the judgment of the donor and the center) and when the donor is well informed.<sup>107</sup> In this case, the long-term risks of prior HCV infection to donor kidney function are uncertain. The donor selection team should examine the donor urine and laboratory workup for possible evidence of prior or ongoing glomerular injury. Depending on the age of the donor, duration of HCV infection, and other findings from the medical evaluation, the donor selection team may consider kidney biopsy to rule out HCV-related injury to the kidney.

In the US context, we also affirm that the term “HCV-positive” may cause confusion as to whether the term references patients with detectable HCV antibody, HCV nucleic acid, or both. In the setting of kidney transplantation candidates, recipients and donors, only positive HCV NAT should be considered consistent with current HCV infection. Therefore, we recommend that “HCV-viremic” be substituted to refer to patients specifically with detectable HCV nucleic acid.

### Use of Maintenance Immunosuppressive Regimens in HCV-Infected Kidney Transplant Recipients

#### 4.3 Use of maintenance immunosuppressive regimens

- 4.3.1 We suggest that all conventional current induction and maintenance immunosuppressive regimens can be used in HCV-infected kidney transplant recipients (2C).

#### Commentary

We support guideline statement 4.3 that all contemporary induction and maintenance immunosuppression regimens can be used in HCV-infected kidney transplant recipients.

### Management of HCV-Related Complications in Kidney Transplant Recipients

#### 4.4 Management of HCV-related complications in kidney transplant recipients

- 4.4.1 We recommend that patients previously infected with HCV who achieved SVR before transplantation be tested by NAT 3 months after transplantation or if liver dysfunction occurs (1D).

- 4.4.2 Untreated HCV-positive kidney transplant recipients should have the same liver disease follow-up as HCV-positive non-transplant patients, as outlined in the American Association for the Study of Liver Diseases (AASLD) guidelines (*Not Graded*).
- 4.4.3 HCV-infected kidney transplant recipients should be tested at least every 6 months for proteinuria (*Not Graded*).
- 4.4.3.1 We suggest that patients who develop new-onset proteinuria (either urine protein-to-creatinine ratio > 1 g/g or 24-hour urine protein > 1 g on 2 or more occasions) have an allograft biopsy with immunofluorescence and electron microscopy included in the analysis (2D).
- 4.4.4 We recommend treatment with a DAA regimen in patients with post-transplant HCV-associated glomerulonephritis (1D).

### Commentary

Recommendation 4.4 addresses the management of kidney transplant recipients with HCV infection before and/or after kidney transplantation. We are not aware of any high-quality evidence supporting routine HCV NAT after transplantation for kidney transplant recipients who achieved SVR<sub>12</sub> before transplantation. Specifically, we neither support that kidney transplant candidates who have already been cured of HCV should be counseled that kidney transplantation might cause HCV infection to recur nor do we think that routine posttransplantation HCV NAT should be performed to confirm that HCV RNA remains undetectable. However, we support HCV NAT at least once after transplantation in specific situations, including: (1) transplantation with an HCV-viremic kidney, (2) transplantation from an anti-HCV antibody-positive/NAT-negative donor, (3) transplantation with an increased risk kidney (as defined by the US Public Health Service), (4) liver dysfunction posttransplantation, and (5) glomerulonephritis posttransplantation.

In the US context, we affirm that DAA treatment should be initiated posttransplantation for all recipients with HCV viremia to prevent the many potential complications of HCV infection in the setting of immunosuppression. Although no specific evidence basis can support the exact timing of DAA treatment, we think that treatment should be initiated as early as possible posttransplantation (eg, weeks to months posttransplantation) regardless of evidence of glomerulonephritis, proteinuria, or other clinical findings. The THINKER and EXPANDER trials of transplanting HCV-viremic kidneys to uninfected recipients provide relevant evidence that treatment in the first week posttransplantation can be comfortably integrated into usual posttransplantation care, with the caveat that these favorable early outcomes were obtained within the structure of a clinical trial.<sup>67,99</sup> This early treatment approach may avoid potential injury to the liver or allograft or other

adverse outcomes, including diabetes mellitus. Although the risks and benefits of transplanting HCV-infected organs into HCV-negative recipients are not yet fully defined, there is suggestive evidence and biological plausibility that deferring DAA treatment until months after transplantation may elevate the risks for other viral infections such as cytomegalovirus and polyoma virus and of liver injury such as fibrosing cholestatic hepatitis.<sup>67,99,101–105,108</sup> Therefore, in the setting of de novo donor-derived HCV infection with kidney transplantation, we advocate for treatment with DAAs as early as the first week posttransplantation. To facilitate the early posttransplantation initiation of DAA therapy in patients consenting to accept a kidney from an HCV-viremic donor, we suggest that the process of obtaining approval by third-party payer be initiated in the pretransplantation period.

After HCV infection cure, these kidney recipients should be treated according to usual center guidelines as far as proteinuria screening and indications for kidney biopsy. Specific considerations related to liver disease care should be performed according to prevailing US general population HCV guidelines for patients who have achieved SVR<sub>12</sub>.

