Executive summary of the 2018 KDIGO Hepatitis C in CKD Guideline: welcoming advances in evaluation and management

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Infection with the hepatitis C virus (HCV) has adverse liver, kidney, and cardiovascular consequences in patients with chronic kidney disease (CKD), including those on dialysis therapy and in those with a kidney transplant. Since the publication of the original Kidney Disease: Improving Global Outcomes (KDIGO) HCV Guideline in 2008, major advances in HCV management, particularly with the advent of direct-acting antiviral therapies, have now made the cure of HCV possible in CKD patients. In addition, diagnostic techniques have evolved to enable the noninvasive diagnosis of liver fibrosis. Therefore, the Work Group undertook a comprehensive review and update of the KDIGO HCV in CKD Guideline. This Executive Summary highlights key aspects of the guideline recommendations.

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The complete *KDIGO 2018 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease* is published simultaneously in *Kidney International Supplements*, volume 8, issue 3, 2018, which is available online at www.kisupplements.org.

Received 20 June 2018; accepted 29 June 2018

Kidney International (2018) **94,** 663–673; https://doi.org/10.1016/j.kint.2018.06.011

KEYWORDS: antivirals; chronic kidney disease; cryoglobulinemia; dialysis; direct-acting antivirals; glomerular diseases; guideline; hemodialysis; hepatitis C virus; infection control; KDIGO; kidney transplantation; liver testing; nosocomial transmission; screening; systematic review

The high prevalence of hepatitis C virus (HCV) in the chronic kidney disease (CKD) population has been recognized since diagnostic testing became available in the early 1990s, as was its transmission within dialysis units. Subsequent studies identified the adverse consequences of HCV infection in the CKD population, as well as its detrimental effect on recipient and graft outcomes following kidney transplantation. Although screening of blood products for HCV reduced its acquisition by blood transfusion, the unique aspects of the epidemiology of HCV infection in the CKD population were apparent. Studies established that transmission was frequent in dialysis patients and typically reflected insufficient attention to body fluid precautions. Also confounding the management of HCV in the CKD population was an absence of biochemical liver dysfunction in most

HCV-infected hemodialysis patients, which contributed to the lack of recognition of its presence and clinical significance. Furthermore, the toxicity of interferon (IFN) in this population underscored the need for effective and tolerable antiviral agents to treat HCV.

The initial Kidney Disease: Improving Global Outcomes (KDIGO) guideline, published in 2008, provided recommendations for the prevention, diagnosis, and management of HCV in CKD. Since then, there have been major advances in HCV management, particularly with the advent of direct-acting antiviral (DAA) therapy. In addition, diagnostic testing has evolved for the assessment of chronic liver disease. Therefore, we undertook a comprehensive review and update of the KDIGO HCV Guideline in patients with CKD.[1] All guideline recommendations are listed in Box 1, but it is beyond the scope of this Executive Summary to discuss each recommendation statement. Instead, we highlight significant concepts underlying the recommendations.

Chapter 1: Detection and evaluation of HCV in CKD

Initial screening. The majority of individuals with HCV infection are asymptomatic, making screening necessary to detect infection in high-risk populations; this is particularly true for hemodialysis patients in whom signs or symptoms of acute HCV infection are rarely recognized. Indeed, the prevalence of HCV infection is greater in CKD patients than in the general population, especially in those with advanced CKD who are not yet on dialysis therapy. In addition, HCV has been identified as an independent risk factor for both CKD onset and rapid CKD progression in multiple studies. Thus, HCV screening is recommended at the time of initial evaluation of CKD. HCV screening is also indicated for patients starting in-center maintenance hemodialysis and for those who transfer from another dialysis facility or modality. In dialysis units with a high prevalence of HCV, initial nucleic acid testing (NAT) should be considered. An HCV antibody (anti-HCV)−negative, NAT-positive profile strongly suggests acute HCV infection.

Screening of peritoneal dialysis and home hemodialysis patients should be considered upon initiation of dialysis to document baseline HCV infection status. If these patients transiently receive in-center hemodialysis, they should undergo HCV infection screening as per the recommendations for in-center hemodialysis patients. Kidney transplantation candidates should be tested for HCV infection during evaluation for transplantation for optimal management and planning.

