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**KDIGO 2018 Clinical Practice Guideline for the Prevention, Diagnosis,
Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease**

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KDIGO 2018 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease

- 91 KDIGO 2018 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease
Kidney Disease: Improving Global Outcomes (KDIGO) Hepatitis C Work Group





**KDIGO 2018 CLINICAL PRACTICE GUIDELINE
FOR THE PREVENTION, DIAGNOSIS, EVALUATION,
AND TREATMENT OF HEPATITIS C
IN CHRONIC KIDNEY DISEASE**



KDIGO 2018 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease

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Supplementary material is linked to the online version of the article at www.kisupplements.org.

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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 ^a	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.

^aThe additional category "not graded" is 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. They should not be interpreted as being weaker recommendations than Level 1 or 2 recommendations.

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to 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 defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. CKD is classified based on cause, GFR category (G1–G5), and albuminuria category (A1–A3), abbreviated as CGA.

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR
and albuminuria categories:
KDIGO 2012

				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
GFR categories (ml/min/1.73 m ²), description and range	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 × conversion factor = SI unit.

ALBUMINURIA CATEGORIES IN CKD

Category	AER (mg/24 h)	ACR (approximate equivalent)		Terms
		(mg/mmol)	(mg/g)	
A1	<30	<3	<30	Normal to mildly increased
A2	30–300	3–30	30–300	Moderately increased ^a
A3	>300	>30	>300	Severely increased ^b

ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease.

^aRelative to young adult level.

^bIncluding nephrotic syndrome (albumin excretion usually > 2200 mg/24 h [ACR > 2200 mg/g; > 220 mg/mmol]).

INTERPRETATION OF HCV ASSAYS

Anti-HCV	HCV-NAT	Interpretation
Positive	Positive	Acute or chronic HCV infection depending on the clinical context
Positive	Negative	Resolution of HCV infection (i.e., successfully treated or spontaneously cleared)
Negative	Positive	Early acute HCV infection; chronic HCV in the setting of immunosuppressed state; false anti-HCV negative or false HCV-NAT positive
Negative	Negative	Absence of HCV infection

Anti-HCV, HCV antibody; HCV, hepatitis C virus; NAT, nucleic acid testing.

Abbreviations and acronyms

AASLD	American Association for the Study of Liver Diseases	GRADE	Grading of Recommendations Assessment, Development and Evaluation
ALT	alanine aminotransferase	GT	genotype
Anti-HCV	HCV antibody	HAV	hepatitis A virus
APRI	aspartate aminotransferase–platelet ratio index	HBcAb	antibody to hepatitis B core antigen
ASN	American Society of Nephrology	HBsAb	antibody to hepatitis B surface antigen
AUC	area under the curve	HBsAg	hepatitis B surface antigen
BSI	bloodstream infection	HBV	hepatitis B virus
CDC	Centers for Disease Control and Prevention	HCC	hepatocellular carcinoma
CI	confidence interval	HCV	hepatitis C virus
CKD	chronic kidney disease	HIV	human immunodeficiency virus
CKD G4	chronic kidney disease GFR category 4	HR	hazard ratio
CKD G5	chronic kidney disease GFR category 5	IFN	interferon
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration	IU	international unit
CNI	calcineurin inhibitor	KDIGO	Kidney Disease: Improving Global Outcomes
CPG	clinical practice guideline	MMF	mycophenolate mofetil
CrCl	creatinine clearance	MN	membranous nephropathy
DAA	direct-acting antiviral	MPGN	membranoproliferative glomerulonephritis
DOPPS	Dialysis Outcomes and Practice Patterns Study	NAT	nucleic acid test(ing)
EASL	European Association for the Study of the Liver	NS5A	nonstructural protein 5A
eGFR	estimated glomerular filtration rate	NS5B	nonstructural protein 5B
ERT	evidence review team	OR	odds ratio
ESKD	end-stage kidney disease	PrOD (3D regimen)	paritaprevir/ritonavir/ombitasvir and dasabuvir
FDA	Food and Drug Administration	RBV	ribavirin
GFR	glomerular filtration rate	RCT	randomized controlled trial
GN	glomerulonephritis	RR	relative risk
		SVR (weeks)	sustained virologic response (at stated weeks)
		US	United States

Notice

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon literature searches last conducted in May 2017, supplemented with additional evidence through July 2018. It is designed to assist decision making. It is not intended to define a standard of care, and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Health care professionals using these recommendations should decide how to apply them to their own clinical practice.

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Foreword



Kidney International Supplements (2018) **8**, 91–165; <http://dx.doi.org/10.1016/j.kisu.2018.06.001>

With the growing awareness that chronic kidney disease (CKD) 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 virus (HCV) in the CKD population was recognized once diagnostic testing became 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 transplantation. 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 most 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 because interferon, 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 for 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 now disappeared. In addition, diagnostic testing has evolved in chronic liver disease to the extent that fibrosis can now be assessed with noninvasive techniques such as transient elastography. Because of these advances in diagnostics and therapeutics, it was deemed appropriate to undertake a comprehensive review and update of the KDIGO HCV guideline in patients with kidney disease. It has been KDIGO’s philosophy to provide recommendations based on the best available clinical evidence without direct consideration of costs, as they vary widely across countries. The recent Lancet Commission on Essential Medicines articulated the importance and challenges of providing access to safe, effective, and affordable essential medicines, including treatments for combating HCV.¹ In this vein, the World Health Organization has issued its first global report to offer practical steps to expand access for such treatments.²

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 the independent evidence review team led by Ethan Balk, MD, MPH, Craig Gordon, MD, MS, Amy Earley, BS, and Mengyang Di, MD, PhD, who made this guideline possible.

In keeping with KDIGO’s policy for transparency and rigorous public review during the guideline development process, its scope and the draft guideline were both made available for open commenting. The feedback received was carefully considered by the Work Group members who critically reviewed the public input and revised the guideline as appropriate for the final publication.

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Abstract

The *Kidney Disease: Improving Global Outcomes (KDIGO) 2018 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease* represents a complete update of the prior guideline published in 2008. This guideline is intended to assist the practitioner caring for patients with hepatitis C virus (HCV) and chronic kidney disease (CKD), including those who are on chronic dialysis therapy and individuals with a kidney transplant. Specifically, the topic areas for which new recommendations are issued include detection and evaluation of HCV in CKD; treatment of HCV infection in patients with CKD; management of HCV-infected patients before and after kidney transplantation; prevention of HCV transmission in hemodialysis units; and diagnosis and management of kidney diseases associated with HCV infection. Development of this guideline update followed an explicit process of evidence review and appraisal. Treatment approaches and guideline recommendations are based on systematic reviews of relevant studies, and appraisal of the quality of the evidence and the strength of recommendations followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Limitations of the evidence are discussed, with areas of future research also presented.

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

CITATION

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Summary of recommendation statements

Chapter 1: Detection and evaluation of HCV in CKD

1.1 Screening patients with CKD for HCV infection

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

1.1.1.1: We recommend using an immunoassay followed by nucleic acid testing (NAT) if immunoassay is positive (1A).

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

1.1.2.1: We recommend using NAT alone or an immunoassay followed by NAT if immunoassay is positive (1A).

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

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

1.2 Follow-up HCV screening of in-center hemodialysis patients

1.2.1: We recommend screening for HCV infection with immunoassay or NAT in in-center hemodialysis patients every 6 months (1B).

1.2.1.1: Report any new HCV infection identified in a hemodialysis patient to the appropriate public health authority (Not Graded).

1.2.1.2: In units with a new HCV infection, we recommend that all patients be tested for HCV infection and the frequency of subsequent HCV testing be increased (1A).

1.2.1.3: We recommend that hemodialysis patients with resolved HCV infection undergo repeat testing every 6 months using NAT to detect possible re-infection (1B).

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

1.2.2.1: We suggest that hemodialysis patients have ALT level checked monthly (2B).

1.3 Liver testing in patients with CKD and HCV infection

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

1.3.2: We recommend an initial noninvasive evaluation of liver fibrosis (1B).

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

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

1.4 Other testing of patients with HCV infection

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

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

1.4.2: If there is no evidence of kidney disease at initial evaluation, patients who remain NAT-positive should undergo repeat screening for kidney disease (Not Graded).

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

1.4.4: We recommend that all CKD patients with a history of HCV infection, whether NAT-positive or not, be screened and, if appropriate, vaccinated against hepatitis A virus (HAV) and hepatitis B virus (HBV), and screened for human immunodeficiency virus (HIV) (1A).

Chapter 2: Treatment of HCV infection in patients with CKD

2.1: We recommend that all CKD patients infected with HCV be evaluated for antiviral therapy (1A).

2.1.1: We recommend an interferon-free regimen (1A).

- 2.1.2: We recommend that the choice of specific regimen be based on HCV genotype (and subtype), viral load, prior treatment history, drug–drug interactions, glomerular filtration rate (GFR), stage of hepatic fibrosis, kidney and liver transplant candidacy, and comorbidities (1A).
- 2.1.3: Treat kidney transplant candidates in collaboration with the transplant center to optimize timing of therapy (Not Graded).
- 2.2: We recommend that patients with GFR ≥ 30 ml/min per 1.73 m² (CKD G1–G3b) be treated with any licensed direct-acting antiviral (DAA)-based regimen (1A).
- 2.3: Patients with GFR < 30 ml/min per 1.73 m² (CKD G4–G5D) should be treated with a ribavirin-free DAA-based regimen as outlined in Figure 1.
- 2.4: We recommend that all kidney transplant recipients infected with HCV be evaluated for treatment (1A).
- 2.4.1: We recommend treatment with a DAA-based regimen as outlined in Figure 1 (1A).
- 2.4.2: We recommend that the choice of regimen be based on HCV genotype (and subtype), viral load, prior treatment history, drug–drug interactions, GFR, stage of hepatic fibrosis, liver transplant candidacy, and comorbidities (1A).
- 2.4.3: We recommend avoiding treatment with interferon (1A).
- 2.4.4: We recommend pre-treatment assessment for drug–drug interactions between the DAA-based regimen and other concomitant medications including immunosuppressive drugs in kidney transplant recipients (1A).
- 2.4.4.1: We recommend that calcineurin inhibitor levels be monitored during and after DAA treatment (1B).

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

Figure 1 | Recommended direct-acting antiviral (DAA) treatment regimens for patients with chronic kidney disease (CKD) G4–G5D and kidney transplant recipients (KTRs), by hepatitis C virus (HCV) genotype^a. Duration of therapy for all above regimens is usually 12 weeks but readers should consult Association for the Study of Liver Diseases (AASLD) or European Association for the Study of the Liver guidelines for latest guidance. ^aWe recommend that CKD patients with glomerular filtration rates (GFRs) ≥ 30 ml/min per 1.73 m² (CKD G1T–G3bT) be treated with any licensed DAA regimen. ^bThere is little published evidence to guide treatment regimens in KTRs with GFR < 30 ml/min per 1.73 m² (CKD G4T–G5T). Regimens in KTRs should be selected to avoid drug–drug interactions, particularly with calcineurin inhibitors. ^cBased on Reau *et al.*³ ^dAs suggested in AASLD guidelines (<https://www.hcvguidelines.org/>). CKD G, chronic kidney disease (GFR category); HD, hemodialysis; n/a, no data or evidence available; PD, peritoneal dialysis.

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

Chapter 3: Preventing HCV transmission in hemodialysis units

- 3.1: We recommend that hemodialysis facilities adhere to standard infection control procedures including hygienic precautions that effectively prevent transfer of blood and blood-contaminated fluids between patients to prevent transmission of blood-borne pathogens (see Table 1) (*1A*).

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

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

- 3.1.1: We recommend regular observational audits of infection control procedures in hemodialysis units (*1C*).
- 3.1.2: We recommend *not* using dedicated dialysis machines for HCV-infected patients (*1D*).
- 3.1.3: We suggest *not* isolating HCV-infected hemodialysis patients (*2C*).
- 3.1.4: We suggest that the dialyzers of HCV-infected patients can be reused if there is adherence to standard infection control procedures (*2D*).
- 3.2: We recommend that hemodialysis centers examine and track all HCV test results to identify new cases of HCV infections in their patients (*1B*).
- 3.2.1: We recommend that aggressive measures be taken to improve hand hygiene (and proper glove use), injection safety, and environmental cleaning and disinfection when a new case of HCV is identified that is likely to be dialysis-related (*1A*).
- 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

- 4.1 Evaluation and management of kidney transplant candidates regarding HCV infection
- 4.1.1: We recommend kidney transplantation as the best therapeutic option for patients with CKD G5 irrespective of presence of HCV infection (*1A*).
- 4.1.2: We suggest that all HCV-infected kidney transplant candidates be evaluated for severity of liver disease and presence of portal hypertension (if indicated) prior to acceptance for kidney transplantation (*2D*).
- 4.1.2.1: We recommend that HCV-infected patients with compensated cirrhosis (without portal hypertension) undergo isolated kidney transplantation (*1B*).
- 4.1.2.2: We recommend referring HCV-infected patients with decompensated cirrhosis for combined liver-kidney transplantation (*1B*) and deferring HCV treatment until after transplantation (*1D*).
- 4.1.3: Timing of HCV treatment in relation to kidney transplantation (before vs. after) should be based on donor type (living vs. deceased donor), wait-list times by donor type, center-specific policies governing the use of kidneys from HCV-infected deceased donors, HCV genotype, and severity of liver fibrosis (*Not Graded*).
- 4.1.3.1: We recommend that all HCV-infected patients who are candidates for kidney transplantation be considered for DAA therapy, either before or after transplantation (*1A*).
- 4.1.3.2: We suggest that HCV-infected kidney transplant candidates with a living kidney donor can be considered for treatment before or after transplantation according to HCV genotype and anticipated timing of transplantation (*2B*).
- 4.1.3.3: We suggest that if receiving a kidney from an HCV-positive donor improves the chances for transplantation, the HCV NAT-positive patient can undergo transplantation with an HCV-positive kidney and be treated for HCV infection after transplantation (*2B*).

4.2 Use of kidneys from HCV-infected donors

- 4.2.1: We recommend that all kidney donors be screened for HCV infection with both immunoassay and NAT (if NAT is available) (1A).
- 4.2.2: We recommend that transplantation of kidneys from HCV NAT-positive donors be directed to recipients with positive NAT (1A).
- 4.2.3: After the assessment of liver fibrosis, HCV-positive potential living kidney donors who do not have cirrhosis should undergo HCV treatment before donation; they can be accepted for donation if they achieve sustained virologic response (SVR) and remain otherwise eligible to be a donor (*Not Graded*).

4.3 Use of maintenance immunosuppressive regimens

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

4.4 Management of HCV-related complications in kidney transplant recipients

- 4.4.1: We recommend that patients previously infected with HCV who achieved SVR before transplantation be tested by NAT 3 months after transplantation or if liver dysfunction occurs (1D).
- 4.4.2: Untreated HCV-positive kidney transplant recipients should have the same liver disease follow-up as HCV-positive non-transplant patients, as outlined in the American Association for the Study of Liver Diseases (AASLD) guidelines (*Not Graded*).
- 4.4.3: HCV-infected kidney transplant recipients should be tested at least every 6 months for proteinuria (*Not Graded*).
 - 4.4.3.1: We suggest that patients who develop new-onset proteinuria (either urine protein-to-creatinine ratio > 1 g/g or 24-hour urine protein > 1 g on 2 or more occasions) have an allograft biopsy with immunofluorescence and electron microscopy included in the analysis (2D).
- 4.4.4: We recommend treatment with a DAA regimen in patients with post-transplant HCV-associated glomerulonephritis (1D).

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

- 5.1: We recommend that a kidney biopsy be performed in HCV-infected patients with clinical evidence of glomerular disease (*Not Graded*).
- 5.2: We recommend that patients with HCV-associated glomerular disease be treated for HCV (1A).
 - 5.2.1: We recommend that patients with HCV-related glomerular disease showing stable kidney function and/or non-nephrotic proteinuria be treated initially with DAA (1C).
 - 5.2.2: We recommend that patients with cryoglobulinemic flare, nephrotic syndrome, or rapidly progressive kidney failure be treated, in addition to DAA treatment, with immunosuppressive agents with or without plasma exchange (1C).
 - 5.2.3: We recommend immunosuppressive therapy in patients with histologically active HCV-associated glomerular disease who do not respond to antiviral therapy, particularly those with cryoglobulinemic kidney disease (1B).
 - 5.2.3.1: We recommend rituximab as the first-line immunosuppressive treatment (1C).

Chapter 1: Detection and evaluation of HCV in CKD

1.1 Screening patients with CKD for HCV infection

Patients receiving maintenance hemodialysis and subgroups of CKD patients not yet on dialysis are known to have a high prevalence of 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 on 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 an immunoassay followed by nucleic acid testing (NAT) if immunoassay is positive (1A).

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

1.1.2.1: We recommend using NAT alone or an immunoassay followed by NAT if immunoassay is positive (1A).

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

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

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 an immunoassay followed by nucleic acid testing (NAT) if immunoassay is positive (1A).

Any CKD patient who has a risk factor for HCV infection should be tested.⁴ Additionally, HCV testing is warranted for the evaluation of CKD because: (i) the prevalence of HCV infection may be higher in patients with CKD not yet on dialysis than in the general population;^{5,6} (ii) HCV infection increases the risk of developing CKD;⁷ and (iii) HCV infection can accelerate progression of CKD.^{8–10}

Diagnosis of HCV infection relies on various assays.^{11,12} Serological assays that detect HCV antibody (anti-HCV) are based on enzyme immunoassays or chemoluminescence

immunoassays. Anti-HCV tests are unable to distinguish between resolved HCV infection and current HCV infection. Detection of HCV viremia relies on NAT technologies. Qualitative and quantitative HCV RNA methods are available and have similar limits of detection (10–20 international units [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).^{11,13–15}

The most usual strategy for diagnosis of HCV infection consists of initial screening with an inexpensive serological assay and, if the assay is positive, subsequent NAT. However, in high prevalence settings or very high risk groups, immediate NAT is an appropriate alternative.

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

1.1.2.1: We recommend using NAT alone or an immunoassay followed by NAT if immunoassay is positive (1A).

The prevalence of HCV infection in patients undergoing hemodialysis (CKD G5 on dialysis) is higher than in the general population^{16,17} and has been associated with the number of years one has been on hemodialysis. Patient-to-patient transmission of HCV infection in outpatient hemodialysis centers has occurred repeatedly despite widespread knowledge of this risk and published guidelines for prevention. Identification of HCV transmission within a dialysis facility should prompt immediate reevaluation of infection control practices and determination of appropriate corrective action (see Chapter 3).^{18–22} The majority of persons with HCV infection are asymptomatic, making screening necessary to detect infection in high-risk populations, particularly in 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 the United States (US) Centers for Disease Control and Prevention (CDC) and also the US Preventive Services Task Force.^{23,24} Goals of screening in this patient population include early detection of HCV infection, treatment of infection, and detection of dialysis-related transmission. HCV screening is indicated in patients starting in-center maintenance hemodialysis and also in patients who transfer from another dialysis facility or modality. In dialysis units with a high prevalence of HCV, initial testing with NAT should be considered. An anti-HCV–negative, HCV RNA–positive (i.e., NAT–positive) profile strongly suggests acute HCV infection.

