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KDOQI COMMENTARY

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

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KDIGO (Kidney Disease: Improving Global Outcomes) is an international initiative with a key mission of developing clinical practice guidelines in the area of chronic kidney disease (CKD). KDIGO recently published evidence-based clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C virus infection in individuals with CKD. The process of adaptation of international guidelines is an important task that, although guided by general principles, needs to be individualized for each region and country. Therefore, the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (KDOQI) convened a multidisciplinary group to comment on the application and implementation of the KDIGO guidelines for patients with CKD in the United States. This commentary summarizes the process undertaken by this group in considering the guidelines in the context of health care delivery in the United States. Guideline statements are presented, followed by a succinct discussion and annotation of the rationale for the statements. Research recommendations that are of particular interest to the United States are then summarized to highlight future areas of inquiry that would enable updating of the guidelines.

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THE NEED FOR A US KDOQI COMMENTARY ON THE KDIGO HEPATITIS C GUIDELINES

KDIGO (Kidney Disease: Improving Global Outcomes) is an international initiative with a mission to "improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practices guidelines."[1] The recent KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis

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C virus (HCV) infection in patients with chronic kidney disease (CKD) appeared in *Kidney International* (Issue 109, April 2008).[2] To describe and adopt international guidelines within a local US environment, the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (KDOQI) convened a multidisciplinary group. The resulting document describes the specific guideline recommendations, rationale, and statements regarding applicability to the US situation. The intention is to ensure that a US KDQOI perspective is available for use by local physicians and care providers.

The burden of HCV in the United States is substantial, with an estimated 3.2 million Americans chronically infected with the virus.[3] HCV infection is associated with an increased prevalence of reduced kidney function[4] and albuminuria[5] and an increased risk of developing end-stage renal disease.[6] Moreover, HCV infection is associated with increased mortality in patients on hemodialysis (HD) therapy[7] and kidney transplant recipients.[8] Thus, how to manage HCV infection in patients with CKD is a relevant question in the US context.

KDIGO GUIDELINE PROCESS

KDIGO developed evidence-based clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of HCV infection in patients with CKD. KDIGO defined CKD as including patients with CKD stages 1 to 5, as well as those on dialysis therapy (HD or peritoneal dialysis) and kidney transplant recipients, a terminology we adopt in this text.

In July 2005, two work group co-chairs assembled a panel of international experts in HCV and nephrology, hepatology, and virology to undertake a systematic review of the literature and produce clinical practice guidelines for the care of patients with CKD and HCV infection. An international team of methodologists coordinated the methods and analytical process and prepared the evidence report. Liaisons from the Centers for Disease Control and Prevention (CDC), World Health Organization, and National Institutes of Health (NIH) participated in the iterative process of evidence review and guideline development.

The work group focused on 5 aspects of management of patients with CKD with respect to HCV infection: diagnosis; treatment; preventing transmission in HD facilities; management of infected patients before and after kidney transplantation; and management of kidney diseases associated with HCV infection. Specific questions were formulated addressing these topics to form the basis of systematic reviews. For most topics, eligible studies evaluated patients with any CKD stage being tested or treated for HCV infection. For treatment-related topics, the work group primarily considered clinical outcomes (including adverse events) or sustained virological response (SVR).

The guideline document included detailed evidence tables summarizing the overall conclusions and quality of evidence for all studies that met the inclusion criteria. With the assistance of the Evidence Review Team, work group members rated the quality of the individual studies. A modification of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method[9] was applied to appraise the quality of evidence for key outcomes of interest and of the overall body of evidence for each guideline statement. Guideline statements were then formulated and their strength was rated as "strong," "moderate," or "weak" based on the quality of evidence and other considerations, including the size of the effect estimate and values and preferences. Costs were not formally considered.

The guidelines were endorsed by the international work group and the KDIGO Board. The HCV guidelines underwent external peer review by individuals and organizations worldwide. Subsequent to that process, feedback was incorporated and a final document was published in *Kidney International*.[2]

KDOQI PROCESS FOR ADAPTATION OF HCV GUIDELINES

Although the KDIGO guidelines were produced through a robust process of evidence review, it is imperative that they be reviewed regarding their applicability and implementation to a particular context, ie, for the United States. Differences in the target population, prevalence of disease, availability of various diagnostic tests, therapeutic interventions, and organization of health services can result in reasonable varia-

tions in how evidence is interpreted and guideline recommendations are formulated and applied, even when they are based on the same best available evidence.[10] Local adaptation of international guidelines has received increasing attention.[10,11] It requires consideration of how specific medical, organizational, legislative, and cultural issues impact on the applicability of the recommendations.