Follow-up screening. Hemodialysis patients who are not infected with HCV should be screened for the presence of new HCV infection every 6 months using immunoassay. Acute HCV infection in a hemodialysis patient should be reported to the appropriate public health authorities, and all other patients in the same facility should promptly be evaluated by NAT to identify additional cases.

For anti-HCV-positive patients with chronic HCV infection who become HCV NAT-negative with a sustained virologic response (SVR) to DAA therapy, NAT screening should be initiated 6 months after documentation of SVR. SVR is assessed based on the results of NAT testing ≥12 weeks after the conclusion of therapy.

For patients with spontaneous resolution of acute HCV infection as documented by a negative test for HCV RNA at ≥6 months after the onset of acute infection, NAT screening should begin 6 months after documented resolution of infection.

Monthly monitoring of serum alanine aminotransferase is an inexpensive way to ensure that hemodialysis patients are assessed for possible acquisition of infection between regular antibody or NAT screenings. Even minor, unexplained alanine aminotransferase increases should raise the suspicion of acute HCV infection.

Evaluation of liver disease. All HCV-infected patients with kidney failure should undergo a noninvasive biochemical and/or morphological evaluation to stage liver fibrosis, determine the role and timing of antiviral therapies, and facilitate the choice of kidney or combined liver/kidney transplantation in cirrhotic patients. When biochemical and morphological evaluations yield discordant results or when liver comorbidities are suspected, liver biopsy is suggested.

Other testing. Although HCV infection predominantly causes liver disease, it is also associated with extrahepatic manifestations, including kidney disease. However, the relationship between HCV infection and CKD is complex. Based on current evidence, patients with HCV infection should be considered at increased risk of CKD, regardless of the presence of conventional risk factors for kidney disease. As such, all patients should be assessed for kidney disease at the time of HCV infection diagnosis with urinalysis and estimated glomerular filtration rate (eGFR) with repeat follow-up screenings if they are still viremic. Patients with HCV and CKD should be followed regularly to monitor progression of kidney disease.

An increasing body of evidence has implicated HCV infection in CKD progression.[1] Based on epidemiologic data, repeat testing for proteinuria and of eGFR in anti-HCV−positive/HCV NAT−positive patients is recommended. Overall, multiple studies have shown that HCV infection is associated with an increased risk of developing CKD, probably by multiple pathways, including accelerated atherosclerosis.

HCV is a blood-borne pathogen and shares routes of transmission with hepatitis B virus (HBV) and HIV. Although hepatitis A virus (HAV) infection is frequently benign in healthy individuals, superinfection with HAV and HBV in patients with liver disease (including chronic HCV infection) may result in significant morbidity and mortality. Thus, as HAV and HBV infections are preventable by vaccine, appropriate vaccination should be encouraged. However, it should be noted that response rates to vaccinations are diminished in patients with advanced CKD.

Chapter 2: Treatment of HCV infection in patients with CKD

Treatment recommendations are presented by CKD GFR category. For most CKD patients, as in the general population, the potential benefits of DAA treatment outweigh

Box 1 | Summary of KDIGO HCV Recommendations

CHAPTER 1: DETECTION AND EVALUATION OF HEPATITIS C VIRUS IN CHRONIC KIDNEY DISEASE

1.1: Screening patients with chronic kidney disease (CKD) for hepatitis C virus (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*).**
  - **1.1.2.1: We recommend using NAT alone or an immunoassay followed by NAT if immunoassay is positive (*1A*).**
- **1.1.3: We suggest screening all patients for HCV infection upon initiation of peritoneal dialysis or home hemodialysis (*2D*).**
- **1.1.4: We recommend screening all patients for HCV infection at the time of evaluation for kidney transplantation (*1A*).**

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 hemodialysis patients have ALT level checked monthly *(2B)*.**

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*).**

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*).**

potential harms. However, some patients may not be expected to live long enough to benefit from therapy (e.g., those with metastatic cancer). The Work Group was hesitant to specify a minimum life expectancy that would justify treatment, given the inaccuracy of predictions and the need to individualize treatment decisions.

IFN is often poorly tolerated in CKD G4–G5 patients who have prolonged IFN exposure due to decreased renal clearance. Ribavirin is also associated with substantial adverse events. Because DAAs are effective, well tolerated, and some regimens do not require dose reductions in those with CKD, it is clearly desirable to avoid IFN completely in all patients and to minimize the use of ribavirin in patients with advanced CKD.