Samples collected to test for HCV by NAT should be drawn before dialysis, because hemodialysis sessions reduce viremia level, although the mechanism remains unclear.²⁵

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

HCV transmission has typically been described in the context of in-center hemodialysis. In this setting, blood contamination on the hands of staff members or of medications, supplies, and equipment can contribute to HCV transmission. The current risk of health care–related HCV infection among patients who receive peritoneal dialysis or home hemodialysis has not been quantified. 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 transplantation. Determination of HCV status in recipients is essential for optimal management and potentially for acceptance of kidneys from HCV-infected donors (see Chapter 4).

1.2 Follow-up HCV screening of in-center hemodialysis patients

1.2.1: We recommend screening for HCV infection with immunoassay or NAT in in-center hemodialysis patients every 6 months (1B).

1.2.1.1: Report any new HCV infection identified in a hemodialysis patient to the appropriate public health authority (Not Graded).

1.2.1.2: In units with a new HCV infection, we recommend that all patients be tested for HCV infection and the frequency of subsequent HCV testing be increased (1A).

1.2.1.3: We recommend that hemodialysis patients with resolved HCV infection undergo repeat testing every 6 months using NAT to detect possible re-infection (1B).

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

1.2.2.1: We suggest that hemodialysis patients have ALT level checked monthly (2B).

Rationale

1.2.1: We recommend screening for HCV infection with immunoassay or NAT in in-center hemodialysis patients every 6 months (1B).

1.2.1.1: Report any new HCV infection identified in a hemodialysis patient to the appropriate public health authority (Not Graded).

1.2.1.2: In units with a new HCV infection, we recommend that all patients be tested for HCV infection and the frequency of subsequent HCV testing be increased (1A).

1.2.1.3: We recommend that hemodialysis patients with resolved HCV infection undergo repeat testing every 6 months using NAT to detect possible re-infection (1B).

Patients who are not infected with HCV should be screened for presence of new infection every 6 months.²³ This recommendation includes anti-HCV–negative patients and anti-HCV–positive, HCV RNA–negative patients screened initially by immunoassay, as well as HCV RNA–negative patients screened initially by NAT. Patients who are anti-HCV–positive and HCV RNA–negative (i.e., NAT–negative) have resolved infection but remain at risk for re-infection if exposed.²⁶ Therefore, these patients should also undergo repeat screening. For dialysis patients who are anti-HCV–positive and HCV NAT–negative, screening for HCV reinfection should be conducted every 6 months using NAT.

The purpose of the repeat screening is to identify new infections (i.e., newly acquired 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 whether there was a change in infection status indicating a new infection, and results must be communicated to the patient. Any patient with a 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. Reporting may be mandated by law, as in the US, where a documented negative HCV antibody or NAT laboratory test result followed within 12 months by a positive HCV test result (test conversion) must be reported to public health authorities.²⁷ Acute HCV infection in a hemodialysis patient should be investigated and considered health care–related until proven otherwise.²⁸ Behavioral risk factors, along with dialysis and nondialysis health care exposures, should be evaluated by public health authorities. Molecular sequencing of HCV RNA from other patients in the facility may help to identify a source.^{22,29–31}

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 patients

previously known to be uninfected should be retested for HCV infection. The frequency of repeat screening should also be increased for a limited time: for example, monthly testing for 3 months, followed by testing again in 3 months, and then resumption of screening every 6 months if no additional infections are identified.^{20,23} This strategy can help to identify delayed seroconversions (from the same exposure period as the index case) or other cases resulting from recurrent breaches. Use of this strategy has led to the detection of additional new cases in several reported outbreaks.^{22,32}

For anti-HCV-positive patients with chronic HCV infection who become HCV NAT-negative with a sustained virologic 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 that patients have serum alanine aminotransferase (ALT) level checked upon initiation of in-center hemodialysis or upon transfer from another facility (2B).

1.2.2.1: We suggest that hemodialysis patients have ALT level checked monthly (2B).

A baseline serum ALT test, followed by monthly testing, in susceptible patients has been recommended to enable early detection of new HCV infection in hemodialysis patients.²³ 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., to 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 has been assessed in a single study and found to be moderate.³³ However, ALT monitoring is an inexpensive way to ensure that hemodialysis patients are assessed for possible acquisition of infection between regular antibody or NAT screenings. Because few hemodialysis patients with a new HCV infection 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 has not been studied.

1.3 Liver testing in patients with CKD and HCV infection

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

1.3.2: We recommend an initial noninvasive evaluation of liver fibrosis (1B).

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

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

Rationale

Evaluation of liver fibrosis in HCV-infected patients with CKD. In the prior Kidney Disease: Improving Global Outcomes (KDIGO) HCV guideline published in 2008,³⁴ liver biopsy had been considered the gold standard to assess liver fibrosis in patients with CKD, including candidates for transplantation and transplant recipients. 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.

Current evidence suggests that biochemical noninvasive markers (FibroTest/FibroMeter, aspartate aminotransferase-platelet ratio index [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 as in the general population.³⁵ Noninvasive methods, especially elastography, are sufficiently reliable to detect extensive fibrosis and/or cirrhosis (F3–F4)^{36,37} though noninvasive tests other than elastography may be less accurate (Supplementary Tables S1 and S2). 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. Liver biopsy use in HCV-infected patients generally has declined.

Because SVR can now 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 necroinflammation and may even result in regression of cirrhosis, potentially resulting in decreased disease-related morbidity and improved survival.³⁸ Even in the absence of regression of cirrhosis, kidney transplantation alone is feasible in the absence of major complications of portal hypertension, just like in patients with hepatitis B virus (HBV)-related cirrhosis.³⁹

Thus, the role of liver biopsy in evaluation of liver fibrosis in HCV-infected patients with CKD G4–5 will evolve given the high SVR rates obtained with current DAA regimens. Defining the severity of cirrhosis involves assessment for clinically significant portal hypertension (hepatic-vein wedge-pressure gradient of ≥ 10 mm Hg).⁴⁰ Methods include upper endoscopy, noninvasive radiological evaluation, or direct portal pressure measurement. Based on the Baveno VI consensus,⁴¹ portal hypertension is very unlikely (and hence an upper endoscopy can be avoided with $> 90\%$ reliability) in patients with compensated cirrhosis but elastography < 20 kPa and platelet

count $> 150,000/\text{mm}^3$. 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.⁴²

1.4 Other testing of patients with HCV infection

Although HCV infection predominantly causes liver disease, it is also associated with extrahepatic manifestations including kidney disease.⁴³ HCV has been shown to infect both hepatocytes and lymphocytes; thus, lymphoproliferative disorders such as lymphoma and mixed cryoglobulinemia are linked to HCV infection.⁴⁴ 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.⁴⁵

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 HIV-infected patients.⁴⁶ A meta-analysis⁷ of observational studies^{47–55} demonstrated a relationship between anti-HCV-positive serologic status and an increased incidence of CKD in the adult general population, with an adjusted hazard ratio (HR) of 1.43 (95% confidence interval [CI]: 1.23–1.63). 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.

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

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

1.4.2: If there is no evidence of kidney disease at initial evaluation, patients who remain NAT-positive should undergo repeat screening for kidney disease (Not Graded).

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

1.4.4: We recommend that all CKD patients with a history of HCV infection, whether NAT-positive or not, be screened and, if appropriate, vaccinated against hepatitis A virus (HAV) and hepatitis B virus (HBV), and screened for human immunodeficiency virus (HIV) (1A).

Rationale

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

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

The prevalence of CKD, defined by a reduction in eGFR and/or increased urinary albumin excretion,⁵⁶ exceeds 10% in the adult general population, according to numerous population-based studies. The prevalence of low GFR alone is around 5% to 6% but increases sharply with older age. 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; the demographic/clinical characteristics of the representative patient population were variable as well. According to 3 studies performed in the US,^{47,52,55} the unadjusted prevalence of low GFR ($< 60 \text{ ml/min per } 1.73 \text{ m}^2$) ranged at baseline between 5.1% and 8.0% among middle-aged anti-HCV-seropositive individuals. The unadjusted prevalence of renal insufficiency (serum creatinine $> 1.5 \text{ mg/dl}$ [$> 133 \text{ }\mu\text{mol/l}$]) in one large study of anti-HCV-seropositive veterans from the US was 4.8%.⁵⁷ In another large cohort of HCV-positive, HIV-positive patients from North America, the unadjusted frequency of low GFR ($< 60 \text{ ml/min per } 1.73 \text{ m}^2$) at baseline ranged between 3.7% and 4.0%.⁵⁸

Kidney involvement in HCV infection was first recognized more than 2 decades ago; however, the association between HCV and CKD (low GFR or presence of proteinuria) in the adult general population was controversial until a few years ago. An increasing body of evidence has recently highlighted the detrimental impact of HCV infection on the risk of CKD (Supplementary Tables S3 and S4). One meta-analysis⁷ reported an HR of 1.43 (95% CI: 1.23–1.63) between positive HCV serologic status and increased incidence for CKD, while another recent study⁵⁹ demonstrated that patients with HCV had a 27% increased risk of CKD compared with patients without HCV. This study also revealed that HCV-positive patients experienced a 2-fold higher risk of membranoproliferative glomerulonephritis (MPGN) and a nearly 17-fold higher risk of cryoglobulinemia. Effective antiviral treatments have been shown to reduce risk for development of CKD by 30%. Cohort studies performed in patients with HIV and HCV co-infection,¹⁰ patients with diabetes,^{8,60} and patients with biopsy-proven chronic glomerulonephritis (GN)⁹ have confirmed a significant relationship between anti-HCV-positive serologic status and accelerated progression of

CKD. The prevalence of anti-HCV in serum was significantly greater in patients with CKD before reaching end-stage kidney disease (ESKD) than in a healthy population.^{5,6} Among liver transplant recipients infected with HCV who were treated with antiviral therapy, SVR led to improved eGFR in those with CKD G2 (GFR 60–89 ml/min per 1.73 m²) before treatment.⁶¹ HCV co-infection is a risk factor for increased health care resource utilization in HIV-infected individuals in the US; a multivariate Poisson model showed that HCV co-infection was associated with higher frequency of emergency department visits: adjusted relative risk (RR) 2.07 (95% CI: 1.49–2.89). In particular, emergency department visits related to kidney disease were much more common among co-infected patients (37%) than among those with HIV infection alone (10%).⁶² Another meta-analysis of observational studies⁶³ reported a relationship between positive anti-HCV serologic status and an increased risk of reduced GFR among HIV-infected individuals, with an adjusted HR of 1.64 (95% CI: 1.28–2.0), compared with those having HIV infection alone.

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 testing for proteinuria or GFR in anti-HCV-positive, HCV NAT-positive patients comes from epidemiologic data. In one study, serial measurements of eGFR and proteinuria were obtained in a large cohort of US metropolitan residents. The prevalence of CKD was greater among anti-HCV-positive, HCV NAT-positive patients compared with matched anti-HCV-negative controls (9.1% vs. 5.1%, $P = 0.04$).⁶⁴ In addition, using data from the Third National Health and Nutrition Examination Survey, at least 2 studies have observed an increased risk of albuminuria in patients with HCV.^{65,66} Classically, HCV infection predisposes to cryoglobulinemic MPGN; however, HCV-positive individuals may also be at risk for kidney injury related to decompensated cirrhosis, injection drug use, and HIV or HBV co-infection. Overall, multiple studies have now shown that HCV infection is associated with an increased risk of developing CKD, as summarized in a recent meta-analysis.⁷ It is possible that accelerated atherosclerosis also contributes to the increased risk of developing kidney disease among HCV-infected individuals.⁶⁷

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

Although studies are heterogeneous and some controversy persists,⁶⁸ overall, HCV-infected patients appear to be at greater risk for incidence and progression of kidney disease and require monitoring as outlined in the KDIGO CKD guideline.⁵⁶ 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) compared with women who were seronegative.⁶⁹

Of note, antiviral therapy for HCV significantly improves hepatic and extrahepatic outcomes in the general population^{70,71} and among patients co-infected with HIV and HCV.⁷² Six studies have addressed the impact of interferon (IFN)-based regimens on the progression of CKD.^{64,73–77} Five multivariate analyses^{64,73–76} suggested that treatment of HCV infection may improve renal survival *per se*. In a nationwide cohort study from Taiwan, patients who had received antiviral treatment (pegylated IFN plus ribavirin [RBV]) had a calculated 8-year cumulative incidence of ESKD of 0.15% versus 1.32% in untreated patients ($P < 0.001$).⁷⁵ Multivariate-adjusted Cox regression revealed that antiviral treatment was associated with lower risks of ESKD (HR: 0.15; 95% CI: 0.07–0.31). Antiviral treatment was also associated with an adjusted HR of 0.77 (95% CI: 0.62–0.97) for acute coronary syndrome, and 0.62 (95% CI: 0.46–0.83) for ischemic stroke.⁷⁵ These favorable associations were not observed in patients treated for less than 16 weeks, suggesting that shorter-duration therapy was inadequate.

In a study on 650 Japanese patients with liver cirrhosis,⁷³ multivariate Cox proportional hazards analysis showed that failure to achieve SVR was a predictor of development of CKD, with an adjusted HR of 2.67 (95% CI: 1.34–5.32). In a hospital-based study from the US, 552 HCV-infected 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 (odds ratio [OR]: 0.18; 95% CI: 0.06–0.56).⁶⁴ Finally, a recent meta-analysis of controlled and uncontrolled studies (11 studies; $n = 225$ patients) that evaluated efficacy and safety of antiviral treatment for HCV-related glomerular disease found that the summary estimate of the mean decrease in serum creatinine levels was 0.23 mg/dl (20 μ mol/l) (95% CI: 0.02–0.44) after IFN α -based therapy.⁷⁸

1.4.4: We recommend that all CKD patients with a history of HCV infection, whether NAT-positive or not, be screened and, if appropriate, vaccinated against HAV and HBV, and screened for human immunodeficiency virus (HIV) (1A).

HCV is a blood-borne pathogen and shares routes of transmission with HBV and HIV. Although hepatitis A virus (HAV) infection is frequently mild in healthy individuals, superinfection with HAV and HBV in patients with liver disease (including chronic HCV) may result in significant morbidity and mortality.⁷⁹ Thus, as HAV⁸⁰ and HBV⁸¹ are vaccine-preventable infections, appropriate vaccination should be encouraged, although response rates to vaccination are diminished in patients with advanced CKD.

Research recommendations

- Studies are needed to examine HCV antigen testing as an alternative to NAT to diagnose HCV viremic infection.
- The 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 and the additive value of ALT screening to the current generation of immunoassays or NAT testing should be investigated. Data should already exist to address this question among dialysis providers that perform routine screening of their patients. The utility of ALT testing after resolved HCV infection should be studied.
- With the availability of effective treatments for HCV, the role of DAAs in preventing and slowing the progression of CKD in HCV-infected population should be assessed.

Chapter 2: Treatment of HCV infection in patients with CKD

The recommendations are presented below by GFR category. GFR can be measured GFR or estimated GFR. 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.⁸²

Because multiple studies from the general population have found a strong correlation between mortality and SVR,⁸³ regulatory agencies such as the US Food and Drug Administration (FDA) have generally accepted SVR response as a surrogate endpoint for trials used in their drug approval process.⁸⁴ The FDA recently replaced SVR at 24 weeks after cessation of therapy (SVR24) with SVR at 12 weeks (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 HIV co-infection.⁸⁵ Currently, duration of therapy for DAA regimens is usually 12 weeks but may change in the future.

For most CKD patients, as in the general population, the potential benefits of antiviral treatment outweigh potential harms.⁸⁶ However, some patients may not be expected to live long enough to benefit from therapy (e.g., those with metastatic cancer). The Work Group was hesitant to specify a minimum life expectancy that would justify treatment, given the inaccuracy of predictions and the need to individualize this decision. However, as noted in the American Association for the Study of Liver Diseases/Infectious Diseases Society of America (AASLD/IDSA) guidance, little evidence exists to support initiation of HCV treatment in patients with a limited life expectancy (<12 months).⁸⁷

IFN is often poorly tolerated in advanced CKD (CKD G4–G5) patients who 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 G3b–G5 and can be severe. The 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 erythropoiesis stimulating agents (ESAs). Because DAAs are effective, well-tolerated, and often do not require dose reductions in those with CKD, it is clearly desirable to avoid IFN completely in all patients and to minimize use of RBV in patients with advanced CKD.

- 2.1: We recommend that all CKD patients infected with HCV be evaluated for antiviral therapy (IA).**
 - 2.1.1: We recommend an interferon-free regimen (IA).**
 - 2.1.2: We recommend that the choice of specific regimen be based on HCV genotype (and subtype), viral load, prior treatment history, drug–drug interactions, glomerular filtration rate (GFR), stage of hepatic fibrosis, kidney and liver transplant candidacy, and comorbidities (IA).**
 - 2.1.3: Treat kidney transplant candidates in collaboration with the transplant center to optimize timing of therapy (Not Graded).**
- 2.2: We recommend that patients with GFR \geq 30 ml/min per 1.73 m² (CKD G1–G3b) be treated with any licensed direct-acting antiviral (DAA)-based regimen (IA).**
- 2.3: Patients with GFR < 30 ml/min per 1.73 m² (CKD G4–G5D) should be treated with a ribavirin-free DAA-based regimen as outlined in Figure 1.**
- 2.4: We recommend that all kidney transplant recipients infected with HCV be evaluated for treatment (IA).**
 - 2.4.1: We recommend treatment with a DAA-based regimen as outlined in Figure 1 (IA).**
 - 2.4.2: We recommend that the choice of regimen be based on HCV genotype (and subtype), viral load, prior treatment history, drug–drug interactions, GFR, stage of hepatic fibrosis, liver transplant candidacy, and comorbidities (IA).**
 - 2.4.3: We recommend avoiding treatment with interferon (IA).**
 - 2.4.4: We recommend pre-treatment assessment for drug–drug interactions between the DAA-based regimen and other concomitant medications including immunosuppressive drugs in kidney transplant recipients (IA).**
 - 2.4.4.1: We recommend that calcineurin inhibitor levels be monitored during and after DAA treatment (IB).**
- 2.5: All treatment candidates should undergo testing for HBV infection prior to therapy (Not Graded).**
 - 2.5.1: If hepatitis B surface antigen [HBsAg] is present, the patient should undergo assessment for HBV therapy (Not Graded).**

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

Figure 1 | Recommended direct-acting antiviral (DAA) treatment regimens for patients with chronic kidney disease (CKD) G4–G5D and kidney transplant recipients (KTRs), by hepatitis C virus (HCV) genotype^a. Duration of therapy for all above regimens is usually 12 weeks but readers should consult Association for the Study of Liver Diseases (AASLD) or European Association for the Study of the Liver guidelines for latest guidance. ^aWe recommend that CKD patients with glomerular filtration rates (GFRs) ≥ 30 ml/min per 1.73 m² (CKD G1T–G3bT) be treated with any licensed DAA regimen. ^bThere is little published evidence to guide treatment regimens in KTRs with GFR < 30 ml/min per 1.73 m² (CKD G4T–G5T). Regimens in KTRs should be selected to avoid drug–drug interactions, particularly with calcineurin inhibitors. ^cBased on Reau *et al.*³ ^dAs suggested in AASLD guidelines (<https://www.hcvguidelines.org/>). CKD G, chronic kidney disease (GFR category); HD, hemodialysis; n/a, no data or evidence available; PD, peritoneal dialysis.