KDOQI convened a multidisciplinary group to comment on the application and implementation of the KDIGO clinical practice guidelines in the United States, as well as to serve as a model for adaptation of future KDIGO guidelines. The original KDIGO guideline recommendations for HCV diagnosis, evaluation, and treatment are presented verbatim with the strength that was originally assigned to them and with references to additional tables or algorithms contained in the KDIGO guidelines, which are not reproduced here. After each set of recommendations, a rationale commentary is provided that comments on their applicability in the United States. The target population is patients with CKD of all stages, including HD patients and kidney transplant recipients. The target audience is the practitioners caring for these patients in the United States. The process included comparison of the KDIGO guidelines with other United States–based guidelines for HCV infection, including those published by the American Association for the Study of Liver Diseases (AASLD),[12] American Gastroenterological Association (AGA),[13] NIH,[14] and the CDC.[15,16]

The KDOQI panel considered the medical care delivery system in the United States and has attempted to describe here for US practitioners the key guidelines regarding HCV diagnosis, evaluation, and treatment. Explicit consideration of cost implications of the recommendations warrants detailed analysis and is beyond the scope of this report.

GUIDELINE 1: DETECTION AND EVALUATION OF HCV IN CKD

1.1.1 It is suggested that CKD patients be tested for HCV. (Weak)

1.1.2 Testing for HCV should be performed in patients on maintenance HD therapy (CKD Stage 5D) and kidney transplant candidates. (Strong)

1.2.1 Patients on HD therapy should be tested when they first start HD or when they transfer from another HD facility. (Strong)

- In HD units with a low prevalence of HCV, initial testing with enzyme immunoassay [EIA]; (if positive, followed by nucleic acid testing [NAT]) should be considered (see Algorithm 1 in the KDIGO guideline). (Moderate)
- In HD units with a high prevalence of HCV, initial testing with NAT should be considered (see Algorithm 1 in the KDIGO guideline). (Moderate)

1.2.2 For patients on HD therapy who test negative for HCV, retesting every 6 to 12 months with EIA should be considered. (Moderate)

1.2.3 Testing for HCV with NAT should be performed for HD patients with unexplained abnormal aminotransferase(s) levels. (Strong)

1.2.4 If a new HCV infection in an HD unit is suspected to be nosocomial, testing with NAT should be performed in all patients who may have been exposed. (Strong)

- Repeated testing with NAT is suggested within 2 to 12 weeks in initially NAT-negative patients. (Weak)

RATIONALE

The detection and evaluation of HCV in a patient with CKD is important because HCV may be the cause of CKD and may be linked to poor clinical outcomes. The recommendations suggest the most appropriate testing strategy and frequency in patients with different stages of CKD. The evidence base is relatively modest in the area of diagnosis and evaluation, but the statements reflect best practices and recommendations, which incorporate risk to the patient, risk to others, and both diagnostic and prognostic aspects.

Even if hepatitis C is unrelated to the cause of CKD, it can still be an independent predictor of

more rapid progression of CKD, as shown in patients with diabetes mellitus.[17] Therefore, testing may be reasonable in this population. However, there is little evidence to support the practice of routine HCV testing in all patients with CKD based on the unproven benefits in the face of possible substantial costs. Still, as outlined in the AASLD guideline for the general population, it is recommended that HCV testing be performed in patients with CKD at risk of acquiring HCV. This includes persons who have injected illicit drugs in the recent or remote past, persons who received a blood transfusion or organ transplant before July 1992, and persons with human immunodeficiency virus infection, among others.[12]

In a small proportion of individuals with CKD, HCV infection is the cause of CKD, which may manifest as membranoproliferative glomerulonephritis (MPGN) with or without cryoglobulinemia, focal and segmental glomerulosclerosis, or membranous glomerulopathy.[18] Therefore, individuals with glomerular hematuria or proteinuria of unknown cause should be tested for HCV (Guideline 1.1.1) as part of the evaluation of the cause of CKD.

Routine testing in HD patients is recommended (1.1.2). Patients on HD therapy should be tested for HCV when they first start HD therapy and also when they transfer between HD facilities (1.2.1). This KDIGO recommendation is applicable to the US context because the prevalence of HCV in patients on maintenance HD therapy in the United States is 10-fold greater than that of the general population.[3,19] Patients may acquire HCV before initiating HD therapy or be infected through nosocomial transmission in HD facilities. In addition, HCV infection is associated with increased mortality in HD patients.[7] Testing serves 2 purposes: to identify and manage those with active HCV infection and provide surveillance to detect nosocomial transmission in the HD facility.

