



kidney

INTERNATIONAL



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

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

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Disclaimer

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINES

These Clinical Practice Guidelines are based on the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of care, and should not be construed as one, nor should they be interpreted as prescribing an exclusive course of management.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or a type of practice. Every health-care professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation. The recommendations for research contained within this document are general and do not imply a specific protocol.

SECTION II: DISCLOSURE

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the Work Group.

Specifically, all members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as actual or perceived conflicts of interest. This document is updated annually and information is adjusted accordingly. All reported information is published in its entirety at the end of this publication in the Work Group members' Biographical and Disclosure Information section and are on file at the National Kidney Foundation (NKF).

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Abbreviations and acronyms

AASLD	American Association for the Study of Liver Disease	HIV	Human immunodeficiency virus
ACEI	Angiotensin-converting enzyme inhibitor(s)	INR	International normalized ratio
ADA	American Diabetes Association	IVDU	Intravenous drug user
ALT	Alanine aminotransferase	KDIGO	Kidney Disease: Improving Global Outcomes
ARB	Angiotensin receptor blocker(s)	KDOQI	Kidney Disease Outcomes Quality Initiative
AST	Aspartate aminotransferase	MGN	Membranous glomerulonephritis
AUC	Area under the curve	MPGN	Membranoproliferative glomerulonephritis
CARI	Caring for Australians with Renal Impairment	NAT	Nucleic acid test(ing)
CDC	Centers for Disease Control and Prevention	NHANES III	Third National Health and Nutrition Survey
CKD	Chronic kidney disease	NIH	National Institutes of Health
CSN	Canadian Society of Nephrology	NODAT	New-onset diabetes after transplantation
DOPPS	Dialysis Outcomes and Practice Patterns Study	PCR	Polymerase chain reaction
EBPG	European Best Practice Guidelines	RCT	Randomized controlled trial
EDTA	Ethylenediaminetetraacetic acid	ROC	Receiver operating characteristics
EIA	Enzyme immunoassay	RR	Relative risk
GFR	Glomerular filtration rate	SVR	Sustained virologic response
GN	Glomerulonephritis	SQ	Subcutaneous(ly)
GRADE	Grades of Recommendation, Assessment, Development and Evaluation	TLR-3	TOLL-like receptor 3
HBV	Hepatitis B virus	TMA	Transcription-mediated amplification
HCV	Hepatitis C virus	UK-RA	United Kingdom Renal Association
		USRDS	United States Renal Data System
		WHO	World Health Organization

Reference Keys

Stages of chronic kidney disease

Stage	Description	GFR ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)	Treatment
1	Kidney damage with normal or \uparrow GFR	≥ 90	
2	Kidney damage with mild \downarrow GFR	60-89	
3	Moderate \downarrow GFR	30-59	1-5T if kidney transplant recipient
4	Severe \downarrow GFR	15-29	
5	Kidney failure	< 15 (or dialysis)	5D if dialysis (HD or PD)

CKD, chronic kidney disease; GFR, glomerular filtration rate; \uparrow , increased; \downarrow , decreased.

Conversion factors of metric units to SI units

	Metric Unit	Conversion Factor	SI Units
Creatinine	mg dl^{-1}	88.4	$\mu\text{mol/L}$
Glucose	mg dl^{-1}	0.0555	mmol/L

Note: Metric units \times conversion factor=SI units.

Levels of strength of recommendations

Strength of Recommendation	Wording of Recommendation	Basis for Strength of Recommendation
Strong	An intervention "should" be done	"High" quality evidence and/or other considerations support a strong guideline ^a
Moderate	An intervention "should be considered"	"Moderate" quality evidence and/or other considerations support a moderate guideline ^a
Weak	An intervention "is suggested"	"Low" or "Very Low" quality evidence; predominantly based on expert judgment for good clinical practice ^a

^aSee Appendix 2: Grading the strength of the recommendations, p. S85.

Foreword

Kidney International (2008) **73** (Suppl 109), S1–S2; doi:10.1038/ki.2008.81

Kidney Disease: Improving Global Outcomes (KDIGO) is an independently incorporated nonprofit foundation, governed by an international board of directors, that was established in 2003 with the 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 rationale for focusing on guidelines was the increasing and convincing information that rigorously developed evidence-based clinical practice guidelines, when implemented, improve patient outcomes and favorably affect the efficiency of health-care delivery. The rationale for a global initiative was the mounting epidemiologic data that kidney disease is common worldwide and its harmful complications are universal. Further, the science- and evidence-based care of these patients are independent of geographical location and national borders. As such, international cooperation in the development of evidence-based guidelines can improve the efficiency and broaden the expertise base of guideline development, thereby saving regional resources for use in their implementation, rather than duplicating a review of essentially the same database. The rationale for focusing on patients with kidney disease is that it allows for the development of guidelines that are of maximum benefit to patients if resources were unlimited. In reality, that is never the case because available resources do vary, and—even in the wealthiest countries—there are always regional considerations that limit the adoption of ideal guidelines. Given that the KDIGO guidelines are meant to be global, trade-offs in applying individual interventions must be prioritized and determined regionally. KDIGO is committed to share the evidentiary basis of the guidelines and assist local Guideline Development Groups to determine and adopt the recommendations that are appropriate for regional implementation. This is the approach recommended by the World Health Organization (WHO) in its *Guidelines on Guidelines*, and the approach adopted by the KDIGO Board. Essentially, the objective is to globalize and share the evidence, but localize the decision for their adoption and implementation.

Now, we are proud to present the first product of what has been an unprecedented undertaking of the international renal community. It has been a rigorous process from the outset that took two years to launch. After much debate, the KDIGO Board decided to avoid duplication of existing guidelines in nephrology and selected the topic of infectious diseases as a heretofore orphan topic of worldwide interest. Five major infectious diseases were considered: human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV), tuberculosis, and malaria. Ultimately, HCV was selected because (i) of the larger number of available studies

on the subject; (ii) HCV is an infection that can detrimentally affect patients throughout the spectrum of chronic kidney disease (CKD) and can itself cause kidney disease; and (iii) HCV is a problem of worldwide clinical relevance in developed and developing countries.

At the same time as the board was deliberating the choice of a guideline topic, it commissioned a group of experts to develop a rigorous and consistent approach for the development and grading of the evidence and recommendations of nephrology guidelines, in general, and those of KDIGO, in particular. The recommendation of this expert group, based on the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach, is the process that was followed in developing the present guidelines. Essentially, the guideline development process was guided by (i) the level of scientific evidence and methodologic rigor of the available literature; (ii) the Work Group charged with developing the guidelines being interdisciplinary, international, and independent throughout the process; and (iii) ascertainment of openness of the entire development process, especially during its review phase.

The guidelines were subjected to a three-step review process. At every step of the review process, all comments received were carefully reviewed, considered, and discussed by the Work Group; where appropriate, they are integrated into the final version of the guidelines. As a first step, the Board reviewed an early draft of the questions to be addressed in December 2005. In the second phase, a first draft of the final guidelines was reviewed by the Board and representatives of Caring for Australians with Renal Impairment (CARI), United Kingdom Renal Association (UK-RA), Canadian Society of Nephrology (CSN), Kidney Disease Outcomes Quality Initiative (KDOQI), and European Best Practice Guidelines (EBPG) in December 2006.

In the third and final phase, the draft guidelines were submitted for public review and comment by any interested individual or party. All comments received were considered and discussed by the Work Group. Where appropriate, changes were made in this final document. This is an important step in the development of guidelines, as it increases the base of expertise that goes into their development. We owe a special debt of gratitude to all those who took time out of their busy schedules to share their comments with us. They have been instrumental in improving the final guidelines.

A major problem that plagues the development of guidelines, in general, and in nephrology, in particular, is the relatively small number of available high-level randomized clinical trials (RCTs) that address all the pertinent clinical issues needed for the care of patients. To convey the level of evidence for each guideline statement, the HCV Guideline Development

Work Group elected to specify it in parentheses at the end of each statement and detail it in the rationale that follows. Guideline statements specified as ‘Strong’ refer to those where the quality of the evidence is high and assumes that most well-informed individuals will make the same choice. Statements specified as ‘Moderate’ refer to those where the quality of the evidence is moderate or low, but additional considerations support a recommendation to consider the specific intervention, with the assumption that a majority of well-informed individuals will consider its use. Statements specified as ‘Weak’ refer to consensus-based recommendations where the evidence is low, very low, or absent, with the expectation that consideration would be given to follow the suggested judgment-based recommendation on an individual basis. The table below summarizes the interpretation of the three levels of recommendations. To assist the reader, this table is repeated with each set of statements. In the final analysis, it is absolutely essential to keep in mind the definition of guidelines: ‘Guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for special conditions.’ As such, these are merely guidelines and not standards or mandates. In clinical practice, the decision to follow any guideline statement, independent of the level of its supporting evidence, must be made individually for each patient.

Levels of strength of recommendations

Strength of recommendation	Wording of recommendation	Basis for strength of recommendation
Strong	An intervention ‘should’ be done	‘High’ quality evidence and/or other considerations support a strong guideline ^a
Moderate	An intervention ‘should be considered’	‘Moderate’ quality evidence and/or other considerations support a moderate guideline ^a
Weak	An intervention ‘is suggested’	‘Low’ or ‘Very Low’ quality evidence; predominantly based on expert judgment for good clinical practice ^a

^aSee Appendix 2: Grading the Strength of the Recommendations, p. S85.

On behalf of KDIGO, we acknowledge the immense effort and contributions of those who made it all possible. In particular, we acknowledge the following: the members of the Guideline Development Work Group and the Evidence Review Team, without whose tireless effort and dedication this first set of KDIGO guidelines would not have been possible; the KDIGO Board, whose leadership, vision, and guidance were instrumental at every step of preparing the guidelines; and the exceptional support of the National Kidney Foundation staff assigned to KDIGO who worked so diligently in resolving logistic problems, arranging activities, and attending the innumerable conference calls and meetings that went into bringing the process to fruition. Specifically, we acknowledge Donna Fingerhut, Michael Cheung, and Dekeya Slaughter-Larkem who were instrumental in coordinating the whole project.

A very special debt of gratitude is owed to Michel Jadoul and David Roth, Co-Chairs of the Guideline Development Work Group, for their leadership, countless hours of work, dedicated commitment, invaluable expertise, and intellectual rigor; and to Ethan Balk, Craig Gordon, and Amy Earley for their relentless vigilance in providing methodologic rigor and guidance in developing the evidentiary basis and grading the final guideline statements.

In a voluntary and multidisciplinary undertaking of this magnitude, numerous others have made valuable contributions to these guidelines, but cannot be acknowledged individually. To each and every one of them, we express our sincerest appreciation and thanks.

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Executive summary

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Levels of strength of recommendations

Strength of recommendation	Wording of recommendation	Basis for strength of recommendation
Strong	An intervention 'should' be done	'High' quality evidence and/or other considerations support a strong guideline ^a
Moderate	An intervention 'should be considered'	'Moderate' quality evidence and/or other considerations support a moderate guideline ^a
Weak	An intervention 'is suggested'	'Low' or 'Very Low' quality evidence; predominantly based on expert judgment for good clinical practice ^a

^aSee Appendix 2: Grading the Strength of the Recommendations, p. S85.

The above table summarizes the interpretation of the three levels of recommendations. Each statement strength is matched with specific wording and with a given basis for the strength. For further clarity, in the lists of statements Strong statements are in bold print, Moderate statements are in regular print, and Weak statements are in italics.

GUIDELINE 1: DETECTION AND EVALUATION OF HCV IN CKD

Guideline 1.1: Determining which CKD patients should be tested for HCV:

- 1.1.1 *It is suggested that CKD patients be tested for HCV. (Weak)*
- 1.1.2 **Testing for HCV should be performed in patients on maintenance hemodialysis (CKD Stage 5D) and kidney transplant candidates. (Strong)**

Guideline 1.2: HCV testing for patients on maintenance hemodialysis:

- 1.2.1 **Patients on hemodialysis should be tested when they first start hemodialysis or when they transfer from another hemodialysis facility. (Strong)**
 - In hemodialysis units with a low prevalence of HCV, initial testing with EIA (if positive, followed by NAT) should be considered (see Algorithm 1). (Moderate)
 - In hemodialysis units with a high prevalence of HCV, initial testing with NAT should be considered (see Algorithm 1). (Moderate)
- 1.2.2 For patients on hemodialysis who test negative for HCV, retesting every 6–12 months with EIA should be considered. (Moderate)
- 1.2.3 **Testing for HCV with NAT should be performed for hemodialysis patients with unexplained abnormal aminotransferase(s) levels. (Strong)**

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

- *Repeat testing with NAT is suggested within 2–12 weeks in initially NAT-negative patients. (Weak)*

GUIDELINE 2: TREATMENT OF HCV INFECTION IN PATIENTS WITH CKD

Guideline 2.1: Evaluation of HCV-infected CKD patients for antiviral treatment

- 2.1.1 *It is suggested that CKD patients with HCV infection be evaluated for antiviral treatment. (Weak)*
- 2.1.2 *It is suggested that the decision to treat be based on the potential benefits and risks of therapy, including life expectancy, candidacy for kidney transplantation, and comorbidities. (Weak)*
- 2.1.3 *It is suggested that in CKD patients—except kidney transplant recipients—who develop an acute HCV infection, a waiting period beyond 12 weeks to observe spontaneous clearance (by NAT) is not justified, and that antiviral treatment should be started. (Weak)*
- 2.1.4 *It is suggested that HCV-infected patients accepted for kidney transplantation be treated (see Guideline 4). (Weak)*
- 2.1.5 *It is suggested that treatment of HCV-infected kidney transplant recipients be considered only when the benefits of treatment clearly outweigh the risk of allograft rejection due to IFN-based therapy (for example, fibrosing cholestatic hepatitis, life-threatening vasculitis). (Weak)*
- 2.1.6 *It is suggested that antiviral therapy be considered for patients with HCV-related GN (see Guideline 5.3). (Weak)*

Guideline 2.2: Basing HCV treatment on CKD stage

- 2.2.1 *For HCV-infected patients with CKD Stages 1 and 2, combined antiviral treatment using pegylated IFN and ribavirin is suggested, as in the general population. (Weak)*
 - *It is suggested that ribavirin dose be titrated according to patient tolerance. (Weak)*
- 2.2.2 *For HCV-infected patients with CKD Stages 3, 4, and 5 not yet on dialysis, monotherapy with pegylated IFN with doses adjusted to the level of kidney function is suggested. (Weak)*
- 2.2.3 *For HCV-infected patients with CKD Stage 5D on maintenance hemodialysis, monotherapy with standard IFN that is dose-adjusted for a GFR <15 ml per min per 1.73 m² is suggested. (Weak)*

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

Guideline 2.3: Monitoring the response to HCV treatment in CKD patients

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

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

- For patients on maintenance hemodialysis, repeat testing with NAT every 6 months is suggested. (Weak)

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

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

GUIDELINE 3: PREVENTING HCV TRANSMISSION IN HEMODIALYSIS UNITS

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

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

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

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

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

Guideline 4.1: Evaluation and management of kidney transplant candidates regarding HCV infection

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

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

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

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

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

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

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

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

Guideline 4.2: Use of kidneys from HCV-infected donors

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

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

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

Guideline 4.3: Use of maintenance immunosuppressive regimens

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

Guideline 4.4: Management of HCV-related complications in kidney transplant recipients

- 4.4.1 *It is suggested that HCV-infected kidney transplant recipients more than 6 months after transplant have their liver disease evaluated at least annually. (Weak)*
- 4.4.2 *For HCV-infected kidney transplant recipients in whom the benefits of antiviral treatment clearly outweigh the risks (see Guidelines 2.1.5 and 2.2.4), monotherapy with standard IFN is suggested. (Weak)*
- 4.4.3 *It is suggested that HCV-infected kidney transplant recipients be screened for the development of hyperglycemia after transplantation. (Weak)*
- 4.4.4 *It is suggested that HCV-infected kidney transplant recipients be tested at least every 3–6 months for proteinuria. (Weak)*
- *It is suggested that patients who develop new onset proteinuria (either urine protein/creatinine ratio > 1 or 24-h urine protein greater than 1 g on two or more occasions) have an allograft biopsy*

with immunofluorescence and electron microscopy included in the analysis. (Weak)

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

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

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

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

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

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

Introduction

Kidney International (2008) **73** (Suppl 109), S6–S9; doi:10.1038/ki.2008.83

I. HEPATITIS C VIRUS INFECTION IN THE GENERAL POPULATION

HCV, an RNA virus

Hepatitis C virus (HCV) is a small single-stranded RNA virus with a lipid envelope (E) containing glycoproteins (E1 and E2) and a core with a genome consisting of 9500 nucleotides. HCV components are both structural (core, E1, and E2) and nonstructural (NS; P7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B). The nonstructural genes encode various enzymes including a polymerase responsible for replication of HCV. HCV isolates are classified into six distinct genotypes depending on sequence homology.

In the absence of HCV cell cultures, until very recently, studies of infectivity have relied on the chimpanzee. Exposure of chimpanzees to HCV is followed by the appearance of HCV RNA in serum within 1–2 weeks, with increase of serum alanine aminotransferase (ALT) 3–6 weeks later and subsequent seroconversion with antibodies developing mainly against HCV core, NS3, and NS4. As for other RNA viruses, the genetic sequence of HCV is characterized by a high rate of spontaneous mutations, with major implications for escape from the human immune system and the development of an effective vaccine.

Testing for HCV

After the identification of the hepatitis B virus (HBV) in the 1960s, it soon became apparent that many cases of post-transfusional hepatitis remained unexplained, including the so-called ‘non-A, non-B hepatitis.’ The causative agent remained unknown for more than 15 years until a group, after screening over one million clones of a library of cDNA complementary to total RNA extracted from a chimpanzee infected with serum from a patient with post-transfusional non-A, non-B hepatitis, identified a single reactive clone of a virus called HCV.¹ This led to the first-generation enzyme immunoassay (EIA) that detected antibodies against a single nonstructural HCV protein (C100-3).² It was already apparent at that time that the presence of antibodies coincided with the presence of viral RNA and that antibodies were thus not protective.

Subsequently, second- and third-generation immunoblots and EIAs were developed, which detect antibodies against multiple HCV nonstructural proteins as well as HCV core. Both sensitivity and specificity improved dramatically as the second-generation EIA became available, and slightly more so with the third-generation EIA. Overall, first-generation EIA tests are now considered obsolete and most countries rely exclusively on third-generation EIA. Given the good performance of third-generation EIA tests, immunoblot tests have also become obsolete in clinical practice.³ The increased sensitivity of the last generation of HCV assays has

dramatically reduced the risk of HCV transmission by blood components and also reduced the detection time between acquisition of infection and the development of anti-HCV antibodies (the ‘serologic window’) from 82 days to 66 days.^{4,5} Fourth-generation tests, which will soon become available, would allow the simultaneous detection of HCV antibodies and HCV core protein. These tests should further reduce the serologic window. In some populations, with frequent polyclonal hypergammaglobulinemia, there may be discrepancies among third-generation EIA tests. Thus, in pregnant women in Cameroon, HCV positivity using only one third-generation EIA test was 4.9%, but it decreased to 1.9% when two third-generation EIA tests were performed; HCV RNA was present in 75% of women having concomitantly two positive EIA tests and was 0% in those having only one positive EIA test.⁶

Nucleic acid testing (NAT) is based either on qualitative HCV RNA detection or on HCV RNA quantitation. Qualitative detection assays are based on the principle of target amplification using conventional polymerase chain reaction (PCR), real-time PCR, or transcription-mediated amplification (TMA). All commercially available assays can detect 50 IU ml⁻¹ of HCV RNA or less and have equal sensitivity for the detection of all HCV genotypes.⁷ The lower limit of detection of the qualitative conventional PCR-based assays or their semiautomated version is 50 IU ml⁻¹; that of real-time PCR assays (which are able to simultaneously qualify and quantify HCV RNA) is 10–30 IU ml⁻¹; and that of the TMA-based assay is 10 IU ml⁻¹. Quantitative assays are based either on target amplification techniques (conventional PCR or real-time PCR) or on signal amplification techniques (branched DNA). Branched DNA and most quantitative conventional PCR-based assays have detection limits higher than those of qualitative detection assays.⁸

Epidemiology of HCV infection in the general population

Hepatitis C virus is a blood-borne pathogen that appears to be endemic in most parts of the world. There are, however, substantial geographic and temporal variations in the incidence and prevalence of HCV infection, largely due to differences in regional risk factors for the transmission of HCV. The World Health Organization (WHO) estimates that the global prevalence of HCV infection averages 3%, or around 170 million infected persons worldwide. However, population-based surveys are not available for most parts of the world, and prevalence estimates are based on testing of selected populations such as blood donors. Prevalence of confirmed EIA positivity in blood donors ranges from less than 0.1% in Northern Europe to 0.1–0.5% in Western Europe, North America, parts of Central and South America,

Australia, and a few regions of Africa. Intermediate rates (1–5%) have been reported from Brazil, Eastern Europe, the Mediterranean area, the Indian subcontinent, and parts of Africa and Asia.⁹ The highest prevalence of HCV has been found in Egypt (17–26%).⁹ A few population-based studies such as the Third National Health and Nutrition Survey (NHANES III) in the United States and similar small-sized studies from other countries, such as France and Italy, have clearly shown that prevalence estimates based on blood donors underestimate the actual prevalence of HCV in the general population by up to threefold.^{10–12}

Globally, the major risk factors for HCV infection are blood transfusions from unscreened donors and intravenous drug use. However, exposure to HCV-infected blood from other health-care-related procedures and regional cultural practices are increasingly recognized as having an important function in HCV transmission in some parts of the world. Since the introduction and improvement in the 1990s of the screening of blood donors, HCV transmission by blood transfusions is now exceedingly rare (around or less than one per million) in developed countries.^{13,14} Unfortunately, the screening of blood donors for HCV is not yet routinely performed by some blood banks in developing countries.¹⁵ Most new cases in developed countries are related to intravenous drug use. Health-care-related procedures leading to nosocomial HCV transmission are not restricted to hemodialysis facilities. Several reports from Western countries have clearly documented nosocomial transmission of HCV through inadvertent sharing of multidose vials or unsterilized instruments, among others.^{16,17} Similar nosocomial transmission of HCV outside dialysis units is certainly not less likely to occur in developing countries but has not been reported until now. Additional risk factors for HCV transmission include occupational exposure, especially by accidental needlestick, as well as perinatal transmission (about 6%), whereas the transmission of HCV by sexual activity appears relatively inefficient.^{9,18}

Natural history of HCV in the general population

Acute HCV infection is often mild and frequently does not prompt medical consultation, resulting in diagnostic delay. Unfortunately, HCV infection frequently becomes chronic, defined as the continued presence of HCV RNA for 6 months or longer after the estimated onset. Subsequent spontaneous loss of virus is unusual. Chronicity rates range from 50 to 90%, with somewhat lower rates in children and young healthy women (50–60%) and higher rates in older individuals and African Americans.^{19,20} Despite several studies, the natural history of chronic HCV infection remains poorly defined. The major long-term complications of chronic HCV infection are liver fibrosis and cirrhosis, portal hypertension and liver failure, and a high risk for hepatocellular carcinoma. The development of cirrhosis in published studies in the general population has ranged from 2 to 42%.^{21,22} In this regard, it should be noted that available studies do not yet extend beyond the first two decades after

infection. Factors associated with an increased risk of progressive fibrosis include older age, male gender, white race, coinfection with human immunodeficiency virus (HIV) or HBV, chronic alcoholism, and coexistence of other comorbid conditions such as obesity and diabetes.

Treatment in the general population

Interferon- α (IFN- α) was approved for the treatment of chronic hepatitis C in 1991. The rate of sustained virologic response (SVR), defined as the absence of HCV RNA in serum at least 6 months after IFN- α withdrawal, is unfortunately low, usually <20%. The subsequent inclusion of ribavirin in the therapeutic regimen has been shown to improve SVR rates to 40–45%.^{23–25} The long-acting pegylated IFNs were introduced more recently. Owing to their longer half-life, pegylated IFN can be given as a weekly dose. In large trials of pegylated IFN, either alfa-2a (Pegasys; Roche, Basel, Switzerland) or alfa-2b (PEG-Intron; Schering-Plough, Kenilworth, NJ, USA), the rate of SVR after a 48-week course of combined pegylated IFN and ribavirin was 54 and 56%, respectively, as compared with 44 and 47% with IFN and ribavirin, and only 29% with pegylated IFN alone.^{23,26,27} Response rates were higher in patients with HCV genotype 2 or 3 (75–80%) than genotype 1 (40–45%). Recently, it was shown that patients with genotype 2 or 3 could be treated with 800 mg rather than 1000–1200 mg ribavirin daily, and for 24 weeks rather than 48 weeks, without reducing SVR (about 80%) rates.^{28–30} Absolute contraindications to therapy with IFN or pegylated IFN and ribavirin include pregnancy and breastfeeding. Relative contraindications include decompensated liver disease, major neuropsychiatric disease, coronary or cerebrovascular disease, active substance or alcohol abuse, and a history of kidney or heart transplantation. The most common adverse effects of pegylated IFN are muscle aches and fatigue. Additional side effects include depression, anxiety, and sleep disturbances. The most common side effect of ribavirin is hemolysis with anemia, requiring dose reduction.

II. HCV IN CHRONIC KIDNEY DISEASE

Relevance of the topic in CKD patients

Soon after the discovery of HCV as the major cause of non-A non-B hepatitis, HCV was recognized as an important cause and consequence of chronic kidney disease (CKD). Indeed, HCV is a significant cause of some forms of glomerulonephritis (GN), especially membranoproliferative GN (MPGN). The initial recognition of this association came from case series of patients with MPGN, in which the prevalence of HCV infection appeared much higher than expected. Subsequent population-based studies have found an association between HCV positivity and markers of CKD, such as albuminuria or proteinuria. This has been documented in the United States (NHANES III) and Taiwan.³¹ These studies obviously did not have data on kidney histology, so it is unclear whether the association is mainly due to MPGN or other factors.³²

In addition, HCV infection is a frequent consequence of CKD. Blood transfusions (before effective screening of blood

donors for HCV was instituted), nosocomial transmission in dialysis units, and transmission by kidney grafts all have contributed to the much higher prevalence of HCV infection in CKD Stage 5D and transplant patients than in the general population.

Epidemiology of HCV infection in the various stages of CKD

As in the general population, the prevalence of HCV in CKD Stage 5D patients varies worldwide, ranging from as low as 1% to as high as over 70% (see Table 1). Overall, the current prevalence of HCV is below 5% in most of Northern Europe, around 10% in most of Southern Europe and the US, between 10 to 50% and up to 70% in many parts of the developing world, including many Asian, Latin American, and North African countries (Table 1). It is important to emphasize that the prevalence of HCV is highly variable from unit to unit within the same country, with recent reports from some dialysis units in the US reporting prevalences above 20%.³³

Consistent risk factors for the presence of anti-HCV antibodies and/or HCV RNA include blood transfusions given before efficient testing for HCV and the total time spent on dialysis. Additional risk factors include a history of kidney transplantation, intravenous drug use, and having been dialyzed in a high-prevalence region.

Some studies from various European countries showed a decrease of the prevalence of anti-HCV during the 1990s. In contrast, the prevalence of anti-HCV antibodies, as recorded by the voluntary registration program of the Centers for Disease Control and Prevention (CDC), has apparently not changed significantly over the last 10 years, remaining around 8–10%.³⁴ The evolution of the epidemiology of HCV in CKD Stage 5D patients in other countries is poorly defined.

Table 1 | Prevalence of HCV infection in hemodialysis patients from various countries

Country	Prevalence of HCV (+)	Year(s) of testing	Reference
Brazil	17%	2002–2005	Santos and Souto ³⁹
Belgium	7%	2000	Jadoul <i>et al.</i> ³⁸
France	15%	1997–2001	Fissell <i>et al.</i> ⁴⁰
Germany	7%	1996–1997	Hinrichsen <i>et al.</i> ⁴¹
India	12–42%	2001	Saha and Agarwal ⁴²
Iran	9%	2004	Shamshirsaz <i>et al.</i> ⁴³
Italy	22%	1997–2001	Fissell <i>et al.</i> ⁴⁰
Japan	20%	1997–2001	Fissell <i>et al.</i> ⁴⁰
New Zealand	5%	1992	Blackmore <i>et al.</i> ⁴⁴
Poland	42%	1992	Hruby <i>et al.</i> ⁴⁵
Saudi Arabia	68%	1994	Huraib <i>et al.</i> ⁴⁶
South Africa	21%	1994	Cassidy <i>et al.</i> ⁴⁷
Spain	22%	1997–2001	Fissell <i>et al.</i> ⁴⁰
Thailand	20%	1994	Luengrojanakul <i>et al.</i> ⁴⁸
The Netherlands	3%	1997	Schneeberger <i>et al.</i> ⁴⁹
Tunisia	20%	2001–2003	Hmaied <i>et al.</i> ⁵⁰
United States	14%	1997–2001	Fissell <i>et al.</i> ⁴⁰
United Kingdom	3%	1997–2001	Fissell <i>et al.</i> ⁴⁰

HCV, hepatitis C virus.

Figures are only indicative, as only small-sized studies are available in some countries; data not based on systematic review.

The reported incidence of newly acquired HCV infection, usually detected by seroconversion, was high in the early 1990s, ranging from 1.4% to more than 20% per year.^{35,36} Recent data show that the incidence of seroconversion for HCV has decreased to less than 1–2% in many developed countries.^{34,37,38}

Not surprisingly, the prevalence of HCV infection in CKD transplant patients is also high. Consistent risk factors include the total time spent on dialysis and a history of and/or the number of blood transfusions. The prevalence in a given population of CKD transplant patients parallels the prevalence in the general population of the same country or region. Recent population-based estimates of the prevalence of HCV infection in CKD transplant patients are not available.

Even less is known of the prevalence of HCV in the various stages of CKD before dialysis or transplantation. It is, however, apparent from several case series—admittedly relatively small-sized—that patients with CKD Stages 3–5 have a disproportionately high prevalence of HCV infection compared with the general population.

Natural history of HCV infection in CKD

Multiple observational studies have shown an independent and significant association between HCV positivity and lower patient survival, despite adjustment for a number of comorbid conditions. The major complications of HCV-related chronic liver disease (cirrhosis and hepatocellular carcinoma) have been implicated in the lower survival of anti-HCV-positive CKD Stage 5D patients. Similarly, HCV-infected CKD transplant patients have lower long-term graft and patient survival than uninfected CKD transplant patients. In addition, the presence of HCV RNA in CKD transplant patients has been implicated in the development of post-transplant immune complex GN and a higher incidence of post-transplant diabetes mellitus. Very little is known of the natural history of chronic HCV infection and its prognostic impact in the earlier stages of CKD (see Guideline 2).

Liver biopsy in patients with CKD

Liver biopsy is not without risk and complications, especially hemorrhagic. In patients with CKD, hepatocellular dysfunction, drugs with antiplatelet activity, and uremic platelet dysfunction, all may contribute to this risk. The place of liver biopsy in the diagnostic strategy, the prevention of complications of the procedure, and the scoring of liver biopsies are discussed in Appendix 1.

Treatment of HCV infection in CKD

Treating chronic HCV infection in CKD patients is associated with a number of challenges. As glomerular filtration rate (GFR) decreases, the half-life of both IFNs and ribavirin increases, resulting in potentially poorer tolerance and the need for dosage adaptations in severe CKD. In kidney graft recipients, the use of IFNs and immunostimulating agents

further entails a substantial risk of rejection. These issues are discussed extensively in Guideline 2.

HCV infection in children with CKD

Very little is known about HCV infection in infants and children with CKD. Only a few reports describe the basic epidemiologic characteristics of HCV infection in children with CKD Stage 5D and transplant recipients.^{51,52} This very limited information implies that the current guidelines do not apply directly and completely to this specific population. Pediatric nephrologists and other physicians in charge of caring for children with CKD should carefully evaluate the extent to which the current guidelines may be extrapolated to children.

Management of potential occupational exposure to HCV

Hepatitis C virus is not easily transmitted through occupational exposure to blood. The average incidence of anti-HCV seroconversion after accidental percutaneous exposure to an HCV-positive source is 1.5% (range 0–7%).⁵³ Transmission rarely occurs from mucosal exposure to blood, and no transmission has been documented from intact or nonintact skin exposure to blood. Postexposure prophylaxis (unlike for HIV) is not recommended, either with immunoglobulins or with antiviral agents (IFNs or ribavirin).

In the absence of postexposure prophylaxis for HCV, recommendations for postexposure management aim at

identifying early actual HCV infection. Cohort studies in the general population strongly suggest that early antiviral treatment (at the stage of acute hepatitis C) is associated with a very high (over 90%) rate of cure for hepatitis C.⁵⁴ For HCV postexposure management, the HCV status of the source and the exposed health-care worker should be determined. For health-care workers exposed to an HCV-positive source, follow-up testing should be performed to determine if hepatitis C develops. The minimal recommendation is to perform tests for ALT and EIA (and/or NAT) monthly for 4 months after exposure.⁵⁵ In the case of acute HCV infection, the health-care worker should be referred urgently to a specialist for appropriate management. This does not imply that the viral treatment will always be immediately started, as acute hepatitis C may resolve spontaneously in 15–20% of cases within 3 months,⁵⁶ but close follow-up is essential.

III. FORMAT OF GUIDELINE STATEMENTS

Each listing of guideline statements is accompanied by a table that summarizes the interpretation of the three levels of recommendations used. Each statement strength is matched with specific wording and with a given basis for the strength. For further clarity in the lists of statements, Strong statements are in bold print, Moderate statements are in regular print, and Weak statements are in italics.

Guideline 1: Detection and evaluation of HCV in CKD

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INTRODUCTION

The prevalence of HCV infection is higher in most subgroups of CKD patients than in the general population.^{36,57,58} The reasons for testing CKD patients for HCV include diagnostic evaluation of the cause of CKD (specifically, HCV-associated GN), infection control in hemodialysis units, and optimal care before and after kidney transplantation. Treating HCV infection as early as possible is another major reason for testing all CKD patients who may benefit from antiviral treatment. The specifics of diagnostic testing for HCV in various CKD populations are discussed below, taking into account the presumed prevalence of HCV infection in each population and its characteristics (especially immune deficiency).

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

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

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

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

Levels of strength of recommendations

Strength of recommendation	Wording of recommendation	Basis for strength of recommendation
Strong	An intervention 'should' be done	'High' quality evidence and/or other considerations support a strong guideline ^a
Moderate	An intervention 'should be considered'	'Moderate' quality evidence and/or other considerations support a moderate guideline ^a
Weak	An intervention 'is suggested'	'Low' or 'Very Low' quality evidence; predominantly based on expert judgment for good clinical practice ^a

^aSee Appendix 2: Grading the Strength of the Recommendations, p. S85.

1.1 Determining which CKD patients should be tested for HCV

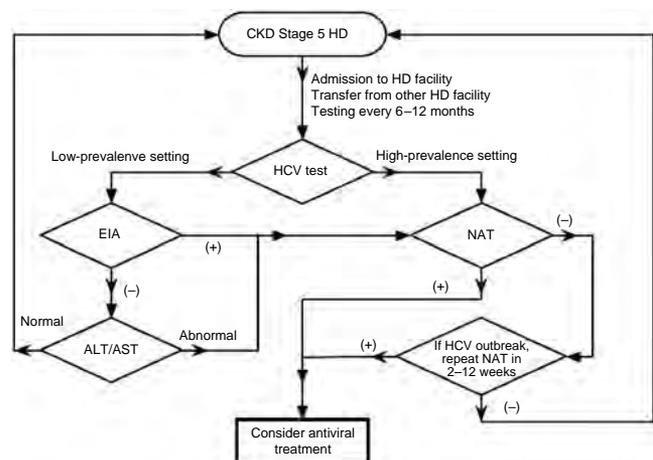
1.1.1 *It is suggested that CKD patients be tested for HCV. (Weak)*

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

1.2 HCV testing for patients on maintenance hemodialysis:

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

- In hemodialysis units with a low prevalence of HCV, initial testing with EIA (if positive, followed by NAT) should be considered (see Algorithm 1). (Moderate)
- In hemodialysis units with a high prevalence of HCV, initial testing with NAT should be considered (see Algorithm 1). (Moderate)



Algorithm 1. CKD Stage 5 hemodialysis diagnostic algorithm.

Please refer to the rationale text for a detailed explanation of the impact of pretest probability of HCV + on the choice of HCV test. In particular, note that after a negative primary NAT, a patient can be considered to be at low probability of HCV infection (unless other factors change) so that subsequent testing by EIA is appropriate. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD: chronic kidney disease; EIA: enzyme immunoassay; HCV: hepatitis C virus; NAT: nucleic acid test.

BACKGROUND

Worldwide, HCV is the major etiologic agent of chronic hepatitis that can lead to the development of liver cirrhosis and hepatocarcinoma. According to the American Association for the Study of Liver Disease (AASLD),⁵⁹ individuals who should be tested for HCV infection include those

- who have injected illicit drugs in the recent or remote past;

- with conditions associated with a high prevalence of HCV infection, including
 - HIV infection,
 - hemophilia treated by clotting factor concentrates before the availability of heat-treated concentrates,
 - CKD Stage 5 ever treated by hemodialysis,
 - unexplained abnormal aminotransferase levels,
 - recipients of a transfusion or organ transplant, specifically those
 - who have been notified that they had received blood from a donor who later tested positive for HCV infection,
 - who have received a transfusion of blood or blood products before the systematic testing of blood donors with second-generation EIA or more recent tests,
 - who have received an organ transplant before the systematic testing of organ donors with second-generation EIA or more recent tests;
 - who are suspected of having chronic HCV infection;
 - children born to HCV-infected mothers;
 - health-care, emergency-medical, and public safety workers after a needlestick injury or mucosal exposure to HCV-positive blood;
 - sexual partners of HCV-infected persons.

RATIONALE

1.1 Determining which CKD patients should be tested for HCV:

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

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

HCV infection has been associated with various types of GN, such as cryoglobulinemic GN,⁶⁰ MPGN, focal and segmental glomerulosclerosis, and membranous GN.^{31,61} Thus, testing for HCV appears logical in CKD patients with either hematuria or proteinuria indicative of the possibility of GN. In addition, in diabetic patients with CKD, HCV infection is an independent predictor of a more rapid decrease of GFR.^{62,63} Finally, the prevalence of HCV infection tends to be higher in patients with CKD not yet on dialysis than in the general population.^{64,65} Thus, testing such patients with CKD is associated with the additional advantage of potentially offering antiviral treatment to all those who are able to benefit from it.

The prevalence of HCV infection is much higher in hemodialysis patients (CKD Stage 5D) than in the general population⁵⁸ and is associated with an increased mortality rate.^{66,67} Although HCV infection results in an increase in ALT, levels are generally lower in hemodialysis patients⁶⁶⁻⁶⁸ and kidney transplant patients⁶⁹ than in the general population, and the reasons for this are unknown. Therefore, a single measurement of ALT level is not a good tool to

detect or rule out either acute or chronic HCV infection in these patients. Treating HCV infection after kidney transplantation is associated with an increased risk of rejection. This, taken together with the need for optimal selection of kidney transplant recipients, makes testing for HCV mandatory as part of the pretransplant evaluation. Moreover, patients in all stages of CKD frequently have abnormal liver enzyme levels and also an increased prevalence of HCV infection. Thus, testing for HCV is also mandatory in the post-transplant period.

1.2 HCV testing for patients on maintenance hemodialysis:

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

- In hemodialysis units with a low prevalence of HCV, initial testing with EIA (and, if positive, followed by NAT) should be considered (see Algorithm 1). (Moderate)
- In hemodialysis units with a high prevalence of HCV, initial testing with NAT should be considered (see Algorithm 1). (Moderate).