2.5.2: If HBsAg is absent but markers of prior HBV infection (HBcAb-positive with or without HBsAb) are detected, monitor for HBV reactivation with serial HBV DNA and liver function tests during DAA therapy (Not Graded).

Rationale

CKD G1–G3b (GFR ≥ 30 ml/min per 1.73 m²). For mild to moderate decreases in kidney function, patients with CKD can generally be treated as per evidence-based guidelines for the general population. Currently in the US, the AASLD/IDSA guidelines recommend few dosage modifications for people with mild to moderate reductions in GFR. For CKD G1–G3b (GFR ≥ 30 ml/min per 1.73 m²), no dosage adjustment is required when using daclatasvir (60 mg); daily fixed-dose combination of elbasvir (50 mg) and grazoprevir (100 mg); daily fixed dose combination of glecaprevir (300 mg) and pibrentasvir (120 mg); fixed dose combination of sofosbuvir

(400 mg) with either ledipasvir (90 mg) or velpatasvir (100 mg); simeprevir (150 mg); fixed-dose combination of sofosbuvir (400 mg), velpatasvir (100 mg), and voxilaprevir (100 mg); or sofosbuvir (400 mg). At the time of publication, regimens including velpatasvir have not been formally approved for use in patients with CKD G1–G3 in some jurisdictions, however.

The 2018 European Association for the Study of the Liver (EASL) guideline⁴² also recommends no dosage modifications of DAAs for CKD G1–G3 patients, but recommends that these patients should be carefully monitored.

In summary, for patients with CKD G1–G3 the choice of DAA is not restricted. However, it must be stressed that recommended drugs and dosage are constantly evolving, and clinicians should consult the latest guidelines from AASLD (<https://www.hcvguidelines.org/unique-populations/renal-impairment>) or EASL (<http://www.easl.eu/research/our-contributions/clinical-practice-guidelines>) for the most up-to-date treatment information.

CKD G4–G5 and G5D (Advanced CKD: GFR < 30 ml/min per 1.73 m² and those on hemodialysis). DAAs have variable renal elimination; thus, advanced CKD, if present, is an important determinant in the choice of agent. Until recently, patients with advanced CKD had limited options for HCV therapy. Importantly sofosbuvir, which had been the cornerstone of most DAA regimens, is predominantly renally cleared (80%) and is licensed for use only in individuals with GFR \geq 30 ml/min per 1.73 m² (CKD G1–G3b).

A regimen combining a nonstructural protein 5A (NS5A) replication complex inhibitor (elbasvir) and a new-generation nonstructural protein NS3/4A protease inhibitor (grazoprevir) has been licensed for patients infected with HCV genotypes (GTs) 1 and 4, with safety and efficacy data available in patients with advanced CKD. Both agents are metabolized by CYP3A and primarily (>90%) excreted in feces with minimal renal clearance (<1%). Although pharmacokinetic analyses show that area under the curves (AUCs) are higher in individuals with advanced CKD requiring hemodialysis (up to 46% higher compared with individuals with normal kidney function), these changes in exposure to the drugs are not considered clinically relevant.⁸⁸ Of note, Reddy *et al.*⁸⁹ identified 32 patients with CKD G3a/G3b included in trials with grazoprevir and elbasvir and found no evidence of deterioration of kidney function as a result of treatment with these agents.

Grazoprevir is a substrate of OATP1B1/3, and co-administration with drugs that inhibit OATP1B1/3 (such as enalapril, statins, digoxin, some angiotensin-receptor blockers) 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 (such as rifampin, phenytoin, and St John's wort) is contraindicated, as it may result in decreased plasma concentrations and potentially reduced antiviral activity of both agents. The Hepatitis 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.

In contrast to sofosbuvir, agents such as grazoprevir-elbasvir, paritaprevir-ritonavir-ombitasvir with or without dasabuvir, simeprevir, daclatasvir as well as glecaprevir/pibrentasvir can be safely used in CKD G4 and G5 patients (Supplementary Tables S5 and S6). Data on several regimens have been published in patients with advanced CKD (CKD G4–G5D). In the C-SURFER trial, a phase 3 placebo-controlled, randomized, multicenter trial, 12-week treatment with grazoprevir and elbasvir was evaluated in HCV GT1-infected patients with advanced CKD (81% with eGFR < 15 ml/min per 1.73 m² [CKD G5] and 76% on hemodialysis [CKD G5D]), including 6% of patients with cirrhosis.⁹⁰ The majority of them were infected with GT1a (52%), and 80% were treatment-naïve. SVR12 was 99% (95% CI: 95.3–100.0; 115 of 116), with 1 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 on dialysis therapy. Tolerability was excellent. The most common adverse events (\geq 10% frequency) were headache, nausea, and fatigue, and were comparable in the treatment versus control arms. The frequencies of hemoglobin levels < 8.5 g/dl (< 85 g/l) were also comparable between treated and untreated groups (4.5% and 4.4%, respectively), and similar proportions of patients in both groups required treatment with ESAs. 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.^{90,91} These RCT results have recently been confirmed in a real-world French cohort study.⁹² The combination of ritonavir-boosted paritaprevir with ombitasvir and dasabuvir (“PrOD” or 3D regimen) has been evaluated in a small single-arm study as well as in observational cohorts demonstrating excellent efficacy in patients infected with HCV GT1 and CKD G4 and G5.⁹³ RBV may be required when using the PrOD regimen in patients infected with HCV GT1a. However, 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 ESAs.⁹⁴

Virological factors that may impact response to HCV therapy especially in GT1a-infected patients include the presence of resistance-associated variants.⁹⁵ 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), prolonging duration of therapy to 16 weeks and the use of RBV, if possible, to avoid a reduction in SVR12 (from 99% with RBV to 88% without in 1 study) is suggested.⁹⁶

In the RUBY II trial presented at the 2016 AASLD Annual Meeting, dialysis patients with HCV GT1a were treated with ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir, and those infected with GT4 were treated with the first 2 agents without dasabuvir. RBV was not included in the regimen. Of the 13 treated subjects, 12 achieved SVR (92%). The remaining patient who discontinued antiviral therapy elected to undergo kidney transplantation.⁹⁷ 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 (CKD G4–G5), 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 or G5, 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 1 treatment failure was nonvirological (death after the end of the treatment unrelated to the treatment). The only patient who relapsed was a GT1-infected patient with advanced liver 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 nine patients due to anemia; 4 received ESAs. No blood transfusions were required.⁹⁴

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 for kidney function is needed with NS5A inhibitors such as daclatasvir and protease inhibitors such as simeprevir.

Prior to the recent introduction of glecaprevir-pibrentasvir, a sofosbuvir-based regimen had been the only option for patients with CKD G4 and G5 infected with HCV GTs 2, 3, 5, and 6, particularly those with cirrhosis and those with a history of prior nonresponse to IFN-based therapies. However, the glecaprevir-pibrentasvir regimen is pan-genotypic, with no dose reduction necessary for diminished GFR. In the EXPEDITION-4 trial, which included 104 patients with CKD G4–G5 and HCV GTs 1–6 of whom 82% were receiving hemodialysis therapy,⁹⁸ subjects received the combination of glecaprevir, a protease inhibitor, and pibrentasvir, an NS5A inhibitor, for 12 weeks. Forty-two percent of subjects had been treated previously, including 2 who had received sofosbuvir-based therapy; 19% of patients had compensated cirrhosis. SVR12 was 98%; of the 2 patients who did not achieve SVR, 1 received only 4 weeks of therapy and the other died of an unrelated cause shortly after completion of therapy. Detection of resistance-associated variants, present in 29% of subjects, did not impact SVR, although HCV GT 3 patients with prior therapy failure had been excluded from inclusion.

We recognize that preferred regimens such as grazoprevir-elbasvir and glecaprevir-pibrentasvir for CKD G4–G5D patients may not be available in some countries or regions, and sofosbuvir-based regimens may be all that is available despite the fact that they are not licensed for use in CKD G4–G5D patients. Sofosbuvir 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, and the 4-hour hemodialysis extraction ratio is about 53%.⁹⁹ For creatinine clearance (CrCl) < 30 ml/min, pharmacokinetics data showed marked plasma overexposure of sofosbuvir (AUC_{0-IFN} 171% higher), and particularly SOF-007 (AUC_{0-IFN} 451% higher) after a single dose of 400 mg, as compared with subjects with normal kidney function.¹⁰⁰

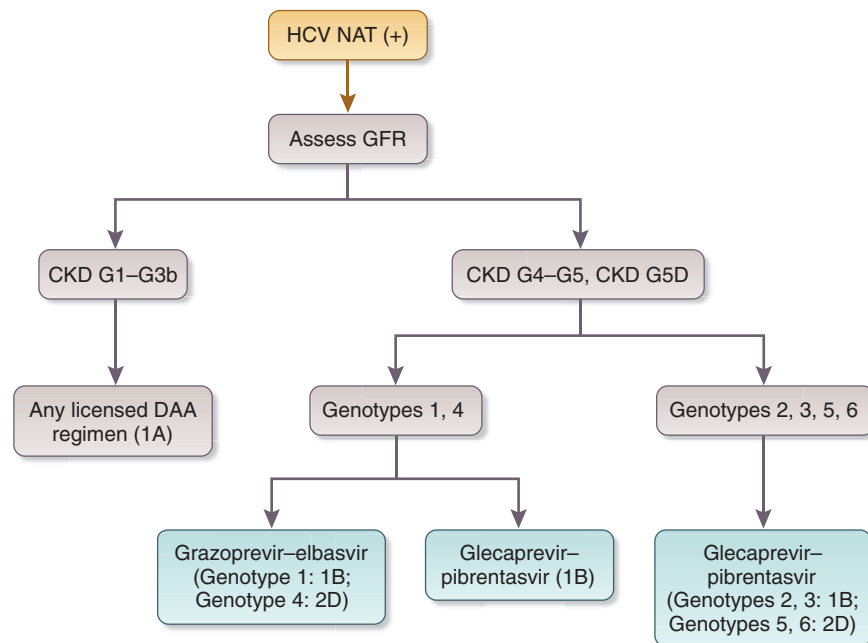
Despite these pharmacokinetics studies, there are preliminary data with sofosbuvir-based regimen in CKD patients suggesting that sofosbuvir with a daily or 3-times weekly regimen is safe and well tolerated in HCV-infected patients, most with cirrhosis, who require hemodialysis.^{100–107} In a recent 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.¹⁰⁵ 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.

Additional experience with reduced sofosbuvir doses, such as 200 mg daily or 400 mg 3 times weekly, suggests 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 advanced CKD (9 infected with HCV GT1 and 1 with HCV GT3, all with CrCl < 30 ml/min) receiving sofosbuvir, 200 mg daily, combined with RBV, 200 mg daily.¹⁰⁰ This schedule resulted in 6 relapses in HCV GT1-infected patients. In 2 case reports, Perumpail *et al.* reported the successful treatment of 2 liver transplant patients on hemodialysis therapy who received sofosbuvir, 200 mg and 400 mg daily, respectively, with simeprevir at standard dose.^{103,104} Bhamidimarri *et al.*¹⁰⁶ evaluated 2 different schedules in 15 patients with advanced CKD ($n = 3$) or requiring hemodialysis ($n = 12$). Eleven patients received sofosbuvir, 200 mg daily, and 4 patients received sofosbuvir, 400 mg 3 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.¹⁰² Very recently, a larger study ($n = 50$) also suggested that sofosbuvir-based antiviral therapy, with a reduced dose of sofosbuvir, is reasonably safe and effective for the treatment of HCV patients with ESKD, including hemodialysis patients.¹⁰⁸

Use of full-dose off-label use of sofosbuvir daily has been reported in HCV patients on dialysis and in those at high risk of treatment failure such as those with cirrhosis, previously pretreated or nonresponders and those infected with GT3. Such patients should be closely monitored, with clinical, biological, and cardiac assessment.¹⁰⁹

A related and unresolved issue is whether use of sofosbuvir in patients with advanced CKD may accelerate its progression. Most of the studies that examined this issue were conducted in patients with moderate CKD. Gonzalez-Parra and colleagues¹¹⁰ observed a significant mean decrease in GFR of 9 ml/min per 1.73 m² in 35 patients treated with a sofosbuvir-based regimen with a baseline GFR of 30 to 60 ml/min per 1.73 m², whereas no significant decline in GFR occurred in 8 patients treated with the PrOD regimen. Rosenblatt *et al.*¹¹¹ also reported that in a series of 90 patients, a baseline CrCl < 60 ml/min 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 eGFR ≤ 45 ml/min per 1.73 m² treated with sofosbuvir.¹⁰⁷ Mallet *et al.*,¹¹² in a retrospective study of 814 HCV patients mostly with baseline eGFR ≥ 60 ml/min per 1.73 m², reported a mean eGFR decrease of 2.6 and 1.7 ml/min per 1.73 m² over a maximum of 37 months in patients treated with sofosbuvir-based and non-sofosbuvir-based regimens, respectively. In contrast, Sise



Algorithm 1 | Treatment scheme for chronic kidney disease (CKD) G1–G5D. Recommendation grading is provided for each specific treatment regimen and hepatitis C virus (HCV) genotype. CKD G, chronic kidney disease, GFR category; DAA, direct-acting antiviral; GFR, glomerular filtration rate; NAT, nucleic acid testing.

*et al.*¹¹³ recently reported that in patients with CKD G3a–G3b who received sofosbuvir-based regimens, HCV cure was associated with a 9.3 ml/min per 1.73 m² improvement in eGFR during the 6-month post-treatment follow-up period. Despite these conflicting findings, if a sofosbuvir-based regimen is selected, monitoring of kidney function should be performed with serial serum creatinine measurements during therapy, although it is unclear whether dose reduction or withdrawal is indicated if GFR declines further.

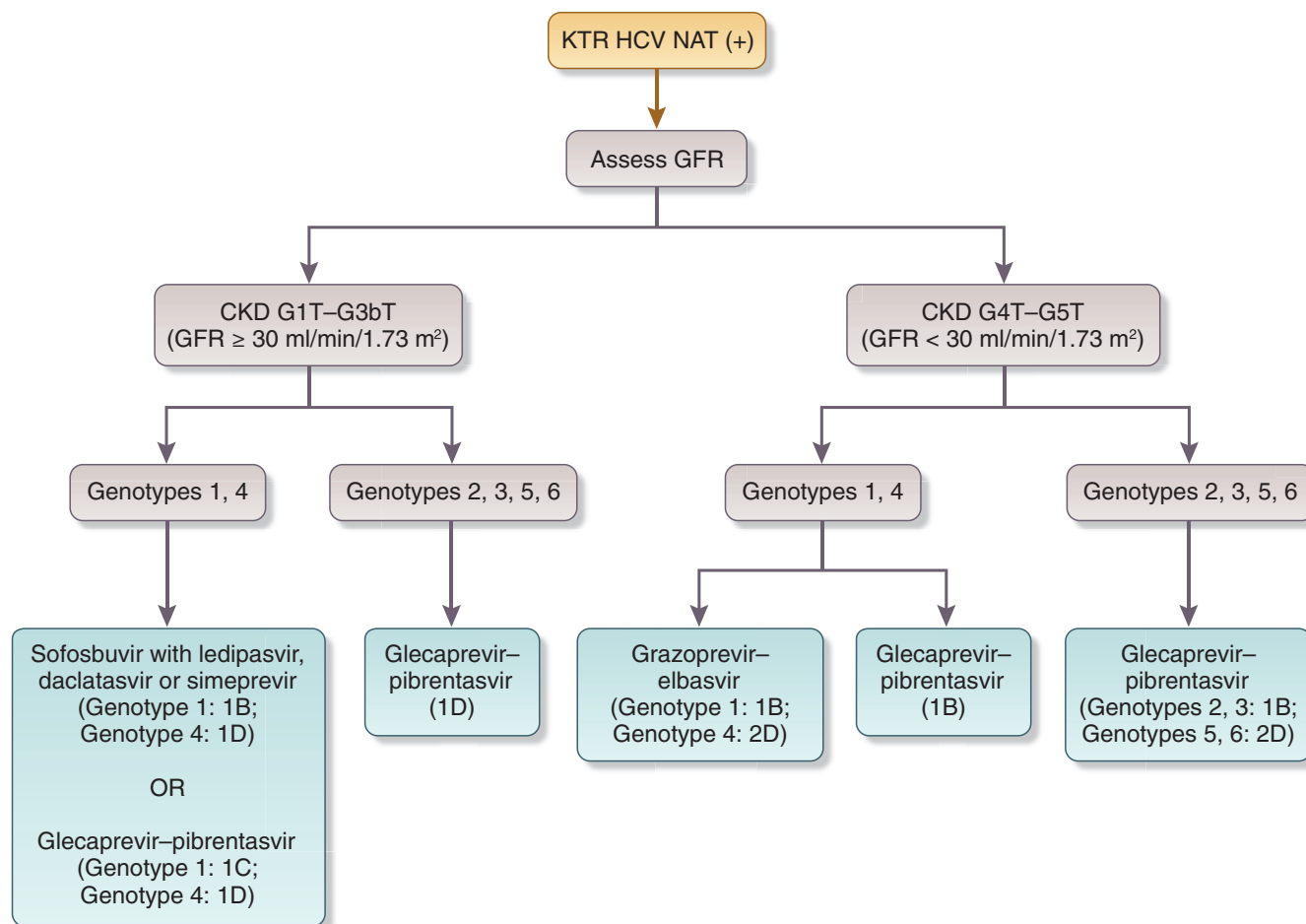
Algorithm 1 summarizes the recommended choice of DAAs according to the level of kidney function and HCV GT. The Work Group recognizes that not all preferred regimens are available in all jurisdictions, and as such we have also recommended alternate regimens to provide further potential treatment options. There is no evidence to support specific DAA regimens in patients on peritoneal dialysis, but it is reasonable to follow guidance for patients on hemodialysis.¹¹⁴

In summary, we recommend that patients with CKD G4–G5 and G5D be treated with a RBV-free DAA-based regimen. Glecaprevir-pibrentasvir has pan-genotypic efficacy including in patients with prior sofosbuvir treatment and cirrhosis. Grazoprevir-elbasvir and the PrOD regimen are also approved for use in CKD G4–G5 and G5D patients with GTs 1 and 4. Although there are studies reporting the use of sofosbuvir in patients with CKD G4–G5D, in jurisdictions where there is availability of well-tolerated regimens (i.e., grazoprevir-elbasvir and glecaprevir-pibrentasvir), its use is not recommended given the limited information about its safety in this population. Our guidance is in general concordance with those provided by AASLD (<https://www.hcvguidelines.org/unique-populations/renal-impairment>) and EASL (<http://www.easl.eu/research/our-contributions/clinical-practice-guidelines>), but given that recommended drugs and dosage are constantly evolving, clinicians should consult these resources for the most up-to-date treatment information.