CKD G1–G3b. For patients with CKD G1–G3b (eGFR $\geq$ 30 ml/min per 1.73 m^2), the choice of DAA is not

Box 1 | Summary of KDIGO HCV Recommendations

CHAPTER 2: TREATMENT OF HCV INFECTION IN PATIENTS WITH CKD

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*).**

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

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

Kidney function	HCV genotype	Recommended regimen(s)	Strength of evidence	Alternate regimen(s)	Strength of evidence
CKD G4–G5 (GFR < 30 ml/min per 1.73 m^2) including HD, KTR[b]	1a	Grazoprevir/elbasvir	1B	Ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir (also known as PrOD or 3D regimen) with ribavirin	2D
		Glecaprevir/pibrentasvir	1B	Daclatasvir/asunaprevir	2C
	1b	Grazoprevir/elbasvir	1B	Ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir (also known as ProD or 3D regimen)	2D
		Glecaprevir/pibrentasvir	1B	Daclatasvir/asunaprevir	2C
	2,3	Glecaprevir/pibrentasvir	1B		
	4	Grazoprevir/elbasvir	2D		
		Glecaprevir/pibrentasvir	1B		
	5,6	Glecaprevir/pibrentasvir	2D		
CKD G5 PD	n/a (reasonable to follow proposed regimens for HD)				
KTR (GFR ≥ 30 ml/min per 1.73 m^2)	1a	Sofosbuvir with ledipasvir, daclatasvir or simeprevir	1B	Sofosbuvir/ribavirin	2D
		Glecaprevir/pibrentasvir[c]	1C		
	1b	Sofosbuvir with ledipasvir, daclatasvir or simeprevir	1B		
		Glecaprevir/pibrentasvir[c]	1C		
	2, 3, 5, 6	Glecaprevir/pibrentasvir[c]	1D	Sofosbuvir/daclatasvir/ribavirin[d]	2D
	4	Sofosbuvir with ledipasvir, daclatasvir or simeprevir	1D		
		Glecaprevir/pibrentasvir[c]	1D		

Figure 1 | Recommended direct-acting antiviral (DAA) treatment regimens for patients with chronic kidney disease (CKD) G4–G5D and kidney transplant recipients (KTRs), by hepatitis C virus (HCV) genotype.[a] Duration of therapy for all these regimens is usually 12 weeks, but readers should consult American Association for the Study of Liver Diseases (AASLD) or European Association for the Study of the Liver guidelines for the latest information. [a]We recommend that CKD patients with glomerular filtration rates (GFRs) ≥ 30 ml/min per 1.73 m^2 (CKD G1T–G3bT) be treated with any licensed DAA regimen. [b]There is little published evidence to guide treatment regimens in KTRs with GFR < 30 ml/min per 1.73 m^2 (CKD G4T–G5T). Regimens in KTRs should be selected to avoid drug–drug interactions, particularly with calcineurin inhibitors. [c]Based on Reau *et al.*[3] [d]As suggested in AASLD guidelines (https://www.hcvguidelines.org). HD, hemodialysis; n/a, no data/evidence available; PD, peritoneal dialysis.

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*).**

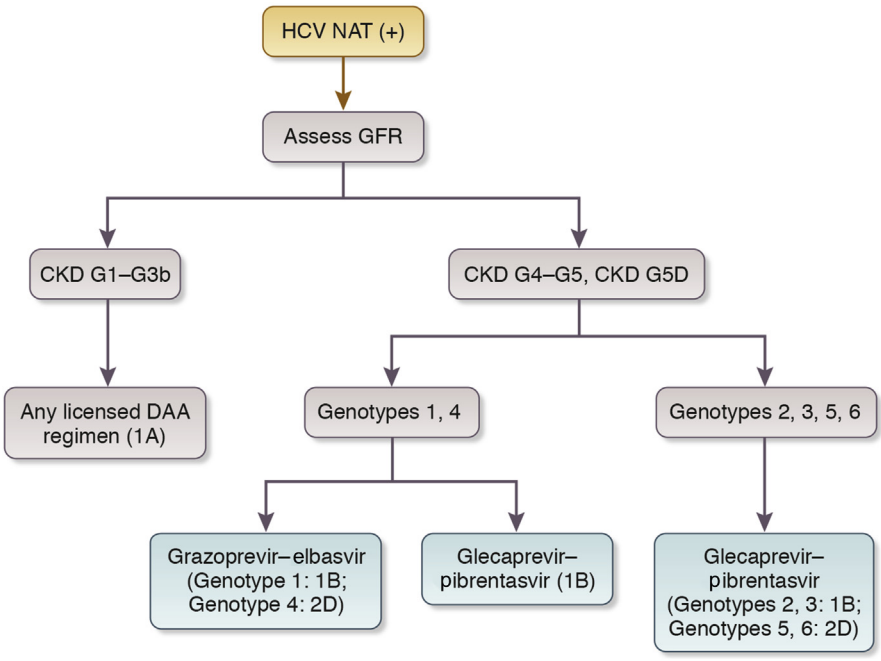
2.4.3: We recommend avoiding treatment with interferon (*1A*).
2.4.4: We recommend pre-treatment assessment for drug−drug interactions between the DAA-based regimen and other concomitant medications, including immunosuppressive drugs in kidney transplant recipients (*1A*).
2.4.4.1: We recommend that calcineurin inhibitor levels be monitored during and after DAA treatment (*1B*).
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*).