The prevalence of HCV infection in patients on hemodialysis is highly variable but clearly much higher than in the general population of the respective countries. In phase one of the Dialysis Outcomes and Practice Patterns Study (DOPPS)—a prospective, observational study of adult hemodialysis patients randomly selected from 308 representative dialysis facilities in France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States—an overall HCV prevalence of 13% was found in 8615 patients.⁴⁰ The HCV prevalence varied from 3% (the United Kingdom, Germany) to 23% (Italy, Spain). In some developing countries, the prevalence of HCV in dialysis patients is even higher: Brazil 24–47%,⁷⁰ India 12–45%,⁴² Jordan 35%,⁷¹ Saudi Arabia 43%.⁷²

The prevalence of HCV infection is influenced, among other factors, by

- dialysis modalities, that is, hemodialysis (center > home hemodialysis) > peritoneal dialysis;
- hemodialysis vintage;
- history of blood transfusions or organ transplantation before effective screening of donors with second-generation EIA or more recent tests;
- prevalence of HCV infection in the dialysis unit.

Testing for HCV in all patients initiating hemodialysis or transferring to a new facility should be part of the infection control strategy of each hemodialysis facility (see Guideline 3).

The detection of anti-HCV antibodies is based on the use of third-generation EIA that detects antibodies directed against various HCV epitopes. EIA tests are reproducible, inexpensive, and suitable for use in the diagnosis of HCV infection. Given the good performance of third-generation EIA tests, immunoblot tests have become obsolete in clinical practice.³ The increased sensitivity of the last generation of HCV assays has dramatically reduced the risk of HCV

transmission by blood components and reduced the time between acquisition of infection and detection of anti-HCV antibodies (the 'serologic window') from 82 to 66 days.^{4,5} In the near future, fourth-generation tests will be available, allowing the simultaneous detection of HCV antibodies and HCV core protein. These tests should further reduce the serologic window. In some populations with frequent polyclonal hypergammaglobulinemia, there may be discrepancies among third-generation EIA tests. Thus, in pregnant women in Cameroon, HCV-positive determination using only one third-generation EIA test was 4.9%, but it decreased to 1.9% when requiring positive results of two third-generation EIA tests; HCV RNA was present in 75% of women having concomitantly two positive EIA tests and 0% in those having only one positive EIA test.⁶

NAT is based either on qualitative HCV RNA detection or on HCV RNA quantitation. Qualitative detection assays are based on the principle of target amplification using conventional PCR, real-time PCR, or TMA. All commercially available assays can detect 50 IU ml⁻¹ or less of HCV RNA, and have equal sensitivity for the detection of all HCV genotypes.⁷ The lower limit of detection of the qualitative conventional PCR-based assays or their semiautomated version is 50 IU ml⁻¹; that of real-time PCR assays, which are able at the same time to qualify and quantify HCV RNA, is 10–30 IU ml⁻¹; and that of TMA-based assay is 10 IU ml⁻¹. Quantitative assays are based either on target amplification techniques (conventional PCR or real-time PCR) or on signal amplification techniques (branched DNA). Branched DNA and most quantitative conventional PCR-based assays have detection limits higher than those of qualitative detection assays.

NAT should be performed in laboratories that have facilities specifically designed for that purpose. Serum or plasma samples must be collected, processed, and stored in a manner suitable for minimizing false-negative results obtained from NAT. Serum or ethylenediaminetetraacetic acid (EDTA) plasma must be separated from cellular components within 2–6 h after collection. Storage of serum or EDTA plasma at 2–5 °C should be limited to 72 h; for longer storage, freezing at –20 or –70 °C is recommended. Samples collected for serologic testing can be used only if these conditions are met.⁷³ Since heparin is an inhibitor of PCR,^{74,75} samples from hemodialysis patients should be obtained before the dialysis session and from a peripheral vein in patients with a central catheter locked with heparin.

Tests other than classical EIA or NAT may become clinically available in the relatively near future.⁷⁶ Among the potential test candidates is one for the core protein, which is a structural HCV protein whose sequence is highly conserved across HCV genotypes.⁷⁷ The HCV core antigen test, in hemodialysis patients, has a sensitivity and specificity of 84 and 89%, respectively.⁷⁸ There is now an HCV test that combines the simultaneous detection of HCV core antigen and anti-HCV antibodies, and also enables an early detection of HCV infection during the so-called 'window period' compared to anti-HCV assays. This test could be a useful

alternative to HCV RNA detection or HCV core antigen assays for diagnosis or blood screening when NAT or HCV core antigen detection is not implemented.⁵ However, these tests are not yet routinely available.

How should hemodialysis patients be tested?

The consequences of variable diagnostic accuracy are not purely academic. Patients with positive diagnostic tests will be further assessed, including, if indicated, a liver biopsy, and eventually will receive appropriate treatment, with its own associated benefits and harm. Patients with false-positive results might be subjected to further inappropriate testing—in particular, liver biopsies—and eventually unnecessary treatment. Patients with false-negative results might lose an opportunity for intervention (with possible increased morbidity and mortality of undiagnosed HCV infection) while on dialysis and after kidney transplant. The sensitivity and specificity of EIA as compared with the reference standard of NAT have been examined in a meta-analysis of relevant published papers (Tables 2–4). This analysis made several assumptions. While acknowledging that EIA and NAT measure different conditions (antibody response to present or past infection and viremia, respectively), in practice these two tests are both used primarily as markers of HCV infection. This analysis assumes that EIA is used as a cheaper, more readily accessible alternative to the more definitive NAT. Thus, sensitivity and specificity of EIA are based on NAT as the reference standard. It is important to realize that there are a number of conditions where EIA and NAT accurately disagree (such as continued antibody response after a cleared infection or immunodeficiency with active viremia). However, for the purpose of this analysis, it is assumed that both tests are being considered as alternatives for making new diagnoses of HCV infection. Patients for whom EIA is considered an inaccurate test for active infection, due to severe immunodeficiency, should be tested with NAT alone. In the relevant published studies, the sensitivity of EIA varied from 53 to 100% and the specificity from 85 to 100%, with pooled sensitivity and specificity of 75 and 95%, respectively (Figure 1). Across studies, there was no association between HCV prevalence and reported sensitivity and specificity.

Implications with consideration of unit prevalence

Figure 2 depicts how the estimates of HCV prevalence can change after an EIA test and vary depending on the actual prevalence of HCV and the sensitivity and specificity of EIA. In each graph, the upper curve indicates the prevalence of HCV among patients with a positive EIA over the full range of true HCV prevalence (that is, the positive predictive value of EIA). The lower curves indicate the prevalence of HCV among patients with a negative EIA (or 1—negative predictive value). Figure 2b uses a theoretical midpoint in both sensitivity and specificity from the summary receiver operating characteristics curve, based on the summary estimates among the 12 studies (sensitivity 75%, specificity 95%), whereas approximate extreme values are used in Figure 2a and c.

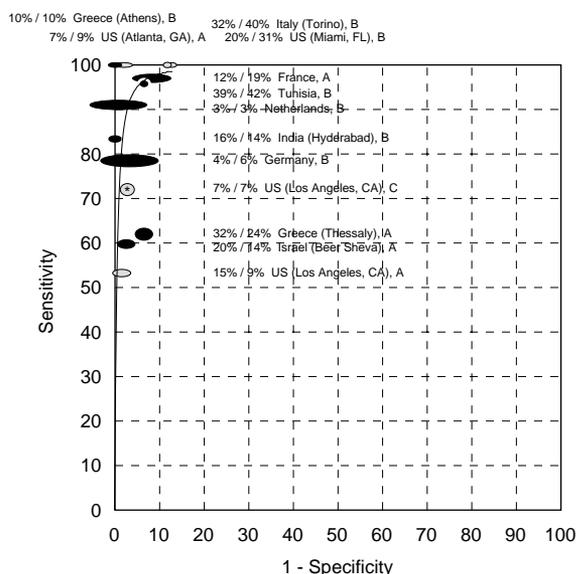


Figure 1 | Summary receiver operating characteristic curve: EIA vs NAT. *For Khan (at Sn 72%, Sp 97%), the oval size is for the actual numbers analyzed. For each study, the prevalence of HCV per NAT/EIA testing, and the quality are noted. Black ovals indicate 3rd generation EIA, grey ovals indicate 2nd generation EIA.

The graphs also highlight several theoretical pretest prevalence values. The pretest values refer to the best guess estimate of the likelihood of HCV infection before the test is performed. A starting point for this estimate can be the recent prevalence of disease in a dialysis unit or in a region. The pretest prevalence values graphed include the mean (13%) and extreme values of 3% and 23% in DOPPS⁴⁰ as well as a 40% prevalence taken to represent higher prevalence settings. Using Figure 2b, at low pretest prevalence values (3%, 10%) when the EIA is negative, the post-test prevalence (the likelihood of infection after the test) remains less than 5%. However, as pretest prevalence increases to 23% or 40%, the post-test prevalence among those with a negative EIA increases to 15% (in Figure 2b). Thus, with higher baseline prevalence rates of disease, there is an increasing proportion of false-negative EIA results.

Furthermore, in the low pretest prevalence setting, a positive EIA results in only a 30–65% post-test prevalence of HCV. As pretest prevalence increases, a positive EIA results in increasing post-test prevalence of HCV. For example, at a pretest prevalence of 40%, a positive EIA results in about a 90% post-test prevalence of HCV infection. Thus, in low-prevalence settings, there is a relatively high risk of false-positive EIA results.

However, uncertainty exists about the true sensitivity and specificity of EIA testing of hemodialysis patients. Figure 2a demonstrates the post-test prevalence estimates of HCV as a function of pretest prevalence when EIA has a low sensitivity (53%) and high specificity (99%). Using these performance characteristics, the curves are shifted to the upper left. With increasing pretest prevalence of HCV, the post-test prevalence of HCV when EIA is negative increases to as high as 24% in the highest prevalence setting. As a result, there is a marked increase in false-negative EIA test results as pretest prevalence rises.

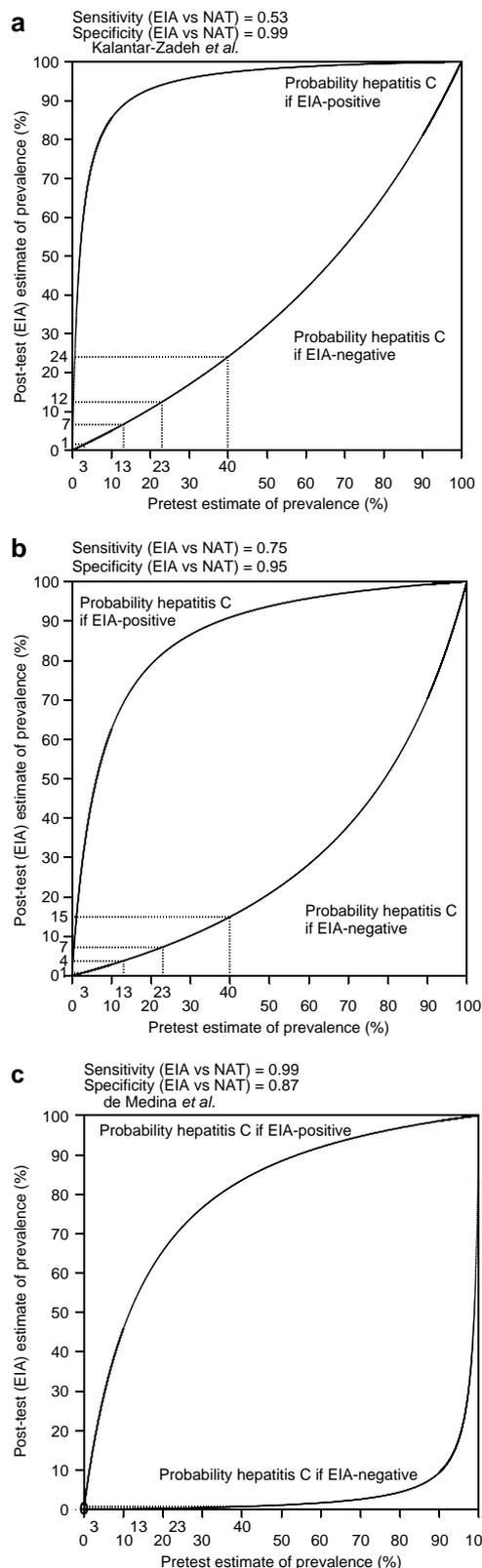


Figure 2 | Probability of HCV infection based on population prevalence and EIA test accuracy. (a) Low sensitivity, high specificity; (b) approximated from pooled estimates of sensitivity and specificity; (c) high sensitivity, low specificity. Abbreviations: EIA: enzyme immunoassay; NAT: nucleic acid test.

Conversely, there is a low rate of false-positive testing (that is, nearly all positive EIA results represent true HCV infection).

Figure 2c depicts the scenario where sensitivity is high and specificity relatively low (sensitivity 99%, specificity 87%), where the curves are shifted to the lower right. Here, a negative EIA result likely represents a true negative in all but the highest (>80%) prevalence settings. However, a positive EIA result has a high likelihood of being a false positive in the range of prevalence common in dialysis units. For instance, in the 3–13% range, a positive EIA results in only a 15–50% prevalence of disease.

In summary, in low-prevalence settings, EIA is adequate to rule out HCV infection when the test is negative, but a positive EIA would need confirmation with NAT. In this setting, only relatively few patients will require NAT testing, as most patients without HCV will test negative on EIA. In higher prevalence settings, a negative EIA becomes increasingly unreliable to rule out HCV infection; thus, initial testing with NAT becomes appropriate to avoid missing HCV infections. However, given the uncertainties regarding the sensitivity of EIA to predict NAT-positive patients and given the differing preferences regarding the acceptable risks of missing HCV infections in hemodialysis patients, no single threshold can be used to distinguish between high- and low-prevalence settings.

In addition, it is important to note that this discussion refers only to patients who have not been recently tested for HCV. Patients who were previously tested negative for HCV (by EIA or NAT) and who have not had an intervening event placing them at increased risk can be considered to be at low risk for HCV and should be tested with EIA when necessary (see rationale for Guideline 1.2.2). Conversely, patients with recently elevated ALT/AST levels or with another event that has placed them at high risk for HCV infection (where their likelihood of infection is greater than the threshold used for high prevalence) should be tested with NAT.

Hemodialysis patients are tested for HCV to identify infected patients, who may be treatment candidates, and to identify newly infected cases for the purposes of infection control. The consideration of which test (EIA or NAT) to use should depend on the prevalence of HCV in the dialysis unit to minimize false-positive and false-negative results. The implications of a false-negative EIA test (whether due to test error or to immune dysfunction in the setting of viremia) include a delay or failure of diagnosis of HCV infection. Not identifying HCV-infected hemodialysis patients has important implications, as HCV infection is associated with increased mortality (relative risk (RR) = 1.57)⁷⁹ on hemodialysis and after kidney transplantation (RR = 1.79).⁸⁰ Moreover, non-recognition of HCV-infected hemodialysis patients can increase the risk of transmission to other dialysis patients (particularly if the infection was due to, in part, poor infection control in the dialysis unit). On the other hand, a false-positive EIA test (based on test error as opposed to a previous history of HCV infection) will lead to unnecessary additional testing (NAT).

In high-prevalence settings, high false-negative rates call into question the value of EIA as a screening test for HCV in a dialysis unit. In these settings, a high percentage of patients with

a negative EIA are, in fact, HCV RNA-positive. For example, in a setting with a pretest prevalence of HCV of 40%, of those who test negative by EIA, 15% will be HCV RNA positive when a NAT is performed. Furthermore, in high-prevalence settings, a large percentage of patients will require additional testing with NAT due to positive EIA tests (both true positives and false positives), mitigating the cost savings of starting with EIA.

In low-prevalence settings, there is an increased likelihood of false-positive EIA testing (whether due to test error or to previously cleared HCV infection). However, owing to the low prevalence of disease, the actual number of false-positive results (as well as the number of true positives) will be low; thus, there will be only a small additional expense of further testing. For example, in a setting with 5% prevalence, if specificity is 95%, less than 5% of patients will require confirmation with NAT.

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

How should regular testing be performed?

Patients who are EIA-negative and NAT-negative should be considered in a low-risk (that is, low prevalence) group unless a change in clinical status that increases the likelihood of acute HCV infection occurs, for example, elevated ALT/AST levels or other traditional risk factors for acquiring HCV such as intravenous drug user (IVDU), and so on. In most countries, the incidence rate of new HCV infection varies from 0 to 3.6% in most units (DOPPS 1 (1996–2001): Italy, 3.6%; the United States, 3.1%; the United Kingdom, 1.1%; Japan and Spain, 3%; France, 1.9%; Germany, 1.7%). Other, more recent studies indicate incidence rates of Italy, 2%; Japan, 0.3%;⁸¹ Tunisia, 0.5%.⁵⁰ However, in some units prevalence is as high as 75%, suggesting a persistently high incidence (for example, Casablanca, Morocco).⁸² Thus, in most countries and units, there is a very low likelihood of acquiring new HCV infection in a 6-month to 1-year period even in dialysis units with the highest prevalence. Consequently, repeat NAT testing on an annual or biannual basis will likely detect very few cases and will not be cost-effective. The proposed interval of 6–12 months between tests for HCV may probably be extended in the few patients treated exclusively by home hemodialysis. Monthly ALT testing to identify those patients with increased likelihood of acute HCV infection should be adequate when combined with biannual EIA testing. These patients are in a low-prevalence state if they have had a one-time negative NAT. A patient whose ALT/AST levels increase acutely would be managed as having a higher likelihood of HCV infection in the period in which the ALT/AST levels increase. Also, travel to regions where the prevalence of HCV is high in dialysis centers is unlikely to be associated, in a brief period of time on hemodialysis, with such an increase of the risk that the high-prevalence threshold is reached. Thus, NAT testing on return to the primary unit is not necessary (in the absence of elevated aminotransferase levels). This approach may be adapted if the incidence/prevalence in the hemodialysis

unit where the patient is visiting is extremely high and/or the stay prolonged (several months).

This usually raises the issue of previous HCV testing with EIA. If one-time NAT testing of the entire cohort of EIA-negative hemodialysis units is adopted, does a history of previous EIA negativity decrease the likelihood of a positive NAT? In theory, repeated EIA-negative results might be hypothesized to lower the likelihood of a positive NAT, but this would require that the performance characteristics of this test on sequential samples are independent. However, it is likely that this is not the case. False-negative EIA results are relatively rare in immunocompetent individuals; thus, the false-negative results in hemodialysis patients likely represent an impaired immune response to HCV infection. Consequently, an EIA-negative patient who is actually NAT-positive would be more likely to have repeated false-negative results during ongoing testing. Thus, NAT testing of EIA-negative patients from high-prevalence settings would be anticipated to detect additional HCV RNA patients.

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

In suspected acute HCV infection, a negative anti-HCV test does not exclude HCV infection. After an exposure to HCV, HCV RNA can be detected within 1–2 weeks, whereas antibodies to HCV are detectable only, on average, 8 weeks later in immunocompetent subjects.⁵⁹

ALT levels increase in acute HCV infection. Although a single measurement is not useful as a screening method for HCV, ALT levels are regularly measured in CKD Stage 5D patients, and an elevation of ALT levels compared to baseline values may suggest a recent infection.^{83–85} Even though in hemodialysis patients the ALT levels are lower than those in patients without kidney disease,⁵⁹ an unexplained elevation of aminotransferase levels from baseline should prompt testing by NAT.

In CKD Stage 5D patients, the serologic window, that is, the time lag between acute HCV infection and seroconversion, may have a duration of up to several months.^{83,84} In a recent study in CKD Stage 5D patients, the median interval between NAT positivity and EIA positivity was 246 and 154 days for second- and third-generation EIA, respectively.⁸⁶

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

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

If the nosocomial transmission of HCV to a patient on hemodialysis is suspected, the early recognition of other cases of acute HCV infection within the facility would provide an additional clue to ongoing HCV transmission; hence, there is urgency to audit and reinforce the basic hygienic precautions to prevent HCV transmission. In addition, the early diagnosis of acute HCV infection should prompt early treatment in suitable candidates, with a much better chance of therapeutic success (see Guideline 2).

A negative sensitive NAT test in a person with a positive EIA most likely indicates that the HCV infection has resolved.⁵⁹ Other interpretations are that the anti-HCV immunoassay is falsely positive, the NAT test is falsely negative, or rarely, that a person has intermittent or low-level viremia. The latter situation is most unlikely when using TMA. As the implications of missing actual HCV viremia may be substantial, a repeat testing of EIA-positive NAT-negative patients is recommended.

Summary of recommendations

- Dialysis units with a known high prevalence of HCV should ensure that all patients have been tested once with NAT (as it is likely that some EIA-negative patients are actually HCV RNA-positive).
- Incident dialysis patients with a high likelihood of being HCV infected and without a documented NAT should have NAT testing performed on admission to the unit.
- EIA-negative patients who are believed to be at high risk (using the same threshold as for high prevalence) of HCV infection due to changes in risk factors or exposures should be tested with NAT.
- Patients in low-prevalence units, from low-prevalence regions or countries, and those who remain at low risk of infection (below the threshold for high prevalence) should be tested with EIA.

RESEARCH RECOMMENDATIONS

- Additional studies are required to better delineate the actual prevalence of HCV infection and distribution of HCV genotypes at various stages of CKD.
- The sensitivity of EIA testing for the detection of HCV infection along the various (especially early) stages of CKD should be investigated.
- The impact of CKD stage on the natural history of HCV viremia should be studied further.

Table 2 | Summary table of baseline characteristics of hemodialysis patients tested for HCV (EIA vs NAT)

Author (year)	Country of study	Sample size	Mean age (years)	Race	Male gender (%)	Mean duration of HD (months)	Genotype prevalence					N
							1	2	3	4	5	
EIA 3 vs NAT test												
Hanuka (2002) ⁸⁷	Israel	310	ND	ND	ND	ND	67 ^a	7	14	3		
Hinrichsen (2002) ⁴¹	Germany	2796	61	ND	53	54	93	5	1	1		17
Schneeberger (1998) ⁸⁸	The Netherlands	2653	ND	ND	ND	ND	70 ^b	17	7	4		1
Salama (2000) ⁸⁴	France	1323	65	ND	60	36				ND		
Rigopoulou (2005) ⁸⁹	Greece	366	61	ND	66	49				ND		
Bouzgarrou (2005) ⁷⁸	Tunisia	175	ND ^c	ND	ND ^c	ND	91	2	2	5		ND
Garinis (1999) ⁹⁰	Greece	161	43	ND	52	114 ^d				ND		
Reddy (2006) ⁹¹	India	111	ND	ND	ND	ND				ND		
Dalekos (1998) ⁹²	Greece	15 EIA+ 81 EIA-	55 61	ND ND	67 67	81 55				ND ND		
Abdelnour (1997) ⁹³	Lebanon	108	ND	ND	ND	ND				ND		
de Medina (1998) ⁹⁴	United States	128	21–76 (range)	52% Black	59	3–108 (range)				ND		
EIA 2 vs NAT test												
Kalantar-Zadeh (2005) ⁹⁵	United States	314	53	30% Black	52	37				ND		
Kelley (2002) ⁹⁶	United States	257	63	ND	'Approximately half'	80% for >1 year	94	6				2
Khan (2004) ⁹⁷	United States	269	ND	ND	ND	ND				ND		
de Medina (1997) ⁹⁸	United States	88	52	57% Black 22% Hispanic 14% White 1% Asian	75	34				ND		
Boero (1995) ⁹⁹	Italy	75	63	ND	53	63				ND		
Sypsa (2005) ⁸⁶	Greece	562	57	ND	58	31	50	3	24	22		20
Fabrizi (1998) ¹⁰⁰	United States	375	61	63% Black 19% White 12% Hispanic 6% Asian	56	27				ND		

EIA, enzyme immunoassay; HCV, hepatitis C virus; HD, hemodialysis; NAT, nucleic acid test; ND, not documented.

^aNine percent of patients had genotypes 1b+3a.

^bThese percentages are out of a total of 71 patients. Further breakdown by genotype is as follows: 1a, 24%; 1b, 46%; 2a, 13%; 2b, 1%; 2, 3%. Also, 6% of the patients had multiple genotypes.

^cThese parameters were not documented on the entire cohort. The 76 patients who ultimately were EIA-positive had the following characteristics: 52% men, mean age of 47 years.

^dThis duration of dialysis is the mean duration of those patients who were shown to be HCV-positive in at least one of the three screening and/or confirmatory assays ($n=19$).

Table 3 | Summary table of testing for HCV in hemodialysis patients (EIA vs NAT)

Author (year), country of study	N	Description of HCV diagnostic test				Outcomes of interest			Quality	
		Diagnostic test	Reference standard (Sensitivity threshold)	Reference standard	Diagnostic test		Sn Sp			
					EIA(+)	EIA(–)				
<i>EIA 3 vs NAT test</i>										
Salama (2000), ⁸⁴ France	1323	EIA 3 (multiple, different tests used)	RT-PCR (Cobas Amplicor 2.0) (50 IU ml ⁻¹)	NAT(+) NAT(–)			152 ^a 94 ^a PPV: ~62%	5 1072 NPV: 99.5%	Sn: 97% Sp: 92%	A
Rigopoulou (2005), ⁸⁹ Greece	366	EIA 3	TMA (Versant) (10 IU ml ⁻¹)	NAT(+) NAT(–)			72 16 PPV: 82%	44 234 NPV: 84%	Sn: 62% Sp: 94%	A
Hanuka (2002), ⁸⁷ Israel	310 ^b	EIA 3	RT-PCR (Cobas Amplicor 2.0) (50 IU ml ⁻¹)	NAT(+) NAT(–)			37 6 PPV: 86%	25 242 NPV: 91%	Sn: 60% Sp: 98%	A
Hinrichsen (2002), ⁴¹ Germany	2796	EIA 3	RT-PCR (Cobas Amplicor 2.0) (50 IU ml ⁻¹)	NAT(+) NAT(–)			~87 ~84 PPV: ~51%	~24 ~2591 NPV: ~99%	Sn: ~78% Sp: ~97% ^c	B
Schneeberger (1998), ⁸⁸ The Netherlands	2653 ^d	EIA 3	RT-PCR (in-house) (ND)	NAT(+) NAT(–)			61 ^e 18 PPV: 77%	6 2568 NPV: 99.8%	Sn: 91% Sp: 99%	B
Bouzzgarrou (2005), ⁷⁸ Tunisia	175	EIA 3	RT-PCR (Platinum Taq kit) (ND)	NAT(+) NAT(–)			66 7 PPV: 90%	3 ^f 99 NPV: 97%	Sn: 96% Sp: 93%	B
Garinis (1999), ⁹⁰ Greece	161	EIA 3	RT-PCR (HCV Amplicor) (ND)	NAT(+) NAT(–)			16 0 PPV: 100%	0 145 NPV: 100%	Sn: 100% Sp: 100%	B
Reddy (2006), ⁹¹ India	111	EIA 3	RT-PCR (Amplicor 2.0) (ND)	NAT(+) NAT(–)			15 0 PPV: 100%	3 93 NPV: 97%	Sn: 83% Sp: 100%	B
Dalekos (1998), ⁹² Greece	15 EIA+	EIA 3	RT-PCR (DEIA) (100 copies)	EIA(+)	N=15	NAT(+) NAT(–)	13 2 PPV: 87%			C
	81 EIA–			EIA(–)	N=81	NAT(+) NAT(–)		0 81 NPV: 100%		
Abdelnour (1997), ⁹³ Lebanon	17 EIA+	EIA 3	RT-PCR (in-house) (ND)	EIA(+)	N=17	NAT(+) NAT(–)	11 6 PPV: 65%			C
	29 of 91 EIA–			EIA(–) without signs and symptoms of HCV	N=29 (of 91)	NAT(+) NAT(–)		3 26 ^g NPV: 90%		
de Medina (1998), ⁹⁴ United States	35 EIA+ ^h	EIA 3	RT-PCR (Amplicor Monitor) (50 IU ml ⁻¹)	NAT(+) NAT(–)			29 6 PPV: 83%			C

Table 3 | Continued

Author (year), country of study	N	Description of HCV diagnostic test			Outcomes of interest			Quality	
		Diagnostic test	Reference standard (Sensitivity threshold)	Reference standard	Diagnostic test		Sn Sp		
					EIA(+)	EIA(-)			
<i>EIA 2 vs NAT test</i> Kalantar-Zadeh (2005), ⁹⁵ United States	314	EIA 2	TMA (Versant) (signal to cutoff ratio > 1)	NAT(+) NAT(-)	25 4	22 263	Sn:53% Sp: 99%	A	
Kelley (2002), ⁹⁶ United States	257	EIA 2	RT-PCR (Amplacor) (50 IU ml ⁻¹)	NAT(+) NAT(-)	19 5	0 233	PPV: 86% NPV: 92%	Sn: 100% Sp: 98%	A
de Medina ¹ (1997), ⁹⁸ United States	88	EIA 2	bDNA (Quantiplex) (3.5 × 10 ⁵ equiv. ml ⁻¹)	NAT(+) NAT(-)	18 9	0 61	PPV: 67% NPV: 100%	Sn: 100% Sp: 87%	B
Boero (1995), ⁹⁹ Italy	75	EIA 2	RT-PCR (DEIA) (ND)	NAT(+) NAT(-)	24 6	0 45	PPV: 80% NPV: 100%	Sn: 100% Sp: 88%	B
Sypsa (2005), ⁸⁶ Greece	562 EIA+ ^j	EIA 2 ^k	RT-PCR (Amplacor) (50 IU ml ⁻¹)	NAT(+) NAT(-)	110 53		PPV: 67%		C
Fabrizi (1998), ¹⁰⁰ United States	375 EIA- ^l	EIA 2	bDNA (Quantiplex) (3.5 × 10 ⁵ equiv. ml ⁻¹)	NAT(+) NAT(-)		6 369	NPV: 98%		C
Khan (2004), ⁹⁷ United States	269	EIA 2	RT-PCR (in-house) (ND)	NAT(+) NAT(-)	110 59	2 (43) ^m 98 (2109) ^m	PPV: 65% NPV: 98%	Sn ^m : (72)% Sp: (97)%	C

bDNA, branched DNA; DEIA, DNA enzyme immunoassay; EIA, enzyme immunoassay; HD, hemodialysis; NAT, nucleic acid test; ND, not documented; NPV, negative predictive value; PPV, positive predictive value; RT-PCR, reverse transcription-polymerase chain reaction; Sn, sensitivity; Sp, specificity; TMA, transcription-mediated amplification.

^aPatients were tested with two different EIA 3 tests and were classified as positive (both tests positive), negative (both tests negative), or discordant (one test positive and one test negative). For analysis, positive and discordant groups combined EIA-positive cells. If discordant results were analyzed as EIA-negative, Sn and Sp remained unchanged.

^bAlso reported results of 319 patients in a hepatology clinic but not described here.

^cSp and negative predictive value are determined from approximations in EIA+/NAT- and EIA-/NAT- cells. A total of 2591 patients were negative by both tests. Nineteen patients had EIA testing only and 10 had NAT testing only. Thus, the negative predictive value and Sp are estimates based on the 2591 value. We then performed Sn analysis by adding the 10 patients with incomplete data into each of the four cells of a 2 × 2 table. Estimates of negative predictive value and Sp changed by less than 1%. Sn varied from 72 to 80% when the 10 patients were added to the EIA-/NAT+ and EIA+/NAT+ cells, respectively.

^dTotal sample size includes 2108 hemodialysis patients and 545 peritoneal dialysis patients. Results were not distinguished between these two groups.

^eThis group included all EIA-positive test results regardless of confirmation assay, which demonstrated five indeterminate and four negative results in patients who were EIA-positive. There is no difference in Sn or positive predictive value when these results were considered EIA-negative.

^fThese three patients were diagnosed with acute HCV infection and later seroconverted to EIA-positive. When reanalyzed with these results in EIA-positive RNA-positive cell, Sn was 91%, Sp was 100%, positive predictive value was 100%, and negative predictive value remained unchanged at 93%.

^gVerification bias was possible because 29 patients were selected from among 91 EIA-negative patients. There was no discussion of whether they were randomly selected.

^hRNA not tested in 93 EIA 3-negative patients.

ⁱPrimary focus of the study was comparing bDNA with RT-PCR, but also looked at EIA 2.

^jPatients (399) were EIA-negative and did not have a NAT test performed.

^kCompared EIA 2 and EIA 3 results in a randomly selected cohort of 189 patients. Discordant results were seen in 9 of 189 patients (8 of 9 were EIA 3-positive and EIA 2-negative; only 1 patient was EIA 2-positive and EIA 3-negative).

^lSeventy-four patients were EIA-positive and did not have a NAT test performed.

^mEIA-negative patients (100) were chosen at random from total of 2152 EIA-negative patients. In parentheses is the value after the conversion to the entire population of people who were tested by EIA 2.

Table 4 | Evidence profile for diagnostic testing for HCV in hemodialysis patients

Outcome	No. of studies and study design	Total N of patients	Methodologic quality of studies	Consistency across studies	Directness of the evidence, including applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Description of findings	Importance of outcome
Sn and Sp of EIA (NAT used as reference standard)	13 (+5 without Sn/Sp) ^a (high)	10 012	Some limitations ^b (–1)	No important inconsistencies ^c (0)	Direct ^d (0)	Absence of clear reference standard	Moderate	EIA 3: range of Sn was 60–100% and range of Sp was 86–100%. EIA 2: range of Sn was 53–100% and range of Sp was 87–99%	High
Total N		10 012							
Balance of potential benefits and harm: N/A (refer to text discussion about implications of false-positive and false-negative tests results)							Quality of overall evidence: Moderate		

EIA, enzyme immunoassay; N/A, not applicable; NAT, nucleic acid test; Sn/Sp, sensitivity or specificity.

^aFive studies (1114 patients, all C quality) contributed information on positive predictive value and negative predictive value, but were not considered for this outcome because they did not report sensitivity and specificity.

^bVerification bias in C-grade studies did not contribute, but there were incomplete data and inconsistencies between text and tables of some articles.

^cWide variability in result of performance characteristics across studies, but unable to explain the rationale for these differences adequately after careful review of study.

^dStudies occurred in a variety of prevalence settings and used different EIA and NAT tests which improved applicability.

Guideline 2: Treatment of HCV infection in patients with CKD

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Guideline 2.1: Evaluation of HCV-infected CKD patients for antiviral treatment

INTRODUCTION

Despite the increased prevalence of HCV infection in CKD patients compared to that of the general population, the indications for treatment and optimal antiviral regimens in terms of safety and efficacy in CKD are not well defined. The following recommendations are based on an evaluation of the available literature focusing on HCV-infected CKD patients; however, extrapolation of data from the non-CKD population was also necessary in situations where only limited information was available. This was done in accordance with the KDIGO position statement on extrapolating evidence from studies on the general population.¹⁰¹ A variety of IFN-based regimens with differing treatment durations have been used in CKD, which makes comparison among studies more difficult. In these situations, the best available information from the CKD population was used together with data from the general population where extrapolation was considered to be appropriate to make the following recommendations.

Levels of strength of recommendations

Strength of recommendation	Wording of recommendation	Basis for Strength of recommendation
Strong	An intervention 'should' be done	'High' quality evidence and/or other considerations support a strong guideline ^a
Moderate	An intervention 'should be considered'	'Moderate' quality evidence and/or other considerations support a moderate guideline ^a
Weak	An intervention 'is suggested'	'Low' or 'Very Low' quality evidence; predominantly based on expert judgment for good clinical practice ^a

^aSee Appendix 2: Grading the Strength of the Recommendations, p. S85.

- 2.1.1 *It is suggested that CKD patients with HCV infection be evaluated for antiviral treatment. (Weak)*
- 2.1.2 *It is suggested that the decision to treat be based on the potential benefits and risks of therapy, including life expectancy, candidacy for kidney transplantation, and comorbidities. (Weak)*
- 2.1.3 *It is suggested that in CKD patients—except kidney transplant recipients—who develop an acute HCV infection, a waiting period beyond 12 weeks to observe spontaneous clearance (by NAT) is not justified and that antiviral treatment should be started. (Weak)*

- 2.1.4 *It is suggested that HCV-infected patients accepted for kidney transplantation be treated (see Guideline 4). (Weak)*
- 2.1.5 *It is suggested that treatment of HCV-infected kidney transplant recipients be considered only when the benefits of treatment clearly outweigh the risk of allograft rejection due to IFN-based therapy (for example, fibrosing cholestatic hepatitis, life-threatening vasculitis). (Weak)*
- 2.1.6 *It is suggested that antiviral therapy be considered for patients with HCV-related GN (see Guideline 5.3). (Weak)*

BACKGROUND

HCV infection is more prevalent in patients with CKD than in the general population, and thus treatment of either acute or chronic HCV infection in patients with CKD is an important consideration. Unfortunately, all major RCTs for the treatment of HCV infection have specifically excluded patients with abnormal kidney function. Accordingly, the available data that critically evaluate the indications for treatment and determine the most efficacious and safe treatment protocols in CKD patients are limited.

Nevertheless, the issue of treatment in the CKD population is an important one, as HCV infection has been implicated in the pathogenesis of various forms of immune complex GN and has been shown to adversely affect patient survival in the maintenance hemodialysis population. Furthermore, HCV-infected patients who receive a kidney transplant have an inferior survival compared with non-HCV-infected patients. In addition, they are at greater risk of developing *de novo* GN of the allograft as well as increased risk for new-onset diabetes after transplantation (NODAT). Thus, there are compelling reasons to diagnose and treat specific groups of HCV-infected CKD patients with the goal of clearing viremia and obtaining SVR.

RATIONALE

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

The decision to treat HCV infection in the CKD patient should be based on liver histology, age, comorbidities, and ability to tolerate therapy. The revised National Institutes of Health (NIH) consensus statement from 2002, updated from the 1997 original, suggests that a liver biopsy may not be necessary in all patients before treatment. It was the judgment of the experts who updated the recommendations that, whereas a biopsy is recommended in patients infected with HCV genotypes 1 and 4, it may not be necessary in

patients infected with genotypes 2 and 3 in whom the response rate to treatment is quite high (~80%) (<http://www.consensus.nih.gov/2002/2002HepatitisC2002116main.htm>). It must be noted that the studies from which these recommendations were derived excluded patients with CKD from participation, and thus any applicability to the CKD population is inferred and not based on data obtained from clinical trials with CKD patients.

Relevant information from a liver biopsy include the grade of necrosis and inflammatory activity, and the stage of fibrosis, both of which are determining factors in advising therapy for individual patients. The AASLD guidelines for the treatment of patients with HCV infection are generally in agreement with those of the NIH (<https://www.aasld.org/eweb/docs/hepatitisc.pdf>). The AASLD guidelines recommend that patients who have chronic hepatitis C with significant fibrosis (Metavir score ≥ 2 , Ishak score ≥ 3) should receive antiviral therapy, as this is predictive of progression to more advanced histology, whereas patients with lesser degrees of fibrosis should ordinarily not be treated. They also recommend that treatment with IFN and ribavirin may be contraindicated in certain groups of patients. These include those individuals with major, uncontrolled depressive illness or concurrent disease, such as severe hypertension, heart failure, significant coronary artery disease, poorly controlled diabetes, obstructive pulmonary disease, uncontrolled seizures, or untreated hyperthyroidism. Also, patients >60 years of age are in a higher risk group for the development of serious adverse reactions to IFN and require individual decision-making. In addition, the AASLD guidelines recommend that treatment in patients with CKD 'should be individualized' and that 'HCV should not be treated in kidney transplant recipients.'

There are limited data available on patient survival in HCV-infected CKD patients who are on dialysis. Studies performed in the general population without kidney disease¹⁰² have shown that untreated HCV-infected patients with compensated cirrhosis have 3-, 5-, and 10-year survivals of 96, 91, and 79%, respectively. Five-year survival drops to 50% in patients with decompensated cirrhosis. Although these data cannot be extrapolated to the entire CKD population, it is reasonable to assume that survival in the majority of patients with CKD Stage 1 and most patients with CKD Stage 2 is not significantly different from that of the general population with normal kidney function and that the available data from the general population apply to these two stages. For patients with CKD Stage 3, 5-year survival in those without HCV infection has been reported to be 76%.¹⁰³ This allows for extrapolation from the general population for some of these patients, although if other comorbidities are present (diabetes, coronary artery disease, and so on), then the anticipated survival must be considered individually in the decision to offer antiviral therapy. In patients with CKD Stage 4, survival at 5 years has been reported to be about 54%. In this setting, the decision to treat must take into account comorbidities that might significantly worsen survival and lessen the

importance of a therapy whose benefit is measured in long-term survival gain. In contrast to CKD Stages 1–4, Stage 5 patients have a markedly reduced survival compared with the general population with normal kidney function. In this context, the decision to treat these patients must take into account anticipated patient survival (age, comorbidities, and so on) and the goals of therapy (that is, SVR before transplantation) before a decision to treat is made.

