KDIGO 2017 CLINICAL PRACTICE GUIDELINE ON THE PREVENTION, DIAGNOSIS, EVALUATION AND TREATMENT OF HEPATITIS C IN CKD

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PUBLIC REVIEW DRAFT

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SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

Note: This draft version of the KDIGO 2017 Clinical Practice Guideline on the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in CKD is *not final*. Please do not quote or reproduce any part of this document.

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NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as **Level 1**, **Level 2**, or **Not Graded**, and the quality of the supporting evidence is shown as **A**, **B**, **C**, or **D**.

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

* The additional category "Not Graded" was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

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

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is <u>defined</u> as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is <u>classified</u> based on <u>C</u>ause, <u>G</u>FR category (G1-G5), and <u>A</u>lbuminuria category (A1-A3), abbreviated as CGA.

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m^2) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

CONVERSION FACTORS OF CONVENTIONAL UNITS TO SI UNITS

	Conventional Unit	Conversion Factor	SI Unit
Creatinine	mg/dl	88.4	µmol/l

Note: Conventional unit x conversion factor = SI unit

ABBREVIATIONS AND ACRONYMS

AASLD	American Association for the Study of Liver Disease
AKI	Acute kidney injury
ALT	Alanine aminotransferase
APRI	Aspartate aminotransferase/platelet ratio index
AUC	Area under the curve
BSI	Bloodstream infection
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CKD	Chronic kidney disease
CKD G4, CKD G5	Chronic kidney disease GFR category 4; chronic kidney disease GFR category 5
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNI	Calcineurin inhibitor
CPG	Clinical practice guideline
CrCl	Creatinine clearance
DAA	Direct-acting antiviral
DOPPS	Dialysis Outcomes and Practice Patterns Study
EASL	European Association for the Study of the Liver
eGFR	Estimated glomerular filtration rate
ERT	Evidence Review Team
ESRD	End-stage renal disease
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
GN	Glomerulonephritis
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
GT	Genotype
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
IDSA	Infectious Diseases Society of America
IFN	Interferon
IU	International unit
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
MC	Mixed cryoglobulinemia
MMF	Mycophenolate mofetil
MGN	Membranous glomerulonephritis
MPGN	Membranoproliferative glomerulonephritis
NAT	Nucleic acid test(ing)
NHSN	National Healthcare Safety Network
NS5A	Nonstructural protein 5A
NS5B	Nonstructural protein 5B
OR	Odds ratio
RAS	Resistance associated substitutions
RBV	Ribavirin
RCT	Randomized controlled trial
RR	Relative risk
SVR(weeks)	Sustained virologic response(weeks)
US	United States

PREFACE

With the growing awareness that chronic kidney disease is an international health problem, Kidney Disease: Improving Global Outcomes (KDIGO) was established in 2003 with its stated 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 practice guidelines."

The high prevalence of hepatitis C (HCV) in the chronic kidney disease (CKD) population was recognized once diagnostic testing become available in the early 1990s, as was its transmission within dialysis units. A series of publications subsequently identified the adverse consequences of HCV infection in the CKD population as well as its detrimental effect on recipient and graft outcomes following kidney transplant. Although screening of blood products for HCV reduced its acquisition by blood transfusion, the unique aspects of its epidemiology in the CKD population were apparent. Studies also 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 HCV-infected hemodialysis patients which contributed to the lack of recognition of its presence and clinical significance. An additional difficulty was the lack of effective and tolerable antiviral agents to treat HCV in patients with CKD as interferon, and especially in combination with ribavirin, had considerable toxicity. Furthermore interferon was implicated in graft dysfunction in kidney transplant recipients.

KDIGO convened a group of experts in this area to develop guideline recommendations on the prevention, diagnosis and management of HCV in CKD a decade ago, which resulted in the publication of the very first KDIGO guideline in 2008. Since then there have been major advances in HCV management particularly in antiviral therapy. As a result much of the hesitancy in advising therapy for HCV infected patients with CKD and following kidney transplant has diminished. In addition diagnostic testing has evolved in chronic liver disease including in HCV such that assessment of extent of fibrosis can now be established with noninvasive techniques such as transient elastography.

Because of these advances in diagnostics and therapeutics it was felt appropriate to undertake a comprehensive review and update of the KDIGO HCV guidelines in patients with kidney disease. We thank Michel Jadoul MD and Paul Martin MD for leading this important initiative and we are especially grateful to the Work Group members who provided their time and expertise to this endeavor. In addition, this Work Group was ably assisted by colleagues from KDIGO including Bert Kasiske MD and the independent evidence review team (ERT) led by Ethan Balk MD and his colleagues, Craig Gordon MD, Amy Earley BS, and Mengyeng Di MD, PhD. This teamwork made this guideline possible.

In keeping with KDIGO's policy for transparency and rigorous public review, the draft guideline presented here is now available for commentary. The feedback received will be carefully considered by the Work Group members who will critically review the public input and revise the guideline as appropriate for final publication.

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SUMMARY OF RECOMMENDATION STATEMENTS

CHAPTER 1: DETECTION AND EVALUATION OF HCV IN CKD

HCV screening of patients with CKD

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

1.1.1.1: We recommend using immunoassay followed by nucleic acid testing (NAT). (*1A*)

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

1.1.2.1: We recommend using NAT, or immunoassay followed by NAT. (*1A*)

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

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

Follow-up HCV screening of in-center hemodialysis patients

1.2.1: We recommend screening in-center hemodialysis patients for HCV 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: If a new HCV infection is identified in a hemodialysis facility, we recommend all patients within the facility who were NAT negative be tested for HCV infection and the frequency of subsequent HCV testing for these patients be increased. (*1A*)

1.2.1.3: We recommend hemodialysis patients with resolved HCV infection undergo repeat testing every 6 months using NAT. (*1B*)

1.2.2: We suggest patients have serum alanine aminotransferase (ALT) level checked upon initiation of in-center hemodialysis or upon transfer to another facility or modality. We suggest NAT-negative hemodialysis patients have serum alanine aminotransferase (ALT) level checked monthly. (*2B)*

Liver testing in patients with CKD and HCV infection

1.3.1: We recommend HCV-infected patients with CKD be assessed for liver fibrosis. (*1A*)

1.3.2: We recommend an initial non-invasive evaluation of liver fibrosis. (*1B*)

1.3.3: When the cause of liver disease is uncertain or non-invasive testing results are discordant, consider liver biopsy. (*Not Graded*)

1.3.4: We recommend assessment of portal hypertension in CKD patients with suspected advanced fibrosis (F3-4). (*1A*)

Other testing of patients with HCV infection

1.4.1: We recommend that all patients be assessed for kidney disease at the time of HCV 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 regularly to assess for 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 for HAV and HBV, and screened for HIV. (*1A*)

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 choice of specific regimen be based on HCV genotype (and subtype), viral load, drug-drug interactions, eGFR category, 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 eGFR > 30 ml/min/1.73 m^2 be treated with any licensed DAA-based regimen. (*1A*)

2.3: We recommend that patients with eGFR < 30 ml/min/1.73 m^2 be treated with DAA-based regimens, preferentially ribavirin-free (*1B*), as follows:

2.3.1: We recommend for HCV genotype 1 subtype A the use of grazoprevir/elbasvir (*1A*) and for HCV genotype 1 subtype B, grazoprevir/elbasvir (*1A*) or the "PROD" regimen (the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir) (*1B*) for 12 weeks.

2.3.2: We suggest for HCV genotype 4 the use of grazoprevir/elbasvir or the "2D" regimen (the combination of ritonavir-boosted paritaprevir, ombitasvir regimen) for 12 weeks. (*2D*)

2.3.3: Treat patients with HCV genotypes 2, 3, 5, and 6 on a case-by-case basis. (*Not Graded*)

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

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

2.4.2: We recommend the choice of regimen be based on HCV genotype (and subtype), viral load, drug-drug interactions, eGFR category, stage of hepatic fibrosis, liver transplant candidacy, and comorbidities. (*1A*)

2.4.3: We recommend that treatment with interferon be avoided. (*1A*)

2.5: 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*)

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

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. (*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*)

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 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*)

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

Evaluation and management of kidney transplant candidates regarding HCV infection

4.1: We recommend kidney transplantation as the best therapeutic option for patients with end-stage renal disease (ESRD) irrespective of presence of HCV infection. (*1A*)

4.2: We suggest that all HCV-infected kidney-transplant candidates be evaluated for severity of liver disease and, if indicated, portal hypertension prior to acceptance for an isolated kidney or combined kidney-liver transplantation. (*2D*)

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

4.2.2: We recommend to refer HCV-infected patients with decompensated cirrhosis for combined liver-kidney transplantation (*1B*) and to defer HCV treatment until after transplantation. (*1D*)

4.3: Timing of HCV treatment in relation to kidney transplantation (before vs. after) should be based on donor type (living vs. deceased donor), waitlist times by donor type, center-specific policies for using or not kidneys from HCV-infected deceased donors, HCV genotype, and severity of liver fibrosis. (*Not Graded*)

4.3.1: For all HCV-infected patients who are candidates for kidney transplantation, we recommend they be considered for antiviral therapy, either before or after transplantation. (*1A*)

4.3.2: For HCV-infected kidney-transplant candidates with a living kidney donor, we suggest they can be considered for treatment before or after transplantation according to HCV genotype and anticipated timing of transplantation. (*2D*)

4.3.3: We suggest that, if receiving a kidney from a HCV-positive donor improves the chances for transplantation, the HCV RNA-positive patient can undergo transplantation with a HCV-positive kidney and be treated for HCV infection after transplantation. (*2D*)

Use of kidneys from HCV-infected donors

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

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

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

Use of maintenance immunosuppressive regimens

4.5: We suggest that all conventional current induction and maintenance immunosuppressive regimens can be considered for use in HCV-infected kidney transplant recipients. (*2C*)

Management of HCV-related complications in kidney transplant recipients

4.6.1: 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*)

4.6.2: Untreated HCV-positive kidney-transplant recipients should have the same liver disease follow-up as HCV-positive non-transplant patients, per AASLD guidelines. (*Not Graded*)

4.6.3: HCV infected kidney transplant recipients should be tested at least every 6 months for proteinuria. (*Not Graded*)

4.6.3.1: We suggest that patients who develop new onset proteinuria (either urine protein/creatinine ratio > 1 or 24-hour urine protein > 1 g on two or more occasions) have an allograft biopsy with immunofluorescence and electron microscopy included in the analysis. (*2D*)

4.6.4: We recommend treatment with a DAA regimen in patients with post-transplant HCV-associated glomerulonephritis. (*1D*)

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. (*1B*)

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. (*1B*)

5.2.2: We recommend that patients with cryoglobulinemic flare, nephrotic syndrome, or progressive kidney failure be treated with both DAA and immunosuppressive agents and/or plasma-exchange. (*1B*)

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. (*1A*)

5.2.3.1: We recommend rituximab as the first-line immunosuppressive treatment. (*1B*)

CHAPTER 1: DETECTION AND EVALUATION OF HCV IN CKD

HCV screening of patients with CKD

Patients receiving maintenance hemodialysis and subgroups of CKD patients not yet on dialysis are known to have a high prevalence of hepatitis C (HCV) infection. The reasons for testing CKD patients for HCV infection include early detection and treatment of HCV infection, diagnostic evaluation of the cause of CKD, identification of infection control lapses in hemodialysis centers, and guidance of decisions surrounding kidney transplantation care.

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 immunoassay followed by nucleic acid testing (NAT). (*1A*)

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

1.1.2.1: We recommend using NAT, or immunoassay followed by NAT. (*1A*)

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

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

RATIONALE

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 immunoassay followed by nucleic acid testing (NAT). (1A)

Any CKD patient who has a risk factor for HCV infection should be tested (www.cdc.gov/hepatitis/HCV/guidelinesC.htm). HCV testing is additionally warranted for the evaluation of CKD because: (1) the prevalence of HCV infection may be higher in patients with CKD not yet on dialysis than in the general population;[1, 2] (2) HCV infection increases the risk of developing CKD;[3] (3) HCV infection can accelerate progression of CKD.[4-6]

Testing and diagnosis of HCV infection rely on different assays.[7, 8] Serological assays that detect HCV antibody are based on enzyme-immunoassays or chemoluminescence-immunoassays. HCV antibody tests are unable to distinguish between resolved HCV infection and current HCV infection. Detection of HCV viremia relies on nucleic acid testing (NAT) technologies. Qualitative and quantitative HCV RNA methods are available and have similar limits of detection (10 – 20 IU/ml). HCV antigen tests that detect core antigen alone or in combination with other HCV proteins have the potential to be less costly than NAT, but their limit of detection is higher (equivalent to about 150-3000 IU/ml).[7, 9-11]

The most usual strategy for diagnosis of HCV infection consists of initial screening with a serological assay and, if positive, followed by NAT. However, in high prevalence settings or very high risk groups, immediate NAT is an appropriate alternative. Studies are needed to use HCV antigen test as an alternative to NAT to diagnose HCV viremic infection.

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

1.1.2.1: We recommend using NAT, or immunoassay followed by NAT. (1A)

The prevalence of HCV infection in patients undergoing hemodialysis (CKD G5 on dialysis) is higher than in the general population[12, 13] and has been associated with the number of years of hemodialysis.[12, 13] Patient-to-patient transmission of HCV infection has been documented to occur within outpatient hemodialysis centers.[14-18] The majority of persons 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. Screening of maintenance hemodialysis patients for HCV infection is recommended by United States (US) Centers for Disease Control and Prevention (CDC) and also the US Preventive Services Task Force.[19, 20] Goals of screening in this patient population include early detection of HCV infection, treatment of infection, and detection of dialysis-related transmission. Identification of HCV transmission within a dialysis facility should prompt reevaluation of infection control practices and need for corrective action (Chapter 3). HCV screening is indicated in patients starting in-center maintenance hemodialysis and also in patients who transfer to another facility or modality. In countries with a high prevalence of HCV, initial testing with NAT should be considered. An HCV antibody-negative, HCV RNA-positive profile strongly suggests acute HCV infection. Samples for HCV NAT should be drawn pre-dialysis, since the virus can adhere to the dialyzer membrane.

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

HCV transmission has typically been described in the context of in-center hemodialysis, where healthcare personnel hands, and medications, supplies, and equipment used for one patient can become contaminated with another patient's blood. The current risk of healthcare-related HCV infection among patients who receive peritoneal dialysis or home hemodialysis is unclear. Many of these patients will require in-center hemodialysis at some point during their care, and may be at risk of acquiring HCV infection during that time. 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, with consideration of continued screening until 6 months after the completion of in-center hemodialysis (and transition to a different modality).

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

Kidney transplantation candidates should be tested for HCV infection during evaluation for transplant. Determination of HCV status in recipients is essential for optimal management and potentially acceptance of kidneys from HCV-infected donors (Chapter 4).

Follow-up HCV screening of in-center hemodialysis patients

1.2.1: We recommend screening in-center hemodialysis patients for HCV 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: If a new HCV infection is identified in a hemodialysis facility, we recommend all patients within the facility who were NAT negative be tested for HCV infection and the frequency of subsequent HCV testing for these patients be increased. (*1A*)

1.2.1.3: We recommend hemodialysis patients with resolved HCV infection undergo repeat testing every 6 months using NAT. (*1B*)

1.2.2: We suggest patients have serum alanine aminotransferase (ALT) level checked upon initiation of in-center hemodialysis or upon transfer to another facility or modality. We suggest NAT-negative hemodialysis patients have serum alanine aminotransferase (ALT) level checked monthly. (*2B*)

RATIONALE

1.2.1: We recommend screening in-center hemodialysis patients for HCV 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: If a new HCV infection is identified in a hemodialysis facility, we recommend all patients within the facility who were NAT negative be tested for HCV infection and the frequency of subsequent HCV testing for these patients be increased. (1A)

1.2.1.3: We recommend hemodialysis patients with resolved HCV infection undergo repeat testing every 6 months using NAT. (1B)

Patients who are not infected with HCV should be rescreened for presence of new infection every 6 months.[19] This includes HCV antibody-negative patients and HCV antibody-positive, HCV RNA-negative patients screened initially by immunoassay, as well as HCV RNA negative patients screened initially by NAT. Patients who are HCV antibody-positive and HCV RNA-negative have resolved infection but remain at risk for re-infection if exposed.[21] As a result, these patients should also undergo repeat screening. For dialysis patients who are anti-HCV positive and HCV RNA negative, screening for HCV reinfection should be conducted every six months using NAT (See Recommendation 1.2.3).

The purpose of the repeat screening is to identify new infections that could represent transmission within the dialysis center. The baseline HCV testing results should be reviewed for any patient who has a positive HCV screening test result to determine if there was a change in infection status indicating a new infection, and results must be communicated to the patient. Any patient with current infection, whether new or pre-existing, should be linked to HCV care and considered for antiviral therapy.

Acute HCV infection in a hemodialysis patient should be reported to the appropriate public health authority. In the US, a documented negative HCV antibody or NAT laboratory test result followed within 12 months by a positive HCV test result (test conversion) is reportable to public health.[22] Acute HCV infection in a hemodialysis patient should be

investigated and considered healthcare-related until proven otherwise.[23] Behavioral risk factors, along with dialysis and non-dialysis healthcare exposures may be evaluated by public health authorities. Molecular sequencing of HCV RNA from other patients in the facility might also be conducted to try to identify a source.[18, 24-26]

Acute HCV infection should also prompt immediate evaluation of all other patients in the same facility to identify additional cases. The status of all patients should be reviewed at the time a new infection is identified and all uninfected patients should be tested for HCV infection. The frequency of repeat screening should be increased for a limited time. For example, monthly testing for 3 months, following by testing again in 3 months, and then resumption of screening every 6 months if no additional infections are identified.[16, 19]

For anti-HCV-positive patients with chronic HCV infection who become HCV RNA negative with a sustained viral response (SVR) to HCV therapy, initiate NAT screening 6 months after documentation of SVR. SVR is determined based on 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.

1.2.2: We suggest patients have serum alanine aminotransferase (ALT) level checked upon initiation of in-center hemodialysis or upon transfer to another facility or modality. We suggest NAT-negative hemodialysis patients have serum alanine aminotransferase (ALT) level checked monthly. (2B)

Baseline followed by monthly testing of serum ALT in susceptible patients has been recommended to enable early detection of new HCV infection in hemodialysis patients.[19] Newly infected patients may have an increase in ALT levels prior to antibody conversion, which should prompt additional evaluation. If an unexplained elevation (i.e., greater than upper limit normal) of ALT occurs, the patient should be tested for HCV infection. The exact predictive value of ALT screening for detection of HCV infection is unknown. However, ALT monitoring is a reasonable way to assure hemodialysis patients are assessed for possible acquisition of infection between regular antibody or NAT screenings. Because few hemodialysis patients newly infected with HCV report symptoms or have symptoms documented in their dialysis medical records, ALT levels are also often used retrospectively to define the likely exposure period for patients who acquired infection. Thus, monthly ALT levels are valuable to help narrow the focus of an HCV case investigation to the most likely exposure and source. The value of monthly ALT testing in patients who have resolved HCV

infection in unknown. No recommendation can be made for routine ALT testing in this subgroup.

RESEARCH RECOMMENDATIONS

- Clinical utility of HCV antigen immunoassays and antigen and antibody combination assays should be determined.

- The predictive value of different levels of ALT for identifying HCV infection, should be investigated, along with the additive value of ALT screening to current generation immunoassays or NAT testing. Data should already exist to address this question among dialysis providers that perform routine screening of their patients.

Liver testing in patients with CKD and HCV infection

1.3.1: We recommend HCV-infected patients with CKD be assessed for liver fibrosis. (*1A*)

1.3.2: We recommend an initial non-invasive evaluation of liver fibrosis. (*1B*)

1.3.3: When the cause of liver disease is uncertain or non-invasive testing results are discordant, consider liver biopsy. (*Not Graded*)

1.3.4: We recommend assessment of portal hypertension in CKD patients with suspected advanced fibrosis (F3-4). (*1A*)

RATIONALE

Evaluation of liver fibrosis in HCV-infected patients with renal impairment

In the prior KDIGO HCV guideline published in 2008,[27] liver biopsy had been considered the gold standard to assess liver fibrosis in patients with renal impairment, including candidates for transplantation or in transplant recipients. Generally biochemical non-invasive markers (the Fibrotest/Fibrometer but also APRI, Forns or FIB-4 index) and morphological evaluation (liver stiffness by elastography) may have comparable accuracy in evaluating liver fibrosis in patients with CKD G4-5 than in the general population.[28] The primary objective of liver biopsy in patients with advanced CKD had been to diagnose cirrhosis. Because of the risk of liver-related mortality after kidney transplantation, cirrhosis

had been considered a contraindication to kidney transplantation alone and led to consideration of combined liver-kidney transplantation.

Noninvasive methods, especially elastography, are sufficiently reliable to detect extensive fibrosis/cirrhosis (F3-F4);[29, 30] although, noninvasive tests other than elastography may be less accurate (Evidence Profile 1 and Summary Table 1). Furthermore, although serious complications of liver biopsy are uncommon, patients are often reluctant to consider it and its validity may be diminished by sampling as well as interpretation errors. Its use in HCV infected patients generally has declined.[31, 32]

Now that a SVR can be anticipated in the vast majority of patients treated for HCV, the management of the HCV infected kidney transplant candidate even with cirrhosis has evolved. SVR is associated with sustained and long-lasting suppression of necro-inflammation and may even result in regression of cirrhosis potentially resulting in decreased disease-related morbidity and improved survival.[33] Even in absence of regression of cirrhosis, kidney transplantation alone is feasible in the absence of major complications of portal hypertension, as is recommended for hepatitis B (HBV)-related cirrhosis.[34]

Thus, the role of liver biopsy in evaluatation of liver fibrosis in HCV-infected patients with CKD G4-5 will evolve given the high SVR rates obtained with current direct-acting antiviral (DAA) regimens. Defining the severity of cirrhosis involves assessment for clinically significant portal hypertension. Methods include upper endoscopy, non-invasive radiological evaluation or direct portal pressure measurement. Based on the Baveno VI consensus,[35] portal hypertension is very unlikely (and hence an upper endoscopy can be avoided with > 90% reliability) in patients with compensated cirrhosis but elastography < 20 Kpas and platelet count > 150000/mm^3. Whether this approach is also valid for patients on hemodialysis remains unknown.

In summary, all HCV-infected patients with kidney failure should undergo a noninvasive biochemical and/or morphological evaluation to stage fibrosis and determine the role of antiviral therapies (see Chapter 2) and to facilitate the choice of kidney or combined liver/kidney transplantation in cirrhotic patients. When results between biochemical and morphological evaluation are discordant or when liver comorbidities are suspected, liver biopsy is suggested.