restricted by impaired kidney function. However, recommended drugs and dosages are constantly evolving, and clinicians should consult the latest guidelines from the American Association for the Study of Liver Diseases (AASLD; www.hcvguidelines.org/unique-populations/renal-impairment) or European Association for the Study of the Liver (EASL; www.easl.eu/research/our-contributions/clinical-practice-guidelines) for the most up-to-date information.

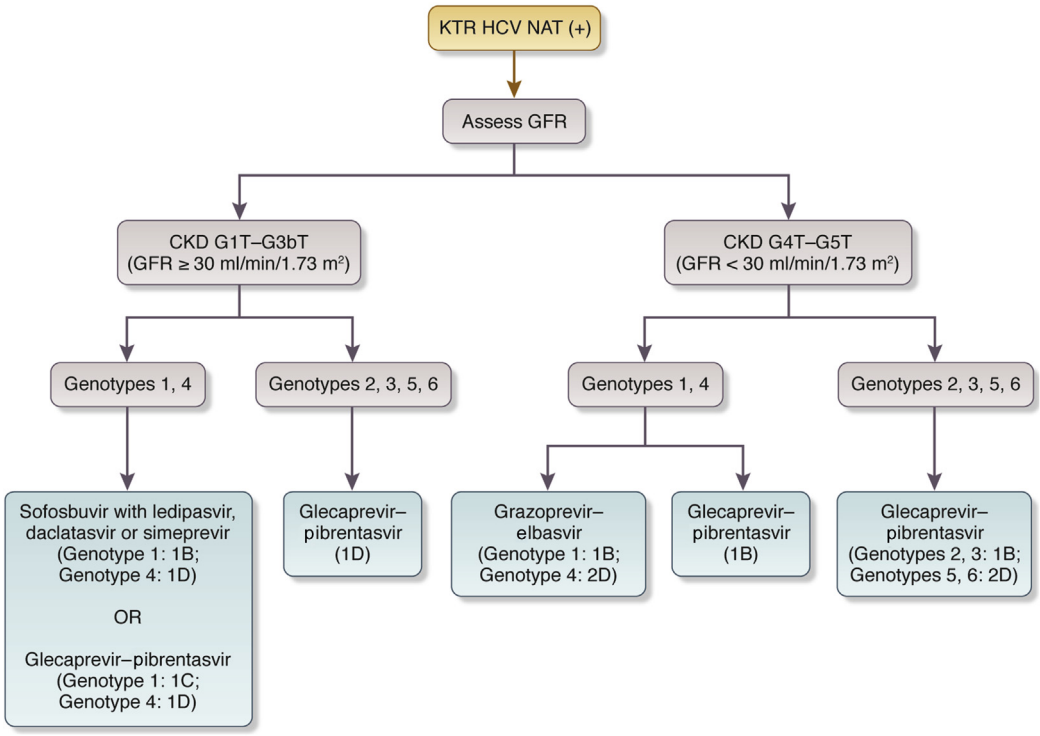
CKD G4–G5 and G5D. Because DAAs have variable renal elimination, advanced CKD (CKD G4−G5D), when present, is an important determinant in the choice of agent. Algorithm 1 summarizes the recommended choices of DAAs according to the level of kidney function and HCV genotype. We recommend that patients with CKD G4–G5 (eGFR < 30 ml/min per 1.73 m^2) and G5D (on dialysis) be treated with a ribavirin-free, DAA-based regimen. As before, clinicians should consult the AASLD and EASL guidelines for the most current treatment information.