There is some information on the association between anti-HCV-seropositive serologic status and survival in patients on maintenance hemodialysis. The quality of evidence in support of treatment is low. In fact, an accurate assessment of the natural history of HCV in dialysis patients and renal transplant recipients has been difficult to obtain. HCV infection in dialysis patients and transplant recipients is usually asymptomatic with an apparently indolent course. The natural history of HCV infection extends over decades rather than years,^{20,102} whereas CKD patients generally have higher morbidity and mortality rates than those of the general population due to age and comorbid conditions,¹⁰³ making the long-term consequences of HCV infection difficult to establish. Accurate evaluation of HCV infection is further complicated in this setting by the observation that aminotransferase values are typically lower in the dialysis than in the nonuremic populations. Dialysis patients who have detectable serum HCV RNA have aminotransferase levels greater than those who do not, although values are typically within the normal range.^{104,105} In addition, the recent advances in antiviral therapy for hepatitis C support the antiviral treatment of HCV in the CKD population; this will hamper the implementation of large trials on the natural history of HCV in this population.

Seven observational studies have shown an independent and significant association between anti-HCV-positive serologic status and diminished patient survival.^{67,106–111} These studies have appropriate follow-up and size. In one study, HCV RNA-positive patients had a RR of 1.78 (95% confidence interval (CI), 1.01–3.14) for death compared to nonviremic hemodialysis patients.¹¹¹ This was confirmed in another study that found a RR for death of 1.41 (95% CI, 1.01–1.97) in anti-HCV-positive hemodialysis patients.¹¹⁰ The major complications of HCV-related chronic liver disease (cirrhosis and hepatocellular carcinoma) have been implicated in the lower survival of seropositive patients. These results are consistent with evidence from other sources. A recent survey (DOPPS) of patients on long-term dialysis in three continents reported an independent and significant association between anti-HCV status and mortality (RR, 1.17; $P < 0.02$).¹¹²

Similarly, HCV-infected kidney transplant recipients have diminished long-term graft and/or patient survival compared to uninfected controls.^{113–120} The higher mortality observed in HCV-positive recipients has been linked to liver dysfunction. Furthermore, positive anti-HCV serologic status in the kidney transplant recipient has been implicated in the development of acute glomerulopathy¹²¹ and *de novo* immune complex GN in the allograft.^{122–125} Positive

anti-HCV serologic status has also been associated with an increased incidence of serious infections¹²⁶ and diabetes mellitus after renal transplantation,^{127–132} making it desirable to treat the HCV-infected kidney transplant candidate before transplantation in an attempt to achieve SVR.

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

Potential benefits of successful therapy include slowing the progression of liver disease and reducing the risk of post-transplant complications associated with HCV. However, given the generally indolent progression of HCV, treatment is not recommended for the patient with less than a 5-year estimated survival due to comorbidities such as cardiovascular disease. This is particularly the case if liver histology shows an absence of extensive fibrosis.

The decision to treat an HCV-infected patient with CKD must be made in the context of the patient's clinical situation. In some patients, there are good data to support treatment; for example, in the pretransplant patient (see rationale for Guideline 2.1.4) or in the patient with HCV-associated GN with or without cryoglobulinemia (see Guideline 5). For others with HCV infection and CKD Stages 1–4, it might be reasonable to adapt the recommendations for treatment that apply to the general population, as there are no studies available that target this specific population (<https://www.aasld.org/eweb/docs/hepatitisc.pdf>). The 5-year mortality of patients with CKD Stages 2, 3, and 4 has been reported to be 19.5, 24, and 46%, respectively.¹⁰³ This well exceeds the reported 5-year mortality of HCV-infected patients with compensated cirrhosis (9%) in the general population. In this context, a patient with CKD Stage 4 is five times more likely to die from a CKD-associated event (for example, cardiovascular disease) than from liver failure, assuming that they already show Metavir ≥ 3 on biopsy. Patients with lesser degrees of liver fibrosis would have an even greater chance of dying from a complication related to CKD than liver disease. Thus, a decision to treat patients with advanced stages of CKD for their HCV infection must take into consideration the significant mortality associated with CKD, a burden of disease that can only be made worse by the added comorbid condition of HCV infection. It is the judgment of the Work Group that CKD patients should be considered candidates for antiviral therapy since, as a group, they have a substantially elevated risk of mortality, which would likely be further elevated by progressive liver disease. The patients should be appropriately informed of the risks and benefits of antiviral therapy and should also participate in the decision-making process.

The benefits and risks of antiviral therapy with IFN-based regimens in HCV-infected patients on maintenance hemodialysis have been evaluated in several studies of appropriate study size (Tables 8–10). The quality of evidence in this area is moderate for SVR, but very low overall (Table 10). It has been

suggested that tolerance to IFN is lower in dialysis than in non-CKD patients with chronic hepatitis C. Also, the profile of side effects to IFN therapy in dialysis patients seems different from normal controls. In addition to flu-like symptoms, other common side effects leading to interruption of IFN therapy in CKD patients are neurologic and cardiovascular disorders.⁷⁹ Nevertheless, approximately one-third of hemodialysis patients with chronic hepatitis C have obtained SVR with standard IFN monotherapy (Tables 9A, 10).^{79,133} This is in contrast to SVR rates in patients without kidney disease of 42–46% in genotype 1 infections and 76–82% in those with genotypes 2 and 3 using combination therapy with pegylated IFN and ribavirin.^{26,167}

There is significant geographical variability in the prevalence of the six major HCV genotypes. Whereas genotype 1 is the most common isolate in the United States and Europe (60–70%), genotype 3 is encountered more often in India, the Far East, and Australia. Genotype 4 is found more commonly in Africa and the Middle East, genotype 5 in South Africa, and genotype 6 in Hong Kong, Vietnam, and Australia.⁴¹² Although genotype does not predict the outcome of infection, it has been shown to both predict the probability of response to and determine the necessary duration of therapy. Infections with HCV genotypes 1 and 4 are less responsive to IFN-based therapy and require 48 weeks of treatment (<http://www.consensus.nih.gov/2002/2002HepatitisC2002116main.htm>). In contrast, genotypes 2 and 3 are far more responsive to treatment and require only 24 weeks of therapy to achieve SVR. In patients with HCV genotype 3 who did not reach HCV RNA clearance within 24 weeks of therapy, a prolonged treatment (up to 48 weeks) is recommended at present, especially in those patients with high viral load. HCV genotype 5 appears to have a response similar to genotypes 2 and 3 but requires 48 weeks of therapy. Genotype 6 responds better than genotype 1 but not so well as genotypes 2 and 3. These results have been obtained in patients with HCV infection and normal kidney function (<http://www.consensus.nih.gov/2002/2002HepatitisC2002116main.htm>). In a meta-analysis of patients on maintenance hemodialysis, the overall summary estimate for SVR was 37% in the whole group and 30% in those patients with HCV genotype 1.⁷⁹ In another review, the pooled SVR rate was 33% in the whole group and 26% with HCV genotype 1.¹³³

The quality of evidence on efficacy and safety of IFN therapy of hepatitis C in CKD patients is very low (Tables 9A, 10). Several studies, including three RCTs, have been published on this issue.^{134–136} The size of the study group was appropriate in most trials.^{137–145} However, there is still concern about the applicability of these results to all dialysis patients, as most of the subjects included in these studies were on the waiting list for kidney transplantation and were younger and probably healthier than the general dialysis population. Furthermore, only one study was from North America¹⁴⁶ where many CKD patients are African American. This is of special relevance, as there are racial differences in the response to IFN therapy in subjects with

normal kidney function.¹⁴⁷ Thus, whereas the impact of race on the efficacy and tolerability of antiviral therapy in CKD patients remains undefined, the available data from the general population should be considered in making a decision in individual cases of CKD.

Early virologic response (that is, virologic response obtained 12 weeks after initiation of antiviral therapy with at least a 2 log fall in the HCV viral titer) has been demonstrated to be highly predictive of SVR in HCV-infected patients with normal kidney function (<http://www.consensus.nih.gov/2002/2002HepatitisC2002116main.htm>). As there are no data regarding the predictive value of early viral response in evaluating the response of HCV-infected CKD patients to antiviral therapy, a recommendation to determine early viral response in the CKD population must be made by extrapolating data from the general population. In studies of patients without kidney disease, 65% of patients treated with pegylated IFN- α -2a who achieved an early viral response went on to have SVR. Among those without an early viral response, 97% failed to achieve SVR. Furthermore, in studies using pegylated IFN- α -2b, of those not having an early viral response, none achieved SVR (<https://www.aasld.org/eweb/docs/hepatitisc.pdf>). These data are compelling and the consensus of the Work Group is that the failure to obtain an early viral response can be used in making a decision not to continue treatment beyond 12 weeks in patients with CKD. If an early viral response is obtained and treatment is continued, it is recommended that the AASLD guidelines be followed and treatment for 48 weeks in CKD patients infected with HCV genotypes 1 and 4, and 24 weeks for patients infected with genotypes 2 and 3 be completed.

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

There are patients with CKD who will become acutely infected with HCV. This might occur in the community setting from horizontal transmission, transfusion of infected blood products, or from nosocomial transmission in the hemodialysis unit (see Guideline 3). The quality of evidence for the treatment of CKD patients who acquire acute HCV infection is very low. Preliminary data support the use of antiviral therapy in maintenance hemodialysis patients who acquire HCV while on dialysis. Paradoxically, the SVR rate has been reported to be higher in this group of patients than in patients with chronic HCV infection who are not on dialysis, but this remains to be substantiated.^{148–150}

In one prospective, controlled clinical trial, the SVR (in acute HCV) was higher in IFN-treated patients compared to untreated controls: 39% (19/49) vs 5.6% (1/18), $P=0.001$.¹⁴⁸ High-dose IFN (10 MU thrice weekly) gave SVR rate of 50% compared with 26% in the low-dose IFN group

(3 MU thrice weekly) and 5.6% in the untreated control group. In another prospective cohort trial, the SVR rate was 72%.¹⁵⁰

It remains unclear whether SVR is linked with other typical outcomes (that is, biochemical response and improved liver histology). In addition, the relationship between SVR and improved patient survival has not been evaluated in CKD patients with acute HCV infection.

The information on acute HCV infection in dialysis patients is limited. Recent reports have noted that spontaneous and permanent clearance of HCV RNA occurs in about 5–30% of patients.^{148,151,152} HCV RNA clearance was observed at 12 weeks after the onset of acute HCV infection and all these patients maintained SVR at 12 months.¹⁵¹ The available data suggest that the rate of spontaneous SVR is lower in dialysis patients (5–30%) than in the general population (up to 50%).²⁰ Thus, a waiting period of 12 weeks is recommended to determine whether spontaneous HCV RNA clearance will occur before starting antiviral therapy in CKD patients.

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

HCV-infected kidney transplant recipients have reduced long-term patient and graft survivals compared to uninfected controls.^{113–120} Positive anti-HCV serologic status after kidney transplantation is implicated in the pathogenesis of acute glomerulopathy,¹²¹ *de novo* graft HCV-associated nephropathy,^{122,123,125} NODAT,^{127–129,131,132,153} and a higher incidence of chronic allograft nephropathy.¹⁵⁴ In the context of these extra hepatic complications, the impetus to treat the HCV-infected kidney transplant candidate is different than it is in the general population where the risks of post-transplant diabetes, *de novo* GN of the allograft, and chronic allograft nephropathy are not pertinent. For this reason, it is recommended that patients be treated with lesser degrees of fibrosis than suggested in the AASLD guidelines (<https://www.aasld.org/eweb/docs/hepatitisc.pdf>). For HCV-infected patients with CKD who are kidney transplant candidates, antiviral therapy is recommended even for those with a pattern of histologic injury that does not meet the recommended degree of fibrosis to qualify for therapy in the general population (that is, Metavir score <2 and Ishak score <3).

Information in support of antiviral therapy of kidney transplant candidates is based on three controlled clinical trials.^{130,154,155} The quality of evidence on this issue is very low because patient allocation was not randomized. In one controlled clinical trial, pretransplant antiviral therapy resulted in a lower incidence of *de novo* HCV-related GN in kidney transplant recipients. Of 15 HCV-positive recipients who received pretransplant IFN therapy, 10 (67%) had SVR; only 1 (7%) of these 15 treated patients, who remained viremic, developed *de novo* GN. Among the 63 untreated HCV-positive allograft recipients, all of whom were HCV

RNA viremic at the time of transplantation, 12 (19%) developed *de novo* GN ($P < 0.0001$).¹⁵⁵

Pretransplant antiviral therapy of HCV-infected transplant recipients appears to lower the incidence of NODAT. In a controlled trial,¹³⁰ the frequency of NODAT was higher in the group of HCV-positive recipients who had not received IFN than in those who were treated with IFN before transplantation (25% (10/40) vs 7% (1/14), $P = 0.009$).

In a relatively large cohort ($n = 50$) of kidney transplant recipients, a higher proportion of nontreated controls developed chronic allograft nephropathy compared with IFN-treated patients (41% (13/32) vs 6% (1/18), $P = 0.009$). In the logistic regression analysis, the absence of IFN therapy before kidney transplantation was a risk factor for chronic allograft nephropathy with an odds ratio of 12 ($P = 0.02$).¹⁵⁴

In patients with well-compensated cirrhosis, the decision of whether to treat is a difficult one. Most Work Group members do not feel that these patients represent reasonable transplant candidates and, as such, the benefit of treatment in this setting is difficult to measure. However, improved liver histology (from Metavir 4 to Metavir 2) was seen in 5 of 64 (7.8%) patients with normal kidney function and three of four HCV-infected dialysis patients with cirrhosis after receiving antiviral therapy that achieved SVR.¹⁵⁶ Thus, if improvement in liver histology can be documented after antiviral therapy that achieves SVR, it is suggested that the patient's candidacy for transplant be re-evaluated in the context of the most recent liver biopsy. If the patient with well-compensated cirrhosis remains viremic, kidney transplantation alone is not recommended. The patient may become a candidate for combined kidney–liver transplantation at a later date.

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

Graft dysfunction and failure are frequent side effects of IFN therapy administered after transplant (Table 13). Dropouts during antiviral therapy are mostly related to IFN-induced acute rejection, which is frequently steroid-resistant and irreversible. Graft rejection has been reported after IFN monotherapy or combined (IFN plus ribavirin) therapy after kidney transplantation (Tables 11–14).^{1,4} The AASLD specifically recommends that kidney transplantation is a contraindication to IFN therapy for HCV infection (<https://www.aasld.org/eweb/docs/hepatitisc.pdf>). The quality of evidence is very low in this area (Tables 11–14). Controlled¹⁵⁷ and cohort (prospective or retrospective) studies^{158–163} have addressed this issue in kidney transplant recipients. Combined antiviral therapy (IFN plus ribavirin) was used in some studies.^{164,165}

The SVR rate ranged from 0¹⁵⁷ to 50%^{162,166} across the published trials (Tables 11–14).^{1,4} It remains unclear whether

SVR in kidney transplant recipients was linked to an improved patient or graft survival. It is recommended that antiviral therapy with IFN-only be considered in patients with fibrosing cholestatic hepatitis or life-threatening vasculitis in whom the risk of not treating justifies the possible loss of the allograft. The patient must be carefully informed of these risks before initiating treatment. There are limited data on the use of pegylated IFN (with ribavirin if the creatinine clearance is > 50 ml per min per 1.73 m^2) in this clinical setting.

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

LIMITATIONS

- The limited information available in the literature on HCV infection in the CKD population has made it necessary to extrapolate evidence from the non-CKD population. The natural course of HCV infection in the CKD population may differ substantially from the general population with normal kidney function.
- Many studies are retrospective in design and have small numbers of patients.
- There is no clear information on several parameters (such as HBV/HIV coinfection, mode of HCV acquisition, alcohol use) that potentially affect the course of HCV infection in the CKD population.
- There are no data on the course of HCV infection in the CKD population with repeated liver biopsies.
- In the context of the reduced life expectancy of maintenance hemodialysis patients and the slowly progressive course of chronic HCV infection, there are no studies that address the impact of antiviral therapy on long-term survival. There was inconsistent reporting of mortality in many of the articles reviewed with variable follow-up times.
- Many of the studies on treatment of hemodialysis patients with IFN are from Europe where most of the patients are Caucasian. This is of importance, as there are racial differences in the predicted response to IFN therapy. Thus, the impact of race on the efficacy and tolerability of antiviral therapy in CKD patients remains undefined.
- Information on the rate of adverse effects during antiviral (IFN) therapy in dialysis patients is unsatisfactory. It remains unclear whether the adverse effects in dialysis patients with HCV are related to IFN activity *per se* or to the high prevalence of comorbid conditions typical of dialysis patients.

RESEARCH RECOMMENDATIONS

- Prospective trials of antiviral therapy in HCV-infected CKD patients are needed to determine whether the benefit of therapy is realized in a patient population with significantly reduced long-term survival.

- Few studies examining the safety and efficacy of IFN in hemodialysis patients are from North America, where there are substantial numbers of non-Caucasian patients in the CKD Stage 5 population. In the context that there are racial differences in the response to IFN, studies are needed with larger numbers of non-Caucasian patients to confirm the results obtained from the largely European studies of IFN-based therapy in hemodialysis patients.
- Prospective studies involving the treatment of HCV infection in peritoneal dialysis patients are needed. Essentially, all information available on the treatment of dialysis patients comes from studies in the hemodialysis population.
- Prospective studies are needed to determine whether treating the pretransplant candidate with lesser degrees of fibrosis on biopsy (Metavir ≤ 2) than is generally recommended for the non-CKD population is beneficial in terms of post-transplant adverse outcomes such as NODAT and allograft glomerulopathy.
- Prospective, controlled studies in dialysis patients are required to compare the rate of adverse effects during antiviral (IFN-based) therapy vs those patients who do not receive antiviral therapy. These types of studies would more definitively clarify the nature of the adverse effects observed by some investigators.

Guideline 2.2: Basing HCV treatment on CKD stage

INTRODUCTION

The prevalence of HCV infection is higher in the CKD population compared to the general population. In this context, many CKD patients are candidates for antiviral therapy. Importantly, the level of kidney function in the CKD population plays a crucial role on the pharmacokinetics of antiviral drugs targeted at HCV. Kidney filtration and catabolism have a significant contribution to the clearance of IFN and ribavirin such that these products must be used with caution in patients with CKD, and appropriate dosing adjustments must be made (Table 5).

Levels of Strength of Recommendations

Strength of recommendation	Wording of recommendation	Basis for strength of recommendation
Strong	An intervention 'should' be done	'High' quality evidence and/or other considerations support a strong guideline ^a
Moderate	An intervention 'should be considered'	'Moderate' quality evidence and/or other considerations support a moderate guideline ^a
Weak	An intervention 'is suggested'	'Low' or 'Very Low' quality evidence; predominantly based on expert judgment for good clinical practice ^a

^aSee Appendix 2: Grading the Strength of the Recommendations, p. S85.

- 2.2.1 For HCV-infected patients with CKD Stages 1 and 2, combined antiviral treatment using pegylated IFN and ribavirin is suggested, as in the general population. (Weak).
 - It is suggested that the ribavirin dose be titrated according to patient tolerance. (Weak).
- 2.2.2 For HCV-infected patients with CKD Stages 3, 4, and 5 not yet on dialysis, monotherapy with pegylated IFN with doses adjusted to the level of kidney function is suggested. (Weak).
- 2.2.3 For HCV-infected patients with CKD Stage 5D on maintenance hemodialysis, monotherapy with standard IFN that is dose-adjusted for a GFR < 15 ml per min per 1.73 m² is suggested. (Weak).
- 2.2.4 For HCV-infected kidney transplant recipients in whom the benefits of antiviral treatment clearly outweigh the risks (see Guideline 2.1.5), monotherapy with standard IFN is suggested. (Weak).

RATIONALE

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

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

In RCTs of HCV-infected patients with intact kidney function, the highest overall SVRs to date have been achieved with the combination of weekly subcutaneous injections of pegylated IFN and oral ribavirin. This represents the current standard of care for HCV infection (<https://www.aasld.org/eweb/docs/hepatitisc.pdf>). This recommendation is based on the results of three large randomized trials that were completed in IFN-naive patients with normal kidney function.^{26,27,167} In the first of these trials, standard IFN- α -2b plus ribavirin (1000–1200 mg day⁻¹) was compared with pegylated IFN- α -2b (1.5 μ g kg⁻¹ week⁻¹ for 4 weeks followed by 0.5 μ g kg⁻¹ week⁻¹) plus ribavirin (1000–1200 mg day⁻¹) or pegylated IFN- α -2b (1.5 μ g kg⁻¹ week⁻¹) plus ribavirin (800 mg day⁻¹).²⁷ The overall SVR rate was 47, 47, and 54% for the standard, 0.5, and 1.5 μ g kg⁻¹ groups, respectively. The result was significantly different for the 1.5 μ g kg⁻¹ group vs the other two. The SVR rate was approximately 80% for patients infected with genotypes 2 and 3 vs 42% for those with genotype 1. In the second major study in the general population infected with HCV, the efficacy of pegylated IFN- α -2a (180 μ g week⁻¹ subcutaneously (SQ)) plus ribavirin (1000–1200 mg day⁻¹) was compared with standard IFN- α -2b plus ribavirin or pegylated IFN- α -2a monotherapy.²⁶ All patients were treated for 48 weeks. The patients receiving pegylated IFN plus ribavirin obtained SVR more often than either of the other two groups (56 vs 44 and 29%, respectively, for the standard IFN plus ribavirin and pegylated-IFN monotherapy groups). As was seen in the first trial, the response rate for patients with genotypes 2 and

3 was significantly higher than those with genotype 1 (76 vs 46%). Finally, the third major trial randomly assigned patients to either pegylated IFN- α -2a (180 μ g week⁻¹) plus ribavirin (either 800 or 1200 mg daily) for 24 or 48 weeks.¹⁶⁷ The highest SVR for patients with genotype 1 was obtained with the higher dose of ribavirin for the 48-week treatment period. Patients with genotypes 2 and 3 responded equally well at 24 or 48 weeks to the lower dose of ribavirin. The results from these three trials form the basis for the current recommendations for treatment by the AASLD.

No data exist in the literature to guide therapy for HCV in patients with CKD Stages 1 and 2. However, in patients with a GFR >50 ml per min per 1.73 m², impaired kidney function does not have a major impact on the efficacy and safety of combined IFN and ribavirin therapy. As such, the results reported in patients with normal kidney function treated with pegylated IFN plus ribavirin should apply to CKD Stages 1 and 2 (Table 5).

patients with advanced CKD not yet on dialysis requiring a dosage adjustment. A single-dose study of pegylated IFN- α -2a in patients with stable chronic renal failure showed no significant difference in apparent body clearance between patients with normal kidney function (creatinine clearance >100 ml min⁻¹) and those with significant reductions in kidney function (creatinine clearance 20–40 ml min⁻¹).¹⁷² Reduced kidney function (estimated GFR <60 ml per min per 1.73 m²) in CKD Stages 3 and 4 would be expected to worsen the side effects of combined antiviral therapy with IFN and ribavirin. Ribavirin use is limited by hemolytic anemia that can be particularly dangerous in CKD patients, who often have anemia as well as other comorbidities (for example, cardiac ischemia) at baseline. The use of ribavirin in patients with a GFR <50 ml per min per 1.73 m² is not recommended in other guidelines (<https://www.aasld.org/eweb/docs/hepatitisc.pdf>). Recent data support its use in CKD patients with GFR <50 ml per min per 1.73 m² in a cautious and very well-monitored setting; however, these preliminary findings

Table 5 | Recommended treatment of HCV infection in patients with CKD and their associated adverse events

Stage of CKD	IFN ^a	Ribavirin ^b	Common adverse events
1 and 2	Pegylated IFN α -2a: 180 μ g SQ q week Pegylated IFN α -2b: 1.5 μ g kg ⁻¹ SQ q week	800–1200 mg day ⁻¹ in two divided doses	IFN: headache, flu-like illness, depression Ribavirin: worsened anemia due to hemolysis
3 and 4	Pegylated IFN α -2a: 135 μ g SQ q week Pegylated IFN α -2b: 1 μ g kg ⁻¹ SQ q week	Stage 3: 400–800 mg day ⁻¹ in two divided doses Not recommended for eGFR <50 ml per min per 1.73 m ²	IFN: same as above Ribavirin can cause hemolytic anemia and its use must be supported with increased erythropoietin as needed
5	Pegylated IFN α -2a: 135 μ g SQ q week Pegylated IFN α -2b: 1 μ g kg ⁻¹ SQ q week	Not recommended	IFN: same as above
5D	Alfa-2a IFN: 3 mU SQ 3 times per week Alfa-2b IFN: 3 mU SQ 3 times per week	Not recommended	IFN: same as above
5T 1–5	Not recommended unless treating fibrosing cholestatic hepatitis or life-threatening vasculitis	Not recommended	IFN has been associated with allograft rejection and failure

eGFR, estimated glomerular filtration rate; IFN, interferon; SQ, subcutaneous; q week, every week.

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

^bSee text for a detailed discussion of ribavirin usage and dosing in patient with CKD Stages 3–5. Patients with genotypes 2 and 3 infection should receive 800 mg day⁻¹ with Stages 1 and 2 CKD. Patients infected with genotypes 1 and 4 should receive 1000–1200 mg day⁻¹ with Stages 1 and 2 CKD.

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

Extensive data do not exist about the use of combination antiviral therapy (pegylated IFN plus ribavirin) in CKD Stages 3–5 patients. The available data on combined therapy (standard IFN or pegylated IFN plus ribavirin) in the CKD population derive mostly from studies of patients on maintenance hemodialysis (Tables 8 and 9, bottom; other referenced studies were not summarized because they were retrospective or too small).^{168–171} There are limited data on the clearance of IFN in patients with CKD Stages 3 and 4. However, available evidence indicates that there is impaired clearance of standard IFN in patients on maintenance hemodialysis. Therefore, it would be reasonable to assume that IFN clearance might be reduced in

will need confirmation in larger trials. Of interest, however, is one study that evaluated the pharmacokinetics of ribavirin by a two-compartment model in patients with normal and reduced levels of kidney function.¹⁷³ The authors reported a ribavirin half-life of approximately 100 h with normal kidney function and >300 h with very reduced creatinine clearance. In addition, there was a large volume of distribution resulting in a time to steady-state concentration of almost 3 months in patients with reduced creatinine clearance. On the basis of their findings, the authors developed a table (Table 6) for dosing of ribavirin based on creatinine clearance and targeted steady-state concentration of ribavirin. According to this analysis, estimated GFR was a significantly better predictor of ribavirin clearance than body weight alone. This ribavirin-dosing schedule has been promoted by data showing that the probability of response to ribavirin increases with increasing ribavirin concentration.^{168,174}

Table 6 | Ribavirin dosing based on creatinine clearance and targeted steady-state concentration of ribavirin

Target C _{ss}	CrCl (ml per min per 1.73 m ²)					
	120	100	80	60	40	20
6 μmol l ⁻¹	600	600	400	400	200	200
10 μmol l ⁻¹	1000	800	800	600	400	400+200
14 μmol l ⁻¹	1400	1200	1000	800	600	400

CrCl, creatinine clearance; C_{ss}, ribavirin concentration at steady state.

The patient's weight is set at 70 kg. For considerable deviations from 70 kg or creatinine clearance < 20 ml per min per 1.73 m², use the equations provided in the text. Dosing is total ribavirin in mg per day. 400+200 denotes 400 mg 1 day alternating with 200 mg the next day.

Adapted from Bruchfeld *et al.*¹⁷³

For patients with creatinine clearance < 20 ml per min per 1.73 m², the authors recommend the use of the following equations to determine the ribavirin dose:

Ribavirin dose =

$$0.24 \times C_{ss} \text{Target} \times \text{dose interval} \times \text{ribavirin clearance}$$

Ribavirin clearance =

$$0.122 \times \text{creatinine clearance} + (0.0414 \times \text{weight (kg)})$$

These data have not been verified in large numbers of CKD patients. Furthermore, the assay to measure steady-state ribavirin levels has very limited availability.

For the patient with CKD Stage 3 with a GFR > 50 ml per min per 1.73 m², combination therapy with pegylated IFN and ribavirin is recommended with the precautions indicated above. For the patient with CKD Stage 4, combination therapy using markedly reduced doses of ribavirin as estimated from the equations above may be tried, although extreme caution must be used. At this level of kidney function, concentration-controlled dosing of ribavirin should also be used. If ribavirin levels cannot be obtained, its use in patients with a GFR < 50 ml per min per 1.73 m² is not recommended. If ribavirin is not tolerated, it is recommended that monotherapy with pegylated IFN be the treatment of choice for patients with CKD Stages 3 and 4. There are no good data available on the treatment of patients with CKD Stage 5 not yet on dialysis. It is the judgment of the Work Group that these patients should be treated with pegylated IFN, with doses adjusted to the level of GFR (Table 5).

2.2.3 For HCV-infected patients with CKD Stage 5D on maintenance hemodialysis, monotherapy with standard IFN that is dose-adjusted for a GFR < 15 ml per min per 1.73 m² is suggested. (Weak).

The available data in the literature support monotherapy with standard IFN in patients on maintenance hemodialysis. The virologic response to monotherapy with standard IFN is higher in dialysis patients than in non-CKD patients with chronic hepatitis C infection. In three randomized controlled trials, the SVR ranged from 21 to 58% for patients treated for 6 or 12 months with standard IFN monotherapy.¹³⁴⁻¹³⁶ Similar SVRs were obtained in 14 prospective

noncomparative cohort trials (Tables 8-10). The viral response to monotherapy with standard IFN in maintenance hemodialysis patients (summary estimate of 37%), as demonstrated in a recent meta-analysis,⁷⁹ is higher than that observed in patients with chronic hepatitis C and normal kidney function (7-16%) who received standard IFN monotherapy.^{24,175,176} However, the viral response to monotherapy with standard IFN in dialysis patients is lower than that observed in patients with chronic hepatitis C treated with combined therapy (conventional or pegylated IFN plus ribavirin) in the general population. Several mechanisms account for the relatively higher response to IFN in patients receiving maintenance hemodialysis. Dialysis patients with HCV usually have a lower viral load;¹⁰⁴ the infection is frequently associated with milder forms of histologic liver disease;¹⁷⁷ clearance of IFN is lower in dialysis patients than in non-CKD patients;¹⁷⁸ and an increase in endogenous IFN release from circulating white blood cells during hemodialysis sessions has been reported.¹⁷⁹ A marked and prolonged release of hepatocyte growth factor (or other cytokines) caused by hemodialysis could play an additional role.¹⁸⁰

Although response rates to conventional IFN are better in the dialysis population, tolerance to IFN monotherapy appears lower in patients on maintenance hemodialysis than in non-CKD individuals (Tables 8-10). The summary estimate of dropout rate was 17% in dialysis patients who received standard IFN monotherapy,⁷⁹ whereas the frequency of side effects requiring IFN discontinuation ranged between 5 and 9% in non-CKD patients with chronic hepatitis C who received a usual dose of standard IFN monotherapy (3 MU thrice weekly for 6 months SQ).^{24,175} The altered pharmacokinetic parameters of IFN in the hemodialysis population,¹⁷⁸ higher age, and high rate of comorbid conditions may, to some extent, explain the higher frequency of side effects leading to IFN discontinuation. The IFN-alfa half-life was longer in dialysis than in normal controls, 9.6 vs 5.3 h ($P = 0.001$) and the area under the curve was twice that of patients with normal kidney function.¹⁷⁸

There are limited data on monotherapy with pegylated IFN for HCV-infected patients on maintenance hemodialysis (Tables 15,17). The quality of evidence is very low. However, in two randomized clinical trials, the SVR was 75% in the pegylated IFN group vs 8% in the untreated control group¹⁸¹ and 22 vs 0% in patients treated with 1.0 vs 0.5 μg kg⁻¹, respectively.¹⁴⁶ It has been observed that pegylated-IFN-alfa-2a kinetics do not seem to be affected significantly by kidney function. Regression analyses of pharmacokinetic data from 23 patients with creatinine clearance values ranging from greater than 100 to 20 ml min⁻¹ showed no significant relationship between the pharmacokinetics of pegylated IFN-alfa-2a and creatinine clearance.¹⁷² In another study of single-dose pharmacokinetics using pegylated IFN-alfa-2b, significant differences were noted between patients with creatinine clearance > 80 ml min⁻¹ and those with creatinine clearance 10-29 ml min⁻¹. Pegylated IFN mean area under the curve and

C_{max} were increased by up to two-fold in patients with renal impairment compared to controls, and mean half-life increased by up to 40%. In a separate analysis of hemodialysis patients in the same study, it was shown that dialysis had negligible effects on pegylated IFN- α -2b clearance.¹⁸² A single-dose study in patients on maintenance hemodialysis identified no additional toxicity, although there was a 30% reduction in IFN clearance.¹⁸³ The conclusion of this study was that the pharmacokinetic profile of pegylated IFN- α -2a (40 kDa) in patients on maintenance hemodialysis is similar to that in healthy individuals with only a 30% relative reduction in clearance. The pharmacokinetics of pegylated IFN during hemodialysis may vary in dialysis patients, depending on the permeability and dialyzer pore size.¹⁸⁴ In this study, 40 kDa pegylated IFN- α -2a was not cleared through low-flux/small-pore size and high-flux/middle- to large-pore size dialyzers and was partially cleared through intermediate permeability/large-pore size dialyzers. In contrast, 12 kDa pegylated IFN- α -2b was cleared (40–80%) through poly(methyl methacrylate) dialyzers with pore size $>60 \text{ \AA}$. Neither pegylated IFN- α -2a nor 2b was removed after three hemodialysis sessions using 27/31 \AA and 33 \AA polysulfone dialyzers.

Just as it appears that pegylated IFN does not provide an added benefit in terms of virologic response in comparison with standard IFN monotherapy, treatment discontinuation due to adverse events was also similar (Tables 15, 17). In three RCTs of standard IFN, 21–53% of patients discontinued the drug owing to adverse events^{134–136} compared with 0–44% of patients in two RCTs of pegylated IFN.^{146,181} Importantly, mortality was not reported in the pegylated IFN trials. One small clinical trial looked at patients after liver transplant with serum creatinine $>1.8 \text{ mg per } 100 \text{ ml}$ ($159 \mu\text{mol l}^{-1}$) who were treated with pegylated IFN- α -2b ($1 \mu\text{g kg}^{-1} \text{ week}^{-1}$). In this study, two of nine patients obtained SVR, although eight of nine patients were intolerant to treatment and discontinued IFN within 3 months of starting.¹⁸⁵

Few studies have evaluated combined therapy (pegylated or standard IFN plus ribavirin) in patients on maintenance hemodialysis (Tables 9A, 16, 17). The quality of evidence on this issue is very low. The results provided in some trials^{168–171,186} have been encouraging in terms of efficacy and safety, but the limited size of the study groups does not allow definitive recommendations. Ribavirin therapy in this setting is not recommended. (<https://www.aasld.org/eweb/docs/hepatitisc.pdf>). The Work Group feels that if a decision is made to use ribavirin in patients on maintenance hemodialysis, it should be used very cautiously and only after the implementation of several precautions, including: (i) very low ribavirin dose (about 200 mg day^{-1} or 200 mg thrice weekly); (ii) weekly monitoring of hemoglobin levels; and (iii) high doses of erythropoietin to treat anemia.

In summary, it is recommended that standard IFN (3 MU thrice weekly SQ) be used for the treatment of HCV-infected maintenance hemodialysis patients (Table 5). Recommendations present in the AASLD guidelines for liver biopsy and

length of therapy based on HCV genotype (48 weeks for genotypes 1 and 4, and 24 weeks for genotypes 2 and 3) should be extrapolated to the hemodialysis population. In addition, it is recommended to determine if an early treatment response is achieved at 12 weeks ($>2 \text{ log}$ decrease in the viral titer) to decide if therapy should be continued out to 24 or 48 weeks.

For the kidney transplant candidate, the recommendation is the same as that stated above (Table 5) with the exception that all HCV-infected patients should have a liver biopsy regardless of genotype. Furthermore, contrary to AASLD guidelines, it is suggested that all patients whose liver biopsy shows Metavir <3 be evaluated for antiviral therapy to try and achieve SVR. This more aggressive approach is based on the evidence demonstrating a decreased incidence of post-transplant diabetes, *de novo* GN, and chronic allograft nephropathy in the transplant recipient who is no longer viremic.

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

IFN-based regimens are contraindicated after kidney transplantation (<https://www.aasld.org/eweb/docs/hepatitisc.pdf>). In four prospective trials using IFN monotherapy, the rate of treatment discontinuation ranged from 21 to 56% and allograft loss occurred in 6–15% of patients (Tables 11–14).^{14,157,187,188} In one trial combining IFN with ribavirin, there were no reported graft losses, although 27% of the patients discontinued therapy due to adverse events.¹⁶⁵ However, the development of HCV-related fibrosing cholestatic hepatitis may be an indication for IFN use after kidney transplantation, as fibrosing cholestatic hepatitis has an ominous course. In this setting, the potential benefits of treatment may outweigh the risks of rejection and graft failure.¹⁸⁹ In any circumstance, this course of therapy should be undertaken only after the patient has been properly informed of the risks of both treatment and electing not to treat.

Alternative regimens based on drugs other than IFN have been proposed, but no proof of their efficacy has been provided (Tables 11–14).^{1,4} No impact on viral response was seen with ribavirin monotherapy^{187,190} even though a biochemical response was observed.^{187,190} The benefits of antiviral therapy on liver histology were small^{187,190} or absent.¹⁹¹ Similarly, amantadine monotherapy after kidney transplantation has been reported to have no impact on either HCV viremia or liver histology.¹⁹² These alternative regimens are not recommended.

LIMITATIONS

- The limited information available in the literature on HCV infection in the CKD population made it necessary to extrapolate evidence from the non-CKD population.

The natural course of HCV infection in the CKD population may differ substantially from the general population with normal kidney function.

- There are few RCTs of antiviral treatment in patients with CKD Stages 1–5. Most of the available literature on treatment is limited to patients on hemodialysis. In addition, many of these patients were awaiting kidney transplantation so that they were, in all likelihood, healthier than the general hemodialysis population. Patients with impaired kidney function were specifically excluded from the large randomized clinical trials that demonstrated the efficacy of combination therapy with IFN and ribavirin to treat HCV infection.
- In the context of the reduced life expectancy of maintenance hemodialysis patients and the slowly progressive course of chronic HCV infection, there are no studies that address the impact of antiviral therapy on long-term survival.
- Although many studies demonstrated improved SVR compared to untreated patients, often no information on critical outcomes, including mortality, were reported. In addition, there were significant but self-limited adverse events reported.
- Only one study was from North America where many CKD patients are non-Caucasian. This is of special relevance as there are racial differences in the response to IFN therapy in subjects with normal kidney function. It is not known if the reported outcomes would apply to regions with a higher prevalence of non-Caucasian patients.