*et al.*¹¹³ recently reported that in patients with CKD G3a–G3b who received sofosbuvir-based regimens, HCV cure was associated with a 9.3 ml/min per 1.73 m² improvement in eGFR during the 6-month post-treatment follow-up period. Despite these conflicting findings, if a sofosbuvir-based regimen is selected, monitoring of kidney function should be performed with serial serum creatinine measurements during therapy, although it is unclear whether dose reduction or withdrawal is indicated if GFR declines further.

Kidney transplant recipients: CKD G1T–G5T (see also Chapter 4). Although published data on DAAs in kidney transplant recipients are less abundant,¹¹⁵ the study results seem as satisfactory as those observed in liver transplant recipients (Supplementary Tables S7 and S8). In a recent trial comparing 12 and 24 weeks of sofosbuvir and ledipasvir in 114 kidney transplant recipients infected with HCV GTs 1 and 4 (96% GT1) with an eGFR of 40 ml/min per 1.73 m² or greater (median eGFR 56 ml/min per 1.73 m²), the 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.¹¹⁶ Smaller cohort studies recently also reported excellent results in kidney transplant recipients with sofosbuvir-based regimens.^{117–119} Sofosbuvir/velpatasvir has also been shown to be highly effective and well tolerated in liver transplant recipients with GTs 1–4 and may be considered for kidney transplant recipients in the future, although at the present, efficacy and safety data for the latter group are lacking.¹²⁰ Reau *et al.*³ have recently described the use of glecaprevir/pibrentasvir in 100 organ transplant recipients, 20 of whom had received a kidney transplant with high SVR and excellent tolerability.

In transplant recipients, drug–drug interactions with immunosuppressive agents may result in increased or diminished plasma levels of immunosuppressive agents, with



Algorithm 2 | Treatment scheme for kidney transplant recipients (KTRs). Recommendation grading is provided for each specific treatment regimen and hepatitis C virus (HCV) genotype. Chronic kidney disease (CKD) G, CKD glomerular filtration rate (GFR) category (suffix T denotes transplant recipient); NAT, nucleic acid testing.

consequent 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, tacrolimus, and everolimus. There are no significant drug-drug interactions with these protease inhibitors and mycophenolate mofetil (MMF). No significant interactions between NS5A and polymerase inhibitors such as sofosbuvir and calcineurin inhibitors (CNIs) have been described, but close monitoring of immunosuppressive drugs is mandatory because changes in liver metabolism concurrent with HCV eradication may require modification of immunosuppressive drug doses.

Overall, drug-drug interactions are an important factor in 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 CNIs and mTOR inhibitors.^{93,121}

Nonstructural protein 5B (NS5B) inhibitors such as sofosbuvir or 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 Hepatitis 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.

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, it may be better to receive a kidney transplant from an HCV-positive donor than to face a long wait for an HCV-negative kidney. It has been suggested that an HCV-positive transplant candidate should forego treatment of HCV until after kidney transplantation, to allow receipt of a kidney transplant from an HCV-positive deceased donor. Adoption of this strategy would expand the deceased donor organ pool as well as diminish wait times as suggested by Kucirka *et al.*¹²²

If an HCV-negative transplant candidate has a potential living donor who is HCV NAT-positive, then it seems reasonable for the donor to be treated for HCV, and donate the kidney after SVR has been achieved. Because 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. Another consideration is the use of a kidney from an HCV NAT-positive donor in an HCV-negative recipient with prompt DAA treatment after transplant, as recently reported by Goldberg *et al.*¹²³ and Durand *et al.*¹²⁴ in 2 encouraging small case series. This approach requires further study before it can be endorsed.

In summary, kidney transplant recipients with GFR \geq 30 ml/min per 1.73 m² (CKD G1T–G3bT) and HCV GTs 1 or 4 can utilize sofosbuvir-based regimens and glecaprevir-pibrentasvir. For those with HCV GTs 2, 3, 5, and 6, we recommend glecaprevir-pibrentasvir. For kidney transplant recipients with GFR < 30 ml/min per 1.73 m² (CKD G4T–G5T), the same regimens proposed for patients with CKD G4–G5D apply (i.e., grazoprevir-elbasvir for GTs 1 and 4 and glecaprevir-pibrentasvir for all GTs). Our guidance is in general concordance with those provided by AASLD (<https://www.hcvguidelines.org/unique-populations/kidney-transplant>) and EASL (<http://www.easl.eu/research/our-contributions/clinical-practice-guidelines>), but given that recommended drugs and dosage are constantly evolving, clinicians should consult these resources for the most up-to-date treatment information. Algorithm 2 summarizes the recommended choice of DAAs for kidney transplant recipients according to the level of kidney function and HCV GT.

Reactivation of HBV infection after DAA therapy. A number of reports have recently described apparent reactivation of HBV infection in individuals following successful therapy of HCV infection with DAA-based therapy.^{125,126} This has

prompted an FDA warning.¹²⁷ As part of routine evaluation of patients with HCV and CKD, serum markers of HBV infection (i.e., hepatitis B surface antigen [HBsAg] and HBV DNA) should be obtained prior to antiviral therapy. Initiation of therapy with an oral HBV suppressive agent is recommended if criteria for HBV therapy are met, based on initial testing prior to HCV therapy or during follow-up after HCV. If HBsAg is initially absent but markers of prior HBV infection (positive antibody to hepatitis B core antigen [HBcAb-positive] with or without antibody to hepatitis B surface antigen [HBsAb]) are detected, patients should be monitored for HBV reactivation with serial HBV DNA and liver function tests during DAA therapy (see also <https://www.hcvguidelines.org/evaluate/monitoring>).

Research recommendations

- Further studies should be conducted on whether RBV is required after kidney transplantation in some specific groups such as prior nonresponders infected with HCV GT1a. Treatment of NS5A-resistant variants after kidney transplantation should also be evaluated.
- Optimal timing of antiviral therapy before or after transplantation in candidates for kidney transplantation should be clarified. Because the time to transplantation with kidneys from deceased donors is unpredictable, delaying treatment carries higher vascular, metabolic, and malignancy risks as well as the risk of drug–drug interactions with CNIs after transplantation. As such, treatment before transplantation may be more appropriate. However, in regions where the prevalence of anti-HCV-positive donors is high, post-kidney transplant therapy should be considered.
- Use of organs from HCV-positive donors for HCV-negative recipients with DAA therapy needs to be further explored.
- The impact of treating HCV infection on CKD progression should be further 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 (see Table 1) (1A).

3.1.1: We recommend regular observational audits of infection control procedures in hemodialysis units (1C).

3.1.2: We recommend *not* using dedicated dialysis machines for HCV-infected patients (1D).

3.1.3: We suggest *not* isolating HCV-infected hemodialysis patients (2C).

3.1.4: We suggest that the dialyzers of HCV-infected patients can be reused if there is adherence to standard infection control procedures (2D).

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

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

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.¹²⁸ HCV prevalence rates range from about 4%–9% in most high-income countries, but is significantly higher in other countries,

particularly those in the Middle East, North and Sub-Saharan Africa, Asia, and Eastern Europe^{16,129,130,131} (Table 2). Rates also vary during times of social crisis, war, or economic downturn.^{132–134} 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 per 100 patient-years: 4.44 per 100 patient-years in low- to middle-income countries, and 0.99 per 100 patient-years in high-income countries.¹³⁵

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 ESAs,¹³⁶ leaving nosocomial transmission as the main method of spread of HCV in dialysis units. Several studies have confirmed nosocomial transmission in dialysis units using epidemiologic and phylogenetic data obtained by viral sequencing.^{21,34,137–140} 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 using sensitive, specific new-generation serological tests.^{17,141} 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 other European countries including France (42% to 30%), Italy (28% to 16%), and Sweden (16% to 9%).¹⁴¹ Table 2 provides an overview of HCV prevalence in hemodialysis patients as summarized from some recent studies.

Nevertheless, more than 50% of all health care–associated HCV outbreaks from 2008 to 2015 reported to the CDC occurred in hemodialysis settings.¹⁴² As a result, the CDC recently provided guidance on improving infection control practices to stop HCV transmission in dialysis units.¹⁴³

Infection control. Infection control lapses responsible for HCV transmission contribute to transmission of other pathogens; hence implementation of improvement efforts will

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

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

Table 2 | Recent reported HCV prevalence in hemodialysis patients

Country	N	Year of testing	HCV prevalence (%)	Source
Australia-New Zealand	393	2012	3.8	DOPPS 5 ¹⁴⁷
Belgium	485	2012	4.0	DOPPS 5 ¹⁴⁷
Brazil	798	2011	8.4	Rodrigues de Freitas ¹⁴⁸
Canada	457	2012	4.1	DOPPS 5 ¹⁴⁷
China	1189	2012	9.9	DOPPS 5 ¹⁴⁷
Cuba	274	2009	7.6	Santana ¹⁴⁹
Egypt	–	2007–2016	5.0	Ashkani-Esfahan ^{149a}
France	501	2012	6.9	DOPPS 4 ¹⁴⁷
Germany	584	2012	4.5	DOPPS 5 ¹⁴⁷
Gulf Cooperation Council	910	2012	19.3	DOPPS 5 ¹⁴⁷
India	216	2012	1.6	NephroPlus
	1050	2013	1.1	
	3068	2014	0.8	
Iran	–	2006–2015	1.2	Ashkani-Esfahan ^{149a}
Iraq	–	2008–2015	2.0	Ashkani-Esfahan ^{149a}
	7122	2015	1.0	
	7673	2016	0.9	
Italy	485	2012	11.5	DOPPS 5 ¹⁴⁷
Japan	1609	2012	11.0	DOPPS 5 ¹⁴⁷
Jordan	–	2007–2015	3.5	Ashkani-Esfahan ^{149a}
Lebanon	3769	2010–2012	4.7	Abou Rached ¹⁵⁰
Libya	2382	2009–2010	31.1	Alashek ¹⁵¹
Nigeria	100	2014	1.5	Ummate ¹⁵²
Palestine	–	2010–2016	1.8	Ashkani-Esfahan ^{149a}
Romania	600	2010	27.3	Schiller ¹⁵³
Russia	486	2012	14.0	DOPPS 5 ¹⁴⁷
Saudi Arabia	–	2007	1.9	Ashkani-Esfahan ^{149a}
Senegal	106	2011	5.6	Seck ¹⁵⁴
Syria	–	2009	5.4	Ashkani-Esfahan ^{149a}
Spain	613	2012	8.9	DOPPS 5 ¹⁴⁷
Sweden	426	2012	6.0	DOPPS 5 ¹⁴⁷
Turkey	383	2012	7.0	DOPPS 5 ¹⁴⁷
United Kingdom	397	2012	4.6	DOPPS 5 ¹⁴⁷
United States	2977	2012	7.3	DOPPS 5 ¹⁴⁷

DOPPS, Dialysis Outcomes and Practice Patterns Study; HCV, hepatitis C virus.

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.

Three systematic reviews have examined the reasons behind transmission of HCV in hemodialysis units.^{34,140,144} Root cause analysis of confirmed nosocomial outbreaks^{22,29,31,145,146} 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 3). Other causes of infection such as undergoing dialysis during travel to developing countries, and nondialysis health care exposures (e.g., procedures performed in a common vascular access surgical center) can occur and

Table 3 | Factors and 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 1 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

HCV, hepatitis C virus.

are considered before concluding that transmission occurred in the dialysis unit.

Mishandling of parenteral medications has been implicated frequently 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. The US CDC's *One & Only Campaign* on safe injection practices (<http://www.oneandonlycampaign.org/>) should help address the former issue by promoting single use of syringes. The latter issue concerning contamination 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 hand washings of dialysis personnel.^{155–161} Blood that is visible or not visible to the naked eye, as evidenced by chemical tests, has also been detected on dialysis treatment station surfaces that underwent routine cleaning procedures following an outbreak of HCV.²¹ HCV can persist in an infectious state for at least 16 hours, and potentially much longer, on surfaces at room temperature.^{160,162} Hand hygiene also plays an important role in prevention of nosocomial transmission.¹⁶³ Lack of adherence to standard practices, such as hand-washing and glove use and removal practices, has been documented in several audits. In most HCV outbreaks in US hemodialysis centers reported to the CDC, multiple lapses in infection control were identified, involving practices such as hand hygiene and glove use, injectable medication handling, and environmental surface disinfection.¹⁴²

Petrosillo *et al.*¹⁶⁴ conducted a multicenter study in 58 Italian hemodialysis centers and found that the adjusted 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. A study of 87 US hemodialysis centers similarly found that baseline HCV prevalence of greater than 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.¹⁶⁵

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 1. The CDC has checklists and audit tools to assist facilities in implementing and assessing many of these practices.¹⁶⁶

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, including the use of a dedicated dialysis machine, personnel, room, or shift, and/or other barrier precautions (e.g., aprons, gowns, or gloves) by health care professionals attending these patients.

Whereas the complete isolation of HBV-infected patients (by room, thus including machine, equipment, and staff) has proven invaluable in halting the nosocomial transmission of HBV within hemodialysis units,¹⁶⁷ there are multiple reasons that argue against recommending isolation of HCV-positive patients:¹⁶⁸

- (i) 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 (BSIs) or transmission of multi-drug resistant organisms or other blood-borne pathogens.
- (ii) Segregating patients on the basis of HBV and HCV would create four separate cohorts, which creates a significant logistic challenge. The treatment of HCV infection in dialysis patients raises an additional logistical difficulty of how to cohort patients undergoing therapy.
- (iii) Isolating only on HCV infection status may expose the isolated patient to infection with a second HCV GT.
- (iv) HCV seroconversion may be delayed for several months in newly infected hemodialysis patients and serological testing cannot be relied on to exclude recent infection.¹⁶⁹
- (v) Starting and maintaining isolation is likely to impose large costs on already expensive dialysis programs.

The evidence for the use of isolation of HCV-infected patients during hemodialysis is weak, based on very low-quality evidence (Supplementary Tables S9 and S10). The KDIGO 2008 HCV guideline³⁴ 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 health care-acquired transmission, where a local isolation policy may be deemed necessary).

A recent Cochrane review¹⁷⁰ examined the impact of isolation as a strategy for controlling transmission of HCV infection in hemodialysis units. Of the 123 full-text articles

identified, the authors could find only 1 randomized controlled trial (RCT).¹⁷¹ 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. 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 versus nondedicated machines (calculated using chi-square test), based on a more standard risk ratio analysis, the Cochrane review concluded that the use of dialysis machines dedicated for HCV-infected individuals, as compared with the use of nondedicated machines made no difference in terms of reducing the incidence of HCV infection during the follow-up period. In addition, the quality of evidence was rated as “very low” due to several methodological issues.

Other studies examining isolation as a means of reducing HCV transmission reported a reduction of transmission, but they were observational and had very poor-quality evidence with methodological challenges.^{172–174} The isolation policies studied included implementing the isolation or cohorting of infected patients in a separate room; using exclusive machines; or employing dedicated machines, room, and staff. Most studies have adopted a “before-and-after” design, and compared their results with their own historical controls.^{175–178} Thus, it is unclear whether the reported improvement resulted from the isolation policy or rather from the simultaneous raising of awareness and reinforcement of the application of hygienic precautions. Furthermore, in some studies, there might be other contributing factors such as changes in baseline prevalence and injection safety and hygienic practices over time.

In contrast to these studies, a DOPPS (Dialysis Outcomes and Practice Patterns Study) multicenter study and an Italian multicenter study both concluded that isolation did not protect against transmission of HCV in hemodialysis patients,^{16,164} and some prospective observational studies have shown reduction of transmission after adoption of universal precautions.¹⁷⁹ 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.¹⁸⁰

The CDC does not recommend the isolation of HCV-infected patients in its infection-prevention guidelines.²³ The UK Renal Association also states that patients with HCV do not need to be dialyzed 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.¹⁸¹ The European Best Practice Work Group considers implementation of universal hygienic measures to be the standard of care.¹⁸²

Finally, several experts and guidelines acknowledge that because transmission can be effectively prevented by adherence to currently recommended practices, considering isolation of seropositive patients indicates a 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.

Dedicated dialysis machines. Evidence of HCV transmission through internal pathways of the modern single-pass dialysis machine has not been demonstrated.³⁴ Transmission would require the virion to cross the intact dialyzer membrane, migrate from the drain tubing to the fresh dialysate circuit, and pass again through the dialyzer membrane of a second patient. However, 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 back-filtration 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.²¹

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.¹⁸³ 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, and 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, or prime waste container) are lapses commonly identified in these outbreaks. In some investigations, transmission involving the dialysis machine was essentially ruled out.¹³⁷ 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, diminishing the purported value of using dedicated machines. Similar to the concern about the risks of isolating dialysis patients with HCV, it should be stressed that using dedicated machines may trigger the perception that there is no longer a risk of nosocomial HCV transmission and thus reduce the attention devoted by hemodialysis staff members to body fluid precautions.

Table 4 | 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 or 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 (e.g., between modules or behind the 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.

Reuse. During the reuse procedure, patient-to-patient transmission can take place if the dialyzers or blood port caps are switched between patients and not sterilized effectively or 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 labeling. Two large studies have not identified reuse as a risk factor for HCV transmission,^{180,184} whereas a weak association was shown in 1 study, likely due to unmeasured confounders.¹⁸⁵

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 guideline³⁴ 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.²³ 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 events³⁴ (Table 4). We reaffirm our previous recommendation.

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 the CDC or the dialysis company) as part of their continuous quality improvement process.

Although there are no RCTs that examined 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 BSIs following implementation of regular audits and an evidence-based intervention

package. In a study from the US, 17 centers reported monthly event and denominator data to the National Healthcare Safety Network 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. Modeled rates decreased 32% ($P < 0.01$) for BSIs and 54% ($P < 0.001$) for access-related BSIs.¹⁸⁶ In a follow-up study, the reduction in access-related BSI rates was sustained for 4 years after the initial intervention implementation.¹⁸⁷ 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 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 1 particular outcome, such as HCV transmission, and permits wider implementation of infection control measures.

Audits done in other dialysis center studies routinely show suboptimal adherence to hygienic practices. A Spanish study showed that gloves were used on 93% of occasions, and hands were washed only 36% of the time after patient contact and only 14% of the time before patient contact.¹⁸⁸ In a 2002 US survey, only 53% of US outpatient ESKD 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.¹⁸⁴ A survey of 420 dialysis personnel from 45 facilities reported on hand hygiene practices and knowledge regarding HCV infection risk.¹⁸⁹ 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, 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, when 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. The CDC recommends that 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 changes. 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.¹⁹⁰ 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.

It is known that hand hygiene practices improve when study participants are aware they are under observation. 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.¹⁹¹ 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. The CDC recommends that all maintenance hemodialysis patients be screened for anti-HCV and ALT level upon admission and that anti-HCV testing be repeated semiannually and ALT testing be repeated monthly for susceptible patients.¹⁹² This is discussed in Chapter 1. Detection of seroconversions should prompt an aggressive evaluation of infection control practices to correct lapses and prevent additional cases from occurring (Table 5).²⁸ Importantly, HCV screening should not be used as a substitute for regular infection control audits.

