KDIGO 2022 CLINICAL PRACTICE GUIDELINE UPDATE
FOR THE PREVENTION, DIAGNOSIS, EVALUATION, AND
TREATMENT OF HEPATITIS C
IN CHRONIC KIDNEY DISEASE

CONFIDENTIAL: DO NOT DISTRIBUTE

PUBLIC REVIEW DRAFT
FEBRUARY 2022
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tables and Figures</td>
<td>iii-iv</td>
</tr>
<tr>
<td>KDIGO Executive Committee</td>
<td>vi</td>
</tr>
<tr>
<td>Reference Keys</td>
<td>vii</td>
</tr>
<tr>
<td>CKD Nomenclature</td>
<td>viii</td>
</tr>
<tr>
<td>Conversion Factors</td>
<td>ix</td>
</tr>
<tr>
<td>Abbreviations and Acronyms</td>
<td>x</td>
</tr>
<tr>
<td>Notice</td>
<td>xi</td>
</tr>
<tr>
<td>Foreword</td>
<td>xii</td>
</tr>
<tr>
<td>Work Group Membership</td>
<td>xiii</td>
</tr>
<tr>
<td>Abstract</td>
<td>xiv</td>
</tr>
<tr>
<td>Summary of Recommendation Statements</td>
<td>xv</td>
</tr>
<tr>
<td>Chapter 2: Treatment of HCV Infection in Patients with CKD</td>
<td>1</td>
</tr>
<tr>
<td>Chapter 4: Management of Patients with HCV before and after Kidney Transplantation</td>
<td>24</td>
</tr>
<tr>
<td>Chapter 5: Diagnosis and Management of Kidney Diseases Associated with HCV Infection</td>
<td>48</td>
</tr>
<tr>
<td>Methods for Guideline Development</td>
<td>72</td>
</tr>
<tr>
<td>Appendix 1</td>
<td>92</td>
</tr>
<tr>
<td>Disclosure Information</td>
<td>96</td>
</tr>
</tbody>
</table>
TABLES

Table 1. Direct-acting antiviral (DAA) regimens with evidence of effectiveness for various CKD populations.... 3
Table 2. Systematic review topics and screening criteria................................................................. 74
Table 3. Hierarchy of outcomes........................................................................................................ 76
Table 4. Work products for the guideline.......................................................................................... 79
Table 5. Classification of study quality............................................................................................ 80
Table 6. GRADE system for grading quality of evidence................................................................. 82
Table 7. Final grade for overall quality of evidence......................................................................... 83
Table 8. Balance of benefits and harms........................................................................................... 83
Table 9. KDIGO nomenclature and description for grading recommendations................................. 84
Table 10. Determinants of strength of recommendation................................................................. 85
Table 11. The Conference on Guideline Standardization (COGS) checklist for reporting clinical practice guidelines................................................................................................................. 87
FIGURES

Figure 1. Summary of currently available DAA treatment targets on HCV life cycle ........................................... 6
Figure 2. Proposed strategy in a HCV-infected kidney transplant candidate .......................................................... 29
Figure 3. Indications for biopsy in patients with HCV and severe glomerulonephritis ........................................... 50
Figure 4. Search yield.................................................................................................................................................. 78
APPENDIX

Appendix 1. Online search strategies ........................................................................................................ 92
KDIGO EXECUTIVE COMMITTEE

Garabed Eknoyan, MD
Norbert Lameire, MD, PhD
Founding KDIGO Co-Chairs

David C. Wheeler, MD, FRCP
Immediate Past Co-Chair

Michel Jadoul, MD
KDIGO Co-Chair

Wolfgang C. Winkelmayer, MD, MPH, ScD
KDIGO Co-Chair

Gloria Ashuntantang, MD
Mustafa Arici, MD
Tara I. Chang, MD, MS
Irene de Lourdes Noronha, MD, PhD
Jennifer E. Flythe, MD, MPH
Masafumi Fukagawa, MD, PhD
Morgan E. Grams, MD, MPH, PhD
Fan Fan Hou, MD, PhD
Joachim Ix, MD, MAS

Meg Jardine, MBBS, PhD
Markus Ketteler, MD, FERA
Jolanta Małyszko, MD, PhD
Laura Solá, MD
Paul E. Stevens, MB, FRCP
Sydney C.W. Tang, MD, PhD, FRCP, FACP, FHKCP, FHKAM
Irina Tchokhonelidze, MD
Marcello A. Tonelli, MD, SM, MSc, FRCPC

KDIGO Staff

John Davis, Chief Executive Officer
Danielle Green, Executive Director
Michael Cheung, Chief Scientific Officer
Melissa Thompson, Chief Operating Officer
Amy Earley, Guideline Development Director
Kathleen Conn, Director of Communications
Tanya Green, Events Director
Coral Cyzewski, Events Coordinator
REFERENCE KEYS

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as Level 1 or Level 2, and the quality of the supporting evidence is shown as A, B, C, or D.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Patients</strong></td>
</tr>
<tr>
<td><strong>Level 1 ‘Strong’</strong></td>
<td>Most people in your situation would want the recommended course of action and only a small proportion would not.</td>
</tr>
<tr>
<td>“We recommend”</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Clinicians</strong></td>
</tr>
<tr>
<td><strong>Level 1 ‘Strong’</strong></td>
<td>Most patients should receive the recommended course of action.</td>
</tr>
<tr>
<td>“We recommend”</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Policy</strong></td>
</tr>
<tr>
<td><strong>Level 1 ‘Strong’</strong></td>
<td>The recommendation can be evaluated as a candidate for developing a policy or a performance measure.</td>
</tr>
<tr>
<td>“We recommend”</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Patients</strong></td>
</tr>
<tr>
<td><strong>Level 2 ‘Weak’</strong></td>
<td>The majority of people in your situation would want the recommended course of action, but many would not.</td>
</tr>
<tr>
<td>“We suggest”</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Clinicians</strong></td>
</tr>
<tr>
<td><strong>Level 2 ‘Weak’</strong></td>
<td>Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.</td>
</tr>
<tr>
<td>“We suggest”</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Policy</strong></td>
</tr>
<tr>
<td><strong>Level 2 ‘Weak’</strong></td>
<td>The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.</td>
</tr>
<tr>
<td>“We suggest”</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>Quality of evidence</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High</td>
<td>We are confident that the true effect is close to the estimate of the effect.</td>
</tr>
<tr>
<td>B</td>
<td>Moderate</td>
<td>The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.</td>
</tr>
<tr>
<td>C</td>
<td>Low</td>
<td>The true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>D</td>
<td>Very low</td>
<td>The estimate of effect is very uncertain, and often it will be far from the true effect.</td>
</tr>
</tbody>
</table>
CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is classified based on Cause, GFR category (G1-G5), and Albuminuria category (A1-A3), abbreviated as CGA.

<table>
<thead>
<tr>
<th>GFR categories (mL/min/1.73 m²)</th>
<th>Description and range</th>
<th>Persistent albuminuria categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Normal or high</td>
<td>A1: Normal to mildly increased, A2: Moderately increased, A3: Severely increased</td>
</tr>
<tr>
<td>G2</td>
<td>Mildly decreased</td>
<td>A1: &lt; 30 mg/g, A2: 30–300 mg/g, A3: &gt; 300 mg/g</td>
</tr>
<tr>
<td>G3a</td>
<td>Mildly to moderately decreased</td>
<td>A1: &lt; 3 mg/mmol, A2: 3–30 mg/mmol, A3: &gt; 30 mg/mmol</td>
</tr>
<tr>
<td>G3b</td>
<td>Moderately to severely decreased</td>
<td>A1: 30–44 mg/mmol, A2: 15–29 mg/mmol</td>
</tr>
<tr>
<td>G4</td>
<td>Severely decreased</td>
<td>A1: 45–59 mg/mmol, A2: 15–29 mg/mmol</td>
</tr>
<tr>
<td>G5</td>
<td>Kidney failure</td>
<td>A1: 60–89 mg/mmol, A2: 30–44 mg/mmol</td>
</tr>
</tbody>
</table>

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.
CONVERSION FACTORS OF CONVENTIONAL UNITS TO SI UNITS

<table>
<thead>
<tr>
<th>Conventional unit</th>
<th>Conversion factor</th>
<th>SI Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>88.4</td>
<td>µmol/l</td>
</tr>
</tbody>
</table>

Note: Conventional unit x conversion factor = SI unit

ALBUMINURIA CATEGORIES IN CKD

<table>
<thead>
<tr>
<th>Category</th>
<th>AER (mg/24 hours)</th>
<th>ACR (approximate equivalent) (mg/mmol)</th>
<th>ACR (approximate equivalent) (mg/g)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>&lt; 30</td>
<td>&lt; 3</td>
<td>&lt; 30</td>
<td>Normal to mildly increased</td>
</tr>
<tr>
<td>A2</td>
<td>30-300</td>
<td>3-30</td>
<td>30-300</td>
<td>Moderately increased*</td>
</tr>
<tr>
<td>A3</td>
<td>&gt; 300</td>
<td>&gt; 30</td>
<td>&gt; 300</td>
<td>Severely increased**</td>
</tr>
</tbody>
</table>

ACR, albumin:creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease
*Relative to young adult level
**Including nephrotic syndrome (albumin excretion usually >2200 mg/24 h [ACR >2200 mg/g; >220 mg/mmol]