RESEARCH RECOMMENDATIONS

- RCTs are needed to determine the optimal antiviral therapy for HCV-infected hemodialysis patients. The information available in the literature is largely with the use of standard IFN. Studies using pegylated IFN in the CKD Stage 5 population are needed to address efficacy and safety, especially in the context of uremia and the prolonged half-life of the pegylated product compared to standard IFN. In addition, the data on the pharmacokinetics of pegylated IFN in dialysis patients are very limited and require further study.
- Studies in which non-Caucasian patients are better represented are needed to confirm the outcomes achieved with IFN in largely Caucasian populations of hemodialysis patients.
- Prospective studies involving the treatment of HCV infection in peritoneal dialysis patients are needed. Essentially all information available on the treatment of dialysis patients is based on the hemodialysis population.
- Combined therapy with pegylated IFN and ribavirin is the gold standard of treatment in the general population (<https://www.aasld.org/eweb/docs/hepatitisc.pdf>) However, ribavirin is not recommended for use with GFR < 50 ml per min per 1.73 m². Several small studies in hemodialysis patients have suggested that ribavirin

can be used cautiously in low doses with careful monitoring for worsened anemia in patients with more advanced kidney disease. The higher efficacy of combined antiviral therapy (standard or pegylated IFN plus ribavirin) as compared to IFN monotherapy for hepatitis C in patients with normal renal function is likely related to the synergistic activity played by ribavirin. However, the activity of ribavirin appears to be dose-dependent, and the recent evidence that has been accumulated suggests that low doses of ribavirin can be safely used in dialysis patients. Thus, the effective role of low-dose ribavirin in enhancing the antiviral activity of IFN in dialysis patients remains to be determined. Prospective controlled studies designed to answer this important question should be performed.

- There are no studies addressing the role of early (week 12) virologic response in CKD patients who receive antiviral therapy. Abundant information on this issue exists in the nonuremic population, where the negative predictive value of early virologic response has been emphasized. Many CKD patients who receive antiviral therapy are potential renal transplant candidates but they cannot be wait-listed for transplant while receiving antiviral therapy. Thus, the failure to achieve a virologic response 12 weeks after the initiation of antiviral therapy can support an early interruption of antiviral treatment, giving the patient the possibility of rapid inclusion in the waiting list for transplant. Prospective studies on the clinical utility of early changes in the viral load, measured as absolute viral loads or change in viral load from baseline, are required in CKD-infected patients who receive antiviral therapy.
- Prospective cohort trials are needed to study the durability of the pretransplant SVR after renal transplantation. The evidence supporting the durability of a pretransplant SVR after renal transplantation provides encouraging results; however, it is based mostly on uncontrolled trials that need to be confirmed in prospective studies.
- Clinical studies are needed to assess the efficacy and safety of combined antiviral therapy (conventional or pegylated IFN plus ribavirin) in HCV-infected kidney transplant recipients where the benefits of antiviral therapy outweigh the risks (for example, fibrosing cholestatic hepatitis, life-threatening vasculitis).

Guideline 2.3: Monitoring the response to HCV treatment in CKD patients

INTRODUCTION

CKD patients who have been treated with antiviral therapy for chronic HCV infection must have their response to therapy monitored. It is recommended that the guidelines available for the general population be applied to the CKD population (<https://www.aasld.org/eweb/docs/hepatitisc.pdf>).

Levels of Strength of Recommendations

Strength of Recommendation	Wording of Recommendation	Basis for Strength of Recommendation
Strong	An intervention 'should' be done	'High' quality evidence and/or other considerations support a strong guideline ^a
Moderate	An intervention 'should be considered'	'Moderate' quality evidence and/or other considerations support a moderate guideline ^a
Weak	An intervention 'is suggested'	'Low' or 'Very Low' quality evidence; predominantly based on expert judgment for good clinical practice ^a

^aSee Appendix 2: Grading the Strength of the Recommendations, p. S85.

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

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

- For patients on maintenance hemodialysis, repeat testing with NAT every 6 months is suggested. (Weak)

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

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

RATIONALE

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

The viral response to therapy measured by NAT to demonstrate sustained clearance of viremia at 6 months after discontinuing treatment remains the gold standard to evaluate the efficacy of antiviral therapy in patients with hepatitis C and normal kidney function (<http://www.consensus.nih.gov/2002/2002HepatitisC2002116main.htm>). It is suggested that the most sensitive NAT assay available be used. RCTs in HCV-infected patients on maintenance hemodialysis have shown that the SVR rate is significantly higher in patients who received antiviral therapy compared to untreated patients.^{134–136} In a recent meta-analysis, a sensitivity analysis of more homogeneous trials in which 24 weeks of therapy was used demonstrated no significant difference for the summary estimate of response to treatment from the primary analysis of all of the trials (39 vs 37%, respectively). These findings suggested that longer duration of IFN therapy in hemodialysis patients may not give improvement in response rates. However, the limited number

of trials with patients receiving 48 weeks of therapy limits the applicability of these conclusions.⁷⁹

Controlled and cohort trials have reported that treatment of HCV with IFN monotherapy gives SVR in 19–71% of hemodialysis patients (see Table 7). There are no equivalent data available for the CKD population.

Achieving SVR may improve clinical outcomes (improved survival, lowered rate of hepatocellular carcinoma) in patients with HCV and normal kidney function.^{193–197} No data are available to indicate that obtaining SVR translates into improved survival in the CKD population with HCV infection. However, there are reports that successful antiviral therapy can improve other outcomes (for example, liver histology). Pretransplant SVR after IFN therapy is associated with improved liver histology in patients who remain on dialysis^{143,151} and in those who go on to receive a kidney transplant.¹³⁶ An association between SVR after IFN therapy and improved liver histology has also been observed in HCV-infected dialysis patients with cirrhosis.¹⁵⁶ Improvement in ALT/AST levels with successful therapy has also been demonstrated. Controlled clinical trials have shown that patients on maintenance hemodialysis treated with IFN had ALT normalization, whereas no change in ALT/AST levels were observed in untreated controls.^{134,135} Controlled and cohort studies have shown that antiviral therapy targeted at HCV results in sustained biochemical response (ALT normalization that persists at least 6 months after completion of antiviral therapy) in 40–100% of patients with CKD Stage 5D.⁷⁹

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

- For patients on maintenance hemodialysis, repeat testing with NAT every 6 months is suggested. (Weak)

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

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

The literature is limited on long-term virologic response after IFN-based therapy in CKD patients with HCV. For patients with CKD Stages 1–5 who have attained SVR, annual testing is suggested to assess the durability of the viral response. For patients with CKD Stage 5D, it is recommended that NAT be repeated every 6 months (see Guideline 1). This is primarily for reasons of infection control in the hemodialysis unit. There are no data available for follow-up testing of patients with CKD Stages 1–5, and this recommendation is extrapolated from the AASLD guidelines (<https://www.aasld.org/eweb/docs/hepatitisc.pdf>).

Table 7 | Monotherapy with conventional IFN in dialysis patients

Author (year)	IFN schedule	SVR rate
Koenig (1994) ¹⁴²	5 MUI 3 times per week for 4 months	30% (11/37)
Pol (1995) ¹⁴³	3 MUI 3 times per week for 6 months	20% (3/15)
Raptopoulou-Gigi (1995) ¹⁹⁸	3 MUI 3 times per week for 6 months	68% (13/19)
Fernandez (1997) ¹³⁵	1.5–3 MUI 3 times per week for 6 months	21% (3/14)
Izopet (1997) ¹⁹⁹	3 MUI 3 times per week for 6 months (n=12)	52% (12/23)
	3 MUI 3 times per week for 12 months (n=11)	
Chan (1997) ²⁰⁰	3 MUI 3 times per week for 6 months	27% (3/11)
Huraib (1999) ²⁰¹	3 MUI 3 times per week for 12 months	71% (12/17)
Campistol (1999) ¹³⁴	3 MUI 3 times per week for 6 months	42% (8/19)
Espinosa (2001) ²⁰²	3 MUI 3 times per week for 12 months	46% (6/13)
Casanovas-Taltavull (2001) ¹³⁸	3 MUI 3 times per week for 6 months then	62% (18/29)
	1.5 MUI 3 times per week for 6 months	
Hanrotel (2001) ¹⁴¹	3 MUI 3 times per week for 12 months	33% (4/12)
Degos (2001) ¹³⁹	3 MUI 3 times per week for 12 months (n=12)	19% (7/37)
	1.5 MUI 3 times per week for 12 months (n=6)	
Kamar (2003) ²⁰³	3 MUI 3 times per week for 6 (or 12) months	38% (21/55)
Rivera (2005) ²⁰⁴	3 MUI 3 times per week for 6 (or 12) months	40% (8/20)
Mahmoud (2005) ¹⁵⁴	3 MUI 3 times per week for 6 months	44% (8/18)
Ozdemir (2004) ²⁰⁵	6 MUI 3 times per week for 6 months (n=10)	40% (8/20)
	3 MUI 3 times per week for 12 months (n=10)	
Grgurevic (2006) ¹⁴⁰	3 MUI 3 times per week for 6 months (n=8)	40% (6/15)
	5 MUI 3 times per week for 3 months then	
	5 MUI 1 time per week for 3 months (n=7)	
Buargub (2006) ¹³⁷	3 MUI 3 times per week for 12 months	26% (9/35)
Rocha (2006) ¹⁴⁴	3 MUI 3 times per week for 12 months	22% (10/46)
Yildirim (2006) ¹⁴⁵	3 MUI 3 times per week for 6 months	54% (20/37)

IFN, interferon; MUI, million units (international); SVR, sustained virologic response.

This is a nonsystematic review of studies and did not follow the methodology described in Appendix 2.

In a long-term follow-up on 20 HCV-infected patients on maintenance hemodialysis for a period of 6 years, 15 (75%) showed HCV RNA clearance at the end of treatment, but 7 of them (47%) had viral relapse and only 8 (40%) had SVR at final follow-up.²⁰⁵

Recent data indicate that pretransplant SVR is well sustained after transplantation despite intense immunosuppressive therapy.^{187,206} There are additional reports (all prospective cohort studies) giving information on a total of 58 patients. The relapse rate of HCV RNA after kidney transplantation in these trials ranged between 0 and 33%.^{108,134,138,154,187,204}

The annual assessment of HCV viremia is especially important for those patients who have received antiviral therapy and are on the waiting list for kidney transplantation. HCV-infected patients with CKD who relapse after having obtained an on-treatment viral response should be re-treated before kidney transplantation (see Guideline 2.1.1). There are no clinical trials on response to antiviral therapy in patients on maintenance hemodialysis who relapse, but the information available from patients with HCV and normal kidney function supports this approach. Those who relapse should receive antiviral treatment for at least 1 year (see Guideline 2.2.3). A similar approach should be used for patients who achieve an end-of-treatment response but not SVR.

LIMITATIONS

- The limited information available in the literature on HCV infection in the CKD population made it

necessary to extrapolate evidence from the non-CKD population. The natural course of HCV infection in the CKD population may differ substantially from that in the general population.

- No data are available to indicate that obtaining SVR translates into improved survival in the CKD population with HCV infection.

RESEARCH RECOMMENDATIONS

- There are no clinical trials on the response to antiviral therapy in patients on maintenance hemodialysis who relapse, but the information available from patients with HCV and normal kidney function supports this approach. The optimal treatment for this group of patients needs further study.
- Prospective cohort trials are needed to study the durability of the pretransplant SVR after renal transplantation. The evidence supporting the durability of a pretransplant SVR after renal transplantation provides encouraging results; however, it is based mostly on uncontrolled trials that need to be confirmed in prospective studies.
- Epidemiologic studies are needed to demonstrate that achieving SVR in the hemodialysis population translates into improved long-term survival. Similarly, the literature is limited on long-term virologic response after IFN-based therapy in CKD patients with HCV. Studies to better understand the virologic course of the disease are needed.

Table 8 | Summary table of baseline characteristics of hemodialysis patients with chronic HCV infection receiving IFN-based regimens

Author (year)	Country of study	Sample size	Mean age	Race	Male gender (%)	Mean duration of HD (months)	Mean duration of HCV infection (months)	Genotype prevalence					N
								1	2	3	4	5	
Fernandez (1997) ¹³⁵	Argentina	14 treatments 9 controls	45 49	ND	36 67	45 57	20 20	54 78	15 22	23	8		1 0
Campistol (1999) ¹³⁴	Spain	19 treatments 17 controls	42 48	ND	47 59	77 96	ND	94 100		6			1 9
Huraib (2001) ¹³⁶	Saudi Arabia	11 treatments 10 controls	40 38	ND	62	32 30	ND	40 ^a			60 ^a		
Rocha (2006) ¹⁴⁴	Brazil	46	46	ND	61	60	72	100					27
Yildirim (2006) ¹⁴⁵	Turkey	37	44	ND	62	92	26	86	5	8			
Degos (2001) ¹³⁹	France	37	45	ND	68	ND	94	83	14	3			2
Koenig (1994) ¹⁴²	Austria	37	54	ND	59	84	ND						37
Buargub (2006) ¹³⁷	Libya	35	40	ND	57	24	24	35		5	60		15
Casanovas-Taltavull (2001) ¹³⁸	Spain	29	45	ND	62	70	ND	100					3
Izopet (1997) ¹⁹⁹	France	23	47	ND	74	99	89	57	17	4	17	4	
Ozdemir (2004) ²⁰⁵	Turkey	20	45	ND	55	47	ND	67	25	8			8
Pol (1995) ²⁰⁷	France	19	45	ND	74	94	ND	67	13	7	7	7	4
Espinosa (2001) ²⁰²	Spain	13	34	ND	54	96	72	86				14	
Chan (1997) ²⁰⁰	Hong Kong	11	42	ND	73	122	> 60	91	9				
Raptopoulou-Gigi (1995) ¹⁹⁸	Greece	19	ND	ND	ND	ND	ND						19
Hanrotel (2001) ¹⁴¹	France	12	38	ND	67	88	ND	67	17	8	8		
Benci (1998) ²⁰⁸	Italy	10	38	ND	40	ND	ND						10
Mousa (2004) ¹⁷⁰	Saudi Arabia	20	52	ND	45	66	68	38			62		12

HCV, hepatitis C virus; HD, hemodialysis; NA, not applicable; ND, not documented; NS, not significant.

^aGenotype proportion from original cohort of 30 patients.

Table 9A | Summary table of IFN-based regimens in hemodialysis patients with chronic HCV infection: main outcomes

Author (year), country study design	Mean follow-up N (months)		Description of HCV		Intervention		Outcomes								Quality	
	N	(months)	RNA assay (sensitivity threshold)	Mean baseline HCV RNA	Dose ^a	Duration of therapy (months)	Efficacy outcomes		Treatment discontinued due to adverse events (%)	Adverse outcomes						
							SVR (%)	Other outcomes		Systemic	Adverse events ^{b,c} (N (%))					
IFN																
Randomized controlled trials																
Fernandez (1997) ¹³⁵ Argentina	14	12 ^d	Qualitative nested RT-PCR (ND)	ND	1.5 MU ^e	6	21	^g	21	1 (7%)	1 (7%)		1 (7%) ^h	1 (11%)	A	
Campistol (1999), ¹³⁴ Spain	19	19 ⁱ	Qualitative RT-PCR (ND)	ND	3 MU	6	58*	^g	53	4 (21%)	4 (21%)	ND	1 (5%)	1 (5%)	B	
Huraib (2001), ¹³⁶ Saudi Arabia ^k	11	12 ^l	Quantitative bDNA (Quantiplex) (0.2 mequiv. ml ⁻¹)	1.1 mequiv. ml ⁻¹ 1.0 mequiv. ml ⁻¹	3 MU	12	36 ^m	^g	0		1 (9%)	ND			B	
Prospective, noncomparative cohort studies																
Rocha (2006), ¹⁴⁴ Brazil	46	6	ND	ND	3 MU	12	22*	^g	24	44 (96%)	6 (13%)		7 (15%)	31 (67%)	B	
Yildirim (2006), ¹⁴⁵ Turkey	37	15	Qualitative RT-PCR (ND)	ND	3 MU	>6	54 ^{kk}		3 ^{ll}				1 (3%)		B	
Degos (2001), ¹³⁹ France	37	6	Quantitative RT-PCR (Amplicor Monitor) (ND)	5.1 log copies per ml	3 MU	12	19*		51 ⁿ	10 (27%)		1 (3%)	1 (3%)	7 (19%)	B	
Koenig (1994), ¹⁴² Austria	37	5	Qualitative nested RT-PCR (ND)	ND	5 MU	4	30 ^o		35 ^p	10 (27%)				3 (8%)	B	
Buargub (2006), ¹³⁷ Libya	35	6	Quantitative RT-PCR (Versant (3200 HCV RNA copies per ml)	5.95 log copies per ml	3 MU	12	26		9					3 (9%)	B	
Casanovas- Taltavull (2001), ¹³⁸ Spain	29	ND ^q	Qualitative RT-PCR (Amplicor) (ND)	ND	3 MU followed by 1.5 MU ^f	12	62		24				1 (3%)	1 (3%)	7 (24%)	B
Izopet (1997), ¹⁹⁹ France	23	19	Quantitative RT-PCR (Amplicor monitor) (2.7 log copies per ml)	4.7 log copies per ml	3 MU	6 (N=12) or 12 (N=11)	57*	^g	13	2 (9%)			1 (4%)	2 (9%)	B	

Table 9A | Continued

Author (year), country study design	Description of HCV		Intervention		Outcomes							Quality		
	Mean follow-up N (months)	RNA assay (sensitivity threshold)	Mean baseline HCV RNA	Dose ^a	Duration of therapy (months)	Efficacy outcomes		Treatment discontinued due to adverse events (%)	Adverse outcomes					
						SVR (%)	Other outcomes		Systemic	Adverse events ^{b,c} (N (%))				
									Hemato- logic	Seizures	Psychiatric	Others		
Ozdemir (2004), ²⁰⁵ Turkey	20	76	Qualitative RT-PCR (RT-Amplisensor) (ND)	ND	6 MU (N=10) or 3 MU (N=10) ^f	6 (N=10) or 12 (N=10) ^f	40	^g	0					B
Pol (1995), ²⁰⁷ France	19 ^v	18	Quantitative bDNA (Quantiplex) (3.5 × 10 ⁵ equiv. ml ⁻¹)	1.4 × 10 ⁶ equiv. ml ^{-1w}	3 MU	6	20 ^x		5	1 (5%) ^y	1 (5%)			B
Espinosa (2001), ²⁰² Spain	13	53 ^z	Qualitative RT-PCR (Amplicor) (ND)	ND	3 MU	12	46 ^{aa}		23	1 (8%)	1 (8%)	1 (8%)		B
Chan (1997), ²⁰⁰ Hong Kong	11	24	Quantitative bDNA (Quantiplex) (3.5 × 10 ⁵ equiv. ml ⁻¹)	< 3.5 × 10 ⁵ equiv. ml ⁻¹ in responders, 12.2 × 10 ⁵ equiv. ml ⁻¹ in relapsers	Starting: 1.5 MU, and then 3 MU maintenance	Starting: 0.5 months, then 6 months maintenance	27 [*]		0	8 (73%) ^{bb}	8 (73%) ^{cc}			B
Raptopoulou- Gigi (1995), ¹⁹⁸ Greece	19	14	Qualitative nested RT-PCR (ND)	ND	3 MU ^{dd}	6	68 [*]	^g	32	3 (16%)	1 (5%)		4 (21%)	C
Hanrotel (2001), ¹⁴¹ France	12	6	Quantitative RT-PCR (Amplicor Monitor) (ND)	564 018 equiv. copies ml ⁻¹	3 MU	12	33 [*]		8				1 (8%)	C
Benci (1998), ²⁰⁸ Italy	10	6	ND	ND	1 MU	12	20 ^{ff}		10	1 (10%)				C
IFN plus ribavirin														
Prospective, noncomparative cohort studies														
Mousa (2004), ¹⁷⁰ Saudi Arabia	20	12	Qualitative RT-PCR (Amplicor) (ND)	ND	3 MU+200 mg RBV TIW	6 (N=9) 12 (N=11)	55	^g	0		3 ^{jj} (15%)			C

*Primary outcome.

bDNA: branched-chain DNA signal amplification assay; HD, hemodialysis; IFN, interferon; MU, million units; NA, not applicable; ND, not documented; NS, not significant; RBV, ribavirin; RCT, randomized controlled trial; RT-PCR, reverse transcription-polymerase chain reaction; SVR, sustained virologic response; TIW, three times weekly.

^aAll studies administered IFN three times per week in the dialysis unit.^bPatients may have contributed to more than one adverse event.^cSystemic symptoms include flu-like syndrome, fever, arthralgia, fatigue, anorexia, and asthenia. Hematologic adverse events include leukopenia, anemia, and thrombocytopenia of sufficient severity to be reported. Hematologic adverse events of lesser severity were reported but without rates in some studies. Psychiatric adverse events include depression, confusion, and lethargy. Other adverse events include cardiovascular, gastrointestinal adverse events, plus rejection/necrosis of nonfunctional kidney allograft.^dFollow-up period was 6 months for all treated patients and 12 months for patients who achieved SVR. Control patients were followed during their treatment with placebo.^eDecreased to 3 MU if no response at 3 months.^fControl patients received albumin placebo with identical volume and administration schedule to IFN.

Table 9A | Continued

^gSee Table 9B.

^hOne patient had depression and asthenia. A total of three patients reported adverse events.

ⁱFollow-up reported is the average of the follow-up time for patients who remained on HD and those who underwent kidney transplantation.

^kAuthors report the results of 21 patients who were followed for 12 months after kidney transplant. An additional nine (four treated and five control) patients had not yet reached this endpoint.

^lDuration of follow-up between end of treatment and transplantation not documented. Patients were followed for 12 months after kidney transplant.

^mReported SVR of 36% extrapolated from post-transplant results assuming all HCV RNA-negative transplant recipients were HCV RNA-negative 6 months after treatment.

ⁿStudy terminated prematurely by promoting institution because of side effects requiring discontinuation of treatment in 51% of patients.

^oOf 37 patients, 11 were HCV RNA-negative 5 months after treatment. SVR result extrapolated from this finding.

^pTreatment terminated in one additional patient because kidney transplantation was performed.

^qTreated patients who underwent kidney transplantation were followed for a mean of 41 months after transplant.

^rPatients treated with 6 months of 3 MU followed by 6 months of 1.5 MU.

^tTen patients were treated with 6 MU TIW for 6 months. Ten patients were treated with 3 MU TIW for 12 months.

^vOf 19 patients, four were HCV-negative by RT-PCR before treatment; 3 of 19 had acute HCV.

^wOf 19 patients, 11 had measurable HCV RNA by bDNA test (compared with 15 of 19 by RT-PCR). The reported average is among all patients (including those who were bDNA negative).

^xFifteen patients were HCV RNA-positive at start of treatment. SVR was calculated using only these patients and was 3 of 15 (20%).

^ySame patient reported adverse events of fatigue and anemia. There was only one patient who reported adverse events.

^zMean duration of follow-up (range 12–72 months).

^{aa}All patients (46% of cohort treated) who achieved SVR remained HCV RNA-negative for entire duration of follow-up (12–72 months).

^{bb}Eight patients complained of persistent malaise, myalgia, and poor appetite during IFN therapy.

^{cc}Eight patients were treated for anemia.

^{dd}Dose reduced to 1 MU in the case of side effects in five patients who then completed the treatment at this lower dose.

^{ff}Post-treatment HCV RNA only tested in patients with a persistent normalization of transaminases 6 months after treatment.

^{jj}Three patients had anemia from hemolysis attributed by the authors to ribavirin not IFN.

^{kk}SVR result may be a slight underestimate as it includes HCV RNA results at last follow-up. Nine patients relapsed after end of treatment response at 7 ± 5 (range 1–17) months after treatment discontinuation.

^{ll}Treatment discontinued after 6 months in six additional patients due to lack of virologic response.

Table 9B | Summary table of IFN-based regimens in hemodialysis patients with chronic HCV infection: other outcomes described

Author (year), country, study design	Other efficacy outcomes
IFN	
<i>Randomized controlled trials (other outcomes for treatment arm only)</i>	
Fernandez (1997), ¹³⁵ Argentina	End of treatment response: 29%; SVR: 21%; HCV RNA-negative 12 months after treatment: 14% ^g
Campistol (1999), ¹³⁴ Spain	HCV remained negative in 3 patients until the day of kidney transplantation at 7, 12, and 27 months after IFN, respectively. Two of these patients remained HCV-negative 3 and 24 months after transplantation; 1 became HCV-positive 20 months after transplantation. In 5 patients, HCV RNA remained negative while on hemodialysis (~27 months)
Huraib (2001), ¹³⁶ Saudi Arabia	Four of 11 (36%) patients had undetectable HCV RNA at the end of treatment and 12 months after transplant (time between end of treatment and kidney transplantation was not documented) ^m
<i>Prospective, noncomparative cohort studies</i>	
Rocha (2006), ¹⁴⁴ Brazil	An end-of-treatment response was seen in 41% of patients. SVR was 34% in patients completing treatment
Izopet (1997), ¹⁹⁹ France	SVR: 42% of patients treated for 6 months and 64% of patients treated for 12 months
Ozdemir (2004), ²⁰⁵ Turkey	HCV RNA became undetectable in 15 of 20 (75%) of patients at the end of treatment. At the end of final follow-up (76 months), the 8 (40%) patients who had achieved SVR remained HCV RNA-negative
Raptopoulou-Gigi (1995), ¹⁹⁸ Greece	Of the 13 patients who achieved SVR, one had a relapse and became HCV RNA positive in 14 months after treatment; the rest remained negative
<i>IFN plus Ribavirin</i>	
<i>Prospective, noncomparative cohort studies</i>	
Mousa (2004), ¹⁷⁰ Saudi Arabia	Seven of 20 (35%) patients were HCV RNA-negative 12 months after treatment completed, although 12 month data were not reported for all patients, including some who had achieved SVR

For footnotes 'g' and 'm', see Table 9A.

Table 10 | Evidence profile of treatment with IFN-based regimens in hemodialysis patients with chronic HCV infection

Outcome	No. of studies and study design	Total N of patients on treatment	Methodologic quality of studies	Consistency across studies	Directness of the evidence, including applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Survival	ND	ND					Very low ^l	Inconsistent reporting of mortality in text of articles with variable follow-up times and no documentation of how mortality was ascertained	Critical
Sustained virologic response	3 RCT 15 prospective (high)	412	Some limitations ^a (−1)	No important inconsistencies ^b (0)	Some uncertainty about directness of evidence ^c (−1)	Consistently higher SVR than in untreated controls. Suggestion of a dose response relationship. (+1)	Moderate ^d	Range of SVR for RCTs was 21–58% Range of SVR for prospective, noncomparative, cohort studies was 19–62%	High
Adverse events	3 RCT 14 prospective 1 not reported (high)	Total: 392 Systemic ^e : 248 Hematologic ^f : 172 Seizures: 102 Psychiatric ^g : 205 Others ^h : 234	Some limitations ⁱ (−1)	Important inconsistencies ^j (−1)	Some uncertainty about directness of evidence ^k (−1)		Very low ^l	Total of 93 adverse events were seen in 274 patients ^m Systemic adverse events were documented in 85 (34%) Hematologic adverse events were documented in 26 (15%) Seizures were documented in 4 (4%) Psychiatric adverse events were documented in 15 (7%) Other adverse events were documented in 57 (24%)	High
Treatment discontinued due to adverse events	3 RCT 14 prospective 1 not reported (high)	401	Some limitations (−1)	Important inconsistencies ^b (−1)	Some uncertainty about directness of evidence ^c (−1)		Very low ^l	Treatment was discontinued in 69 patients (17%) due to adverse events	High
Change in liver histology	NA	NA						There was inconsistent reporting of change in liver histology as an outcome. There were a small number of studies reporting this outcome and a variety of different histologic scoring systems (Knodell, HAI, Ishak, Metavir) were used	Low

Table 10 | Continued

Outcome	No. of studies and study design	Total N of patients on treatment	Methodologic quality of studies	Consistency across studies	Directness of the evidence, including applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Total N		412							
Balance of potential benefits and harm: Improved SVR compared with untreated patients, but no information on critical outcomes including mortality. In addition, there are significant, but self-limited adverse events reported.							Quality of overall evidence: Very low		

NA, not applicable (not summarized in Table 9); ND, no data; RCT, randomized controlled trial; SVR, sustained virologic response.

^aSmall samples sizes. There were only three RCTs with problems of allocation concealment. Some studies not analyzed by intention to treat. There were inconsistencies between text and tables of articles.

^bSVR was consistently higher in treated individuals than untreated controls. There was heterogeneity in genotype, dose, duration, and disease severity, but suggestion of dose-response relationship.

^cStudies investigated a small discrete subset of dialysis patients and may not apply to all hemodialysis patients. No studies of peritoneal dialysis patients.

^dUpgraded by the Work Group because, in spite of few RCTs, the rate of spontaneous viral clearance in the RCTs was low and thus the results of prospective studies could be upgraded for the outcome of SVR.

^eSystemic symptoms include flu-like syndrome, fever, arthralgia, fatigue, anorexia, and asthenia.

^fHematologic adverse events include leukopenia, anemia, and thrombocytopenia of sufficient severity to be reported. Hematologic adverse events of lesser severity were reported but without rates in some studies.

^gPsychiatric adverse events include depression, confusion, and lethargy.

^hOther adverse events include cardiovascular, gastrointestinal adverse events, plus rejection/necrosis of nonfunctional kidney allograft.

ⁱReporting bias, publication bias, small samples sizes. There were only three RCTs, and only one administered placebo to patients in the control group. There was inconsistent reporting of rates of adverse events.

^jInconsistent reporting of adverse events in studies resulted in inconsistent results of rate of adverse events.

^kStudies investigated a small discrete subset of dialysis patients and may not apply to all hemodialysis patients.

^lNot upgraded in a manner consistent with SVR as an outcome because there was no compelling reason to believe that outcomes would be similar in RCTs.

^mMore than one adverse event may have occurred in each patient.

Table 11 | Summary table of baseline characteristics of kidney transplant recipients with chronic HCV infection receiving therapy

Author, year	Country of study	Sample size	Mean age	Race	Male gender (%)	Mean duration of HCV infection (months)	Genotype prevalence					N
							%					
							1	2	3	4	5	ND
IFN monotherapy												
Rostaing (1995) ¹⁵⁷	France	14 treatment 14 controls	48 45	ND	64 43	ND					ND	
Rostaing (1996) ¹⁸⁸ and Rostaing (1995) ²¹⁰	France	16	49	ND	63	106					ND	
Ribavirin monotherapy												
Kamar (2003) ¹⁸⁷	France	16 treatment 32 control	48 49	ND	75 63	199 158	44 84	31 9	6 3	19 3		
IFN plus ribavirin therapy												
Shu (2004) ¹⁶⁵	Taiwan	11	42	ND	72	ND	67	33				2

NA, not applicable; ND, not documented; NS, not significant.

Table 12 | Summary table of treatment in kidney transplant recipients with chronic HCV infection

Author (year), country, study design	N	Mean follow-up (months)	Description of HCV		Intervention		Outcomes					Quality
			RNA assay (sensitivity threshold)	Mean baseline HCV RNA	Dose ^a	Duration of therapy (months)	Efficacy outcomes		Adverse outcomes			
							HCV RNA- negative after IFN (%)	Other outcomes	Tx D/C due to AEs	Increased serum creatinine ^b	Allograft loss (return to HD)	
IFN												
Comparative study												
Rostaing (1995), ¹⁵⁷ France Prospective	14	12	Qualitative HCV RNA (Amplicor) (ND)	ND	3 MU	6	0%	^c	21% ^d	36% ^e	7%	C
	14				Untreated		ND		0%	0%	0%	
Noncomparative study												
Rostaing (1996) ¹⁸⁸ and (1995), ²¹⁰ France Prospective	16	2	HCV RNA (Amplicor) (ND)	ND	3 MU	6	0%		56% ^f	38% ^g	19%	C
Ribavirin												
Comparative study												
Kamar (2003), ¹⁸⁷ France Prospective	16	12	Quantitative RT-PCR (Amplicor Monitor) (ND)	5.9 log copies per ml 5.5 log copies per ml	1000 mg day ⁻¹ in two divided doses ^h	12	ND	ⁱ	25%	↓ 19 μmol l ⁻¹ (<i>P</i> =0.075)	6%	C
	32				Untreated		ND		ND	↑ 14 μmol l ⁻¹ (<i>P</i> =0.002)	ND	
IFN plus Ribavirin												
Noncomparative study												
Shu (2004), ¹⁶⁵ Taiwan Prospective	11	32	Quantitative RT-PCR (Amplicor Monitor) (600 copies per ml)	2.8 × 10 ⁴ copies per ml	IFN: 1 MU+ ribavirin: 600 mg day ⁻¹	12	27%	^j	27% ^k	9%	0%	C

AE, adverse events; D/C, discontinued; HD, hemodialysis; IFN, interferon; KTR, kidney transplant recipient; MU, million units; NA, not applicable; ND, not documented; NS, not significant; RT-PCR, reverse transcription-polymerase chain reaction; SVR, sustained virologic response; Tx, treatment.

^aAll studies of IFN administered it three times per week in the dialysis unit.

^bDefinition of this outcome specified in footnote of individual articles when reported.

^cAt end of treatment, HCV RNA was negative in 4 of 14 (29%) treated patients. Within 1 month of cessation of IFN, all four had relapsed and were HCV-RNA positive.

^dPercent out of the total treated with IFN; 3 of 14 (21%) patients treated with IFN dropped out of the study due to adverse events.

^eCreatinine increased more than 20% above baseline in 5 of 14 (36%) treated patients. Despite receiving pulse methylprednisolone, one required HD, two had stable or increasing serum creatinine and two had improving serum creatinine.

^fA total of nine patients did not complete the study. Four patients dropped out due to adverse events, whereas five dropped out due to acute kidney failure.

^gCreatinine increased more than 25% above baseline in 6 of 16 (38%) treated patients. Pulse methylprednisolone was given with improvement of kidney function in two, stabilization in one, and ongoing increase in three, who subsequently required HD.

^hDosage reduced for anemia despite erythropoietin support.

ⁱNumber of patients who achieved negative HCV RNA not documented but the mean HCV viremia did not differ (5.7 copies per ml at the end of treatment). Liver fibrosis worsened on the Metavir scoring system after treatment with ribavirin.

^jOf 11 patients, five were HCV RNA-negative at end of treatment; 3 of 11 (27%) remained HCV RNA-negative in 52, 59, and 60 weeks after treatment, respectively.

^kOne patient developed increased creatinine 2 weeks after treatment initiated but improved after pulse steroids. Two patients were withdrawn from the study due to urosepsis.

Table 13 | Summary table of adverse events leading to discontinuation of treatment in kidney transplant recipients with chronic HCV infection

Author (year) country	N	Intervention		Increase in serum creatinine ^c	Adverse events N (%) ^a		Total D/C of therapy due to AE
		Dose ^b	Duration of therapy (mo)		Allograft loss (return to HD)	Other AE	
IFN							
Comparative Study							
Rostaing (1995) ¹⁵⁷ France	14 ^d	3 MU	6	5 (36%) ^e	1 (7%)	12 (86%) persistent fatigue, 3 (21%) anorexia, 2 (14%) weight loss >10%, 2 (14%) sleep disturbances, 1 (7%) sexual impotence, 1 (7%) partial alopecia	3 (21%) ^f
Noncomparative study							
Rostaing (1996) ¹⁸⁸ Rostaing (1995), ²¹⁰ France	16	3 MU	6	6 (38%) ^g	3 (19%)	5 (31%) developed acute kidney failure ^h , 4 (25%) anorexia	9 (56%)
Ribavirin							
Comparative study							
Kamar (2003), ¹⁸⁷ France	16	1000 mg day ⁻¹ in 2 divided doses	12	↓ 19 μmol l ⁻¹ (P=0.075) ⁱ	1 (6%) ^j	3 (19%) anemia	4 (25%)
IFN plus ribavirin							
Noncomparative study							
Shu (2004) ¹⁶⁵ Taiwan	11	IFN: 1 MU+ribavirin: 600 mg day ⁻¹	12	1 (9%) ^k	0 (0%)	2 (18%) urosepsis	3 (27%)

AE, adverse events; Δ, change; D/C, discontinued; HD, hemodialysis; IFN, interferon; KTR, kidney transplant recipient; MU, million units NA, not applicable; ND, not documented; NS, not significant.

^aBecause patients may have experienced more than one adverse event, the percentages may add up to > 100%.

^bAll studies administered IFN three times per week in the dialysis unit.

^cDefinition of this outcome specified in footnote of individual articles when reported.

^dOut of 28 patients enrolled, 14 patients received IFN treatment vs 14 receiving no treatment.

^eCreatinine increased more than 20% above baseline in 5 of 14 (36%) treated patients. Despite receiving pulse methylprednisolone, one required HD, two had stable or increasing serum creatinine, and two had improving serum creatinine.

^fOf 14 treated patients, three dropped out of the study due to severe side effects (anorexia, weight loss). This figure does not include the five patients whose serum creatinine increased.

^gCreatinine increased more than 25% above baseline in 6 of 16 (38%) treated patients. Pulse methylprednisolone was given with improvement of kidney function in two, stabilization in one, and ongoing increase in three, who subsequently required HD.

^hOf 16 patients, five developed acute kidney failure during treatment. One of 16 had increase in serum creatinine first documented after treatment was completed.

ⁱThis analysis does not include the serum creatinine of the patient with allograft loss.

^jAllograft loss 2 months after initiating ribavirin due to thrombosis of a preexisting severe artery stenosis.

^kOne patient developed increased creatinine 2 weeks after treatment initiated but improved after pulse steroids.

Table 14 | Evidence profile for treatment regimens in kidney transplant recipients with chronic HCV infection

Outcome	No. of studies and study design	Total N of patients on treatment	Methodologic quality of studies	Consistency across studies	Directness of the evidence, including applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Survival	ND	ND					Very low	Inconsistent reporting of mortality in text of articles with variable follow-up times and no documentation of how mortality was ascertained.	Critical
Allograft loss (return to HD)	4 prospective (high)	30	Some limitations (–1) ^d	Important inconsistencies (–1) ^b	Some uncertainty about directness of the evidence ^c (–1)	None	Very low	Rate of allograft loss ranged from 7–19% in patients treated with IFN. Rate of allograft loss was 6% in patients treated with ribavirin. Rate of allograft loss was 0% in patients treated with IFN plus ribavirin. Rate on allograft loss was 0% in untreated controls.	Critical
HCV RNA negative after treatment	4 prospective (high)	57 (46 untreated controls)	Some limitations (–1) ^a	Important inconsistencies (–1) ^b	Some uncertainty about directness of the evidence ^c (–1)	None	Very low	Rate of HCV RNA negativity after IFN was 0% in 2 studies. Rate of HCV RNA negativity after ribavirin was not documented. Rate of HCV RNA negativity after treatment with IFN plus ribavirin was 27%.	High
Increased serum creatinine	4 prospective (high)	57	Serious limitations (–2) ^e	Important inconsistencies (–1) ^f	Some uncertainty about directness of the evidence ^c (–1)	None	Very low	Rate of increased serum creatinine ranged from 36–38% in patients treated with IFN. Rate of increased serum creatinine was not documented in patients treated with ribavirin. Rate of increased serum creatinine was 9% in patients treated with IFN plus ribavirin. Rate of increased serum creatinine was 0% in untreated controls.	High
Other adverse events	4 prospective (high)	Total: 57 Systemic ^g : 30 Hematologic ^h : 16 Other ⁱ : 25	Serious limitations (–2) ^j	Important inconsistencies (–1)	Some uncertainty about directness of the evidence (–1)	None	Very low	Systemic symptoms ranged from 25–86% in patients treated with IFN. Rate of hematologic adverse events was 19% in patients treated with ribavirin. The rate of other adverse events was 14% in patients treated with IFN and 18% in patients treated with IFN plus ribavirin. Adverse events were not reported in untreated patients.	High

Table 14 | Continued

Outcome	No. of studies and study design	Total N of patients on treatment	Methodologic quality of studies	Consistency across studies	Directness of the evidence, including applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Treatment discontinued due to adverse events	4 prospective (high)	57	Some limitations (−1)	Important inconsistencies (−1)	Some uncertainty about directness of the evidence (−1)	None	Very low	Rate of treatment discontinuation ranged from 21–56% in patients treated with IFN, was 25% in patients treated with ribavirin, and was 27% in patients treated with IFN plus ribavirin.	High
Total N		57							
Balance of benefit and harm: Unable to assess the balance between benefit and harm ^k							Quality of overall evidence: Very low		

HCV, hepatitis C virus; HD, hemodialysis; ND, no data.