### Implementation and Challenges

Recommendation 4.4 encompasses a wide range of issues relevant to the management of HCV infection in the setting of kidney transplantation. Important and somewhat controversial questions are addressed in this guideline, specifically the optimal timing to treat an HCV-viremic dialysis patient who is a candidate for transplantation and the equitable and safe allocation of kidneys recovered from HCV-viremic donors. Going forward, the single largest challenge to those making these decisions and developing policy will be to obtain the necessary short- and long-term clinical outcomes data from an appropriate number of patients who acquired HCV infection from their donor at the time of transplantation. Education of both the public and health professionals about the utility of transplanting organs from the unfortunate victims of the ongoing opioid epidemic in the United States must continue to be a priority as additional data become available. Cooperation from third-party payors and insurance carriers is of paramount importance to ensuring that recipients of these organs have quick and reliable access to the necessary DAAs in the posttransplantation period.

### Future Research Recommendations

The optimal timing to initiate posttransplantation antiviral therapy has not been determined. Studies that are more comprehensive will be necessary to fully understand the benefits, risks, and short- and long-term outcomes of transplanting kidneys from HCV-viremic donors into HCV-negative recipients. In addition, it may become necessary to revisit the inclusion of donor HCV status in the kidney donor profile index. This important question should be studied more carefully because the

assignment of the donor kidney donor profile index has a significant impact on the kidney allocation sequence for that organ.

### Kidney Biopsy in HCV-Infected Patients With Clinical Evidence of Glomerular Disease

5.1 We recommend that a kidney biopsy be performed in HCV-infected patients with clinical evidence of glomerular disease (*Not Graded*).

#### Commentary

Patients with HCV-associated cryoglobulinemic glomerular disease typically have a histologic lesion resembling membranoproliferative glomerulonephritis (MPGN), which can present clinically in an indolent manner with asymptomatic non-nephrotic-range proteinuria and hematuria with or without reduction in eGFR. Alternatively, the patient may have a more aggressive presentation including nephrotic syndrome (~20%) or rapidly progressive glomerulonephritis in <10%.<sup>109–111</sup> Data from the interferon and ribavirin era guide our understanding of the important role of viral clearance in ameliorating proteinuria and stabilizing GFR in patients with HCV-related MPGN.<sup>112</sup> Other glomerular diseases, such as membranous nephropathy, have been reported in association with HCV infection; however, the response to antiviral or immunosuppressive therapy in these situations is not well defined.

### Treatment of Patients With HCV-Associated Glomerular Disease

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 function 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).

#### Commentary

Because the combination of interferon and ribavirin had SVR<sub>12</sub> rates of only ~40%, the 2008 KDIGO guideline recommended that steroids, cyclophosphamide, or rituximab-based immunosuppression be used first-line in

addition to antiviral therapy for patients with HCV-related MPGN. In the context of the current availability of highly effective DAA therapy that results in rapid viral clearance (within 2–4 weeks of starting therapy) with >95% SVR, the 2018 guideline (statement 5.2) now recommends that first-line therapy for patients with MPGN who have milder manifestations (ie, non-nephrotic-range proteinuria without a rapidly declining eGFR) should be DAAs alone. Translating this into clinical practice would mean that the large majority of patients with MPGN should be spared first-line immunosuppression. This is a critically important change from the 2008 guideline, particularly given that patients with advanced liver disease may be at higher risk for infectious complications associated with potent immunosuppression. Patients presenting with severe manifestations, including rapidly progressive glomerulonephritis and pulmonary hemorrhage or those with nephrotic syndrome should begin both immunosuppression and DAA treatment as first-line therapy. Clearance of cryoglobulins with plasma exchange should be considered for patients with life-threatening presentations.

#### Clinical Utility

The guideline notes the importance of close follow-up of patients after the completion of successful anti-HCV therapy. This recommendation derives from studies demonstrating that there are patients who will fail to achieve remission of proteinuria and hematuria with antivirals alone.<sup>113,114</sup> Relapse of vasculitis symptoms and even de novo vasculitis developing after an SVR<sub>12</sub> was achieved in patients who did not previously have evidence of cryoglobulinemic MPGN are well documented.<sup>115,116</sup> Furthermore, de novo glomerulopathies, including lupus nephritis and focal segmental glomerulosclerosis, have been described in HCV-infected patients.<sup>117–120</sup> In the context of strong clinical trial evidence from the interferon-ribavirin era that rituximab provides superior outcomes for cryoglobulinemic MPGN, the 2018 guideline recommends rituximab as a first-line option for patients who do not respond to antiviral therapy alone or as part of first-line therapy for patients with severe manifestations of cryoglobulinemic vasculitis who require up-front immunosuppression.<sup>121,122</sup>

#### Implementation and Challenges

Identification of HCV infection as part of the evaluation of patients presenting with a nephritic and/or nephrotic clinical picture is essential to highlighting patients who might benefit from DAA therapy. Continued education of health professionals who might be involved in the flow of health care before the patient being seen by a nephrologist (primary care physician, hospitalist, and emergency department physician) is important and must be ongoing. Furthermore, increasing awareness of the linkage of HCV infection with kidney disease in care settings in which HCV infection is being treated (ie, hepatologists and

infectious disease specialists) is also essential so that proper referral of the patient to a nephrologist can be accomplished.

### Future Research Recommendations

We agree with KDIGO that future work should assess the efficacy and safety of DAA therapies and/or immunosuppressive agents in treating HCV-associated glomerulonephritis, ideally in larger controlled clinical studies that have longer follow-up durations. Additionally, given the rapid antiviral activity of DAA regimens, more clarification is needed regarding the role of immunosuppressive agents in the management of aggressive HCV-related glomerular disease such as in nephrotic syndrome and when there is a precipitous decrease in GFR.

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