Kidney transplant recipients. Although published data on DAAs in kidney transplant recipients are less abundant, the results appear as satisfactory as those observed in liver transplant recipients. Drug−drug interactions are an important factor in the choice of a DAA regimen, and clinicians should systematically consult this online resource (http://www.hep-druginteractions.org). Algorithm 2 summarizes the recommended choices of DAAs for kidney transplant recipients according to the level of kidney function and HCV genotype. Again, clinicians should consult the AASLD and EASL guidelines for the most current treatment information.

Reactivation of hepatitis B virus infection after DAA therapy. Several reports have described apparent reactivation of HBV infection in individuals after successful therapy for HCV infection with DAA-based therapy. As part of routine evaluation of patients with HCV and CKD, serum markers of HBV infection (e.g., hepatitis B surface antigen [HBsAg], HBV DNA) should be assessed before starting



Algorithm 1 | Treatment scheme for chronic kidney disease (CKD) G1 to G5D. (See Algorithm 2 for kidney transplant recipients.) Recommendation grades (1−2) and strength of evidence (A−D) are provided for each recommended treatment regimen and hepatitis C virus (HCV) genotype; see full guideline.[1] DAA, direct-acting antiviral; GFR, glomerular filtration rate; NAT, nucleic acid testing.



Algorithm 2 | Treatment scheme for kidney transplant recipients (KTRs). Recommendation grade (1−2) and strength of evidence (A−D) are provided for each recommended treatment regimen and hepatitis C virus (HCV) genotype; see full guideline.[1] Chronic kidney disease (CKD) G, glomerular filtration rate (GFR) category (suffix T denotes transplant recipient); NAT, nucleic acid testing.

antiviral therapy. Initiation of therapy with an oral HBV suppressive agent is recommended if criteria for HBV therapy are met based on initial testing before HCV therapy or during follow-up after HCV. If HBsAg is initially absent, but markers of previous HBV infection (positive antibody to hepatitis B core antigen [HBcAb] with or without antibody to hepatitis B surface antigen [HBsAb]) are detected, patients should be monitored for HBV reactivation with serial HBV DNA and liver function tests during DAA therapy.

Chapter 3: Preventing HCV transmission in hemodialysis units

The prevalence of HCV infection in hemodialysis patients is usually higher than in the general population. HCV is transmitted parenterally, primarily through percutaneous exposure to blood. Several studies confirmed nosocomial HCV transmission in dialysis units using epidemiological and phylogenetic data from viral sequencing. These data were further supported by the observed decline in infection rates after routine implementation of infection control practices and virological follow-up to detect anti-HCV using sensitive, specific, new-generation serological tests. Nevertheless, according to data from the US Centers for Disease Control and Prevention (CDC), >50% of all health care−associated HCV outbreaks in the US reported to the CDC from 2008 to 2015 occurred in hemodialysis settings. Nosocomial transmission of HCV was also repeatedly observed in hemodialysis units from other high-, low-, and middle-income countries.[2]

Infection control. Infection control lapses responsible for HCV transmission contribute to transmission of other pathogens; hence, improvement efforts will have broader salutary effects. HCV transmission can effectively be prevented through adherence to currently recommended general infection control practices. Root cause analyses of confirmed nosocomial outbreaks that revealed lapses in infection control were associated with transmission of HCV infection among patients in dialysis units. Mishandling of parenteral medications was implicated frequently in transmissions.

It should be emphasized that blood contamination of both environmental surfaces and equipment can be present even in the absence of visible blood. In most reported HCV outbreaks in hemodialysis centers, multiple lapses in infection control were identified, and involved practices such as hand hygiene and glove use, injectable medication handling, and environmental surface disinfection.

Implementation of infection control practices can be advanced by establishing a list of evidence-based interventions as discussed in the full guideline[1] and by regularly assessing and reinforcing adherence to practice through observational audits.

Isolation. Isolating HCV-infected patients (or patients awaiting HCV screening results) during hemodialysis sessions is defined as physical segregation from others for the express purpose of limiting direct or indirect transmission of HCV.

Box 1 | Summary of KDIGO HCV Recommendations

CHAPTER 3: PREVENTING HCV TRANSMISSION IN HEMODIALYSIS UNITS

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*).