^aPublication bias, reporting bias, and inconsistent reporting of outcomes.

^bInconsistent results with different treatment regimens.

^cStudies investigated a discrete subset of transplant recipients and may not apply to all transplant recipients.

^dPublication bias, reporting bias.

^ePublication bias, reporting bias, and inconsistent reporting of outcomes. In addition, one study only reported mean change in serum creatinine after treatment.

^fDefinition of increased creatinine varies across studies resulting in inconsistent results.

^gSystemic symptoms include fatigue, anorexia, weight loss, and sleep disturbance.

^hThe hematologic adverse event was defined as anemia.

ⁱOther adverse events include partial alopecia, sexual impotence, and urosepsis.

^jInconsistent reporting of adverse events.

^kBecause of very low quality.

Table 15 | Summary table of pegylated-IFN monotherapy in hemodialysis patients with chronic HCV infection

Author (year), country, study design	Applicability					Description of HCV			Intervention		Outcomes			
	N	Mean age (mean)	Male gender (%)	Mean duration of HD (months)	Mean duration of HCV infection (months)	Genotype	Mean follow- up (mo)	RNA assay (sensitivity threshold)	Mean baseline HCV RNA	Dose	Duration of therapy (months)	Efficacy outcomes	Adverse outcomes	Quality
												SVR	Treatment discontinued due to adverse events	
Pegylated IFN RCT														
Kokoglu (2006), ¹⁸¹ Turkey	12	37	92	67	ND	1 (100%)	6	Quantitative RT-PCR (Amplicor Monitor) (600 copies per ml)	8.4×10^5 copies per ml	135 μg once weekly	12	75%*	0% ^b	B
	13	49	62	66	ND	1 (100%)	8.1×10^5 copies per ml		Untreated ^a			8%*	ND	
Russo (2006), ¹⁴⁶ United States	9	43	67	ND	ND	1 (89%) 2 (11%)	6	Quantitative RT-PCR (Amplicor Monitor) (600 copies per ml)	$\sim 100\,000$ IU ml ⁻¹	1.0 μg kg ⁻¹ once weekly	12	22%*	44% ^c	B
	7	50	57	ND	ND	1 (100%)	$\sim 200\,000$ IU ml ⁻¹		0.5 μg kg ⁻¹ once weekly			0%*	29% ^c	
Prospective cohort study														
Sporea (2006), ²⁰⁹ Romania	10	40	40	ND	ND	ND	6	Quantitative RT-PCR (Roche) (600 IU ml ⁻¹)	409 872 IU ml ⁻¹	180 μg once weekly	12	30%*	40% ^d	B

IFN, interferon; IU: international units; NA, not applicable; ND, not documented; NS, not significant; PEG-IFN, pegylated IFN; RCT, randomized controlled trials; RT-PCR, reverse transcription-polymerase chain reaction; SVR, sustained virologic response.

*Primary outcome.

^aControl group consisted of six patients who refused treatment and seven who were not candidates for kidney transplant. SVR was assessed at the same time in both treated and untreated patients.

^bPatients (75%) had anemia, 33% thrombocytopenia, 33% leukopenia, and 58% fatigue, but treatment was not discontinued.

^cAdverse events were reported without specifying to which group each subject belonged. One subject died of cardiac arrest due to a hypoglycemia-associated seizure, but this was not considered a treatment adverse event because subject was not taking PEG-IFN at the time of the event. Two subjects developed uncontrolled hypertension during treatment. One subject developed catheter-related bacteremia during treatment but was not neutropenic. One subject developed pneumonia but was not neutropenic. One subject developed severe constitutional symptoms during treatment. One subject developed possible ischemia to nonfunctioning kidney allograft.

^dTreatment discontinued due to patient death in four cases sepsis (three), hemorrhagic cerebrovascular accident (one), due to serious adverse events in seven patients (one case each of anemia, thrombocytopenia, pancytopenia, depression, hemorrhagic stroke, sepsis, and abdominal pain) and due to patient intolerance due to minor adverse events in 25 patients.

Table 16 | Summary table of pegylated IFN plus ribavirin in hemodialysis patients with chronic HCV infection

Author (year), country, study design	Applicability				Description of HCV			Intervention		Outcomes		Quality		
	N	Mean age (mean)	Male gender (%)	Mean duration of HD (months)	Mean duration of HCV infection	Genotype	Mean follow-up (months)	RNA assay (sensitivity threshold)	Mean baseline HCV RNA	Dose	Duration of therapy (months)		Efficacy outcomes	Adverse outcomes
													SVR	Treatment discontinued due to adverse events
<i>Pegylated IFN plus ribavirin</i>														
<i>Prospective, comparative study; non-RCT^a</i>														
Rendina (2007), ¹⁸⁶ Italy	35	46	54	120	84	1 (46%) Non-1 (54%)	6	Quantitative RT-PCR (Amplicor Monitor) (600 IU ml ⁻¹)	324 000 IU ml ⁻¹	PEG-IFN: 135 µg week ⁻¹ +ribavirin 200 mg day ⁻¹	6 or 12 ^b	97%*	6% ^c	B
	35 ^a	49	57	132	72	1 (43%) Non-1 (57%)			281 000 IU ml ⁻¹	Untreated		0%	ND	

IFN, interferon; IU: International Units; ND, not documented; PEG-IFN, pegylated IFN; RT-PCR, reverse transcription-polymerase chain reaction; SVR, sustained virologic response.

*Primary outcome.

^aThe control patients were selected from treatment candidates who met inclusion criteria but refused treatment.

^bPatients received treatment for 12 months if they were infected with HCV genotype 1. All genotype non-1 patients received treatment for 6 months.

^cOne patient discontinued treatment due to uncontrolled anemia after 3 months of treatment. One patient had severe dermatitis at month 4 and also discontinued treatment. Two patients discontinued treatment because they received a renal transplant at month 5 and treatment was stopped due to lack of response after month 6 of treatment in one patient. These three were not included in 6% reported in the summary table.

Table 17 | Evidence profile for treatment with pegylated-IFN monotherapy or pegylated IFN plus ribavirin in hemodialysis patients with chronic HCV infection

Outcome	No. of studies and study design	Total N of patients on treatment	Methodologic quality of studies	Consistency across studies	Directness of the evidence, including applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Survival	ND	ND					Very low	Inconsistent reporting of mortality in text of articles with variable follow-up times and no documentation of how mortality was ascertained	Critical
Sustained virologic response	2 RCT 1 comparative (non-RCT) 1 prospective (high)	73	Some limitations (−1) ^a	No important inconsistencies (0) ^b	Some uncertainty about the directness of the evidence (−1) ^c	Consistently higher SVR than in untreated controls. Suggestion of a dose–response relationship (+1)	Moderate	Range of SVR in treatment arm of RCTs of PEG-IFN was 13–75% ^d . SVR for the prospective, noncomparative, cohort study of PEG-IFN was 30%. SVR in the treatment arm of the comparative (non-RCT) study of PEG-IFN plus ribavirin was 97%	High
Treatment discontinued due to adverse events	2 RCT 1 comparative (non-RCT) 1 prospective (high)	73	Some limitations (−1) ^a	No important inconsistencies (0)	Some uncertainty about the directness of the evidence (−1) ^c	None	Low	Treatment was discontinued in 12 patients (16%) due to adverse events	High
Total N		73							
Balance of potential benefits and harm: Improved SVR compared with untreated patients, but no information on critical outcomes including mortality. In addition, there are significant, but self-limited adverse events reported.							Quality of overall evidence: Very low		

ND, no data; PEG-IFN, pegylated IFN; RCT, randomized controlled trial; SVR, sustained virologic response.

^aSmall sample sizes and publication bias.

^bSVR was consistently higher in treated individuals than untreated controls. There was heterogeneity in the dose of pegylated IFN used.

^cStudies investigated a small discrete subset of dialysis patients and may not apply to all hemodialysis patients. No studies of peritoneal dialysis patients.

^dThe treatment arms of Russo *et al.* were combined resulting in an overall SVR of 13%.

Guideline 3: Preventing HCV transmission in hemodialysis units

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INTRODUCTION

Dialysis units have responsibility for ensuring that blood-borne viruses are not transmitted among the patients in their care.

Levels of strength of recommendations

Strength of recommendation	Wording of recommendation	Basis for strength of recommendation
Strong	An intervention 'should' be done	'High' quality evidence and/or other considerations support a strong guideline ^a
Moderate	An intervention 'should be considered'	'Moderate' quality evidence and/or other considerations support a moderate guideline ^a
Weak	An intervention 'is suggested'	'Low' or 'Very Low' quality evidence; predominantly based on expert judgment for good clinical practice ^a

^aSee Appendix 2: Grading the Strength of the Recommendations, p. S85.

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

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

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

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

BACKGROUND

Transmission of HCV is primarily via percutaneous exposure to infected blood. HCV can remain viable in the environment (on equipment, clothing, and so on) for at least 16 hours.²¹¹

The prevalence of HCV infection in hemodialysis patients is significantly higher than in the general population.^{36,58} Transfusions before donor blood screening for HCV undoubtedly caused many cases of HCV in dialysis units. Still, correlation between HCV infection and time on dialysis, higher prevalence in hemodialysis than peritoneal dialysis or home hemodialysis, and the highly variable prevalence from unit to unit all suggest that nosocomial transmission has also contributed to the high prevalence.^{36,212,213} The occurrence of nosocomial transmission was confirmed when phylogenetic analysis identified clusters of closely related isolates of HCV, both in studies of individual units with high seroconversion rates^{214,215} and multicenter studies.^{216,217} Parts of the HCV genome (especially hypervariable region 1) are highly variable and lend themselves to fingerprinting of each isolate or quasispecies using nucleic acid sequencing. This may be used to establish a firm basis for studies of spread and routes of infection by HCV.^{218,219}

Since the dramatic reduction in the 1990s of the risk of post-transfusional HCV, nosocomial transmission is the most likely source when hemodialysis patients develop HCV antibodies. Tables 20 and 21 show the results of a systematic review of studies of HCV infections in hemodialysis in which nosocomial transmission was confirmed by phylogenetic analysis, and the route of transmission was investigated by the authors.

RATIONALE

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

Nosocomial transmission of HCV in hemodialysis units has been confirmed using epidemiology and/or molecular virology by many authors (see Background). The most likely cause of HCV transmission between patients treated in the same dialysis unit is cross-contamination from supplies and surfaces (including gloves) as a result of failure to follow infection-control procedures within the unit. Transmission via the internal pathways of the dialysis machine can be excluded for most machines (see below). Other possible transmission routes are direct contact between the patients, a common infected blood donor, and invasive procedures outside the unit with contaminated material used for both the source and the newly infected patient.²¹⁹ The two latter

Table 18 | Hygienic precautions for hemodialysis (general)**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 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.
- Appropriate information on infection control should also be given to nonclinical staff, patients, caregivers, and visitors.

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 antiseptic alcohol gel 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.
- Where practical, patients should also clean their hands, or use an alcohol gel rub, when arriving at and leaving the dialysis station.

Equipment management (for management of the dialysis machine, see Table 19)

- Single-use items required in the dialysis process should be disposed of after use on one patient.
- Nondisposable items should be disinfected after use on one patient. Items that can not be disinfected easily (for example, adhesive tape, tourniquets) should be dedicated to a single patient.
- The risks associated with the use of physiologic monitoring equipment (e.g., blood pressure monitors, weight scales, access flow monitors) for groups of patients should be assessed and minimized. Blood pressure cuffs should be dedicated to a single patient or made from a light-colored, wipe-clean fabric.
- Medications and other supplies should not be moved between patients. 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 management

- Needles should be disposed of in closed, unbreakable containers that 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.
- 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. If it is necessary to drain the circuit, or to remove any components for reprocessing, this should be done in a dedicated area away from the treatment and preparation areas.

causes are currently very unusual^{220–222} and can generally be excluded using the patient's medical records. The sharing of a contaminated medication vial was identified as the transmission route in one study involving the simultaneous infection of five patients.²²³

A systematic review of molecular virology papers that included both confirmation of the source patient(s) and an investigation of possible transmission routes was carried out. Twenty studies, involving between 1 and 22 newly diagnosed cases of HCV, were identified (see Tables 20 and 21). The authors of all 20 studies were unable to conclusively establish the specific transmission route(s), but all considered breaches in infection control, including failure to decontaminate pressure ports in one case,²²⁴ to be the probable cause of the outbreak.

Transmission of the virus via internal fluid pathways of the dialysis machine was considered to be a possibility in only one study,²²⁵ whereas in 18 of 20 studies, the authors reported that some or all patients with new HCV infection had never shared the dialysis machine with the source patient (see Table 21), either because they dialyzed at the same time or because the unit policy was to assign HCV-positive patients to separate machines.

Overall, the evidence from this systematic review of molecular virology studies strongly suggests that the internal hemodialysis machine circuit is, at most, a minor contributor to the nosocomial transmission of HCV among hemodialysis patients. There is no reason to believe that a publication bias has suppressed the reporting of nosocomial transmission related to the dialysis equipment or favored reporting of transmission due to breaches in infection-control procedures.

- *The isolation of HCV-infected patients is not recommended as an alternative to strict infection-control procedures for preventing transmission of blood-borne pathogens. (Weak).*

In the absence of any good RCTs of the impact of isolation on the risk of transmission of HCV to hemodialysis patients, the available evidence is limited to observational studies.

Many authors have reported a reduction (but not full prevention) of HCV transmission in hemodialysis after the adoption of an isolation policy, either dedicated machines for HCV-infected patients or a separate ward. All these studies were of the after-before (or before-after) type and none included a control group.^{226–228} Thus, it is unclear whether

Table 19 | Hygienic precautions for hemodialysis (dialysis machines)

Definitions

The 'transducer protector' is a filter (normally a hydrophobic 0.2- μ m 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 becomes 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.

External cleaning

After each session, the exterior of the dialysis machine should be cleaned with a low-level disinfectant if not visibly contaminated.

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

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

Disinfection of the internal fluid pathways

It is not necessary for the internal pathways of a single-pass dialysis machines to be disinfected between patients, unless a blood leak has occurred, in which case both the internal fluid pathways and the dialysate-to-dialyzer (Hansen) connectors should be disinfected before the next patient.

If machines are not subjected to an internal disinfection procedure, staff should ensure that sufficient time is available between patients for the external surfaces to be disinfected.

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

the reported improvement resulted from the adoption of an isolation policy or rather from the simultaneous raising of awareness and reinforcement of the application of hygienic precautions.

Currently, the best available evidence on the impact of isolation measures on HCV transmission to hemodialysis patients derives from two large prospective observational studies. The DOPPS⁴⁰ and an Italian study²²⁹ concur that, after multivariate adjustment for potential confounders—especially the prevalence of HCV infection within each hemodialysis unit—isolation does not protect against HCV transmission in hemodialysis patients.

Some prospective observational studies^{230,231} have reported a reduction of HCV transmission after the reinforcement of basic hygienic precautions, without any isolation measures. In particular, one Belgian prospective multicenter study²³⁰ showed a reduction from 1.4 to 0% of the yearly incidence of seroconversion for HCV. This demonstrated that complete prevention of HCV transmission to hemodialysis patients was possible in the absence of any isolation policy.

Additional arguments against relying on the use of isolation to prevent transmission of HCV include the possibility of increased risk of HCV infection with more than one genotype and the time between infection and seroconversion. The seroconversion time ('window') can be

over a year²³² and has a median length of 5 months in hemodialysis patients even with third-generation EIA tests.⁸⁶ This will result in inadequate selection of patients to be isolated, unless costly NAT is performed frequently.

If nosocomial transmission continues to occur, despite reinforcement and audit of the precautions listed in Tables 18 and 19, a local isolation policy may be deemed necessary. HCV-infected patients should be treated by dedicated staff in a separate room, area, or shift (morning, afternoon, or evening), as there is no rationale for using dedicated machines. It should be realized that accepting the 'need' for isolation equates to accepting the impossibility of full implementation of basic hygienic precautions, a regrettable situation that entails the risk of transmission of pathogens other than HCV.

- The use of dedicated dialysis machines for HCV-infected patients is not recommended. (Moderate)

In theory, it is almost impossible for a virus to pass through the dialyzer membrane of an infected patient and migrate from the drain tubing to the fresh dialysate circuit to pass through the dialyzer membrane to infect another patient. The impermeability of an intact dialyzer membrane and the requirement for backfiltration in the second session add to the improbability of this mode of transmission.

Of the studies summarized in Table 20, the majority were able to discount transmission via the internal pathways of the dialysis machine easily as the patients involved in the outbreak were dialyzed at the same time and/or on separate machines. Interestingly, several of these reports (Table 20) documented nosocomial HCV transmission despite the existence of a policy of dedicated monitors for HCV-infected patients. This underscores the substantial limitations of such a policy.

Only two studies considered that the machine may have been involved in the transmission of HCV. One concluded that lack of internal disinfection between patients was a possible (but not proven) transmission route, although one of the three confirmed cases of nosocomial transmission that were followed up never dialyzed on the same machine as the source patient.²²⁵ Breaches in infection-control procedures, such as failure to change gloves in emergencies, were also cited and thus appear as an alternative (more likely) explanation.

The strongest case for nosocomial transmission via the dialysis machine was reported in one study.²²⁴ The infected patient was not dialyzed at the same time as the source patient in the period when infection took place, but was dialyzed on the same machine 21 times. However, transmission via the internal pathways could be excluded as the machine was disinfected between shifts. Environmental contamination could not be excluded, but the authors concluded that contamination of the venous pressure port was the likely transmission route. If the precautions in Table 19 are followed, transmission via this route will be prevented without the need to use dedicated machines for patients with HCV.

The high quality of the evidence against transmission of HCV via the internal pathways of the dialysis machine is the basis for the recommendations on disinfection in Table 19 and the recommendation that dedicated machines should not be used for patients with HCV infection.

A single study has claimed that the random assignment of hemodialysis units to dedicated machines for HCV-infected patients reduced the incidence of seroconversion for HCV.⁴³ However, the authors did not disclose details of the randomization procedure, the policy of the participating units before randomization (four to use of dedicated machines, eight to shared machines), or whether the patients who seroconverted had actually shared machines with infected patients. In addition, the authors stated that machines in all units were disinfected with bleach between sessions and that interviews with nurses revealed some deviation from the CDC guidelines on hygienic precautions. One unit in the group using shared machines was eliminated from the analysis due to nonadherence with CDC guidelines. The incidence of seroconversion for HCV was substantial, even in the dedicated machines group, for a relatively low prevalence at study start. Overall, this strongly suggests that the transmission was related to breaches in infection-control procedures and not to the sharing of machines.

The possibility that use of dedicated machines acts as a reminder to the staff to implement procedures cannot be discounted, but it should be possible to raise awareness using

methods that do not (i) restrict the availability of dialysis or (ii) restrict the choice of dialysis location, shift, or treatment modality of HCV-positive patients compared to uninfected patients.

- *Where dialyzer reuse is unavoidable, it is suggested that the dialyzers of HCV-infected patients can be reused provided there is implementation of, and adherence to, strict infection-control procedures. (Weak).*

The main risk for HCV transmission associated with the reprocessing of dialyzers is to the staff involved (beyond the scope of this guideline). Theoretically, contaminated blood could be transferred if dialyzers or blood port caps²³³ that have not been sterilized effectively are switched between patients, but this should not occur if procedures are followed correctly. In addition, there are risks associated with the transport of contaminated equipment, but these risks should be eliminated by strict adherence to hygienic precautions (Table 19).

Dialyzer reuse was not identified as a risk factor for seroconversion for HCV in the CDC surveillance data³⁴ or in the Belgian prospective multicenter study.²³⁴ The weak association of dialyzer reuse with HCV infection in one study carried out in Portugal²³⁵ may reflect an association with unmeasured confounders, such as the degree of actual implementation of basic hygienic precautions.

3.2. Infection-control procedures should include hygienic precautions that effectively prevent the transfer of blood—or fluids contaminated with blood—between patients, either directly or via contaminated equipment or surfaces. (Strong)

As HCV is transmitted by percutaneous exposure to infected blood, effective implementation of the hygienic precautions detailed in Tables 18 and 19 should prevent nosocomial transmission. The precautions listed differ very little from the extensive recommendations of the CDC⁵³ and the rather brief guidelines provided by the European Renal Association.²³⁶

The recommendation of the CDC is that ‘single-pass’ machines do not require disinfection between shifts on the same day, even when a blood leak has occurred. There is a very low risk that a virus leaving the dialyzer could be trapped in the Hansen connector and transferred to the fresh dialysate side through accidental misconnection. Under normal conditions, the dialyzer membrane should provide an effective barrier and make the risk of transmission negligible, but when a blood leak occurs, the risk is slightly greater. Although the extra disinfection may be unnecessary, as blood leaks are now relatively rare, it is unlikely to affect the management of the unit.

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

There are few published studies of observational audits of infection control in hemodialysis. One study in Spain²³⁷

audited hand hygiene in nine hemodialysis units and showed gloves were used on 93% of occasions indicated by unit policy. Hands were washed only 36% of the time after patient contact and only 14% of the time before patient contact.

Observational audits of hygienic precautions were carried out in two of the outbreak investigations in Table 20.^{85,238}

Both identified a range of problems, including

- lack of basic hand hygiene;
- failure to change gloves when touching the machine interface to obtain biologic parameters, or when urgently required to deal with bleeding from a fistula;
- carrying contaminated blood circuits through the ward unbagged;
- lack of routine decontamination of the exterior of machines and other surfaces even when blood spillage had occurred;
- failure to change the internal transducer protector when potentially contaminated.

Where hygienic practice was reviewed through interviewing staff after an outbreak²³⁹ rather than by observation, no obvious breaches in procedure could be identified.

If HCV-negative patients are routinely screened for seroconversion, the absence of new infections can provide evidence of adherence to the procedures in units with high prevalence. Screening results are not a substitute for regular assessment of the implementation of hygienic precautions, especially in units with few or no infected patients. The frequency at which routine audits of infection-control procedures should be carried out will depend on staff turnover and training, and on the results of previous audits. When setting up a new program, audits should be at intervals of no more than 6 months to enable staff to gain experience with the process and ensure that any remedial actions taken have been effective.

IMPLEMENTATION ISSUES

- 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.
- 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 have no difficulty obtaining gloves in an emergency.
- When selecting new equipment, ease of disinfection should be taken into account.

- There are indications from the literature that the rate of failure to implement hygienic precautions increases with understaffing.^{72,229} One study⁸⁵ describes how a large HCV outbreak occurred when an expansion in patient capacity that led to understaffing was aggravated by rapid staff turnover. 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.

RESEARCH RECOMMENDATIONS

- Large national or international prospective observational studies (such as the DOPPS) could be used to capture important epidemiologic data (HCV infection in new patients and seroconversions in prevalent patients). This information is expected to show a significant trend toward infection occurring before starting dialysis and lower rates of subsequent seroconversion.
- If studies such as DOPPS can also capture the hemodialysis unit's isolation policies, and the routine methods through which the use of strict infection-control procedures is reiterated and monitored, the correlation between practice and nosocomial transmission could be strengthened.
- The systematic review carried out during the development of this guideline was limited to papers where nosocomial transmission was confirmed through molecular virology and some attempt had been made to identify the route of transmission. It is reasonable to assume that, unless the patient has other significant risk factors, all new infections in hemodialysis patients are the result of nosocomial transmission and that an investigation should be undertaken. If units are prepared to share their findings, the publications would provide useful educational material and help inform auditors.
- In addition to epidemiologic studies and reporting of outbreak investigations, generic educational materials, operating procedures, and audit tools that can be adapted for local implementation should be developed and made available in a range of languages.

Table 20 | Summary table of virologic investigations of HCV outbreaks in hemodialysis units

Author (year), country	New infections confirmed as nosocomial	Source shared room and shift/day?	Source used machine in previous shift?	Machines disinfected between shifts?	Multidose vials used?	Isolation procedures for HCV?	Infection control procedures investigated	Route suggested
Allander (1994), ²¹⁸ Sweden	5	All (same day)	Never	Yes	ND	None	Yes	No specific routes identified
Abacioglu (2000), ²⁴⁰ Turkey	3	All (same day)	2 occasionally, 1 never	No	Yes	None	ND	Lack of environmental decontamination, failure to change gloves in emergencies
Castell (2005), ²⁴¹ Spain	18	All (same day)	Never initially, possibly while undiagnosed	Yes	Yes	Separate staff and machines	Yes	Contaminated shared medication vial suspected for initial event, further transmission due to poor hand hygiene and failure to disinfect surfaces after blood spillage
de Lamballerie (1996) ²⁴² and Olmer (1997), ²⁴³ France	2	All (same shift)	Never	Yes	ND	None	ND	Failure to follow precautions strictly in emergencies
Delarocque-Astagneau (2002), ²³⁸ France	9	All (same day)	7 possibly, 2 never	Yes	No	None	Yes	Failure to change gloves, poor waste management, lack of systematic environmental decontamination, failure to decontaminate pressure ports after blood ingress
Halfon (2002), ²⁴⁴ France	2	All (same day)	Never	Yes	ND	Separate machines	ND	No specific routes identified
Hmaied (2006), ⁵⁰ Tunisia	1	Same shift, different room	Never	ND	ND	Separate room and machines	ND	Failure to change gloves, understaffing
Hosokawa (2000) ²⁴⁵ and Iwasaki (2000), ²⁴⁶ Japan	2	All (same shift)	Never	ND	ND	None	ND	No specific routes identified
Irish (1999), ²⁴⁷ United Kingdom	1	Same shift, but case patient in side room	Never	Yes	No	None	ND	No specific routes identified
Izopet (2005), ⁸³ France	9	All (same shift)	Never	ND	ND	ND	Yes	No specific routes identified
Izopet (1999), ²³⁹ France	10	All (same shift)	Never	ND	No	None	Yes	Failure to decontaminate surfaces or instruments during busy times or emergencies
Katsoulidou (1999), ²⁴⁸ Greece	5	Only 1 on same shift as source	Never on same day	Yes	ND	None	Yes	Failure to change gloves
Kokubo (2002), ²⁴⁹ Japan	10	All (same shift), if outbreak was a single event	None, if outbreak was a single event	Yes	Yes	None	ND	Contamination of a shared medication vial suspected or possibly accidental use of instruments contaminated with HCV-positive blood
Kondili (2006), ²⁵⁰ Italy	3	All (same day)	Never	ND	Yes	None	ND	Sharing of multidose vials
Le Pogam (1998), ²²⁵ France	3	1 same shift, 2 same day	1 never, 2 probably	No	ND	None	ND	Failure to change gloves in emergencies, lack of machine disinfection between patients
McLaughlin (1997), ²⁵¹ United Kingdom	4	2 same shift, 2 same day	Never	Yes	No	Separate machines	ND	Direct transmission between adjacent patients or failure to implement precautions
Mizuno (1998), ²⁵² Japan	2	All (same shift)	Never	ND	ND	None	ND	No specific routes identified
Sartor (2004), ²²⁴ France	1	Never on same shift	21 times in study period	Yes	No	None	Yes	Contamination of the venous pressure-monitoring system
Savey (2005), ⁸⁵ France	22	All (same day)	Some possible	Yes	No	None	Yes	Inadequate hand washing, lack of glove use, sharing equipment such as clamps, cluttered carts that were hard to disinfect, lack of systematic environmental decontamination, failure to decontaminate pressure ports after blood ingress
Schneeberger (2000), ⁴⁹ (1999) ²¹⁷ The Netherlands	5	All (same shift)	Never	Yes	ND	None	Yes	Failure to change gloves even when possibly contaminated with blood

HCV, hepatitis C virus; NA, not applicable; ND, not documented; NS, not significant.

Table 21 | Summary table of epidemiologic investigations of HCV outbreaks in hemodialysis units

Author (year), country of study	No. of new nosocomial HCV infections investigated	Region of genome investigated	Description of phylogenetic analysis	Timing of investigation compared with outbreak
Allander (1994), ²¹⁸ Sweden	4	E2/NS1 HVR1	Three identical, 1 patient; 1.3% different	Few months
	1		2% different from previous outbreak	Probably immediate
Abacioglu (2000), ²⁴⁰ Turkey	3	NS5b	98.4% sequence similarity	ND
Castell (2005), ²⁴¹ Spain	18	NS5b	98% similarity	< 6 months
De Lamballerie (1996) ²⁴² and Olmer (1997), ²⁴³ France	2	E2/NS1 HVR1	ND	< 1 year
Delarocque-Astagneau (2002), ²³⁸ France	2	NS5b and E2/HVR1	Mean pairwise nucleotide genetic distance, 0.011	~ 1 month
	7		Mean pairwise nucleotide genetic distance, 0.0038	
Halfon (2002), ²⁴⁴ France	1	HVR1	Bootstrap value: 95%	Probably ~ 2 years
	1			Probably a few months
Hmaied (2006), ⁵⁰ Tunisia	1	E2/HVR1	Bootstrap value: 100%	< 1 year
Hosokawa (2000) ²⁴⁵ and Iwasaki (2000), ²⁴⁶ Japan	2 ^a	HVR 1	ND	2-4 years
Irish (1999), ²⁴⁷ United Kingdom	1	NS5	88% similarity	< 1 month
Izopet (2005), ⁸³ France	9	E2/HVR1	ND	< 1 year
Izopet (1999), ²³⁹ France	4		Bootstrap value: 99.7% 1st wave	
	2	E2/HVR1	Bootstrap value: 100% 2nd wave	ND
	4		Bootstrap value: 99.8% 3rd wave or < 99.8%	
Katsoulidou (1999), ²⁴⁸ Greece	5	NS5	Bootstrap value: 100%	ND
Kokubo (2002), ²⁴⁹ Japan	10	E1 region	< 1.1% unweighted substitutions per 100 nucleotides	~ 2 months
Kondili (2006), ²⁵⁰ Italy	3 ^b	E2 region	Genetic distances 0.4–1.7%	< 6 months
Le Pogam (1998), ²²⁵ France	2	NS5b	ND	ND
	1			
McLaughlin (1997), ²⁵¹ United Kingdom	2	NS5	100% 'identical' with source patient	Few months
	2		100% 'identical' with source patient	
Mizuno (1998), ²⁵² Japan	2	E2/HVR1	ND	ND
Sartor (2004), ²²⁴ France	1	NS5b	Bootstrap value: 100%	Probably < 1 month
Savey (2005), ⁸⁵ France	4	E2/HVR1	Mean pairwise nucleotide genetic distance: 0.0040	< 8 months
	5		Mean pairwise nucleotide genetic distance: 0.0000	
	9		Mean pairwise nucleotide genetic distance: 0.0092	
	4		Mean pairwise nucleotide genetic distance: 0.0043	
Schneeberger (2000), ⁴⁹ (1999) ²¹⁷ The Netherlands	5	E2/HVR	94%	ND

HCV, hepatitis C virus; HVR, hypervariable region; NA, not applicable; ND, not documented; NS, not significant.

^aPatients 39 and 44 seroconverted in 1994 but no source was identified. We have assumed that one of these patients infected the other (one incidence of nosocomial transmission), although it is possible that both were infected by a third patient. There was insufficient evidence to confirm nosocomial transmission in the case of patient 19.

^bOne newly infected patient (HCV-1) dialyzed on the same machine as the source patient on the following shift, but was negative for HCV-E2 gene amplification, so nosocomial transmission could not be confirmed.

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

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Guideline 4.1: Evaluation and management of kidney transplant candidates regarding HCV infection

INTRODUCTION

HCV infection is present in a higher proportion of patients with CKD Stage 5 than in the general population. As a consequence, many of these patients present for consideration of kidney transplantation with either previously undiagnosed disease or never having had a thorough evaluation of their liver disease. In some studies, almost 25% of these patients already have significant fibrosis or cirrhosis on liver biopsy. The impact of HCV infection on the candidacy and post-transplant outcomes of the viremic patient with CKD Stage 5 remains a challenging clinical issue.

Levels of strength of recommendations

Strength of recommendation	Wording of recommendation	Basis for strength of recommendation
Strong	An intervention 'should' be done	'High'-quality evidence and/or other considerations support a strong guideline ^a
Moderate	An intervention 'should be considered'	'Moderate' quality evidence and/or other considerations support a moderate guideline ^a
Weak	An intervention 'is suggested'	'Low' or 'very low' quality evidence; predominantly based on expert judgment for good clinical practice ^a

^aSee Appendix 2: Grading the Strength of the Recommendations, p. S85.

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

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

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

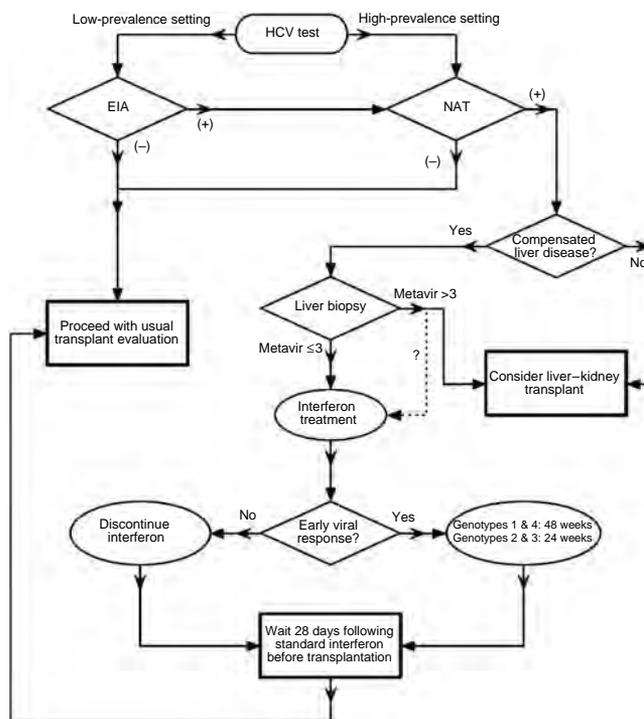
4.1.3 It is suggested that HCV-infected kidney transplant candidates undergo a liver biopsy before transplantation. (Weak)

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

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

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

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



Algorithm 2. Pretransplant evaluation for HCV infection. Early viral response patients have a >2 log decrease in viral titer. EIA, enzyme immunoassay; HCV, hepatitis C virus; IFN, interferon; NAT, nucleic acid test.

transplantation when compared to uninfected kidney transplant recipients (Table 23).^{114,115,118,159,261–264} The increased mortality after kidney transplantation in this population has, in part, been attributed to progressive liver disease after transplantation.^{118,159,264} However, extrahepatic post-transplant complications of HCV infection, such as NODAT,^{127,128,132,265,266,267,268} post-transplant GN,^{122,123,125,269–271} and sepsis,²⁶⁴ are additional complications that contribute to the inferior outcomes observed in these patients. In light of the clinically significant impact that HCV infection has on kidney transplant outcomes, it is recommended that kidney transplant candidates who are HCV-infected should be informed and counseled about the associated hepatic and extrahepatic risks, the need for additional diagnostic studies and therapeutic interventions before and after transplantation, and possible delay in transplantation.

Recipient HCV viremia and impact on donor kidney allocation (also see guideline 4.2)

The HCV status of a transplant candidate directly impacts donor selection. There is good evidence that HCV can be transmitted from infected donors to recipients by organ transplantation.^{272–274} This may occur as a new infection in a previously uninfected recipient or superinfection with a different genotype in an HCV-infected recipient.²⁷⁵ As such, it is preferable to transplant kidneys from HCV-infected donors to recipients who are viremic. The present logistics dictate that deceased donors are only screened with EIA for evidence of HCV antibodies. However, a positive anti-HCV test in donors does not distinguish active viremia from antibody acquired after previously cleared infection. Blanket policies excluding the use of HCV antibody-positive donors have the potential to therefore result in the unnecessary discarding of kidneys from seropositive individuals, who in reality may have no detectable viremia. Moreover, available data indicate that the transplantation of kidneys from HCV-infected donors to HCV-infected candidates is associated with improved survival compared to the remaining wait-listed and dialysis-dependent candidates (Table 24).²⁷⁶

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

Studies in kidney transplant recipients demonstrate that post-transplant immunosuppressive therapy has a permissive effect on viral replication.^{272,277,278} This has the potential to accelerate liver injury after transplantation. Despite this, it is recommended that HCV infection should not be considered a contraindication to transplantation for the following reasons:

1. Three retrospective studies of HCV-infected patients have demonstrated that survival is improved with transplantation compared to the remaining wait-listed on dialysis in HCV-infected patients with kidney failure (Table 22).^{110,253,254} Compared to maintenance hemodialysis, no published studies have shown a lack of survival benefit from transplantation in this patient population.

This survival advantage in favor of transplantation over dialysis is the basis for considering transplantation as the treatment of choice for patients with CKD Stage 5 and HCV infection.

2. Liver disease does not progress in many patients after kidney transplantation. Clinical and histologic progression of chronic liver disease is generally slow when and if it does occur. Whereas progressive liver disease does impact patient outcomes, it usually occurs over many years and thereby affects long-term survival. In single center studies of HCV-infected transplant recipients, the reported increased rates of death due to liver disease occurred in the second and third decade after kidney transplantation.^{114,115,118,120,159,262–264} However, many of these studies are retrospective and examined outcomes in patients in whom a diagnosis of HCV infection was made only after transplantation. This could have resulted in under-recognition of more advanced cases of liver disease at the time of transplantation, accounting for increased rates of decompensated liver disease in the reported cohorts. In contrast, there are a few recent single-center reports where sequential post-transplant liver biopsies have shown that in as many as 80% of the patients, hepatic injury does not progress after kidney transplantation.^{279,280}

It is absolutely essential that these considerations are explained and discussed with potential recipients before a joint decision is made to proceed with transplantation.

Although the evidence supporting this guideline recommendation is limited and the quality is graded as ‘weak,’ the majority of the Work Group felt that this statement be upgraded to ‘moderate’ strength based on four criteria: (i) there are three retrospective studies showing a survival benefit of transplantation over dialysis for HCV-infected CKD Stage 5 patients; (ii) there are no published studies demonstrating a worse outcome with transplantation compared to dialysis for these patients; (iii) it is extremely unlikely that an RCT comparing transplantation to dialysis for long-term treatment of HCV-infected CKD Stage 5 patients will ever be performed; and (iv) the practice of transplantation over dialysis has evolved into the universal standard of care for CKD Stage 5 patients with HCV infection.

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

Because of the poor sensitivity of HCV antibody testing in patients with kidney failure,⁴¹ a decision to perform a liver biopsy should be based on the presence of a positive NAT. In the absence of supportive or contrary data, it was the judgment of the Work Group that all persistently viremic HCV-infected kidney transplant candidates should undergo pretransplant liver biopsy. A liver biopsy performed before kidney transplantation is necessary to determine the severity of hepatic injury and thereby to assess the prognosis and management of the patient both before and after transplan-

tation (see Algorithms 2 and 3). This recommendation is contrary to the AASLD guideline that recommends liver biopsy for patients with genotypes 1 and 4, but considers it unnecessary for patients infected with genotypes 2 and 3 (<https://www.aasld.org/eweb>).