Infrastructure requirements. Audit data show that despite the existence of guidelines to prevent transmission of infections in hemodialysis units, their implementation remains suboptimal, leading to a large preventable burden of infections that not only adversely impacts clinical outcomes, but imposes large costs on the health care system. Experience from public health interventions shows that interventions

Table 5 | Steps to initiate concurrently and undertake following identification of a new HCV infection in a hemodialysis patient (adapted from CDC Health Alert²⁸)

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- A. Report the infection to appropriate public health authority.
- Assess risk factors of the affected patient in conjunction with public health.
- B. Determine HCV infection status of all patients in the hemodialysis unit.
- 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 those subsequently transferred or discharged may be warranted.
- C. Conduct a thorough root cause analysis of the infection and address infection control lapses.
- 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.
 - Share findings with all staff members and take action to address lapses. Staff education and retraining may be necessary.
 - 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.
 - Conduct regular audits to ensure improved adherence to recommended practice.
 - Demonstrations of cleaning adequacy such as use of Glo Germ™ (Moab, UT) 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.
-

CDC, Centers for Disease Control and Prevention; HCV, hepatitis C virus.

that depend on behavior change require large effort, which can undermine their impact. In contrast, making systemwide changes, such as imposition of regulations and creating an environment that discourages unhealthy behavior, is likely to have greater impact. This impact has been shown in many fields such as smoking cessation and containing HIV infection.¹⁹³ Examples in the 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 the National Healthcare Safety Network are critical for

comparisons and to facilitate interventions. Other systemwide changes that are likely to have a 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

Table 6 | 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-to-patient ratio (e.g., 1:4 in France). Formal health care 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.

The following are useful CDC and WHO 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-508.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>

http://www.who.int/gpsc/5may/hh_guide.pdf (See Figure 9 of document and pp. 44–49)

CDC, Centers for Disease Control and Prevention; US, United States; WHO, World Health Organization.

Table 7 | Key hygienic precautions for hemodialysis staff^a**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 techniques) 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 or 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 4)

- Single-use items required in the dialysis process should be disposed of after use on 1 patient.
- Nondisposable items should be disinfected after use on 1 patient. Items that cannot be disinfected easily (e.g., adhesive tape and tourniquets) should be dedicated to a single patient and discarded after use.
- The risks associated with use of physiologic monitoring equipment (e.g., blood pressure monitors, weight scales, and 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.

^aIn addition to standard precautions.

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 are 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 6). Table 7 provides a summary of important hygienic precautions for hemodialysis center staff to follow.

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.¹³⁹ A study that

modeled HCV transmission in hemodialysis centers found that HCV prevalence influenced incidence (as did staff-to-patient ratio), but the compliance rate with hand hygiene and glove change between patients was a much stronger determinant of transmission.¹⁶³ 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 are likely to have a deleterious effect on observance of routine infection control practices, leading to paradoxically increased risk of transmission. Furthermore, reliance on HCV treatment to prevent transmission goes against the principle of treating patients primarily for their individual benefit. Use of treatment alone as an infection control measure might place patients at increased risk of HCV and other blood-borne infections from other sources.

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.¹⁸⁹ Personnel also were much more likely to report knowing how to protect themselves from acquiring a blood-borne 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.*¹⁸⁸ 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 7). As mentioned above, implementation is more likely when guidelines are accompanied by changes in regulations.

Research recommendations

- Further observation studies should be conducted to ascertain features of facilities that do not have incident cases (e.g., staffing, physical layout, policies and practices, and baseline prevalence).
- Large, multicenter long-term RCTs of good quality are required to answer the questions concerning the benefits and harms of isolating HCV-positive patients during hemodialysis. These studies should ideally evaluate 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. The above-suggested trials remain of interest because HCV therapies may not be universally available, affordable, or prioritized for all hemodialysis patient populations. In particular, we need innovative, effective strategies to improve infection control, and it is still important to overcome barriers to identification and treatment of all infected patients (e.g., costs and reimbursement for screening and treatment regimens) in hemodialysis centers; this has implications for improved infection control practices for other endemic and emerging infections even if HCV is eradicated from hemodialysis patient populations.
- Studies should determine whether isolation of HCV-positive patients influences rates of transmission of HCV or other infections.
- The costs and impact of improved facility staffing strategies, including higher staff-to-patient ratios, on HCV transmission should be further evaluated.
- Future research should examine standard measures for detecting dialysis-associated HCV infection that do not require viral sequencing and phylogenetic analysis.
- Future research should devise innovative approaches that accurately measure infection control processes at a reasonable cost.

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

HCV infection remains more prevalent in CKD G5 patients compared with the general population. Although HCV infection can cause HCV-associated glomerular disease resulting in CKD G5D (ESKD),^{128,194} kidney transplant candidates may also have acquired HCV infection within a dialysis unit¹⁹⁵ or may have been infected when they had received a previous transplant or were transfused in the era before systematic screening for HCV.^{194,196,197} Because of the deleterious effects of HCV infection in dialysis and kidney transplant patients, evaluation of disease severity and need for antiviral therapy is crucial.^{198–204} Screening for HCV in kidney transplant candidates has been addressed in Chapter 1.

4.1 Evaluation and management of kidney transplant candidates regarding HCV infection

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

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

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

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

4.1.3: Timing of HCV treatment in relation to kidney transplantation (before vs. after) should be based on donor type (living vs. deceased donor), wait-list times by donor type, center-specific policies governing the use of kidneys from HCV-infected deceased donors, HCV genotype, and severity of liver fibrosis (Not Graded).

4.1.3.1: We recommend that all HCV-infected patients who are candidates for kidney transplantation be considered for DAA therapy, either before or after transplantation (1A).

4.1.3.2: We suggest that HCV-infected kidney transplant candidates with a living kidney

donor can be considered for treatment before or after transplantation according to HCV genotype and anticipated timing of transplantation (2B).

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

Rationale

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

Several studies have shown that kidney transplantation is the best therapeutic option for patients with ESKD (Supplementary Tables S11 and S12). Survival is significantly greater in CKD G5 patients who have undergone kidney transplantation compared with those who have remained on the waiting list irrespective of recipient age and/or comorbidities.^{205,206} As in the uninfected population, in patients with HCV it has also been clearly shown that survival is significantly lower in dialysis patients than in kidney transplant recipients.^{198,207,208} Thus, eligible patients should be considered for kidney transplantation regardless of their HCV status. In addition, the DAAs for HCV treatment in dialysis and kidney transplant patients (see Chapter 2) allow successful HCV clearance in nearly all patients before or after transplantation. Patients who achieve SVR before transplantation do not relapse after transplantation, despite the use of potent immunosuppressive drugs.^{209,210}

Although the survival of patients with persistent HCV replication after kidney transplantation is inferior compared with HCV-negative kidney transplant patients,^{200,201,204} it remains higher than if they had remained on dialysis.^{198,207,208} Graft survival is also significantly decreased in HCV-positive kidney transplant patients compared with HCV-negative patients (Supplementary Tables S13 and S14).^{200–202,204,211,212} Although liver fibrosis progression in HCV-infected kidney transplant patients is variable, development of cirrhosis and hepatocellular carcinoma (HCC) has been reported.^{213–216} 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.

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

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

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

HCV-positive patients who are candidates for kidney transplantation should be evaluated for the presence of cirrhosis using either a noninvasive fibrosis-staging method or, on occasion, a liver biopsy. The choice of method is discussed in Chapter 1. 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. Absence of varices on endoscopy and portal pressure gradient < 10 mm Hg suggests that cirrhosis is compensated.

In patients with compensated cirrhosis without portal hypertension, isolated kidney transplantation is recommended. HCV clearance halts the progression of liver disease and may even induce regression of liver fibrosis.²¹⁷ 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.²¹⁸ Severe portal hypertension has been defined as a hepatic-vein wedge-pressure gradient of ≥ 10 mm Hg.⁴⁰ The Portal Hypertension Collaborative Group stated that hepatic venous-pressure gradient predicts clinical decompensation in patients with compensated cirrhosis.²¹⁹ Patients with cirrhosis who, despite having achieved SVR, have major hepatic complications such as ascites, hepatic encephalopathy, or worsening hepatocellular function should be evaluated for combined liver-kidney transplantation.

4.1.3: *Timing of HCV treatment in relation to kidney transplantation (before vs. after) should be based on donor type (living vs. deceased donor), wait-list times by donor type, center-specific policies governing the use of kidneys from HCV-infected deceased donors, HCV genotype, and severity of liver fibrosis (Not Graded).*

4.1.3.1: *We recommend that all HCV-infected patients who are candidates for kidney transplantation be considered for DAA therapy, either before or after transplantation (1A).*

4.1.3.2: *We suggest that HCV-infected kidney transplant candidates with a living kidney donor can be considered for treatment before or after transplantation according to HCV genotype and anticipated timing of transplantation (2B).*

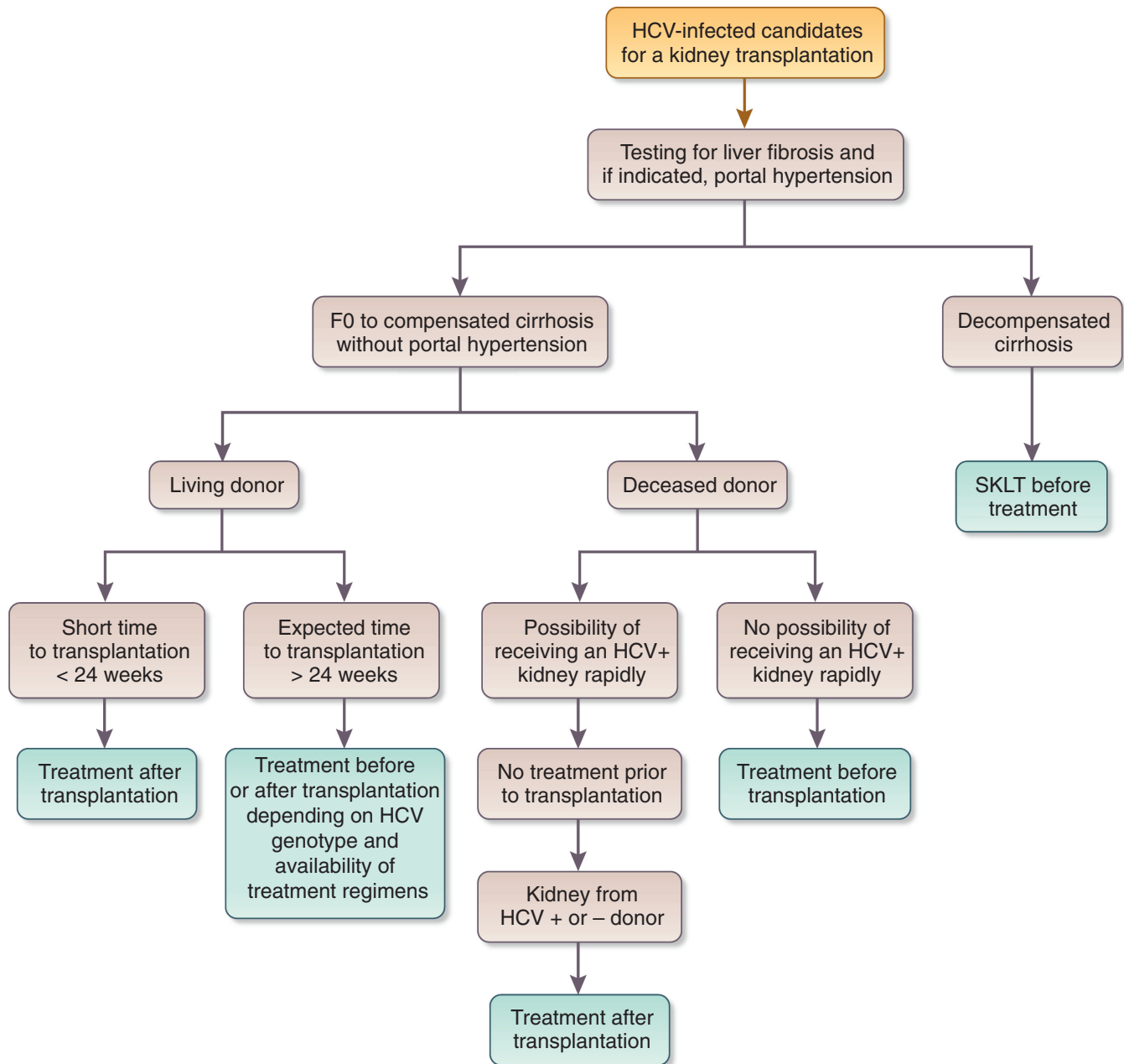
4.1.3.3: *We suggest that if receiving a kidney from an HCV-positive donor improves the chances for transplantation, the HCV NAT-positive patient can undergo transplantation with an HCV-positive kidney and be treated for HCV infection after transplantation (2B).*

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.²²⁰ Hence, it was recommended that candidates for kidney transplantation be treated with IFN before transplantation.³⁴ The use of DAAs has completely changed this situation because HCV clearance is feasible in the vast majority of patients before and after kidney transplantation (see Chapter 2). The current issue is timing of HCV therapy in relationship to transplantation. Considerations for planning therapy include living versus deceased donor, wait-list time by donor type, center-specific policy for acceptance of organs from HCV-positive deceased donors, specific HCV GT, and severity of liver fibrosis (see Algorithm 3). Other factors such as candidate sensitization and patient preference can be also considered for choosing the timing of treatment.

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 (to allow 12 weeks of therapy and 12 weeks of follow-up to prove SVR), then HCV therapy can be offered before or after transplantation based on specific HCV GT and proposed treatment regimen.

In a potential recipient with compensated cirrhosis without portal hypertension and 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.²²¹ 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, or when the anticipated time to obtain a kidney from an HCV-negative donor is long, the patient should be offered HCV therapy before transplantation.

Twice-yearly surveillance for HCC is indicated in cirrhotic patients. In addition, endoscopic surveillance for varices is indicated. Evaluation for complications of cirrhosis is



Algorithm 3 | Proposed strategy in a hepatitis C virus (HCV)-infected kidney transplant candidate. SKLT, simultaneous kidney-liver transplantation.

indicated irrespective of whether the patient receives antiviral therapy or not.

Specific HCV GTs may also influence timing of HCV therapy, depending on the availability of individual drugs in some countries. If the pan-genotypic glecaprevir-pibrentasvir is available, the GT will not influence the timing of DAA treatment. If glecaprevir-pibrentasvir is not available, as discussed in Chapter 2, DAAs (grazoprevir plus elbasvir, daclatasvir plus asunaprevir, or 3D regimen) that are approved to treat HCV infections in CKD G4–G5 patients are efficacious in GTs 1 and 4. For other GTs, only a sofosbuvir-based therapy can be proposed. The off-label use of sofosbuvir-based therapy at reduced doses in CKD G4–G5 patients with

GTs 2, 3, 5, or 6 has been reported, though it is not licensed for patients with an GFR < 30 ml/min per 1.73 m² (see Chapter 2). Hence, in HCV-infected patients with GTs 2, 3, 5, and 6, if possible, treatment should be postponed until after transplantation.

4.2 Use of kidneys from HCV-infected donors

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

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

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

Rationale

4.2.1: We recommend that 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.¹⁹⁶ 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.²²² For this reason, organ procurement organizations and international guidelines have strongly recommended that all organ donors should be tested for HCV infection.^{34,223}

The diagnosis of HCV infection is made by the detection of anti-HCV by enzyme-linked immunosorbent assay.^{34,223} The majority of patients who are seropositive for anti-HCV 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;^{34,223} thus, in many cases, only anti-HCV is tested in potential organ donors prior to transplantation.

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

There has been a consensus that kidneys from HCV NAT-positive donors should not be transplanted into anti-HCV-negative recipients. Kidneys from donors with anti-HCV who are HCV NAT-negative can generally be used safely in negative anti-HCV patients. Nowak *et al.* recently reported a case series of 21 anti-HCV-positive kidneys (20 donors) who were HCV NAT-negative. In no case did the use of those kidneys lead to *de novo* HCV infection in HCV-negative recipients.²²⁴ However, there have been isolated cases of HCV transmission reported to Disease Transmission Advisory Committee (DTAC) from HCV aviremic (i.e., anti-HCV-positive and NAT-negative) donors; these are currently under investigation, but the risk of transmission is probably very low.²²⁵ The problem was and remains that the demand for kidney transplantation clearly surpasses the supply, and this is a particular concern in areas with a high prevalence of HCV infection.³⁴ Universally discarding kidneys from HCV-positive donors could lead to the loss of up to 4.2% of organs.²²⁶ A recent retrospective study of 9290 donors for whom both anti-HCV and NAT data were available estimated that using anti-HCV-positive, NAT-negative donors at the same rate as anti-HCV-negative,

NAT-negative donors could result in 48 more kidney donors. Thus, there is a potential for expanding donor pools by using organs from carefully selected anti-HCV-positive, NAT-negative donors.²²⁷

A related issue was whether organs harvested from HCV NAT-positive donors could be safely transplanted in HCV NAT-positive recipients.²²² An experience in Spain of transplanting kidneys with positive HCV antibodies into HCV-positive recipients^{228,229} 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 NAT-negative had received organs from HCV NAT-positive donors.²²⁹ As a result of these findings, Spanish groups modified their policy, limiting the use of kidneys from HCV-positive donors to HCV NAT-positive recipients. This strategy was supported by international guidelines.^{34,223} Therefore, the HCV RNA (i.e., NAT) status of the donor is critical for optimal allocation of HCV-positive organs.

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,^{230–236} 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.²³⁵ 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.²³²

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.²³⁷ These results were comparable to a single-center experience in the US, showing that donor HCV status does not influence graft, patient survival or eGFR in HCV-positive recipients.²³⁸ 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.²³⁹ The US experience using kidneys from HCV-positive donor demonstrated that the benefit of transplantation is limited to HCV-positive recipients older than 50 years (Supplementary Table S15).²⁴⁰ Recently, it has been shown that kidneys from anti-HCV-positive donors can be considered for transplant into HCV-infected recipients followed by early post-transplant treatment with DAA agents.²⁴¹

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.²⁴² However, with the current availability of highly effective DAA regimens, matching by GT may be less of a serious concern.²²⁶

Despite international recommendations^{34,223} 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 (e.g., long history of kidney disease and high immunological risk). Kucirka *et al.* have reported that kidneys from HCV-positive donors were 2.6 times more likely to be discarded than those from HCV-negative donors.¹²²

In summary, the use of kidneys from HCV NAT-positive donors into HCV NAT-positive recipients (limiting the risk of transmission without loss of organs from the donor pool), is an acceptable approach. The capacity to use DAAs shortly after transplantation should allow safe use of these organs. Use of HCV NAT-positive kidneys for HCV NAT-positive recipients has been included in the algorithms to establish the policy of DAA therapy before or after transplantation.^{243,244}

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

Potential living donors with HCV infection should be treated as in the general population. First, liver fibrosis should be assessed, and then, if there is no evidence of cirrhosis, they can receive DAAs based on GT (see Chapter 2).

SVR can then be assessed at 12 weeks with monitoring of kidney function and proteinuria during and after DAA therapy. In the absence of severe hepatic fibrosis, living donation is then feasible.

The scarcity of donor organs for transplantation results in long waiting times for kidney transplantation.³⁴ In addition, individual patient characteristics, such as high sensitization, may contribute to delays in transplantation. Longer time on hemodialysis and on wait-list 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 analysis of the US Organ Procurement and Transplant Network database through 2012 demonstrated inferior outcomes in HCV-negative recipients who had received an HCV-positive donor compared with HCV-negative recipients transplanted with HCV-negative donors.²⁴⁵ This practice has been considered unacceptable.^{34,223} However, the availability of current DAAs for HCV infections has led to a reconsideration of this prohibition.