The prevalence of HCV in individual HD centers should guide the choice between EIA or NAT for HCV RNA as the initial test. The overall prevalence of HCV in HD patients in the United States is 14%,[19] but varies across centers. The positive and negative predictive values of EIA testing vary by local prevalence of HCV, which determines the pretest probability. In dialysis centers with a high prevalence of HCV infection, more cases of false-negative EIA test results may occur. Thus, initial testing with NAT should be considered. This differs from the CDC recommendation that EIA be the initial test in all patients on HD therapy.[15]

Rates of HCV infection generally are lower for patients on peritoneal dialysis therapy; therefore, guidelines for HCV testing may not be applicable to this population, except for those who have changed modalities from HD. Data for HCV rates for home HD patients are limited, but it is likely that the rates are lower than for in-center HD patients.

CONSIDERATIONS FOR US DIALYSIS FACILITY–SPECIFIC IMPLEMENTATION

There is considerable cost associated with the universal implementation of these guidelines on testing. Given the variation in HCV prevalence and the direct relationship between the dialysis facility prevalence and incidence rates of new cases,[20] it seems reasonable to implement this guideline based on dialysis facility–specific criteria: eg, HCV prevalence in the dialysis facility population and the risk-factor profile for HCV infection in the facility's population, among others. For example, testing of individuals transferring from 1 facility to another in the same geographic area with low HCV rates might not be necessary. In addition, testing patients who transfer from another facility, but have documentation of results from recent testing, also may not be necessary.

Repeated HCV Testing in Seronegative HD Patients

For patients on HD therapy who test negative for HCV, repeated testing every 6 to 12 months using EIA may be considered (1.2.2). Unless an event has occurred in the meantime, these patients have a low pretest probability of infection; therefore, the expensive NAT is unnecessary. This is consistent with the CDC recommendation that patients on HD therapy undergo HCV testing every 6 months and monthly aminotransferase testing.[15] NAT should be performed for HD patients with unexplained abnormal aminotransferase levels (1.2.3), who thus have an increased probability of HCV infection. This guideline is

similar to the CDC recommendation that testing for NAT should be considered in EIA-negative patients with a persistent increase in alanine aminotransferase levels.[15]

In the setting of suspected nosocomial HCV infection in an HD facility, testing with NAT should be performed in all patients who may have been exposed (1.2.4). Repeated testing with NAT is suggested within 2 to 12 weeks in initially NAT-negative patients because of the risk of false-negative NAT test results early after infection.

Applicability of Guideline 1 to the United States

HCV testing of patients with CKD should be performed in patients with unexplained proteinuria, microscopic hematuria, increased aminotransferase levels, or risk factors for HCV acquisition. The choice of initial test (EIA versus NAT) for HD patients should be individualized to facility-specific prevalence because of moderate rates of false-negative EIA test results in high-prevalence units. The optimal frequency of follow-up testing for HCV in US-based HD facilities requires further study, but for now, should follow CDC recommendations.

GUIDELINE 2: TREATMENT OF HCV INFECTION IN PATIENTS WITH CKD

2.1.1 It is suggested that CKD patients with HCV infection be evaluated for antiviral treatment. (Weak)

2.1.2 It is suggested that the decision to treat be based on the potential benefits and risks of therapy, including life expectancy, candidacy for kidney transplantation, and comorbidities. (Weak)

2.1.3 It is suggested that in CKD patients—except kidney transplant recipients—who develop an acute HCV infection, a waiting period beyond 12 weeks to observe spontaneous clearance (by NAT) is not justified, and that antiviral treatment should be started. (Weak)

2.1.4 It is suggested that HCV-infected patients accepted for kidney transplantation be treated (see Guideline 4). (Weak)

2.1.5 It is suggested that treatment of HCV-infected kidney transplant recipients be considered only when the benefits of treatment clearly outweigh the risk of allograft rejection due to interferon (IFN)-based therapy (for example, fibrosing cholestatic hepatitis and life-threatening vasculitis). (Weak)

2.1.6 It is suggested that antiviral therapy be considered for patients with HCV-related glomerulonephritis (see Guideline 5.3). (Weak)

2.2.1 For HCV-infected patients with CKD stages 1 and 2, combined antiviral treatment using pegylated (PEG)-IFN and ribavirin is suggested, as in the general population. (Weak)

- It is suggested that ribavirin dose be titrated according to patient tolerance. (Weak)

2.2.2 For HCV-infected patients with CKD Stages 3, 4, and 5 not yet on dialysis therapy, monotherapy with PEG-IFN with doses adjusted to the level of kidney function is suggested. (Weak)

2.2.3 For HCV-infected patients with CKD Stage 5D on maintenance HD therapy, monotherapy with standard IFN that is dose-adjusted for a glomerular filtration rate (GFR) <15 mL/min/1.73 m^2 is suggested. (Weak)