INTERPRETATION OF HCV ASSAYS

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

Anti-HCV, HCV antibody; HCV, hepatitis C; NAT, nucleic acid testing.
## Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AASLD</td>
<td>American Association for the Study of Liver Diseases</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>HCV antibody</td>
</tr>
<tr>
<td>APASL</td>
<td>Asian Pacific Association for the Study of the Liver</td>
</tr>
<tr>
<td>ASN</td>
<td>American Society of Nephrology</td>
</tr>
<tr>
<td>ASV</td>
<td>asunaprevir</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the curve</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
</tr>
<tr>
<td>CKD G4</td>
<td>chronic kidney disease GFR category 4</td>
</tr>
<tr>
<td>CKD G5</td>
<td>chronic kidney disease GFR category 5</td>
</tr>
<tr>
<td>CKD G5ND or G5D</td>
<td>chronic kidney disease GFR category 5 non-dialysis or dialysis</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>Chronic Kidney Disease Epidemiology Collaboration</td>
</tr>
<tr>
<td>CNI</td>
<td>calcineurin inhibitor</td>
</tr>
<tr>
<td>COGS</td>
<td>Conference on Guideline Standardization</td>
</tr>
<tr>
<td>CPG</td>
<td>clinical practice guideline</td>
</tr>
<tr>
<td>DAA</td>
<td>direct-acting antiviral</td>
</tr>
<tr>
<td>DCV</td>
<td>daclatasvir</td>
</tr>
<tr>
<td>EASL</td>
<td>European Association for the Study of the Liver</td>
</tr>
<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
</tr>
<tr>
<td>ELB</td>
<td>elbasvir</td>
</tr>
<tr>
<td>ERA-EDTA</td>
<td>European Renal Association-European Dialysis and Transplant Association</td>
</tr>
<tr>
<td>ERT</td>
<td>evidence review team</td>
</tr>
<tr>
<td>ESKD</td>
<td>end-stage kidney disease</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
</tr>
<tr>
<td>GLE</td>
<td>glecaprevir</td>
</tr>
<tr>
<td>GN</td>
<td>glomerulonephritis</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development and Evaluation</td>
</tr>
<tr>
<td>GRZ</td>
<td>grazoprevir</td>
</tr>
<tr>
<td>GT</td>
<td>genotype</td>
</tr>
<tr>
<td>HBeAb</td>
<td>antibody to hepatitis B core antigen</td>
</tr>
<tr>
<td>HBsAb</td>
<td>antibody to hepatitis B surface antigen</td>
</tr>
<tr>
<td>HBsAg</td>
<td>hepatitis B surface antigen</td>
</tr>
<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
</tr>
<tr>
<td>HCC</td>
<td>hepatocellular carcinoma</td>
</tr>
<tr>
<td>HCV</td>
<td>hepatitis C virus</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>IDSA</td>
<td>Infectious Diseases Society of America</td>
</tr>
<tr>
<td>KDIGO</td>
<td>Kidney Disease: Improving Global Outcomes</td>
</tr>
<tr>
<td>LDV</td>
<td>ledipasvir</td>
</tr>
<tr>
<td>MMF</td>
<td>mycophenolate mofetil</td>
</tr>
<tr>
<td>MPGN</td>
<td>membranoproliferative glomerulonephritis</td>
</tr>
<tr>
<td>mTOR</td>
<td>mammalian target of rapamycin</td>
</tr>
<tr>
<td>NAT</td>
<td>nucleic acid test(ing)</td>
</tr>
<tr>
<td>NS</td>
<td>nonstructural protein</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PIB</td>
<td>pibrentasvir</td>
</tr>
<tr>
<td>PrOD (3D regimen)</td>
<td>paritaprevir/ritonavir/ombitasvir and dasabuvir</td>
</tr>
<tr>
<td>RBV</td>
<td>ribavirin</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>SOF</td>
<td>sofosbuvir</td>
</tr>
<tr>
<td>SVR (weeks)</td>
<td>sustained virologic response (at stated weeks)</td>
</tr>
<tr>
<td>VEL</td>
<td>velpatasvir</td>
</tr>
</tbody>
</table>
NOTICE

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon literature searches last conducted in December 2020, supplemented with additional evidence through May 2021. It is designed to assist decision making. It is not intended to define a standard of care and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Healthcare professionals using these recommendations should decide how to apply them to their own clinical practice.

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 from an outside relationship or a personal, professional, or business interest of a member of the Work Group. 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 or are actual 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 document in the Work Group members’ Disclosure section, and is kept on file at KDIGO.

Note: This draft version of the KDIGO 2022 Clinical Practice Guideline Update for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease is not final. Please do not quote or reproduce any part of this document.
FOREWORD

Reflecting the growing awareness that chronic kidney disease (CKD) is an international health problem, Kidney Disease: Improving Global Outcomes (KDIGO) was established in 2003. Its stated mission is to “improve the care and outcomes of patients with kidney disease worldwide through the development and implementation of global clinical practice guidelines.”

More than 15 years ago, KDIGO convened an expert group of nephrologists, hepatologists, virologists, and specialists from other relevant disciplines to develop guideline recommendations for the prevention, diagnosis, and management of HCV in CKD, which resulted in the publication of the very first KDIGO guideline in 2008. Since then, major advances in HCV therapy have made treatment of an increasing number of CKD patients with HCV feasible irrespective of specific genotype or severity of liver disease. Advances in diagnostic testing in liver disease, most notably non-invasive evaluation of hepatic fibrosis, have further simplified the management of HCV. The KDIGO guideline was first updated in 2018 and incorporated many of these changes and innovations. However, given the rapid evolution of HCV therapies since then as well as the accumulating new information about HCV treatment in transplant recipients and the potential use of HCV-positive donor kidneys, it became evident that another focused update would be needed for these guidelines to remain current.

Today I am thrilled to present to the global kidney community an updated version of the HCV in CKD clinical practice guideline. Just like the previous iteration, this update was led by our colleagues, Paul Martin, MD, and Michel Jadoul, MD, and carried out by a global panel of Work Group members who provided their time and expertise to this endeavor. In addition, this Work Group was ably assisted by colleagues from the independent evidence review team led by Ethan Balk, MD, MPH, Craig Gordon, MD, MS, and Gaelen Adam, MLIS, MPH, whose diligent work made this guideline possible. Finally, I would like to thank our KDIGO colleagues, Michael Cheung, Amy Earley, and Melissa Thompson, for their tireless and detail-oriented management and support of this important effort.

In keeping with KDIGO’s policy for transparency and rigorous public review during the guideline development process, the draft guideline here is now made available for open commenting. The feedback received from the public review will be carefully considered by the Work Group members and the guideline will be revised as appropriate for the final publication.

Wolfgang C. Winkelmayer, MD, MPH, ScD
KDIGO Co-Chair
WORK GROUP MEMBERSHIP

Work Group Co-Chairs

Michel Jadoul, MD
Cliniques Universitaires Saint Luc
Université Catholique de Louvain
Brussels, Belgium

Paul Martin, MD
Miller School of Medicine
University of Miami
Miami, FL, USA

Work Group

Ahmed A. Awan, MD, FACP
Baylor College of Medicine
Houston, TX, USA

Marina C. Berenguer, MD
La Fe University Hospital, IIS La Fe
University of Valencia-CIBERehd
Valencia, Spain

Annette Bruchfeld, MD, PhD
Linköping University
Linköping, Sweden;
Karolinska University Hospital and
CLINTEC Karolinska Institutet
Stockholm, Sweden

Fabrizio Fabrizi, MD
Maggiore Policlinico Hospital and
IRCCS Cà Granda Foundation
Milan, Italy

David S. Goldberg, MD
Miller School of Medicine
University of Miami
Miami, FL, USA

Jidong Jia, MD, PhD
Capital Medical University
Beijing, China

Nassim Kamar, MD, PhD
Toulouse Rangueil University Hospital;
INSERM UMR 1291, Toulouse Institute for
Infectious and Inflammatory Disease (Infinity);
Paul Sabatier University
Toulouse, France

Rosmawati Mohamed, MD, MRCP, MIntMed, MBBS
University Malaya Medical Centre
Kuala Lumpur, Malaysia

Mário Guimarães Pessôa, MD, PhD
University of São Paulo School of Medicine
São Paulo, Brazil

Stanislas Pol, MD, PhD
Université de Paris et Département d’Hépatologie
Hôpital Cochin, APHP
Paris, France

Meghan E. Sise, MD, MS
Massachusetts General Hospital
Boston, MA, USA

Methods Chair

Marcello Tonelli, MD, SM, MSc, FRCPC

Evidence Review Team

Center for Evidence Synthesis in Health, Brown University School of Public Health

Providence, RI, USA

Ethan M. Balk, MD, MPH, Project Director, Evidence Review Team Director
Craig E. Gordon, MD, MS, Assistant Project Director, Evidence Review Team Associate Director
Gaelen Adam, MLIS, MPH, Information Specialist and Research Associate
The Kidney Disease: Improving Global Outcomes (KDIGO) 2022 Clinical Practice Guideline Update for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease represents a focused update of the 2018 guideline. It is intended to assist the practitioner caring for patients with hepatitis C virus (HCV) and kidney disease, including those who are on dialysis therapy, and kidney transplant candidates and recipients. Topic areas for which recommendations are updated include: Chapter 2: Treatment of HCV infection in patients with CKD; Chapter 4: Management of patients with HCV before and after kidney transplantation; and Chapter 5: Diagnosis and management of kidney diseases associated with HCV infection. Previous chapters on the detection and evaluation of HCV in CKD (Chapter 1) and prevention of HCV transmission in hemodialysis units (Chapter 3) have been deemed current and their content has therefore remained unchanged. Development of this guideline update followed an explicit process of evidence review and appraisal. Treatment approaches and guideline recommendations are based on systematic reviews of relevant studies, and appraisal of the quality of the evidence and the strength of recommendations followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Limitations of the evidence are discussed, with areas of future research also presented.

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

CHAPTER 2: TREATMENT OF HCV INFECTION
IN PATIENTS WITH CKD

2.1: We recommend that all patients with CKD (G1-G5D, including those on dialysis therapy) and kidney transplant recipients (G1T-G5T) with HCV be evaluated for direct-acting antiviral (DAA)-based therapy as outlined in Table 1 (IA).

2.1.1: We recommend that the choice of specific regimen be based on prior treatment history, drug–drug interactions, GFR, stage of hepatic fibrosis, kidney and liver transplant candidacy, and comorbidities (IA). If pangenotypic regimens are not available, HCV genotype (and subtype) should guide the choice of treatment (Table 1).

2.1.2: Treat kidney transplant candidates in collaboration with the transplant center to optimize timing of therapy (Not Graded).

2.1.3: We recommend pre-treatment assessment for drug–drug interactions between the DAA-based regimen and other concomitant medications including immunosuppressive drugs in kidney transplant recipients (IA).

2.1.4: We recommend that calcineurin inhibitor levels be monitored during and after DAA treatment in kidney transplant recipients (IB).