Table 1 | Infection control practices ("hygienic precautions") particularly relevant for preventing HCV transmission

- Proper hand hygiene and glove changes, especially between patient contacts, before invasive procedures, and after contact with blood and potentially blood-contaminated surfaces/supplies
- Proper injectable medication preparation practices following aseptic techniques and in an appropriate clean area, and proper injectable medication administration practice
- Thorough cleaning and disinfection of surfaces at the dialysis station, especially high-touch surfaces
- Adequate separation of clean supplies from contaminated materials and equipment

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*).
3.2: We recommend 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*).
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*).

Although the complete isolation of HBV-infected patients (by room, thus including machines, equipment, and staff) has proven invaluable in halting the nosocomial transmission of HBV within hemodialysis units, evidence for using isolation of HCV-infected patients during hemodialysis is weak. In fact, isolation would have a negative impact on the implementation and reinforcement of basic hygiene measures in the unit as a whole. Several experts and guidelines acknowledge that, as HCV transmission can effectively be prevented by adherence to currently recommended practices, considering isolation of HCV-positive patients indicates failure of adherence to the current standard.

Dedicated dialysis machines. Evidence of HCV transmission through internal pathways of the modern single-pass dialysis machine has not been demonstrated. Although contaminated external surfaces of dialysis machines may facilitate the spread of HCV, other surfaces in the dialysis treatment station are likely to have the same impact, which diminishes the purported value of using dedicated machines. In addition, using dedicated machines may trigger the perception that there is no longer a risk of nosocomial HCV transmission, and thus reduce the attention devoted by hemodialysis staff members to body fluid precautions.

Reuse. During the reuse procedure, patient-to-patient transmission can take place if: (i) the dialyzers or blood port caps are switched between patients and not sterilized effectively; (ii) if there is spillage of contaminated blood; or (iii) mixing of reused dialyzers occurs during transport. These situations can be eliminated by adherence to standard hygienic precautions and appropriate labeling.

Other considerations. Audits and use of surveillance data to implement prevention steps are critical to any infection control program. Although no randomized controlled trials have examined the impact of audits on transmission of HCV infection in dialysis units, observational studies showed reduction in the rates of bloodstream infections after implementation of regular audits and evidence-based intervention. Screening for HCV infection is essential for identifying transmission in hemodialysis units, as discussed in Chapter 1 of the Guideline.

With the availability of DAAs, dialysis units may reasonably start HCV-infected patients on these agents in the hope of curing the infection and preventing transmission to uninfected patients. However, use of treatment alone as an infection control measure may place patients at increased risk of HCV and other blood-borne infections from other sources. Indeed, even in the setting of low HCV prevalence, rigorous adherence to key infection control practices is necessary (Table 1).

Despite compelling evidence about the benefits of infection control practices, adherence to recommended practices

Box 1 | Summary of KDIGO HCV Recommendations

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

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 transplantation 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*).**

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*).**

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*).**

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*).**

remains suboptimal. Improved training and education is needed to address knowledge and adherence gaps.

Chapter 4: Management of HCV-infected patients before and after kidney transplantation

HCV infection remains more prevalent in CKD G5 (eGFR < 15 ml/min per 1.73 m^2) patients compared with the general population. Kidney transplant candidates may have acquired HCV infection before developing CKD or requiring dialysis, within a dialysis unit, when they received a previous transplant, or if they received a blood transfusion in the era before systematic screening for HCV. Because of the deleterious effects of HCV infection in dialysis and kidney transplant patients, it is critical to

evaluate disease severity and the need for antiviral therapy.

Evaluation and management. In patients with HCV infection, survival is significantly lower when they are being treated by dialysis than when they are kidney graft recipients. Thus, eligible patients should be considered for kidney transplantation regardless of their HCV status. DAAs now allow successful HCV clearance in nearly all patients before or after transplantation.

Anti-HCV-positive patients who are candidates for kidney transplantation should be evaluated for the presence of cirrhosis using either a noninvasive fibrosis-staging method, or, on occasion, a liver biopsy. The choice of method is discussed in Chapter 1 of the Guideline.[1]

In patients with compensated cirrhosis without portal hypertension, isolated kidney transplantation is recommended. HCV clearance halts the progression of liver disease and may even induce regression of liver fibrosis. Patients with cirrhosis who have major hepatic complications, despite having achieved SVR, should be evaluated for combined liver–kidney transplantation.