Other testing of patients with HCV infection

1.4.1: We recommend that all patients be assessed for kidney disease at the time of HCV 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 regularly to assess for 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 for HAV and HBV, and screened for HIV. (*1A*)

INTRODUCTION

Although HCV infection predominantly causes liver disease, it is also associated with extrahepatic manifestations including kidney disease.[36] HCV has been shown to infect both hepatocytes and lymphocytes; thus, lymphoproliferative disorders such as lymphoma and mixed cryoglobulinemia (MC) are linked to HCV infection.[37] HCV has also been implicated in derangements of multiple organ systems including cardiovascular, endocrine, muscular, nervous, ocular, respiratory, skeletal, cutaneous and urinary systems. In addition, HCV can have a deleterious impact on psychosocial status.[38]

The relationship between HCV infection and CKD is complex. HCV infection and CKD are prevalent in the general population and associated in various ways: patients on chronic hemodialysis are at increased risk of acquiring HCV and some types of kidney disease are precipitated by HCV infection. Conventional risk factors for CKD such as aging, diabetes, hypertension and metabolic syndrome do not fully explain the current frequency of CKD in the adult general population of developed countries. In addition to these conventional risk factors, accumulating evidence in the last decade has implicated HCV infection as a cause of kidney disease. HCV co-infection has also been implicated as a risk factor for CKD in human immunodeficiency virus (HIV)-infected patients.[39] A meta-analysis[3] of observational studies (n = 9 longitudinal studies; 1,947,034 unique patients)[40-48] demonstrated a relationship between anti-HCV-positive serologic status and an increased incidence of CKD in the adult general population, the summary estimate for adjusted hazard ratio (aHR) was 1.43 (95% confidence

interval [CI]: 1.23-1.63, $P = 0.0001$), according to a random-effects model. Significant heterogeneity was noted and this precluded more definitive conclusions. The observed association between HCV infection and an increased risk for kidney disease could be biased by residual confounding. As an example, information on some covariates (such as injection drug use, exposure to nephrotoxic drugs, etc.) was not available in all included studies. Based on current information, patients with HCV infection should be regarded as being at increased risk of CKD, regardless of the presence of conventional risk factors for kidney disease.

RATIONALE

1.4.1: We recommend that all patients be assessed for kidney disease at the time of HCV diagnosis. (1A)

1.4.1.1: Screen for kidney disease with urinalysis and estimated glomerular filtration rate (eGFR). (Not graded)

The prevalence of CKD, defined by a reduction in estimated glomerular filtration rate (eGFR) and/or increased urinary albumin excretion,[49] exceeds 10% in the adult general population, according to numerous population-based studies. Testing for CKD appears logical in HCV infected individuals as many authors have suggested a potential role of HCV infection as a cause of CKD. However, epidemiologic supporting data regarding the prevalence of CKD in HCV-infected patients were until recently limited and used variable criteria for the definition of CKD; also, the demographic/clinical characteristics of the representative patient population were variable too. According to three studies performed in the US a few years ago,[40, 45, 48] the unadjusted prevalence of low glomerular filtration rate (GFR < 60 ml/min/1.73 m^2) ranged at baseline between 5.1% and 8.0% among anti-HCV seropositive individuals. The unadjusted prevalence of renal insufficiency (serum creatinine >1.5 mg/dl [> 133 µmol/l]) in a large study of anti-HCV seropositive veterans from the US was 4.8%.[50] In a large cohort of HCV-positive/HIV-positive patients from North America, the unadjusted frequency of low GFR (GFR < 60 ml/min/1.73 m^2) at baseline ranged between 3.7% and 4%.[51]

Kidney involvement in HCV infection was first recognized more than two decades ago however the association between HCV and CKD (low eGFR or abnormal proteinuria) in the adult general population was controversial until a few years ago. An increasing body of evidence has recently highlighted the detrimental role of HCV infection on the risk of CKD (Evidence Profile 2 and Summary Tables 2, 3). Cohort studies performed in patients with HIV and HCV co-infection,[6] diabetics,[4, 52] and patients with biopsy-proven chronic glomerulonephritis (GN)[5] have confirmed a significant relationship between anti-HCV-positive serologic status and accelerated progression of CKD. The prevalence of anti-HCV antibody in serum was significantly greater in patients with CKD before reaching end-stage renal disease

(ESRD) than in a healthy population.[1, 2] Among liver transplant recipients infected with HCV treated with antiviral therapy, SVR led to improved eGFR in HCV-infected liver transplant recipients with CKD G2 before treatment.[53] HCV co-infection is a risk factor for increased healthcare resource utilization in HIV-infected individuals in the USA; multivariate Poisson model showed that HCV co-infection was associated with higher frequency of emergency department visits, adjusted relative risk (aRR) 2.07 (95% CI: 1.49- 2.89), $P < 0.001$. In addition to liver injury, kidney disease (37% vs. 12%) played a larger role.[54] Another meta-analysis of observational studies (n = 8 longitudinal studies; 105,462 unique patients)[55]reported a relationship between positive anti-HCV serologic status and an increased risk of reduced GFR among HIV-infected individuals, the summary estimate for adjusted HR was 1.64 (95% CI: 1.28- 2.0, $P < 0.001$) in HIV-HCV co-infected individuals compared with those having HIV mono-infection.[51, 56-62] No heterogeneity was noted between studies.

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)

The recommendation to repeat renal testing in anti-HCV-positive/HCV RNA-positive patients comes from epidemiologic data; based on modified Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, serial measurements of eGFR and proteinuria were obtained in a large cohort of metropolitan residents in the US- the prevalence of CKD was greater among anti-HCV-positive/HCV RNA-positive patients compared to (age-, race-, and gender-matched) anti-HCV-negative controls, 9.1% vs. 5.1%, $P < 0.04$.[63] In addition, using data from the Third National Health and Nutrition Examination Survey, at least two studies have observed an increased risk of albuminuria in patients with HCV.[64, 65] Classically, HCV infection predisposes to cryoglobulinemic membranoproliferative glomerulonephritis (MPGN); however, HCV-positive individuals may also be at risk for kidney injury related to decompensated cirrhosis, injection drug use, concomitant HIV or HBV co-infection. Also, accelerated atherosclerosis may increase the risk of developing kidney disease among HCV-infected individuals.

Another potential independent risk factor for incident and progressive CKD is acute kidney injury (AKI). According to an analysis of hospitalized adults with HCV, CKD was a predictor of dialysis-requiring AKI, adjusted odds ratio (OR), 2.17 (95% CI: 2.03-2.33, $P < 0.001$) in a nationwide inpatient sample analysis. There were 4,603,718 adult hospitalizations with an associated HCV diagnosis from 2004 to 2012 in the US. The proportion of HCV-positive hospitalizations complicated by dialysis-requiring AKI increased significantly from 0.86% in 2004 to 1.28% in 2012. In-hospital mortality was significantly greater in HCV-positive hospitalizations complicated by dialysis-requiring AKI vs. those without (27.38% vs. 2.95%; adjusted OR: 2.09; 95% CI: 1.74–2.51).[66]

There is also evidence about the role of HCV in extrahepatic disease, including metabolic derangements and, more recently, accelerated atherosclerosis. A possible role of an infectious agent in the development of experimental atherosclerosis in rodents was postulated more than a century ago[67] with renewed interest recently.[68] It is likely that HCV promotes atherogenesis through several direct and indirect biological mechanisms. HCV RNA sequences have been isolated from carotid plaques:[69] HCV could play a direct atherogenic role by inducing arterial inflammation. Chronic HCV infection causes hepatic fibrosis, systemic inflammation and hepatic steatosis which is currently considered an early mediator of atherosclerosis. Steatosis promotes the development of atherosclerosis through multiple factors including insulin resistance, hypo-adiponectinemia, metabolic syndrome, oxidative stress, hyper-homocysteinemia, and increased synthesis of tumor necrosis factor-alpha.[70-73] These activities occur independently of traditional known risk factors such as smoking, hypercholesterolemia, and hypertension. In addition to local hepatic inflammation, a concomitant low-grade systemic inflammation has been mentioned in several reports, as suggested by activation of blood monocytes, higher levels of systemic markers of inflammation, particularly fibrinogen, C-reactive protein, erythrocyte sedimentation rate, and N-terminal pro-brain natriuretic peptide.

An atherogenic activity of HCV has been also invoked to explain an excess risk of cardiovascular and cerebrovascular mortality.[74] An increased cardiovascular risk has been observed in HCV-infected patients on maintenance dialysis.[75] According to a meta-analysis of clinical observational studies (n = 14; 145,608 unique patients), positive anti-HCV serologic status was an independent significant risk factor for death among patients on maintenance dialysis.[75] The summary estimate for aRR (all-cause-mortality) was 1.36 with 95% CI: 1.25-1.47 ($P < 0.001$). Stratified analysis showed that the adjusted RR for liver disease-related death was 3.82 (95% CI: 1.92-7.61). The aRR for cardiovascular mortality was 1.26 (95% CI: 1.10-1.45), no heterogeneity was found.[75] Interestingly, SVR achieved in HCV-infected Child-Pugh Class A cirrhotic patients reduced the risk of vascular events by 50% at 3 and 5 years post-treatment.[76]

1.4.3. We recommend that all CKD patients with a history of HCV infection, whether NAT positive or not, be followed regularly to assess for progression of kidney disease. (1A)

.Although studies are heterogeneous and some controversy persists,[77] overall, HCV-infected patients appear at greater risk for incidence and progression of kidney disease and require monitoring as outlined in the KDIGO CKD Guideline.[49] In the Women's Interagency HIV study, anti-HCV-positive serologic status was independently associated with a net decrease in eGFR of approximately 5% per year (95% CI: 3.2-7.2) relative to women who were seronegative.[78]

Of note, antiviral therapy for HCV significantly improves hepatic and extrahepatic outcomes in the general population[79, 80] and among patients co-infected with HIV and HCV.[81] A total of six studies have addressed the impact of interferon (IFN)-based regimens on the progression of CKD.[63, 82-86] Five multivariate analyses[63, 82-85] suggested that treatment of HCV infection may improve renal survival *per se*. In a nationwide cohort study from Taiwan, a total of 12,384 eligible patients who had received antiviral treatment (pegylated interferon plus ribavirin [RBV]) towards HCV were matched 1:2 with 24,768 untreated controls.[84] The treated and untreated cohorts were followed up for a mean duration of 3.3 ($\pm$2.5) and 3.2 ($\pm$2.4) years, respectively. The calculated 8-year cumulative incidence of ESRD in treated and untreated patients was 0.15% vs. 1.32% ($P < 0.001$). This association remained significant after adjustment for various confounders that included death as a competing cause of risk. Multivariate-adjusted Cox regression revealed that antiviral treatment was associated with lower risks of ESRD (HR, 0.15; 95% CI: 0.07-0.31; P < 0.001). Antiviral treatment was also associated with an adjusted HR of 0.77 (95% CI: 0.62-0.97, $P = 0.026$) for acute coronary syndrome, and 0.62 (95% CI: 0.46-0.83, $P = 0.001$) for ischemic stroke, respectively.[84] These favorable associations were not observed in patients treated for less than 16 weeks, suggesting therapy was inadequate. The authors had been able to analyze the Taiwan National Health Insurance Research Database, a single payer system that covers nearly the entire population of Taiwan.

Studies reported from other countries are similar; in a study on 650 Japanese cirrhotics,[82] multivariate Cox proportional hazards analysis showed failure to achieve SVR was a predictor of development of CKD, aHR 2.67 (95% CI:1.43-5.32, $P < 0.005$). In a hospital-based study from the US, 552 HCV-infected American patients were evaluated and 159 received IFN therapy during a 7-year follow-up. Multivariate logistic regression indicated that a history of IFN treatment was a significant independent negative predictor for CKD (OR, 0.18; 95% CI: 0.06-0.56, $P < 0.003$).[63]

An improvement in extrahepatic outcomes has also been observed. In a recent meta-analysis of controlled and uncontrolled studies (11 studies; n = 225 patients) evaluating efficacy and safety of antiviral treatment for HCV-related glomerular disease, the authors found that the summary estimate of the mean decrease in serum creatinine levels was 0.23 mg/dl [20 μmol/l] (95% CI: 0.02-0.44, $P = 0.03$) after IFNα-based therapy.[87]

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 for HAV and HBV, and screened for HIV. (1A)

HCV is a blood-borne pathogen and shares routes of transmission with HIV and HBV. Superinfection with hepatitis A (HAV) and B (HBV) in patients with liver disease (including chronic HCV) may result in higher morbidity and mortality than among individuals without pre-existing liver disease.[88] HAV[89] and HBV[90] are vaccine-preventable infections and appropriate vaccination should be encouraged although response rates are diminished in patients with advanced CKD.

RESEARCH RECOMMENDATION

- With the availability of effective DAAs for the treatment of HCV, it will be possible to assess the role of treatment/cure in preventing and managing CKD in HCV-infected population.

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 choice of specific regimen be based on HCV genotype (and subtype), viral load, drug-drug interactions, eGFR category, 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 eGFR > 30 ml/min/1.73 m^2 be treated with any licensed DAA-based regimen. (*1A*)

2.3: We recommend that patients with eGFR < 30 ml/min/1.73 m^2 be treated with DAA-based regimens, preferentially ribavirin-free (*1B*), as follows:

2.3.1: We recommend for HCV genotype 1 subtype A the use of grazoprevir/elbasvir (*1A*) and for HCV genotype 1 subtype B, grazoprevir/elbasvir (*1A*) or the "PROD" regimen (the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir) (*1B*) for 12 weeks.

2.3.2: We suggest for HCV genotype 4 the use of grazoprevir/elbasvir or the "2D" regimen (the combination of ritonavir-boosted paritaprevir, ombitasvir regimen) for 12 weeks. (*2D*)

2.3.3: Treat patients with HCV genotypes 2, 3, 5, and 6 on a case-by-case basis. (*Not Graded*)

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

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

2.4.2: We recommend the choice of regimen be based on HCV genotype (and subtype), viral load, drug-drug interactions, eGFR category, stage of hepatic fibrosis, liver transplant candidacy, and comorbidities. (*1A*)

2.4.3: We recommend that treatment with interferon be avoided. (*1A*)

2.5: 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*)

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

RATIONALE

These recommendations are based on GFR, which can be measured GFR or estimated GFR (eGFR). If eGFR is used, we suggest using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula or the creatinine and cystatin C based CKD-EPI formula.[91]

For most CKD patients the potential benefits of treatment outweigh potential harm. However, some patients, e.g., patients with metastatic cancer, may not be expected to live long enough to benefit from therapy. 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 this decision. However as in the AASLD/IDSA guidance, life expectancy of at least 12 months should be anticipated.[92]

IFN is often poorly tolerated in CKD patients who may have prolonged IFN exposure due to decreased renal clearance. RBV is also associated with adverse events. Hemolytic anemia induced by RBV is especially common in patients with CKD and can be severe. RBV dose needs to be reduced in patients with advanced CKD, but dose reductions can only be approximated. An initial starting dose of 200 mg daily is typical but does not preclude development of anemia, despite initiation or increased dosing of erythropoietin. Since DAAs are effective, well tolerated, and often do not require dose reductions, it is clearly desirable to avoid IFN completely and RBV if at all possible in patients with CKD (Evidence Profiles 3 and 4, Summary Tables 4 and 5).

For mild-to-moderate decreases in kidney function, patients with CKD can generally be treated per evidence-based guidelines for the general population. In the US the AASLD/IDSA guideline recommends few dosage modifications for mild/moderate reductions in eGFR:

- "For creatinine clearance (CrCl) 30-80 ml/min, no dosage adjustment is required when using daclatasvir, fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg), or fixed-dose combination of paritaprevir (150 mg)/ritonavir (100

mg)/ombitasvir (25 mg) with (or without for HCV genotype [GT] 4 infection) twice-daily dosed dasabuvir (250 mg), grazoprevir/elbasvir combination, simeprevir, or sofosbuvir to treat or retreat HCV infection in patients with appropriate GTs. (Class I, Level A)"[93]

In Europe the EASL guideline[32, 94] also recommends few dosage modifications for CKD patients with mild-to-moderate reductions in kidney function:

- No dose adjustment of simeprevir, sofosbuvir and ledispavir, or daclatasvir is required in patients with mild, moderate or severe renal impairment. The appropriate dose of sofosbuvir for patients with eGFR < 30 ml/min/1.73 m^2 is not yet established.

- Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir or grazoprevir/elbasvir combination is cleared by hepatic metabolism and can be used in patients with severe renal disease.

Waiting times for deceased donor kidney transplantation are very long in many parts of the world, and many transplant candidates die while waiting for a deceased donor transplant. (See Chapter 4). Survival after transplantation is generally better than survival on dialysis including for HCV infected patients. With access to DAA for an individual recipient it may be better to receive a renal graft from a HCV-positive donor than to face a long wait for an HCV-negative kidney, even if the recipient is HCV negative and may acquire HCV infection from the transplanted kidney. If infected, the recipient can be effectively treated for HCV (Evidence Profiles 5 and 6, Summary Tables 6 and 7). This approach remains experimental. It has also been suggested that an HCV-positive transplant candidate should forego treatment of HCV until after kidney transplantation, to allow receipt of a renal graft from an HCV-positive deceased donor. However, there is no guarantee that such a kidney would be available soon and in the meantime the HCV-positive candidate may develop progressive liver disease or extrahepatic complications. Unfortunately, there are no data to suggest which of these potential strategies may be optimal for individual patients.

If a HCV-negative transplant candidate has a potential living donor who is HCV RNA-positive, then it seems reasonable for the donor to be treated for HCV, and donate the kidney after SVR has been achieved. Since the probability of SVR is very high, and the time it takes to achieve SVR is only 12 weeks, this strategy makes intuitive sense even if there are no supporting data. The potential donor also requires careful evaluation of severity of liver disease.

Drug-drug interactions can determine the choice of a DAA regimen. Protease inhibitors are associated with significant risk for drug-drug interactions, particularly in patients

who are treated with immunosuppressive agents such as calcineurin inhibitors (CNIs) and mTOR inhibitors.

Nonstructural protein 5B (NS5B) inhibitors such as sofosbuvir or nonstructural protein 5A (NS5A) inhibitors such as ledipasvir and daclatasvir are associated with a low risk of drug-drug interaction with CNIs and mTOR inhibitors, but may have interactions with other concomitant medications. The HEP Drug Interactions website from the University of Liverpool (http://www.hep-druginteractions.org), or another reliable expert source should be accessed to determine the risk and management recommendations for drug-drug interactions (Table 1).

Table 1. Drug-drug interactions between HCV DAAs and immunosuppressants

	SOF	SOF/ LDV	SOF/ VEL	3D	GZR/ EBR	DCV	SIM
Azathioprine	◆	◆	◆	◆	◆	◆	◆
Cyclosporine	◆	◆	◆	■	●	◆	●
Etanercept	◆	◆	◆	◆	■	◆	◆
Everolimus	◆	■	■	●	■	■	■
Mycophenolate	◆	◆	◆	■	◆	◆	◆
Sirolimus	◆	◆	◆	■	■	◆	■
Tacrolimus	◆	◆	◆	■	■	◆	■

SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; SOF/VEL, sofosbuvir plus velpatasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir; GZR/EBR, grazoprevir plus elbasvir; DCV, daclatasvir; SIM, simeprevir.

Colour legend

◆ No clinically significant interaction expected.

■ Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring.

● These drugs should not be co-administered.

Notes:

- *Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.*
- *The symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on www.hep-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for a more extensive range of drugs, detailed pharmacokinetic interaction data and dosage adjustments, refer to the above-mentioned website.*

Reproduced from EASL[94] In the opinion of the Work Group, for grids that are not labeled green the clinician should carefully review the available evidence prior to co-prescribing the relevant drugs since potential interactions (brown) may in some cases lead to very serious interactions.

DAAs have variable renal metabolism, thus severe renal impairment if present, helps determine choice of agent. Patients with severe renal impairment (eGFR < 30 ml/min/1.73 m^2 and those on hemodialysis) had limited options for HCV therapy until recently. Importantly sofosbuvir, the cornerstone of most anti-HCV DAA regimens, is predominantly renally cleared (80%) and thus remains licensed for use only in individuals with eGFR > 30 ml/minute/1.73 m^2.

Despite this pharmacokinetic profile, there is preliminary clinical data with sofosbuvir-based regimen in CKD patients suggesting that sofosbuvir with a daily or three times weekly regimen may be tolerated in HCV-infected patients who require hemodialysis. A sofosbuvir-based regimen may be the only option at present for patients with CKD G4 and G5 infected with HCV GT2, 3, 5 and 6, particularly those with cirrhosis and those with a history of prior non-response to IFN-based therapies. Consideration should be paid to the potential risk and benefits of using a sofosbuvir-based regimen in patients with CKD G4 and G5.

In contrast to sofosbuvir, other agents such as elbasvir, grazoprevir, paritaprevir, ombitasvir, dasabuvir, simeprevir or daclatasvir can be safely used in CKD G4 and G5 patients. Data on 2 regimens (ritonavir-boosted paritaprevir, ombitasvir and dasabuvir ["PROD" regimen]; elbasvir and grazoprevir) have been published in patients with severe renal impairment (eGFR< 30 ml/min/1.73 m^2 and those on hemodialysis). In the C-SURFER trial, a phase 3 placebo controlled, randomized, multicenter trial, 12-week treatment with grazoprevir and elbasvir was evaluated in GT1 infected patients with advanced CKD (81.3% with eGFR < 15 ml/min/1.73 m^2 and 76.2% on hemodialysis), including 6% of patients with cirrhosis). The majority were infected with GT1a (n = 122, 52%) and 189 (80%) were treatment naïve. Of the 122 patients receiving grazoprevir and elbasvir, six were excluded from the primary efficacy analysis for non-virological reasons. SVR12 was 99% (95% CI: 95.3–100.0; 115/116), with one relapse 12 weeks after end of treatment with no significant difference between GTs 1a and 1b, nor between those undergoing hemodialysis and those with advanced CKD not requiring it. Tolerability was excellent. The most common adverse events (≥ 10% frequency) were headache, nausea, and fatigue, and were comparable in the treatment vs control arms. The frequencies of hemoglobin < 8.5 g/dl (< 85 g/l) were also comparable between both groups (4.5% and 4.4%, respectively) and similar proportions of patients in both groups required erythropoietin. Renal events such as a rise in serum creatinine and/or blood urea nitrogen, change in eGFR, and need to start hemodialysis were comparable between both groups.[95] The combination of ritonavir-boosted paritaprevir, ombitasvir with dasabuvir has been evaluated in a small single-arm study as well as in real-life cohorts demonstrating excellent efficacy in patients infected with HCV GT1 and CKD G4 and G5.[96] RBV may be required when using the ritonavir-boosted paritaprevir, ombitasvir with dasabuvir regimen in patients infected with HCV GT1a but even with a reduced dose of 200 mg RBV daily, further dosing reduction was required in half of the treated patients despite the use of erythropoietin.[97]

Virological factors which may impact response to HCV therapy especially in GT1a include the presence of resistance-associated substitutions (RAS).[98] Resistance testing may not be available in some centers and if use of RBV is not feasible due to baseline anemia, extension of therapy with grazoprevir/elbasvir to 16 weeks for patients infected with HCV GT1a should be considered.

In HCV GT1a patients with high viral load (> 800,000 IU/ml) or pre-existing RAS, prolonging duration of therapy to 16 weeks and the use of RBV, if possible, to avoid a reduction in SVR12 from 99% to 88% is suggested. In the RUBY II trial presented at the 2016 AASLD Annual Meeting, dialysis patients with HCV GT1a were treated with paritaprevir, ombitasvir and dasabuvir and those infected with GT4 were treated with the first two agents without dasabuvir. Of the 13 treated subjects, 12 achieved SVR (92%). The remaining patient who discontinued antiviral therapy elected to undergo kidney transplant.[99]

In summary, in patients with GFR > 30 ml/min/1.73 m^2, the choice of DAA is not restricted. In those with a GFR < 30 and > 15 ml/min/1.73 m^2, only ritonavir-boosted paritaprevir, ombitasvir and dasabuvir or a grazoprevir plus elbasvir regimen are approved. However, there are studies reporting the use of all currently licensed regimens even with a eGFR < 30 ml/min/1.73 m^2, though clinical experience is limited.