2.2: All patients with CKD (G1-G5D, including those on dialysis therapy) and kidney transplant recipients (G1T-G5T) with HCV should undergo testing for hepatitis B virus (HBV) infection prior to DAA therapy (Not Graded).

2.2.1: If hepatitis B surface antigen [HBsAg] is present, the patient should undergo assessment for HBV therapy (Not Graded).

2.2.2: If HBsAg is absent but markers of prior HBV infection (HBcAb-positive with or without HBsAb) are detected, exclude HBV reactivation with HBV DNA testing if liver function tests rise during DAA therapy (Not Graded).
Table 1. Direct-acting antiviral (DAA) regimens with evidence of effectiveness for various CKD populations.

<table>
<thead>
<tr>
<th>CKD Populations</th>
<th>Direct Acting Antiviral Regimens*</th>
<th>HCV Genotypes</th>
<th>Certainty of Evidence†</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1–G3b, not KTR</td>
<td>Any licensed DAA regimen</td>
<td>All</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>G4–G5ND, including KTRb,c</td>
<td>Glecaprevir / Pibrentasvir, 8 or 12 wk</td>
<td>All</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir / Daclatasvir, 12 or 24 wk†</td>
<td>All</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Elbasvir / Grazoprevir, 12 wk</td>
<td>1a, 1b, 4</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir / Ledipasvir, 12 wk</td>
<td>All</td>
<td>Very Low</td>
</tr>
<tr>
<td>G5Dd</td>
<td>Sofosbuvir / Velpasvir, 12 wk</td>
<td>All</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir / Daclatasvir, 12 or 24 wk†</td>
<td>All</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir / Ledipasvir, 12 wk</td>
<td>All</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Glecaprevir / Pibrentasvir, 8 or 12 wk§</td>
<td>All</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Elbasvir / Grazoprevir, 12 wk</td>
<td>1a, 1b, 4</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>PrO±D, 12 wk</td>
<td>1a, 1b, 4</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Daclatasvir / Asunaprevir, 24 wk</td>
<td>1b</td>
<td>Low</td>
</tr>
<tr>
<td>KTR, G1–G3be</td>
<td>Sofosbuvir / Ledipasvir, 12 or 24 wk†</td>
<td>All</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir / Daclatasvir, 12 or 24 wk†</td>
<td>All</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>PrO±D, 12 wk</td>
<td>1a, 1b, 4</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

* 12 weeks for patients with cirrhosis, genotype 3, or prior DAA treatment failure.
† 24 weeks for patients with cirrhosis and genotype 3.
‡ 24 weeks for patients with cirrhosis.
§ 12 weeks for patients with cirrhosis, genotype 3, or prior DAA treatment failure.
* 24 weeks for genotypes 1a or 4, cirrhosis, or prior DAA treatment failure.
The table includes only regimens that were evaluated by at least 2 studies in the specific CKD population and for which summary SVR12 was >92%. Sofosbuvir monotherapy is excluded as DAA regimens incorporate at least 2 agents.

Other regimens may be appropriate for the above populations. Readers are encouraged to consult the Association for the Study of Liver Diseases (AASLD) or European Association for the Study of the Liver (EASL) guidelines for the latest information on various regimens.

†The order of HCV regimens does not indicate a ranking or preferential order of selection. The regimens are presented in order of the certainty of evidence (as per GRADE methodology), then by HCV genotype, then alphabetically. The differences in certainty of evidence primarily relate to small differences in methodological quality of the underlying studies and numbers of evaluated patients (see Evidence Profiles A, B and C).

a GFR <30 ml/min per 1.73 m², not dialysis-dependent
b Regimens in KTRs should be selected to avoid drug–drug interactions, particularly with calcineurin inhibitors
c Strength of evidence for KTR with CKD G4-G5ND is very low for all regimens
d Evidence primarily for patients on hemodialysis. Very few patients were on peritoneal dialysis
e GFR ≥30 ml/min per 1.73 m²

CKD, chronic kidney disease; D, dialysis; G, CKD GFR category; GFR, glomerular filtration rate; HCV, hepatitis C; KTR, kidney transplant recipient; ND, non-dialysis; PrO±D, ritonavir-boosted paritaprevir and ombitasvir with or without dasabuvir; SVR, sustained virologic response.
CHAPTER 4: MANAGEMENT OF PATIENTS WITH HCV BEFORE AND AFTER KIDNEY TRANSPLANTATION

4.1 Evaluation and management of kidney transplant candidates regarding HCV infection

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

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

4.1.2.1: We recommend that patients with HCV, compensated cirrhosis and no portal hypertension undergo isolated kidney transplantation while patients with decompensated cirrhosis or clinically significant portal hypertension (i.e., hepatic venous pressure gradient ≥10 mm Hg or evidence of portal hypertension on imaging or exam) undergo a simultaneous liver-kidney transplantation (1B). Those with mild-to-moderate portal hypertension should be determined on a case-by-case basis.

4.1.2.2: We recommend referring patients with HCV and decompensated cirrhosis for combined liver-kidney transplantation (1B).

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

4.1.3.1: We recommend that all kidney transplant candidates with HCV be considered for DAA therapy, either before or after transplantation (1A).

4.1.3.2: We suggest that HCV-infected kidney transplant candidates with a living kidney donor be considered for treatment before or shortly after transplantation depending on the anticipated timing of transplantation (2B).
4.2 Use of kidneys from HCV-infected donors

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

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

4.2.3: We recommend that kidneys from HCV-infected donors be considered regardless of HCV status of potential kidney transplant recipients (1C).

4.2.4: When transplanting kidneys from HCV-infected donors into HCV-uninfected recipients, transplant centers must ensure that patients receive education and are engaged in discussion with sufficient information to provide informed consent. Patients should be informed of the risks and benefits of transplantation with an HCV-infected kidney, including the need for DAA treatment (Not Graded).

4.2.5: When transplanting kidneys from HCV-infected donors into HCV-uninfected recipients, transplant centers should confirm availability of DAAs for initiation in the early-post transplant period (Not Graded).

4.3 Use of maintenance immunosuppressive regimens

4.3.1: We recommend that kidney transplant recipients being treated with DAAs be evaluated for the need for dose adjustments of concomitant immunosuppressants (1C).

4.4 Management of HCV-related complications in kidney transplant recipients

4.4.1: We suggest that patients previously infected with HCV who achieved SVR before transplantation undergo testing by NAT 3 months after transplantation or if liver dysfunction occurs (2D).

4.4.2: Kidney transplant recipients with cirrhosis should have the same liver disease follow-up as non-transplant patients, as outlined in the American Association for the Study of Liver Diseases (AASLD) guidelines (Not Graded).
4.4.3: HCV-infected kidney transplant recipients should be tested at least every 6 months for proteinuria (Not Graded).

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

4.4.4: We recommend treatment with a DAA regimen in patients with post-transplant HCV-associated glomerulonephritis (1D).
CHAPTER 5: DIAGNOSIS AND MANAGEMENT OF KIDNEY DISEASES ASSOCIATED WITH HCV INFECTION

5.1: HCV-infected patients with a typical presentation of immune-complex proliferative glomerulonephritis (GN) can be managed without a confirmatory kidney biopsy. However, a biopsy may be indicated in certain clinical circumstances (Figure 3) (Not Graded).

5.2: We recommend that patients with HCV-associated glomerulonephritis receive antiviral therapy (1A).

5.2.1: We recommend that patients with HCV-associated glomerulonephritis, stable kidney function, and without nephrotic syndrome be treated with DAAs prior to other treatments (1C).

5.2.2: We recommend that patients with cryoglobulinemic flare or rapidly progressive glomerulonephritis be treated with both DAAs and immunosuppressive agents with or without plasma exchange (1C).

5.2.2.1: The decision whether to use immunosuppressive agents in patients with nephrotic syndrome should be individualized (Not Graded).

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

5.2.3.1: We recommend rituximab as the first-line immunosuppressive treatment (1C).
Figure 3. Indications for biopsy in patients with HCV and severe GN. Algorithm above assumes that patient with HCV and CKD is already receiving DAA treatment. Systemic signs of cryoglobulinemia include skin lesions such as purpura, arthralgias, and weakness.

HCV, hepatitis C virus; GFR, glomerular filtration rate; GN, glomerulonephritis; IS, immunosuppression; RPGN, rapidly progressive glomerulonephritis; SVR, sustained virologic response
CHAPTER 2: TREATMENT OF HCV INFECTION IN PATIENTS WITH CKD

Introduction of highly effective, well-tolerated oral direct-acting antiviral (DAA) regimens has enabled treatment of patients with hepatitis C virus (HCV) across all stages of chronic kidney disease (CKD) and has made interferon and ribavirin obsolete. Current DAA regimens always incorporate two or more drugs with different mechanisms of action to disrupt HCV replication, with the goals of enhancing efficacy and preventing emergence of viral resistance. Although recent studies indicate that most DAA regimens can be used irrespective of kidney function, glomerular filtration rate (GFR) measurements or estimations may still be relevant depending on accessibility to specific drugs in different parts of the world and how they may be labelled for use in people with reduced GFR. If eGFR is used, we suggest using the combined creatinine and cystatin C-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula or, alternatively, the creatinine-based CKD-EPI formulae,1, 2 bearing in mind that creatinine-based formulas do not perform well in patients with cirrhosis.3, 4

Multiple studies have established a survival benefit in patients with HCV who achieve sustained virologic response (SVR),5 an endpoint for clinical trials and drug approval.6 SVR at 12 weeks is considered a virological cure.7

For most CKD patients, as in the general population, the potential benefits of antiviral treatment outweigh possible harm.8 However, some patients may not be expected to live long enough to benefit from therapy (e.g., those with metastatic cancer). The Work Group was hesitant to specify a minimum life expectancy that would justify treatment, given the inaccuracy of predictions and the need to individualize this decision. However, as noted in the American Association for the Study of Liver Diseases/Infectious Diseases Society of America (AASLD/IDSA) guidance, little evidence exists to support initiation of HCV treatment in patients with a limited life expectancy (<12 months).9
2.1: We recommend that all patients with CKD (G1-G5D, including those on dialysis therapy) and kidney transplant recipients (G1T-G5T) with HCV be evaluated for direct-acting antiviral (DAA)-based therapy as outlined in Table 1 (IA).