Treatment with DAAs is an established common practice in the general population and in liver transplant recipients.²⁴³ There is limited information about the use of DAAs in the early period after kidney transplantation.²⁴¹ Preliminary information using DAAs in long-functioning kidney transplant patients with HCV infection indicates excellent SVR12 of 90% to 100%.^{118,119} In liver transplantation, fibrosing cholestatic hepatitis has been successfully treated with DAAs.²⁴⁴ A clinical trial using HCV-positive kidneys into HCV-negative recipients has started very recently in Philadelphia.¹²³ In this pilot study (THINKER), 10 patients with negative anti-HCV were given

kidneys from donors who were HCV-NAT-positive for GT1. At day 3 post-transplantation, all patients had detectable HCV RNA and were given grazoprevir-elbasvir. SVR12 was observed in all patients.¹²³ This novel strategy raises several questions regarding what the optimal informed consent process should be, the potential risk for viral complications, and the cost implications of post-transplant use of DAAs.²⁴⁶ Encouraging results from another trial (EXPANDER-1) of kidneys from HCV NAT-positive donors for HCV-negative recipients were also reported,¹²⁴ but until more information is available regarding long-term safety of this approach, this practice should be considered strictly investigational.

4.3 Use of maintenance immunosuppressive regimens

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

Rationale

In HCV-infected kidney transplant recipients, viral load increases after transplantation because immunosuppression facilitates viral replication.³⁴ Roth *et al.* 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.²¹⁶ These data suggest caution in the choice of immunosuppressive protocol in these patients³⁴ given the frequent high immunological risk profile of HCV-infected recipients.

Antibody induction, particularly antilymphocyte preparations, had been associated with an increased risk of developing liver disease in HCV-infected transplant recipients.¹⁹⁶ 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 (Supplementary Table S16).^{247–250} In addition, the HR for death dropped from 2.51 over the first 6 months after transplant to 0.32 during the 7- to 84-month posttransplant period, in the study using induction therapy noted above.²¹⁶

There are only limited data on the influence of steroids in kidney transplant patients with HCV infection. In a US study, mortality was not different among patients who received steroids as part of immunosuppression protocol versus those who did not.²⁵⁰ In the setting of liver transplantation, discontinuation of steroids after surgery was associated with a reduced rate of post-transplant diabetes.²⁵¹ It is thus plausible that steroid 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.³⁴ However, it should be noted that

the risk of post-transplant diabetes mellitus is higher in HCV-positive patients treated with tacrolimus,²⁵² and cyclosporine inhibits HCV replication on cultured hepatocytes.²⁵³

Increased serum HCV RNA concentrations have been reported in patients who received MMF in place of azathioprine.²⁵⁴ However, MMF is considered part of the standard immunosuppression given to kidney transplant patients no matter what their HCV status is.²¹⁶ Published information on clinical use of mTOR inhibitors (sirolimus and everolimus) in kidney transplant patients with HCV is scarce, and therefore the influence of mTOR inhibitors on HCV-positive 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–drug interaction with immunosuppressive agents. Indeed, cyclosporine, tacrolimus, sirolimus, and everolimus are metabolized in the liver by the cytochrome P450. Thus, for most DAAs substrate competition can occur, influencing their elimination. The use of currently licensed DAAs can affect CNI levels and may require dose adjustment. As such, the Work Group suggests that the Hepatitis Drug Interactions website from the University of Liverpool (<http://www.hep-druginteractions.org>) be consulted for the latest guidance on potential drug–drug interactions prior to DAA use.

4.4 Management of HCV-related complications in kidney transplant recipients

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

4.4.2: Untreated HCV-positive kidney transplant recipients should have the same liver disease follow-up as HCV-positive non-transplant patients, as outlined in the American Association for the Study of Liver Diseases (AASLD) guidelines (Not Graded).

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

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

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

Rationale

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

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

4.4.2: *Untreated HCV-positive kidney transplant recipients should have the same liver disease follow-up as HCV-positive non-transplant patients, as outlined in the American Association for the Study of Liver Diseases (AASLD) guidelines (Not Graded).*

Kidney transplantation in patients with active HCV infection may be complicated by liver disease and also by extrahepatic complications.¹⁹⁴ These patients exhibited a lower graft and patient survival and an increased risk of severe liver disease compared with HCV-negative recipients.^{34,194,223,255} 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. Preliminary publications of the use of DAAs in kidney transplant patients have exhibited SVR of almost 100% without important side effects.^{118,119} More recently, a trial compared 12 and 24 weeks of sofosbuvir and ledipasvir in 114 kidney transplant recipients infected with HCV GTs 1 and 4 (96% GT1) with an eGFR of 40 ml/min per 1.73 m² or greater (median eGFR: 56 ml/min per 1.73 m²). The 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.¹¹⁶

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

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

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

HCV infection has been reported as a risk factor for the development of proteinuria in kidney transplant recipients.²⁵⁶ Several glomerular lesions have been described after kidney transplantation in HCV RNA-positive patients including recurrent or *de novo* cryoglobulinemic or non-cryoglobulinemic MPGN,²⁵⁷ membranous nephropathy (MN),²⁵⁸ acute transplant glomerulopathy,¹⁹⁴ anti-cardiolipin related thrombotic microangiopathy,²⁵⁹ and chronic transplant glomerulopathy.²⁶⁰ MPGN and MN are the most

frequent lesions related to HCV infection. The most common presentation is proteinuria with or without microhematuria, or nephrotic syndrome. The pathogenesis of MPGN and MN seems to be related to the deposition of immune complexes containing HCV RNA in the glomerulus.³⁴

After HCV NAT–positive patients have undergone kidney transplantation, clinicians should screen for proteinuria and microhematuria. In the case of urine protein-to-creatinine ratio > 1 g/g or 24-hour urine protein (protein excretion rate) greater than 1 g on 2 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.^{194,260}

For HCV-related glomerular disease, DAA therapy is indicated.^{261–270} In severe HCV-related cryoglobulinemic MPGN, in addition to antiviral therapy with DAAs, rituximab and, in severe cases, plasmapheresis should be considered.¹⁹⁴ This is discussed in detail in Chapter 5.

Research recommendations

- Prospective studies should assess the best timing for HCV treatment in kidney transplant candidates: before or after transplantation?
- Studies should examine whether accepting a kidney from an HCV-positive donor would reduce the time on the waiting list. Further studies are required in different countries because the prevalence of HCV in donors is highly variable worldwide.
- Future research should evaluate the impact of delaying HCV treatment on HCV-induced morbidity (e.g., liver disease) and patient survival in HCV-positive kidney transplant candidates who are not given DAA therapy in order to be grafted with a kidney from a positive donor.
- Prospective larger studies under investigational protocols should be conducted to corroborate the encouraging preliminary results obtained using kidneys from HCV-positive donors for HCV-negative recipients treated with DAAs. Studies should also examine the cost-effectiveness of this policy with different DAA treatment strategies.
- SVR should be assessed in a large cohort of HCV-positive patients who receive a kidney allograft from a positive donor and who are given DAA therapy after transplantation. In this setting, the optimal timing for starting DAA therapy should be determined.
- In patients presenting with an HCV-associated kidney disease after transplant, the effect of DAAs on the kidney graft should be assessed in a large series.

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

In addition to chronic liver disease, HCV infection also leads to extrahepatic manifestations including kidney disease and mixed cryoglobulinemia.²⁷¹ Although chronic HCV infection has been identified as an important cause of tubulo-interstitial injury in a large case-control study,²⁷² HCV-associated glomerular disease is the most frequent type of kidney disease associated with HCV.

HCV-induced glomerular disease occurs frequently in the context of HCV-associated mixed cryoglobulinemia, a systemic vasculitis characterized by involvement of small and, less frequently, medium-size vessels.^{273–277} Mixed cryoglobulinemia represents 60% to 75% of all cryoglobulinemia cases and is observed in connective tissue diseases and infectious or lymphoproliferative disorders, all grouped under the term “secondary mixed cryoglobulinemia.” After its identification, HCV has been recognized as the cause of 80% to 90% of idiopathic mixed cryoglobulinemia.^{273,276} In general, HCV is associated with type II mixed cryoglobulinemia (cryoglobulins consisting of polyclonal IgG and monoclonal IgM with rheumatoid factor activity), although it is also less frequently associated with type III mixed cryoglobulinemia (cryoglobulins consisting of polyclonal IgG and polyclonal IgM). In the absence of an identified etiology (currently <10% of mixed cryoglobulinemia), 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.^{274,275} The incidence of HCV-associated glomerular disease is probably low even if the available information is scanty. In an autopsy series of 188 consecutive patients with HCV infection, the frequency of MPGN was 11%, MN 2%, and mesangial proliferative GN 17%.²⁷⁸

A large 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 patients without HCV (controls).²⁷⁹ 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 MN (0.33% vs. 0.19%, $P = 0.86$) was found among patients with HCV. According to a prospective Norwegian study, the rate of CKD G5 due to MPGN was 0.2%.²⁸⁰ It has been further shown that anti-HCV seropositive status was more common in patients

with non-cryoglobulinemic MPGN and MN (18%–20%) than that observed in the general population of the same area (7%) after correction for age.²⁸¹ A large meta-analysis of 107,356 patients⁷ 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]).^{65,66,282–285} Another pooled analysis⁶³ demonstrated that anti-HCV-positive serology was an independent risk factor for proteinuria among HIV-infected patients with an adjusted effect estimate of 1.23 (95% CI: 1.18–1.28).^{286–291}

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

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

5.2.1: We recommend that patients with HCV-related glomerular disease showing stable kidney function and/or non-nephrotic proteinuria be treated initially with DAA (1C).

5.2.2: We recommend that patients with cryoglobulinemic flare, nephrotic syndrome, or rapidly progressive kidney failure be treated, in addition to DAA treatment, with immunosuppressive agents with or without plasma exchange (1C).

5.2.3: We recommend immunosuppressive therapy in patients with histologically active HCV-associated glomerular disease who do not respond to antiviral therapy, particularly those with cryoglobulinemic kidney disease (1B).

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

Rationale

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

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.^{292,293}

The main reasons for recommending a kidney biopsy in patients with HCV infection and signs of glomerular disease are not markedly different from the usual reasons prompting a kidney biopsy for other glomerular diseases.²⁹⁴ Kidney biopsy remains invaluable to assess the precise histological picture of the disease and the probability that the observed lesions are causally related to HCV-infection. Other glomerular diseases (including diabetic nephropathy and other types) are indeed not infrequently reported among patients with HCV infection.²⁹⁵ In addition, the histology will provide an assessment of the extent of active or hyperactive lesions requiring urgent immunosuppressive treatment, and of chronic lesions that are unlikely to be reversible under immunosuppression. Thus, some patients might be spared from immunosuppression in the presence of severe chronic lesions when there is no extrarenal indication for immunosuppression.²⁹⁴

The most common type of HCV-related GN is immune complex-mediated 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 subendothelial 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 electron microscopy, large subendothelial deposits are present. Vasculitis of small renal arteries is present in 30% of cases.²⁹⁶

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.²⁹⁶

Some investigators have reported cases of HCV-associated MPGN without cryoglobulinemia.²⁷⁵ In these patients, the clinical picture, histological features and laboratory data are indistinguishable from “classical” idiopathic immune complex-mediated 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.

MN is also observed in association with chronic HCV infection.²⁵⁸ 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 MN. 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,²⁹⁷ IgA nephropathy,²⁹⁸ thrombotic microangiopathy,²⁹⁹ rapidly progressive nephritis,²⁹⁹ fibrillary GN, and immunotactoid glomerulopathy.³⁰⁰ However, these likely correspond to sporadic cases and their pathogenic link with HCV remains even more uncertain than for MN.

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.³⁰¹ 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 MN.³⁰¹ 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.³⁰² Viral antigens have been found by immunohistochemistry,³⁰³ *in situ* hybridization,³⁰³ and laser capture microdissection.³⁰⁴

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. RCTs remain sparse; the evidence on the impact of antiviral treatment of HCV-related glomerular disease was until recently limited and consisted mostly of anecdotal reports and small-sized observational studies (Supplementary Tables S17 and S18). Initial reports adopted monotherapy with conventional IFN,³⁰⁵ but the combined regimen (pegylated IFN plus RBV) superseded monotherapy.³⁰⁶ With the arrivals of DAAs, IFN-based regimens are now considered obsolete, though these antiviral studies^{306–308} provided valuable insight on the etiological role of HCV in the pathogenesis of GN.

Some evidence supporting the antiviral therapy of HCV-associated glomerular disease has been provided by a meta-analysis of comparative studies of various study designs

comparing antiviral versus immunosuppressive regimens for HCV-induced GN.³⁰⁹ However, even with pooling of study results, the effect of IFN (vs. corticosteroid therapy) on reducing proteinuria is highly imprecise: OR 1.92; 95% CI: 0.39–9.57. In a sensitivity analysis including only controlled trials using standard IFN doses, the OR was 3.86 (95% CI: 1.44–10.3). Of note, in all patients with proteinuria reduction, HCV RNA clearance was observed at the end of antiviral therapy.³⁰⁹

In another meta-analysis,⁷⁸ antiviral therapy based on IFN- α 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 hr (95% CI: 1.38–4.04). 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 did 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, and a large variety of histological lesions was found.³¹⁰ According to an updated review, a total of 36 reports based on 47 unique patients were retrieved.^{311–317} 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.³¹⁸ Additional, albeit limited, information on antiviral treatment of HCV-related glomerular disease in kidney,²⁵⁷ liver,^{319–321} and liver/kidney transplanted population³²² and among pediatric individuals exists. Recombinant IFN given for treatment of HCV may exacerbate proteinuria in some patients with underlying glomerulopathies.³²³

Regardless of the regimens used (IFN-based or DAAs), antiviral treatment of HCV-related glomerular disease has limitations. First, the impact of antiviral therapy on the long-term outcomes of kidney disease remains uncertain. Second, the clinical benefit in patients who reached SVR may be transient and/or a dissociation between viral and renal responses can occur.^{275,324–326} Two recent long-term (1- to 2-year) studies reported high rates of marked improvement on various cryoglobulinemia-related manifestations after SVR with DAAs, but confirmed that relapses of vasculitis may occur despite achieving SVR.^{327,328}

5.2.1: We recommend that patients with HCV-related glomerular disease showing stable kidney function and/or non-nephrotic proteinuria be treated initially with DAA (1C).

The development of kidney disease among patients with mixed cryoglobulinemia has particular importance because kidney involvement confers a poor prognosis to such

patients.^{329–331} Clinically, HCV-associated mixed cryoglobulinemia is characterized by the triad of purpura, arthralgia, and weakness. The natural history of HCV-induced mixed cryoglobulinemia is clinically variable: some patients have an indolent course while others develop vasculitic lesions in various organs including kidneys. Extrarenal features of mixed cryoglobulinemia include neuropathy, hepatomegaly, sicca syndrome, and central nervous system and gut involvement. Overt pulmonary involvement is infrequent. Although extrarenal signs of mixed cryoglobulinemia vasculitis usually precede the kidney manifestations, often by years, in 29% of cases, kidney and extrarenal involvement are concurrent.³³¹ Kidney disease occurs in 8% to 58% of patients with mixed cryoglobulinemia, and in a minority of cases can be the first manifestation of mixed cryoglobulinemia. Patients with HCV-associated cryoglobulinemic glomerular disease can present with nephritic syndrome, asymptomatic non-nephrotic proteinuria or hematuria, and/or reduced GFR. Acute nephritic and nephrotic syndrome can be a presenting feature in 25% and 20% of patients, respectively. Arterial hypertension is frequent (affecting >50% of patients at the time of diagnosis) and is often resistant to antihypertensive drugs; the severity of hypertension often mirrors the severity of kidney disease.³³⁰ Around 10% of patients present oliguric kidney failure.^{330,331}

Type II mixed cryoglobulinemia 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.³³² 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 disease, and cardiovascular diseases.^{330,331}

RCTs are lacking to help 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.

Given that remission of hematuria, proteinuria, and improvement of GFR in patients with HCV-associated GN who obtained sustained HCV RNA clearance by DAAs has been reported,^{261–270} antiviral therapy with DAA regimens should be considered the first-line choice in patients with non-nephrotic proteinuria and relatively stable kidney function (Supplementary Tables S17 and S18). In addition, anti-proteinuric agents such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers should be given. Treatment including diuretics and antihypertensive 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 rapidly progressive kidney failure be treated, in addition to DAA treatment, with immunosuppressive agents with or without plasma exchange (1C).

Immunosuppressive agents have been administered to patients with serious, life-threatening complications of mixed cryoglobulinemia, 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 has been employed to remove circulating cryoglobulins from the plasma and consequently to reduce the deposition of immune complexes to the kidneys.

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 DAA therapy. Potential regimens include rituximab (375 mg/m² weekly for 4 weeks) with or without corticosteroids (see below), or cyclophosphamide (2 mg/kg/d for 2–4 months) plus methylprednisolone pulses 0.5 to 1 g/d for 3 days. According to the decision of the clinician, immunosuppressive regimen alone or combined therapy (immunosuppressive agents plus DAA therapy) is suggested as the initial approach.

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 mixed cryoglobulinemia vasculitis and renal involvement was evaluated throughout a median follow-up of 72 months since kidney biopsy.³³⁰ Positive anti-HCV serologic status was reported in 85% of patients. About 80% of patients underwent treatment with oral or pulse intravenous steroids and/or cytotoxic agents, whereas 67% were 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.³³⁰ By 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.³³⁰ Other case reports have also documented improvement following the administration of a combination of steroids and antivirals (IFN and RBV) or of the 3D regimen combined with plasmapheresis, corticosteroids, and rituximab.^{333,334}

5.2.3: We recommend immunosuppressive therapy in patients with histologically active HCV-associated glomerular disease who do not respond to antiviral therapy, particularly those with cryoglobulinemic kidney disease (1B).

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

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 [$n = 2$]).^{325,335} All patients reached SVR, but serum cryoglobulins persisted in 3 patients; also, the benefits on renal signs were partial. MPGN remitted in 3 patients 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 of 7 patients with symptomatic mixed cryoglobulinemia and GN (5 had a biopsy-proven MPGN and 2 were diagnosed clinically) underwent sofosbuvir-based regimens (6 with sofosbuvir and simeprevir and 1 with sofosbuvir and RBV).²⁶⁵ Only 1 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 of 7 patients.

In another cohort of 44 consecutive patients with HCV-associated mixed cryoglobulinemia, 4 patients had renal involvement.²⁶³ The treatment of HCV-associated mixed cryoglobulinemia with sofosbuvir-based DAA therapy appeared to be highly effective (SVR12, 100%) and safe with some improvement of kidney disease.^{262,263} These studies suggest that IFN-free therapies can give high viral and clinical responses in a difficult-to-treat condition such as HCV-associated mixed cryoglobulinemia 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. However, it is clear that we need larger and controlled studies to confirm these results. Combining DAA therapy with rituximab and other immunosuppressants might be of value for cases with severe or obstinate manifestations of cryoglobulinemic vasculitis.