Antiviral therapy and progression of kidney failure

Following oral administration, sofosbuvir is well absorbed, with peak plasma concentration at ~0.5–2.0 h post-dose. It undergoes extensive hepatic metabolism and is biotransformed to the pharmacologically active nucleotide analog uridine-triphosphate (SOF-007TP), which once dephosphorylated results in the formation of the predominant sofosbuvir inactive metabolite GS-331007 (SOF-007). SOF-007 is mainly eliminated through the renal route. The 4-h hemodialysis extraction ratio is ~53%.[100] In ESRD, previous pharmacokinetics data showed marked plasma overexposure of sofosbuvir (area under the curve: $AUC_{0\text{-}IFN}$ 171% higher), and particularly SOF-007 ($AUC_{0\text{-}IFN}$ 451% higher) after one single dose of 400 mg, as compared with subjects with normal kidney function.[101]

Despite these pharmacokinetics studies, there are preliminary data with sofosbuvir-based regimen in CKD patients suggesting that sofosbuvir with a daily or three times weekly regimen is safe and well tolerated in HCV-infected patients, most with cirrhosis, who require hemodialysis.[101-108] In a recent prospective study, 2 dosing regimens, sofosbuvir full dose (400 mg daily, n = 7) and 3 times a week (n = 5) after hemodialysis with simeprevir, daclatasvir, ledipasvir or RBV, were compared in hemodialysis patients.[106] While both groups showed higher SOF-007 plasma concentrations than those previously reported in patients with normal kidney function, plasma concentrations of sofosbuvir or its inactive metabolite SOF-007 did

not accumulate with either regimen between hemodialysis sessions or throughout the treatment course. SOF-007 extraction ratio (52%) was consistent with historical data. In one patient receiving once-daily regimen, SOF-007 half-life was slightly higher (38h) than for patients with normal kidney function receiving a full dose. Hemodialysis did not remove other anti-HCV agents. Clinical and biological tolerance was good for all patients. Two relapses occurred with the 3 times a week regimen and none with the once daily.

Additional experience with reduced sofosbuvir doses, such as 200 mg daily or 400 mg three times weekly, suggest that while very well tolerated, these suboptimal doses may lead to inferior SVR rates. In one study, Gane *et al.* presented results for 10 patients with severe renal impairment (9 infected with HCV GT1 and 1 with HCV GT3) receiving sofosbuvir, 200 mg daily, combined with RBV, 200 mg daily.[101] This schedule resulted in 6 relapses in HCV GT1-infected patients. In two case reports, Perumpail *et al*. reported the successful treatment of 2 liver transplant patients on hemodialysis who received sofosbuvir, 200 mg and 400 mg daily respectively with simeprevir at standard dose.[104, 105] Bhamidimarri *et al*.[108] evaluated 2 different schedules in 15 patients with severe renal impairment (n = 3) or requiring hemodialysis (n = 12). Eleven patients received sofosbuvir, 200 mg daily, and 4 patients received sofosbuvir, 400 mg three times weekly, all with simeprevir at a standard dose. Two relapses occurred, one in each group. Finally, preliminary results from another case series in 11 patients requiring hemodialysis receiving sofosbuvir, 400 mg daily, and simeprevir reported no relapse.[103] Very recently a larger study (n = 50) also suggests that sofosbuvir-based antiviral therapy, with a reduced dose of sofosbuvir, is reasonably safe and effective for the treatment of HCV patients with ESRD, including hemodialysis patients.[109]

Thus, in HCV-infected patients requiring hemodialysis and receiving a DAA-containing regimen, full-dose off-label use of sofosbuvir daily is an alternative option, particularly in patients at high risk of treatment failure such as those with cirrhosis, previously pretreated or non-responders and those infected with GT3. Patients should be closely monitored, with clinical, biological, and cardiac survey.[110]

A related and unresolved issue is whether use of sofosbuvir in patients with advanced CKD may accelerate progression of renal impairment. Gonzalez-Parra and colleagues[111] observed a significant mean decrease in GFR of 9 mls/min in 35 patients treated with a sofosbuvir-based regimen with a baseline GFR between 30-60 mls whereas no decline in GFR occurred in 8 patients treated with the PROD regimen. Rosenblatt *et al*.[112] in a series of 81 patients noted a baseline GFR < 60/ml/minute predicted a decline in kidney function with sofosbuvir therapy. Saxena *et al.* also observed a decline in kidney function in 73 patients with a baseline GFR $\leq$ 45 ml/min/1.73 m^2 treated with sofosbuvir.[113] If a sofosbuvir-based regimen is selected, monitoring of kidney function should be performed with serial creatinine measurements during therapy although it is unclear whether dose reduction or withdrawal is

indicated if GFR declines. Reddy *et al*. identified 32 patients with CKD G3 included in trials with grazoprevir and elbasvir and found no evidence of deterioration of kidney function as a result of treatment with these agents.[114]

A regimen combining an NS5A replication complex inhibitor (elbasvir) and a new-generation NS3/4A protease inhibitor (grazoprevir) is licensed for patients infected with HCV GT1 and 4, with safety and efficacy data available in patients with severe renal impairment. Both agents are metabolized by CYP3A and primarily (> 90%) excreted in feces with minimal renal clearance (< 1%). Although pharmacokinetic analyses show that AUCs are higher in individuals with advanced CKD requiring hemodialysis or not (up to 46% higher compared to individuals with normal kidney function), these changes in exposure to the drugs are not considered clinically relevant.[115]

Grazoprevir is a substrate of OATP1B1/3 and co-administration with drugs that inhibit OATP1B1/3 may result in increased levels of grazoprevir that may lead to clinically significant hyperbilirubinemia. Elbasvir and grazoprevir are substrates of CYP3A and co-administration with strong CYP3A inducers is contraindicated as it may result in decreased plasma concentrations and potentially reduced antiviral activity of both agents.

All components of the combination regimen containing ombitasvir, paritaprevir, ritonavir, and dasabuvir (used in GT1 and without dasabuvir in GT4) are predominantly excreted in the feces with < 11% renal clearance, thus pharmacokinetics are not significantly altered in advanced CKD (eGFR < 30 ml/min/1.73 m^2) and no dose adjustment is recommended. In a single-arm, multicenter study of treatment-naïve adults with HCV GT1 infection, without cirrhosis and with CKD G4 (eGFR 15–30 ml/min/1.73 m^2) or G5 (eGFR, <15 ml/min/1.73 m^2 or requiring hemodialysis), 20 patients were treated with this regimen for 12 weeks. Patients with HCV GT1a infection also received RBV (n = 13), whereas those with GT1b infection did not (n = 7). Eighteen of the 20 patients achieved SVR12 (90%; 95% CI: 69.9–97.2), but one treatment failure was non virological (death after the end of the treatment unrelated to the treatment). The only patient who relapsed case was a GT1-infected patient with advanced fibrosis on hemodialysis. Adverse events were primarily mild or moderate, and no patient discontinued treatment due to an adverse event. RBV therapy was interrupted in 9 patients due to anemia; 4 received erythropoietin. No blood transfusions were required.[97]

Similar to other protease inhibitors (simeprevir and paritaprevir), grazoprevir is contraindicated in decompensated patients with Child-Turcotte-Pugh class B or C due to diminished hepatic metabolism and risk of adverse event, particularly hepatic toxicity.

In practice, no dose adjustment to kidney function is needed with NS5A inhibitors such as daclatasvir and protease inhibitor such as simeprevir.

Table 2 summarizes the putative choice of DAA according to the kidney function, co-medications (especially in kidney transplant recipients) and to the GT.

A report by Gane *et al*. at the 2016 AASLD Annual Meeting described the use of glecaprevir, a protease inhibitor, and pibrentasvir, an NS5A inhibitor, in patients with advanced CKD infected with a variety of HCV GTs and 82% of whom were already on dialysis. Overall SVR12 was 98% with good tolerance demonstrated. This pangenotypic regimen, once licensed, will expand treatment choices for non-1, non-4 GTs in patients with CKD.[116]

Treatment of HCV in kidney transplant recipients (see Chapter 4)

Although published data on DAAs in kidney recipients are scarce,[117] the results seem as satisfactory as those observed in liver transplant recipients. In a recent systematic review including eleven studies with a total of 360 kidney transplant recipients (88% infected with HCV GT1), the overall SVR rate achieved with sofosbuvir-based regimens was 94% (95% CI: 88-97%). In a recent international trial comparing 12 and 24 weeks of sofosbuvir and ledipasvir in 114 kidney transplant recipients infected with HCV GT1 and 4 (96% GT1) with a GFR above 40 ml/min/1.73 m^2 (median eGFR 56 ml/min/1.73 m^2, range 35-135 ml/min/1.73 m^2), therapy was very well tolerated and SVR rates were close to 100% without differences between arms suggesting that a 12-week regimen is also indicated in kidney transplant recipients.[118] Smaller cohort studies recently also reported excellent results in kidney transplant recipients with sofosbuvir-based regimens.[119-121]

In transplant recipients, DDI with immunosuppressive agents may result in increase or diminished plasma levels of immunosuppressive agents, with consequential risk of toxicity or graft rejection, respectively. For instance, concurrent use of elbasvir/grazoprevir and cyclosporine is not recommended as it results in a 15-fold increase in grazoprevir AUC and 2-fold increase in elbasvir AUC. Elbasvir/grazoprevir increases levels of tacrolimus by 43%, thus close monitoring of levels is indicated and dose reductions of tacrolimus may be needed. Other protease inhibitors such as simeprevir and paritaprevir have similar drug-drug interactions with cyclosporine and tacrolimus. There are no significant drug-drug interactions with these protease inhibitors and mycophenolate mofetil (MMF) and no data are available for other immunosuppressant agents such as sirolimus and everolimus. No significant interactions between NS5A and polymerase inhibitors such as sofosbuvir and CNIs have been described but close monitoring of immunosuppressive drugs is mandatory as changes in liver metabolism concurrent with HCV eradication may result in modifications of immunosuppression trough levels.

Table 2. Use of HCV DAAs when kidney function is impaired

GFR > 30 ml/min/1.73 m^2: All available therapeutic options
GFR < 30 ml/min/1.73 m^2: • GT1a: GZP/EBV 12 weeks • GT1b: GZP/EBV or PROD 12 weeks • GT4: GZP/EBV or '2D' regimen 12 weeks • GT2/3/5/6: Consider SOF-based regimen
Kidney transplant recipients: • GFR > 30 ml/min/1.73 m^2: o GT1/2/5/6: SOF + LDV 12 weeks o GT1 or 4: GZP/EBV 12 weeks PROD 12 weeks with adjustments of calcineurin inhibitors — No data o GT3: SOF + DCV 12 weeks • GFR <30 ml/min/1.73 m^2: o GT1a: GZP/EBV 12 weeks o GT1b: GZP/EBV or PROD 12 weeks with adjustments of calcineurin inhibitors — No data o GT4: GZP/EBV or '2D' regimen 12 weeks o GT2/3/5/6: Consider SOF-based regimen

2D, ritonavir-boosted paritaprevir, ombitasvir; DCV; daclatasvir; EBV, elbasvir; GFR, glomerular filtration rate; GT, genotype; GZP, grazoprevir; LDV, ledipasvir; NS5A, nonstructural protein 5A; PROD, ritonavir-boosted paritaprevir, ombitasvir and dasabuvir; SOF, sofosbuvir.

Multiple studies from the general population have found a strong correlation between mortality and SVR.[122] As a result regulatory agencies such as the US Food and Drug Administration (FDA) have accepted SVR response as a surrogate endpoint for trials used in their drug approval process.
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm225333.pdf

The US FDA recently replaced SVR at 24 weeks after cessation of therapy (SVR24) with SVR12. Although there are no data demonstrating that SVR12 reduces mortality in CKD, a meta-analysis showed that SVR24 predicted mortality not only in the general population, but also in patients with cirrhosis and patients with co-infection.

RESEARCH RECOMMENDATIONS

- In patients with CKD G4-5 infected with HCV GTs 2, 3, 5 and 6, there are no therapies that are currently licensed. Further investigation for non-sofosbuvir regimens are needed for these patients.

- Whether RBV is required after kidney transplantation in some specific groups such as prior non-responders infected with HCV GT1a is still an unresolved issue. Treatment of NS5A resistant variants after kidney transplantation has not been evaluated to date.

- Timing of antiviral therapy before or after transplantation in candidates for kidney transplantation should be clarified. Because the time to kidney transplantation is unpredictable, and the higher risk of vascular, metabolic and tumor disease as well as the risk of drug-drug interactions with CNIs, treatment should be obtained before transplantation. However, in regions where the prevalence of anti-HCV-positive donors is high, post-kidney transplant therapy should be considered.

- The impact of treating HCV infection on CKD progression should be investigated.

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. (*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*)

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 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*)

RATIONALE

The prevalence of HCV infection in hemodialysis patients is usually higher than in the general population.[123] According to a recent systematic review of studies in hemodialysis patients based on data up to 2006, the overall global incidence rate of HCV infection was 1.47/100 patient-years: 4.44/ 100 patient-years in low- to middle-income countries, and 0.99/ 100 patient-years in high-income countries.[124] The HCV prevalence rates vary in different parts of the world from < 5% in most Northern European countries,[12, 125] 8% in US, to over

70% in some parts of the world, including countries in Asia, Latin America and North Africa,[126, 127] and during times of social crisis, war, or economic downturn.[128-130]

HCV-infected hemodialysis patients are at increased risk of liver or cardiovascular disease-related death compared with non-infected patients,[123] and with increased morbidity and mortality after kidney transplantation.[131-133]

HCV is easily transmitted parenterally, primarily through percutaneous exposure to blood. Dramatic reductions were noted in the incidence following introduction of screening for HCV in blood donors and reduction in blood transfusion requirements following introduction of erythropoiesis-stimulating agent therapy,[134] leaving nosocomial transmission as the main method of spread of HCV in dialysis units. Several studies have confirmed the nosocomial transmission in dialysis units using epidemiologic and phylogenetic data obtained by viral sequencing.[17, 27, 135-138] These data are further supported by the observation of decline in infection rates following routine implementation of infection control practices and virological follow-up to detect anti-HCV antibodies using sensitive, specific new-generation serological tests (Evidence Profile 7 and Summary Table 8).[13, 139] A multicenter survey revealed that prevalence of anti-HCV positivity for a Belgian cohort of hemodialysis patients (n = 1710) dropped steadily from 13.5% in 1991 to 6.8% in 2000, and the same survey revealed significant drops in many other countries including France (42% to 30%), Italy (27% to 16%), and Sweden (16% to 9%).[140] Table 3 provides an overview of HCV prevalence in hemodialysis patients as summarized from some recent studies.

Still, according to data from the US CDC, more than 50% of all healthcare associated HCV-outbreaks from 2008 to 2015 reported to CDC occurred in hemodialysis settings.[141] As a result, the US CDC recently provided guidance on improving infection control practices to stop HCV transmission in dialysis units.[142]

Infection control

At least 3 systematic reviews have examined the reasons behind transmission of HCV in hemodialysis units.[27, 143] The nosocomial nature of spread of infection has been confirmed using epidemiology and/or molecular virology techniques.[18, 24, 26, 144, 145] Root-cause analysis of these outbreaks has revealed lapses in infection control to be associated with transmission of HCV infection between patients in dialysis units. For several reasons, including the long latency period of HCV infection, the number of dialysis treatments occurring during a patient's likely exposure period (based on multiple treatments per week), and sparse documentation of details in the dialysis treatment record, retrospective investigation to determine an exact cause of dialysis-related HCV acquisition is challenging. Rarely, the exact cause can be surmised using epidemiologic and molecular virology data. More often, transmission is documented among patients in the same clinic, who lack other common exposures and/or risk factors, and

lapses in infection control are identified in the clinic that could logically lead to transmission (Table 4). Other causes of infection such as undergoing dialysis during travel to developing countries, and non-dialysis healthcare exposures (e.g., procedures performed in a common vascular access surgical center) can occur and are considered before concluding that transmission occurred in the dialysis unit.

Table 3. Recent reported HCV prevalence in hemodialysis patients

Country	N pts	Year of testing	Anti-HCV prevalence (%)	Source
Australia-New Zealand	393	2012	3.8	DOPPS 5
Belgium	485	2012	4	DOPPS 5
Brazil	798	2011	8.4	Rodrigues de Freitas
Canada	457	2012	4	DOPPS 5
China	1189	2012	9.9	DOPPS 5
Cuba	274	2009	76	Santana
France	501	2012	6.9	DOPPS 4
Germany	584	2012	4.5	DOPPS 5
Gulf Cooperation Council	910	2012	19.3	DOPPS 5
India	216 1050 3068 7122 7673	2012 2013 2014 2015 2016	16 11 8 10 9	NephroPlus
Italy	485	2012	11.4	DOPPS 5
Japan	1609	2012	11	DOPPS 5
Lebanon	3769	2010-2012	4.7	Abou Rached
Libya	2382	2009-2010	31.1	Alashek
Nigeria	100	2014	15	Unmate
Romania	600	2010	27.3	Schiller
Russia	486	2012	13.7	DOPPS 5
Senegal	106	2011	5.6	Seck
Spain	613	2012	8.9	DOPPS 5
Sweden	426	2012	6	DOPPS 5
Turkey	383	2012	6.6	DOPPS 5
United Kingdom	397	2012	4.4	DOPPS 5
United States	2977	2012	7.4	DOPPS 5

Table 4. Lapses in infection control practices associated with transmission of HCV infection in dialysis units

• Preparation of injections in a contaminated environment (including at patient treatment station)
• Reuse of single dose medication vial for more than one patient
• Use of mobile cart to transport supplies or medications to patients
• Inadequate cleaning or disinfection of shared environmental surfaces between patients
• Failure to separate clean and contaminated areas
• Failure to change gloves and perform hand hygiene between tasks or patients
• Hurried change over processes
• Low staff to patient ratio

Mishandling of parenteral medications has been frequently implicated in transmission. Medication vials can become contaminated with HCV when accessed with used needles or syringes, or through environmental or touch contamination of the vial diaphragm by health care personnel hands. This latter mechanism is more likely to occur when medications are stored or prepared in contaminated areas and blood-contaminated items are handled in close proximity. Sharing of multidose heparin or other medication vials or spring triggered devices for glucose monitoring can lead to transmission. Inadequate cleaning and disinfection of shared environmental surfaces also increases risk of transmission. This may include failure to adequately clean and disinfect external surfaces of hemodialysis machines, treatment chairs, and other surfaces in the treatment station, and failure to clean blood spills.

It should be emphasized that blood contamination of environmental surfaces and equipment both at the patient treatment station and outside the immediate treatment area can be present, even in the absence of visible blood. HCV RNA has been detected on external surfaces of dialysis machines, a dialysate connector, on a shared waste cart and in handwashings of dialysis personnel.[146-152] Both visible and invisible blood has also been detected on dialysis treatment station surfaces that underwent routine cleaning procedures following an outbreak of HCV.[17] HCV can persist in an infectious state for at least 16 hours, and potentially much longer, on surfaces at room temperature.[151, 153] Hand hygiene also plays an important role in prevention of nosocomial transmission.[154] Lack of adherence to standard practices, such as handwashing and glove use and removal practices has been documented in several audits. In most HCV outbreaks in US hemodialysis centers reported to CDC, multiple lapses in infection control were identified, involving practices such as hand hygiene and glove use, injectable medication handling, and environmental surface disinfection.[141]

Petrosillo *et al*.[155] conducted a multicenter study in 58 Italian hemodialysis centers, and found that after correction for all factors, the risk of transmission was correlated with dialysis in units with a high prevalence of HCV-infected patients at baseline and those with a low personnel-patient ratio. They concluded that these factors were more likely to be associated with breaks in infection control practices. A study of 87 US hemodialysis centers similarly

found that baseline HCV prevalence of ≥ 10%, low staff-to-patient ratio, and ≥ 2-year duration of treatment in the facility were independently associated with frequency of HCV infections that were likely to be acquired in the facility.[156] The same study also found the following practices to be associated with dialysis-related HCV infections: lack of cleaning or disinfecting priming containers between uses; preparation of medications or storage of clean supplies in or adjacent to area where blood specimens were handled; and use of mobile medication carts to transport injectable medications in the patient treatment area.

Infection control lapses responsible for HCV transmission contribute to transmission of other pathogens; hence implementation of improvement efforts will have broader salutary effects. Most importantly, HCV transmission can be prevented effectively through adherence to currently recommended infection control practices. There are no reports of transmission of HCV in dialysis units that had all infection control practices in place. Publication bias is unlikely to explain this observation. Additionally, in the experience of the authors, centers that have had HCV transmission identified and that subsequently responded with increased attention to appropriate infection control practices have not had continued transmission. This observation applies to unpublished outbreaks and transmission events.

Implementation of infection control practices can be advanced by establishing a list of evidence-based interventions, such as those recommended by the CDC and regularly assessing and reinforcing adherence to practice through observational audits. Infection control practices that may be most critical to improve (based upon observation of breaches in outbreak situations that are likely to transmit HCV) are shown in Table 5. CDC has checklists and audit tools to assist facilities in implementing and assessing many of these practices.[157]

Table 5. Infection control practices particularly relevant in improving HCV transmission

• Proper hand hygiene and glove changes, especially between patient contacts, before invasive procedures, and after contact with blood and blood-contaminated surfaces/supplies
• Proper injectable medication preparation practices following aseptic technique and in an appropriate clean area, and 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

Isolation

Isolating HCV-infected patients (or patients awaiting HCV screening results) during hemodialysis is defined as physical segregation from others for the express purpose of limiting direct or indirect transmission of HCV. The traditional definition of contact isolation is that used for HBV infections in hemodialysis centers- i.e., dedicated room, machine, equipment, gowns, and personnel. However, "isolation" as considered for HCV control has involved multiple, varied approaches, and policies may include use of a dedicated dialysis machine, personnel, room, or shift, or other barrier precautions (such as aprons, gowns, or gloves), by healthcare professionals attending these patients. These strategies may be implemented alone or in combination.

The evidence for or against the use of isolation of HCV-infected patients during hemodialysis is weak. The KDIGO 2008 HCV Guideline[27] stated that hemodialysis units should ensure implementation of and adherence to strict infection-control procedures designed to prevent transmission of blood-borne pathogens, including HCV, but isolation of HCV-infected patients was not recommended as an alternative to strict infection-control procedures (unless in cases of continued hospital-acquired transmission, where a local isolation policy may be deemed necessary).

A recent Cochrane Review[158] examined the impact of isolation as a strategy for controlling transmission of HCV infection in hemodialysis units. Isolation was defined as the physical segregation of these patients from others with the express purpose of limiting direct or indirect transmission of HCV to other patients. Isolation policies could include a number of strategies with different grades of intensity, such as the use of a dedicated dialysis machine, personnel, room or dialysis shift. Of the 123 full-text articles, they could find only one randomized controlled trial (RCT).[159] This cluster RCT included a total of 12 hemodialysis centers (593 patients) assigned to either dedicated hemodialysis machines for HCV-infected patients or no dedicated machines. The randomization was as follows: the group with dedicated dialysis machines involved four centers: 297 patients, 267 negative and 30 positive for HCV, and the group with non-dedicated machines included 8 centers: 296 patients, 275 negative and 21 positive for HCV at baseline. Two follow-up periods were included in the study and each was 9 months long. Staff was educated on standard infection control practices.