2.1.1: We recommend that the choice of specific regimen be based on prior treatment history, drug–drug interactions, GFR, stage of hepatic fibrosis, kidney and liver transplant candidacy, and comorbidities (IA). If pangenotypic regimens are not available, HCV genotype (and subtype) should guide the choice of treatment (Table 1).

2.1.2: Treat kidney transplant candidates in collaboration with the transplant center to optimize timing of therapy (Not Graded).

2.1.3: We recommend pre-treatment assessment for drug–drug interactions between the DAA-based regimen and other concomitant medications including immunosuppressive drugs in kidney transplant recipients (IA).

2.1.4: We recommend that calcineurin inhibitor levels be monitored during and after DAA treatment in kidney transplant recipients (IB).

2.2: All patients with CKD (G1-G5D, including those on dialysis therapy) and kidney transplant recipients (G1T-G5T) with HCV should undergo testing for hepatitis B virus (HBV) infection prior to DAA therapy (Not Graded).

2.2.1: If hepatitis B surface antigen [HBsAg] is present, the patient should undergo assessment for HBV therapy (Not Graded).

2.2.2: If HBsAg is absent but markers of prior HBV infection (HBcAb-positive with or without HBsAb) are detected, exclude HBV reactivation with HBV DNA testing if liver function tests rise during DAA therapy (Not Graded).
Table 1. Direct-acting antiviral (DAA) regimens with evidence of effectiveness for various CKD populations.

<table>
<thead>
<tr>
<th>CKD Populations</th>
<th>Direct Acting Antiviral Regimens*</th>
<th>HCV Genotypes</th>
<th>Certainty of Evidence †</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1–G3b, not KTR</td>
<td>Any licensed DAA regimen</td>
<td>All</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>G4–G5ND, a</td>
<td>Glecaprevir / Pibrentasvir, 8 or 12 wk&lt;sup&gt;1&lt;/sup&gt;</td>
<td>All</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir / Daclatasvir, 12 or 24 wk&lt;sup&gt;4&lt;/sup&gt;</td>
<td>All</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Elbasvir / Grazoprevir, 12 wk</td>
<td>1a, 1b, 4</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir / Ledipasvir, 12 wk</td>
<td>All</td>
<td>Very Low</td>
</tr>
<tr>
<td>G5D&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Sofosbuvir / Velpatasvir, 12 wk</td>
<td>All</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir / Daclatasvir, 12 or 24 wk&lt;sup&gt;2&lt;/sup&gt;</td>
<td>All</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir / Ledipasvir, 12 wk</td>
<td>All</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Glecaprevir / Pibrentasvir, 8 or 12 wk&lt;sup&gt;4&lt;/sup&gt;</td>
<td>All</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Elbasvir / Grazoprevir, 12 wk</td>
<td>1a, 1b, 4</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>PrO ± D, 12 wk</td>
<td>1a, 1b, 4</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Daclatasvir / Asunaprevir, 24 wk</td>
<td>1b</td>
<td>Low</td>
</tr>
<tr>
<td>KTR, b</td>
<td>Sofosbuvir / Ledipasvir, 12 or 24 wk&lt;sup&gt;3&lt;/sup&gt;</td>
<td>All</td>
<td>High</td>
</tr>
<tr>
<td>G1–G3b&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Sofosbuvir / Daclatasvir, 12 or 24 wk&lt;sup&gt;5&lt;/sup&gt;</td>
<td>All</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>PrO±D, 12 wk</td>
<td>1a, 1b, 4</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

<sup>1</sup> 12 weeks for patients with cirrhosis, genotype 3, or prior DAA treatment failure.
<sup>2</sup> 24 weeks for patients with cirrhosis and genotype 3.
<sup>3</sup> 24 weeks for patients with cirrhosis.
<sup>4</sup> 12 weeks for patients with cirrhosis, genotype 3, or prior DAA treatment failure.
<sup>5</sup> 24 weeks for patients with cirrhosis.
<sup>6</sup> 24 weeks for genotypes 1a or 4, cirrhosis, or prior DAA treatment failure.
*The table includes only regimens that were evaluated by at least 2 studies in the specific CKD population and for which summary SVR12 was >92%. Sofosbuvir monotherapy is excluded as DAA regimens incorporate at least 2 agents.

Other regimens may be appropriate for the above populations. Readers are encouraged to consult the Association for the Study of Liver Diseases (AASLD) or European Association for the Study of the Liver (EASL) guidelines for the latest information on various regimens.

†The order of HCV regimens does not indicate a ranking or preferential order of selection. The regimens are presented in order of the certainty of evidence (as per GRADE methodology), then by HCV genotype, then alphabetically. The differences in certainty of evidence primarily relate to small differences in methodological quality of the underlying studies and numbers of evaluated patients (see Evidence Profiles A, B, and C).

a GFR <30 ml/min per 1.73 m², not dialysis-dependent
b Regimens in KTRs should be selected to avoid drug–drug interactions, particularly with calcineurin inhibitors
c Strength of evidence for KTR with CKD G4-G5ND is very low for all regimens
d Evidence primarily for patients on hemodialysis. Very few patients were on peritoneal dialysis
e GFR ≥30 ml/min per 1.73 m²

CKD, chronic kidney disease; D, dialysis; G, CKD GFR category; GFR, glomerular filtration rate; HCV, hepatitis C; KTR, kidney transplant recipient; ND, non-dialysis; PrO±D, ritonavir-boosted paritaprevir and ombitasvir with or without dasabuvir; SVR, sustained virologic response.
RATIONALE

Development of DAA therapy has been based on mapping the HCV genome which contains non-structural (NS) proteins and the identification of its replication cycle which includes amplification of the HCV genome by the RNA polymerase NS5B. Several protease inhibitors, which all end in “-previr,” are active against the NS3/NS4 serine protease; these have been introduced with more recent additions having a high barrier to antiviral resistance and greater efficacy (Figure 1). The NS5A protein, although not an enzyme, is key to the assembly of virions and these NS5A inhibitors, which all have “-asvir” in the suffix, have excellent antiviral activity but a relatively low barrier to antiviral resistance. A key event in HCV replication is amplification of the HCV genome by the RNA polymerase NS5B. Its actions can be disrupted by nucleotide or non-nucleotide inhibitors whose names end in “-buvir” (Figure 1). A number of studies have been published which have established the safety and efficacy of DAA therapy in CKD. As will be discussed, some regimens are effective against all HCV genotypes (“pangenotypic”) while others are limited by specific genotype (GT), thus necessitating GT determination prior to DAA therapy.
Figure 1. Summary of currently available DAA treatment targets on HCV life cycle.

Infection is initiated by (1): virus binding and internalization, followed by (2) cytoplasmic release and uncoating; (3) translation and polyprotein processing; (4) RNA replication; (5) packaging and assembling; and (6) virion maturation and release. Adapted with permission from Stanciu et al.¹⁰

NS3/4A, nonstructural protein protease inhibitor; NS5A, nonstructural protein 5A complex inhibitor; NS5B, nonstructural protein polymerase inhibitor.

CKD G1–G3b (GFR ≥ 30 ml/min per 1.73 m²)

Patients with CKD G1-G3b can be treated using the evidence-based guidelines for the general population. The AASLD/IDSA and the 2020 European Association for the Study of the Liver (EASL) guidelines recommend no dosage modifications for individuals with mild to moderate reductions in GFR.⁹,¹¹ As recommended drugs and dosage may change, clinicians should consult the latest guidelines from AASLD/IDSA (https://www.hcvguidelines.org/unique-populations/renal-impairment) or EASL¹¹ (http://www.easl.eu/research/our-contributions/clinical-practice-guidelines) for the most up-to-date treatment information.
DAAs have variable renal elimination, although recent evidence shows that the clinical importance of reduced renal elimination in CKD G4-G5 is limited. However advanced CKD, if present, may be a consideration in the choice of agent depending on drug labeling in the local jurisdiction.

**Pangenotypic regimens**

* Sofosbuvir-based regimens

Sofosbuvir (SOF), a polymerase inhibitor, is the cornerstone of several DAA regimens. It is predominantly renally cleared (80%) and thus, had previously been licensed for use only in individuals with GFR $\geq 30$ ml/min per 1.73 m$^2$ (CKD G1–G3b). However recent data on SOF-based regimens in patients with advanced CKD (G4-G5D) suggest that SOF is well-tolerated and safe, including for those who require hemodialysis (Summary Tables 2.1-2.5). In an early study, reduced-dose of SOF (400 mg three times a week or 400 mg every other day) was efficacious and well tolerated in 62 hemodialysis patients. Other studies have come to the same conclusion in advanced CKD. More recent studies have provided further reassurance about the safety and efficacy of SOF in advanced CKD at full dose. Dose adjustment of SOF in patients with CKD G4-G5 and G5D is not required. Across 13 studies that evaluated SOF-based regimens, no serious adverse events were reported in 774 hemodialysis patients and only one patient was reported to have discontinued treatment due to adverse events (Summary Table 2.3 and Evidence Profile B). Similarly, across five studies of patients with CKD G4-G5ND (non-dialysis), no serious adverse events were reported in 210 patients and only four patients discontinued treatment due to adverse events (Summary Table 2.1 and Evidence Profile A). SOF is currently licensed for all stages of CKD in several countries, including the United States.

SOF-based regimens that have been evaluated by at least two studies that reported SVR12 and safety information specifically in CKD G4-G5ND or CKD G5D populations include SOF/DCV (daclatasvir), SOF/LDV (ledipasvir), and SOF/VEL [velpatasvir] (in
CKD G5D only). Other regimens have been evaluated by single studies only, with similar findings (SOF/SIM [simeprevir] and SOF/VEL, in CKD G4-G5ND; Summary Tables 2.1-2.5 and Evidence Profiles A and B). Monotherapy with SOF alone is not recommended due to inferior efficacy (SVR12 72% in CKD G4-G5ND, inconsistent efficacy in CKD G5D; Summary Tables 2.1 and 2.3, Evidence Profiles A and B).