Considerations for planning therapy include a living donor versus a deceased donor, wait-list time by donor type, center-specific policy for acceptance of organs from HCV-positive deceased donors, specific HCV genotype, and severity of liver fibrosis.

In patients with compensated cirrhosis without portal hypertension, if living donor kidney transplantation is anticipated without a long wait, HCV therapy can be deferred until after transplantation. If living donor kidney transplantation is likely to be delayed >24 weeks (to allow 12 weeks of therapy and 12 weeks of follow-up to prove SVR), then HCV therapy can be offered before or after transplantation, based on specific HCV genotype and proposed treatment regimen.

Twice yearly surveillance for hepatocellular carcinoma is indicated in cirrhotic patients. In addition, endoscopic surveillance for varices is indicated. Evaluation for complications of cirrhosis is indicated, irrespective of whether the patient receives antiviral therapy.

Use of kidneys from HCV-infected donors. The use of kidneys from NAT-positive donors into NAT-positive recipients will limit the risk of HCV transmission from these donors without loss of organs from the donor pool. Such use of kidneys from NAT-positive donors is an acceptable approach. The capacity to use DAAs shortly after transplantation should allow safe use of these organs.

Potential living donors with HCV infection should be treated as in the general population. First, the extent of liver fibrosis should be established, and then, if there is no evidence of cirrhosis, they can receive DAAs based on genotype. SVR can then be assessed at 12 weeks with monitoring of kidney function and proteinuria during and after DAA therapy. In the absence of severe hepatic fibrosis, living donation is then feasible.

Two clinical trials on the use of HCV-positive donor kidneys in HCV-negative recipients followed by treatment with DAAs have been reported, but until more information is available regarding long-term safety of this approach, it should be considered strictly investigational.

Maintenance immunosuppressive regimens. In HCV-infected kidney transplant recipients, viral load increases after transplantation because immunosuppression facilitates viral replication. There are limited data on the influence of steroids in kidney transplant patients with HCV infection. One important concern with new DAAs for the treatment of HCV infection in kidney transplant patients is drug–drug interaction with immunosuppressive agents. Because these agents are metabolized in the liver by cytochrome P450, as are most DAAs, substrate competition can occur, which influences their elimination. We suggest consulting the Hepatitis Drug Interactions website (www.hep-druginteractions.org) for the latest guidance on potential drug–drug interactions before DAA use.

Box 1 | Summary of KDIGO HCV Recommendations

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

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

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

- **5.2.1: We recommend that patients with HCV-related glomerular disease showing stable kidney 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*).**

Management of HCV-related complications. Kidney transplantation outcomes in patients with HCV without extensive fibrosis, who are successfully treated before transplantation, should be equivalent to outcomes in uninfected transplant recipients. With achievement of SVR, viral relapse is unlikely, although kidney transplant recipients with unexplained hepatic dysfunction should undergo HCV and HBV testing.

Kidney transplantation in patients with active HCV infection may result in liver disease and extrahepatic complications. Therefore, patients with persistent HCV RNA should be re-evaluated for liver disease and possible DAA treatment.

HCV infection has been reported as a risk factor for the development of proteinuria in kidney transplant recipients. After HCV NAT-positive patients have undergone kidney transplantation, clinicians should screen for proteinuria and microhematuria. For HCV-related glomerular disease, DAA therapy is indicated as well, as discussed in the next section.

Chapter 5: Diagnosis and management of kidney diseases associated with HCV infection

In addition to chronic liver disease, HCV also leads to extrahepatic manifestations, including kidney disease and mixed cryoglobulinemia. Glomerular disease is the most frequent type of kidney disease associated with HCV.

A kidney biopsy should be performed in HCV-positive patients with clinical evidence of glomerular disease. Patients with mild or moderate forms of HCV-associated glomerulonephritis with stable kidney function and/or non-nephrotic proteinuria should be managed first with a DAA regimen. Patients with severe cryoglobulinemia or severe glomerular disease induced by HCV (i.e., nephrotic proteinuria or rapidly progressive kidney failure) should be treated with immunosuppressive agents (generally with rituximab as the first-line agent) with or without plasma exchange in addition to DAA therapies. Patients with HCV-related glomerular disease who do not respond to or are intolerant of antiviral treatment should also be treated with immunosuppressive agents. In all cases, achievement of SVR after DAA treatment, changes in kidney function, evolution of proteinuria, and side effects from antiviral therapy must be carefully monitored. Treatment with antiproteinuric agents such as angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers should be given to patients with HCV-associated glomerular disease. When appropriate, diuretics and antihypertensive drugs should be administered to achieve recommended target blood pressure goals for patients with CKD.