Although the original article reported a significant reduction in the proportion of new infections in the second follow-up period among the facilities using dedicated vs. non-dedicated machines (calculated using chi-square test), the Cochrane review showed that the 95% CI for the RR for both follow up periods of the study included 1, suggesting this was not statistically significant. The Cochrane analysis concluded that the use of dialysis machines dedicated for HCV infected individuals, as compared with the use of non-dedicated machines

made no difference in terms of reducing the incidence of HCV infection during the follow-up period. The quality of evidence, however, was rated as "very low," as the authors did not disclose details of the method of randomization, and blinding of outcome assessors was not reported. The original study investigators also excluded a center from the analysis after randomization, and failed to account for clustering in the analysis. Importantly there was a high risk of bias due to incomplete outcome data (i.e., loss to follow-up), and the estimation of the effect of the intervention was deemed to be imprecise. As in many other observational studies of isolation, incidence density was not calculated to account for differences in patient exposure time. Although the Cochrane reviewers also determined that the lack of blinding of participants and patients to the intervention in the study was a source of bias, most studies of isolation will be unable to truly blind facility participants to the intervention.

Other studies examining isolation as a means of reducing HCV transmission are largely observational and have very poor quality evidence with methodological challenges.[160-162] The isolation policies studied include: implementing the isolation or cohorting of infected patients in a separate room; using exclusive machines; or dedicating machines, room and staff. These studies have reported some reduction of HCV transmission, seroconversions, or other measure of HCV infection in hemodialysis after the adoption of an isolation policy. Most of these studies have adopted a "before-and-after" design, and compared their results with their own historical controls. For example, one study implemented isolation of HCV-infected patients in a separate room (but together with HBV-infected patients) in a single hospital-based dialysis unit and found lowered rates of new HCV infection over time.[163] The intervention period (2003-2006) was compared to a distant historical control period (1993-1998). Although the authors claimed no changes occurred other than the intervention between the two time periods (and the exposure time of patients to the unit was significantly less in the latter time period), it is difficult to imagine that infection control practices had not evolved over a decade. One study[164] compared isolation versus universal precautions assessed through questionnaires. Over a 6-month follow-up period, the prevalence diminished from 10% to 0 in units with universal precautions and from 24% to 10% in those following isolation. In another study, HCV-infected patients (both hemodialysis and peritoneal dialysis) were isolated in separate rooms with dedicated machines and the authors examined outcomes during the 3 years preceding complete isolation and the subsequent 7 years.[165] The authors demonstrated substantial reductions in HCV prevalence over time; HCV seroconversions were rare in the pre-intervention period and absent in the post-intervention period. No significant difference in seroconversion rate was demonstrated and a steady reduction in HCV prevalence over ten years was likely the result of multiple factors, including population prevalence. One study had three sets of patients: one set without isolation, a second set with a dedicated area and a dedicated machine in the same room and a third set of patients isolated in a separate room, and showed that isolation in a different room was better than dedicated machines.[166] The "before-and-after" study design and lack of a control group in almost all of these studies, makes it

unclear to judge whether the reported improvement resulted from the adoption of an isolation policy or rather from the simultaneous raising of awareness and reinforcement of the application of hygienic precautions. Further, in some studies, there might be other contributing factors such as changes in baseline prevalence and injection safety and hygienic practices in dialysis and other healthcare settings over time.

In contrast to these studies, a DOPPS multicenter study and the Italian multicenter study both concluded that isolation does not protect against transmission of HCV in hemodialysis patients,[12, 155] and some prospective observational studies have shown reduction of transmission after adoption of universal precautions.[167] A prospective observational study showed a reduction in the annual incidence of HCV seroconversion from 1.4% to 0% after the reinforcement of basic hygienic precautions, without any isolation measures.[168]

The CDC does not recommend the isolation of HCV-infected patients in its infection-prevention guidelines.[19] The UK Renal Association states that patients with HCV do not need to be dialysed in a segregated area; however, more experienced staff should be assigned. They further recommend that if nosocomial transmission continues to occur despite reinforcement and audit of the precautions, a local segregation policy may be deemed necessary. The European Best Practice Work Group considers implementation of universal hygienic measures to be the standard of care. Some investigators support isolating patients with HCV infection in a specific hemodialysis room, or suggest that the no-isolation policy should not be generalized.

There are additional reasons that argue against recommending isolation of HCV-positive patients):[169]

1. Isolation purely for HCV will have no impact on transmission of other infections. Segregation of patients can create a false sense of reassurance around practices that could easily result in bloodstream infections, or transmission of multi-drug resistant organisms or other blood-borne pathogens.

2. Segregating patients on the basis of HBV and HCV would create 4 separate cohorts which creates a logistic nightmare. The treatment of HCV infection in dialysis patients raises an additional logistical challenge of how to cohort patients undergoing therapy.

3. Isolating only on HCV-infection status exposes the isolated patient to infection with a second HCV GT.

4. HCV infection has a relatively long incubation period, and patients in the window period of conversion will be incorrectly cohorted as uninfected patients.

5. Starting and maintaining isolation is likely to impose large costs on already expensive dialysis programs.

Finally, several experts and guidelines acknowledge that as transmission can be effectively prevented by adherence to currently recommended practices, considering isolation of positive patients indicates failure of adherence to the current standard, and would have a negative impact on the implementation and reinforcement of basic hygienic measures in the unit as a whole. In these situations, maintenance of chronic hemodialysis programs is highly challenging.

Dedicated dialysis machines

The theory of HCV transmission through internal pathways of the modern single pass dialysis machine has been discounted.[27]. Transmission would require the virion to cross intact dialyzer membrane, migrate from the drain tubing to fresh dialysate circuit, and pass again through the dialyzer membrane of a second patient – a theoretical and practical impossibility. The virus does not cross the intact membrane, and even in the event of a blood leak, transmission would require HCV to reach fresh dialysate used for a subsequent patient and enter the blood compartment for that patient through backfiltration across the dialyzer membrane, a highly unlikely scenario. Almost all the studies included in the various systematic reviews have conclusively excluded transmission via the internal dialysis pathway. In a few cases, a role for the dialysis circuit could not be excluded, but the environmental surfaces are more likely to have contributed to transmission.[17]

Receiving dialysis next to, rather than sharing the same dialysis machine with an HCV infected patient, has been found to be a risk factor for HCV acquisition.[170] In outbreak investigations with phylogenetic viral sequencing analysis, transmission is sometimes documented from an infected patient to a subsequent patient treated at the same station on the next shift, but also from an infected patient to patients treated in nearby stations during the same or subsequent shifts, which indicates transmission independent of the machine. Hurried and incomplete disinfection of external machine surfaces and other surfaces at the station (e.g., side table, dialysis chair, blood pressure cuff, prime waste container) are lapses commonly identified in these outbreaks. In some investigations, data collected essentially ruled out transmission involving the dialysis machine.[135] In several studies included in the systematic reviews of HCV transmission, nosocomial spread was documented despite the existence of a policy of dedicated machines. Taken together, this information confirms that contamination of dialysis machine components cannot be the sole contributor to transmission, and may have little to no role in HCV spread. While contaminated external surfaces of dialysis machines might facilitate HCV spread, other surfaces in the dialysis treatment station are likely to have the same impact.

A single study that claimed reduction[159] in incidence of HCV transmission with dedicated machines was found to have important deficiencies – such as lack of details about the randomization procedure, policy of participating units before randomization, whether patients who had seroconverted actually shared machines with infected patients, lack of adherence to standard machine disinfection procedures as well as deviations from infection prevention guidelines. The seroconversion rates were very high even in the dedicated machine group. The summary of evidence suggests the transmission was likely due to poor infection control.

Reuse

The risk of transmission during reuse procedure is more to the staff rather than to other patients. Patient-to-patient transmission can take place if the dialyzers or blood port caps are switched between patients and not sterilized effectively, if there is spillage of contaminated blood, or mixing of reused dialyzers during transport. These situations can be eliminated by adherence to standard hygienic precautions and appropriate labelling. Two large studies have not identified reuse as a risk factor for HCV transmission,[168, 171] whereas a weak association was shown in one study – likely due to unmeasured confounders.[172]

Management of a dialyzer membrane defect leading to blood leak

As HCV is transmitted by percutaneous exposure to blood from an infected person, effective implementation of the dialysis precautions recommended in the 2008 KDIGO HCV guideline[27] and by the CDC should prevent nosocomial transmission. The risk that the virus leaving the dialyzer could be trapped in the Hansen connector and transferred to the fresh dialysate side through accidental misconnection is vanishingly low, hence the CDC does not recommend disinfection of 'single-pass' machines between treatments on the same day, even when a blood leak has occurred.[19] The 2008 KDIGO HCV guideline, however, recommends disinfection of both the internal fluid pathways and the Hansen connectors before the next patient if a leak has occurred as a matter of abundant caution, and justified it based on the rarity of such events.[27] (Table 6)

Table 6. Hygienic precautions for hemodialysis (dialysis machines)

Definitions The 'transducer protector' is a filter (normally a hydrophobic 0.2-μm filter) that is fitted between the pressure monitoring line of the extracorporeal circuit and the pressure-monitoring port of the dialysis machine. The filter allows air to pass freely to the pressure transducer that gives the reading displayed by the machine, but it resists the passage of fluid. This protects the patient from microbiologic contamination (as the pressure monitoring system is not disinfected) and the machine from ingress of blood or dialysate. An external transducer protector is normally fitted to each pressure-monitoring line in the blood circuit. A back-up filter is located inside the machine. Changing the internal filter is a technical job.

A 'single-pass machine' is a machine that pumps the dialysate through the dialyzer and then to waste. In general, such machines do not allow fluid to flow between the drain pathway and the fresh pathway except during disinfection. "Recirculating" machines produce batches of fluid that can be passed through the dialyzer several times.

Transducer protectors

External transducer protectors should be fitted to the pressure lines of the extracorporeal circuit.

Before commencing dialysis, staff should ensure that the connection between the transducer protectors and the pressure-monitoring ports is tight, as leaks can lead to wetting of the filter.

Transducer protectors should be replaced if the filter become wet, as the pressure reading may be affected. Using a syringe to clear the flooded line may damage the filter and increase the possibility of blood passing into the dialysis machine.

If wetting of the filter occurs after the patient has been connected, the line should be inspected carefully to see if any blood has passed through the filter. If any fluid is visible on the machine side, the machine should be taken out of service at the end of the session so that the internal filter can be changed and the housing disinfected.

Some blood tubing sets transmit pressure to the dialysis machine without a blood-air interface, thus eliminating the need for transducer protectors.

External cleaning

After each session, the exterior of the dialysis machine and all surfaces in the dialysis treatment station should be cleaned with a low-level disinfectant if not visibly contaminated. Pay particular attention to high-touch surfaces that are likely to come into contact with the patient (e.g., arm rests, blood pressure cuff) or staff members hands (e.g., machine control panel).

Disinfection of external machine surfaces should not commence until the patient has left the dialysis treatment station. A complete (unit–wide) patient-free interval between shifts might facilitate more thorough cleaning and disinfection of the unit.

If a blood spillage has occurred, the exterior should be disinfected with a commercially available tuberculocidal germicide or a solution containing at least 500 p.p.m. hypochlorite (a 1:100 dilution of 5% household bleach) if this is not detrimental to the surface of dialysis machines. Advice on suitable disinfectants, and the concentration and contact time required, should be provided by the manufacturer.

If blood or fluid is thought to have seeped into inaccessible parts of the dialysis machine (for example, between modules, behind blood pump), the machine should be taken out of service until it can be dismantled and disinfected.

Disinfection of the internal fluid pathways

It is not necessary for the internal pathways of a single-pass dialysis machines to be disinfected between patients, even in the event of a blood leak. Some facilities may still opt to disinfect the dialysate-to-dialyzer (Hansen) connectors before the next patient.

Machines with recirculating dialysate should always be put through an appropriate disinfection procedure between patients.

Audits

Audits and use of surveillance data to implement prevention steps are critical to any infection control program. Routine observational audits of various infection control practices, combined with feedback of results to clinical staff, allows for regular assessment of actual practices and identification of gaps. Data from audits can facilitate immediate interventions to correct practice and should also inform broader quality improvement efforts, including unit-wide staff education and retraining. In the US, most dialysis centers use infection control audit tools (including tools developed by CDC or the dialysis company) as part of their continuous quality improvement process.

Although there are no RCTs of the impact of audits on transmission of HCV infection in dialysis units, observational studies as part of quality improvement programs have shown reduction in the rates of bloodstream infections following implementation of regular audits and evidence-based intervention package. In a study from the US, 17 centers reported monthly event and denominator data to the National Healthcare Safety Network (NHSN) and received guidance from the CDC. The feedback included advice on chlorhexidine use for catheter exit-site care, staff training and competency assessments focused on catheter care and aseptic technique, hand hygiene and vascular access care audits, and feedback of infection and adherence rates to staff. The pooled mean bloodstream infection (BSI) and access-related BSI rates decreased from 1.09 and 0.73 events per 100 patient-months to 0.89 and 0.42 events per 100 patient-months, respectively. Modeled rates decreased 32% ($P < 0.01$) for BSIs and 54% ($P < 0.001$) for access-related BSIs.[173] In a follow-up study, the reduction in access-related BSI rates was sustained for 4 years after the initial intervention implementation.[174] The over-representation of hospital-based centers and lack of a control group limit generalization of these data. However, the ongoing simplification of audit tools for ease of reporting with the use of information technology – as used in this current study – precludes the need of infection control professionals on site, and leaves little justification to not recommend implementation of audits. Moreover, the scope of such audits goes beyond measuring one particular outcome, such as HCV transmission, and permit wider implementation of infection control measures.

Audits done in other dialysis center studies routinely show suboptimal adherence to hygienic practices. A Spanish study showed gloves were used on 93% of occasions, hands were washed only 36% of the time after patient contact and only 14% of the time before patient contact.[175] In a 2002 survey in US, only 53% of US outpatient ESRD facilities reported preparing injected medications in a dedicated room or area separated from the treatment area; 25% prepared these medications at a medication cart or other location in the treatment area, and 4% prepared medications at the dialysis station.[171] A survey of 420 dialysis personnel from 45 facilities reported on hand hygiene practices and knowledge regarding HCV infection risk.[176] At these facilities, percentages of dialysis staff reported to always wash their hands and

change gloves during the following activities were: 47% when going from one patient treatment station to another, 55% between administering intravenous medications to different patients, and 57% immediately before starting patients on dialysis. Other studies have shown similar findings.

Observational audits of hygienic precautions that were carried out in outbreak investigations have identified a range of problems, including lack of basic hand hygiene, failure to change gloves when touching the machine interface to obtain biologic parameters, or when urgently required to deal with bleeding from a fistula; carrying contaminated blood circuits through the ward unbagged; lack of routine decontamination of the exterior of machines and other surfaces even when blood spillages had occurred; and failure to change the internal transducer protector when potentially contaminated. On the other hand, where hygienic practice was reviewed through interviewing staff after an outbreak rather than by observation, no obvious breaches in procedure could be identified.

The frequency at which routine audits of infection-control procedures should be carried out will depend on audit type, staff turnover and training, and on the results of previous audits. When setting up a new program, audits should be at intervals of no greater than 6 months to enable staff to gain experience with the process and ensure that any remedial actions taken have been effective. CDC recommends audits be performed as often as monthly to establish and constantly reinforce recommended practices. Observational audits should be conducted on various days of the week and different shifts to capture all staff, and should include particularly busy times of day such as shift change. These factors and the number of opportunities (e.g., for hand hygiene) and procedures (e.g., injectable medication administration) observed will determine the representativeness of the results.

The CDC website (http://www.cdc.gov/dialysis/prevention-tools/audit-tools.html) has a number of audit tools and checklists intended to promote CDC-recommended practices for infection prevention in hemodialysis facilities. The audit tools and checklists can be used by individuals when assessing staff practices. They can also be used by facility staff themselves to help guide their practices. In some centers, audit tools have been shared with patients, who are asked to assess staff practice as a means of engaging patients in the infection control efforts of the facility and improving the culture of safety in units.[177] Patients should be educated on correct practices and should feel empowered to speak up when they observe a breach in hand hygiene or other staff practice.

Hand hygiene monitoring is known to be subject to the Hawthorne effect and it is difficult for an individual to observe practices within a dialysis unit without staff awareness that they are being observed. In one study, video monitoring of hand hygiene (performed via review of video surveillance footage) was shown to be a more accurate method than direct

observation.[178] Video surveillance for hand hygiene adherence should be considered, and other innovative approaches to monitoring staff adherence to recommended infection control practices should be explored.

Screening

Screening for HCV infection is essential to identifying transmission in hemodialysis units. CDC recommends that all maintenance hemodialysis patients be screened for anti-HCV and ALT level upon admission and that anti-HCV testing be repeated semi-annually and ALT testing be repeated monthly for susceptible patients. Although serum ALT levels frequently are normal in the setting of chronic HCV infection, most hemodialysis patients with new HCV infection have increased transaminase levels.[19, 179]. A majority of the known outbreaks would not have been identified in the absence of anti-HCV screening. Detection of seroconversions should prompt an aggressive evaluation of infection control practices to correct lapses and prevent additional cases from occurring.[23] (Table 7) This should occur in parallel with investigation of the affected patient's risk factors to determine whether the infection was likely acquired in the hemodialysis unit. In most instances, a symptomatic new HCV infection or HCV antibody seroconversion in a chronic hemodialysis patient represents dialysis-related transmission, and thus, a dialysis source should be assumed until proven otherwise. Because most HCV infections are asymptomatic and there is no laboratory test to distinguish acute HCV infection, routine screening tests obtained on admission and serially over time are the only way to identify transmission and determine its extent within a facility. However, HCV screening should not be used as a substitute for regular infection control audits.

Table 7. Steps to initiate concurrently and undertake following identification of a new HCV infection in hemodialysis patient (Adapted from CDC Health Alert[23])

A.	Report the infection to appropriate public health authority. o Assess risk factors of the affected patient in conjunction with public health.
B.	Determine HCV infection status of all patients in the hemodialysis unit. o Test all patients treated in the center for HCV infection (Chapter 1) unless they are already known to have active infection. Follow-up and testing of patients who were treated in the center and subsequently transferred or discharged may be warranted.
C.	Conduct a thorough root cause analysis of the infection and address infection control lapses. o Perform rigorous assessments of staff infection control practices to identify lapses. This should minimally include assessments of hand hygiene and glove change practices; injectable medication preparation, handling, and administration; and environmental cleaning and disinfection practices. o Share findings with all staff members and take action to address lapses. Staff education and retraining may be necessary. o Consider hiring a consultant with infection prevention expertise to provide recommendations for improvement of practices and work flow and/or to help implement actions to address identified lapses. o Conduct regular audits to ensure improved adherence to recommended practice.

- Demonstrations of cleaning adequacy such as use of GloGerm or Luminol might be helpful for staff education.

D. Communicate openly with patients.
   - Inform all patients of the reason for additional HCV testing and the results of their HCV tests.
   - If transmission within the center is suspected or confirmed, inform all patients of this. Patients should also be made aware of steps being taken to assess and improve practices.

HCV, hepatitis C.

Regulatory requirement

Audit data show that despite existence of guidelines to prevent transmission of infections in hemodialysis units, their implementation remains suboptimal, leading to large preventable burden of infections that not only adversely impacts clinical outcomes, but imposes large costs on the healthcare system. Experience from public health interventions show that interventions that depend on behavior change require large effort that can undermine their impact. In contrast, making system-wide changes, such as imposition of regulations and creating an environment that discourages unhealthy behavior is likely to have greater impact. This has been shown in many fields such as smoking cessation, and containing HIV infection.[180] Examples in dialysis field include endorsement of Dialysis Event BSI measure by the US National Quality Forum, and implementation of the Medicare Quality Initiative. Recommendation of uniform validated measures such as those used by NHSN are critical for comparisons and to facilitate interventions. Other system-wide changes that are likely to have beneficial impact on infection prevention and control practices include increasing staff-to-patient ratios and instituting staff training and education requirements. Physical infrastructure changes to facilities might also be beneficial-- for example, establishing minimum space requirements between treatment stations, creating walls around individual treatment stations to establish separate rooms instead of large open spaces and using walls to separate clean and dirty processes (e.g., separate room for medication preparation). Such possibilities should be explored, along with strategies to improve work flow and reduce unnecessary staff maneuvers that add to the already substantial number of occasions during dialysis care when glove change and hand hygiene is warranted. As such, regulatory and accrediting agencies should issue and/or incorporate recommendations to favor compliance with basic infection control practices in dialysis units, and efforts to make the desired infection control behavior the simplest or most logical approach to care processes should be pursued (Table 8). Table 9 provides a summary of important hygienic precautions for hemodialysis center staff to follow.

Table 8. Strategies to support adherence to infection control recommendations in hemodialysis centers

- It is important for the designers of dialysis units to create an environment that makes infection-control procedures easy to implement. Adequate hand-washing facilities must be provided, and the machines and shared space should make it easy for staff to visualize individual treatment stations. Certain jurisdictions specify the area around a hemodialysis machine.
- The unit should ensure that there is sufficient time between shifts for effective decontamination of the exterior of the machine and other shared surfaces.
- The unit should locate supplies of gloves at enough strategic points to ensure that staff has no difficulty obtaining gloves in an emergency.
- When selecting new equipment, ease of disinfection should be considered.
- There are indications from the literature that the rate of failure to implement hygienic precautions increases with understaffing. Understaffing has been associated with hepatitis C outbreaks. Certain jurisdictions specify a specific nurse patient ratio (for example: 1:4 in France). Formal healthcare training of all staff should be required (e.g., in the US, technicians provide most direct hemodialysis care but lack standardized training). Dialysis units that are changing staff-to-patient ratios, or introducing a cohort of new staff, should review the implications on infection-control procedures and educational requirements.
- Resource problems should be handled by carrying out a risk assessment and developing local procedures. For example, if blood is suspected to have penetrated the pressure monitoring system of a machine but the unit has no on-site technical support and no spare machines, an extra transducer protector can be inserted between the blood line and the contaminated system so that the dialysis can continue until a technician can attend to the problem.

Below are useful CDC informational resources to improve hand hygiene, environmental cleaning and disinfection and injection safety.

http://www.cdc.gov/dialysis/PDFs/collaborative/Env_notes_Feb13.pdf
http://www.cdc.gov/dialysis/PDFs/collaborative/Env_checklist-508.pdf
http://www.cdc.gov/dialysis/PDFs/dialysis-Station-Disinfect-Tool-7-2015.pdf
http://www.cdc.gov/dialysis/PDFs/collaborative/Hemodialysis-Hand-Hygiene-Observations.pdf
http://www.cdc.gov/dialysis/PDFs/collaborative/Hemodialysis-InjectionSafety-Checklist.pdf
http://www.cdc.gov/dialysis/PDFs/collaborative/Hemodialysis-InjectionSafety-Observations.pdf

CDC, Centers for Disease Control and Prevention; US, United States.

Table 9. Key hygienic precautions for hemodialysis*

Definitions

A "dialysis station" is the space and equipment within a dialysis unit that is dedicated to an individual patient. This may take the form of a well-defined cubicle or room, but there is usually no material boundary separating dialysis stations from each other or from the shared areas of the dialysis unit.

A "potentially contaminated" surface is any item of equipment at the dialysis station that *could* have been contaminated with blood, or fluid containing blood, since it was last disinfected, even if there is no visual evidence of contamination.

Education

A program of continuing education covering the mechanisms and prevention of crossinfection should be established for staff caring for hemodialysis patients.

Staff should demonstrate infection control competency for the tasks they are assigned. Infection control competencies (e.g., use of aseptic technique) should be assessed upon hire and at least yearly thereafter.

Appropriate information on infection control should also be given to nonclinical staff, patients, caregivers, and visitors. Patients should be encouraged to speak up when they observe an infection control practice that is concerning to them.

Hand hygiene

Staff should wash their hands with soap or an antiseptic hand-wash and water, before and after contact with a patient or any equipment at the dialysis station. An alcohol-based hand rub may be used instead when their hands are not visibly contaminated.