**Glecaprevir/Pibrentasvir (GLE/PIB)**

The pangenotypic regimen GLE/PIB was studied in the open-label EXPEDITION-4 study which included 102 patients with CKD G4-G5, 82% of whom were dialysis dependent. Duration of treatment was 12 weeks. SVR12 was 100% on modified intention-to-treat analysis and no serious adverse events related to the regimen were reported17 (see Table 1). EXPEDITION-5 was another open-label, non-randomized, multicenter study that included a shorter treatment arm where 84 non-cirrhotic patients (out of 101) with CKD G3b-G5 were treated for 8 weeks as long as they did not have GT 3. Cirrhotics, treatment-experienced and GT 3 patients were treated for 12 weeks (13 patients) or 16 weeks (4 patients) duration. SVR12 was 97.0% in the study.18 However, EXPEDITION-4 was excluded from our analysis of SVR12 because results were not reported separately for the CKD G4-G5ND and CKD G5D populations. EXPEDITION-5 was excluded from our analysis of CKD G4-G5ND because patients with CKD G3b were included in their analysis.

In the pooled estimate of the two studies included in our evidence review, 8-week treatment with GLE/PIB in CKD G4-G5ND patients had a SVR12 of 97.9% (95% CI: 92.1-99.5). One of the studies reported no serious adverse events, but two patients (6.3%) discontinued the drug due to adverse events (Summary Table 2.1 and Evidence Profile A).19 Across eight studies with 409 CKD G5D patients, our meta-analysis demonstrated a SVR12 of 96.7% (95% CI: 94.5-98.4). Adverse events were rare; 0.6% (2/333) reported serious adverse events and 1.9% (4/279) discontinued DAAs due to adverse events (Summary Table 2.3 and Evidence Profile B). Therefore, GLE/PIB combination can be safely used in patients with CKD G4-G5ND and G5D without dose adjustment. A treatment duration of 8 weeks is sufficient for most patients without cirrhosis.
Genotype-specific regimens

Since not all regimens are pangenotypic, other regimens such as elbasvir-grazoprevir, paritaprevir-ritonavir-ombitasvir with or without dasabuvir (PrOD), and daclatasvir-asunaprevir can also be safely used in CKD G4-G5ND and G5D patients (Table 1 and Evidence Profiles A and B)

Grazoprevir/Elbasvir (GRZ-ELB)

Grazoprevir-elbasvir (GRZ-ELB) combination is licensed for patients with HCV GTs 1 and 4, with safety and efficacy data available in patients with CKD G4-G5 and G5D. Both agents are metabolized by CYP3A and primarily (>90%) excreted in feces with minimal renal clearance (<1%).

The C-SURFER trial evaluated 12 weeks of this combination in patients with CKD G4-G5ND and G5D with HCV GT 1; 81% of patients had CKD G5 and 76% were on hemodialysis. Patients were randomized in this double-blind trial to either immediate 12 weeks therapy or deferred treatment. The majority had GT 1a (52%), and 80% were treatment-naïve. SVR12 was 99%, with 1 relapse 12 weeks after end of treatment, with no significant difference between GTs 1a and 1b, nor between those undergoing hemodialysis and those with advanced CKD not on dialysis therapy. Tolerability was excellent and adverse events were comparable in the treatment and control arms. Renal events such as acute kidney injury, decrease in GFR, and need to start hemodialysis were comparable in both groups. These results have been confirmed in a real-world French cohort study. For patients with CKD G4-G5ND, across five studies (n = 857) SVR12 was 96.7% (95% CI: 95.4-97.8); however, only one of these studies (n = 14) reported on adverse events (Summary Table 2.1 and Evidence Profile A). For patients with CKD G5D, across nine studies (n = 936), SVR12 was 96.5% (95% CI: 94.8-97.9) with only 0.7% (1/136) experiencing serious adverse events (Summary Table 2.3 and Evidence Profile A).

Ritonavir-boosted paritaprevir with ombitasvir and dasabuvir (PrOD)

The combination of ritonavir-boosted paritaprevir with ombitasvir and dasabuvir (PrOD, also known as 3D regimen) for 12 weeks was evaluated in the open label RUBY-
1 study in patients with HCV GT 1 and CKD G4-G5 including hemodialysis patients, which demonstrated excellent efficacy with SVR12 of 90%. One treatment failure was nonvirological (unrelated death after conclusion of treatment) and there was one relapse.\textsuperscript{24, 25} Ribavirin (RBV) was used in combination with the PrOD regimen in patients with HCV GT 1a. However, even with a reduced dose of 200 mg RBV daily, 9 out of 13 GT 1a patients had to interrupt RBV treatment due to anemia, and four patients required erythropoiesis-stimulating agents.\textsuperscript{25}

The RUBY-2 trial investigated a 12-week RBV-free treatment course of PrO±D in 19 CKD G4 and G5 patients (including dialysis) with HCV GT 1a or 4.\textsuperscript{26} The SVR12 rate in this trial was also high, even among GT 1a patients, and there were no adverse events due to anemia.

Real-world PrOD regimen data from the ERCHIVES study and several case series also demonstrated high SVR rates.\textsuperscript{27-33} Our meta-analysis included 16 studies conducted in patients with CKD G5D (n = 582) in which PrOD was used with or without RBV for 12 weeks to treat HCV GTs 1 and 4. SVR12 was 96.8% (95% CI: 95.2-98.1), with 0.2% (1/406) having serious adverse events and 1.8% patients (n = 446) discontinuing DAAs due to adverse events (Summary Table 2.3 and Evidence Profile B). PrOD has been less extensively evaluated in patients with CKD G4-5ND. Across three studies (n = 103), the estimate of SVR12 is somewhat imprecise (89.4%; 95% CI: 75.7-97.8), with no serious adverse events or discontinuations due to adverse events reported (Summary Table 2.1 and Evidence Profile A).

\textit{Daclatasvir/asunaprevir (DCV/ASV)}

Daclatasvir (DCV, an NS5A inhibitor) and asunaprevir (ASV, an NS3/NS4A protease inhibitor) in combination have been studied primarily in Japanese patients with HCV GT 1b on hemodialysis with SVR rates reported between 76-100%. A large post-marketing study of all patients receiving DCV/ASV in Japan reported an overall SVR rate of 88.4% with 24 weeks of treatment with this regimen.\textsuperscript{34-36} but adverse events were more frequent in patients with eGFR < 30 ml/min/1.73 m\textsuperscript{2} (implicitly including both dialysis and non-dialysis patients). Concerns associated with this regimen include
possible lower SVR in patients with HCV GT 1b with resistance-associated variants.\textsuperscript{37-39} For the general population, the Asian Pacific Association for the Study of the Liver (APASL) suggests this regimen can be used in patients with HCV GT 1b and impaired kidney function if resistance-associated variants are absent.\textsuperscript{40} Among patients on dialysis, our meta-analysis across 9 studies (n = 341) conducted mostly in Japan SVR12 was 93.6\% (95\% CI: 89.5-96.8) with 0.4\% (n = 274) reporting a serious adverse event, but 3.8\% (n = 341) discontinuing treatment due to an adverse event (Summary Table 2.3 and Evidence Profile B). The regimen has not been adequately evaluated in patients (n = 10) with CKD G4-G5 not on dialysis (Summary Table 2.1).

**Toxicity**

A particular concern with SOF had been the putative cardiac toxicity\textsuperscript{41,42} although subsequent analyses could not confirm such observations.\textsuperscript{43} However, post-marketing symptomatic bradycardia has been reported when it was administered with amiodarone.\textsuperscript{44} Another early concern had been whether DAA therapy might accelerate the decline of kidney function in CKD but recent data has provided reassurance regarding SOF. Sise et al.\textsuperscript{45} reported that in patients with CKD G3a–G3b who received SOF-based regimens, HCV cure was associated with a 9.3 ml/min per 1.73 m\textsuperscript{2} improvement in eGFR during the 6-month post-treatment follow-up. Other reports have also indicated that loss of eGFR is not a consequence of SOF use.\textsuperscript{43,46-50} Our review suggests that serious adverse events, discontinuations due to adverse events, or decrements in kidney function were rare in CKD G4-G5ND and CKD G5D patients (Summary Tables 2.1-2.5 and Evidence Profiles A and B).

No evidence of a deleterious effect of other DAAbs on eGFR has been reported with non-SOF-based regimens.\textsuperscript{51} Reddy et al.\textsuperscript{52} identified 32 patients with CKD G3a-G3b included in trials with GRZ/ELB and found no evidence of deterioration of kidney function as a result of treatment with these agents. Summary Table 2.2 lists various studies of patients with CKD G4-G5ND that reported mean change in GFR across various stages of CKD after treatment with various DAAbs, including SOF 200 mg and 400 mg (in combination with DCV, LDV, VEL), PrOD and GLE/PIB. There was no
significant decline in GFR at the end of treatment with any regimen, and in one study, CKD G4 patients had a small improvement in mean GFR (1.6 ml/min; 95% CI: −0.1 to 3.3) after treatment with a SOF 400 mg/VEL regimen.50

Protease inhibitors (“-previrs” such as simeprevir, paritaprevir and grazoprevir) are contraindicated in cirrhotic patients, Child-Turcotte-Pugh class B or C, due to hepatotoxicity.53

In summary, we recommend treatment of HCV in patients with CKD G4–G5ND and G5D with a RBV-free DAA-based regimen. The combination SOF-based regimens SOF/DCV and SOF/LDV have been shown to be safe and effective in patients with CKD G4-G5, with or without dialysis (Evidence Profiles A and B). SOF/VEL has also been shown to be safe and effective in CKD G4-G5ND patients. In Europe and the United States, labeling for SOF has been expanded to include patients with CKD G4-G5, including those on dialysis43 (see SOF/VEL, SOF/VEL/voxilaprevir, SOF/LED in https://www.ema.europa.eu/en and United States product inserts)

Regimens such as GLE/PIB and for patients with GT 1 or 4, GRZ/ELB are also safe and effective in patients with CKD G4-G5ND and G5D. In addition, for dialysis patients, PrOD (for GTs 1 and 4) and DCV/ASV (for GT 1b) are safe and effective (Evidence Profiles A and B).