Immunosuppressive therapies are suggested typically for patients with HCV-associated mixed cryoglobulinemia showing severe disease manifestations, such as progressive glomerular disease. In addition to conventional immunosuppressants, which target inflammation at the 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.^{336–341} Rituximab interferes with synthesis of cryoglobulins, monoclonal IgM, and renal deposition of immune complexes. An important pathogenetic feature of mixed cryoglobulinemia (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 RCTs have demonstrated the superiority of rituximab monotherapy as compared with conventional immunosuppressive therapy (i.e., corticosteroids, azathioprine,

cyclophosphamide, methotrexate, and plasma exchange) for the treatment of HCV-associated cryoglobulinemic vasculitis in patients for whom prior IFN 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.^{339,341} Rituximab was well tolerated and was effective in 71.4% to 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, 16 patients with cryoglobulinemic nephropathy (diffuse MPGN and mixed cryoglobulinemia) received rituximab at a dose of 375 mg/m², according to a “4 + 2” protocol (days 1, 8, 15, and 22 plus one dose 1 and 2 months later).³³⁷ No other immunosuppressive drugs were used. Safety and efficacy of rituximab was evaluated over a long-term follow-up (mean: 72.5 months). A significant improvement of cryoglobulinemic GN was found, starting from the second 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 hr, *P* < 0.05).³³⁷ 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, 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,³⁴² or more frequently, HBV. The risk of reactivation of HBV infection has been added to the existing black box warning on the rituximab label by the FDA in 2013.³⁴³ Infections with ominous course after rituximab therapy have been observed in kidney transplant recipients and in the non-transplant setting. However, 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 per 1.73 m², and concomitant high-dose corticosteroids) and were fatal in some patients.³⁴⁴ Cholestatic liver disease due to HCV reactivation by rituximab has been also observed after kidney transplant.³⁴²

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.^{345,346}

In summary, a kidney biopsy should be performed in HCV-positive patients with clinical evidence of glomerular disease. Patients with mild or moderate forms of HCV-associated GN with stable kidney function and/or non-nephrotic proteinuria should be managed first with a DAA regimen.

Patients with severe cryoglobulinemia or severe glomerular disease induced by HCV (i.e., nephrotic proteinuria or rapidly progressive kidney failure) should be treated with immunosuppressive agents (generally with rituximab as the first-line agent) and/or plasma exchange in addition to DAA therapies. Patients with HCV-related glomerular disease who do not respond to or are intolerant of antiviral treatment should also be treated with immunosuppressive agents. In all cases, achievement of SVR after DAA treatment, changes in kidney function, evolution of proteinuria, and side effects from antiviral therapy must be carefully monitored. Treatment with antiproteinuric agents such as angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers should be given to patients with HCV-associated glomerular disease. When appropriate, diuretics and antihypertensive drugs should be administered to achieve recommended target blood pressure goals for patients with CKD.

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.³⁴⁷ We need large-sized studies with appropriate technology to assess the relationship between occult HCV and glomerular disease.
- The efficacy and safety of DAA therapies and/or immunosuppressive agents for the treatment of HCV-associated GN should be assessed, preferably in larger, controlled clinical studies, with longer follow-up.
- 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; hence, further studies of various DAAs are warranted in late CKD/ESKD for various GTs in patients with HCV-associated GN. Typically, patients with HCV-related glomerular disease receive a high number of concomitant drugs, including cytotoxic agents. Potential drug–drug interaction is another challenge to clinicians using DAA regimens for HCV-induced GN.
- The role of immunosuppressive agents in the management of aggressive HCV-related glomerular disease (i.e., nephrotic syndrome, rapidly progressive decline of GFR) needs to be further clarified in light of the rapid antiviral activity provided by DAA regimens.
- Numerous questions regarding the use of rituximab in HCV-positive glomerular disease remain. For example, what is the optimal timing and dosing 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 patients who are older than 50 years, have kidney disease, and report concomitant use of high-dose corticosteroids. Future studies should delineate how best to avoid infections associated with immunosuppression 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, rationale text, and a summary of systematically generated evidence on relevant pre-defined clinical topics. The general guideline development method is described below.

Overview of process

The development process for the *KDIGO 2018 CPG for 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 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.^{348,349}

The Work Group Co-Chairs and the ERT met for a 2-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 2 separate 2-day meetings to finalize review topics, 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 nephrology, transplant nephrology, hepatology, virology, infection control, and public health. The Brown University Center for Evidence Synthesis in Health in Providence,

Rhode Island, 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,³⁴ which the ERT also had helped to develop (when it was based at Tufts Medical Center in Boston, MA). The Work Group and ERT further developed and refined each topic and its eligibility criteria, literature search strategies, and data extraction forms (Table 8).

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 8.

Ranking of outcomes. The Work Group ranked outcomes of interest on the basis of their importance for informing clinical decision making (Table 9).

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, HCV, and study designs. Searches were conducted in Medline, Embase, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. For topics covered in the 2008 KDIGO HCV CPG,³⁴ 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 Supplementary Appendix A. In addition, the ERT searched for existing relevant systematic reviews. The final searches were conducted in May 2017. The search yield was also supplemented by focused searches for DAAs, conference abstracts from the 2016 and 2017 American Society of Nephrology (ASN) and AASLD meetings, and articles provided by Work Group members through July 2018.

For selection of studies, all members of the ERT screened the abstracts in duplicate using an open-source online screening

Table 8 | Systematic review topics and screening criteria**Hepatitis C treatment**

Population	CKD G3a–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-wk), hepatocellular carcinoma, graft loss, NODAT, QoL, adverse events (including treatment discontinuation), pharmacokinetics/dynamics
Study design	Continuous (HCV-associated GN only): kidney function, proteinuria 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 ³⁵⁰ and ≥ 2012

Liver testing

Population	Tests for cirrhosis: CKD (all stages); pre-transplant biopsy: CKD G4–G5 pre-transplantation (or equivalent)
Intervention/comparator	Noninvasive liver testing, including upper endoscopy (for varices), liver biopsy
Outcome	Noninvasive test performance characteristics, change in management strategy, patient mortality, graft loss
Design	Any
Minimum N of subjects	Noninvasive testing: $N \geq 10$, pre-transplant biopsy: $N \geq 5$
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	$N \geq 30$ patients
Publication dates	≥ 2008 (plus studies in 2008 KDIGO CPG)

Early versus late transplantation

Population	HCV-infected transplantation candidates
Intervention	Transplantation (“now”)
Comparator	Remaining on wait-list or awaiting HCV-negative status
Outcome	Patient mortality, graft loss
Design	Any, multivariable analysis
Minimum duration of follow-up	None
Minimum N of subjects	$N \geq 100$
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	$N \geq 100$
Publication dates	Any

Predictor analyses

Population	Predictors of CKD progression: any (including general population) <i>except</i> CKD G5D (dialysis); HCV as predictor: kidney transplant recipients
Predictor	HCV-infection (untreated), other predictors of CKD progression (if HCV-infected)
Outcome	CKD progression (change in GFR, SCr doubling, ESKD), 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)

2008 KDIGO CPG, 2008 KDIGO clinical practice guideline on hepatitis C³⁴; CKD, chronic kidney disease; DAA, direct-acting antiviral; ESKD, end-stage kidney 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 virologic response.

Table 9 | Hierarchy of outcomes

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

CKD, chronic kidney disease; ESKD, end-stage kidney disease; HCV, hepatitis C virus; SVR, sustained virologic response.

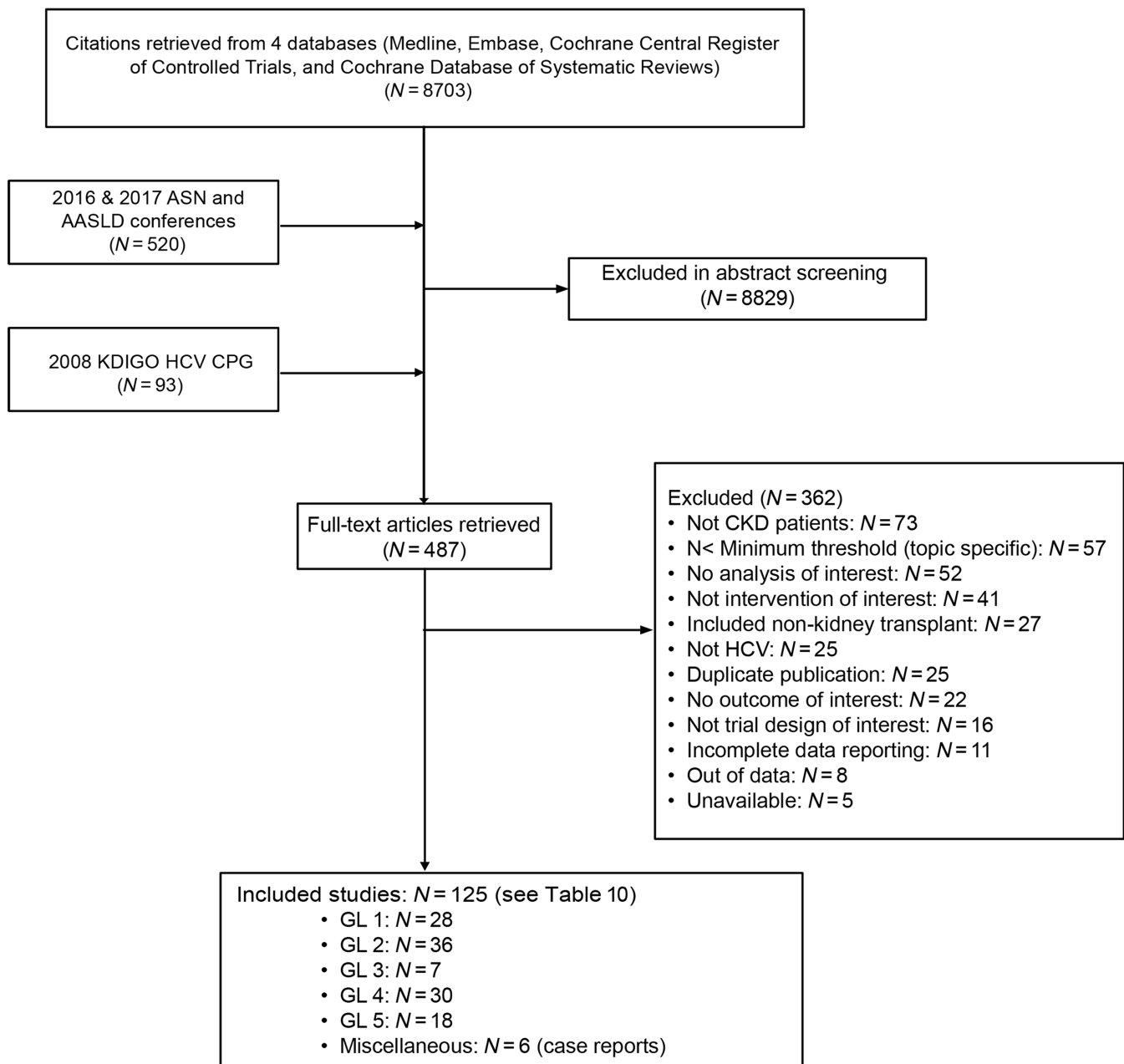


Figure 2 | Search yield. AASLD, American Association for the Study of Liver Diseases; ASN, American Society of Nephrology; CKD, chronic kidney disease; GL, guideline; HCV, hepatitis C virus; KDIGO HCV CPG, Kidney Disease: Improving Global Outcomes hepatitis C virus clinical practice guideline.

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 8703 citations from the databases were screened, in addition to 520 conference abstracts and 93 studies included in the 2008 KDIG HCV CPG (Figure 2). Journal articles reporting original data or systematic reviews were selected for evidence review, based on *a priori* criteria for eligible evidence. Of these, 487 were selected for consideration for inclusion. In total, 125 studies met eligibility criteria for extraction.

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 online repository SRDR (Systematic Review Data Repository); the data are 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 outcomes were tabulated separately.

Work Group members reviewed and confirmed all summary table data and quality assessments. Summary tables are available as supplementary material at www.kisupplements.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 2 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 10, together with the number of included studies.

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 3-level classification system for quality assessment was used to grade the overall study quality and quality of all relevant outcomes in the study (Table 11). 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,³⁵¹ 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

Table 10 | Work products for the guideline

Topics	Summary table	Included studies ^a , 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 Noninvasive versus invasive tests for cirrhosis in CKD	+	11	+
1.4 HCV as predictor of CKD progression	+	16	+
1.4 Other predictors of CKD progression	+	1	–
2. HCV treatment			
2 HCV treatment (DAA, CKD nontransplant including hemodialysis)	+	11	+
2 HCV treatment (peg-interferon, hemodialysis)	+	6	+
2 HCV treatment (DAA, kidney transplant)	+	5	+
2 HCV treatment (interferon, kidney transplant)	+	4	+
2 DAA drug dosing	–	10 PK studies	–
3. HCV transmission			
3 Dialysis isolation	+	7	+
4. Kidney transplantation			
4.1.1 Transplantation versus wait-list	+	5	+
4.1.1 HCV as predictor, patient mortality	+	5	+
4.1.1 HCV as predictor, graft loss	+	7	+
4.1.2 Pre-transplant liver biopsy	–	1	–
4.1.3 Timing of HCV treatment versus kidney transplantation	–	(based on GL 2)	–
4.2 HCV-positive versus negative donor kidneys	+	8	–
4.3 DAA and immunosuppression interaction	+	4	–
4.4 HCV-related complications	–	(not searched)	–
5. HCV-associated glomerulonephritis			
5.1 HCV-associated kidney disease prevalence	+	5	–
5.2 HCV-associated glomerulonephritis management	+	13	+

CKD, chronic kidney disease; DAA, direct-acting antiviral; GL, guideline; HCV, hepatitis C virus; peg, pegylated; PK, pharmacokinetic.

^aPlus 6 case reports on miscellaneous topics.

Table 11 | 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.

RCT, randomized controlled trial.

Table 12 | 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	<i>Study quality</i> -1 level if serious limitations -2 levels if very serious limitations	<i>Strength of association</i> +1 level if strong, ^a no plausible confounders	High = further research is unlikely to change confidence in the estimate of the effect
Observational study = low	<i>Consistency</i> -1 level if important inconsistency <i>Directness</i> -1 level if some uncertainty -2 levels if major uncertainty	+2 levels if very strong, ^b no major threats to validity <i>Other</i> +1 level if evidence of a dose-response gradient	Moderate = further research is likely to have an important impact on confidence in the estimate of effect, and may change the estimate
Any other evidence = very low	<i>Other</i> -1 level if sparse or imprecise data ^c -1 level if high probability of reporting bias	+1 level if all residual plausible confounders would have reduced the observed effect	Low = further research is very likely to have an important impact on confidence in the estimate, and may change the estimate Very low = any estimate of effect is very uncertain

GRADE, Grading of Recommendations Assessment, Development and Evaluation.

^aStrong evidence of association is defined as “significant relative risk of > 2 (< 0.5)” based on consistent evidence from 2 or more observational studies, with no plausible confounders.

^bVery strong evidence of association is defined as “significant relative risk of > 5 (< 0.2)” based on direct evidence with no major threats to validity.

^cSparse if there is only 1 study or if total *N* < 500, and 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.³⁵³

Table 13 | 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.

adjustment for different lengths of follow-up.³⁵² Based on these characteristics an overall assessment was made whether the study was of good, fair, or poor quality (Table 11).

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.

Grading the quality of evidence and the strength of a guideline recommendation. A structured approach, based on GRADE^{353–355} 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.³⁵⁴

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 4 grades: high, moderate, low, or very low (Table 12).

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 4 final categories for the quality of overall evidence were A, B, C, or D (Table 13).

Table 14 | 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 nonstatistically 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.

Table 15 | KDIGO nomenclature and description for grading recommendations

Grade ^a	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.

KDIGO, Kidney Disease: Improving Global Outcomes.

^aThe 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. They should not be interpreted as being weaker recommendations than Level 1 or 2 recommendations.

Table 16 | 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.

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 14). The assessment of net benefit also involved the judgment of the Work Group and the ERT.

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 multistep process during face-to-face meetings and by subsequent drafts by e-mail. Relevant recommendations from the AASLD and EASL guidelines on management of HCV were reviewed to maximize consistency between guidelines. The final draft was sent for external public review. Based on

feedback, it was further revised by the Work Group Co-Chairs and members. All Work Group members provided feedback on initial and final drafts of the recommendation statements and guideline text and 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 15 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 16 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 vs. benefit), values, and preferences, and costs. Formal decision analyses including cost analysis were not conducted.

Table 17 | The Conference on Guideline Standardization (COGS) checklist for reporting clinical practice guidelines

Topic	Description	Discussed in 2018 KDIGO HCV in CKD CPG
1. Overview material	Provide a structured abstract that includes the guideline’s release date, status (original, revised, updated), and print and electronic sources.	See <i>Abstract</i> and <i>Methods for Guideline Development</i> .
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 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 deaths, 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 infection.
5. Target population	Describe the patient population eligible for guideline recommendations and list any exclusion criteria.	Adults with CKD and HCV infection; CKD patients on dialysis therapy.
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 individuals involved in the guideline’s development are disclosed in the <i>Biographic and Disclosure Information</i> .
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. Financial disclosures of Work Group members are published in <i>Biographic and Disclosure Information</i> section of the guideline.
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 (i) systematic review, (ii) systematic search followed by narrative summary, or (iii) 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 <i>Methods for Guideline Development</i> chapter. The search was updated through May 2017 and supplemented by articles identified by Work Group members through July 2018. 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 3-tiered grading system (see Table 11). Quality of evidence and strength of recommendations were graded following the GRADE approach (Tables 12, 13, and 15). The Work Group could provide general guidance in the form of 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.

Topic	Description	Discussed in 2018 KDIGO HCV in CKD CPG
11. Prerelease review	Describe how the guideline developer reviewed and/or tested the guidelines prior to release.	The guideline had undergone external public review in February 2017. Public review comments were compiled and fed back to the Work Group, which considered 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.	The requirement for an update will be assessed periodically from the publication date or earlier if important new evidence becomes available in the interim. Such evidence might, for example, lead to changes to the recommendations or may modify information provided on the balance between benefits and harms of a particular therapeutic intervention.
13. Definitions	Define unfamiliar terms and those critical to correct application of the guideline that might be subject to misinterpretation.	See <i>Abbreviations and Acronyms</i> .
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,” indicate 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.	Algorithms were developed where applicable (see Chapters 2 and 4).
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.

CKD, chronic kidney disease; CPG, clinical practice guideline; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HCV, hepatitis C virus; KDIGO, Kidney Disease: Improving Global Outcomes.

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 2 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 1 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.

Limitations of approach

Although the literature searches were intended to be comprehensive, they were not exhaustive. Medline, Embase, and Cochrane databases were searched, but other specialty or regional databases were not. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched. Recent conference abstracts were screened from ASN and AASLD, but older conference abstracts and other conference meetings were not specifically screened. We relied on Work Group members to provide the ERT with conference abstracts from recent EASL meetings. However, any important studies known to domain experts that were missed by the electronic literature searches were added to retrieved articles and reviewed by the Work Group.