In addition to hand washing, staff should wear disposable gloves when caring for a patient or touching any potentially contaminated surfaces at the dialysis station. Gloves should always be removed when leaving the dialysis station.

Patients should also clean their hands with soap and water, or use an alcohol-based hand rub/sanitizer, when arriving at and leaving the dialysis station.

Injection Safety

Medication preparation should be done in a designated clean area.

All vials should be entered with a new needle and a new syringe, which should be discarded at point of use.

Medications should be administered aseptically, after wearing a disposable glove and disinfecting the injection port with an antiseptic.

Hand hygiene must be performed before and after administration of injection

All single dose vials must be discarded and multidose vials, if used, should not be stored or handled in the immediate patient care area.

Equipment management (for management of the dialysis machine, see Table 6)

Single-use items required in the dialysis process should be disposed of after use on one patient.

Nondisposable items should be disinfected after use on one patient. Items that can't be disinfected easily (for example, adhesive tape, tourniquets) should be dedicated to a single patient and discarded after use.

The risks associated with use of physiologic monitoring equipment (for example, blood pressure monitors, weight scales, access flow monitors) for groups of patients should be assessed and minimized. Blood pressure cuffs should be dedicated to a single patient or made from a light-colored, wipe-clean fabric.

Medications and other supplies should not be moved between patients (e.g., on carts or by other means). Medications provided in multiple-use vials, and those requiring dilution using a multiple-use diluent vial, should be prepared in a dedicated central area and taken separately to each patient. Items that have been taken to the dialysis station should not be returned to the preparation area.

After each session, all potentially contaminated surfaces at the dialysis station should be wiped clean with a low-level disinfectant if not visibly contaminated. Surfaces that are visibly contaminated with blood or fluid should be disinfected with a commercially available tuberculocidal germicide or a solution containing at least 500 p.p.m. hypochlorite (a 1:100 dilution of 5% household bleach).

Waste and specimen management

Needles should be disposed of in closed, unbreakable containers which should not be overfilled. A "no-touch" technique should be used to drop the needle into the container as it is likely to have a contaminated surface. If this is difficult due to the design of the container, staff should complete patient care before disposing of needles.

All blood and other biologic specimen handling should occur away from dedicated clean areas, medications, and clean supplies.

The used extracorporeal circuit should be sealed as effectively as possible before transporting it from the dialysis station in a fluid-tight waste bag or leak-proof container for disposal. Avoid draining or manipulating the used circuit. If it is necessary to drain the circuit to comply with local regulatory requirements, or to remove any components for reprocessing, this should be done in a dedicated area away from the treatment and preparation areas.

*****In addition to standard precautions.

Treatment of HCV infection as a means for prevention of transmission

With the availability of DAAs, there is a possibility that dialysis units might take recourse to starting HCV infected patients on these agents with the hope that this will cure the infection and prevent transmission to uninfected patients. Several studies have shown that facility prevalence of HCV infection is associated with incidence of infection. Thus, it stands to reason that successful treatment of patients could reduce the likelihood of HCV spread in dialysis centers. However, it should be noted that transmission can occur even in centers with very low HCV prevalence. In many outbreak investigations, what is considered the baseline prevalence includes cases of incident HCV infection that occurred in the center under investigation, but prior to the investigation period. A published summary of several US outbreaks of HCV infection included an outbreak in a dialysis center with only one prevalent HCV case.[137] A study that modeled HCV transmission in hemodialysis centers found that HCV prevalence influenced incidence (as did staff:patient ratio), but the compliance rate with hand hygiene and glove change between patients was a much stronger determinant of transmission.[154] Thus, even in the setting of low HCV prevalence, rigorous adherence to infection control practices is necessary. HCV prevention programs that focus solely on treatment of patients likely do so at the cost of routine infection-control practices and go against the principle of treating patients primarily for their individual benefit, keeping in mind the small, but definite risk of harm.

Implementation issues

Despite such strong data, adherence to recommended practices remains suboptimal – often due to misconceptions of the dialysis staff. A survey of 420 dialysis personnel from 45 hemodialysis facilities showed that only 35% of dialysis personnel strongly believed that patients were at risk of acquiring HCV infection in the hemodialysis facility. In contrast, 46% strongly perceived themselves to be at risk of acquiring HCV infection through occupational exposure.[176] Personnel also were much more likely to report knowing how to protect themselves from acquiring a bloodborne pathogen infection than knowing how to protect their patients. On the basis of their observational results, which included high compliance with glove use (93%) in contrast to poor hand hygiene compliance (36%), Arenas *et al*.[175] similarly concluded that dialysis personnel had greater concern for patient-to-staff transmission and lacked awareness of their role in facilitating pathogen transmission to patients. These data support the need for improved training and education to address knowledge gaps, as well as other initiatives focused on optimizing adherence to recommended infection control practices (Table 8). As mentioned above, implementation is more likely when guidelines are accompanied by change in regulations.

RESEARCH RECOMMENDATIONS

In the era of widespread treatment of HCV infection, and possible eradication of HCV infection from certain dialysis patient populations, the question of isolation may become less relevant. Assuming that HCV therapies are not universally available, affordable, or prioritized for hemodialysis patient populations, we offer the following recommendations for higher quality studies on isolation. Large, multicenter long-term RCTs of good quality are required to answer the questions concerning the benefits and harms of isolation of HCV-infected patients during hemodialysis. These studies should evaluate mortality, costs, patient perceptions, and complications associated with isolation. These studies should ensure the physical separation of either the center or room, or separation by treatment shift; these programs should have strict isolation strategies in place that include staff. Studies should randomize centers to either the standard of care (i.e., efforts to adhere to recommended infection control practices) or the standard of care plus isolation; they should describe the infection control efforts and compliance rates in both sets of centers, and should ensure data assessors are blinded to the interventions.

Observational studies
Would help to determine features of facilities that do not have incident cases: For example, staffing, physical layout, policies and practices, baseline prevalence

Interventional trials

- Need innovative, effective strategies to improve infection control
- Still important to pursue for the following reasons:
    - Barriers to identification and treatment of all infected patients (e.g., costs and reimbursement for screening and treatment regimens) in hemodialysis centers
    - Other endemic and emerging infections necessitate improved infection control practices, even if HCV is eradicated from hemodialysis patient populations

Cost effectiveness studies comparing different interventions (increased/improved staffing vs. treating HCV infections)

Effects of HCV isolation or cohorting on rates of other infection

Measurement

- Need innovative approaches to accurately measuring infection control processes
- Standard measures of dialysis-associated HCV infection (that doesn't require viral sequencing and phylogenetic analysis)

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

HCV infection remains more prevalent in CKD G5 patients compared to the general population. Although HCV infection can cause HCV-associated glomerular disease resulting in ESRD,[123, 181] kidney transplant candidates may have acquired HCV infection within a dialysis unit[182] or may have been infected when they had received a previous transplant or were transfused in the era before systematic screening for HCV.[181, 183, 184] Because of the deleterious effects of HCV infection in dialysis and kidney-transplant patients, evaluation of disease severity and need for antival therapy is crucial.[185-191] Screening for HCV in kidney-transplant candidates has been discussed in a previous section (Chapter 1).

Evaluation and management of kidney transplant candidates regarding HCV infection

4.1: We recommend kidney transplantation as the best therapeutic option for patients with end-stage renal disease (ESRD) irrespective of presence of HCV infection. (*1A*)

4.2: We suggest that all HCV-infected kidney-transplant candidates be evaluated for severity of liver disease and, if indicated, portal hypertension prior to acceptance for an isolated kidney or combined kidney-liver transplantation. (*2D*)

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

4.2.2: We recommend to refer HCV-infected patients with decompensated cirrhosis for combined liver-kidney transplantation (*1B*) and to defer HCV treatment until after transplantation. (*1D*)

4.3: Timing of HCV treatment in relation to kidney transplantation (before vs. after) should be based on donor type (living vs. deceased donor), waitlist times by donor type, center-specific policies for using or not kidneys from HCV-infected deceased donors, HCV genotype, and severity of liver fibrosis. (*Not Graded*)

4.3.1: For all HCV-infected patients who are candidates for kidney transplantation, we recommend they be considered for antiviral therapy, either before or after transplantation. (*1A*)

4.3.2: For HCV-infected kidney-transplant candidates with a living kidney donor, we suggest they can be considered for treatment before or after transplantation according to HCV genotype and anticipated timing of transplantation. (*2D*)

4.3.3: We suggest that, if receiving a kidney from a HCV-positive donor improves the chances for transplantation, the HCV RNA-positive patient can undergo transplantation with a HCV-positive kidney and be treated for HCV infection after transplantation. (*2D*)

RATIONALE

4.1: We recommend kidney transplantation as the best therapeutic option for patients with end-stage renal disease (ESRD) irrespective of presence of HCV infection. (1A)

Several studies have shown that kidney transplantation is the best therapeutic option for patients with ESRD (Evidence Profile 8 and Summary Table 9). Survival is significantly greater in CKD G5 patients who have undergone kidney transplantation compared to those who have remained on the waiting list irrespective of recipient age and/or comorbidities.[192, 193] In HCV infected patients, it has also been clearly shown that survival is significantly lower in HCV-positive RNA-positive dialysis patients compared to HCV-positive RNA-positive kidney-transplant recipients.[185, 194, 195] In addition, the all-oral anti-HCV regimens in dialysis and kidney-transplant patients (Chapter 2) allow successful HCV clearance in nearly all patients before or after transplantation. Patients who achieve a SVR before transplantation do not relapse after transplantation, despite the use of potent immunosuppressive drugs.[196, 197]

Although the survival of patients with persistent HCV replication after kidney transplantation is inferior compared to HCV-negative kidney-transplant patients,[187, 188, 191] it remains, however, higher than if they had remained on dialysis.[185, 194, 195] Graft survival is also significantly decreased in HCV-positive kidney-transplant patients compared to HCV-negative patients (Evidence Profile 9 and Summary Table 10).[187-189, 191, 198, 199] Although liver fibrosis progression in HCV-infected kidney-transplant patients is variable, development of cirrhosis and hepatocellular carcinoma (HCC) have been reported.[200-203] As HCC typically develops only in HCV infected patients with Stage 3 or 4 fibrosis, surveillance for HCC should be offered if extensive fibrosis is present.

4.2: We suggest that all HCV-infected kidney-transplant candidates be evaluated for severity of liver disease and, if indicated, portal hypertension prior to acceptance for an isolated kidney or combined kidney-liver transplantation. (2D)

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

4.2.2: We recommend to refer HCV-infected patients with decompensated cirrhosis for combined liver-kidney transplantation (1B) and to defer HCV treatment until after transplantation. (1D)

HCV-positive patients who are candidates for kidney transplantation should be evaluated for the presence of cirrhosis using either a non-invasive fibrosis-staging method or on occasion, a liver biopsy. The choice of method is discussed in Chapter 1. In addition, measurement of hepatic-vein wedge-pressure gradient is useful when deciding whether single kidney transplantation or simultaneous liver-kidney transplantation should be proposed.

In patients with compensated cirrhosis without portal hypertension, isolated kidney transplantation is recommended. In patients with compensated cirrhosis, HCV clearance may induce regression of liver fibrosis.[204] The Consensus Conference Group on simultaneous liver-kidney transplantation proposed that combined liver-kidney transplantation should be performed if patients have decompensated cirrhosis and/or severe portal hypertension.[205] Severe portal hypertension has been defined as a hepatic-vein wedge-pressure gradient of $\geq$ 10 mm Hg. The Portal Hypertension Collaborative Group stated that hepatic venous-pressure gradient predicts clinical decompensation in patients with compensated cirrhosis.[206] In patients with decompensated cirrhosis who despite having achieved SVR, remain symptomatic of ascites persists despite intensive dialysis, combined liver-kidney transplantation should be advised.

4.3: Timing of HCV treatment in relation to kidney transplantation (before vs. after) should be based on donor type (living vs. deceased donor), waitlist times by donor type, center-specific policies for using or not kidneys from HCV-infected deceased donors, HCV genotype, and severity of liver fibrosis. (Not Graded)

4.3.1: For all HCV-infected patients who are candidates for kidney transplantation, we recommend they be considered for antiviral therapy, either before or after transplantation. (1A)

4.3.2: For HCV-infected kidney-transplant candidates with a living kidney donor, we suggest they can be considered for treatment before or after transplantation according to HCV genotype and anticipated timing of transplantation. (2D)

4.3.3: We suggest that, if receiving a kidney from a HCV-positive donor improves the chances for transplantation, the HCV RNA-positive patient can undergo transplantation with a HCV-positive kidney and be treated for HCV infection after transplantation. (2D)

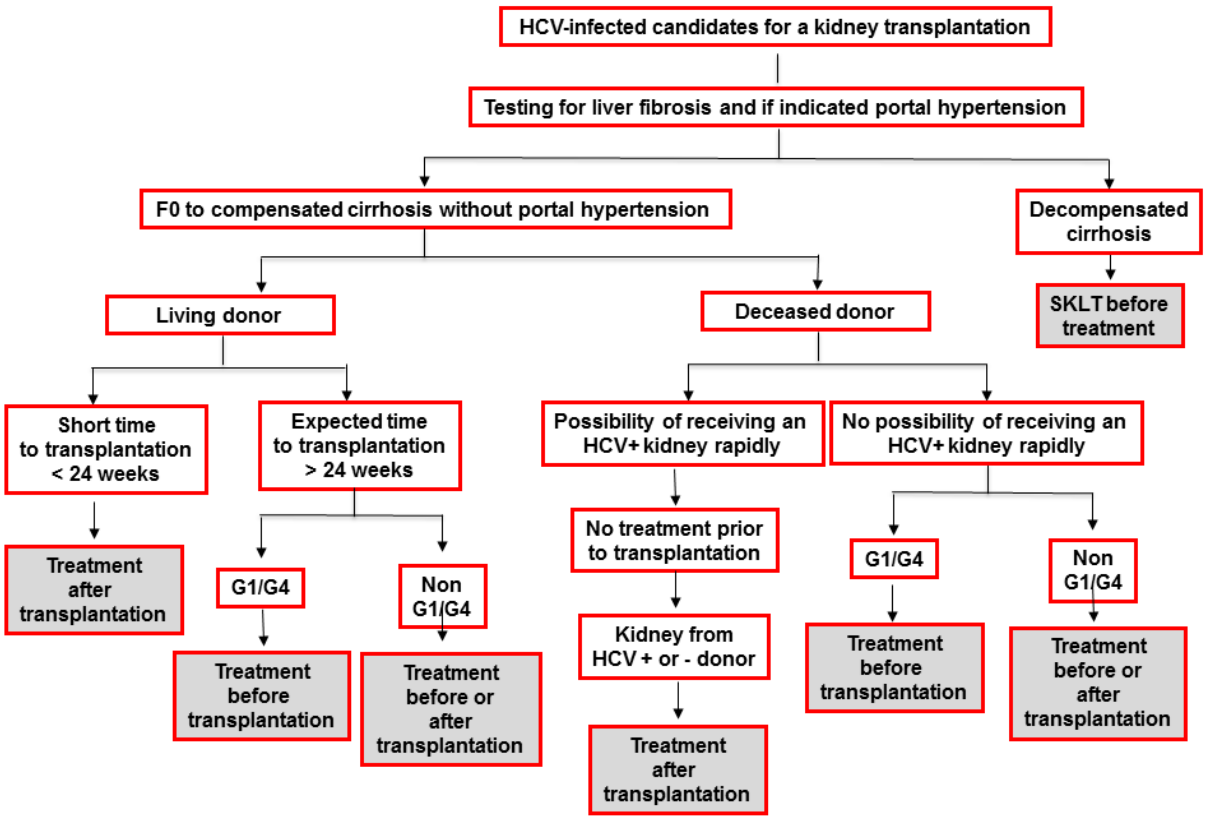
Until recently, only IFN-based therapy was available to treat HCV infection. The use of IFN was contraindicated after kidney transplantation (except in cases of fibrosing cholestatic hepatitis) because of its immunostimulatory properties, which increase the risk of graft rejection.[207] Hence, it was recommended that candidates for kidney transplantation be treated with IFN before transplantation.[27] The use of DAAs has completely changed this situation as HCV clearance is feasible in vast majority of patients before and after kidney transplantation (Chapter 2). The current issue is timing of HCV therapy in relationship to transplant. Considerations for planning therapy include living vs. deceased donor, waitlist time by donor type, center-specific policy for acceptance of organs from HCV-positive deceased donors and specific HCV GT (see Algorithm 1).

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 more than 24 weeks (12 weeks therapy and 12 weeks follow-up), then HCV therapy can be offered before or after transplant based on specific HCV GT and proposed treatment regimen.

In a potential recipient with compensated cirrhosis without portal hypertension listed for kidney transplantation from a deceased donor at a center where it is possible to obtain a kidney allograft from an HCV-positive donor without a long wait, the potential recipient can defer antiviral therapy to allow receipt of an organ from an HCV-positive donor. However, the patient needs to provide written informed consent for this approach. In contrast, when kidney allografts from HCV-positive donors are not or cannot be used because of local policy, and when the anticipated time to obtain a kidney from an HCV-negative donor is long, the patient should be offered anti-HCV therapy before transplantation. Biannual evaluation for complications of cirrhosis is indicated irrespective of whether the patient receives antiviral therapy or not.

Specific HCV GT also influences timing of an anti-HCV therapy. As discussed in Chapter 2, DAAs (grazoprevir plus elbasvir, daclatasvir plus asunaprevir, or 3D combination) that are approved to treat HCV infections in CKD G4 and CKD G5 patients are efficacious in GTs 1 and 4. For non GTs 1-4, only a sofosbuvir-based therapy can be proposed. However,

although it had been used off-label at reduced doses in CKD G4 and CKD G5 patients, it is not licensed for patients with an estimated GFR < 30 ml/min/1.73 m^2 (see Chapter 2). Hence, in non GTs 1-4-infected patients, if possible, treatment should be postponed until after transplantation.



Algorithm 1. Proposed strategy in HCV infected kidney transplant candidate.
G1, genotype 1; G4, genotype 4; HCV, hepatitis C; SKLT, simultaneous kidney-liver transplantation

Use of kidneys from HCV-infected donors

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

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

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

RATIONALE

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

In 1991 Pereira *et al*. demonstrated that HCV was transmitted by organ transplantation.[183] Several experiences published soon after the first description on the transplantation of kidneys from HCV RNA positive donors corroborated unequivocally the transmission of HCV infection by organ transplantation.[208] For this reason, organ procurement organizations and international guidelines have strongly recommended that all organ donors should be tested for HCV infection.[27, 209]

The diagnosis of HCV infection is made by the detection of anti-HCV antibodies by enzyme-linked immunosorbent assay.[27, 209] The majority of patients who are positive for anti-HCV antibodies also have detectable HCV RNA in the serum. Performing NAT as an emergency test in potential deceased donors is optimal but is not widely available due to time constraints,[27, 209] thus in many cases, only anti-HCV antibodies are tested in potential organs donors prior to transplantation.

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

There has been a consensus that kidneys from HCV-positive donors should not be transplanted into anti-HCV antibodies negative recipients. The problem was and remains that the demand for kidney transplantation clearly surpasses the supply.[27] In this way, universally discarding kidneys from HCV-positive donors, could lead to the loss of up to 4.2% of organs. This is a concern given the continued shortage of donor organs, particularly in areas with a

high prevalence of HCV infection.[27] A related issue was whether organs harvested from HCV-positive donors could be safely transplanted in HCV-positive recipients.[208]

An experience in Spain of transplanting kidneys from HCV antibodies positive into HCV-positive recipients[210, 211] provided some initial insights. When serum HCV RNA was retrospectively assessed in donor and recipients (by NAT) it was recognized that some HCV-positive recipients who were HCV RNA negative had received organs from HCV RNA positive donors.[211] As a result of these findings Spanish groups modified their policy, limiting the use of kidneys from HCV-positive donors to HCV RNA positive recipients. This strategy was supported by international guidelines.[27, 209] In recognition of the importance of HCV RNA status of anti-HCV-positive recipient, the HCV RNA status of the donor is critical for optimal allocation of HCV-positive organs. Indeed, Nowak *et al*. recently reported a case series of 21 anti-HCV-positive kidneys (20 donors) who were HCV RNA-negative. In no case did the use of those kidneys lead to *de novo* HCV infection in HCV-negative recipients.[212]

Several studies from the US (registry or hospital data) have demonstrated that transplantation of kidneys from HCV-positive donors into HCV-positive recipients reduces the waiting time for transplantation[213-219] but is associated with a small increased risk of death, graft loss and severe liver disease compared with HCV recipients who received kidneys from HCV-negative donors.[218] Notably, despite this increase in risk, HCV-positive recipients transplanted with kidneys from HCV-positive donors have a better chance of survival than HCV-positive patients on the waiting list.[215]

Long-term results of transplantation with HCV-positive donors into HCV-positive recipients have demonstrated that donor anti-HCV seropositivity was not an independent risk factor for patient survival, graft loss and liver disease.[220] These results were comparable to a single center experience in Philadelphia, showing that donor HCV status does not influence graft, patient survival nor eGFR in HCV-positive recipients.[221] Recent data from the US have corroborated these findings and demonstrated again that HCV patients who received kidneys from HCV-positive donors spent less time on the waiting list, which probably contributed to improved death censored graft survival compared with HCV recipients from HCV-negative donors.[222] The Canadian experience using kidneys from HCV-positive donor demonstrated that the benefit of transplantation is limited to HCV-positive recipients older than 50 years (Summary Table 11).[223]

Superinfection by another HCV GT can occur and therefore matching donors and recipients according to their GT could be the next step to improve the safety of this policy that remains somewhat controversial.[224] In the USA, the use of HCV-positive donors is restricted to viremic GT1 recipients (90-95% of HCV infected patients in the US). The availability of

pangenotypic antiviral agents should allow expansion of this strategy in patients with non-GT1 HCV.[225, 226]

Despite international recommendations[27, 209] currently there is underutilization of HCV-positive organs for a variety of reasons including: concerns about HCV transmission, the fear of legal liability, the lack of acceptance of HCV-positive kidneys from another unit and sometimes extensive recipient morbidities (for instance, long history of kidney disease, high immunological risk). Kucirka *et al.* have reported that HCV-positive donors were 2.6 times more likely to be discarded than HCV-negative donors.[227]

In summary, the use of kidneys from HCV RNA-positive donors into HCV-positive recipients (limiting the risk of transmission without loss of organs from the donor pool), seems to be an acceptable approach. The capacity to use DAAs shortly after transplantation should increase the use of these organs. Use of HCV RNA-positive kidneys for HCV-positive recipients has been included in the algorithms to establish the policy of DAA therapy before or after transplantation.[225, 226]

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

Possible living donors with HCV infection should be treated as in the normal population. First, liver fibrosis should be assessed and then if do not have cirrhosis they can receive DAAs based on GT (see Chapter 2).

Although SVR can be confirmed at 12 weeks, it seems reasonable to wait until 24 weeks to reconfirm SVR and to reevaluate the extent of fibrosis. In the absence of hepatic fibrosis once SVR has been achieved, living donation may be feasible.

The scarcity of donor organs for transplantation results in long waiting times for kidney transplantation.[27] In addition, individual patient characteristics, for instance high sensitization, may contribute to delays in transplantation. Longer time on hemodialysis and on waitlist may be an independent risk factor for graft loss and mortality after transplantation. For these reasons kidney transplantation with expanded criteria donors has become a necessity.

A recent national report from the US demonstrated inferior outcomes in HCV-negative recipients who had received a HCV-positive donor compared to HCV-negative recipients transplanted with HCV-negative donors.[228] This practice has been considered unacceptable.[27,

[209] However, the availability of current DAAs for HCV infections has led to a reconsideration of this prohibition.