Our systematic review found no evidence to recommend specific DAA regimens in patients on peritoneal dialysis but it is reasonable to follow guidance for patients on hemodialysis.46

Our guidance is in overall concordance with those provided by AASLD (https://www.hcvguidelines.org/unique-populations/renal-impairment) and EASL (http://www.easl.eu/research/our-contributions/clincial-practice-guidelines), but given that recommended drugs and dosage are constantly evolving, clinicians should consult these resources for the most up-to-date management information.
Kidney transplant recipients (CKD G1T–G5T)

DAA therapy in kidney transplant recipients with HCV is effective and well tolerated (Summary Tables 2.6-2.8 and Evidence Profile C). In a trial comparing 12 and 24 weeks of SOF/LDV in 114 kidney transplant recipients with HCV GTs 1 and 4 (96% GT1) and eGFR $\geq$ 40 ml/min per 1.73 m$^2$ (median 56 ml/min per 1.73 m$^2$), SVR12 rates were close to 100% without differences between arms, suggesting that a 12-week regimen is appropriate in this population.\textsuperscript{54} Smaller cohort studies recently also reported excellent results in kidney transplant recipients with SOF-based regimens.\textsuperscript{55-57} Pooled analysis of 4 studies from India (n = 65) showed that SOF use in combination with RBV alone had a SVR12 of 100% (95% CI: 89-100) in kidney transplant recipients (Summary Table 2.6 and Evidence Profile C). Across studies, 4.8% of patients discontinued treatment due to adverse events (Summary Table 2.6). Across 10 studies (n = 300), SOF/LDV had high SVR12 (97.3%; 95% CI: 94.9-99.0) with few serious adverse events (2.6%; 95% CI: 0.7-5.7) or discontinuations due to adverse events (1.7%; 95% CI: 0.4-3.7) (Summary Table 2.7 and Evidence Profile C). In 3 studies (n = 84) 1.2% (95% CI: 0.2-0.8) of patients on SOF/LDV experienced graft loss and in 4 studies (n = 109), 6.2% (95% CI: 2.3-12.0) experienced acute rejection.

SOF/DCV had a similarly high SVR12 (100%) in 5 studies (n = 275) and no serious adverse events or discontinuation due to adverse events (Summary Table 2.6). In the 2 studies (n = 230) reporting acute rejection and graft loss, SOF/DCV combination had 3.2% rejections and 0% graft loss at the end of treatment (Summary Table 2.7).

Reau et al.\textsuperscript{58} described the use of GLE/PIB in 100 organ transplant recipients, 20 of whom had received a kidney transplant, with high SVR and excellent tolerability. Furthermore, Fabrizi et al.\textsuperscript{59} recently reported that various DAAs were highly effective in a retrospective study on 95 patients after kidney transplantation (SVR 93.7%). These findings are similar to other recent reports.\textsuperscript{60}

In summary, kidney transplant recipients with GFR $\geq$ 30 ml/min per 1.73 m$^2$ (CKD G1T–G3bT) can receive pangenotypic treatments such as SOF-based regimens and GLE/PIB. If they are not available, PrOD can be considered for GTs 1a, 1b and 4, though caution should be exercised with calcineurin inhibitors (CNIs) as elaborated
below. For kidney transplant recipients with GFR < 30 ml/min per 1.73 m² (CKD G4–G5T), the same regimens proposed for patients with CKD G4–G5 not on dialysis therapy apply. Our guidance is in general concordance with those provided by AASLD (https://www.hcvguidelines.org/unique-populations/kidney-transplant) and EASL (http://www.easl.eu/research/our-contributions/clinical-practice-guidelines), but given that recommended drugs and dosage are constantly evolving, clinicians should consult these resources for the most up-to-date treatment information.

**Drug-drug interactions**

Drug–drug interactions are an important factor in the choice of a DAA regimen. Important drug interactions of DAAs occur with immunosuppressants, such as tacrolimus and cyclosporine in transplant recipients which may result in increased or diminished plasma levels of immunosuppressive agents. Protease inhibitors have a significant risk for drug–drug interactions, particularly in patients who are treated with immunosuppressive agents such as CNIs and mammalian target of rapamycin (mTOR) inhibitors.\(^\text{24, 61}\) NS5B inhibitors such as SOF or NS5A inhibitors such as LDV and DCV are associated with a low risk of drug–drug interaction with CNIs and mTOR inhibitors, but may have interactions with other concomitant medications. Concurrent use of GRZ/ELB and cyclosporine is not recommended, as it results in a 15-fold increase in GRZ area under the curve (AUC) and 2-fold increase in elbasvir AUC. GRZ/ELB increases levels of tacrolimus by 43%; thus, close monitoring of levels is indicated, and dose reductions of tacrolimus may be needed. Other protease inhibitors such as paritaprevir have similar drug–drug interactions with cyclosporine, tacrolimus, and everolimus. There are no significant drug–drug interactions with these protease inhibitors and mycophenolate mofetil (MMF). No significant interactions between NS5A and NS5B polymerase inhibitors such as SOF and CNIs have been described, but close monitoring of immunosuppressive drugs is mandatory because changes in liver metabolism concurrent with HCV eradication may require modification of immunosuppressive drug doses.

Of note, GRZ is a substrate of OATP1B1/3, and co-administration with drugs that inhibit OATP1B1/3 (such as enalapril, statins, digoxin, some angiotensin-receptor
blockers) may result in increased levels of GRZ that may lead to clinically significant hyperbilirubinemia. GRZ and ELB are substrates of CYP3A, and co-administration with strong CYP3A inducers (such as rifampin, phenytoin, and St John’s wort) is contraindicated, as it may result in decreased plasma concentrations and potentially reduced antiviral activity of both agents. The Hepatitis Drug Interactions website from the University of Liverpool (http://www.hep-druginteractions.org) is a valuable resource for determining the risk and management recommendations for drug-drug interactions. This tool can inform the selection of optimal DAAs and concomitant medications, and the potential suspension of specific pharmacotherapies in order to avoid drug-drug interactions.

Reactivation of HBV infection after DAA therapy

A number of reports have recently described apparent reactivation of hepatitis B virus (HBV) infection in individuals following otherwise successful therapy of HCV infection with DAA-based regimens,\textsuperscript{62,63} which has prompted a United States FDA warning.\textsuperscript{64} The European Medicine Agency (www.ema.europa.eu), EASL and APASL have issued similar recommendations.\textsuperscript{65} As part of routine evaluation of patients with HCV and CKD, HBV serological markers (i.e., hepatitis B surface antigen [HBsAg], total core antibody (anti-HBc and antiHBs [antibodies to HBV core and surface antigens] should be obtained prior to antiviral therapy. If there is evidence of current or prior HBV infection, additional testing should include markers of replication including HBV DNA. Initiation of therapy with an oral HBV suppressive agent is recommended if standard criteria for HBV therapy are met, based on initial testing prior to HCV therapy or during follow-up after HCV. If HBsAg is initially absent but markers of prior HBV infection (positive antibody to hepatitis B core antigen [HBcAb-positive] with or without antibody to hepatitis B surface antigen [HBsAb]) are detected, HBV reactivation should be excluded with HBV DNA testing if liver function tests rise during DAA therapy (see also https://www.hcvguidelines.org/evaluate/monitoring, https://easl.eu/wp-content/uploads/2018/10/HepB-English-report.pdf\textsuperscript{66})
**RESEARCH RECOMMENDATIONS**

- Studies of patients with CKD should clearly and transparently report separate results for CKD G1-G3, CKD G4-G5ND, and CKD G5D patients. Studies are needed in patients receiving peritoneal dialysis.

- Studies examining understudied DAAs, especially affordable therapies for potential use in low- and middle-income countries,\(^{67}\) should also be investigated in the various CKD populations.

- Studies should be conducted on the re-treatment of DAA regimen failures in CKD. Furthermore optimal therapy prior to and after kidney transplantation in some specific groups such as prior non-responders should be evaluated as well as treatment of NS5A-resistant variants.

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

- Studies should investigate the survival benefit for patients with CKD G5D and HCV following successful DAA therapy.
SUPPLEMENTAL DATA

Summary Table 2.1: DAAs in CKD G4-G5 (non-dialysis) patients, part 1 (SVR12 and adverse events)

Summary Table 2.2: DAAs in CKD G4-G5 (non-dialysis) patients, part 2 (kidney outcomes)

Evidence Profile A: Chapter 2. Treatment with direct-acting antiviral regimens in CKD G4-G5 non-dialysis patients

Summary Table 2.3: DAAs in CKD G5D (dialysis) population, part 1 (SVR12 and adverse events)

Summary Table 2.4: DAAs in CKD G5D (dialysis) population, part 2 (Death)

Summary Table 2.5: DAAs in CKD G5D (dialysis) population, part 3 (Quality of Life)

Evidence Profile B: Chapter 2. Treatment with direct-acting antiviral regimens in CKD G5D (dialysis) patients

Summary Table 2.6: DAAs in kidney transplant recipients, part 1 (SVR12 and adverse events)

Summary Table 2.7: DAAs in kidney transplant recipients, part 2 (graft outcomes and death)

Summary Table 2.8: DAAs in kidney transplant recipients, part 3 (eGFR and proteinuria)

Evidence Profile C: Chapter 2. Treatment with direct-acting antiviral regimens in kidney transplant recipients
REFERENCES


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

HCV infection remains more prevalent in CKD G5 patients compared with the general population. Although HCV infection can cause HCV-associated glomerular disease resulting in kidney failure, kidney transplant candidates may also have acquired HCV infection within a dialysis unit or may have been infected when they had received a previous transplant or were transfused in the era before systematic screening for HCV. Because of the deleterious effects of HCV infection in kidney transplant patients, evaluation of disease severity and need for antiviral therapy is crucial. Screening for HCV in kidney transplant candidates has been addressed in Chapter 1.

4.1 Evaluation and management of kidney transplant candidates regarding HCV infection

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

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

4.1.2.1: We recommend that patients with HCV, compensated cirrhosis and no portal hypertension undergo isolated kidney transplantation while patients with decompensated cirrhosis or clinically significant portal hypertension (i.e., hepatic venous pressure gradient ≥10 mm Hg or evidence of portal hypertension on imaging or exam) undergo a simultaneous liver-kidney transplantation (IB). Those with mild-to-moderate portal hypertension should be determined on a case-by-case basis.

4.1.2.2: We recommend referring patients with HCV and decompensated cirrhosis for combined liver-kidney transplantation (IB).
4.1.3: Timing of HCV treatment in relation to kidney transplantation (before vs. after) should be based on donor type (living vs. deceased donor), wait-list times by donor type, center-specific policies governing the use of kidneys from HCV-infected deceased donors, and severity of liver fibrosis (Not Graded).