The rationale for a liver biopsy is based on the following evidence:

1. Liver injury markers (for example, ALT) do not reliably reflect the histologic severity of disease in this population.²⁸¹
2. Single-center retrospective cross-sectional studies have reported that up to 25% of HCV-infected patients being evaluated for kidney transplantation have bridging fibrosis or cirrhosis on biopsy.^{177,256–260}
3. There are no definitive studies that have examined whether the histologic stage of the pretransplant biopsy predicts post-transplant liver disease and outcome. However, the presence of cirrhosis on pretransplant liver biopsy has been reported to be associated with a 10-year survival of only 26%.¹¹⁸
4. Several studies have shown that 19–64% of HCV-infected kidney transplant recipients have post-transplant liver disease compared with only 1–30% of patients without evidence of HCV infection.^{114,115,118,120,159,262–264} A study from the New England Organ Bank has shown that the RR of post-transplantation liver disease was 5.0 for kidney transplant recipients with anti-HCV antibodies.²⁶⁴ Most of these investigations are retrospective and examined outcomes in patients in whom a pretransplant liver biopsy was not performed. This may have resulted in under-recognition of more advanced liver disease at the time of transplantation, accounting for increased rates of decompensated liver disease in the reported populations.
5. Studies with no pretransplant biopsy, but with sequential post-transplant liver biopsies, have demonstrated that liver histology may progress in about 20% of patients.^{280,282}
6. Liver biopsy before kidney transplantation should be used as a means to guide antiviral therapy (also see treatment Guidelines 2.1.3 and 2.1.4). A high-quality liver biopsy of at least 2 cm in length and containing >5 portal zones is required for adequate Metavir/Ishak scoring.^{283–285}

It is recognized that evaluation of liver injury is an evolving field and that noninvasive tests (for example, Fibroscan[®]) are emerging. The utility of noninvasive studies for assessing liver injury in HCV-infected CKD patients is not currently known.

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

The presence of compensated liver cirrhosis before kidney transplantation has the potential to increase the risk of recipient mortality in terms of operative procedure, marginal post-transplant reserve and nutritional state, and increased suscepti-

bility to post-transplant infectious and metabolic complications, as well as evolution to decompensated liver disease and the subsequent need for a liver transplant. As such, it is recommended that HCV-infected kidney transplant candidates with liver cirrhosis on biopsy only be considered for kidney transplantation under investigational protocol. This is based on the fact that there are very limited outcome data regarding transplantation of a kidney alone in HCV-infected recipients with pre-existing compensated cirrhosis of the liver. A retrospective study reported that patients with liver cirrhosis before kidney transplant had a 10-year rate of survival of only 26%.¹¹⁸ Also, there are no data available to determine whether patients with early cirrhosis on liver biopsy yet well-compensated clinical disease do better if they are transplanted or remain on dialysis. A trial of IFN therapy can be considered for such patients, although regression of fibrosis was demonstrated only in 7.8% of non-CKD patients and in three of four dialysis patients, numbers that are too small to draw any conclusions.¹⁵⁶

HCV-infected patients with evidence of decompensated liver disease should be evaluated for simultaneous liver-kidney transplantation. Transplantation of a kidney alone in this situation is not recommended.

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

Although there is good evidence that HCV-infected kidney transplant recipients have worse patient and allograft survival after transplantation when compared to their uninfected counterparts,^{114,115,118,159,261–264} the evidence that treatment with IFN before transplantation improves outcomes is very poor. The recommendation in this guideline is therefore the judgment of the Work Group.

After kidney transplantation, both hepatic and extrahepatic HCV-related complications have been demonstrated to contribute to the inferior patient and kidney allograft outcomes observed in this patient population. The rationale underlying this guideline is that in HCV-infected kidney transplant candidates, the achievement of a sustained virologic response before transplantation will be durable and reduce the risk of both hepatic and extrahepatic manifestations associated with viremia after transplantation. The evidence supporting this recommendation is as follows:

1. Uncontrolled trials have demonstrated that administration of nonpegylated IFN therapy to dialysis patients with HCV infection achieves SVR in about 40% of cases.^{134,135,138,139,141–143,198–202,286,287}
2. Uncontrolled studies in kidney transplant candidates with HCV infection have shown that SVR achieved before transplantation is sustained in 80–90% of recipients after transplantation.^{134,138,166,201–203} Although no information was given in any of these reports regarding liver biopsy after transplantation, there was no clinical evidence of progressive liver disease.

3. A few retrospective studies have demonstrated that achieving SVR with IFN therapy in kidney transplant candidates was associated with no cases of NODAT.^{203,288}
4. In liver transplant recipients with recurrent HCV infection, insulin resistance has been reported to increase in concert with viral replication,²⁸⁹ whereas achievement of SVR with IFN has been associated with resolution of NODAT.²⁹⁰
5. Available data in nondiabetic, non-CKD, and HCV-infected subjects demonstrate improved glucose tolerance and enhanced insulin sensitivity after 4 months of IFN therapy.²⁹¹
6. In a controlled trial of pretransplant antiviral therapy in CKD Stage 5 patients with HCV infection, patients in whom SVR was achieved before transplantation had a significantly lower incidence of HCV-related GN after transplantation compared to persistently viremic patients.¹⁵⁵
7. In a relatively large retrospective study of HCV-infected kidney transplant recipients, the absence of IFN therapy before kidney transplantation was associated with a significantly increased risk for chronic allograft nephropathy.²⁹²

It is not known whether the potential benefits of treatment with IFN in an effort to achieve SVR are outweighed by the downside of needing to be on inactive status on the waiting list during the course of therapy, thereby missing a potential opportunity to be transplanted. To mitigate this possibility, it is recommended that if an early virologic response is not obtained within 12 weeks of initiating IFN, the treatment can be discontinued. This recommendation is based on studies indicating that the chance of achieving SVR in this population is <10% in the absence of an early viral response at 12 weeks^{139,141} (see Guideline 2).

Moreover, it is recommended that patients should not receive a kidney transplant while they are still receiving IFN. The evidence for this recommendation is limited to several small case series and case reports which indicate that IFN may cause acute kidney injury in 40–100% of kidney transplant recipients.^{157,158,160,293–299} The majority of IFN-induced acute kidney injury appears to be predominantly related to its immunomodulatory properties, leading to increased rates of both cell- and antibody-mediated rejection. Furthermore, the clearance of IFN is delayed in the setting of dialysis, and the risk exists of exposing the transplanted kidney to IFN before the drug has been fully cleared from the system.

The optimal time to wait between completion of standard IFN therapy and proceeding with transplantation in kidney transplant candidates with HCV infection is unknown. A 28-day wait is recommended after terminating or completing standard IFN therapy before proceeding with transplantation, based on avoiding exposure of the transplanted kidney to IFN, as most of the IFN is cleared by the kidneys and its half-life is prolonged in dialysis patients.^{178,287,296,300,301} As it will

not be known whether the patient has achieved SVR until 6 months after the completion of therapy, it is recommended that these patients only receive a kidney from an HCV-negative donor during this period of time. The delayed drug clearance in dialyzed patients, who achieve a higher area under the curve with each dose, also accounts for the high treatment discontinuation rates in this population because of adverse effects induced by this therapy.^{134,139,142,198,286,287}

A single case report suggests that accumulation and bioavailability of IFN may be even greater in the setting of peritoneal dialysis.²⁹⁶ Consequently, transplantation of a kidney before IFN was adequately cleared from the circulation and before its immunomodulatory effects subside could potentially increase the risk of allograft dysfunction due to rejection in the early post-transplant period.

It is also recommended that although patients with HCV infection are being treated with IFN, they should continue to accumulate time on the waiting list toward eventual transplantation.

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

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

Kidneys for transplantation are scarce, and transplantation is a serious and expensive procedure. As such, it is recommended that all patients on the waiting list with an unknown HCV status be tested for HCV infection before transplantation. Patients found to have a positive NAT test result should be placed on-hold status and referred to a hepatologist for evaluation and possible treatment. This recommendation is based on the evidence that SVRs can be obtained after treatment using IFN-based regimens and remain durable after transplantation.²⁰³ For patients in whom SVR was previously obtained, it is important to perform a NAT annually while on the list to confirm durability of the SVR.

Patients who relapse should be placed on hold and referred to a hepatologist for evaluation. Although no data exist on treatment of relapsers with kidney failure, there are data from the general population indicating that these patients can be successfully retreated using a longer course of therapy.

For persistently viremic patients who either failed to achieve SVR or refused IFN therapy, annual re-evaluation should include an assessment of the clinical stability of the liver disease by a hepatologist. Furthermore, it is the judgment of the Work Group that a repeat liver biopsy be performed every 3 years in patients whose baseline liver biopsy (obtained before transplant) showed Metavir Stage 3 and every 5 years for those whose liver biopsy was Metavir Stage 1 or 2. There are no good data to support this recommendation, although it has been demonstrated that liver disease can progress in patients on dialysis.¹¹⁰ With waiting times in some centers now exceeding 5 years, it is entirely possible that liver injury might worsen in the interval between listing and transplantation.

The rationale underlying these recommendations is mainly expert judgment based on the following data:

1. Waiting times for deceased donor kidney transplants have continued to lengthen. The median waiting time for deceased donor kidney transplantation in the United States is currently 3–4 years. Moreover, there is a 6–8% per year risk of mortality of CKD Stage 5 patients awaiting kidney transplantation.³⁰² In the context of these lengthening waiting times, it is imperative that listed patients continue to be monitored before receiving a kidney transplant to ensure medical suitability for transplantation.
2. Most allocation policies currently dictate that wait-listed patients be medically cleared for transplantation on a continued basis until they are actually transplanted.³⁰³ It is recommended that medical clearance follow the above recommendations.
3. A strong epidemiologic link between diabetes and HCV infection is now well established.^{304,305} One large retrospective study demonstrated that HCV-infected patients who remained on the waiting list had a greater risk of mortality than those being transplanted and that this risk escalated with time.²⁵³ The major mortality determinant in this study was the presence of diabetes as a comorbid condition, although progressive liver disease did occur in some cases as well. The co-existence of HCV and diabetes in patients on the kidney transplant waiting list therefore identifies a subgroup at high risk for mortality.
4. Liver disease may progress in patients on dialysis while on the waiting list.^{67,110}

LIMITATIONS

- There are very few randomized, prospective, or longitudinal studies that address the evaluation and management of HCV-infected kidney transplant candidates.
- Many of the published studies include small numbers of patients.

- Most outcome studies are retrospective and included several studies where a diagnosis of HCV infection was made only after transplantation.
- Studies do not always distinguish between patients being evaluated for kidney transplantation alone vs simultaneous liver-kidney transplantation.

RESEARCH RECOMMENDATIONS

- Prospective observational studies are needed to evaluate the natural history of HCV infection after kidney transplantation and to include a histologic, clinical, and biochemical assessment of liver injury both before and after exposure to chronic maintenance immunosuppression.
- RCTs are required in HCV-infected kidney transplant candidates examining the effectiveness of pretransplant IFN-based therapy on post-transplant outcomes, including patient and graft survival, progressive liver disease, NODAT, and glomerulopathy.
- Prospective studies are needed in HCV-infected CKD Stage 5 patients with well-compensated cirrhosis, comparing the safety and effectiveness of kidney transplant alone to remaining on maintenance dialysis.
- Prospective assessment is needed to assess the utility of repeat liver biopsy in HCV-infected kidney transplant candidates who remain on the waiting list.
- Observational outcome studies should be conducted to examine HCV-infected CKD Stage 5 patients coinfecting with HIV or HBV.
- The effect of specific immunosuppressive agents on hepatic and extrahepatic post-transplant complications should be studied.

Guideline 4.2: Use of kidneys from HCV-infected donors

INTRODUCTION

It has been clearly demonstrated that HCV can be transmitted by kidney transplantation. In this context, it is imperative to know the HCV status of both the organ donor and recipient.

Levels of strength of recommendations

Strength of recommendation	Wording of recommendation	Basis for strength of recommendation
Strong	An intervention 'should' be done	'High'-quality evidence and/or other considerations support a strong guideline ^a
Moderate	An intervention 'should be considered'	'Moderate' quality evidence and/or other considerations support a moderate guideline ^a
Weak	An intervention 'is suggested'	'Low' or 'very low' quality evidence; predominantly based on expert judgment for good clinical practice ^a

^aSee Appendix 2: Grading the Strength of the Recommendations, p. S85.

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

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

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

BACKGROUND

HCV infection may be transmitted by transplantation from infected donors to uninfected recipients.^{273,306,307} For this reason, organ procurement organizations routinely screen all potential donors for evidence of HCV infection. The current standard of practice is to screen all donors for HCV antibody. However, antibody testing does not distinguish between donors who are viremic from those who have immunity following a previous infection (see Guideline 1). As such, the current standard of testing does not allow identification of viremic donors who are potentially infectious as opposed to those who are not. The prevalence of HCV infection among deceased donors worldwide ranges from 1 to 11%.³⁰⁶ Variable transmission rates (25–73%) of HCV have been reported. This variability is likely related to several factors, including: (i) incomplete follow-up and testing of recipients after transplantation; (ii) variation in prevalence rates of viremia among different donor populations who are tested only with EIA, where anti-HCV positivity may reflect immunity to prior infection rather than active infection (see Guideline 1); and (iii) the use of pulsatile perfusion for procured donor kidneys, where the perfusate is associated with reduction in HCV RNA levels.³⁰⁸ Recipient outcomes after the transmission of HCV by an infected kidney show that 73% develop HCV viremia, 50% become anti-HCV-positive, and 35% develop abnormal ALT/AST levels.³⁰⁷

The use of kidneys from anti-HCV-positive donors requires a balanced evaluation of the risks of HCV transmission compared to the benefits of being transplanted instead of remaining on dialysis. In all such cases, the recipient should be informed and participate in decision-making. It is also important to inform recipients of any information on the HCV status of the donor that becomes available after transplantation.

RATIONALE

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

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

Antibody testing does not distinguish donors who have active viremia from those who have acquired immunity after a previous infection (see Guideline 1). As such, kidney donors are best screened for HCV infection using NAT, which is the optimal way to distinguish between donors who may or may

not be potentially infectious. This important variation from current practice directly impacts many current donor and recipient allocation policies. The basis for this recommended change in practice is supported by the following evidence:

1. HCV can be transmitted from infected donors to uninfected recipients.²⁷³
2. Recipients of kidneys from HCV-infected donors have an increased risk of liver disease.^{127,273,309,310}
3. Some, but not all, studies indicate that recipients of kidneys from HCV-infected donors have a greater risk of mortality compared to recipients of kidneys from uninfected donors.^{307,311} The increased mortality may be related to higher rates of both liver disease and susceptibility to NODAT in recipients of kidneys from infected donors.¹²⁷

Where NAT is not available or results cannot be obtained expeditiously, third-generation EIA testing should be used as an alternative (see Guideline 1). The performance of the third-generation EIA in the general population is excellent and should be utilized in settings where NAT testing is not available. However, not all anti-HCV-positive donors are viremic, so discarding kidneys from EIA-positive donors will result in the loss of kidneys that could otherwise be used.

The data on the transmission of HCV from living kidney donors are weak. Living donors should be tested for HCV infection using NAT. Those donors who are HCV-infected should not be considered because of the potential risk, although not well studied, of transmitting HCV infection to the recipient. In addition, as HCV has been associated with several glomerulopathies (see Guideline 5), the HCV-infected donor is at increased risk of developing extrahepatic viral manifestations, such as immune complex disease of the native kidneys, as well as diabetes mellitus.

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

Uninfected recipients of kidneys from HCV-infected donors have increased rates of liver disease and diabetes after transplantation.^{127,273,309,310} There is good evidence that HCV infection can be transmitted via transplantation and that acquisition of the virus has the potential to lead to the development of post-transplant liver disease.^{127,273,309,310} A study of Medicare beneficiaries in the United States Renal Data System (USRDS) registry indicates that the transmission of HCV infection via transplantation was associated with an increased risk of NODAT and a reduction in recipient life expectancy.¹²⁷ To avoid these potential but major complications in uninfected recipients, it is suggested that kidneys from HCV-infected donors should not be used in potential recipients without HCV viremia. However, kidneys from donors infected with HCV can be used in potential recipients with evidence of active HCV viremia at

the time of transplantation. This recommendation is based on the following observations:

1. Studies have shown that the use of kidneys from HCV-infected donors in recipients already infected with HCV may shorten waiting times and neither affect short-term survival nor invariably lead to progressive liver disease (Table 24).^{272,312–314} In contrast, a registry analysis demonstrated that recipients of kidneys from HCV-infected donors was associated with a higher rate of mortality, regardless of the anti-HCV antibody status of the recipient.³¹¹ This study, although large, is limited by the absence of information regarding recipient baseline liver histology or comorbidity, or the reason underlying the decision to use an HCV-infected donor kidney in a given situation.
2. Large registry analysis indicates that the use of kidneys from anti-HCV-positive deceased donors in HCV-infected recipients is associated with superior patient survival compared to remaining on dialysis (Table 24).²⁷⁶

The risks and effects of superinfection with an HCV genotype from the donor that is different from the genotype of the potential HCV-infected recipient are unknown. A new genotype superinfection through transplantation has been reported in two single-center investigations.^{275,315} Although one of the studies reported that elevated transaminase levels did occur,²⁷⁵ the other found no impact on patient or graft survival.³¹⁵

The use of pulsatile pump perfusion may reduce the viral load in the donor kidney and has the potential to reduce viral transmission from HCV-infected organs.^{274,308} Wherever possible, this technique for preserving the procured kidney is recommended in situations where the donor is known to be HCV-infected.

As always, potential recipients of kidneys from HCV-infected donors must be fully informed of the involved risks and benefits and participate in the decision to proceed with treatment.

LIMITATIONS

- There are few randomized, prospective, or longitudinal studies that address the safety of using kidneys from HCV-infected deceased donors.
- Many of the published studies include small numbers of patients.
- Most outcome studies are retrospective.
- Registry studies have been based on antibody testing in donors, which does not distinguish between donors who have active viremia from those who have acquired immunity after a previous infection.
- Registry analyses cannot provide information on the baseline liver histology or comorbidity.
- In many of the studies, the reason underlying the decision to use an HCV-infected donor kidney is not given.

RESEARCH RECOMMENDATIONS

- Randomized trials are needed to examine the role of pulsatile perfusion in reducing the rates of viral transmission by the transplantation of HCV-infected deceased donor organs.
- Prospective studies are needed to longitudinally evaluate the rate of superinfection and its clinical impact after transplantation of a kidney from an HCV-infected deceased donor to an HCV-infected recipient. Such studies should include virologic (for example, genotype and viral load) and histologic (for example, serial liver biopsy) assessment, as well as clinical and biochemical markers of liver injury.
- Prospective observational studies are required to examine the effect of kidneys from HCV-infected deceased donors on hepatic and extrahepatic post-transplant recipient outcomes.

Guideline 4.3: Use of maintenance immunosuppressive regimens

INTRODUCTION

The most appropriate immunosuppressive protocol for the HCV-infected recipient has not been determined. In this context, all currently available agents can be used for induction and maintenance therapy.

Levels of strength of recommendations

Strength of recommendation	Wording of recommendation	Basis for strength of recommendation
Strong	An intervention 'should' be done	'High'-quality evidence and/or other considerations support a strong guideline ^a
Moderate	An intervention 'should be considered'	'Moderate' quality evidence and/or other considerations support a moderate guideline ^a
Weak	An intervention 'is suggested'	'Low' or 'very low' quality evidence; predominantly based on expert judgment for good clinical practice ^a

^aSee Appendix 2: Grading the Strength of the Recommendations, p. S85.

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

RATIONALE

By virtue of their mechanisms of action, immunosuppressive therapies have the potential to have a permissive effect on HCV kinetics after transplantation. This may result in differing effects of the various immunosuppressive agents on viral replication, progressive liver disease, extrahepatic manifestations, and patient and graft outcomes after kidney

transplantation in HCV-infected recipients. In addition, diminished drug clearance in the setting of hepatic dysfunction may affect blood levels of commonly used immunosuppressive agents that are metabolized in the liver, such as cyclosporin and tacrolimus. At the present time, there are relatively few studies that examine the impact of immunosuppression on HCV-related outcomes in kidney transplant patients. Although there are studies in liver transplant recipients, the data from these studies cannot be readily extrapolated to the kidney transplant population. Effective immunosuppressive treatment of HCV-infected kidney transplant recipients, therefore, requires consideration of the safety and efficacy of current agents balanced against their potential adverse effects.

Available evidence indicates that all conventional, current maintenance immunosuppressive agents can be used in kidney transplant patients infected with HCV. Viral replication is increased after transplantation in the setting of chronic immunosuppression use, although it is not clear whether or how this impacts liver disease, or patient, or graft survival in kidney transplant recipients.^{277,278,316} For example, studies in HCV-infected liver transplant recipients suggest that treatment with corticosteroid boluses for acute rejection may result in up to a 100-fold increase in HCV RNA concentrations, increased frequency of acute hepatitis, and decreased time to recurrence of disease.^{317,318} However, this has not been established in kidney transplant patients with HCV infection. As far as mycophenolic acid-based therapies in HCV-infected transplant recipients are concerned, there is growing evidence for the rationale of using this adjunctive agent to spare exposure to the potential toxicities of calcineurin inhibitors and steroids, although specific data are limited in this regard. Studies in HCV-infected non-transplant patients suggest that mycophenolic acid therapies may have an inhibitory effect on viral replication, but this has not been established in transplant recipients.³¹⁹ On the other hand, there is no convincing evidence of a specific deleterious effect of mycophenolic acid therapy on either graft or patient outcomes in kidney transplant recipients with HCV infection.^{320,321} In fact, a retrospective registry analysis indicates that mycophenolate mofetil was associated with favorable outcomes, even after adjustment for all possible confounding factors.³²⁰ Trials in liver transplant patients have confirmed the potential clinical outcome benefit associated with mycophenolate mofetil. Regarding calcineurin inhibitors, emerging evidence from retrospective studies suggests that cyclosporin, but not tacrolimus, may inhibit HCV viral replication. However, this remains to be validated in kidney transplant patients. Also, the available studies suggest that tacrolimus is more diabetogenic than cyclosporin in most transplant recipients (see Guideline 4.4.3). Among HCV-infected kidney transplant recipients, the risk of NODAT appears to be especially high in patients being treated with tacrolimus. For patients developing hyperglycemia in the setting of tacrolimus use, conversion to a cyclosporin-based regimen should be considered.

Among antibody therapies commonly used for induction or for treating acute rejection, unfavorable outcomes have been frequently reported in the literature concerning liver transplant patients with HCV infection. In contrast, preliminary registry data of 3706 patients from the United States indicate that antibody induction is associated with improved patient and graft outcomes in HCV-infected kidney transplant recipients.³²²

There are limited data on the use of sirolimus in HCV-infected kidney transplant recipients. This is another area in which more information would be needed before specific recommendations could be made.

On the basis of the available—although sparse—evidence, and even though most immunosuppressive agents increase viral replication, these therapies can all be used in kidney transplant patients with HCV infection. The following recommendations are made for consideration in the management of these patients:

- All currently available maintenance immunosuppressive therapies can be used in kidney transplant recipients with HCV infection.
- Selection of specific immunosuppressive agents should be tailored to the needs of each individual patient, balancing the potential impact on HCV-related hepatic and extrahepatic complications vs the risk of rejection.
- Maintenance immunosuppression should consist of the lowest possible doses of all of the therapies that will provide effective antirejection coverage.
- Patients should be carefully monitored for post-transplant complications and liver disease as described in Guideline 4.4.
- At the present time, it is not clear that the impact of immunosuppression on outcomes in liver transplant patients with HCV infection can automatically be extrapolated to HCV-infected kidney transplant recipients as well. Further investigation will be required in this area.

LIMITATIONS

- There are few randomized, prospective, or longitudinal studies that examine immunosuppression use in HCV-infected kidney transplant recipients.
- Most outcome studies are retrospective.
- Many of the published studies include small numbers of patients.
- Registry analyses do not provide sufficient or adequate information on baseline liver histology or patient comorbidity.
- Very few studies have examined viral replication after kidney transplantation.
- It is unknown whether the impact of immunosuppression in HCV-infected liver transplant recipients can be extrapolated to kidney transplant recipients.

RESEARCH RECOMMENDATIONS

- Prospective randomized trials are required comparing the calcineurin inhibitors, cyclosporine A, and tacrolimus in HCV-infected kidney transplant recipients in terms of efficacy, patient and graft outcomes, and impact on viral kinetics, as well as other HCV-related complications, for example, NODAT or glomerulopathy.
- Prospective studies are needed to examine the impact of antibody induction therapy on virologic, histologic, clinical, and biochemical markers in HCV-infected kidney transplant recipients.
- A prospective study should be conducted to examine the effect of sirolimus and everolimus on viral replication in HCV-infected kidney transplant recipients.

Guideline 4.4: Management of HCV-related complications in kidney transplant recipients

INTRODUCTION

HCV-infected kidney transplant recipients are at increased risk of several complications in the post-transplant period. Worsening liver disease, in addition to several extrahepatic clinical events such as NODAT and glomerular disease of the allograft, has been reported. In this context, close follow-up of the HCV-infected kidney transplant recipient is mandatory.

Levels of Strength of Recommendations

Strength of recommendation	Wording of recommendation	Basis for strength of recommendation
Strong	An intervention 'should' be done	'High'-quality evidence and/or other considerations support a strong guideline ^a
Moderate	An intervention 'should be considered'	'Moderate' quality evidence and/or other considerations support a moderate guideline ^a
Weak	An intervention 'is suggested'	'Low' or 'very low' quality evidence; predominantly based on expert judgment for good clinical practice ^a

^aSee Appendix 2: Grading the Strength of the Recommendations, p. S85.

- 4.4.1 *It is suggested that HCV-infected kidney transplant recipients more than 6 months after transplant have their liver disease evaluated at least annually. (Weak)*
- 4.4.2 *For HCV-infected kidney transplant recipients in whom the benefits of antiviral treatment clearly outweigh the risks (see Guidelines 2.1.5 and 2.2.4), monotherapy with standard IFN is suggested. (Weak)*
- 4.4.3 *It is suggested that HCV-infected kidney transplant recipients be screened for the development of hyperglycemia after transplantation. (Weak)*
- 4.4.4 *It is suggested that HCV-infected kidney transplant recipients be tested at least every 3–6 months for proteinuria. (Weak)*

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

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

BACKGROUND

Although HCV-infected patients fare better with kidney transplant than with maintenance dialysis, there is good evidence that HCV-infected kidney transplant recipients have worse patient and allograft survival after transplantation compared to their uninfected counterparts. Initial reports indicated that patient survival in the short term (within 5 years after transplant) did not differ between kidney transplant recipients with or without HCV infection.^{323–328} However, recent studies with longer term follow-up have demonstrated that HCV infection is associated with a detrimental effect on patient outcomes.^{114,115,117,118,120,159,261–264,320,329,330} The increased mortality after kidney transplantation in this population has, in part, been attributed principally to progressive liver disease after transplantation,^{118,159,264} but extrahepatic complications of HCV infection are also common and collectively contribute to the inferior outcomes observed in this patient population.

Efforts to improve post-transplant outcomes of HCV-infected kidney transplant recipients require the early detection, prevention, and treatment of complications related to chronic HCV infection. These include ongoing monitoring of liver function; selective and cautious use of IFN in the post-transplant setting; prevention, detection, and treatment of extrahepatic complications of NODAT and post-transplant glomerulopathy.

RATIONALE

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

HCV infection generally has an indolent course and the progression of liver disease is gradual.²⁰ Nevertheless, all HCV-infected kidney transplant recipients should have their ALT/AST levels monitored on an ongoing basis after transplantation, based on the following evidence:

1. Many studies, although all retrospective, have demonstrated that HCV-infected kidney transplant recipients

have an increased risk of mortality from liver disease after transplantation.^{118,159,264} Hepatic complications are primarily related to liver injury, manifested by ALT elevations or progressive chronic liver injury.^{114,115,117,118,159,262–264}

In a recent meta-analysis that evaluated the natural history of HCV infection in kidney transplant recipients, mortality due to liver disease (cirrhosis or hepatocellular carcinoma) was increased in HCV-infected patients in six of the eight studies included in the analysis, with a summary estimate for the RR of death of 1.79.⁸⁰ Overall, the rates of liver disease-related deaths ranged from 2.6 to 40% in HCV-infected patients and from 0 to 37% in uninfected patients. The available studies are subject to some important limitations. First, some investigations examined outcomes in kidney transplant recipients in whom a diagnosis of HCV hepatitis was made only after transplantation; second, the majority of studies did not provide adequate detail regarding virology and also did not incorporate liver histology before kidney transplantation. These shortcomings may have resulted in under-recognition of advanced liver disease present at the time of transplantation, leading to increased rates of decompensated liver disease among HCV-infected kidney transplant recipients. Recent publications have provided additional, albeit somewhat conflicting, post-transplant histologic information through the use of sequential liver biopsies in HCV-infected recipients.^{279,280,282} Once again, none of these studies included pretransplant liver biopsies. In the first of these retrospective but case-controlled studies, both liver histologic activity and fibrosis were reported to progress more rapidly in the transplant recipients than those observed among immunocompetent patients without kidney disease.²⁸² In sharp contrast, the second study reported that rates of liver disease progression were lower in transplant recipients than in infected individuals with normal kidney function.²⁷⁹ The most recent study was a prospective cohort analysis, where up to four sequential post-kidney transplant liver biopsies were performed over a 10-year follow-up period.²⁸⁰ This analysis confirmed that the progression of liver disease was gradual and that histologic progression occurred in about 40% of patients, while the majority either had stable histology (40%) or regression (20%). On the basis of the foregoing evidence, it is concluded that kidney transplant recipients with HCV infection are at increased risk for progressive hepatic injury after kidney transplantation, but progressive liver disease is slow and does not occur in all patients.

2. Immunosuppression may increase HCV viral replication after transplantation²⁷⁸ and occasionally results in accelerated liver injury.¹¹⁰ Cases of fibrosing cholestatic hepatitis have been reported in kidney transplant patients with HCV infection,^{189,331} but are not common.

In light of the heightened predisposition to liver-related morbidity and its impact on mortality, coupled with reported cases of fibrosing cholestatic hepatitis, it is recommended that

regular, ongoing post-transplant monitoring of HCV-infected kidney transplant recipients be performed, including follow-up with a hepatologist in the event of clinically worsening liver disease. The following specific recommendations are proposed for managing HCV infection-related liver disease in HCV-infected kidney transplant recipients:

- Liver enzymes should be checked every month for the first 6 months of the post-transplant period and every 3 months thereafter.
- The detection of clinically worsening liver enzymes should prompt early referral for hepatologic evaluation.
- Annual liver ultrasound and α -fetoprotein level to screen for hepatocellular carcinoma should be considered in patients with cirrhosis on liver biopsy.
- Except in special situations, IFN therapy should be avoided after kidney transplantation (see Guideline 4.4.2).
- There is no reason to perform liver biopsies in the post-transplant period, unless: (i) there is evidence of worsening liver disease; or (ii) as part of an investigational protocol.

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

IFN is effective for viral eradication in HCV-infected patients, especially when combined with ribavirin (see Guideline 2). Induction of SVR with IFN in the pretransplant setting frequently persists after kidney transplantation and can be associated with a reduction in HCV-related complications (see Guideline 4.1). However, the administration of IFN after kidney transplantation can be deleterious to the allograft and should generally be avoided in kidney transplant recipients unless there is indication of worsening hepatic injury on biopsy or clinically decompensating liver disease. This suggestion is supported by evidence of kidney graft dysfunction during IFN therapy in at least 12 published, although uncontrolled retrospective or observational studies (Guideline 2, Tables 12–14).^{2–4,142,160,161,163,165,290,293,295,297,298,332,333} Reported rates of kidney graft dysfunction range from 9 to 100%, with most episodes occurring between 0.3 and 8 months after initiation of therapy. In several cases, graft dysfunction limited the benefit of IFN and was followed by graft loss. Most kidney graft dysfunction was related to increased rates of acute rejection associated with the use of this immunostimulatory agent. In nontransplant patients, IFN has also been associated with the exacerbation of cryoglobulinemia³³⁴ as well as acute renal failure³³⁵ and glomerulopathy.³³⁶

On the other hand, patients with worsening liver disease (for example, fibrosing cholestatic hepatitis) are at increased risk for a subsequent liver transplant or even death. In these patients, IFN-based therapy may be potentially lifesaving and

should be administered despite the risk of kidney graft dysfunction. In the studies cited above, HCV viral clearance was achieved 0–50% of the time. In a recent meta-analysis, the summary estimate for SVR was 18%.²⁹⁴ To this end, there is one report of two patients who developed fibrosing cholestatic hepatitis after kidney transplantation, where IFN successfully reversed the acute hepatic insult.¹⁸⁹ There is also one case series of 11 patients where administration of very low-dose IFN (1×10^6 U thrice weekly) achieved SVR in three of the patients, a partial response in another three, and only one patient experienced acute graft dysfunction. Another single case report suggests that SVR was obtained in a kidney transplant recipient with the use of IFN β .³³⁷

On the basis of the above evidence, the following recommendations are made:

- IFN is contraindicated in kidney transplant recipients for the treatment of extrahepatic complications of HCV infection.
- IFN should only be used in the setting of clinically and histologically worsening liver disease, where the potential benefits of treatment (in terms of eradicating virus and attenuating liver injury or preventing liver failure) outweigh the substantial risks of kidney allograft injury and graft loss due to the therapy.

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

The frequency of HCV infection is increased among diabetic patients in the general population.^{338,339} In addition, HCV infection has been strongly associated with new-onset diabetes mellitus, both in the general population and in transplant recipients. In NHANES III, HCV infection was associated with a 3.7-fold increased risk of type 2 diabetes mellitus,³⁰⁵ and others have reported a higher prevalence of impaired fasting glucose among HCV-infected patients compared to uninfected patients.³⁰⁴

The overall reported rates of new-onset diabetes mellitus after solid organ transplantation range from 2 to 53%.³⁴⁰ The wide range stems, in part, from a previous lack of uniform criteria for defining NODAT. Definitions have ranged from the *de novo* requirement for insulin or oral hypoglycemic agents to various target glucose levels not necessarily consistent with American Diabetes Association (ADA) guidelines. Subject to these limitations, several retrospective cohort studies and one registry analysis indicate that the rates of NODAT among HCV-infected kidney transplant recipients range between 10 and 65%, with a three- to fivefold increased risk of NODAT among HCV-infected kidney transplant recipients.^{127,128,132,265,266,341} At least two of these studies suggest that the risk of NODAT in HCV-infected recipients was especially exaggerated in patients being treated with tacrolimus, as opposed to cyclosporine-based maintenance immunosuppression.^{128,341} A similar increased risk of

NODAT has been made in liver transplant recipients with HCV infection.^{289,290,342} As with uninfected kidney transplant recipients, NODAT typically occurs in HCV-infected patients within the first 3 months after transplantation.^{127,128}

The adverse effects of NODAT on morbidity, mortality, and graft survival after transplantation are well established in kidney transplant recipients.^{127,266} However, outcome data in the subset of HCV-infected patients with NODAT are sparse. One analysis of Medicare beneficiaries in the USRDS registry noted that among HCV-infected kidney transplant recipients, the development of NODAT was associated with a significant reduction in lifespan.¹²⁷ In another study of HCV-infected liver transplant recipients, there was a significantly higher cumulative mortality rate of 56% among patients with NODAT compared to 14% in the nondiabetic cohort.²⁹⁰

The available data provide convincing evidence of a relationship between HCV infection and an increased risk of NODAT after kidney transplantation. Although less well supported from the available evidence, it appears that HCV-infected recipients with NODAT have a higher risk of mortality than their nondiabetic counterparts. Also, many studies have demonstrated that, considered separately, both HCV infection and NODAT^{266,343} independently predict a higher risk of mortality in kidney transplant patients. As early detection of NODAT in HCV-infected transplant recipients is desirable to initiate therapy, the following recommendations are made:

- Nondiabetic HCV-infected kidney transplant candidates should have an oral glucose tolerance test during evaluation for a kidney transplant to screen for pre-existing diabetes mellitus. Fasting blood sugars should be obtained weekly during the first 3 months of the post-transplant period, then every other week for months 4–6, and then monthly for months 6–12. After the first post-transplant year, fasting blood glucose and/or glycosylated hemoglobin should be measured at least annually. This is in keeping with the guidelines of the American Society of Transplantation for outpatient surveillance of kidney transplant recipients.³⁴⁴
- The diagnosis of hyperglycemia should be in keeping with current ADA criteria of a fasting blood glucose > 125 mg per 100 ml (6.9 mmol l⁻¹) on two separate occasions.³⁴⁵
- The use of immunosuppressive drugs that are associated with diabetogenic side effects should be balanced to optimize antirejection efficacy while simultaneously minimizing the risk of hyperglycemia.
- Patients with evidence of hyperglycemia as defined by the ADA criteria should be referred to a diabetologist for further evaluation and management.

Whether the use of oral glucose tolerance tests or more frequent glucose monitoring in HCV-positive kidney transplant recipients will lead to earlier diagnosis and treatment of NODAT remains to be determined.

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

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

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

HCV infection has been implicated in the pathogenesis of glomerular disease in both native and transplanted kidneys.³⁴⁶ Among kidney transplant recipients, the prevalence of proteinuria is increased in those with HCV infection compared to uninfected patients.¹²² HCV-infected kidney transplant recipients have an increased risk of post-transplant glomerulopathy, leading to graft dysfunction and loss. Because kidney transplant recipients with HCV infection are predisposed to post-transplant glomerulopathy, a proactive approach to detecting evidence of glomerular injury is specifically recommended:

- Baseline urine protein-to-creatinine ratio and urinalysis should be obtained within the first 2 weeks after transplantation, or as soon as a stable level of kidney function is achieved. Thereafter, patients should be screened for proteinuria at least every 3–6 months for the first post-transplant year and then twice per year thereafter. These recommendations are in keeping with the guidelines published by the American Society of Transplantation.³⁴⁴
- MPGN is commonly observed in kidney allograft biopsies from HCV-infected patients with proteinuria and may be associated with both chronic allograft nephropathy and either *de novo* disease or post-transplant recurrence of the native kidney lesion.³⁴⁶ Distinguishing the cause of MPGN is important as it may influence subsequent therapy. The presence of immune complex deposition favors a diagnosis of MPGN and may result in accelerated graft loss.¹²²
- A biopsy of the kidney allograft should be performed in HCV-infected kidney transplant recipients who are found to have proteinuria (urine protein-to-creatinine ratio >1.0, or 24-h urine protein >1.0 g on two occasions) or microscopic hematuria without other causes identified.
- Kidney biopsy should be studied with light microscopy, immunofluorescence techniques, and electron microscopy.
- Specific glomerular changes characteristic of cryoglobulinemic MPGN may indicate the need to consider specific therapy (see Guideline 5).

IFN-based therapies may be effective in treating HCV-related glomerulopathy in native kidney disease (see Guideline 5.3). However, IFN use in kidney transplant recipients is associated with an increased risk of rejection (see Guideline 4.4.2). The RR of kidney allograft loss from progressive HCV-associated glomerulopathy vs that from IFN-induced rejection is unknown. Emerging data suggest that the administration of IFN to HCV-infected patients before transplantation may prevent post-transplant GN (discussed in Guideline 4.1.5). The limited available data indicate that antiviral therapies such as ribavirin can be anti-proteinuric in kidney transplant recipients.¹⁸⁷ Nonspecific antiproteinuric measures, such as blockade of the renin–angiotensin–aldosterone system with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), may be useful adjuncts. Although these agents have been extensively investigated in native kidney disease, studies in kidney transplant patients are relatively sparse in general and nonexistent in HCV-infected recipients in particular. However, the available data from native kidney disease studies can be extrapolated to the kidney transplant population. Support for this judgment comes from studies in kidney transplant patients showing that treatment with ACEI/ARB reduces proteinuria³⁴⁷ and slows progressive chronic allograft dysfunction and failure.^{348,349} The following recommendations are made on the basis of the above information and the limited number of studies that specifically address optimal therapy of HCV-related post-transplant glomerulopathy:

- Because of the increased risk of allograft dysfunction, it is suggested that treatment with IFN-based therapy generally be avoided in kidney recipients with HCV-associated glomerulopathy. Any decision to use IFN should be individualized, weighing the potential benefit of treatment vs the risk of rejection. If a decision to treat is made, there are limited data on the use of pegylated IFN and ribavirin in this setting; however, in patients with estimated GFR >50 ml per min per 1.73 m², combination therapy with IFN and ribavirin can be considered.
- Ribavirin can reduce proteinuria in HCV-associated glomerulopathy, although its impact on kidney function is unknown and it does not lead to viral clearance.
- Strong consideration should be given to treat HCV-infected kidney transplant candidates in the pretransplant period, as achievement of a pretransplant SVR is frequently durable and appears to be associated with a reduced risk of post-transplant glomerulopathy (see Guideline 4.1.5).
- Antiproteinuric therapy with agents that block the renin–angiotensin–aldosterone system should be used as tolerated. Careful monitoring of kidney function, serum potassium, and hemoglobin during ACEI/ARB therapy is essential, particularly if recipients have impaired kidney function.