Treatment with DAAs is established in the general population and in liver transplant recipients.[225] However, there is no information about the use of DAAs in the early period after kidney transplantation. Preliminary information using DAAs in long-functioning kidney transplant patients with HCV infection indicates excellent SVR 90-100%.[120, 121] We need additional information about DAA efficacy and safety administered shortly after kidney transplant. In liver transplantation, fibrosing cholestatic hepatitis has been successfully treated with DAAs.[226] In addition, a recent editorial commentary focused on this possibility[203] and a clinical trial using HCV-positive kidneys into HCV-negative recipients has been started very recently in Philadelphia.[229] Therefore, until more information, especially regarding long-term safety is available, this practice could be considered as experimental.

Use of maintenance immunosuppressive regimens

4.5: We suggest that all conventional current induction and maintenance immunosuppressive regimens can be considered for use in HCV-infected kidney transplant recipients. (*2C*)

RATIONALE

In HCV-infected kidney transplant recipients, viral load increases after transplantation as immunosuppression facilitates viral replication.[27] Roth *et al.* recently reported an increased rate of death by infection in HCV-positive patients in the first 6 months after kidney transplantation, a period when the impact of induction and high doses of maintenance immunosuppression therapy is greatest.[203] These data suggest caution in the choice of immunosuppressive protocol in these patients[27] given the frequent high immunological risk profile of HCV-infected recipients (Summary Table 12).

Antibody induction, particularly anti-lymphocyte preparations, had been associated with an increased risk of developing liver disease in HCV-infected transplant recipients.[183] However, several studies have suggested that the use of antibody induction has no detrimental effect on survival in HCV-positive patients with post-transplantation chronic liver disease, even in African Americans.[230-233] In addition, the HR for death dropped from 2.51 to 0.32 during the post-transplant period 7 to 84-month period, in the experience from Miami noted above using induction therapy.[203]

There are scarce data on the influence of steroids in kidney transplant patients with HCV infection. In an American study mortality was not different among patients who received steroids as part of immunosuppression protocol and those did not. In the setting of liver transplantation steroids discontinuation after liver transplantation was associated among others with a reduced rate of post-transplant diabetes.[234] It is thus reasonable to think that steroids withdrawal after kidney transplantation in HCV-positive selected patients could be beneficial to reduce post-transplant diabetes.

Concerning CNIs, there are no significant differences in outcomes with cyclosporine versus tacrolimus therapy in HCV-infected transplant recipients.[27] However, it should be noted that the risk of post-transplant diabetes mellitus is higher in HCV-positive patients treated with tacrolimus[235] and cyclosporine inhibits HCV replication on cultured hepatocytes.[236]

Increased HCV viremia has been reported in patients who received MMF in place of azathioprine.[237] In spite of this, MMF as part of maintenance immunosuppressive regimen was associated with better patient survival in an American study using induction, steroids, CNI and MMF.[203] Published information on clinical use of mTOR inhibitors in kidney transplant patients with HCV is scarce and therefore the influence of mTOR inhibitors (sirolimus and everolimus) in HCV-positive patients on patient survival after kidney transplantation is unknown.

One important concern with new DAAs for the treatment of HCV infection in kidney transplant patients is drug-to-drug interactions with immunosuppressive agents (Table 1). Because cyclosporine, tacrolimus, sirolimus and everolimus are metabolized in the liver by the cytochrome P450 as most DAAs do, a problem of substrate competition can occur influencing their elimination.[181] The use of currently licensed DAAs can increase levels of CNI levels and may require dose reduction (HCVGuidelines.org).[181]

Management of HCV-related complications in kidney transplant recipients

4.6.1: 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*)

4.6.2: Untreated HCV-positive kidney-transplant recipients should have the same liver disease follow-up as HCV-positive non-transplant patients, per AASLD guidelines. (*Not Graded*)

4.6.3: HCV infected kidney transplant recipients should be tested at least every 6 months for proteinuria. (*Not Graded*)

4.6.3.1: We suggest that patients who develop new onset proteinuria (either urine protein/creatinine ratio > 1 or 24-hour urine protein > 1 g on two or more occasions) have an allograft biopsy with immunofluorescence and electron microscopy included in the analysis. (*2D*)

4.6.4: We recommend treatment with a DAA regimen in patients with post-transplant HCV-associated glomerulonephritis. (*1D*)

RATIONALE

4.6.1: 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)

Kidney transplantation outcomes in patients with HCV and without extensive fibrosis successfully treated before transplantation should be equivalent to those in uninfected transplant recipients. With achievement of an SVR, viral relapse is unlikely although unexplained hepatic dysfunction should prompt testing for HCV RNA.

4.6.2: Untreated HCV-positive kidney-transplant recipients should have the same liver disease follow-up as HCV-positive non-transplant patients, per AASLD guidelines. (Not Graded)

Kidney transplantation in patients with active HCV infection may be complicated in the early and late period by liver disease and also by extrahepatic complications.[181] These patients exhibited a lower graft and patient survival and an increased risk of severe liver disease compared with HCV-negative recipients.[27, 181, 209, 238] Therefore, patients with persistent HCV RNA because of lack of treatment before transplantation or due to failure of therapy before or after transplantation should be considered for liver disease reevaluation and re-treatment with DAAs. In this way, preliminary publications of the use of DAAs in kidney transplant patients have exhibited a SVR of almost 100% without important side effects.[120, 121] Awaiting further multicenter and prospective studies, these encouraging results support the treatment with DAAs after kidney transplantation.

4.6.3: HCV infected kidney transplant recipients should be tested at least every 6 months for proteinuria. (Not Graded)

4.6.3.1: We suggest that patients who develop new onset proteinuria (either urine protein/creatinine ratio > 1 or 24-hour urine protein > 1 g on two or more occasions) have an allograft biopsy with immunofluorescence and electron microscopy included in the analysis. (2D)

4.6.4: We recommend treatment with a DAA regimen in patients with post-transplant HCV-associated glomerulonephritis. (1D)

HCV infection has been reported as a risk factor for the development of proteinuria in kidney transplant recipients.[239] Several glomerular lesions have been described after kidney transplantation in HCV RNA positive patients including recurrent or *de novo* cryoglobulinemic or non-cryoglobulinemic MPGN,[240] membranous glomerulonephritis (MGN),[241] acute transplant glomerulopathy,[181] anti-cardiolipin related thrombotic microangiopathy[242] and chronic transplant glomerulopathy.[243] MPGN followed by MGN are the most frequent lesions related to HCV infection. The most usual presentation is proteinuria with or without microhematuria or nephrotic syndrome. The pathogenesis of MPGN and MGN seems to be related to the deposition of immune complexes containing HCV RNA in the glomerulus, somewhat surprisingly in imunosuppressed patients.[27]

After HCV RNA positive patients undergo kidney transplantation, clinicians should screen for proteinuria and/or microhematuria. In the case of urine protein/creatinine ratio > 1 or 24-h urine protein greater than 1 g on two or more occasions a graft biopsy is indicated. Pathological examination should include immunofluorescence and electron microscopy. In the case of suspected transplant glomerulopathy electron microscopy is mandatory to make the differential diagnosis with HCV-related MPGN.[181, 243]

For HCV-related glomerular disease, DAA therapy is indicated. In severe HCV-related cryoglobulinemic MPGN, in addition to antiviral therapy with DAAs, rituximab and in severe cases, plasmaphresis should be considered.[181]

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

HCV infection is an important cause of chronic liver disease and its major long-term complications are cirrhosis, liver failure, and HCC.[244] HCV also leads to extrahepatic manifestations including kidney disease and MC.[245] Although chronic HCV infection has been identified as an important cause of tubulo-interstitial injury in a large case-control study,[246] HCV-associated glomerular disease is the most frequent kidney disease associated with HCV. HCV-induced glomerular disease occurs frequently in the context of HCV-associated MC, a systemic vasculitis characterized by involvement of small and, less frequently, medium-size vessels.[247-251] MC represents 60-75% of all cryoglobulinemia cases and is observed in connective tissue diseases and infectious or lymphoproliferative disorders, all grouped under secondary MC. After its identification, HCV has been recognized as the cause of 80-90% of 'idiopathic' MC.[247, 250] In general, HCV is associated with type II MC, although it may also be less frequently associated with type III MC. In the absence of an identified etiology (currently <10% of MC), cryoglobulinemic vasculitis is defined as essential or idiopathic.

Immune complex glomerular diseases such as MPGN are the most frequent kidney diseases associated with chronic HCV infection.[248, 249] The incidence of HCV-associated glomerular disease is probably low even if the available information is scanty. The largest survey has been conducted by El-Serag *et al*. who carried out a hospital-based case-control study among US male veterans from 1992 to 1999 and identified 34,204 patients infected with HCV (cases) and 136,816 randomly selected patient without HCV (controls).[252] A greater fraction of HCV-infected patients had porphyria cutanea tarda (0.77% vs. 0.06%, $P < 0.0001$), vitiligo (0.17% vs. 0.10%, $P = 0.0002$), lichen planus (0.30% vs. 0.13%, $P < 0.0001$), and cryoglobulinemia (0.57% vs. 0.05%, $P < 0.0001$). A greater rate of MPGN (0.36 vs. 0.05%, $P < 0.0001$) but not membranous nephropathy (0.33 vs. 0.19%, $P = 0.86$) was found among patients with HCV. According to a prospective Norwegian study (n=864 patients with community-acquired HCV infection, followed for a median of 7 years) the rate of CKD G5 due to MPGN was 0.2% (2/864).[253] It has been further shown that anti-HCV seropositive status was more common in patients with non-cryoglobulinemic MPGN and membranous nephropathy (18-20%) than that observed in the general population of the same area (7%) after correction for age.[254] A large meta-analysis (n = 6 studies; 107,356 unique patients)[3] reported that anti-HCV-positive serology was an independent risk factor for proteinuria in the adult general population; adjusted OR, 1.51 (95% CI: 1.19-1.89, $P = 0.0001$).[64, 65, 255-258] Another pooled analysis (n = 6 studies; 26,835 unique patients)[55] demonstrated that anti-HCV- positive serology was an independent risk factor for proteinuria among HIV-infected patients; adjusted effect estimate, 1.23 (95% CI: 1.18-1.28, $P = 0.001$).[259-264]

5.1: We recommend that a kidney biopsy be performed in HCV-infected patients with clinical evidence of glomerular disease. (*1B*)

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. (*1B*)

5.2.2: We recommend that patients with cryoglobulinemic flare, nephrotic syndrome, or progressive kidney failure be treated with both DAA and immunosuppressive agents and/or plasma-exchange. (*1B*)

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. (*1A*)

5.2.3.1: We recommend rituximab as the first-line immunosuppressive treatment. (*1B*)

RATIONALE

5.1: We recommend that a kidney biopsy be performed in HCV-infected patients with clinical evidence of glomerular disease. (1B)

The main clinical manifestations of glomerular disease in HCV-infected patients are the presence of proteinuria and microscopic hematuria with or without reduction in GFR. It remains unclear why only a minority of patients with HCV infection develop kidney abnormalities. Glomerular diseases associated with HCV infection have been described in the presence or absence of significant liver disease; however, all patients with HCV-associated glomerular disease show detectable HCV RNA in serum.[265, 266] Early diagnosis and treatment of HCV-associated glomerulopathy may improve clinical outcomes. In a prospective case-series from the US, 30 patients who received liver transplants for HCV-related cirrhosis underwent kidney biopsy during liver engraftment.[267] The majority of them (25 of 30) showed immune complex mediated glomerular disease; MPGN type 1 was found in 12 patients. Of these patients, 10 had normal serum creatinine levels, normal urinalysis, and normal quantitative proteinuria. In the 5 others, the only renal abnormality was an increased serum creatinine level. No patient had cryoglobulins in the blood or kidney. Additional studies are needed to ascertain whether HCV-related glomerular disease goes unrecognized in patients with advanced liver disease induced by HCV.

Symptomatic cryoglobulinemia occurs in about 5-10% of patients with chronic HCV infection, generally in association with high levels of cryoglobulins and rheumatoid factor. Cryoglobulins containing HCV RNA can be detected in up to 50% of patients with HCV-associated MPGN, but generally at very low levels (cryocrit < 3%).[268] Only a small number of patients with cryoglobulinemia develop kidney disease or other systemic symptoms.[268] The prevalence of MPGN in patients with cryoglobulinemia associated with HCV infection is <10% and, in series of kidney biopsies, only MPGN was clearly associated with HCV infection.[266] For other lesions, such as MPGN without cryoglobulinemia or MGN, the prevalence of HCV infection is in the range of 1–10%.[269, 270] Membranous nephropathy has been described occasionally in HCV-infected patients.[271, 272] In a study from Japan, evidence for HCV infection was found in 2 of 24 patients with apparent idiopathic membranous nephropathy.[273] In an autopsy series of 188 consecutive patients with HCV infection, the frequency of MPGN was 11% (n = 21), membranous nephropathy 2% (n = 5), and mesangial proliferative glomerulonephritis 17% (n = 33). Almost normal glomeruli were noted in 85 cases (45.2%).[274]

Laboratory parameters reveal the presence of circulating cryoglobulins- these are most commonly type II cryoglobulins in which the rheumatoid factor is an IgM-k. Serum anti-HCV antibody and HCV RNA are detected in both the serum and the cryoprecipitate. Positive rheumatoid factors are usually present in serum whereas C3 and C4 levels are frequently low. Some patients exhibit normal aspartate aminotransferase and ALT levels or only a modest elevation in liver enzymes.

The most common type of HCV-related GN is type I MPGN usually in the context of type II cryoglobulinemia. Distinctive features of cryoglobulinemic GN, especially in patients with rapidly progressive deterioration of kidney function, include intraglomerular deposits which are commonly seen in a sub-endothelial location, sometimes occluding the capillary lumen (intraluminal thrombi). Glomeruli may show prominent hypercellularity as a result of infiltration of glomerular capillaries by mononuclear and polymorphonuclear leucocytes. Glomeruli frequently show accentuation of lobulation of the tuft architecture with a combination of increased matrix and mesangial cells, capillary endothelial swelling, splitting of capillary basement membrane, and accumulation of eosinophilic material representing precipitated immune complexes or cryoglobulins. The glomerular basement membrane often shows double contours, which are caused by the interposition of monocytes between the basement membrane and the endothelium. On electronic microscopy, large subendothelial deposits are present. Vasculitis of small renal arteries is present in 30% of cases.[275]

Of note, numerous intraluminal thrombi, vasculitis, or both are more commonly observed in patients with an acute nephritic syndrome and rapid progressive kidney failure. Histological features of exudative or lobular MPGN are associated with the occurrence of

nephrotic and/or nephritic syndromes, whereas mesangial proliferation is prevalent in cases with intact kidney function and isolated proteinuria and/or microscopic hematuria.[275]

Some investigators have reported cases of MPGN without cryoglobulinemia.[249] In these patients, the clinical picture, histological features and laboratory data are indistinguishable from idiopathic type I MPGN. Both subendothelial and mesangial immune complexes can be identified by electron microscopy typically without a distinctive substructure. In both forms of HCV-associated GN, immunofluorescence commonly reveals deposition of IgM, IgG, and C3 in the mesangium and capillary walls.

Membranous nephropathy is also noted with chronic HCV infection.[241] Whether this corresponds to a true association or a coincidence is unclear. The clinical presentation, outcome and histopathology are similar to those observed in idiopathic membranous nephropathy. On light microscopy, the characteristic finding is a diffuse and uniform thickening of the glomerular basement membrane without mesangial or endothelial proliferation. Diffuse subepithelial immune deposits can be identified by electron microscopy, and immunofluorescence shows diffuse and granular deposits of IgG, IgA and C3.

Other glomerular diseases that have been occasionally reported in association with chronic HCV infection are acute proliferative GN, focal segmental glomerulosclerosis,[276] IgA nephropathy,[277] thrombotic microangiopathy,[242] rapidly progressive nephritis,[278] fibrillary GN and immunotactoid glomerulopathy.[279] However, these likely correspond to sporadic cases and their pathogenic link with HCV remains even more uncertain than for membranous nephropathy.

The pathogenesis of glomerular disease associated with HCV infection is not completely understood. It appears that HCV binds and penetrates into the renal parenchymal cells via the CD81 and SR-B1 receptors.[280] HCV RNA has been found in mesangial cells, tubular epithelial cells, and endothelial cells of glomerular and tubular capillaries. The deposition of immune complexes containing HCV proteins in the glomerular basement membrane has been cited in the pathogenesis of HCV-associated membranous nephropathy.[280] HCV-related granular protein deposits located in the mesangium have been observed in patients with HCV-related MPGN: they are probably related to higher degrees of proteinuria.[281] Viral antigens have been found by immunohistochemistry,[282] *in situ* hybridization,[282] and laser capture microdissection.[283]

Toll-like receptors (TLR) may also have a role in HCV-associated renal injury. Toll-like receptor 3 messenger RNA expression is increased in the mesangial cells of patients with HCV-related MPGN. TLR4 is constitutively expressed by podocytes.[284] An upregulation of

glomerular expressions of TLR4 and fibronectin was found in two mouse models of cryoglobulinemic GN.[285]

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

In view of the role of HCV in the pathogenesis of cryoglobulinemic GN, antiviral therapy has been used to achieve clearance of HCV and ameliorate the renal injury. The evidence on the impact of antiviral treatment of HCV-related glomerular disease is limited and consists mostly of anecdotal reports and small-sized observational studies, and RCTs are sparse (Evidence Profile 10 and Summary Table 13). Initial reports adopted monotherapy with conventional IFN,[269] but the combined regimen (pegylated IFN plus RBV) superseded monotherapy.[286]

Some evidence supporting the antiviral therapy of HCV-associated glomerular disease has been provided by a meta-analysis of clinical controlled trials comparing antiviral versus immunosuppressive regimens for HCV-induced GN.[287] Pooling of study results indicated that proteinuria decreased more commonly after IFN than corticosteroid therapy even if no significant association was noted, OR = 19.92; 95% CI: 0.39-9.57. In a sensitivity analysis including only clinical controlled trials using standard IFN doses, OR was 3.86 (95% CI: 1.44-10.3, P = 0.007). Of note, in all patients with proteinuria reduction, HCV RNA clearance was observed at the end of antiviral therapy.[287]

In another meta-analysis,[87] antiviral therapy based on IFN-alpha decreased proteinuria in HCV-positive CKD patients. At the end of antiviral therapy, the summary estimate of the mean decrease in proteinuria was 2.71 g/24 h [95% CI: 1.38-4.04, P < 0.0001]. The decrease in proteinuria following antiviral therapy was associated with HCV RNA clearance. Serum creatinine was not significantly decreased with antiviral treatment; however, stabilization of serum creatinine was achieved. Patients receiving combination with IFN plus RBV achieved a higher SVR rate than those with IFN monotherapy regardless of HCV GT.

Additional anecdotal reports on the antiviral treatment of HCV-associated glomerular disease in adults with native kidneys have been published; reports in English language were mostly identified. As listed elsewhere, a large variety of histological lesions was found.[288] According to an updated review, a total of 36 reports (n = 47 unique patients) were retrieved.[289-295] The majority of these patients had improvement of renal changes after clearance of HCV RNA, and this confirms the role of the virus in the pathogenesis of the kidney disease. One report emphasized the spontaneous remission of glomerular lesions; this cannot be excluded in a few cases.[296] Additional, albeit limited, information on antiviral treatment of HCV-related glomerular disease in kidney,[240] liver,[297-299] and liver/kidney

transplanted population[300] and among pediatric individuals exists. Recombinant IFN given for treatment of HCV may exacerbate proteinuria in some patients with underlying glomerulopathies.[301]

Antiviral treatment of HCV-related glomerular disease has numerous limitations. First, the eradication of HCV is not universal as suggested by a systematic review with meta-analysis of clinical observational studies using IFN-based regimens; the summary estimate of SVR was 0.52 with 95% CI: 0.21-0.83 (P = 0.001).[288] Preliminary data suggest that the efficacy of antiviral therapy will improve with the use of IFN-free DAA regimens. Second, the impact of antiviral therapy on the long-term outcomes of kidney disease remains uncertain. Third, the clinical benefit in patients who reached SVR may be transient and/or a dissociation between the viral and renal responses can occur.

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. (1B)

The development of kidney disease among patients with MC has particular importance as kidney involvement confers a poor prognosis to patients with MC.[302-304] Clinically, HCV-associated MC is characterized by the triad of purpura, arthralgia, and weakness. The natural history of HCV-induced MC is clinically variable: some patients have an indolent course while others develop vasculitic lesions in various organs including kidneys. Extrarenal features of MC include neuropathy, hepatomegaly, sicca syndrome, central nervous system and gut involvement. Overt pulmonary involvement is infrequent. Although extrarenal signs of MC vasculitis usually precede the kidney manifestations, often by years, in 29% of cases, kidney and extrarenal involvement are concurrent.[304] Kidney disease occurs in 8-58% of patients with MC, and in a minority of cases, can be the first manifestation of MC. Patients with HCV-induced cryoglobulinemic glomerular disease can present with nephritic syndrome, asymptomatic non-nephrotic proteinuria or hematuria and/or reduced eGFR. Acute nephritic and nephrotic syndrome can be a presenting feature in 25% and 20% of the patients, respectively. Arterial hypertension is frequent (affecting > 50% of patients at the time of diagnosis) and is often resistant to anti-hypertensive drugs - the severity of hypertension often mirrors the severity of kidney disease.[303] Around 10% of patients present oliguric kidney failure.[303, 304]

Type II MC is most common in the fourth or fifth decade of life, and usually is characterized by periods of extrarenal symptoms alternating with periods of quiescence.[305] The exacerbation of extrarenal symptoms often is associated with a flare up of kidney disease, but can occur independently. Patients with cryoglobulinemic GN have a poor prognosis, mainly because of a high incidence of infections, end-stage liver, and cardiovascular diseases.[303, 304]

We need prospective RCTs to establish evidence-based recommendations to treat glomerular lesions associated with HCV infection. Until this information is available, the treatment of HCV-associated GN should probably be driven by the severity of proteinuria and kidney failure. Antiviral therapy with IFN-free regimens should be considered the first-line choice in patients with non-nephrotic proteinuria and relatively stable kidney function. In addition, anti-proteinuric agents such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers should be given to maximally reduce proteinuria. Treatment including diuretics and anti-hypertensive agents should be used to achieve target blood pressure recommended in patients with CKD.

5.2.2: We recommend that patients with cryoglobulinemic flare, nephrotic syndrome, or progressive kidney failure be treated with both DAA and immunosuppressive agents and/or plasma-exchange. (1B)

Immunosuppressive agents have been administered to patients with serious, life-threatening complications of MC, such as MPGN, severe neuropathy or extensive skin disease. Cyclophosphamide has been selected to improve kidney disease by reducing stimulation of B lymphocytes and cryoglobulin synthesis; steroid pulses have been given to treat glomerular inflammation, and plasma-exchange to remove circulating cryoglobulins from the plasma and consequently to reduce the deposition of immune complexes at kidney level.

In patients with nephrotic-range proteinuria and/or rapidly progressive kidney failure and/or acute flare of cryoglobulinemia, control of disease by immunosuppressive agents, with or without plasma exchange (3 liters of plasma thrice weekly for 2-3 weeks), should be considered before the initiation of antiviral therapy. It has been already recommended to consider the use of rituximab (375 mg/m^2 weekly for 4 weeks), or cyclophosphamide (2 mg/kg/day for 2-4 months) plus methylprednisolone pulses 0.5-1 g/day for 3 days. According to the decision of the clinician, immunosuppressive regimen alone or combined therapy (immunosuppressive agents plus antiviral therapy) is suggested as the initial approach. DAA dosage in patients with HCV-related glomerular disease should be adapted to eGFR as stated in Chapter 2.