2.2.4 For HCV-infected kidney transplant recipients in whom the benefits of antiviral treatment clearly outweigh the risks (see Guideline 2.1.5), monotherapy with standard IFN is suggested. (Weak)

2.3.1 SVR, defined as HCV RNA clearance 6 months after completion of antiviral treatment, is suggested for assessing response to antiviral treatment. (Weak)

2.3.2 If SVR is achieved, it is suggested that testing with NAT be performed annually to ensure that the patient remains nonviremic. (Weak)

- For patients on maintenance HD therapy, repeated testing with NAT every 6 months is suggested. (Weak)

2.3.3 All patients with HCV infection, regardless of treatment or treatment response, should be followed up for HCV-associated comorbidities. (Strong)

- Patients who have evidence of clinical or histological cirrhosis should have follow-up every 6 months. (Strong)
- Annual follow-up for patients without cirrhosis is suggested. (Weak)

RATIONALE

General Consideration of Trade-offs Between Benefits and Harms of Treatment

Treatment of HCV in the general population is associated with lower rates of mortality,[21,22] cirrhosis,[23,24] and hepatocellular carcinoma.[21,25] It is uncertain to what extent the benefit from avoiding morbidity and mortality would apply to patients with CKD, who in general have a shorter life expectancy. Patients with CKD traditionally have been excluded from trials, thus making most of these treatment recommendations moderate to weak. Nonetheless, they are consistent with the recommendations of other official bodies that provide guidance on treatment of patients with HCV. Treatment of HD patients who develop acute hepatitis C should be delayed to determine whether spontaneous HCV RNA clearance occurs, but not beyond 12 weeks after infection (2.1.3). Antiviral treatment should then be considered in patients with CKD (2.1.1) after weighing the potential benefits and risks of therapy for individual patients. Consideration should include: kidney function level (based on estimated GFR); the likelihood of successful treatment in terms of clearing HCV RNA; the patient's candidacy for kidney transplantation; medical comorbidities, including psychiatric or hematologic diseases; and estimated life expectancy, among other factors (2.1.2).[12,13] Hepatologists and transplant surgeons may be helpful in

Table 1. Recommended Treatment of HCV Infection in Patients With CKD and Their Associated Adverse Events

CKD Stage	Interferon*	Ribavirin†	Common Adverse Events
1 and 2	Pegylated interferon alfa-2a, 180 μg SC/wk Pegylated interferon alfa-2b, 1.5 μg/kg SC/wk	800-1,200 mg/d in 2 divided doses	Interferon: headache, flu-like illness, depression Ribavirin: worsened anemia due to hemolysis
3 and 4	Pegylated interferon alfa-2a, 135 μg SC/wk Pegylated interferon alfa-2b, 1 μg/kg SC/wk	Stage 3: 400-800 mg/d in 2 divided doses; not recommended for eGFR $<$ 50 mL/min/1.73 m^2	Interferon: same as above Ribavirin can cause hemolytic anemia and its use must be supported with increased erythropoietin as needed
5	Pegylated interferon alfa-2a, 135 μg SC/wk Pegylated interferon alfa-2b, 1 μg/kg SC/wk	Not recommended	Interferon: same as above
5D	Alfa-2a interferon, 3 mU SC 3$\times$/wk Alfa-2b interferon, 3 mU SC 3$\times$/wk	Not recommended	Interferon: same as above
5T 1-5	Not recommended unless treating fibrosing cholestatic hepatitis or life-threatening vasculitis	Not recommended	Interferon has been associated with allograft rejection and failure

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; SC, subcutaneous; mU, million units.

*Patients with genotypes 1 and 4 should receive 48 weeks of interferon therapy if an early viral response is obtained at 12 weeks ($>$2 log fall in viral titer). Genotypes 2 and 3 should be treated for 24 weeks.

†See text for detailed discussion of ribavirin use and dosing in patient with CKD stages 3 to 5. Patients with genotypes 2 and 3 infection should receive 800 mg/d with stages 1 and 2 CKD. Patients infected with genotypes 1 and 4 should receive 1,000 to 1,200 mg/d with stages 1 and 2 CKD.

the decision-making process. Because this is an area of weak evidence and there are trade-offs between potential benefits and harms, it is particularly important to incorporate the patient's preferences and values in this decision.

The selection of HCV treatment agent depends on CKD stage and should be made in consultation with a hepatologist (Table 1). SVR, defined as achieving HCV RNA negativity 6 months after completing treatment, is the accepted measure of treatment success. PEG-IFN and ribavirin combination therapy for 6 to 12 months depending on HCV genotype is the standard treatment for patients with HCV infection in the general population.[12,26,27] However, experience with the use of these agents is limited in certain groups of patients with CKD.