4.1.3.1: We recommend that all kidney transplant candidates with HCV be considered for DAA therapy, either before or after transplantation (1A).

4.1.3.2: We suggest that HCV-infected kidney transplant candidates with a living kidney donor be considered for treatment before or shortly after transplantation depending on the anticipated timing of transplantation (2B).

RATIONALE

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

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

Prior to the era of DAA therapy, survival of patients with persistent HCV viremia after kidney transplantation was inferior compared with HCV-negative kidney transplant patients, but still higher than if they had remained on dialysis. Graft survival is
significantly decreased in untreated HCV-positive kidney transplant patients compared with HCV-negative patients.⁷,¹⁰-¹²,²¹,²² Although liver fibrosis progression in HCV-NAT (nucleic acid testing) positive kidney transplant patients is variable, development of cirrhosis and hepatocellular carcinoma (HCC) has been reported.²³-²⁶ As HCC typically develops only in HCV-infected patients with stage 3 or 4 fibrosis, surveillance for HCC should be offered if extensive fibrosis is present. It is important to note that the above associations between HCV infection and decreased graft and patient survival were derived from the era prior to the advent of DAAs for HCV infection.

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

4.1.2.1: We recommend that patients with HCV, compensated cirrhosis and no portal hypertension undergo isolated kidney transplantation while patients with decompensated cirrhosis or clinically significant portal hypertension (i.e., hepatic venous pressure gradient ≥10 mm Hg or evidence of portal hypertension on imaging or exam) undergo a simultaneous liver-kidney transplantation (1B). Those with mild-to-moderate portal hypertension should be determined on a case-by-case basis.

4.1.2.2: We recommend referring patients with HCV and decompensated cirrhosis for combined liver-kidney transplantation (1B).

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

In patients with compensated cirrhosis without clinically significant portal hypertension (i.e., patients with a hepatic venous pressure gradient ≥10 mm Hg or evidence of portal hypertension on imaging or exam, e.g., ascites, esophageal varices, collaterals on imaging),²⁷,²⁸ isolated kidney transplantation is recommended. HCV
clearance following treatment halts the progression of liver disease and may even induce regression of liver fibrosis.\textsuperscript{29} The Consensus Conference Group on simultaneous liver-kidney transplantation proposed that combined liver-kidney transplantation should be performed if patients have decompensated cirrhosis and/or clinically significant portal hypertension.\textsuperscript{30} Treatment of HCV in patients with decompensated cirrhosis is associated with increased risks of adverse effects, and the benefits in a patient waitlisted for a simultaneous liver-kidney transplantation are outweighed by the risks. The Portal Hypertension Collaborative Group stated that hepatic venous-pressure gradient predicts clinical decompensation in patients with compensated cirrhosis.\textsuperscript{31} Patients with cirrhosis who, despite having achieved SVR, have major hepatic complications such as ascites, hepatic encephalopathy, or worsening hepatocellular function should be evaluated for combined liver-kidney transplantation. Timing of antiviral therapy for HCV in candidates for combined liver transplant should be determined by the transplant program recognizing that organ allocation practices including use of organs from HCV-positive donors vary by country.

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

4.1.3.1: We recommend that all kidney transplant candidates with HCV be considered for DAA therapy, either before or after transplantation (1A).

4.1.3.2: We suggest that HCV-infected kidney transplant candidates with a living kidney donor be considered for treatment before or shortly after transplantation depending on the anticipated timing of transplantation (2B).

The use of DAAs has transformed the paradigm of treating HCV before and after kidney transplantation. DAAs can safely be used in patients on dialysis as well as post-transplant, with similar cure rates (\textgreater 95\%) to the broader population with HCV (see
Chapter 2). The main consideration, currently, is timing of HCV therapy in relationship to transplantation. Other considerations for planning therapy include living versus deceased donor, wait-list time by donor type, center-specific policy for acceptance of organs from HCV-infected deceased donors, and severity of liver fibrosis (Figure 2). Other factors such as candidate sensitization and patient preference can be also considered for choosing the timing of treatment. In HCV-infected patients who elect to undergo transplantation prior to DAA therapy, treatment with DAAs in the early post-transplant period is suggested in order to quickly eradicate HCV and prevent deleterious sequelae of persistent HCV viremia.
Figure 2. Proposed strategy in a hepatitis C virus (HCV)-infected kidney transplant candidate.
*Clinically significant portal hypertension is defined as hepatic venous pressure gradient ≥10 mm Hg or evidence of portal hypertension on imaging or exam, e.g., ascites, esophageal varices, collaterals on imaging. SKLT, simultaneous kidney-liver transplantation.
In patients with compensated cirrhosis without clinically significant portal hypertension, if living-donor kidney transplantation is anticipated without a long wait, HCV therapy can be deferred until after transplantation. If living-donor kidney transplantation is likely to be delayed more than 24 weeks, then HCV therapy can be offered before or after transplantation; this will allow 12 weeks of therapy and 12 weeks of follow-up to confirm SVR12.

Potential kidney recipients with compensated cirrhosis without clinically significant portal hypertension who are listed for kidney transplantation from a deceased donor at a center where kidneys from HCV-infected donors are available without a long wait, may wish to defer antiviral therapy to allow receipt of an organ from an HCV-positive donor. This determination should be made in consultation with a hepatologist to ensure the patient is not at increased risk of progressive liver disease with deferred treatment. However, the patient needs to provide written informed consent to receive a kidney from an HCV-infected donor (even though the patient already is infected), and the increased use of HCV-infected donors in HCV-negative recipients has diminished this waiting time advantage. In contrast, when the expected waiting time for a kidney allograft from an HCV-infected donor is long, the patient should be offered HCV therapy before transplantation.

Twice-yearly surveillance for HCC is indicated in any patient with cirrhosis, regardless of the cause. Evaluation for complications of cirrhosis is indicated irrespective of whether the patient receives antiviral therapy or not.
4.2 Use of kidneys from HCV-infected donors

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

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

4.2.3: We recommend that kidneys from HCV-infected donors be considered regardless of HCV status of potential kidney transplant recipients (1C).

4.2.4: When transplanting kidneys from HCV-infected donors into HCV-uninfected recipients, transplant centers must ensure that patients receive education and are engaged in discussion with sufficient information to provide informed consent. Patients should be informed of the risks and benefits of transplantation with an HCV-infected kidney, including the need for DAA treatment (Not Graded).

4.2.5: When transplanting kidneys from HCV-infected donors into HCV-uninfected recipients, transplant centers should confirm availability of DAAs for initiation in the early-post transplant period (Not Graded).

RATIONALE

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

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

The diagnosis of HCV infection is made by the detection of anti-HCV by enzyme-linked immunosorbent assay. When HCV-NAT testing is widely available,
all deceased donors should be tested for HCV NAT prior to organ procurement, and ideally before the organ is offered to potential recipients.

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

Potential living donors with HCV infection should be treated for HCV as in the general population and liver fibrosis should be assessed (see Chapter 2). Kidney function and proteinuria should be monitored during and after DAA therapy. In the absence of severe hepatic fibrosis, or evidence of kidney disease, living donation is feasible. If both the donor and recipient are infected with HCV, one can delay treatment of the donor if timely transplant has benefits to the recipient (e.g., avoiding dialysis in a recipient with limited vascular access), with little expected harms to the donor. If the recipient is HCV-negative, treatment of the donor should occur prior to transplantation in order to minimize any risks to the recipient, and added costs of treating two patients (donor and recipient).

4.2.3: We recommend that kidneys from HCV-infected donors be considered regardless of HCV status of potential kidney transplant recipients (1C).

4.2.4: When transplanting kidneys from HCV-infected donors into HCV-uninfected recipients, transplant centers must ensure that patients receive education and are engaged in discussion with sufficient information to provide informed consent. Patients should be informed of the risks and benefits of transplantation with an HCV-infected kidney, including the need for DAA treatment (Not Graded).

4.2.5: When transplanting kidneys from HCV-infected donors into HCV-uninfected recipients, transplant centers should confirm availability of DAAs for initiation in the early-post transplant period (Not Graded).

Prior to 2014, kidneys from HCV-infected donors were almost exclusively transplanted into HCV-infected patients. This was due to the limited treatment options, and the increased risk of death, graft loss, and severe liver disease compared with HCV
recipients who received kidneys from HCV-negative donors. However, with the advent of DAA therapy, and the rapid increase in the number of deceased donors infected with HCV in some parts of the world due to the opioid epidemic, kidneys from HCV-infected organs are increasingly being transplanted into HCV-negative patients.

The first two prospective studies of transplanting kidneys from HCV-infected donor into HCV-negative patients were published in 2017 and 2018, each with 10 participants. The THINKER trial transplanted donors with GT 1 or 4 HCV and began DAAs day 3 post-transplant and the EXPANDER trial transplanted donors with any genotype and began DAAs just prior to the transplant surgery; in both trials all patients were cured of HCV (SVR12). Since those initial publications, there have been multiple studies published on the safety and efficacy of transplanting kidneys from HCV-infected donors into HCV-negative patients (Summary Table 4.1). These studies have varied from formal prospective trials with institutional review board approval, registration in clinicaltrials.gov, and prospective ascertainment of outcomes and adverse events, to ‘standard-of-care’ center protocols with retrospective data collection. The published studies have also varied in the DAA regimen used, the timing of initiation of DAAs (ranging from pre-transplant to >90 days post-transplant), and treatment duration (ranging from ultra-short courses [4 days] to full-course therapy of 12 weeks; Summary Table 4.1).

There have been 13 published studies with at least 10 participants in which kidneys from HCV-infected donors were transplanted into HCV-negative recipients. Of the 396 HCV-negative patients who were transplanted with a kidney from an HCV-infected donor, followed by DAA treatment, the HCV cure (SVR12) rate was 99.0% (95% CI: 97.3-99.6%). Post-transplant outcomes were excellent with ≥ 98% 1-year patient and graft survival (Evidence Profile D). However, studies were mostly noncomparative and outcome reporting was typically unclear, resulting in only low strength of evidence in the outcome estimates. Reported hepatic complications were rare, although the retrospective studies did not have formal ascertainment of adverse events and serious adverse events, and/or pre-specified definitions of liver injury. Of the 13 published studies included in our analysis, there were 3 reported cases of fibrosing
cholestatic HCV, all of which occurred in patients with initiation of DAAs more than 30 days post-transplant. The other reported complications are shown in Summary Table 4.1, but overall, are in line with what is expected in kidney transplant recipients.