Until a few years ago, combined therapy with corticosteroids and immunosuppressive agents, for example treatment using sequentially cyclophosphamide and azathioprine, has been used while awaiting the response, if any, to antiviral therapy. In one retrospective study, the clinical outcome of 105 patients with essential MC vasculitis and renal involvement was evaluated throughout a median follow up of 72 months since kidney biopsy.[303] Positive anti-HCV serologic status was ascertained in around 85%. About 80% of patients underwent treatment with oral or pulse intravenous steroids and/or cytotoxic agents, whereas 67% was

treated with plasma-exchange. Despite this aggressive treatment, patient survival was 49% at 10 years after kidney biopsy and only 14% of patients had long-term remission of kidney disease.[303] At multivariate analysis, age >50 years, purpura, splenomegaly, cryocrit levels >10%, C3 plasma levels < 54 mg/dl and serum creatinine >1.5 mg/dl [> 133 μmol/l] were independent risk factors for death or dialysis.[303]

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. (1A)

Limited information exists on the use of DAAs in patients with HCV-associated glomerular disease. Nine patients with symptomatic mixed cryoglobulinemic disease (seven with MPGN) and HCV GT1 underwent triple antiviral therapy [pegylated IFN, RBV, and boceprevir (n = 2) or telaprevir (n = 5) or sofosbuvir (n = 2)].[306, 307] All patients reached SVR but serum cryoglobulins persisted in three patients; also, the benefits on renal signs were partial. MPGN remitted in three after further treatment with corticosteroids or corticosteroids plus rituximab.

More recently, encouraging results have been obtained with IFN-free DAA regimens for HCV-related glomerular disease- a small group (n = 7) of patients with symptomatic MC and GN (five had a biopsy-proven MPGN and two were diagnosed clinically) underwent sofosbuvir-based regimens (sofosbuvir and simeprevir, n = 6), or sofosbuvir and RBV, n = 1).[308] Only one patient was receiving ongoing immunosuppression concurrent with antiviral therapy. All patients had an improvement in eGFR and a reduction in proteinuria, particularly in those whose onset of proteinuria was recent. Also, in all patients HCV RNA was undetectable by week 4 and remained undetectable while on treatment. SVR was reached in 6/7 patients.

In another cohort of 44 consecutive patients with HCV-associated MC, four patients had kidney disease (MPGN, n = 1; nephrotic syndrome n = 1; and non-nephrotic proteinuria, n= 2).[309] The treatment of HCV-associated MC with sofosbuvir-based DAA therapy appeared to be highly effective (SVR12, 100%) and safe with some improvement of kidney disease[309, 310] These studies suggest that IFN-free therapies can give high viral and clinical responses in a difficult-to-treat condition such as HCV-associated MC with renal involvement. In fact, the SVR rates ranging between 83% and 100% are comparable to the SVR12 rates reported with similar regimens in other non-cryoglobulinemic real-world groups. It is clear that we need larger and controlled studies to confirm these results. Association with rituximab and other immunosuppressants might be of value for cases with severe or obstinate manifestations of cryoglobulinemic vasculitis.

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

Immunosuppressive therapies are suggested typically for patients with HCV-associated MC showing severe disease manifestations, such as progressive glomerular disease. In addition to conventional immunosuppressants which target inflammation at glomerular level, encouraging results have been obtained with rituximab, a human-mouse chimeric monoclonal antibody that binds to the B-cell surface antigen CD20 and selectively targets B cells.[311] Rituximab interferes with synthesis of cryoglobulins, monoclonal IgM and renal deposition of immune complexes. An important pathogenetic feature of MC (including cryoglobulinemic GN) is chronic stimulation of B lymphocytes by HCV and widespread auto-antibody synthesis related to HCV-induced lowering of cell activation threshold.

Two prospective RCTs have demonstrated the superiority of rituximab monotherapy as compared to conventional immunosuppressive therapy (i.e., corticosteroids, azathioprine, cyclophosphamide, methotrexate, and plasma exchange) for the treatment of HCV-associated cryoglobulinemic vasculitis in whom prior antiviral therapy failed to induce disease remission, or in patients who were not eligible for IFN therapy. Admittedly, only a minority of the included patients showed renal involvement.[312, 313] Rituximab was well tolerated and was effective in 71.4%-83% of patients with HCV-associated cryoglobulinemic vasculitis. Frequent relapses may occur after rituximab when B cells re-emerge in the peripheral blood; in addition, repeated rituximab infusions may expose patients to opportunistic infections.

In a recent prospective, single-center study, patients (n = 16) with cryoglobulinemic nephropathy (diffuse MPGN and MC) received rituximab at a dose of 375 mg/m^2, according to a '4 + 2' protocol (days 1, 8, 15 and 22 plus 1 dose 1 and 2 months later).[314] No other immunosuppressive drugs were used. Safety and efficacy of rituximab was evaluated over a long-term follow-up (mean, 72.47 months; range, 30-148). A significant improvement of cryoglobulinemic GN was found, starting from the 2nd month after rituximab (serum creatinine from 2.1 ± 1.7 mg/dl [186 ± 150 μmol/l] to 1.5 ± 1.6 mg/dl [133 ± 141 μmol/l], $P < 0.05$; and 24-hour proteinuria from 2.3 ± 2.1 to 0.9 ± 1.9 g/24 h, $P < 0.05$).[314] No clinically relevant side effects were recorded. Re-induction with rituximab was carried out in 9 patients who relapsed after a mean of 31.1 months (12-54), again with beneficial effects. In addition, complete remission of pre-treatment active manifestations was observed in all cases of purpuric lesions and non-healing vasculitic ulcers, and in 80% of the peripheral neuropathies.

A point of caution is important as rituximab, which selectively targets B cells, has been associated with severe infectious complications including reactivation of HCV.[315] The risk of reactivation of HBV infection has been added to the existing black box warning on the rituximab label by the FDA in 2013. Infections with ominous course after rituximab therapy

have been observed in kidney transplant recipients and in the non-transplant setting. Admittedly, these complications were mostly observed in patients under multiple immunosuppressive agents. Infectious episodes have been frequently reported in a patient subgroup (age > 70 years, GFR < 60 ml/min/1.73 m^2, and concomitant high-dose corticosteroids) and were fatal in some patients.[316] Cholestatic liver disease due to HCV reactivation by rituximab has been also observed after kidney transplant.[317]

In addition to conventional or selective immunosuppressive agents, additional immunosuppressive agents, such as MMF, should be evaluated. Preliminary evidence suggests that MMF can be effective for maintaining remission of HCV-associated cryoglobulinemic GN.[318, 319] The key takeaways from this chapter's recommendations are summarized in Table 10.

Table 10. Summary of recommendations

• Patients with mild or moderate HCV-induced glomerulonephritis (non-nephrotic proteinuria and/or moderate kidney failure) should be managed first with interferon-free regimens.
• Patients with acute flares of cryoglobulinemia and/or severe glomerular disease induced by HCV (nephrotic proteinuria and/or progressive kidney failure) should be treated with plasma-exchange, rituximab, and interferon-free antiviral therapies.
• Additional immunosuppressive drugs include steroids, cyclophosphamide, and mycophenolate mofetil.
• Relapses of symptomatic mixed cryoglobulinemia with glomerular disease should be managed with additional doses of rituximab (or other immunosuppressants).
• Patients with HCV-related glomerular disease who are non-responders, or intolerant to antiviral treatment should be treated with rituximab (or other immunosuppressants).
• Low-dose ribavirin (200 mg daily or 200-400 thrice weekly) should be given for the treatment of HCV-induced glomerular disease and creatinine clearance < 50 ml/min with close monitoring of hemoglobin concentration.
• SVR after interferon-free regimens, changes in kidney function, evolution of proteinuria, and side effects of antiviral therapy must be carefully monitored.
• Treatment with antiproteinuric agents such as ACEi and/or ARBs should be given to patients with HCV-associated glomerular disease to maximally reduce urinary protein losses.
• Diuretics and anti-hypertensive drugs should be administered to achieve recommended target blood pressure goals of patients with CKD.

ACEi; angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; HCV, hepatitis C; SVR, sustained virologic response.

LIMITATIONS

1. The efficacy and safety of antiviral therapies for the treatment of HCV-related glomerular disease has been evaluated mostly in small-sized clinical studies.

2. The studies concerning antiviral therapies for HCV-positive glomerular disease commonly have short follow-up.

3. HCV-associated GN is an uncommon disease; this clearly hampers the implementation of prospective RCTs which we need to make evidence-based recommendations for treatment.

RESEARCH RECOMMENDATIONS

- Occult HCV infection (detectable HCV RNA in peripheral blood mononuclear cells and/or in serum after centrifugation) could be involved in the pathogenesis of glomerular disease among patients negative for HCV RNA.[320] We need large-sized studies with appropriate technology to confirm the relationship between occult HCV and glomerular disease, which has various implications from the clinical standpoint.

- The antiviral approach to the treatment of HCV-related glomerular disease is expected to improve with IFN-free and RBV-free regimens. However, some of these drugs are not currently approved in patients with low GFR; thus further studies of various DAAs are warranted in late CKD/ESRD for various GTs.

- Typically, patients with HCV-related glomerular disease receive a high number of concomitant drugs, including cytotoxic agents; potential drug-drug interactions is another challenge to clinicians using IFN-free DAA regimens for HCV-induced GN.

- Numerous questions regarding the use of rituximab in HCV-positive glomerular disease remain: as an example, the timing and dose of periodic rituximab infusions for relapsers. The role of rituximab as first-line or rescue therapy needs to be defined further.

- Severe infections after rituximab therapy frequently occur in a definite clinical setting (patient age >50 years, renal impairment and concomitant use of high-dose corticosteroids). We need to expand such evidence.

- The role of immunosuppressive agents in the management of aggressive HCV-related glomerular disease (nephrotic syndrome, rapidly progressive decline of glomerular filtration) needs further to be clarified in the light of the fast antiviral activity provided by IFN-free DAA regimens.

METHODS FOR GUIDELINE DEVELOPMENT

AIM

The overall aim of this project was to develop an evidence-based clinical practice guideline (CPG) for the management of patients with CKD as pertains to HCV infection. The guideline consists of recommendation statements, rationales, and a summary of systematically generated evidence on relevant pre-defined clinical topics. The general guideline development method is described at http://www.kdigo.org/home/guidelines/development as well as below.

OVERVIEW OF PROCESS

The development process for the *KDIGO 2017 Clinical Practice Guideline on the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in CKD* included the following steps:

- Appointing Work Group members and the evidence review team (ERT)
- Discussing process, methods, and results
- Developing and refining topics
- Identifying populations, interventions or predictors, and outcomes of interest
- Selecting topics for systematic evidence review
- Standardizing quality assessment methodology
- Developing and implementing literature search strategies
- Screening abstracts and retrieving full-text articles on the basis of pre-defined eligibility criteria
- Creating data extraction forms
- Extracting data and performing critical appraisal of the literature
- Grading the methodology and outcomes in individual studies
- Tabulating data from individual studies into summary tables
- Grading quality of evidence for each outcome across studies, and assessing the overall quality of evidence across outcomes with the aid of evidence profiles
- Grading the strength of recommendations on the basis of the quality of evidence and other considerations
- Finalizing guideline recommendations and supporting rationales
- Sending the guideline draft for for public review in February 2017
- Editing the guideline
- Publishing the final version of the guideline

The overall process for conducting the systematic reviews and developing the CPG follow international standards, including those from the Institute of Medicine.[321, 322]

The Work Group Co-Chairs and ERT met for a two-day meeting to go over the guideline development process, evidence review topics, and systematic review findings. Following this, the Work Group, ERT, and KDIGO support staff met for two separate meetings to review the available evidence, formulate recommendation statements, evaluate the quality of the evidence and strength of recommendations, deliberate on rationale for recommendations, and develop consensus.

Commissioning of Work Group and ERT

The KDIGO Co-Chairs appointed the Work Group Co-Chairs, who then assembled the Work Group of domain experts, including individuals with expertise in adult and pediatric nephrology, transplant nephrology, hepatology, virology, infection control, and public health. The Brown University Center for Evidence Synthesis in Health in Providence, Rhode Island, USA, was contracted as the ERT to conduct systematic evidence review and provide expertise in guideline development methodology. The ERT consisted of physician–methodologists with expertise in nephrology and evidence-based clinical practice guideline development, and experienced research associates.

Defining scope and topics

The Work Group Co-Chairs and the ERT defined the overall scope and goals of the guideline (including a list of critical and important interventions and outcomes) and then drafted a preliminary list of topics and key clinical questions. The list of research and recommendation topics was based on the original KDIGO guideline on HCV[27] which the ERT also had helped to develop (when it was based at Tufts Medical Center in Boston, Massachusetts, USA). The Work Group and ERT further developed and refined each topic and specified screening criteria, literature search strategies, and data extraction forms (Table M1).

Establishing the process for guideline development

The ERT performed systematic literature searches and organized abstract and article screening. The ERT also coordinated the methodological and analytical processes and defined and standardized the methodology for performing literature searches, data extraction, and summarizing the evidence. The Work Group took the primary role of writing and grading the recommendation statements and rationales and retained final responsibility for their content.

The Work Group Co-Chairs and the ERT prepared the first draft of the scope of work document as a series of open-ended questions to be considered by Work Group members.

Formulating questions of interest

Questions of interest were formulated according to the PICODD criteria (Population, Intervention, Comparator, Outcome, study Design and Duration of follow-up). Details of the PICODD criteria are presented in Table M1.

Table M1. Systematic review topics and screening criteria

HCV treatment	
Population	CKD G3-5 (including dialysis and transplant) or equivalent; HCV infection
Intervention	DAA (except 1st generation: telaprevir, boceprevir), pegylated interferon ± ribavirin, immunosuppression including induction (in combination with DAA or as treatment of HCV-associated GN)
Comparator	Active or control or none (single arm studies)
Outcome	Categorical: All-cause mortality, SVR (preferably 24 week), hepatocellular carcinoma, graft loss, NODAT, QoL, adverse events (including treatment discontinuation), pharmacokinetics/dynamics Continuous (HCV-associated GN only): kidney function, proteinuria,
Study design	RCT, nonrandomized comparative studies, single group studies; prospective (all topics) or retrospective (immunosuppression or GN topics only). Interferon in dialysis: RCT only.
Minimum duration of follow-up	HCV treatment studies: 12 weeks post-treatment; Other topics: no minimum
Minimum *N* of Subjects	≥10; Immunosuppression topic: Any, including case reports.
Publication dates	All: ≥2008 (plus studies in 2008 KDIGO CPG); Interferon and dialysis topic: Cochrane review[323] and ≥2012.
Liver testing	
Population	Tests for cirrhosis: CKD (all stages); Pre-transplant biopsy: CKD G4-G5 pre-transplantation (or equivalent)
Intervention/ Comparator	Non-invasive liver testing, including upper endoscopy (for varices), liver biopsy
Outcome	Non-invasive test performance characteristics, change in management strategy, patient mortality, graft loss,
Design	Any
Minimum *N* of subjects	Non-invasive testing: N≥10, Pre-transplant biopsy: N≥5
Publication dates	Any
Dialysis isolation	
Population	Hemodialysis (patients or units)
Intervention	Isolation, quarantine, etc.
Comparator	No isolation, less stringent standard
Outcome	HCV transmission
Design	Any
Minimum duration of follow-up	None
Minimum *N* of subjects	N≥30 patients
Publication dates	≥2008 (plus studies in 2008 KDIGO CPG)

Early vs. late transplantation	
Population	HCV-infected transplantation candidates
Intervention	Transplantation ("now")
Comparator	Remaining on waitlist or awaiting HCV-negative status
Outcome	Patient mortality, graft loss
Design	Any, multivariable analysis
Minimum duration of follow-up	None
Minimum *N* of subjects	N≥100
Publication dates	≥2008 (plus studies in 2008 KDIGO CPG)
HCV-infected donors	
Population	HCV-infected kidney transplant recipients
Intervention	HCV-infected donors
Comparator	HCV-negative donors
Outcome	Patient mortality, graft loss
Design	Longitudinal comparative, multivariable analysis
Minimum duration of follow-up	None
Minimum *N* of subjects	N≥100
Publication dates	Any
Predictor analyses	
Population	Predictors of CKD progression: Any (including general population) *except* CKD 5D (dialysis); HCV as predictor: Kidney transplant recipients
Predictor	HCV-infection (untreated), other predictors of CKD progression (if HCV-infected)
Outcome	CKD progression (GFR, SCr doubling, ESRD, graft loss), proteinuria, patient mortality, graft loss, delayed graft function, kidney pathology (HCV-associated GN)
Design	Longitudinal, multivariable analyses; HCV-associated GN: Any (except autopsy studies)
Minimum duration of follow-up	Any
Minimum *N* of subjects	≥100
Publication dates	Predictors of CKD progression: Any; HCV as predictor: ≥2008 (plus studies in 2008 KDIGO CPG)

Abbreviations: 2008 KDIGO CPG, 2008 KDIGO clinical practice guideline on hepatitis C;[27] CKD, chronic kidney disease; DAA, direct acting antiviral; ESRD, end-stage renal disease; GFR, glomerular filtration rate; GN, glomerulonephritis; HCV, hepatitis C virus; NODAT, new-onset diabetes after transplantation; QoL, quality of life; RCT, randomized controlled trial; SCr, serum creatinine; SVR, sustained viral response.

Ranking of outcomes

The Work Group ranked outcomes of interest on the basis of their importance for informing clinical decision making (Table M2).

Table M2. Hierarchy of outcomes

Hierarchy	Outcome
Critical importance	Mortality, graft loss, ESRD
High importance	SVR, treatment discontinuation due to adverse events, serious adverse events, CKD incidence, HCV seroconversion, test performance characteristics
Moderate importance	HCV relapse, kidney function, proteinuria, HCV positivity, hepatocellular carcinoma

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; HCV, hepatitis C virus; SVR, sustained viral response.

Literature searches and article selection

Systematic search strategies were developed by the ERT with input from the Work Group Co-Chairs. Modules were created for kidney disease, hepatitis C, and study designs. Searches were conducted in PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. For topics covered in the 2008 KDIGO HCV CPG,[27] searches were limited to 2008 and later to capture new evidence. For new topics, searches were not limited by publication date. The full literature search strategies are provided in the Supplemental Appendix 1. In addition, the ERT searched for existing relevant systematic reviews. The final searches will be conducted in late November 2016. The search yield was also supplemented by articles provided by Work Group members through January 2017.

For selection of studies, all members of the ERT screened the abstracts in duplicate using an open-source, on-line screening program Abstrackr (http://abstrackr.cebm.brown.edu/). To establish relevance and consensus among reviewers, the entire team screened and achieved consensus on a series of initial batches of 100 abstracts. A total of 7121 citations were screened. Journal articles reporting original data or systematic reviews were selected for evidence review, based on *a priori* criteria for eligible evidence. Of these, 332 were selected for consideration for inclusion.

Data extraction

Data extraction was done by ERT research associates. Extracted data from each study was reviewed by another ERT member to confirm accuracy. The ERT designed forms to capture data on design, methodology, eligibility criteria, study participant characteristics, interventions, comparators, predictors, outcomes, and results of individual studies. Methodology and outcomes were also systematically assessed for risk of bias (see the section on risk of bias assessment below) and recorded during the data extraction process. Data were extracted into the on-line repository SRDR (Systematic Review Data Repository); [upon publication], the data [will be] published and made available for review at http://srdr.ahrq.gov/.

Summary tables

Summary tables were developed for each reviewed topic. Summary tables contain outcomes of interest, relevant population characteristics, description of intervention and comparator (or predictor), results, and quality grading for each outcome. Categorical outcomes and continuous lipid outcomes were tabulated separately.

Work Group members reviewed and confirmed all summary table data and quality assessments. Summary tables are available at www.kdigo.org.

Evidence profiles

Evidence profiles were constructed to assess the quality and record quality grades and descriptions of effect (or association) for each outcome across studies, as well as the quality of overall evidence and description of net benefits or harms of the intervention or comparator across all outcomes. These profiles aim to make the evidence synthesis process transparent. Decisions in the evidence profiles were based on data from the primary studies listed in corresponding summary tables and on judgments of the ERT and Work Group. When the body of evidence for a particular comparison of interest consisted of two or fewer studies, the summary table provided the final level of synthesis and an evidence profile was not generated. Each evidence profile was initially constructed by the ERT and then reviewed, edited, and approved by the Work Group. The work products created by the ERT for summarizing the evidence base are listed in Table M3, together with the number of included studies.

Table M3. Work products for the guideline

Topics	Summary Table	Included Studies*, n	Evidence Profile
1. HCV testing			
1.1. Determining which CKD patients should be tested for HCV	−	(not searched)	
1.2. HCV testing in CKD	−	(not searched)	
1.3. Non-invasive vs. invasive tests for cirrhosis in CKD	+	8	+
1.4. HCV as predictor of CKD progression	+	16	+
1.5. Other predictors of CKD progression	+	1	−
2. HCV treatment			
2.1. HCV treatment (DAA, CKD non-transplant)	+	11	+
2.1. HCV treatment (peg-interferon, hemodialysis)	+	6	+ (dialysis only)
2.1. HCV treatment (DAA, kidney transplant)	+	5	+
2.1. HCV treatment (interferon, kidney transplant)	+	4	+
2.2. DAA drug dosing	−	10 PK studies	−
3. HCV transmission			
3. Dialysis isolation	+	6	+
4. Kidney transplantation			
4.1. Transplantation vs. waitlist	+	5	− (currently)
4.2. HCV as predictor, patient mortality	+	5	+
4.2. HCV as predictor, graft loss	+	7	+
4.3. HCV-positive vs. negative donor kidneys	+	7	−
4.4. Pre-transplant liver biopsy	−	1	−
4.5. DAA and immunosuppression interaction	−	0	−
5. HCV-associated glomerulonephritis			
5.1. HCV-associated kidney disease prevalence	+	5	−
5.2. HCV-associated glomerulonephritis management	+	12	+

Abbreviations: CKD, chronic kidney disease; DAA, direct acting antiviral; HCV, hepatitis C virus.
* Plus 4 case reports on miscellaneous topics.

Grading of quality of evidence for outcomes of individual studies

Methodological quality (internal validity) refers to the design, conduct, and reporting of outcomes of a clinical study. A previously devised three-level classification system for quality assessment was used to grade the overall study quality and quality of all relevant outcomes in the study (Table M4). Grading of individual studies was done by one of the reviewers, then confirmed by another, with discrepancies discussed in conference.

We based the methodological quality of each study on predefined criteria. For RCTs and other comparative studies, the ERT used the Cochrane risk of bias tool,[324] which asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. For observational studies, we also used selected questions from the Newcastle Ottawa Scale about comparability of cohorts, representativeness of the population, and adjustment for different lengths of follow-up.[325] Based on these characteristics an overall assessment was made whether the study was of good, fair, or poor quality (Table M4).

Each reported outcome was then evaluated and given an individual grade depending on the quality of reporting and methodological issues specific to that outcome. However, the quality grade of an individual outcome could not exceed the quality grade for the overall study.

Table M4. Classification of study quality

Good quality	Low risk of bias and no obvious reporting errors; complete reporting of data. Must be prospective. If study of intervention, must be RCT.
Fair quality	Moderate risk of bias, but problems with study or paper are unlikely to cause major bias. If study of intervention, must be prospective.
Poor quality	High risk of bias or cannot rule out possible significant biases. Poor methods, incomplete data, reporting errors. Prospective or retrospective.