RECOMMENDED TREATMENT OF HCV INFECTION IN PATIENTS WITH CKD AND THEIR ASSOCIATED ADVERSE EVENTS

CKD Stages 1 to 5, Nondialysis

Although all HCV-infected patients with CKD should be considered for treatment, patients with HCV-related glomerulonephritis should be specifically targeted for treatment (2.1.6) to possibly reduce proteinuria and slow progressive loss of kidney function. The KDIGO guidelines recommended PEG-IFN and ribavirin combination therapy only for patients with CKD stages 1 and 2 (2.2.1), in part because the Food and Drug Administration package inserts for these agents permit their use at this level of kidney function[28-30] and studies of PEG-IFN and ribavirin excluded subjects with serum creatinine values 1.5 times the upper limit of normal.[26] The Food and Drug Administration suggests that ribavirin be avoided in patients with creatinine clearance less than 50 mL/min because ribavirin is cleared by the kidneys and can cause life-threatening hemolytic anemia.[30] Thus, patients with CKD Stages 3 to 5 may be treated with PEG-IFN (2.2.2) or IFN monotherapy. These recommendations are consistent with those published by the AASLD and the AGA.[12,13]

CKD Stage 5 HD and Kidney Transplant Candidates

Patients on HD therapy, particularly kidney transplant candidates (2.1.4), should be considered for treatment. Patients on HD therapy have SVR rates of 33% to 37%,[31,32] but also a much shorter life expectancy during which any benefits may accrue and a high rate of adverse events.[31,32] Individuals who are kidney transplant candidates are a special subgroup in that their life expectancy is longer than that of other patients on HD therapy and their risk from untreated HCV infection during subsequent immunosuppression is greater. Still, the benefits of treatment have to be weighed against a possible delay in transplantation during the lengthy treatment of patients with HCV infection. The KDIGO guidelines suggest monotherapy with IFN for patients on HD therapy (2.2.3). More recent studies of PEG-IFN in HD patients have found similar SVR rates to those of IFN monotherapy in HD patients.[33-35] However, none of the IFN studies and only 1 of the PEG-IFN studies[34] was conducted in the United States. Thus, it is unclear how directly the results are applicable to US HD patients because of potential differences in patient population, HCV genotype prevalence, and severity of HCV disease. These recommendations are similar to those made by the AASLD and AGA guidelines, which recommend PEG-IFN or IFN, but suggest ribavirin not be used in HD patients.[12,13]

Kidney Transplant Recipients

Potential treatment benefits in kidney transplant recipients have to be weighed against the risk of acute allograft rejection caused by IFN therapy[36,37] and lack of evidence showing the efficacy of both IFN and ribavirin in this population.[36-38] However, IFN can be considered in kidney transplant recipients if the potential benefits of treating life-threatening vasculitis or fibrosing cholestatic hepatitis outweigh a 7% to 19% incidence of allograft loss caused by rejection[36,37] (2.1.5). The AASLD guidelines also recommend against antiviral treatment after kidney transplantation.[12]

Follow-up of Treated Patients, All CKD Populations

Follow-up of treated patients should include assessment of SVR (2.3.1). Periodic testing of HCV RNA in patients who achieved SVR should be performed to monitor for long-term persistence of viral negativity (2.3.2). As in the general population, patients with CKD and cirrhosis presumed to be caused by HCV should be managed in consultation with a hepatologist and should be screened for hepatocellular carcinoma and other sequelae of HCV infection and cirrhosis, as recommended by the AGA and AASLD (2.3.3).[12,13]

Applicability of Guideline 2 to the United States

Although the available evidence supporting HCV treatment is weak as applied to the US population, it favors treatment of appropriate individuals. Thus, after weighing the risks and benefits for the individual patient, treatment is indicated because of the high morbidity and mortality associated with persistent HCV infection. Specifically, patients with CKD stages 1 to 2 are candidates for the current gold standard of PEG-IFN and ribavirin, and HD patients appear to have high SVR rates after IFN monotherapy. Further study is needed to clarify the overall clinical benefit of HCV treatment in US patients with CKD and the optimal treatment strategy for patients at any stage of CKD.