General treatment principles for CKD management should be followed, including target levels of proteinuria, blood pressure, and lipids, as described in guidelines by KDOQI and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

LIMITATIONS

- There are no prospective studies examining the natural history of liver disease progression in HCV-infected kidney transplant recipients, especially in terms of pretransplant liver histology.
- There is a lack of prospective studies evaluating extrahepatic HCV-related complications in kidney transplant recipients.
- Most published studies include small numbers of patients.
- Registry studies are short on detailed and patient-specific data.
- All outcome studies are retrospective.
- It is not known whether practice standards used for the nontransplant population or for liver transplant

recipients with HCV infection can be applied to HCV-infected kidney transplant recipients.

RESEARCH RECOMMENDATIONS

- Prospective studies are needed to evaluate the natural history of HCV infection in kidney transplant recipients in terms of progressive liver disease as well as extrahepatic complications.
- Studies are needed to determine the mechanism of NODAT in HCV-infected transplant recipients as well as possible therapies that may mitigate or prevent this complication.
- Prospective randomized trials of IFN or other emerging antiviral therapies administered to HCV-infected kidney candidates before transplantation are needed to examine the effects on hepatic and extrahepatic complications of HCV developing after transplantation.
- Prospective trials are needed to examine the efficacy of anti-CD20 in post-transplant GN and its effect on viral replication.

Table 22 | Summary table of patient mortality in HCV-positive kidney transplant recipients vs wait-listed HCV-positive hemodialysis patients^a

Author (year), country, study design	N	Test determining HCV status	Mean follow-up (months)	Outcome ^b Mortality
Pereira (1998), ¹¹⁰ United States, Retrospective	111 HCV+ kidney recipients 112 HCV+ patients on waiting list	EIA 3	73 (median)	Transplant vs dialysis ^c Adjusted RR of mortality ^d 0–3 months post-transplant: ~4.8 (significant) 4–6 months post-transplant: ~1.8 (NS) 7–47 months post-transplant: ~0.3 (significant) ≥48 months post-transplant: ~0.8 (NS)
Bloom (2005), ²⁵³ United States, Retrospective	138 HCV+ kidney recipients 177 HCV+ patients on waiting list	EIA 2 or EIA 3	48 (median)	Transplant vs nontransplanted: Actuarial mortality: ~20 vs ~50% (P=0.003)
Knöll (1997), ²⁵⁴ United States, Retrospective	33 HCV+ kidney recipients 25 HCV+ patients on waiting list	EIA 1 or EIA 2	39 35	Transplant vs dialysis ^e : Actuarial mortality: ~15 vs ~30% (P=0.04)

EIA, enzyme immunoassay; HD, hemodialysis; NA, not applicable; ND, not documented; NS: not significant; RR, relative risk.

^aNonsystematic review. No grading.

^bNo data provided on graft survival in these articles.

^cAll-cause mortality figures are for all transplant recipients vs dialysis, but point estimates for HCV-positive and HCV-negative transplant recipients were similar (see Figure 2 in text).

^dEstimated from Figure 2 in text.

^eResults approximate because extrapolated from Figure 1 in text. Eighteen HCV-positive patients who were not transplant candidates were also studied and had a 62% mortality rate in 29 months of follow-up.

Table 23 | Summary table of adjusted mortality and graft loss in HCV-positive vs HCV-negative kidney transplant recipients^a

Author (year), country, study design	N	Test determining HCV status	Mean follow-up (months)	Outcomes	
				Risk-adjusted patient mortality	Risk-adjusted graft loss
Meier-Kriesche (2001), ³⁵⁰ United States Retrospective	535 HCV+ 73 172 HCV–	EIA (unspecified)	ND ^b	HCV+ vs HCV– Adjusted mortality per 1000 patients: 35.7 vs 44.6 ($P < 0.01$)	ND
Abbott (2003), ³²⁰ United States Retrospective	2525 HCV+ ^c 34 431 HCV–	EIA (presumed)	33	HCV+ vs HCV– Adjusted HR of mortality: 1.34 (1.04–1.74)	HCV+ vs HCV– Adjusted HR of graft loss: 0.85 (0.52–1.39)
Batty (2001), ²⁶¹ United States Retrospective	1624 HCV+ 27 068 HCV–	EIA (presumed)	ND ^d	HCV+ vs HCV– Adjusted HR for mortality: 1.23 (1.01–1.49)	ND
Morales (2004), ¹²⁰ Spain Retrospective	488 HCV+ 2877 HCV–	EIA 1, EIA 2, or EIA 3	ND	HCV+ vs HCV– Adjusted RR of mortality: 1.50 (1.12–2.02)	HCV+ vs HCV– Adjusted RR of graft loss: 1.53 (1.17–2.00)
Bruchfeld (2004), ¹¹⁵ Sweden Retrospective	51 HCV+ 520 HCV– ^e	EIA 1, EIA 2, or EIA 3 PCR ^e	ND ^f	HCV+ vs HCV– Adjusted RR of mortality: 2.23 (1.48–3.34)	HCV+ vs HCV– Adjusted RR of graft loss: 1.96 (1.37–2.79)
Legendre (1998), ²⁶³ France Retrospective	112 HCV+ 387 HCV–	EIA 2	79 81	HCV+ vs HCV– Adjusted OR of mortality: 2.8 (1.4–5.7)	ND
Forman (2004), ¹¹⁶ United States Retrospective	26 HCV+ 328 HCV–	EIA (unspecified)	28 (median)	ND	HCV+ vs HCV– Adjusted HR of graft loss: 2.00 (0.73–5.46) ^g
Gentil (1999), ²⁶² Spain Retrospective	85 HCV+ 235 HCV–	EIA 1 or EIA 2	63 57	HCV+ vs HCV– Adjusted RR of mortality: 3.1 (1.2–7.8) ^h	HCV+ vs HCV– Adjusted RR of graft loss: 3.0 (1.8–5.0) ^h
Lin (2004), ³²⁹ Taiwan Retrospective	129 HCV+ 170 HCV–	EIA 1, EIA 2, or EIA 3	67	HCV+ vs HCV– Adjusted RR of mortality: 0.30 (0.13–0.65)	HCV+ vs HCV– Adjusted RR of graft loss: 0.81 (0.48–1.35)
Mahmoud (2004), ²⁹² Egypt Prospective	87 HCV+ 46 HCV–	RT-PCR (Amplicor)	94 98	HCV+ vs HCV– Adjusted OR of mortality: 0.50 (0.1–1.9) ⁱ	HCV+ vs HCV– Adjusted OR of graft loss: 0.50 (0.3–1.2) ^j

EIA, enzyme immunoassay; HD, hemodialysis; HR, hazard ratio; KTR, kidney transplant recipient; NA, not applicable; ND, not documented; NS: not significant; OR, odds ratio; RR, relative risk; RT-PCR, reverse transcription-polymerase chain reaction.

↑, positive association—increase in death or graft loss (not statistically significant); ↓, negative association—decrease in death or graft loss (not statistically significant); ↑ and ↓, statistically significant association ($P < 0.05$).

^aNonsystematic review. No grading.

^bSurvival curves contain data up to 8 years.

^cHCV+ recipients (23%) received HCV+ kidney, 0.8% of HCV– recipients received HCV+ kidneys.

^dSurvival curves contain data up to 3 years.

^eSix patients were EIA-positive but persistently RNA-negative. They were classified as HCV-negative.

^fSurvival curves contain data up to 13 years.

^gIn multivariable models, the following factors had statistically significantly increased adjusted HR for graft loss: panel-reactive antibody $> 20\%$, HLA mismatch ≥ 5 , post-transplant delayed graft function, and acute humoral rejection.

^hText inconclusive of directionality of adjusted RR but reported values are consistent with the directionality of unadjusted risks.

ⁱHCV RNA-positive patients with elevated ALT had OR of mortality: 3.7 (1.0–13.7).

^jHCV RNA-positive patients with elevated ALT had OR of graft loss: 3.0 (1.4–6.7).

Table 24 | Summary table of outcomes following kidney transplantation using HCV-positive donors

Author (year), country, study design	N	Donor HCV EIA status	Recipient HCV EIA status	Applicability	Mean follow-up (months)	Outcome		Quality
						Mortality	Graft loss	
Abbott (2003), ³²⁰ United States Retrospective ^a (USRDS 1996–2001)	873	Positive	Positive (68%) Negative (32%)	Moderate	60	HCV+ vs HCV– donor ^b Adjusted HR mortality: 2.12 (1.72–2.87) ^{c,d}	HCV+ vs HCV– donor Adjusted HR graft loss: 0.77 (0.25–2.42) ^e	B
	36 083	Negative	Positive (5%) Negative (95%)					
Abbott (2004), ²⁷⁶ United States Retrospective ^a (USRDS 1995–2000)	389	Positive	Positive (52%) Negative (48%)	Moderate	38	Adjusted HR of mortality: HCV+ donor: 0.76 (0.60–0.96) HCV– donor: 0.47 (0.44–0.50) Transplant waiting list: 1 (reference)	ND	B
	16 595	Negative	Positive (4%) Negative (96%)					
	17 094	Transplant Waiting List						
Bucci, 2002 ³¹¹ United States Retrospective ^a (USRDS 1994–1998)	484	Positive	Positive (66%) Negative (34%)	Moderate	36	HCV+ vs HCV– donor Adjusted HR mortality: 1.46 (1.04–2.05)	ND	B
	17 213	Negative	Positive (5%) Negative (95%)					
Cosio, 1996 ¹²¹ United States Retrospective	32	Negative ^f	Positive	Moderate	28	ND	26% (NS) 17% (NS) 14% (NS)	C
	48	Positive	Negative					
	204	Negative	Negative					
Roth, 1992 ³⁵¹ United States Retrospective	15 ^g	Positive	Negative (33%) Unknown (67%)	Moderate	41	HCV+ vs HCV– donor 5-year mortality: 22 vs 17% (NS)	HCV+ vs HCV– donor 5-year Graft loss: 35 vs 39% (NS)	C
	120	Negative	Negative					
Bouthot, 1997 ³⁰⁹ United States Retrospective	29	Positive	ND	Moderate	68	HCV+ vs HCV– donor Adjusted RR of mortality: 1.0 (0.5–2.0)	HCV+ vs HCV– donor Adjusted RR of Graft loss: 0.95 (0.5–1.7)	C
	74 ^h	Negative	ND					
Morales, 1995 ²⁷² Spain Prospective	24	Positive	Positive	Moderate	26	HCV+ vs HCV– donor mortality: 0 vs 2% (NS)	HCV+ vs HCV– donor Graft loss 4 vs 7% (NS)	C
	40	Negative	Positive					
Woodside, 2003 ³⁵² United States Retrospective	20	Positive	Positive	Narrow	~31 ⁱ (median)	HCV+ vs HCV– donor 1-year mortality: 11 vs 6% (NS)	HCV+ vs HCV– donor 1-year Graft loss: 11 vs 21% (NS)	C
	20	Negative	Positive					
Mandal, 2000 ³¹³ United States Retrospective	18 ^j	Positive	Positive	Narrow	15	HCV+ vs HCV– donor mortality: 11 vs 10%	HCV+ vs HCV– donor Graft loss ^k 11 vs 30%	C
	10	Negative	Positive					

EIA, enzyme immunoassay; HR, hazard ratio; ND, not documented; NS, not significant, RR, relative risk; USRDS, United States Renal Data System.

^aOverlapping database analyses.

^bAdjusted hazard ratio reported for HCV-positive donor without regard to HCV status of recipient.

^cAdjusted hazard ratio of mortality for HCV-positive recipients of kidneys from HCV-positive donors was 0.51 (0.36–0.73) but became nonsignificant after adjustment for comorbid conditions.

^dHazard ratio of receiving a kidney from an HCV-positive donor was 2.66 ($P=0.003$) after adjustment for comorbid conditions (data since April 1996 on 63% of cohort).

^eAdjusted hazard ratio of graft loss for HCV-positive recipients of kidneys from HCV-positive donors was 1.48 (0.37–5.85).

^fAll but one donor was HCV-negative. No specific information was available on the one HCV-positive recipient of an HCV-positive kidney.

^g31 patients without reported recipient HCV status were not considered.

^hIncludes a combination of kidney, heart, and liver transplantation.

ⁱText of article reads 'Median follow-up was 788 d for hepatitis C seropositive patients receiving a seronegative kidney and 1047 d for those receiving a seronegative kidney'. We calculated an average follow-up time for both groups.

^jOne patient received two transplants during the study. The first (from an HCV+donor) was lost due to accelerated acute rejection. Patient received a second kidney (from an HCV+donor) 11 months later.

^kDeath-censored allograft loss.

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

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INTRODUCTION

Hepatitis C virus infection has been associated with the development of immune complex glomerular diseases, including MPGN and membranous nephropathy. In addition, HCV infection has been strongly linked with the pathogenesis of cryoglobulinemia. In this context, all HCV-infected patients are at increased risk to develop kidney disease and should be screened annually. In addition, patients with vasculitis or glomerular syndromes of uncertain etiology should be screened for HCV infection as part of the initial evaluation.

Levels of strength of recommendations

Strength of recommendation	Wording of recommendation	Basis for strength of recommendation
Strong	An intervention 'should' be done	'High' quality evidence and/or other considerations support a strong guideline ^a
Moderate	An intervention 'should be considered'	'Moderate' quality evidence and/or other considerations support a moderate guideline ^a
Weak	An intervention 'is suggested'	'Low' or 'Very Low' quality evidence; predominantly based on expert judgment for good clinical practice ^a

^aSee Appendix 2: Grading the Strength of the Recommendations, p. S85.

- 5.1 *It is suggested that HCV-infected patients be tested at least annually for proteinuria, hematuria, and estimated GFR to detect possible HCV-associated kidney disease. (Weak)*
- 5.2 *It is suggested that a kidney biopsy be performed in HCV-infected patients with clinical evidence of GN. (Weak)*
- 5.3 *It is suggested that for patients with HCV-associated glomerular diseases, particularly MPGN, antiviral treatment as per Guideline 2.2 be considered. (Weak)*
 - *It is suggested that immunosuppressive agents be considered for patients with cryoglobulinemic kidney diseases. (Weak)*

BACKGROUND

Patients with long-standing HCV infection can develop chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. Several extrahepatic—including hematologic and dermatologic—complications have also been associated with HCV infection, as well as autoimmune and kidney diseases.³⁵³ There is an increasing evidence for the association between HCV infection and glomerular disease in both native and transplanted

kidneys. Type I MPGN associated with type II cryoglobulinemia is the most common form of kidney disease associated with HCV infection.³⁵⁴ Less frequently described lesions are MPGN without cryoglobulinemia and membranous GN (MGN). Also, occasional cases of focal segmental glomerulosclerosis, thrombotic microangiopathy associated with anti-cardiolipin antibodies, and fibrillary and immunotactoid glomerulopathies have been reported.^{60,354–359}

The presence of these renal manifestations of HCV infection is not common and their exact prevalence remains unknown because the available information is limited. Why only some HCV-infected patients develop kidney lesions has not been determined. However, consideration for the use of antiviral therapy in these cases is important, as HCV infection has been implicated in the pathogenesis of the immune complex GN that sometimes develops.⁶⁰ Establishment of the correct histologic diagnoses in patients with suspected HCV-induced GN is essential, as clearing of HCV RNA with SVR can be obtained with the use of appropriate antiviral strategies. In some patients with histologically active lesions (for example, crescents, vasculitis), combined antiviral and immunosuppressive therapies may be effective and should be considered.³⁶⁰

RATIONALE

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

HCV-infected patients, including those with kidney or liver transplants, have an increased risk of glomerulopathy leading to CKD.³⁵⁹ Glomerular lesions associated with HCV infection have been described in the presence or absence of significant liver disease; however, all patients with HCV-associated GN are HCV RNA-positive in the serum.^{60,359,360}

Epidemiologic studies reporting the actual prevalence of CKD in patients with HCV infection are not available. It has been demonstrated that the prevalence of HCV seropositivity in case series of patients with MPGN is about 10 times greater than the reported prevalence of HCV seronegativity.³⁶¹ Furthermore, studies of both live and autopsy series of individuals with HCV infection have shown a higher prevalence of MPGN than those reported for the general population.^{362,363} A recent cross-sectional analysis of the NHANES III data demonstrated an age-dependent

association between HCV seropositivity and albuminuria (adjusted odds ratio of 1.84 for ages 40–59 years and 1.27 for age ≥ 60 years).³² In the ≥ 60 -year age group, 46% of HCV-seropositive individuals had albuminuria compared with 24% of those who were HCV antibody-negative. Of interest, the same study found no significant association between HCV seropositivity and low estimated GFR. Similar findings were reported in a recent study from Taiwan.³¹ In this cross-sectional analysis, nondiabetic subjects who were anti-HCV-positive had an 8.3% prevalence of ≥ 1 positive dipstick proteinuria compared with 5.1% in the seronegative group ($P = 0.002$). In multivariate analysis, the association between anti-HCV-positive status and proteinuria had an odds ratio of 1.84.

Cryoglobulins containing HCV RNA can be detected in up to 50% of patients with HCV-associated MPGN, but generally at very low levels (cryocrit $< 3\%$).³⁶⁴ Symptomatic cryoglobulinemia occurs in about 1% of patients with HCV infection, generally in association with high levels of cryoglobulins and rheumatoid factor. Only a small number of patients with cryoglobulinemia develop kidney disease or other systemic vasculitis symptoms.³⁶⁵ The prevalence of MPGN in patients with cryoglobulinemia associated with HCV infection is $< 10\%$,³⁵⁸ and, in some series of kidney biopsies of different lesions, only MPGN was clearly associated with HCV infection.³⁶¹ For other lesions, such as MPGN without cryoglobulinemia or MGN, the prevalence of HCV infection is in the range of 1–10%.^{366–368} Membranous nephropathy has been described occasionally in HCV-infected patients.^{369,370} In a study from Japan, evidence for HCV infection was found in 2 of 24 patients with apparent idiopathic membranous nephropathy.³⁷¹ In an autopsy series of 188 consecutive patients with HCV infection, the authors reported that MPGN was present in 11%, membranous nephropathy in 2%, mesangial proliferative GN in 17%, and 45% of the kidneys showed no evidence of GN.³⁷²

The principal clinical manifestations of glomerular disease in HCV-infected patients are the presence of proteinuria and microscopic hematuria with or without impaired kidney function. Screening for urinary abnormalities and alterations of kidney function in all HCV-positive patients is recommended, particularly in those with cryoglobulinemia. Early diagnosis and treatment of HCV-associated glomerulopathy may improve clinical outcomes. Supporting this proposition is a prospective study of hepatitis C-infected patients with end-stage cirrhosis undergoing liver transplantation,³⁷³ in which renal biopsies obtained at transplant surgery demonstrated that most patients (25 of 30) had immune complex-mediated GN. The majority of these were MPGN, and most glomerular disease was clinically not apparent before biopsy. This study indicates a potentially large and unrecognized reservoir of kidney diseases in HCV-infected patients, particularly those with advanced liver disease, that could contribute to CKD in conjunction with other kidney injuries such as those consequent to liver transplantation.

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

HCV infection has been associated with glomerular lesions in native and transplanted kidneys.^{32,60,359} In HCV-infected patients with proteinuria and/or hematuria, a kidney biopsy is necessary to determine the histologic pattern of glomerular injury present. Although several glomerular lesions have been described, the most important one is MPGN usually, but not invariably, in the context of cryoglobulinemia. HCV infection is the major cause of mixed cryoglobulinemia, a systemic vasculitis characterized by arthralgias, arthritis, Raynaud's phenomena, purpura, peripheral neuropathy, hypocomplementemia, and kidney disease.³⁵⁶ Cryoglobulins and HCV RNA are usually present. Hypocomplementemia and positive rheumatoid factor can also be observed. Some patients exhibit normal ALT/AST levels or only a mild elevation of liver enzymes (60–70% of cases). Manifestations of kidney involvement include nephrotic or non-nephrotic proteinuria, hematuria, and variable degrees of reduced GFR. Acute nephritic syndrome and nephrotic syndrome can be a presenting feature in 25 and 20% of these patients, respectively.⁶⁰

Pathologic findings of cryoglobulinemic GN typically include evidence of immune complex deposition in the glomeruli and changes of type I MPGN. Glomeruli may demonstrate prominent hypercellularity as a result of massive infiltration of glomerular capillaries with mononuclear and polymorphonuclear leukocytes. Glomeruli show accentuation of lobulation of the tuft architecture and may have a combination of increased matrix and mesangial cells, capillary endothelial swelling, splitting of capillary basement membrane, intracapillary thrombi, and accumulation of eosinophilic material representing precipitated immune complexes or cryoglobulins. Vasculitis of the small- and medium-sized renal arteries can also be present. On electron microscopy, subendothelial immune complexes are usually seen and may have a fibrillar or immunotactoid pattern suggestive of cryoglobulin deposits.^{60,358}

It is important to note that the presence of massive intraluminal thrombi, vasculitis, or both is more commonly observed in patients with acute nephritic syndrome and rapid progression to kidney failure. Histologic findings of exudative MPGN or lobular MPGN are associated with the presence of nephrotic and/or nephritic syndromes, whereas mesangioproliferative GN is associated with proteinuria and microscopic hematuria with preserved kidney function.⁶⁰

In noncryoglobulinemic MPGN, the clinical picture, pathologic features, and laboratory data are indistinguishable from idiopathic type 1 MPGN,³⁵⁸ but are characterized by the presence of HCV antibodies and HCV RNA in the serum. Both subendothelial and mesangial immune complexes can be identified by electron microscopy typically without a distinctive substructure. In both forms of HCV-associated MPGN, immunofluorescence usually demonstrates deposition of IgM, IgG, and C3 in the mesangium and capillary walls.³⁵⁸

MGN is also associated with HCV infection. The clinical presentation, outcome, and pathologic findings are similar to those of idiopathic MGN.^{365,367} On light microscopy, the characteristic finding is a diffuse and uniform thickening of the glomerular basement membrane without mesangial proliferation. Diffuse subepithelial immune deposits can be identified by electron microscopy, and immunofluorescence reveals diffuse and granular deposits of IgG, C3, and IgA.

The pathogenesis of MGN in HCV-infected patients may be related to the deposition of immune complexes containing HCV proteins in the glomerular basement membrane. Viral antigens have been detected by immunohistochemistry,³⁷⁴ and by *in situ* hybridization.³⁷⁵ It has been also reported that laser microdissection is a useful method for measuring HCV RNA genomic sequences and HCV core protein in kidney structures, such as glomeruli and tubules, in patients with HCV-related GN.³⁷⁶ However, these reports of localization of either HCV mRNA or proteins still await confirmation.

Of interest, a recent study found that Toll-like receptor 3 messenger RNA expression was elevated in mesangial cells in HCV-associated GN and was associated with enhanced proinflammatory cytokines. The authors hypothesized that immune complexes containing RNA activate mesangial Toll-like receptor 3 during HCV infection, inducing chemokine and cytokine release and affecting proliferation and apoptosis. The authors suggest a novel role for Toll-like receptor 3 in HCV-associated GN that could establish a link between viral infections and GN.³⁷⁷

Other glomerular diseases that have been occasionally reported in association with HCV infection include acute diffuse proliferative GN,^{358,362} focal segmental glomerulosclerosis,³⁵⁸ rapidly progressive GN,³⁷⁸ IgA nephropathy,³⁵⁸ thrombotic microangiopathy,³⁵⁵ fibrillary GN, and immunotactoid glomerulopathy.³⁵⁷

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

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

Antiviral therapy targeted at achieving clearance of HCV RNA with SVR has been used in patients with HCV-associated GN to treat the underlying kidney disease. Unfortunately, there are limited data regarding antiviral treatment in HCV-associated GN, and the impact of antiviral therapy on long-term outcomes of kidney disease is not well known (Tables 25–28).

Monotherapy with IFN alfa has been used in cryoglobulinemic GN with complete clearance of HCV RNA and improved kidney function; however, recurrence of viremia and relapses of kidney disease were universally observed after IFN was discontinued.^{367,379} The use of steroid pulses and cytotoxic agents, with or without plasma exchange, can be useful in some patients with cryoglobulinemic GN and

systemic manifestations of mixed cryoglobulinemia, but can be associated with a high rate of severe complications such as infection, increased viral replication, and death.³⁶⁰

Combination therapy with pegylated IFN and ribavirin to treat HCV-associated GN has been reported in isolated cases and uncontrolled studies with small numbers of patients. The most recent experience shows promising results with this combination. SVR, decreased HCV RNA viral titers, and improved kidney function and proteinuria have been demonstrated in some patients.^{380–383} However, IFN has been reported to exacerbate proteinuria in some patients with underlying glomerulopathies.³³⁶ Monitoring ribavirin dosage is essential to circumvent ribavirin-induced hemolytic anemia. Ribavirin is not recommended in patients with a creatinine clearance < 50 ml per min per 1.73 m².³⁶⁰ Recently, the anti-CD20 monoclonal antibody rituximab, an agent that selectively targets B cells, has been used in a few noncontrolled studies of cryoglobulinemic MPGN associated with HCV infection.^{360,384–386} Preliminary results are encouraging. Rituximab has not been associated with enhanced viral replication and the side effects of cytotoxic agents such as cyclophosphamide.^{360,387} In fact, the preferential use of rituximab has been recommended by some in spite of the absence of controlled trials. However, a point of caution is important, as the use of rituximab may be associated with the activation of various viral infections, including HCV.^{388–391}

It is clear that prospective multicenter RCTs are mandatory to establish evidence-based recommendations to treat glomerular lesions associated with HCV infection. However, until this information is available, it is suggested that two possible regimens should be considered for the treatment of cryoglobulinemic MPGN, depending on the severity of proteinuria and kidney failure:

- First, in patients with moderate proteinuria and slow but progressive loss of kidney function, therapy for 12 months with standard IFN or pegylated IFN alfa-2a (135 µg week⁻¹ SQ in patients with reduced creatinine clearance) or pegylated IFN alfa-2b (1.5 µg kg⁻¹ week⁻¹ SQ) plus ribavirin (not recommended for a GFR < 50 ml per min per 1.73 m²), with or without erythropoietin support depending on the level of hemoglobin.
- Second, in patients with nephrotic-range proteinuria and/or rapidly progressive loss of kidney function and an acute flare of cryoglobulinemia, it is recommended to consider the use of either plasma exchange (3l of plasma thrice weekly for 2–3 weeks), rituximab (375 mg m⁻² week⁻¹ for 4 weeks), or cyclophosphamide (2 mg kg⁻¹ day⁻¹ for 2–4 months) plus methylprednisolone pulses 0.5–1 g day⁻¹ for 3 days.³⁶⁰ After control of the vasculitic syndrome has been achieved, attention should be focused on treating the HCV infection directly with the antiviral therapy outlined above. In cases of early relapse of viremia, consideration should be given to further treatment with rituximab (375 mg m⁻² week⁻¹ for 4 weeks) with or

without IFN for a longer duration (minimum of 18 months treatment).

- Finally, and in all cases, treatment including diuretics and antihypertensive agents should be used to achieve recommended target blood pressure goals of patients with CKD (see KDOQI Hypertension Guidelines). Additionally, antiproteinuric agents such as ACEI alone or in combination with ARBs should be used to maximally reduce urinary protein losses.

In patients with noncryoglobulinemic MPGN and MGN associated with HCV infection, the use of IFN monotherapy or combination treatment with pegylated IFN plus ribavirin, as outlined above, could be useful. Another possibility could be monotherapy with standard IFN or pegylated IFN alone and the use of ribavirin only in patients remaining HCV RNA-positive after 3 months of therapy with IFN. Symptomatic therapy is also important in these cases, particularly that of antiproteinuric agents to decrease proteinuria.

Ribavirin monotherapy has been used in a few cases of HCV-associated GN with consequent decreased proteinuria, although no improvement in viremia was achieved.³⁶⁰ In patients with reduced kidney function, ribavirin should be administered with caution because of the risk of hemolytic anemia. Its use is not recommended in patients with a creatinine clearance of <50 ml per min per 1.73 m². Owing to the limited data available, more information is needed before the use of ribavirin monotherapy can be recommended in HCV-associated GN.

Summary of recommendations

- Patients with acute flares of cryoglobulinemia and MPGN should be treated with plasma exchange, immunosuppressive drugs, and antiviral therapy.
- Immunosuppressive drugs include steroids, cyclophosphamide, or rituximab.
- Antiviral therapy with standard IFN or pegylated IFN plus ribavirin for at least 12 months is recommended.
- Patients with cryoglobulinemia without systemic disease and MPGN may be treated with standard IFN or pegylated IFN plus ribavirin without immunosuppressive agents.
- Patients with noncryoglobulinemic MPGN and MGN may be treated with standard IFN, pegylated IFN, or IFN plus ribavirin.
- SVR after antiviral therapy, change in kidney function, evolution of proteinuria, and side effects of therapy must be carefully monitored.
- Relapses of systemic cryoglobulinemia and MPGN may be treated with additional doses of rituximab.
- Relapses of HCV infection may be treated with standard or pegylated IFN. Patients who received monotherapy with standard IFN as initial therapy should be considered for treatment with pegylated IFN plus ribavirin if the creatinine clearance is >50 ml per min per 1.73 m².

- Ribavirin is not recommended in patients with impaired kidney function (creatinine clearance <50 ml per min per 1.73 m²) to avoid anemia from hemolysis. If ribavirin is used in patients with CKD Stages 3–5, extreme caution must be used and close monitoring for worsening anemia is required.
- Patients with HCV-associated glomerulopathy should receive therapy with antiproteinuric agents, including ACEI and/or ARBs to reduce proteinuria and antihypertensive treatment to achieve target blood pressure and proteinuria goals established for patients with CKD.

LIMITATIONS

- Limited studies are available; most studies are retrospective analyses with small sample sizes.
- Most of the published literature comes from studies of patients referred with significant proteinuria, hematuria, or reduced kidney function. More thorough screening of the HCV-infected population will likely identify larger numbers of patients with earlier evidence of kidney disease who might have other histologic forms of injury.
- The measure of response to therapy varies significantly across the studies making it difficult to have valid comparisons of outcomes (for example, changes in proteinuria and kidney function).
- Long-term studies of patient and kidney outcomes after treatment of HCV associated glomerular disease are lacking.

RESEARCH RECOMMENDATIONS

- Large epidemiologic studies are needed to determine the prevalence and types of glomerular lesions in HCV-infected patients.
- Epidemiologic studies should be performed to examine the prevalence, risk factors, and outcomes of cryoglobulinemic MPGN.
- Epidemiologic studies are needed to determine whether acute diffuse proliferative GN, focal segmental glomerulosclerosis, rapidly progressive GN, and IgA nephropathy represent a true association or a coincidental association with HCV infection.
- Development of reagents that reliably test the presence of HCV virions, peptides, or RNA in tissues is needed to better understand the pathogenesis of glomerular disease associated with HCV infection.
- Further analyses should be conducted on the cytopathic effect of HCV and its possible interaction with cell-surface receptors such as Toll-like receptor 3.
- The role of HCV quasispecies evolution in promoting the development of cryoglobulinemia, GN, or in modulating the response of patients to various treatment regimens needs to be defined.

- Prospective multicenter RCTs are needed to establish the most efficacious treatment of HCV-associated glomerulopathy.
- Controlled trials of pegylated IFN should be performed to determine the dose and duration of therapy that is most effective with minimal adverse effects.
- Prospective controlled trials are needed to define the role of rituximab in cryoglobulinemic MPGN, and to determine dosage, safety, and effect on kidney disease.
- Controlled trials should be performed to determine the most effective therapy for relapses of cryoglobulinemia and HCV replication after a successful initial course of treatment.

Table 25 | Summary table of baseline characteristics of patients treated for HCV-associated glomerular disease

Author (year)	Country of study	Sample size	Mean age	Race	Male gender (%)	Mean duration of HCV (months)	Genotype prevalence					N
							%					
							1	2	3	4	5	
Mazzaro (2000), ³⁹² RCT	Italy	13	61	ND	62	55	42	50	8		1	
Alic (2004), ³⁸⁰ Prospective	France	25	54	ND	68	199	60	20	12	8		
Johnson (1994), ³⁶⁷ Retrospective	United States	19 ^a	46	ND	59	ND	31	38	7	24	5	
Beddhu (2002), ³⁹³ Retrospective	United States	17	47	ND	65	ND				ND		
Komatsuda (1996), ³⁹⁴ Retrospective	Japan	16	55	ND	68	ND		69	23	8	6	
Bruchfield (2003) ³⁸¹ Retrospective	Sweden	7	47	ND	57	ND	14	43	43			
Quartuccio (2006), ³⁸⁶ Prospective	Italy	5	57	ND	40	ND	60	40				
Stehman-Breen (1995), ³⁷⁰ Retrospective (case reports)	United States	3	41	1 White 1 Black 1 Hispanic	67	ND				ND		

HCV, hepatitis C virus; ND, no data; RCT, randomized controlled trial.

^aOut of the original group of 34, 19 were treated, but criteria for choosing who was treated were not presented. These included patients with primarily glomerular disease with or without systemic manifestations of cryoglobulinemia. All treated patients had evidence of glomerular disease on kidney biopsy. Article also reports treatment with prednisone or cyclophosphamide but outcomes not reported systematically.

Table 26 | Summary table of effect of treatment of HCV-associated glomerular disease

Author (year), country, study design	N	Mean follow-up post-treatment (months)	Pretreatment serum creatinine ($\mu\text{mol l}^{-1}$)	Pretreatment proteinuria (g per 24 h)	Intervention		Outcomes					
					Dose	Duration of therapy (months)	SVR (%)	↓ in serum creatinine by $\geq 18 \mu\text{mol l}^{-1}$ (%) ^a	↓ in proteinuria to $< 1.0 \text{ g per } 24 \text{ h}$ (%) ^a	Doubling of creatinine, or HD (%)	Treatment discontinued due to adverse events (%)	Quality
Mazzaro (2000), ³⁹² Italy, RCT	7	12	150	5.2	IFN: 3 MU	6	14	14 ^a	14 ^a	ND	14	B
Alric (2004), ³⁸⁰ France, Prospective	18	17	115	3.1	Prednisone: 0.2 mg kg ⁻¹ day ⁻¹ IFN: 3 MU+RBV: 600–1000 mg day ⁻¹ (n=14) PEG-IFN: 1.5 $\mu\text{g kg}^{-1}$ week ⁻¹ +RBV 600–1000 mg day ⁻¹ (n=4)	18	67	ND ^d	ND ^e	ND	0	C
Johnson (1994), ³⁶⁷ United States, Retrospective	7	24	133	3.6	Not treated ^c	NA	ND	ND ^d	ND ^e	ND	5	C
Beddhu (2002), ³⁹³ United States, Retrospective	19 ^f	ND	177	5.8	IFN: 3 MU ⁱ	6–12	0	58	37	5	16	C
	11 ^h	27	203	5.0	IFN: 10 MU ⁱ	12	0	9 ^j	18 ^k	9	9 ^l	C
	4 ^h				+Prednisone ⁱ	2	25	50 ^j	50 ^k	0	9 ^l	C
	4 ^h				+cyclophosphamide/ prednisone ⁱ	ND	0	25 ^j	25 ^k	75	ND	ND
Komatsuda (1996), ³⁹⁴ Japan, Retrospective	5 ^m	6	ND	ND	IFN- α : 600 MU day ⁻¹ Prednisolone: 40 mg day ⁻¹	> 6	20	0	0	ND	ND	C
Bruchfield (2003), ³⁸¹ Sweden, Retrospective	11 ^m	12–32 (range)	GFR: 48 ml min ⁻¹	3.9	Antiplatelet drugs (control)	1	0	18 ⁿ	45	ND	ND	ND
	6				IFN: 3 MU+RBV (n=4) PEG-IFN+RBV (n=2) RBV (n=1) ^o	6 (n=5) > 12 (n=2) ^p	71	43 ^q	86 ^r	0	0 ^s	C
Quartuccio (2006), ³⁸⁶ Italy, Prospective	5	> 15	133	1.7	Rituximab: 375 mg m ^{-2t} weekly	1, 2, 4, 6 ^w	ND	60	100 ^u	0	0	C
Stehman-Breen (1995), ³⁷⁰ United States, Retrospective (case reports)	3 ^v	6–12 (range)	124	14.1	IFN: 3 MU		0 ^x	67	33	33	33	C

ACEI, angiotensin-converting enzyme inhibitor; CKD, chronic kidney disease; GFR, glomerular filtration rate; HCV, hepatitis C virus; HD, hemodialysis; IFN, interferon; MU, million units; NA, not applicable; ND, not documented; NS, not significant; PEG-IFN, pegylated IFN; RBV, ribavirin; RCT, randomized clinical trial; SVR, sustained virologic response.

^aThe definitions of decrease in serum creatinine and proteinuria were selected to allow comparison of similar outcome measurements across studies.

^bPatients (71%) had a decrease in creatinine and 50% of patients had a decrease in proteinuria. All but one relapsed after treatment stopped.

^cPatients (67%) had a decrease in creatinine and 50% of patients had a decrease in proteinuria, but all relapsed after treatment stopped.

^dAll patients in both groups were treated during a 3-month run-in period with combination of furosemide, ACEI, steroids, and/or plasmapheresis based on the judgment of their physician. The IFN plus RBV group then began treatment, whereas the other group was managed symptomatically with diuretics as needed.

^eBetween-group comparison of change in serum creatinine was not significant.

^fBetween-group comparison of change in proteinuria was significant ($P < 0.05$). There was a statistically significant reduction in proteinuria in patients who achieved SVR vs nonresponders and controls. Also, there was a statistically significant decrease in pretreatment proteinuria in patients who achieved SVR.

^gOut of the original group of 34, 19 were treated but criteria for choosing who was treated were not presented. These included patients with primarily glomerular disease with or without systemic manifestations of cryoglobulinemia. All treated patients had evidence of glomerular disease on kidney biopsy. Article also reports treatment with prednisone or cyclophosphamide, but outcomes not reported systematically.

^hFive patients were subsequently treated with oral prednisone without improvement of kidney function. Two additional patients were later treated with pulse intravenous steroids with improvement in kidney function (including one patient who had been formerly dialysis-dependent and whose serum creatinine improved to $212 \mu\text{mol l}^{-1}$). In five patients, cytotoxic agents (with or without plasma exchange) were used. No efficacy data were presented, but three of these patients died (etiology: sepsis, pneumonia, and adult respiratory distress syndrome).

ⁱN reported are the total number of HCV-positive patients who received each treatment. Of a total number of 17, 11 were HCV-positive. Data reported are that of the HCV-positive patients only. Some patients received multiple treatments.

^jAll HCV-positive patients (n=11) initially treated with 3 MU IFN for 12 months. Four of those who did not respond or who relapsed were given high-dose IFN (10 MU daily for 2 weeks followed by 10 MU three times weekly for 6 weeks). Eight patients were treated with steroids (n=4) or steroids plus cyclophosphamide (n=4) after not responding to IFN.

^kArticle defined this outcome as stabilization or improvement in kidney function.

^lArticle defined this outcome as 50% reduction in proteinuria.

^mIFN was discontinued in one patient due to psychosis and psychiatric admission, but dose of IFN at the time of the adverse event was not documented.

Table 26 | Continued

^mThirteen total patients are described. Four received both IFN and prednisone sequentially after not responding to first treatment with three patients receiving the prednisone first.

ⁿCreatinine results reported for five patients where steroids were 'effective.' Improvements were seen in two of these five patients. Owing to lack of reporting, it is assumed that the remaining six patients did not have decreased creatinine.

^oPatient 2 did not tolerate IFN (adverse event not documented) and received RBV monotherapy for entire treatment course.