Review of guideline development process

The Conference on Guideline Standardization (COGS) checklist has been developed to assess the quality of the methodological process for systematic review and guideline development.³⁵⁶ Table 17 shows the criteria that correspond to the COGS checklist and how each one is addressed in this guideline. Similarly, Supplementary Appendix B demonstrates the level of concurrence with which this guideline corresponds to the Institute of Medicine's standards for systematic reviews and guidelines.^{348,349}

Biographic and disclosure information



Michel Jadoul, MD (Work Group Co-Chair), received his MD degree in 1983 at the Université Catholique de Louvain (UCL), Brussels, Belgium. Dr. Jadoul trained in internal medicine and nephrology under the mentorship of Professor Charles van Ypersele de Strihou. He has served as chair at the Department of Nephrology of the Cliniques Universitaires Saint-Luc since 2003 and is currently full clinical

professor at UCL. Dr. Jadoul's clinical activities focus on the follow-up of hemodialysis and CKD patients, and his main research interests include β 2-microglobulin amyloidosis, hepatitis C, and other complications (e.g., falls, bone fractures, sudden death) in hemodialysis patients, as well as cardiovascular complications after kidney transplantation and various causes of kidney disease (e.g., drug-induced).

Dr. Jadoul has co-authored over 230 scientific papers, most of them published in major nephrology journals. He is currently serving as a theme editor of *Nephrology Dialysis Transplantation*, and he is also a country co-investigator for the Dialysis Outcomes and Practice Patterns Study (DOPPS) (2001–present). In 2008, he received the international distinguished medal from the US National Kidney Foundation. He was previously a member of the KDIGO Executive Committee (2010–2015) and the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Council (2013–2016). Presently, Dr. Jadoul is the KDIGO Co-Chair Elect.

Consultant: Astellas, GlaxoSmithKline, Merck Sharp & Dohme, Vifor Fresenius Medical Care Renal Pharma

Grant/research support: Alexion, Amgen, Janssen-Cilag, Merck Sharp & Dohme Otsuka, Roche

Speaker: AbbVie, Amgen, Menarini, Merck Sharp & Dohme, Vifor Fresenius Medical Care Renal Pharma

Travel: Amgen

All monies paid to institution.



Paul Martin, MD, FRCP, FRCPI (Work Group Co-Chair), is professor of medicine, Mandel Chair of Gastroenterology, and chief of the Division of Gastroenterology and Hepatology at the University of Miami, USA. He graduated from medical school at University College, Dublin, Ireland and trained in internal medicine and gastroenterology in Dublin and in Canada. He was a

medical staff fellow in the Liver Unit of the National Institutes of Health, where he trained with Dr. Jay Hoofnagle. He is Editor-in-Chief of *Liver Transplantation* and co-editor of *Handbook of Liver Disease*. Dr. Martin was previously a councilor for the American Society of Transplantation and has had a long-standing interest in viral hepatitis and organ transplantation. He was the Sheila Sherlock Lecturer for the Internal Association for the Study of Liver Disease in 2004 and received the Charles Trey Award from the American Liver Foundation in 2001.

Board member: AbbVie, Bayer, Bristol-Myers Squibb

Grant/research support: AbbVie, Bristol-Myers Squibb*, Gilead*, Merck**

**Monies paid to institution.*



Marina C. Berenguer, MD, is a consultant hepatologist at La Fe University Hospital in Valencia, Spain, and professor of medicine at the University of Valencia. She was trained in medicine at the University of Valencia before completing a fellowship at the Veterans Affairs Medical Center / University of California, San Francisco, with Dr. Teresa Wright.

Prof. Berenguer is well recognized for her important contributions to the field of post-transplantation HCV liver disease, where she has been involved in the creation of various consensus documents on viral hepatitis and liver disease. She is also an active committee member for several national and international hepatology and liver transplantation societies. Prof. Berenguer has also coordinated research within a national research network in hepatogastroenterology ("Centro de Investigación Biomédica en Red en Enfermedades Hepáticas y Digestivas," CIBER-ehd) since its creation in 2006.

Prof. Berenguer previously served as associate editor for the *Journal of Hepatology and Liver Transplantation* until December 2014, and is now deputy editor for *Transplantation*. She has authored more than 300 publications in peer-reviewed journals as well as over 70 chapters in international and national textbooks.

Consultant: AbbVie, Gilead, Merck Sharp & Dohme

*Grant/research support: Gilead**

Speaker: AbbVie, Astellas, Gilead, Merck Sharp & Dohme, Novartis

**Monies paid to institution.*



Wahid Doss, MD, is professor of hepatogastroenterology and endemic medicine at Cairo University, Egypt. Dr. Doss became the Head of the National Hepatology Institute, Cairo, from 2006 through 2015, and he is presently the Head of the National Committee for the Control of Viral Hepatitis since 2006. Together with

his colleagues, he established and supervised one of the most comprehensive hepatitis treatment programs worldwide, which has received acclaim from local and international organizations including the World Health Organization. Dr. Doss is a founding member of the gastrointestinal endoscopy unit at Kasr El Aini Hospital, Cairo University, and maintains a special interest in therapeutic endoscopic procedures. A member of EASL, AASLD, and American Society for Gastrointestinal Endoscopy, he is also a founding member and current vice president of the Egyptian Liver Care Society.

Dr. Doss declared no competing interests.



Fabrizio Fabrizi, MD, is staff nephrologist and professor of medicine at Maggiore Policlinico Hospital and IRCCS Foundation, Milan, Italy. His research focus is aimed at the understanding of the epidemiology, natural history, and management of viral hepatitis (HBV and HCV) in the CKD population through laboratory work, clinical research studies, and clinical trials.

He has received grants from the Italian Society of Nephrology and fellowships from the Society of Italian-American Nephrologists as support for his research projects. Dr. Fabrizi has actively participated in the development of numerous national and international guidelines regarding the management of viral hepatitis in CKD patients, including the inaugural 2008 KDIGO HCV guideline. He currently serves on the editorial board of the *International Journal of Artificial Organs* and the *Journal of Nephrology*, and has authored more than 250 publications in peer-reviewed journals such as *Kidney International*, the *American Journal of Kidney Diseases*, and the *Clinical Journal of the American Society of Nephrology*, among others.

Board member: AbbVie, Merck Sharp & Dohme

Consultant: AbbVie



Jacques Izopet, PharmD, PhD, is professor of virology at Toulouse University and head of the Federative Institute of Biology at Toulouse University Hospital, France. He is also head of a research team in the Pathophysiology Center of Toulouse-Purpan – INSERM UMR 1043/CNRS 5282. His primary research area has centered on viral persistence, host response, and pathophysiology, with a

particular focus on HIV tropism and hepatitis E virus infection in immunocompetent and immunocompromised patients. Dr. Izopet has published over 450 papers in international journals.

Dr. Izopet declared no competing interests.



Vivekanand Jha, MBBS, MD, DM, FRCP, FRCP (Edin) FAMS, is the executive director at The George Institute for Global Health India, professor of nephrology at University of Oxford, UK, and the president-elect of the International Society of Nephrology. Prof. Jha received his

internal medicine and nephrology training at the Postgraduate Institute of Medical Education and Research (PGIMER) in Chandigarh, India, and a research fellowship at Harvard University. He was a professor of nephrology, led the Stem Cell Research Facility, and was head of the Department of Translational and Regenerative Medicine at PGIMER.

Prof. Jha focuses on the study of emerging public health threats globally and in India, and in finding solutions using innovative methodologies appropriate for emerging countries. He currently spearheads research projects in more than 20 countries with a particular interest in the understanding of global burden of kidney diseases, the social- and disease-related drivers of diseases and their determinants of outcome. Prof. Jha is an expert in the effect of tropical ecology on kidney diseases and the impact of infections on patients with kidney diseases. He has served as a Work Group member on prior KDIGO guidelines including the management of patients with glomerulonephritis and the care of kidney transplant recipients.

*Consultant: NephroPlus**

Grants/research support: Baxter Healthcare, GlaxoSmithKline**

*Speaker: Baxter Healthcare**

**Monies paid to institution.*



Nassim Kamar, MD, PhD, is a professor of nephrology at Toulouse University Hospital in Toulouse, France, and is the head of the Department of Nephrology and Organ Transplantation at Toulouse University Hospital. Dr. Kamar received his medical degree from Dijon University, France. Thereafter,

he received internship at Toulouse University, France, where he graduated with a specialty in nephrology. Dr. Kamar received additional training in kidney replacement therapy and medical pedagogy. He also completed a 1-year post-doctoral fellowship in basic research at the Department of Nephrology, La Charité Hospital, Berlin, Germany. Dr. Kamar was awarded his PhD in 2006.

Dr. Kamar's interests include the studying of viral infection, particularly hepatitis E virus, HCV, and cytomegalovirus infections that develop after solid organ transplantation. He is also interested in immunosuppression after solid organ transplantation. Dr. Kamar has published over 450 papers in peer-reviewed journals and was a member of The Council of the International Transplant Infectious Disease Society. He has received numerous awards, including la Fondation du Rein (2008), the Grand Prix de Médecine from the Académie des Sciences, Inscriptions et Belles-Lettres de Toulouse (2009), and the Palme de Médecine des CHU (2015).

Board member: Astellas, Merck Sharp & Dohme, Novartis, Shire
Consultant: Novartis

Speaker: AbbVie, Amgen, Astellas, Chiesi, Fresenius, Gilead, Merck Sharp & Dohme, Neovii, Novartis, Roche, Sanofi, Shire



Bertram L. Kasiske, MD, FACP, obtained his undergraduate training at Michigan State University, East Lansing, MI, USA. He received his medical degree from the University of Iowa, Iowa City, IA, USA and completed an internal medicine residency and fellowship training in nephrology at Hennepin County Medical Center, an affiliate hospital of the University of Minnesota in Minneapolis, USA. Dr. Kasiske is former deputy director of the US Renal Data System, former Editor-in-Chief of the *American Journal of Kidney Diseases*, and former Co-Chair of Kidney Disease: Improving Global Outcomes (KDIGO). Currently he is director of nephrology at Hennepin County Medical Center and professor of medicine at the University of Minnesota.

Dr. Kasiske is the principal investigator for a National Institutes of Health grant to study long-term effects of living kidney donation. He is also the director of the Scientific Registry of Transplant Recipients, which is a federal registry of solid organ transplants in the US.

Speaker: Novartis



Ching-Lung Lai, MD, FRCP, FRACP, FHKAM (Med), FHKCP, FAASLD, is the Simon K Y Lee Professor in Gastroenterology and the Chair Professor of Medicine and Hepatology at the Department of Medicine, University of Hong Kong, where he has been working since his graduation with honors from the

university. For the last 4 decades he has been extensively involved in research on various aspects of HBV, including its molecular virology, natural history, treatment, and prevention. Prof. Lai is one of the lead investigators in the pivotal trials of various nucleos(t)ide analogues that have revolutionized the treatment of chronic hepatitis B. More recently he has been involved in studies for the treatment of chronic hepatitis C.

Prof. Lai has published over 500 peer-reviewed papers and reviews in international journals. His publications have been widely cited, and he is one of top scientists in the field of chronic hepatitis B infection. Prof. Lai was also invited to give the Leon Schiff State-of-the-Art Lecture at the 2005 annual meeting of the American Association for the Study of Liver Diseases (AASLD), entitled "The natural history and treatment of chronic hepatitis B: consensus and controversies," and he has co-edited a book entitled *Hepatitis B Virus*.

*Board member: Arrowhead Research Corporation**

Speaker: AbbVie, Gilead Sciences Hong Kong Limited

**Monies paid to institution.*



Jose M. Morales, MD, PhD, is professor of medicine and senior investigator of the Research Institute in the Hospital 12 de Octubre (Madrid, Spain), educational ambassador of the International Society of Nephrology, and associate editor of *Clinical Transplantation*.

He was medical director of the Renal Transplant Program of the Hospital 12 de Octubre in Madrid (one of the largest hospitals in Spain), chief of the Renal Transplant Office, and chief of the Section of Nephrology/Renal Transplantation. Prof. Morales also served as the past president of the Madrid Transplantation Society and a council member of the Spanish Transplantation Society. In addition, he was a council member of ERA-EDTA (1998–2001) and a medical coordinator of Forum Renal from Spain.

Prof. Morales has published over 300 articles in peer-reviewed journals, and he has served as reviewer in the main nephrology and transplantation journals. His principal areas of scientific interest include clinical nephrology/transplantation, and immunosuppression and HCV. Prof. Morales has also been a principal investigator for many important

trials involving immunosuppressive agents such as tacrolimus, extended-release tacrolimus, rapamycin, mycophenolate mofetil, everolimus, and belatacept.

He was a member of the expert group that developed the European Best Practice Guidelines of Renal Transplantation (2000–2002) and a prior member of the Work Group that developed the 2008 KDIGO CPG on HCV in CKD. Recently, Madrid was chosen to host the Transplantation Society Congress in July 2018, and Dr. Morales is president of the local committee and vice chair of the 27th International Congress of the Transplantation Society.

Consultant: Merck Sharp & Dohme

Speaker: Astellas, Merck Sharp & Dohme



Priti R. Patel, MD, MPH, is a medical officer in the Division of Healthcare Quality Promotion at the US Centers for Disease Control and Prevention (CDC), where she leads CDC's dialysis safety efforts. She is also adjunct assistant professor of family and preventive medicine at the Emory University School of Medicine. Dr. Patel earned a Master of Public Health degree from Columbia University and received her medical degree from

Howard University College of Medicine (1999). She completed a residency in internal medicine at the University of Pennsylvania (2002) and residency in preventive medicine at CDC (2005). She received training as an officer in the Epidemic Intelligence Service (EIS) program assigned to CDC's Division of Viral Hepatitis (2004). In her work at CDC, Dr. Patel has supervised numerous outbreak investigations in dialysis centers, has contributed to CDC guidance documents, and develops resources and strategies to help prevent infections among dialysis patients. Dr. Patel has authored more than 80 peer-reviewed publications, largely focused on health care-associated infection prevention and patient safety. She is the director of CDC's Making Dialysis Safer for Patients Coalition and a member of the Nephrologists Transforming Dialysis Safety Project Committee.

Dr. Patel declared no competing interests.



Stanislas Pol, MD, PhD, is professor of hepatology and gastroenterology at Université Paris Descartes, Paris, France, and head of the liver department at Cochin Hospital, Paris, France. He completed hepatology and gastroenterology residency and chief residency at the Necker-Enfants Malades University, and a molecular enzymology fellowship in Henri Mondor Hospital. Dr. Pol completed his MD

thesis on occult HBV infections in 1983 and his PhD thesis on the regulation of iso-enzymes of aspartate aminotransferase in

liver disease in 1992. Dr. Pol's current research interests involve studying the impact of immune deficiency, including HIV, on the natural history of viral hepatitis; the treatment of viral hepatitis; and the reversal of cirrhosis.

He is a co-leader of a research INSERM unit (U1223 of Institut Pasteur) studying the immune pathology of HCV infection.

Dr. Pol is the recipient of several research awards and fellowships and has published more than 350 primary and review articles in the field of liver diseases. He has previously chaired the coordinated action 24 (AC 24) of the French Agency for AIDS and Viral Hepatitis (ANRS: therapeutic trials in viral hepatitis), and he is presently the clinical head of the French ANRS HEPATHER cohort, which includes HBV and HCV patients. He is also the director of the Center of Translational Research of Institut Pasteur since 2015.

Board member: AbbVie, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp & Dohme

Consultant: AbbVie, Gilead

Speaker: AbbVie, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp & Dohme



Marcelo O. Silva, MD, is the head of hepatology and liver transplant units at Austral University Hospital in Pilar, Argentina. He earned his medical degree with honors from the University of Buenos Aires, and completed his post-graduate medical education in internal medicine and

gastroenterology at the University of Buenos Aires Hospital. Dr. Silva obtained hepatology training with a research and clinical fellowship at the Center for Liver Diseases, University of Miami School of Medicine. Upon completion of his fellowship, Dr. Silva served as assistant professor of clinical medicine at the University of Miami, FL.

He has extensive experience in clinical trials involving chronic hepatitis B and C. Dr. Silva has published more than 60 papers in peer-reviewed journals, contributed over 100 abstracts and presentations in scientific meetings, and authored several book chapters. He also developed the Latin American Liver Research Education and Awareness Network to promote research education and awareness of liver diseases in the region. In January 2014, he was appointed as a board member of the World Health Organization Viral Hepatitis Scientific and Technical Advisory Committee Committee.

Board member: AbbVie, Bristol-Myers Squibb, Gilead, Merck Sharp & Dohme

Grants/research support: AbbVie, Bristol-Myers Squibb*, Gilead*, Merck Sharp & Dohme**

Speaker: AbbVie, Bristol-Myers Squibb, Merck Sharp & Dohme
Development of educational presentations: AbbVie, Bristol-Myers Squibb, Merck Sharp & Dohme

Travel: AbbVie, Bristol-Myers Squibb, Gador

KDIGO Co-Chairs



David C. Wheeler, MD, FRCP, is professor of kidney medicine at University College London, UK, an honorary consultant nephrologist at the Royal Free London NHS Foundation Trust, and an honorary professorial fellow of the George Institute for Global Health. He is a clinician scientist with an interest in the complications of CKD, specifically those that increase the burden of cardiovascular disease and/or accelerate progression of kidney failure.

He has participated in the design, roll-out, and monitoring of several large-scale clinical trials including the Study of Heart and Renal Protection (SHARP) and the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE). He currently sits on the steering committee of Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) and is co-chief investigator of the Dapagliflozin in CKD (DAPA-CKD) study. He is clinical lead for Division 2 of the North Thames Clinical Research Network and heads a team of 10 clinical trial nurses and practitioners at the Centre for Nephrology, Royal Free Hospital in London. He has been involved in clinical practice guideline development for several organizations, most recently for KDIGO, of which he is currently Co-Chair. He is past president of the UK Renal Association and past chair of the UK Renal Registry. His other responsibilities include membership of the editorial board of the *Journal of the American Society of Nephrology* and of the Executive Committee of Standardised Outcomes in Nephrology (SONG).

Consultant: Akebia, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daichii-Sankyo, GlaxoSmithKline, Janssen, Vifor Fresenius Medical Care Renal Pharma

Grants/research support: AstraZeneca

Speaker: Amgen, Vifor Fresenius Medical Care Renal Pharma



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Consultant: Akebia, Amgen, AstraZeneca, Bayer, Daichii-Sankyo, Relypsa, Vifor Fresenius Medical Care Renal Pharma
Speaker: FibroGen

Evidence review team



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project director for this guideline, he played a role in providing methodological expertise in the guideline development process and assisted in the collection, evaluation, grading, and synthesis of evidence and the revisions of the final evidence report. Dr. Balk also provided methodological guidance and training of Work Group members regarding topic refinement, key question formulation, data extraction, study assessment, evidence grading, and recommendation formulation. His primary research interests are evidence-based medicine, systematic review, clinical practice guideline development, and critical literature appraisal.

Dr. Balk declared no competing interests.



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Board member: AbbVie

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Dr. Di declared no competing interests.

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Ms. Earley declared no competing interests.

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Participation in the review does not necessarily constitute endorsement of the content of this report by the above individuals or the organizations or institutions they represent.

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