Abbreviation: RCT, randomized controlled trial

Grading the quality of evidence and the strength of a guideline recommendation

A structured approach, based on GRADE[326-328] and facilitated by the use of evidence profiles was used to grade the quality of the overall evidence and the strength of recommendations. For each topic, the discussion on grading of the quality of the evidence was led by the ERT, and the discussion regarding the strength of the recommendations was led by the Work Group Co-Chairs. The "strength of a recommendation" indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm. The "quality of a body of evidence" refers to the extent to which our confidence in an estimate of effect is sufficient to support a particular recommendation.[327]

Grading the quality of evidence for each outcome across studies. Following GRADE, the quality of a body of evidence pertaining to a particular outcome of interest was initially categorized on the basis of study design. For each outcome, the potential grade for the quality of evidence for each intervention–outcome pair started at "high" but was then lowered if there were serious limitations to the methodological quality of the aggregate of studies, if there were important inconsistencies in the results across studies, if there was uncertainty about the directness of evidence including limited applicability of the findings to the population of interest, if the data were imprecise (a low event rate [0 or 1 event] in either arm or a CI spanning a range >1) or sparse (only 1 study or total $N < 500$), or if there was thought to be a high likelihood of bias. The final grade for the quality of the evidence for an intervention–outcome pair could be one of the following four grades: "High", "Moderate", "Low" or "Very Low" (Table M5).

Table M5. GRADE system for grading quality of evidence

Step 1: Starting grade for quality of evidence based on study design	Step 2: Reduce grade	Step 3: Raise grade	Final grade for quality of evidence and definition
Randomized trials = High	*Study quality* −1 level if serious limitations −2 levels if very serious limitations *Consistency* −1 level if important inconsistency *Directness* −1 level if some uncertainty −2 levels if major uncertainty *Other* −1 level if sparse or imprecise data[c] −1 level if high probability of reporting bias	*Strength of association* +1 level if strong[a], no plausible confounders +2 levels if very strong[b], no major threats to validity *Other* +1 level if evidence of a dose–response gradient +1 level if all residual plausible confounders would have reduced the observed effect	High = Further research is unlikely to change confidence in the estimate of the effect
Observational study = Low			Moderate = Further research is likely to have an important impact on confidence in the estimate of effect, and may change the estimate
			Low = Further research is very likely to have an important impact on confidence in the estimate, and may change the estimate
Any other evidence = Very Low			Very Low = Any estimate of effect is very uncertain

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation.

[a] Strong evidence of association is defined as "significant relative risk of >2 (<0.5)" based on consistent evidence from two or more observational studies, with no plausible confounders.

[b] Very strong evidence of association is defined as "significant relative risk of >5 (<0.2)" based on direct evidence with no major threats to validity.

[c] Sparse if there is only one study or if total *N* <500. Imprecise if there is a low event rate (0 or 1 event) in either arm or confidence interval spanning a range >1.

Adapted by permission from Uhlig K, Macleod A, Craig J *et al*.[326]

Grading the overall quality of evidence. The quality of the overall body of evidence was then determined on the basis of the quality grades for all outcomes of interest, taking into account explicit judgments about the relative importance of each outcome. The resulting four final categories for the quality of overall evidence were: "A", "B", "C" or "D" (Table M6).

Table M6. Final grade for overall quality of evidence

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

Assessment of the net health benefit across all important clinical outcomes. The net health benefit was determined on the basis of the anticipated balance of benefits and harms across all clinically important outcomes (Table M7). The assessment of net benefit also involved the judgment of the Work Group and the ERT.

Table M7. Balance of benefits and harms

When there was evidence to determine the balance of medical benefits and harms of an intervention to a patient, conclusions were categorized as follows:

- For statistically significant benefit or harm, report as "benefit [or harm] of intervention".
- For non–statistically significant benefit or harm, report as "possible benefit [or harm] of intervention".
- In instances where studies are inconsistent, report as "possible benefit [or harm] of intervention".
- "No difference" can only be reported if a study is not imprecise.
- "Insufficient evidence" is reported if imprecision is a factor.

Developing the recommendations. Draft recommendation statements were developed by the Work Group Co-Chairs and Work Group members with input from all Work Group members. The health benefits, side effects, and risks associated with each recommendation were considered when formulating the guideline, as well as information on patient preferences when available. Recommendation statements were revised in a multi-step process during face-to-face meetings and by subsequent drafts by email. All Work Group members provided feedback on initial and final drafts of the recommendation. The final draft will be distributed for external peer review and be further revised by the Work Group Co-Chairs and members. All Work Group members approved the final version of the guideline.

Grading the strength of the recommendations. The strength of a recommendation is graded as level 1 or level 2. Table M8 shows the KDIGO nomenclature for grading the strength of a recommendation and the implications of each level for patients, clinicians, and

policy makers. Recommendations can be for or against doing something. Each recommendation includes an explicit link between the quality of the available evidence and the strength of that recommendation. However, Table M9 shows that the strength of a recommendation is determined not only by the quality of the evidence but also by other, often complex judgments regarding the size of the net medical benefit (potential risks versus benefit), values, and preferences, and costs. Formal decision analyses including cost analysis were not conducted.

Table M8. KDIGO nomenclature and description for grading recommendations

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

*The additional category "Not Graded" was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Table M9. Determinants of strength of recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is warranted. The narrower the gradient, the more likely a weak recommendation is warranted.
Quality of the evidence	The higher the quality of evidence, the more likely a strong recommendation is warranted.
Values and preferences	The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a weak recommendation is warranted. Values and preferences were obtained from the literature where possible or were assessed in the judgment of the Work Group where robust evidence was not identified.
Costs (resource allocation)	The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

Ungraded statements. This category was designed to allow the Work Group to issue general advice. Typically an ungraded statement meets the following criteria: it provides guidance based on common sense, it provides reminders of the obvious, and it is not sufficiently specific to allow for application of evidence to the issue and therefore it is not based on systematic evidence review. As such, ungraded statements may be considered to be relatively strong recommendations; they should not be interpreted as weak recommendations based on limited or poor evidence. Common examples include recommendations about frequency of testing, referral to specialists, and routine medical care. We strove to minimize the use of ungraded recommendations.

This grading scheme, with two levels for the strength of a recommendation together with four levels of grading the quality of the evidence, as well as the option of an ungraded statement for general guidance, was adopted by the KDIGO Board in December 2008. The Work Group took on the primary role of writing the recommendations and rationale statements and retained final responsibility for the content of the guideline statements and the accompanying narrative. The ERT reviewed draft recommendations and grades for consistency with the conclusions of the evidence review.

Format for guideline recommendations. Each chapter contains one or more specific recommendations. Within each recommendation, the strength of recommendation is indicated as level 1 or level 2 and the quality of the supporting evidence is shown as A, B, C, or D. The recommendation statements and grades are followed by the rationale text summarizing the key points of the evidence base and the judgments supporting the recommendation. In relevant sections, considerations of the guideline statements in international settings and suggested audit criteria are also provided where applicable. Important key points and research recommendations suggesting future research to resolve current uncertainties are also outlined at the conclusion of each chapter.

Review of guideline development process

Several tools and checklists have been developed to assess the quality of the methodological process for systematic review and guideline development. These include the Appraisal of Guidelines for Research and Evaluation (AGREE 2) criteria, the Conference on Guideline Standardization (COGS) checklist,[329] and the Institute of Medicine's recent Standards for Systematic Reviews and Clinical Practice Guidelines We Can Trust. Table M10 shows the criteria which correspond to the COGS checklist and how each one is addressed in this guideline.

Table M10. The Conference on Guideline Standardization (COGS) checklist for reporting clinical practice guidelines

Topic	Description	Discussed in KDIGO 2017 Clinical Practice Guideline on HCV in Chronic Kidney Disease
1. Overview material	Provide a structured abstract that includes the guideline's release date, status (original, revised, updated), and print and electronic sources.	Abstract and Executive Summary (to be written).
2. Focus	Describe the primary disease/condition and intervention/service/technology that the guideline addresses. Indicate any alternative preventative, diagnostic or therapeutic interventions that were considered during development.	Management of the HCV in terms of treatment, monitoring, and prevention in adults with CKD, including both dialysis and transplant populations.
3. Goal	Describe the goal that following the guideline is expected to achieve, including the rationale for development of a guideline on this topic.	This CPG is intended to assist the practitioner caring for patients with CKD and HCV and to prevent transmission, resolve the infection, and prevent adverse outcomes such as death, graft loss, and progression to kidney failure while optimizing patients' quality of life.
4. User/setting	Describe the intended users of the guideline (e.g., provider types, patients) and the settings in which the guideline is intended to be used.	Target audience is practicing nephrologists and other health care providers for adults with CKD and HCV
5. Target population	Describe the patient population eligible for guideline recommendations and list any exclusion criteria.	Adults with CKD and HCV
6. Developer	Identify the organization(s) responsible for guideline development and the names/credentials/potential conflicts of interest of individuals involved in the guideline's development.	Organization: KDIGO Names/credentials/potential conflicts of interest of Work Group members involved in the guideline's development will be published in the final guideline copy.
7. Funding source/sponsor	Identify the funding source/sponsor and describe its role in developing and/or reporting the guideline. Disclose potential conflict of interest.	This guideline is funded by KDIGO. Potential conflicts of interest of Work Group members involved in the guideline's development will be published in the final guideline copy.

8. Evidence collection	Describe the methods used to search the scientific literature, including the range of dates and databases searched, and criteria applied to filter the retrieved evidence.	Topics were triaged either to a) systematic review, b) systematic search followed by narrative summary, or c) narrative summary. For systematic reviews, we searched PubMed, EMBASE, Cochrane Central Registry for trials, and Cochrane database of systematic reviews. Screening criteria for this and other topics are outlined in the *Methods for Guideline Development* chapter. The search was updated through November 2016 and supplemented by articles identified by Work Group members through January 2017. We also searched for pertinent existing guidelines and systematic reviews.
9. Recommendation grading criteria	Describe the criteria used to rate the quality of evidence that supports the recommendations and the system for describing the strength of the recommendations. Recommendation strength communicates the importance of adherence to a recommendation and is based on both the quality of the evidence and the magnitude of anticipated benefits and harms.	Quality of individual studies was graded in a three-tiered grading system (see Table M4). Quality of evidence and strength of recommendations were graded following the GRADE approach (Tables M5 and M6). The Work Group could provide general guidance in ungraded statements.
10. Method for synthesizing evidence	Describe how evidence was used to create recommendations, e.g., evidence tables, meta-analysis, decision analysis.	For systematic review topics, summary tables and evidence profiles were generated. For recommendations on interventions, the steps outlined by GRADE were followed.
11. Prerelease review	Describe how the guideline developer reviewed and/or tested the guidelines prior to release.	The guideline will undergo external public review in February 2017. Public review comments will be compiled and fed back to the Work Group, which will consider comments in its revision of the guideline.
12. Update plan	State whether or not there is a plan to update the guideline and, if applicable, an expiration date for this version of the guideline.	Following the publication of this guideline, requirement for updating will be assessed on a regular basis to determine if new evidence will lead to changes to the recommendations or may modify information provided herein.
13. Definitions	Define unfamiliar terms and those critical to correct application of the guideline that might be subject to misinterpretation.	Abbreviations and Acronyms.

14. Recommendations and rationale	State the recommended action precisely and the specific circumstances under which to perform it. Justify each recommendation by describing the linkage between the recommendation and its supporting evidence. Indicate the quality of evidence and the recommendation strength, based on the criteria described in Topic 9.	Each guideline chapter contains recommendations for the management of HCV in CKD patients. Each recommendation builds on a supporting rationale with evidence tables if available. The strength of the recommendation and the quality of evidence are provided in parenthesis within each recommendation.
15. Potential benefits and harms	Describe anticipated benefits and potential risks associated with implementation of guideline recommendations.	The benefits and harm for each comparison of interventions are provided in summary tables and summarized in evidence profiles. The estimated balance between potential benefits and harm was considered when formulating the recommendations.
16. Patient preferences	Describe the role of patient preferences when a recommendation involves a substantial element of personal choice or values.	Recommendations that are level 2 or ”discretionary,” indicating a greater need to help each patient arrive at a management decision consistent with her or his values and preferences.
17. Algorithm	Provide (when appropriate) a graphical description of the stages and decisions in clinical care described by the guideline.	Algorithm for management or treatment of HCV in CKD will be presented where appropriate.
18. Implementation considerations	Describe anticipated barriers to application of the recommendations. Provide reference to any auxiliary documents for providers or patients that are intended to facilitate implementation. Suggest review criteria for measuring changes in care when the guideline is implemented.	These recommendations are global. Local versions of the guideline are anticipated to facilitate implementation and appropriate care. Review criteria were not suggested because implementation with prioritization and development of review criteria have to proceed locally. Most recommendations are discretionary, requiring substantial discussion among stakeholders before they can be adopted as review criteria. The decision whether to convert any recommendations to review criteria will vary globally. Research recommendations were also outlined to address current gaps in the evidence base.

Abbreviations: CKD, chronic kidney disease; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HCV, hepatitis C; KDIGO, Kidney Disease: Improving Global Outcomes; RCT, randomized controlled trial.

SUPPLEMENTARY MATERIAL

Supplemental Appendix 1: Online search strategies.

Kidney and HCV module

1. exp kidney glomerulus/
2. exp kidney disease/
3. exp kidney function tests/
4. exp renal replacement therapy/
5. exp kidney transplantation/
6. exp kidney, artificial/
9. renal.af. or renal.tw.
10. nephro$.af. or nephro$.tw.
11. kidney.af. or kidney.tw.
12. ur?emia.af. or ur?emia.tw.
13. h?emodialysis.af. or h?emodialysis.tw.
13a. dialysis.tw
14. (hemofiltr$ or haemofiltr$).af. or (hemofiltr$ or haemofiltr$).tw.
15. or/1-14
16. exp Hepatitis C/
17. hepatitis c.mp.
18. hep c.tw.
19. HCV.af.
20. or/16-19
21. 15 and 20
22. limit to humans

Diagnostic tests

1. (enzyme immunoassay$ or immune, essay$ or EIA or NAT or nucleic acid amplification test$ or test$, nucleic acid or amplification technique$, nucleic acid or tech$, nucleic acid amplification)af.
2. limit 1 to yr-“2008-current”
3. (biops$, liver or liver biops$ or APRI or ((aspartate aminotransferase or ast) and platelet and (ratio or index)) or fibrotest or fibrosure or fibroscan or transient elastography or elastography, transient or elastography).af
4. 2 or 3
5. 4 not (“addresses”[pt] or “autobiography”[pt] or “bibliography”[pt] or “biography”[pt] or “case reports”[pt] or “comment”[pt] or “congresses”[pt] or “dictionary”[pt] or “directory”[pt] or “editorial”[pt] or “festschrift”[pt] or “government publications”[pt] or “historical article”[pt] or “interview”[pt] or “lectures”[pt] or “legal cases”[pt] or “legislation”[pt] or “letter”[pt] or “news”[pt] or “newspaper article”[pt] or “patient education handout”[pt] or “periodical index”[pt] or "comment on" or review[tw] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] or cow[tw] or cows[tw] or chicken*[tw] or horse[tw] or horses[tw] or mice[tw] or mouse[tw] or bovine[tw] or sheep or ovine or murine)
6. 5 and “kidney and HCV module”

Predictor studies

1. (incidence or follow-up studies or prognosis).sh or exp models, statistical or (prognos$ or predict$ or course or diagnosed).tw or cohort.mp
2. 1 not (“addresses”[pt] or “autobiography”[pt] or “bibliography”[pt] or “biography”[pt] or “case reports”[pt] or “comment”[pt] or “congresses”[pt] or “dictionary”[pt] or “directory”[pt] or “editorial”[pt] or “festschrift”[pt] or “government publications”[pt] or “historical article”[pt] or “interview”[pt] or “lectures”[pt] or “legal cases”[pt] or “legislation”[pt] or “letter”[pt] or “news”[pt] or “newspaper article”[pt] or “patient education handout”[pt] or “periodical index”[pt] or "comment on" or review[tw] OR ("Animals"[Mesh]

NOT "Humans"[Mesh]) OR rats[tw] or cow[tw] or cows[tw] or chicken*[tw] or horse[tw] or horses[tw] or mice[tw] or mouse[tw] or bovine[tw] or sheep or ovine or murine)
3. 2 and “kidney and HCV module”

DAA or non-DAA treatment
1. (telaprevir or boceprevir or danoprevir or RG$7227 or faldaprevir or BI201335 or vaniprevir or MK$7009 or sovaprevir or ACH$1625 or simeprevir or TMC435 or asunaprevir or BMS$650032 or paritaprevir or ABT$450 or grazoprevir or MK$5172 or vedroprevir or GS$9451 or daclatasvir or BMS$790052 or ombitasvir or ABT$267 or ledipasvir or GS$5885 or samatasvir or IDX$719 or elbasvir or MK$8742 or GS$5816 or ACH$3102 or sofosbuvir or GS$7977 or mericitabine or RG$7128 or valopicitabine or MK$3682 or setrobuvir or ANA598 or tegobuvir or GS$9190 or filibuvir or PF$868554 or dasabuvir or ABT$333 or deleobuvir or BI$207127 or beclabuvir or BMS$791325 or ABT$072 or GS$9669 or VX$222).af
2. ribavirin.af. or (interferon or IFN).af. or (pegylated interferon or pegylated IFN).af.
3. limit 2 to yr-“2011-current”
4. 1 or 3
5. 4 and (((pre-post[tw] or "pre test*"[tw] or pretest*[tw] or posttest*[tw] or "post test*"[tw] or (pre[tw] and post[tw]))) OR ((pre-workshop[tw] or post-workshop[tw] or (before[tw] and workshop[tw]) or (after[tw] and workshop[tw]))) OR (trial[tw] or ((study[tw] and aim*[tw]) or "our study"[tw])) OR ((before[tw] and (after[tw] or during[tw]))) OR (("quasi-experiment*" or quasiexperiment* or "quasi random*" or quasirandom* or "quasi control*" or quasicontrol* or ((quasi or experimental) and (method or study or trial or design*)))) OR (("time series" and interrupt*)) OR ((time points[tw] and (over[tw] or multiple[tw] or three[tw] or four[tw] or five[tw] or six[tw] or seven[tw] or eight[tw] or nine[tw] or ten[tw] or eleven[tw] or twelve[tw] or month*[tw] or hour*[tw] or day[tw] or days[tw] or "more than"[tw]))) OR pilot[tw]) OR "Pilot Projects"[Mesh]) OR ((clinical trial[pt] or controlled clinical trial[pt] or multicenter study[pt])) OR ((multicentre[tw] or multicenter[tw] or multi-centre[tw] or multi-center[tw])) OR (random*[tw] or controlled[tw])) OR ((control[tw] and (area[tw] or cohort*[tw] or compare*[tw] or condition[tw] or design[tw] or group[tw] or groups[tw] or grouping[tw] or intervention*[tw] or participant*[tw] or study[tw])) NOT ((("comment on" or review[tw] or review [pt])) OR (("Animals"[Mesh] NOT "Humans"[Mesh])) OR ((rat[tw] or rats[tw] or cow[tw] or cows[tw] or chicken*[tw] or horse[tw] or horses[tw] or mice[tw] or mouse[tw] or bovine[tw] or animal*[tw])))) or ("Epidemiologic Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Cohort Studies"[Mesh] or "Cross-Sectional Studies"[Mesh] OR “Case control” OR cohort OR (Follow up AND (study or studies)) OR (observational and (study or studies)) OR Longitudinal OR Retrospective OR cross section* OR cross-section* OR "Prospective Studies"[Mesh] OR "Longitudinal Studies"[Mesh] "Follow-Up Studies"[Mesh] OR (follow-up or followup)) or (systematic[sb] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy* OR metanaly* OR metaanaly* OR met analy* OR (systematic AND (review* OR overview*)) OR "Review Literature as Topic"[Mesh] OR cochrane[tiab] OR embase[tiab] OR (psychlit[tiab] or psyclit[tiab]) OR (psychinfo[tiab] or psycinfo[tiab])OR (cinahl[tiab] or cinhal[tiab]) OR science citation index[tiab] OR bids[tiab] OR cancerlit[tiab] OR reference list*[tiab] OR bibliograph*[tiab] OR hand-search*[tiab] OR relevant journals[tiab] OR manual search*[tiab] OR selection criteria[tiab] OR data extraction[tiab]) or ((pharmacokinetic or pharmacodynamic).tw or exp Clinical Trial, Phase II/ or exp Clinical Trial, Phase III/)
6. 5 and “kidney and HCV module”

Isolation
1. (isolat$ or transmi$ or quarantine or sequestra$ or segregat$ or separat$).af
2. 1 not (addresses or bibliography or biography or comment or dictionary or directory or editorial or festschrift or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or "review" or review, academic or review, tutorial)
3. 2 and “kidney and HCV module”

Transplant topics

1. exp kidney transplantation/
2. (kidney or renal).af
3. exp transplantation/
4. exp allograft/
5. 1 or (2 and (3 or 4))
6. exp Hepatitis C/
7. hepatitis c.mp.
8. hep c.tw.
9. HCV.af.
10. or/6-9
11. 5 and 10
12. limit 11 to humans
13. limit 12 to (addresses or bibliography or biography or comment or dictionary or directory or editorial or festschrift or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or "review" or review, academic or review, tutorial)
14. 12 not 13

Glomerulonephritis

1. glomerulonephritis.mp. or exp Glomerulonephritis/
2. glomerulopathy.tw.
3. immunotactoid glomerulopathy.tw
4. exp Nephrotic Syndrome/
5. exp Glomerulonephritis, Membranous/
6. glomerulonephrit$.tw.
7. exp Glomerulonephritis, Membranoproliferative/
8. membranous nephropathy.tw.
9. (IGA nephropathy or immunoglobulin A nephropathy).mp. or IGAN.tw.
10. exp Glomerulonephritis, IgA/
11. rapidly progressive glomerulonephr$.tw.
12. RPGN.tw.
13. (focal sclerosing glomerulopathy or FSGS).tw.
14. Sclerosing Glomerulonephrit$.tw. or sclerosing glomerulonephritis/
15. glomerulosclerosis.tw.
16. Mesangiocapillary Glomerulonephrit$.tw.
17. (Hypocomplementemia and Glomerulonephritis).tw.
18. Berger's disease.mp. or Bergers.tw.
19. Focal segmental glomerulosclerosis.mp. or focal segmental glomerulo$.tw.
20. Goodpasture syndrome.mp. or Goodpasture.tw.
21. Nephritis.mp. or Nephritis.tw.
22. exp Purpura, Schoenlein-Henoch/
23. (exp Antibodies, Antineutrophil Cytoplasmic/ and vasculitis/et) or (ANCA adj1 vasculitis).tw.
24. exp Glomerulosclerosis, Focal Segmental/
25. exp Nephrosis, Lipoid/
26. Minimal change nephropathy.mp.
27. minimal change disease.mp.
28. churg-strauss syndrome/ or wegener granulomatosis/
29. exp Lupus Nephritis/ or Lupus nephritis.mp.
30. renal vasculitis.tw.
31. fibrillary glomerulonephritis.tw
32. amyloidosis.tw
33. or/1-32

34. exp Hepatitis C/
35. hepatitis c.mp.
36. hep c.tw.
37. HCV.af.
38. or/34-37
39. 33 and 38
40. limit 39 to yr=”2008-current”
41. limit 40 to humans
42. limit 41 to (addresses or bibliography or biography or comment or dictionary or directory or editorial or festschrift or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or "review" or review, academic or review, tutorial)
43. 41 not 42

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