Conclusion

As detailed in this guideline, there have been major advances in the evaluation and therapeutic management of HCV in CKD. However, current access to DAAs remains limited, reaching only 7.4% of those diagnosed globally[4]; low- and middle-income countries (LMICs) accounted for approximately 75% of people living with HCV worldwide in 2016.[5] Financial barriers to treatment adoption persist, although discounts as high as 99% have been achieved in certain LMICs.[6] A multitude of other factors (e.g., availability of generics, company voluntary license discounts, or insurance reimbursement) also account for the large variation in DAA access even within LMICs and upper-middle and high-income countries. It has been the philosophy of KDIGO to provide recommendations based on the best available scientific evidence without direct consideration of costs because they vary widely across countries, and DAA access is likely to evolve quickly over time (e.g., increased market competition, government support programs). Nevertheless, KDIGO recognizes that differences in DAA cost and availability are highly jurisdictional, and as such attempts were made by the Work Group to provide alternative treatment options if available (Figure 1). We hope the guidance from this updated guideline represents another step toward attaining the World Health Organization's goal of eliminating viral hepatitis as a public health problem by 2030.[7]

DISCLOSURE

MJ declared having received consultancy fees from Astellas*, GlaxoSmithKline*, Merck Sharp & Dohme*, and Vifor Fresenius Medical Care Renal Pharma (VFMCRP)*; research support from Alexion*, Amgen*, Janssen-Cilag*, Merck Sharp & Dohme*, Otsuka*, Roche*; speaker honoraria from Abbvie*, Amgen*, Menarini*, Merck Sharp & Dohme*, and VFMCRP*; and travel support from Amgen*. MCB declared having received consultancy fees from Abbvie, Gilead, and Merck Sharp & Dohme; research support from Gilead*; and speaker honoraria from Abbvie, Astellas, Gilead, Merck Sharp & Dohme, and Novartis. FF declared having served as a board member for Abbvie and Merck Sharp & Dohme, and received consultancy fees from Abbvie. VJ declared having received consultancy fees from NephroPlus*; research support from Baxter Healthcare* and GlaxoSmithKline*; and speaker honorarium from Baxter Healthcare*. NK declared having served as a board member for Astellas, Merck Sharp & Dohme, Novartis, and Shire; received consultancy fees from Novartis; and speaker honoraria from Abbvie, Amgen, Astellas, Chiesi, Fresenius, Gilead, Merck Sharp & Dohme, Neovii, Novartis, Roche, Sanofi, and Shire. BLK declared having received speaker honoraria from Novartis. C-LL declared having served as a board member for Arrowhead Research Corporation* and received speaker honoraria from AbbVie and Gilead Sciences Hong Kong Limited. JMM declared having received consultancy fees from Merck Sharp & Dohme, and speaker honoraria from Astellas and Merck Sharp & Dohme. SP declared having served as a board member for Abbvie, Bristol-Myers Squibb, Gilead, Janssen, and Merck Sharp & Dohme; received consultancy fees from Abbvie and Gilead; and speaker honoraria from Abbvie, Bristol-Myers Squibb, Gilead, Janssen, and Merck Sharp & Dohme. MOS declared having served as a board member for Abbvie, Bristol-Myers Squibb, Gilead, and Merck Sharp & Dohme; received research support from Abbvie*, Bristol-Myers Squibb*, Gilead*, and Merck Sharp & Dohme*; speaker honoraria from Abbvie, Bristol-Myers Squibb, and Merck Sharp & Dohme; fees for development of educational presentations from Abbvie, Bristol-Myers Squibb, and Merck Sharp & Dohme; and travel support from Abbvie, Bristol-Myers Squibb, and Gador. CEG declared having served as a board member for Abbvie and received consultancy fees from Alexion. PM declared having served as a board member for Abbvie, Bayer, and Bristol-Myers Squibb, and received research support from Abbvie*, Bristol-Myers Squibb*, Gilead*, and Merck*. *Denotes monies paid to institution. All the other authors declared no competing interests.

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