^pDuration of treatment based on HCV genotype.

^qIncrease in GFR of 10% was used as a surrogate marker for decreased serum creatinine of $18 \mu\text{mol l}^{-1}$. Patients (100%) had either stabilization or improvement of GFR after treatment.

^rReduction in proteinuria to less than 0.5 g in six patients. Patient 7 continued to have nephrotic-range proteinuria (4.6 g) but improved from pretreatment 10 g day^{-1} .

^sIFN discontinued for one patient who continued RBV for remainder of study.

^tPatients 1 and 2 were previously treated with IFN, pegylated IFN, and/or cyclophosphamide. The other patients had not received previous treatment.

^uPatients 3 and 5 were retreated for a second 1-month course due to recurrent proteinuria with improvement. The results reported include the effect of this second treatment.

^vOf four patients reported, three were treated.

^wEach patient followed for a different duration.

^xPatient 3 became HCV RNA-negative at the end of treatment, but follow-up RNA results were not documented.

Table 27 | Summary table of adverse events of treatment in HCV-associated glomerular disease

Author (year), country, study design	N	Mean follow-up post-treatment (months)	Intervention		Treatment discontinued due to adverse events	Quality	
			Dose	Duration of therapy (months)			
Mazzaro (2000), ³⁹² Italy, RCT Prospective	6 7	12	Prednisone: 0.2 mg kg ⁻¹ day ⁻¹ IFN: 3 MU	6	None 1 (14%) thrombocytopenia 'flu-like symptoms in most patients'	0 1 (14%)	B
Alric (2004), ³⁸⁰ France Prospective	18	24	IFN: 3 MU+RBV: 600–1000 mg day ⁻¹ (n=14) PEG-IFN: 1.5 µg kg ⁻¹ week ⁻¹ +RBV 600–1000 mg day ⁻¹ (n=4)	18	8 (44%) anemia	0	C
Johnson (1994), ³⁶⁷ United States, Retrospective	19	ND	IFN: 3 MU	6–12	1 (5%) neuropathy 1 (5%) erythema multiforme 1 (5%) progression to HD	3 (16%)	C
Beddhu (2002), ³⁹³ United States, Retrospective	11 ^a	27	IFN: 3 or 10 MU ^b	12 ^b	2 (18%) flu-like syndrome 1 (9%) psychosis	1 (9%)	C
	4		Prednisone	ND	2 Cushing's syndrome ^c 1 pancreatitis	ND	
	4		Cyclophosphamide+ prednisone	ND	2 neutropenia ^c 1 pneumonia	ND	
Bruchfield (2003), ³⁸¹ Sweden, Retrospective	7	12–32	IFN: 3 MU+RBV (n=4) PEG-IFN+RBV (n=2) RBV (n=1) ^d	6 (n=5) 12+(n=2)	5 (71%) anemia 7 (100%) fever 3 (43%) hyperuricemia	0 ^d	C
Stehman-Breen (1995) ³⁷⁰ United States, Retrospective (case reports)	3 ^e	6	IFN: 3 MU	2, 4, 6 ^f	1 (33%) fatigue, nausea, difficulty managing volume status	1 (33%)	C

Abbreviations: HCV, hepatitis C virus; HD, hemodialysis; IFN, interferon; MU, million units; NA, not applicable; ND, not documented; NS, not significant; PEG-IFN, pegylated IFN; RBV, ribavirin; RCT, randomized controlled trial. ^aN is the number of HCV-positive patients in the study. The total N is 17. Data reported are that of the HCV-positive patients only.

^bAll HCV-positive patients (n=11) initially treated with 3 MU IFN for 12 months. Four of those who did not respond or who relapsed were administered high-dose IFN (10 MU daily for 2 weeks followed by 10 MU three times weekly for 6 weeks). Eight patients were treated with steroids (n=4) or steroids plus cyclophosphamide (n=4) after not responding to IFN.

^cAdverse events reported for entire cohort of HCV-positive and HCV-negative patients. We report overall occurrence of adverse events but without percentages.

^dPatient 2 did not tolerate IFN treatment (adverse event not documented), so it was discontinued and, in turn, patient received RBV monotherapy for entire treatment course.

^eOf four patients reported, three were treated.

^fEach patient followed for a different duration.

Table 28 | Evidence profile for effect of treatment of HCV-associated glomerular disease

Outcome	No. of studies and study design	Total N of patients	Methodologic quality of studies	Consistency across studies	Directness of the evidence, including applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative description of effect	Importance of outcome
SVR	1 RCT 1 prospective 5 retrospective (low)	100	Some limitations (–1) ^a	Important inconsistencies (–1) ^b	Some uncertainty about directness of evidence (–1)		Very low	Range of SVR for IFN was 0–71% SVR for prednisone was 0% SVR for cyclophosphamide and prednisone was 0% SVR was not reported for rituximab SVR for control patients treated with antiplatelet drugs was 0%	High
Doubling of creatinine, or HD	1 Prospective 4 retrospective (low)	51	Some limitations (–1) ^a	Important inconsistencies (–1) ^b	Some uncertainty about directness of evidence (–1)		Very low	Range of doubling of creatinine or progression to HD for IFN was 0–9% Doubling of creatinine or progression to HD for prednisone was 75% Doubling of creatinine or progression to HD for cyclophosphamide and prednisone was 25% Doubling of creatinine or progression to HD for rituximab was 0% Doubling of creatinine or progression to HD for control patients treated with antiplatelet drugs was not documented	High
↓ in serum creatinine by ≥18 μmol l ^{–1}	1 RCT 1 prospective 5 retrospective (low)	80	Some limitations (–1) ^a	Important inconsistencies (–1) ^b	Some uncertainty about directness of evidence (–1)		Very low	Range of decreased serum creatinine for IFN 0–67% Range of decreased serum creatinine with prednisone was 0–25% Decreased serum creatinine with cyclophosphamide and prednisone was 75% Decreased serum creatinine with rituximab was 60% Decreased serum creatinine for control patients treated with antiplatelet drugs was not documented.	Moderate
↓ in proteinuria to <1.0 g per 24 h	1 RCT 1 prospective 5 retrospective (low)	80	Some limitations (–1) ^a	Important inconsistencies (–1) ^b	Some uncertainty about directness of evidence (–1)		Very low	Range of decreased proteinuria for IFN was 0–86% Range of decreased proteinuria for prednisone was 0–45% Decreased proteinuria for cyclophosphamide and prednisone was 25% Decreased proteinuria for rituximab was 100% Decreased proteinuria for control patients treated with antiplatelet drugs was 17%	Moderate
Treatment discontinued due to adverse events	1 RCT 2 prospective 4 retrospective (low)	89	Some limitations (–1) ^a	Important inconsistencies (–1) ^b	Some uncertainty about directness of evidence (–1)		Very low	Range of discontinuation due to adverse events for IFN was 0–33% Discontinuation due to adverse events for prednisone was 0% Discontinuation due to adverse events for cyclophosphamide and prednisone was not documented Discontinuation due to adverse events for rituximab was 0% Discontinuation due to adverse events for control patients treated with antiplatelet drugs was not documented.	Moderate
Total N		100							
Balance of benefit and harm: Unable to assess the balance between benefit and harm ^c							Quality of overall evidence: Very low		

CKD, chronic kidney disease; F/U, follow-up; HD, hemodialysis; ND, no data; RCT, randomized controlled trial; SVR, sustained virologic response; Tx, treatment.

^aReporting bias, publication bias, small sample sizes, and inconsistent definitions of outcomes.

^bHeterogeneous treatment and inconsistent reporting of outcomes.

^cBecause of very low quality.

Appendix 1: Liver biopsy in patients with CKD

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Liver biopsy is essential in the evaluation of patients with liver disease. This is not without risk and complications; however, they are uncommon and, fortunately, usually respond to conservative management (Rockey DC, Caldwell SH, Goodman ZD *et al.* Liver biopsy. AASLD Practice Guidelines. *Hepatology*, in press). Coagulopathy due to hepatocellular dysfunction and thrombocytopenia due to portal hypertension and hypersplenism are major concerns for an increased bleeding risk in patients with more clinically overt liver disease.³⁹⁵ Routine hematologic evaluation before liver biopsy includes reviewing the results of a recent international normalized ratio (INR) and platelet count. Drugs with antiplatelet activity, such as ticlopidine, aspirin, and nonsteroidal anti-inflammatories, need to be discontinued for at least 7 days before biopsy. Warfarin therapy should be discontinued for 3–5 days with documented normalization of INR. Typically, a platelet count <50 000 and an INR >1.5 are regarded as contraindications to blind percutaneous liver biopsy (Rockey DC, Caldwell SH, Goodman ZD *et al.* Liver biopsy. AASLD Practice Guidelines. *Hepatology*, in press). However, there is a controversy in recent medical literature about whether any platelet count level or INR derangement truly separates out those patients with liver disease most likely to bleed after liver biopsy.³⁹⁶

A study performed in the early 1980s in 200 patients undergoing laparoscopic liver biopsy with direct visualization of the site failed to establish any relationship between duration and extent of bleeding and prothrombin times, platelet count, or whole clot time.³⁹⁷ Recently, a systematic review of bleeding, including that associated with liver biopsy, also failed to establish a relationship between risk and conventional tests of coagulation.³⁹⁶ Although attempts at correction of coagulopathy with plasma replacement are common, there is also a lack of evidence that they reduce the risk of bleeding. This uncertainty has prompted a multicenter NIH-funded trial in the United States of plasma replacement in patients with an INR of 1.3–1.9 undergoing invasive hepatic procedures, and this should help determine whether plasma replacement is indicated to reduce the risk of post-liver biopsy bleeding.³⁹⁸ Even with a normal INR and platelet count, there remains a concern about performing liver biopsy because of platelet dysfunction associated with uremia (Rockey DC, Caldwell SH, Goodman ZD *et al.* Liver biopsy. AASLD Practice Guidelines. *Hepatology*, in press). As with most of the other literature regarding liver biopsy, it is impossible to quantify the increased risk, if any, related to uremic platelet dysfunction. Although not supported by data on efficacy, there has been increasing use of desmopressin acetate (also known as DDAVP) (0.3 µg per kg body weight)

infused immediately before liver biopsy in patients with CKD, although no specific serum level of creatinine or degree of reduction in GFR is currently determined for the use of DDAVP.³⁹⁹ The presence of a prolonged INR and/or a platelet count below 100 000 in a patient with liver disease are generally reliable indicators of underlying cirrhosis and may obviate the need for liver biopsy to determine histologic severity in a patient with HCV.

The majority of liver biopsies are currently obtained by the percutaneous transthoracic route. Ultrasound is being increasingly performed to identify the optimal biopsy site, although it remains controversial whether this maneuver increases the safety of the procedure.^{400,401} Typically, transvenous liver biopsy, via the transjugular or transfemoral route, is used in the presence of ascites, coagulopathy, or thrombocytopenia of such severity that a percutaneous approach is considered to be contraindicated, or when additional diagnostic information is required—notably, free and hepatic wedge pressures—to confirm the presence of portal hypertension.

Liver biopsy in patients with chronic HCV infection is indicated not only to assess disease severity with particular attention to the amount of fibrosis and necroinflammatory activity but also to exclude other concomitant causes of hepatic dysfunction, such as nonalcoholic fatty liver disease. A sufficiently large core of tissue is crucial for adequate interpretation to reduce sampling error. Gauge 16 or larger biopsy needles are recommended, ideally with a minimum length of 2.0–2.5 cm, to reduce sampling error. One study evaluated the accuracy of quantification of fibrosis based on biopsy core size, correlating an automated image analysis technique with Metavir score on hepatic resection specimens.⁴⁰² A core length of 2.5 cm allowed a more accurate assessment of fibrosis compared to smaller specimens. Smaller specimens may fail to identify serious liver disease in 20% of patients with liver disease based on a core length of 1.5 cm (Rockey DC, Caldwell SH, Goodman ZD *et al.* Liver biopsy. AASLD Practice Guidelines. *Hepatology*, in press).²⁸⁴ Sampling error is an important concern. A study performed laparoscopic liver biopsies from the right and left lobes of 124 patients with chronic HCV.²⁸⁴ Liver biopsy stage varied by at least 1 on a scale of 0–4 in one-third of patients between the two lobes. Furthermore, in 18 patients (14%), cirrhosis was diagnosed in one lobe, but only stage 3 was observed in the other lobe. Reassuringly, a difference of two stages was observed only in a small minority of patients (3 (2.4%)), suggesting that although there may be intrahepatic variation in histologic severity, it does not usually exceed one stage. To accurately assess the severity of HCV infection, a minimum

of 11 portal tracts are necessary.⁴⁰³ Guidelines on liver biopsy developed by the AASLD recommend a biopsy core that is ideally 3 cm long obtained by a 16-gauge needle (Rockey DC, Caldwell SH, Goodman ZD *et al.* Liver biopsy. AASLD Practice Guidelines. *Hepatology*, in press). Irrespective of who is performing the biopsy, it is imperative that an adequate core of tissue be obtained.

To ensure reproducibility of liver biopsy interpretation, a number of scoring systems have been devised in an attempt to quantify inflammation and fibrosis. An early attempt was a complex scoring system,⁴⁰⁴ and it was the basis for the subsequent Ishak system.⁴⁰⁵ The two most commonly used scoring systems at present are Metavir⁴⁰⁶ and Ishak. The Metavir system assigns a score of 0–4 for fibrosis, whereas the Ishak system scores fibrosis from 0 to 6 ranging from no fibrosis to established cirrhosis (Table 29).⁵⁹ The simpler I–IV scoring system of Metavir has found favor with many pathologists for routine diagnostic use, whereas the more complex Ishak system has found application in large clinical trials of antiviral agents. In case of diagnostic uncertainty, consultation should be sought from a pathologist with expertise in liver biopsy, as up to 25% of cases reviewed by a hepatopathologist at a referral center has led to a substantial

change in interpretation.⁴⁰⁷ Although there is currently considerable interest in noninvasive markers of hepatic fibrosis, they generally are most accurate in patients with either no fibrosis or advanced fibrosis.⁴⁰⁸ There is no information about their use in patients with HCV and CKD, and for now the prognostic information afforded by liver biopsy remains unsurpassed.⁴⁰⁹

Table 29 | Histologic scoring systems of liver fibrosis

Stage	Metavir system	Ishak system
0	No fibrosis	No fibrosis
1	Periportal fibrosis expansion	Fibrous expansion of some portal areas, with or without short fibrous septa
2	P-P septae (> 1 septum)	Fibrous expansion of most portal areas, with or without short fibrous septae
3	P-C septae	Fibrous expansion of most portal areas with occasional P-P bridging
4	Cirrhosis	Fibrous expansion of portal areas with marked bridging (P-P or P-C)
5	—	Marked bridging (P-P or P-C) with occasional nodules (incomplete cirrhosis)
6	—	Cirrhosis

P-C, portal-central; P-P, portal-portal.
Adapted with permission from Strader *et al.*⁵⁹
(<https://www.aasld.org/eweb/docs/hepatitisc.pdf>).

Appendix 2: Methods for guideline development

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AIM

The overall aim of the project was to create a set of guidelines for the prevention, diagnosis, evaluation, and treatment of HCV in CKD. The Work Group sought to create the guidelines using an evidence-based approach. After topics and relevant clinical questions were identified, the available scientific literature on those topics was systematically searched and summarized. The content and strength of the guidelines were based on the evidence, the strength and quality of the evidence and—where evidence was poor or lacking—on the expertise of the Work Group.

OVERVIEW OF PROCESS

The creation of the guidelines included concurrent steps.

- Form the Work Group of domain experts and liaisons, and the Evidence Review Team of experts in the methodology of evidence-based guideline development.
- Confer to discuss process, methods, and results.
- Develop and refine topics.
- Define specific populations, interventions or predictors, and outcomes of interest.
- Formulate key questions to be addressed.
- Create and standardize evidence quality assessment methods.
- Create data extraction forms.
- Develop literature search strategies and run searches.
- Screen abstracts and retrieve full articles based on predetermined eligibility criteria.
- Extract data and perform critical appraisal of the literature.
- Grade quality of each study.
- Tabulate data from articles into summary tables.
- Grade the quality of evidence for each outcome and assess the overall quality of bodies of evidence with the aid of Evidence Profiles.
- Write guideline recommendations and supporting rationale text.
- Grade the strength of the recommendations.

The Work Group, KDIGO Co-Chairs, Evidence Review Team, liaisons, and the National Kidney Foundation (NKF) support staff met for four 2-day meetings for training in the guideline development process, topic discussion, consensus development, and guideline approval. The guidelines were also presented to and reviewed by the KDIGO Executive Committee and then subjected to a public review process.

Creation of groups

The KDIGO Co-Chairs appointed two work group co-chairs who then assembled the Work Group responsible for the development of the guidelines. The Work Group consisted of

domain experts, including individuals with expertise in nephrology, hepatology, pathology, immunology, virology, and hepatitis C disease specifically. The Work Group members were chosen to represent a range of expertise and of countries. In addition, liaisons from the CDC, WHO, and the NIH (National Institute of Diabetes and Digestive and Kidney Diseases) also participated in the Work Group discussions. For support in evidence review, methods expertise, and guideline creation, the NKF contracted with an Evidence Review Team based primarily at the Center for Clinical Practice Guideline Development and Implementation at Tufts-New England Medical Center (Boston, MA, USA). The Evidence Review Team also included methodology, nephrology, and infectious disease experts at the University of Sydney (Sydney, NSW, Australia), and the University of Ioannina School of Medicine (Ioannina, Greece). The Work Group and the Evidence Review Team collaborated closely throughout the project.

The first task of the Work Group was to define the overall topics and goals for the guidelines. Groups of 4–7 individuals were formed and assigned to each topic. The Work Group and Evidence Review Team then further developed and refined each topic, specified screening criteria (Table 30), literature search strategies, and data extraction forms. The Work Group members were the principal reviewers of the literature, and from their reviews and detailed data extractions, they summarized the available evidence and took the primary roles of writing the guidelines and rationale statements.

The Evidence Review Team consisted of physician methodologists with expertise in nephrology, infectious disease, and internal medicine, and research assistants. It instructed and coordinated the Work Group members in all steps of systematic review, critical literature appraisal, and guideline development. The Evidence Review Team also coordinated the methodologic and analytical process of the report, and defined and standardized the methodology of performing literature searches, data extraction, and summarizing the evidence. It performed literature searches, assisted in development of topic and search criteria, organized abstract and article screening, created forms to extract relevant data from articles, organized data extraction for the Work Group members, tabulated and confirmed results, assisted with grading the strength of the evidence, and offered suggestions for guideline development. The Evidence Review Team also performed analyses for selected topics. Throughout the project, the Evidence Review Team led discussions on systematic review, literature searches, data extraction, assessment of quality of articles, evidence synthesis, grading the quality of evidence and the strength of guideline recommendations, and the consensus development process for guideline creation.

Table 30 | Systematic review topics and screening criteria^a

<i>Guideline 1.1</i>	<i>Determining which CKD patients should be tested for HCV</i>
Population	All CKD stages
Predictor, reference standard	EIA, NAT (not liver biochemical tests or HCV core antigen)
Outcomes	Test performance characteristics
Study design	Cross-sectional; prospective or retrospective
No. of subjects	No minimum
<i>Guideline 1.2</i>	<i>HCV testing for patients on maintenance hemodialysis</i>
Population	All CKD stages
Intervention, reference standard	EIA, NAT (not liver biochemical tests or HCV core antigen)
Outcomes	Test performance characteristics
Study design	Cross-sectional or longitudinal; prospective or retrospective
No. of subjects	No minimum
<i>Guideline 2.1</i>	<i>Evaluation of HCV-infected CKD patients for antiviral treatment</i>
Population	All CKD stages
Intervention	IFN, ribavirin, pegylated IFN
Outcomes	Mortality, SVR, adverse events (not change in liver biochemical tests or liver histology)
Study design	RCTs and prospective interventional studies
No. of subjects	≥10
<i>Guideline 2.2</i>	<i>Basing HCV treatment on CKD stage</i>
Population	All CKD stages
Intervention	IFN, ribavirin, pegylated IFN
Outcomes	Mortality, SVR, adverse events (not change in liver biochemical tests or liver histology)
Study design	RCTs and prospective interventional studies
No. of subjects	≥10
<i>Guideline 2.3</i>	<i>Monitoring the response to HCV treatment in CKD patients</i>
Population	All CKD stages
Intervention	IFN, ribavirin, pegylated IFN
Outcomes	Mortality, SVR, adverse events (not liver biochemical tests or change in liver histology)
Study design	RCTs and prospective interventional studies
No. of subjects	≥10
<i>Guideline 3</i>	<i>Preventing HCV transmission in hemodialysis units</i>
Population	CKD Stage 5 dialysis
Predictor	Possible new HCV infection in hemodialysis unit
Outcomes	Molecular epidemiology of HCV outbreak
Study design	Cross-sectional or longitudinal; prospective or retrospective; must report phylogenetic analysis of HCV strains and detailed description of proposed epidemiologic mechanisms of HCV transmission (excluded articles where there was no phylogenetic analysis or where there was phylogenetic analysis but no data on epidemiology)
No. of subjects	No minimum

Refinement of topics and development of materials

The Work Group Co-Chairs prepared the first draft of the scope of work document as a series of open-ended questions to be considered by the Work Group members. At their first 2-day meeting, members added further questions until the initial working document included all topics of interest to the Work Group. The inclusive, combined set of questions formed the basis for the deliberation and discussion that followed. The

Table 30 | Continued

<i>Guideline 4.1</i>	<i>Evaluation and management of kidney transplantation candidates regarding HCV infection^b</i>
Population	Kidney transplantation candidates
Intervention, predictor	Transplantation (vs remaining on kidney transplant waiting list); use of HCV-positive donors
Outcomes	Adjusted mortality, graft survival
Study design	Longitudinal; prospective or retrospective
No. of subjects	≥100
<i>Guideline 4.2</i>	<i>Use of kidneys from HCV-infected donors</i>
Population	Kidney transplant recipients
Predictor	HCV-infected kidney transplant donors (vs. noninfected donors)
Outcomes	Adjusted mortality and graft survival
Study design	Longitudinal; prospective or retrospective
No. of subjects	≥100
<i>Guideline 4.3</i>	<i>Use of maintenance immunosuppressive regimens</i>
Population	Kidney transplant recipients
Intervention	Immunosuppressive regimen
Outcomes	Mortality, graft survival
Study design	Longitudinal; prospective or retrospective
No. of subjects	No minimum
<i>Guideline 4.4</i>	<i>Management of HCV-related complications in kidney transplant recipients</i>
	Covered by searches for Guidelines 2.1, 2.2, and 5
<i>Guideline 5 (background)</i>	<i>Diagnosis of kidney diseases associated with Hepatitis C</i>
Population	All CKD stages
Predictor	HCV infection
Outcome	Prevalence of kidney pathology (excluding autopsy studies)
Study design	Cross-sectional; prospective or retrospective
No. of subjects	No minimum
<i>Guideline 5 (management)</i>	<i>Management of kidney diseases associated with Hepatitis C</i>
Population	All CKD stages
Intervention	IFN, ribavirin, pegylated IFN, corticosteroids, immunosuppressive agents
Outcome	Change in kidney function, change in proteinuria, HCV RNA, treatment discontinuation due to adverse events
Study design	RCTs and prospective interventional studies
No. of subjects	No minimum

CKD, chronic kidney disease; EIA, enzyme immunoassay; HCV, hepatitis C virus; IFN, IFN; NAT, nucleic acid testing; RCT, randomized controlled trial; SVR, sustained virologic response.

^aScreening for all topics included a minimum duration of 6 months (exceptions allowed) and publication dates from 1989 onwards.

^bGuideline 4.1 was a partial systematic review. The topic was determined to be of interest late in the guideline development process; thus a limited systematic review using the above criteria was performed.

Work Group strove to ensure that all topics deemed clinically relevant and worthy of review were identified and addressed.

On the basis of the list of topics, the Work Group and Evidence Review Team developed (i) draft guideline statements; (ii) draft rationale statements that summarized the expected pertinent evidence; and (iii) specific research questions for which systematic review would be performed. For each systematic review topic, the Work Group Co-Chairs

and the Evidence Review Team formulated well-defined systematic review research questions using a well-established system.⁴¹⁰ For each question, clear and explicit criteria were agreed on for the population, intervention or predictor, comparator, and outcomes of interest. Each factor was defined as comprehensively as possible. In general, hard clinical outcomes (such as death or clinical events) were favored over intermediate outcomes (such as laboratory values). In addition, study eligibility criteria were decided on the basis of study design, minimal sample size, minimal follow-up duration, and year of publication, as indicated. The specific criteria used for each topic are described in Table 30. In general, eligibility criteria were determined on the basis of clinical value, relevance to the guidelines and clinical practice, whether a set of studies would affect the guidelines or the strength of evidence, and practical issues such as available time and resources. For example, for topics where randomized trials were known to exist, retrospective or non-comparative studies may have been excluded.

Literature search and article selection

A search through MEDLINE and the *Cochrane Database of Systematic Reviews* was performed to capture all abstracts and articles relevant to the topic of hepatitis C and CKD. The search was updated through 2 January 2007 and supplemented by articles identified by the Work Group members through May 2007. Search terms included kidney, kidney disease, renal replacement therapy, hepatitis C, specific treatments for hepatitis C, and related terms (see Appendix 3). The search was limited to publications since 1989, but not by language.

During citation screening, only full journal articles of original data were included. Editorials, letters, abstracts, single case reports, unpublished reports, and articles published in non-peer-reviewed journals were not included. Selected review articles and key meta-analyses were retained from the searches for background and supplementary material.

MEDLINE search results were screened by members of the Evidence Review Team for relevance using the predefined eligibility criteria. Retrieved articles were screened by the Evidence Review Team. Potentially relevant studies were sent to the Work Group members for rescreening and data extraction, when appropriate. Domain experts (Work Group members), with the assistance of the Evidence Review Team, made the final decision for the inclusion or exclusion of all articles. The same eligibility criteria and processes were applied to articles found by electronic literature search or identified by the Work Group members.

The Work Group members had latitude to review and cite other articles that did not meet the systematic review eligibility criteria. These may have included other narrative and systematic reviews, articles on related topics, studies of other populations, interventions or outcomes, and opinion pieces. However, these articles were not included among the

tabulated studies or considered in evaluating the strength and quality of the evidence.

Data extraction

The Evidence Review Team designed data extraction forms to capture information on various aspects of primary studies. Data fields for all topics included study setting, patient demographics, eligibility criteria, stage of kidney disease, number of subjects, study design, study funding source, description of HCV, descriptions of relevant risk factors or interventions, description of outcomes, statistical methods, results, study quality, and free-text fields for comments and assessment of biases. Training of the Work Group members to extract data from primary articles took place during Work Group meetings and by e-mail and teleconferences. The Work Group members performed primary data extraction of articles.

The Evidence Review Team reviewed and confirmed data extraction and whether the study met eligibility criteria. Discrepancies were resolved with the relevant Work Group members. The Evidence Review Team subsequently condensed the information from the data extraction forms. These condensed forms were returned to the Work Group members to assist them with a review of the evidence. All extracted articles and extraction forms were made available to all the Work Group members.

Summary tables

Summary tables describe the studies according to four dimensions: study size, follow-up duration, results, and methodologic quality. The Evidence Review Team generated summary tables using data from extraction forms and, when necessary, the articles. All summary tables were reviewed by the Work Group members.

In the summary tables, studies were ordered first by subtopic (for example, specific outcome), then by methodologic quality (good to poor), and finally by study size (largest to smallest). Results are presented in their appropriate metric or summary symbols, as defined in the table footnotes.

To provide consistency throughout the summary tables, data were sometimes converted or estimated. All estimated values have been annotated as such.

Baseline characteristic tables

Tables were created to record key descriptive characteristics of the study population. These characteristics include age, race, percentage of men, duration of hemodialysis (where relevant), duration of hepatitis C infection, and genotype distribution within the study population.

Literature yield

The literature searches yielded 2435 citations. Of these, 155 articles were reviewed in full. An additional 36 were added by the Work Group members and reviewed in full. Of the total 191 articles, 113 were extracted by the Work Group members.

Table 31 | Literature search yield of primary articles for systematic review topics

Guideline topic	Search strategy	Abstracts screened in	Full articles retrieved	Articles added by experts	Articles data extracted	Articles included in summary tables ^a
Guideline 1	Kidney and hepatitis C	71	31	4	31	19
Guideline 2	Kidney and hepatitis C	80	39	8	32	24
Guideline 3	Kidney and hepatitis C	87	36	5	26	20
Guideline 4	Kidney and hepatitis C	54	26	18	22	22
Guideline 5	Kidney and hepatitis C	29	23	1	21	7

^aDoes not include articles included in tables other than summary tables or that may have been used as background material in the text.

Of these, 93 studies were included in the summary tables. Details of the yield by topic can be found in Table 31.

Evaluation of individual studies

Study size and duration. The study (sample) size is used as a measure of the weight of the evidence. In general, large studies provide more precise estimates of prevalence and associations. In addition, large studies are more likely to be generalizable; however, large size alone does not guarantee applicability. A study that enrolled a large number of selected patients may be less generalizable than several smaller studies that include a broad spectrum of patient populations. Similarly, longer duration studies may be of better quality and more applicable, depending on other factors.

Methodologic quality. Methodologic quality (internal validity) refers to the design, conduct, and reporting of the clinical study. As studies with a variety of types of design were evaluated, a three-level classification of study quality was used. This classification system has been used for the KDOQI guidelines with which the Tufts-New England Medical Center Evidence Review Team was also associated:

(A) **Good quality:** Least bias; results are valid. A study that mostly adheres to the commonly held concepts of high quality, including the following: a formal study design; clear descriptions of the population, setting, intervention, reference standard, and outcome; proper measurement techniques; appropriate statistical and analytical methods; no reporting errors; no obvious bias. Not retrospective or case series

(B) **Fair quality:** Susceptible to some bias, but not sufficient to invalidate the results. A study that does not meet all the criteria of a good quality study. There are some deficiencies, but none likely to cause major bias

(C) **Poor quality:** Significant bias possible that may invalidate the results. A study with serious errors in design or reporting. These studies may have large amounts of missing information or discrepancies in reporting

The evaluation of questions of interventions included RCTs as well as longitudinal studies. The grading of these studies included a consideration of the methods (that is, duration, degree of blinding, number and reasons for drop outs, and so on), population (that is, does the population studied introduce bias?), outcomes (that is, are the outcomes clearly defined and

properly measured?), thoroughness/precision of reporting, statistical methods (that is, was the study sufficiently powered and were the statistical methods valid?), and the funding source.

Results. The type of results used from a study was determined by the study design, the purpose of the study, and the question(s) being asked for which the results were used. Decisions were based on the screening criteria and outcomes of interest.

Statistical analyses

For the majority of topics, no meta-analyses or other statistical analyses of the studies were conducted. However, for the evaluation of the sensitivity and specificity of EIA compared to NAT for the diagnosis of HCV infection in patients on hemodialysis, various analytical techniques were used.

Studies of second- and third-generation EIA vs NAT were graphed in receiver operating characteristics space (Guideline 1, Figure 1). Qualitative evaluations were performed to determine possible associations between test accuracy and EIA generation, hepatitis C prevalence, study location, and study quality. To assist with the determination of which test may be most appropriate in different settings, graphs of the predictive values of EIA were plotted assuming different test accuracy measurements (Guideline 1, Figure 2). These graphs plotted the pretest estimate of hepatitis C prevalence vs the post-test estimate of prevalence given either a positive or negative test. Three scenarios were tested on the basis of the available studies: those of relatively high specificity and low sensitivity, relatively moderate specificity and sensitivity (which approximated the meta-analyzed summary sensitivity and specificity estimates), and relatively low specificity and high sensitivity. The pre- and post-test estimates for a negative EIA were plotted for a sample of prevalence estimates from the DOPPS study⁴⁰ and from a representative higher prevalence setting (40%).

Rating the quality of evidence and the strength of guideline recommendations

A structured approach, facilitated by the use of evidence profiles and modeled after the GRADE approach,^{101,411} 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 overall evidence and the strength of the recommendations was led by the primary expert reviewer of each topic, with participation by the Work Group chairs, all other Work Group members, and the Evidence Review Team.

Grading the quality of evidence for each outcome. The quality of a body of evidence pertaining to each separate outcome of interest was initially categorized on the basis of study design. For questions of interventions, the initial quality grade was ‘high’ if the body of evidence consisted of RCTs; ‘low’ if it consisted of observational studies; or ‘very low’ if it consisted of studies of other study designs. However, intervention studies of HCV-infected hemodialysis patients that used a prospective, nonrandomized study design were not downgraded because the Work Group determined that the rate of spontaneous HCV clearance in untreated patients was very low; thus, the effects found in these studies were similar in strength to the effects found in randomized trials.

The evidence quality grade for each intervention/outcome pair was then decreased if there were serious limitations to the methodologic 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 limitations to the applicability of the findings to the population of interest; if the data were imprecise or sparse; or if there was thought to be a high likelihood of bias (Table 32). The final grade for the quality of evidence for an intervention/outcome pair could be one of the following four grades: high, moderate, low, or very low.

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 by taking into account explicit judgments about the relative importance of each of the outcomes. The actual results were reviewed for each outcome to judge the balance between benefits and harm. When there was evidence to determine the balance of medical benefits and harm of an intervention to a patient, one of the four conclusions was drawn (Table 33). Four final categories for the quality of overall evidence were used, as defined in Table 32.

Table 33 | Balance of benefit and harm

<i>Net benefits</i>	=the intervention clearly does more good than harm
<i>Trade-offs</i>	=there are important trade-offs between the benefits and harm
<i>Uncertain trade-offs</i>	=it is not clear whether the intervention does more good than harm
<i>No net benefits</i>	=the intervention clearly does not do more good than harm

When data were missing on important benefits or harm (for example, the risk of misclassification as a result of variable performance characteristics of EIA), the expected consequences or potential benefits and harm were described in the Evidence Profile, and the uncertainty in the quality of the evidence was accounted for.

Evidence profiles were constructed by the Evidence Review Team to record decisions about grades and summary effects by the Work Group members. These profiles serve to make transparent to the reader the thinking process of the Work Group in systematically combining evidence and judgments. Each Evidence Profile was filled in by the Work Group experts with Evidence Review Team guidance. Decisions were

Table 32 | GRADE system for grading quality of evidence

Step 1: Starting grade for quality of evidence based on study design

Randomized trials	=High
Observational study	=Low
Any other evidence	=Very low

Step 2: Reduce grade

Study quality	–2 levels if very serious limitations –1 level if serious limitations
Consistency	–1 level if important inconsistency
Directness	–2 levels if major uncertainty –1 level if some uncertainty
Other considerations	–1 level if sparse or imprecise data –1 level if high probability of reporting bias

Step 3: Raise grade

Strength of association	+2 levels if very strong, ^a no major threats to validity +1 level if strong, ^b no plausible confounders +1 level if evidence of a dose-response gradient +1 level if all residual plausible confounders would have reduced the observed effect
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Final grade for quality of evidence and definition

High	=Further research is unlikely to change confidence in the estimate of the effect
Moderate	=Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	=Further research is very likely to have an important impact on confidence in the estimate and may change the estimate
Very low	=Any estimate of effect is very uncertain

GRADE, Grades of Recommendation, Assessment, Development and Evaluation; RR, relative risk.

^aVery strong evidence of association is defined as ‘significant RR of > 5 (<0.2)’ based on direct evidence with no major threats to validity.

^bStrong evidence of association is defined as ‘significant RR of > 2 (<0.5)’ based on consistent evidence from two or more observational studies, with no plausible confounders.

based on facts and findings from the primary studies listed in corresponding Summary Tables, and on judgments of the Work Group. Judgments about the quality, consistency, and directness of evidence were often complex as were the judgments about the importance of an outcome or the summary of effects sizes. The Evidence Profiles provided a structured approach to grading rather than a rigorous method of quantitatively summing up grades. In an effort to balance simplicity with full and transparent consideration of the important issues, footnotes were placed to provide the rationale for grading.

Grading the strength of the recommendations. Each rationale statement was graded according to the quality of evidence for each outcome on which it was based (as described above). The guideline recommendation was graded on the basis of the quality of the overall evidence in the supporting rationale statements as well as additional considerations (Table 34). At the final Work Group meeting, each guideline statement was discussed in relation to its evidence base. For each statement, the Work Group voted on the recommendation and the strength of the recommendation.

Table 34 | Levels of strength of recommendations

Strength of recommendation	Wording of recommendation	Basis for strength of recommendation
Strong	An intervention 'should' be done	'High' quality evidence and/or other considerations support a strong guideline
Moderate	An intervention 'should be considered'	'Moderate' quality evidence and/or other considerations support a moderate guideline
Weak	An intervention 'is suggested'	'Low' or 'Very Low' quality evidence; predominantly based on expert judgment for good clinical practice

Minority opinions were collected and added to the rationale section of each guideline. The strength of each statement was graded Strong, Moderate, or Weak. Strong recommendations are based on high-quality evidence and/or internationally

recognized standards of care supported by strong evidence-based guidelines developed by other bodies, as discussed further below. Strong recommendations state that an intervention 'should' be done. Moderate recommendations are based on moderate quality evidence together with internationally recognized standards of care based on other evidence-based guidelines of weaker strength than strong statements. Moderate recommendations state that an intervention 'should be considered.' Weak recommendations are based predominantly on a consensus in the Work Group for what it considers good clinical practice, when the supporting evidence is of 'low' or 'very low' quality, or where evidence was lacking. Weak guidelines state that an intervention 'is suggested.' In assigning a final strength to all recommendations, the Work Group considered the range of values, judgments, and preferences that users are likely to have. The Work Group also considered all suggestions made during the public review process of the guidelines by patients, clinicians, other individuals, and organizations from different settings and countries.

To incorporate recommendations from existing guidelines, the Work Group evaluated these guidelines to determine their strength. Only explicitly evidence-based guidelines were considered. Where the guidelines assigned grades to the strength of their recommendations, the supporting rationale was reviewed and, if accepted by the Work Group, the grades were adopted. When the guideline or its evidentiary basis was not graded, the Work Group assumed that the guideline was based on Moderate quality evidence.

Format for evidence-based guidelines

Each guideline contains one or more specific statements that represent recommendations to the target audience. Each statement incorporates the strength grade of that statement. The strength of the guideline is also indicated by the wording of the statements. The text following the statements includes the rationale as agreed upon by the Work Group for the set of guidelines, any necessary definitions, the evidentiary basis for the guideline (including the relevant summary tables and evidence profiles), any necessary further elaborations or caveats to the guidelines, and other issues related to implementation. A discussion of future research recommendations from the Work Group is presented at the end of each guideline chapter.

Appendix 3: Hepatitis C search strategy

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1. exp kidney disease/
2. exp kidney/
3. kidney.mp.
4. renal.af.
5. nephro\$.af.
6. exp renal replacement therapy/
7. exp kidney, artificial/
8. (hemodialy\$ or haemodialy\$ or dialy\$).af.
9. (hemofiltr\$ or haemofiltr\$).af.
10. or/1-9
11. exp Hepatitis C/
12. hepatitis c.mp.
13. hep c.tw.
14. HCV.af.
15. or/11-14
16. ribavirin.af.
17. IFN.af.
18. IFN.af.
19. pegylated IFN.af.
20. exp hepatitis/
21. (17 or 18) and 20
22. or/16,19,21
23. 10 and (15 or 22)
24. limit 23 to humans
25. limit 24 to (addresses or bibliography or biography or comment or dictionary or directory or editorial or festschrift or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or 'review' or review, academic or review, tutorial)
26. 24 not 25

Biographic and disclosure information

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Grant/research support: Genzyme

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Consultant: Novartis
Speaker: Astellas Pharma Inc.

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Grant/Research Support: Roche

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Speaker: Astellas Pharma Inc.; Novartis; Wyeth Pharmaceuticals

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Participation in the review does not necessarily constitute endorsement of the content of the report by the individuals or the organization or institution they represent.

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