GUIDELINE 3: PREVENTING HCV TRANSMISSION IN HD UNITS

3.1 HD units should ensure implementation of, and adherence to, strict infection-control procedures designed to prevent transmission of blood-borne pathogens, including HCV. (Strong)

- Isolation of HCV-infected patients is not recommended as an alternative to strict infection-control procedures for preventing transmission of blood-borne pathogens. (Weak)
- The use of dedicated dialysis machines for HCV-infected patients is not recommended. (Moderate)
- When dialyzer reuse is unavoidable, it is suggested that the dialyzers of HCV-infected patients can be reused provided there is implementation of, and adherence to, strict infection-control procedures. (Weak)

3.2 Infection-control procedures should include hygienic precautions (Tables 18 and 19 in the KDIGO guideline[39]) that effectively prevent the transfer of blood or fluids contaminated with blood between patients, either directly or via contaminated equipment or surfaces. (Strong)

- It is suggested to integrate regular observational audits of infection-control procedures in performance reviews of HD units. (Weak)

RATIONALE

Transmission of HCV occurs primarily through percutaneous exposure to infected blood. A systematic review of studies using molecular epidemiology to track the pattern of HCV outbreaks in HD facilities confirmed patient-to-patient transmission as the major route of transmission,[40-42] with only 1 study implicating the internal pathways of the dialysis apparatus.[43] Although none of the studies in the systematic review was performed in the United States, there is little reason to believe that routes of transmission substantially differ in HD centers in or outside of the United States. A recent abstract showed breakdowns in 4 infection control practices as risk factors for HCV outbreaks in HD facilities.[44]

Infection control procedures identical to those used for other blood-borne pathogens, such as hepatitis B virus and human immunodeficiency virus, should be followed to prevent the nosocomial transmission of HCV (3.1). These include staff education, hand hygiene before and after patient contact, and use of single-use vials for medicines. Dialysis stations should be cleaned with low-level disinfectant after treatment sessions, but higher level disinfectants should be used in the event of visible contamination of equipment. The KDIGO guidelines did not explicitly comment on

the risk of HCV infection to staff members in HD centers, but the practice of universal precautions should minimize this risk, as well.

Large prospective studies have not identified isolation of HCV-infected HD patients as an effective measure to reduce nosocomial HCV transmission.[19,45,46] The use of dedicated machines also is not recommended (3.1) because all except 1 study excluded transmission of HCV through the internal pathways of the dialysis apparatus after appropriate disinfection. Dialyzer reuse does not appear to be a risk factor for HCV transmission provided that strict infection-control procedures are used in the sterilization process (3.1).[20,47,48] The KDIGO recommendations are consistent with the CDC recommendation that routine isolation of HCV-infected HD patients is unnecessary.[15]

Applicability of Guideline 3 to the United States

Although few studies of HCV transmission in HD units were performed in the United States, there is little reason to suspect the mechanisms of transmission are different. Moreover, the recommended infection control procedures are identical to those for other blood-borne pathogens, which are already applied in the US setting.

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

4.1.1 All kidney transplant candidates should be evaluated for HCV infection (see Algorithm 2 in the KDIGO guideline). (Strong)

- In low-prevalence settings, initial testing with EIA and follow-up of positive EIA with NAT should be considered. (Moderate)
- In high-prevalence settings, initial testing with NAT should be considered. (Moderate)

4.1.2 HCV infection should not be considered a contraindication for kidney transplantation. (Moderate)

4.1.3 It is suggested that HCV-infected kidney transplant candidates undergo a liver biopsy before transplantation. (Weak)

4.1.4 It is suggested that HCV-infected patients with cirrhosis confirmed by liver biopsy, but clinically compensated liver disease, be considered for kidney transplantation only in an investigational setting. (Weak)

4.1.5 It is suggested that HCV-infected kidney transplant candidates be considered for treatment with standard IFN before transplantation (see Algorithm 2 in the KDIGO guideline). (Weak)

4.1.6 It is suggested that patients on a kidney transplant waiting list be evaluated for HCV infection (see Algorithm 3 in the KDIGO guideline). (Weak)

- For patients who have never been tested for HCV, it is suggested that testing be performed with EIA in low-prevalence settings (with follow-up of positive results by NAT) and NAT in high-prevalence settings (see Guideline 1.1.1). (Weak)
- It is suggested that HCV-infected patients not previously known to be viremic be placed on hold status pending full evaluation of the severity of their liver disease. (Weak)
- It is suggested that patients who had received antiviral treatment before listing and experienced an SVR have testing with NAT repeated at least annually (see Guideline 2.3.2) (Weak); if NAT becomes positive, it is suggested that the patient be put on hold status and have full evaluation of their liver disease. (Weak)
- It is suggested that HCV-infected patients who had prior evaluation with liver biopsy, but either failed or refused antiviral treatment, have repeated liver biopsy performed every 3 to 5 years while on the transplant waiting list, depending on their histological stage. (Weak)

4.2.1 All kidney donors should be tested for HCV infection. (Strong)

- Testing with both EIA and NAT (if NAT is available) is suggested. (Weak)

4.2.2 It is suggested that transplantation of kidneys from donors infected with HCV be restricted to recipients with positive NAT results. (Weak)

4.3 All conventional current maintenance immunosuppressive regimens can be considered for use in HCV-infected kidney transplant recipients. (Weak)

4.4.1 It is suggested that HCV-infected kidney transplant recipients more than 6 months after transplantation have their liver disease evaluated at least annually. (Weak)

4.4.2 For HCV-infected kidney transplant recipients in whom the benefits of antiviral treatment clearly outweigh the risks (see Guidelines 2.1.5 and 2.2.4), monotherapy with standard IFN is suggested. (Weak)

4.4.3 It is suggested that HCV-infected kidney transplant recipients be screened for the development of hyperglycemia after transplantation. (Weak)

4.4.4 It is suggested that HCV-infected kidney transplant recipients be tested at least every 3 to 6 months for proteinuria. (Weak)

- It is suggested that patients who develop new-onset proteinuria (either urine protein/creatinine ratio >1 or 24-hour urine protein greater than 1 g on 2 or more occasions) have an allograft biopsy with immunofluorescence and electron microscopy included in the analysis. (Weak)

4.4.5 Because of the risk of rejection, it is suggested that kidney transplant recipients with HCV-associated glomerulopathy not receive IFN-based therapy, unless it is determined that the benefits of therapy outweigh the risks of treatment. (Weak)

RATIONALE

HCV infection is not a contraindication to kidney transplantation, but all transplant candidates should be evaluated for HCV infection (4.1.1 and 4.1.2). HCV-infected kidney transplant recipients have lower mortality rates than HCV-infected patients on HD therapy and the transplant waiting list.[49-51] Because HCV-infected kidney transplant recipients have greater rates of mortality,[52-54] graft loss,[55,56] posttransplantation diabetes,[57-59] and glomerulonephritis[60,61] than uninfected kidney transplant recipients, treatment of HCV infection is suggested in kidney transplant candidates (4.1.5). The majority of HD patients who achieve SVR after IFN monotherapy remain HCV RNA negative after transplantation.[62-64] Moreover, limited retrospective data suggest that rates of posttransplantation diabetes[62] and glomerular disease[65] are lower in treated patients.

HCV-infected kidney transplant candidates should undergo a liver biopsy to investigate for the presence of cirrhosis (4.1.3). If cirrhosis is detected on liver biopsy, patients could be considered for combined liver and kidney transplantation. KDIGO suggests that in the setting of histological, but not clinical, cirrhosis, kidney transplantation alone can be considered, but only in investigational settings (4.1.4).

Before undergoing transplantation, kidneys from deceased donors should be tested for HCV using EIA because of time constraints or NAT if rapid testing is available (4.2.1). HCV-infected donor kidneys should be restricted to recipients with positive NAT results (4.2.2). This practice is associated with shorter waiting list times[66] without an apparent increase in mortality.[66] The risk of superinfection with a different viral genotype exists, but mixed infection has not been associated with increased mortality.[67]

There are no data suggesting that any immunosuppressive agent is superior to others in HCV-infected kidney transplant recipients (4.3). After transplantation, HCV-infected kidney transplant recipients should be monitored for the development of liver disease (4.4.1), hyperglycemia (4.4.3), and proteinuria (4.4.4). When an allograft biopsy is performed to evaluate proteinuria in HCV-infected kidney transplant recipients, it should also be examined with immunofluorescence and electron micros-

copy to look for pathological states associated with HCV-related kidney disease.

Applicability of Guideline 4 to the United States

The database studies of outcomes associated with kidney transplantation in HCV-infected patients with CKD were performed in US populations. Accordingly, the guidelines for kidney transplantation in HCV-infected patients with CKD and use of HCV-positive donors are applicable to US patients. Posttransplantation testing for diabetes and proteinuria are currently recommended by the American Society of Transplantation.[68]

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

5.1 It is suggested that HCV-infected patients be tested at least annually for proteinuria, hematuria, and estimated GFR to detect possible HCV-associated kidney disease. (Weak)

5.2 It is suggested that a kidney biopsy be performed in HCV-infected patients with clinical evidence of glomerulonephritis. (Weak)

5.3 It is suggested that for patients with HCV-associated glomerular diseases, particularly MPGN, antiviral treatment according to Guideline 2.2 be considered. (Weak)

- It is suggested that immunosuppressive agents be considered for patients with cryoglobulinemic kidney diseases. (Weak)

RATIONALE

The prevalence of glomerular disease in patients infected with HCV is not known. However, HCV is associated with MPGN and possibly with other glomerular diseases.[18] Thus, screening HCV-infected patients for hematuria, proteinuria, or reduced GFR can detect cases of HCV-related CKD (5.1).[69] This screening would have to be carried out by hepatologists, infectious disease specialists, or general internists who care for the majority of HCV-infected patients. Kidney biopsy is indicated when HCV infection is suspected as a cause of hematuria, proteinuria, or reduced GFR (5.2).

When HCV-associated MPGN is diagnosed, it is suggested that antiviral treatment be considered (5.3). The choice of treatment agent should be tailored to the individual patient with consideration of their CKD stage and comorbid diseases. Studies of patients with MPGN primarily have investigated IFN monotherapy and, to a lesser degree, PEG-IFN or ribavirin. For patients with cryoglobulinemic MPGN, immunosuppression with steroids, cyclophosphamide, or rituximab may be considered (5.3). A phase 3 NIH-sponsored study currently is investigating the use of rituximab in patients with MPGN from HCV infection.

Applicability of Guideline 5 to the United States

Many studies of the management of HCV-associated kidney diseases were conducted in the United States. However, the quality of the evidence on these topics was overall low, highlighting the need to individualize treatment.

RESEARCH RECOMMENDATIONS

Because the process of guideline development involves a systematic review of the literature, it also identifies gaps in the evidence and raises important questions for future research. We list several research questions identified by the KDIGO guidelines that have direct relevance for the care of patients with CKD and HCV infection in the United States.

RESEARCH QUESTIONS PERTAINING TO EVALUATION (GUIDELINE 1)

- Knowledge of the pretest probability of HCV in different CKD populations is essential for a better understanding of the utility of both screening and follow-up testing of patients. A study to examine the prevalence of HCV infection in patients with various stages of CKD would allow better assessment of the utility and costs of screening and possibly support a rationale for testing in targeted settings.
- Rates of seroconversion for HCV of long-term HD patients should be defined in US dialysis centers.

- Cost-effectiveness studies should be performed to clarify the optimal pretest prevalence above which initial NAT testing should be used.

RESEARCH QUESTIONS PERTAINING TO TREATMENT (GUIDELINE 2)

CKD Non-HD Populations

- Studies are needed in HCV-infected patients with CKD Stages 3 to 5 without HCV-related kidney disease to identify the optimal treatment strategy.
- Trials also should be performed to determine the best treatment regimen for patients with HCV-associated glomerular diseases with and without cryoglobulinemia.

HD Populations

- Only 1 study has investigated treatment options for patients on HD therapy in the United States, and a large multicenter trial comparing different treatment regimens would be useful. These studies should evaluate both SVR and clinical outcomes, such as mortality. Patients of African-American descent need to be represented in the studies because they make up 37% of the HD population[70] and have greater rates of HCV infection[4] and lower response rates to treatment.[71]
- Trials also should generate observational data for identification of factors predictive of SVR and long-term clinical outcomes after SVR to help select successful treatment candidates.

Kidney Transplant Populations

- Few treatment options for patients with HCV infection are available for kidney transplant recipients. Future studies should consider new agents or combinations of treatments designed to maximize efficacy while minimizing adverse events. The inclusion of kidney transplant recipients in studies of new medications and strategies should be encouraged.

RESEARCH QUESTIONS PERTAINING TO PREVENTION (GUIDELINE 3)

- Studies should be performed in US HD centers using molecular epidemiology methods to clarify whether nosocomial infection in the United States occurs from contact with the external surfaces of the dialysis apparatus or through the internal pathways, with special emphasis on the potential impact of dialyzer reuse practices on nosocomial transmission of HCV infection.

RESEARCH QUESTIONS PERTAINING TO HCV AND KIDNEY TRANSPLANTATION (GUIDELINE 4)

- A registry should track clinical outcomes of HCV RNA–positive recipients who underwent transplantation of an HCV-infected deceased donor kidney to determine the risk of adverse outcomes.

RESEARCH QUESTIONS PERTAINING TO HCV-ASSOCIATED KIDNEY DISEASES (GUIDELINE 5)

- The epidemiology of HCV-associated glomerular diseases needs to be better characterized in terms of prevalence, pathological variants, and the causal connection with HCV.

CONCLUSIONS

We have reviewed the KDIGO clinical practice guidelines on HCV and CKD, which were developed by an international work group composed of experts in HCV and nephrology, hepatology, virology, and guideline methods. The purpose of our review is to determine the applicability of the recommendations to US patients with CKD and HCV infection. We have adapted and contextualized the guidelines to the US health care delivery system. Specifically, we considered the availability of diagnostic tests, therapeutic alternatives, organization of the health care system, and practices related to HD and kidney transplantation.[10]

Similar commentaries on the KDIGO guidelines can be performed for guideline adaptation to other countries or regions. The process of adaptation of international guidelines is an important task that, although guided by general principles, needs to be individualized for each region and country.[10] The KDIGO guidelines offer an excellent framework from which to adapt specific guidelines to clinical practice and from which to develop important research questions that will strengthen the evidence base for a future update of these guidelines.

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