The published data on transplanting kidneys from HCV-infected donors into HCV-negative recipients demonstrates that the practice can be associated with HCV cure rates that equal those with chronic HCV infection, with excellent 1-year post-transplant outcomes.\textsuperscript{33, 40} These data therefore demonstrate that kidneys from HCV-infected donors should not be preferentially offered to patients with HCV infection. However, this recommendation is associated with several caveats. First, the published data have focused on short-term outcomes, and data beyond one year are limited. Secondly, there have been reports of higher-than-expected cytomegalovirus and BK viremia in HCV-negative recipients of a kidney from an HCV-infected donor,\textsuperscript{41} and this needs to be studied in a prospective fashion with matched comparators. Third, all HCV-negative patients received formal education about the risks and unknowns of being transplanted with a kidney from an HCV-infected donor, and this practice, along with a formal informed consent process, must be part of any protocol that involves transplanting kidneys from HCV-infected donors into HCV-negative patients.\textsuperscript{42} Because the only reported cases of fibrosing cholestatic HCV in the setting of transplanting kidneys from HCV-infected donors into HCV-negative recipients occurred with delayed initiation of therapy (two of the cases were >80 days post-transplant), it is recommended to start DAA therapy as early as possible. However, there are insufficient data to determine the exact time point at which DAA therapy should be started (e.g., 3 days vs 7 days vs 28 days). But because of the potential for insurance delays and/or denials for DAA therapy given their off-label use in the setting of transplanting kidneys from HCV-infected donors into HCV-negative recipients, it is critical that any center performing such transplants have a plan to ensure patients can be treated in the setting of insurance denials, or delays that could lead to avoidable HCV-related liver or kidney injury.\textsuperscript{43-45} Lastly, although there have been trials of short-course therapy, more data are needed to determine whether short-course therapy is associated with similar HCV cure rates, and at this time, it is recommended that patients be treated with a full course of DAAs as suggested by the AASLD/IDSA guidelines.
4.3 Use of maintenance immunosuppressive regimens

4.3.1: We recommend that kidney transplant recipients being treated with DAAs be evaluated for the need for dose adjustments of concomitant immunosuppressants (IC).

RATIONALE

DAAs are highly effective and the degree of immunosuppression has not been associated with a reduced probability of HCV cure. DAAs directly act on the virus’s replicative machinery, in contrast to interferon which relied in part on the patient’s own immune system. The primary concern as it relates to immunosuppression and HCV treatment is the interaction between the different DAAs and transplant immunosuppression. The primary interaction is between cyclosporine and DAA therapy. Concomitant use of CNIs and DAAs requires close monitoring and dose reduction given that some DAAs can increase immunosuppressant levels several-fold. Examples include ombitasvir/paritaprevir with dasabuvir. In addition DAA levels may be raised by cyclosporine use, for instance GLE/PIB, and this DAA regimen can raise tacrolimus levels, mandating close monitoring of tacrolimus levels. Further details can be found in the section on drug-drug interactions in Chapter 2 and the reader is advised to consult the Hepatitis Drug Interactions website from the University of Liverpool (http://www.hep-druginteractions.org) or the AASLD/EASL guidelines for the latest guidance.
4.4 Management of HCV-related complications in kidney transplant recipients

4.4.1: We suggest that patients previously infected with HCV who achieved SVR before transplantation undergo testing by NAT 3 months after transplantation or if liver dysfunction occurs (2D).

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

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

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

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

RATIONALE

4.4.1: We suggest that patients previously infected with HCV who achieved SVR before transplantation undergo testing by NAT 3 months after transplantation or if liver dysfunction occurs (2D).

Kidney transplantation outcomes in patients with HCV without extensive fibrosis who are successfully treated before transplantation should be equivalent to those in uninfected transplant recipients. With achievement of SVR12, viral relapse is highly unlikely, although kidney transplant recipients with unexplained hepatic dysfunction should undergo HCV testing as part of the routine diagnostic workup to exclude HCV reacquisition.
4.4.2: Kidney transplant recipients with cirrhosis should have the same liver disease follow-up as non-transplant patients, as outlined in the American Association for the Study of Liver Diseases (AASLD) guidelines (Not Graded).

Kidney transplant recipients with cirrhosis require surveillance for complications of their liver disease such as HCC as outlined in AASLD/EASL guidelines on management of cirrhosis in the general population.

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

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

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

HCV infection has been reported as a risk factor for the development of proteinuria in kidney transplant recipients. Several different types of glomerular lesions have been described after kidney transplantation in HCV RNA–positive patients including recurrent or de novo cryoglobulinemic or non-cryoglobulinemic membranoproliferative glomerulonephritis (MPGN), membranous nephropathy, acute transplant glomerulopathy, anti-cardiolipin related thrombotic microangiopathy, and chronic transplant glomerulopathy. MPGN and membranous nephropathy are the most frequent lesions related to HCV infection. The most common presentation is proteinuria with or without microhematuria, or nephrotic syndrome. The pathogenesis of MPGN seems to be related to the deposition of immune complexes containing HCV RNA in the glomerulus.

After HCV NAT–positive patients have undergone kidney transplantation, clinicians should screen for proteinuria and microhematuria, although there are no data to recommend the exact timing. In the case of urine protein-creatinine ratio > 1 g/g or 24-
hour urine protein (protein excretion rate) greater than 1 g on two or more occasions, a
graft biopsy is indicated. Pathological examination should include immunofluorescence
and electron microscopy. In the case of suspected transplant glomerulopathy, electron
microscopy is mandatory to make the differential diagnosis with HCV-related MPGN.3, 54

For HCV-related glomerular disease, DAA therapy is indicated.55-64 In severe
HCV-related cryoglobulinemic MPGN, in addition to antiviral therapy with DAAs,
rituximab and, in severe cases, plasmapheresis should be considered.3 This is discussed
in detail in Chapter 5.
RESEARCH RECOMMENDATIONS

- Optimal timing of antiviral therapy in candidates for kidney transplantation should be clarified. Because the time to transplantation with kidneys from deceased donors is unpredictable, delaying treatment carries higher vascular, metabolic, and malignancy risks as well as the risk of drug–drug interactions with CNIs after transplantation. As such, treatment before transplantation may be more appropriate. However, in regions where the prevalence of anti-HCV-positive donors is high, post-kidney transplant therapy should be considered.

- Future studies are needed to determine the long-term outcomes of transplantation of HCV-viremic kidneys into HCV-uninfected transplant recipients. The National Institutes of Health is sponsoring a multi-center trial of transplanting kidneys from HCV-infected donors into HCV-negative recipients (NCT04075916) that began on April 15, 2021 that seeks to address several knowledge gaps: a) HCV cure rates with high precision; b) longer-term post-transplant kidney function; c) survival benefit of agreeing to being transplanted with a kidney from an HCV-infected donor; d) risk of post-transplant cytomegalovirus disease versus matched comparators; and e) evidence of chronic kidney pathology in kidneys from HCV-infected donors versus matched comparators.

- Future studies are needed to determine the preferred timing of DAA treatment after transplantation with an HCV-infected kidney, including an assessment of the benefits of earlier DAA therapy (e.g., peri-transplant or immediate post-transplant) and the risks of delayed therapy (e.g., beyond four weeks post-transplant). This would allow better consideration of how long DAA therapy can safely be delayed.

- More data are needed about the safety and efficacy of treating with short-course DAA therapy, including the potential prevention of HCV. Such studies should
also include an examination of the logistics of implementing protocols in standard-of-care practice.
SUPPLEMENTAL DATA

Summary Table 4.1: DAA treatment in HCV-positive donors/HCV-negative recipient kidney transplantation

Evidence Profile D: Chapter 4. DAA treatment for HCV donor-positive to HCV-negative recipients
REFERENCES


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

In addition to chronic liver disease, HCV infection may also lead to extrahepatic manifestations, including kidney disease and mixed cryoglobulinemia. Although chronic HCV infection may result in tubulointerstitial injury, HCV-associated glomerulonephritis (GN) is the most frequent type of kidney disease associated with HCV, MPGN being the most common one.\(^1\)\(^,\)\(^2\) However, the incidence of HCV-associated GN is low, as recently confirmed by large scale studies. Moorman \textit{et al.}\(^3\) found a frequency of nephrotic syndrome of 0.3% in a large cohort of HCV RNA viremic patients. In the same cohort, the frequency of cryoglobulinemia was 0.9%. Identical results have been offered by the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project, which examined the comorbidities in HCV-positive patients hospitalized in the United States during 2004-2011. The rate of ‘nephrotic syndrome or MPGN’ ranged between 0.47% and 0.36%.\(^4\) According to a retrospective cohort study of Veterans Affairs patients with a positive HCV RNA test who received a first course of DAAs between 2012 and 2016 (n = 45,260), the baseline prevalence of GN (ICD-9/10 diagnosis) was around 2.6%.\(^5\)

The extrahepatic burden of HCV infection was also evaluated by El-Serag \textit{et al.}, who performed a hospital-based case-control study among United States male veterans from 1992 to 1999. They identified 34,204 patients infected with HCV (cases) and 136,816 randomly selected patients without HCV (controls).\(^6\) A greater rate of MPGN (0.36% vs. 0.05%, \(P < 0.0001\)) but not membranous nephropathy (0.33% vs. 0.19%, \(P = 0.86\)) was found among patients with HCV. HCV-induced GN occurs frequently in association with mixed cryoglobulinemia, a systemic vasculitis characterized by involvement of small, and less frequently, medium-size vessels.\(^1\)\(^,\)\(^2\)\(^,\)\(^7\)\(^-\)\(^9\) Mixed cryoglobulinemia represents 60% to 75% of all cryoglobulinemia cases and is observed in patients with connective tissue diseases, chronic infections or lymphoproliferative disorders, all grouped under the term “secondary mixed cryoglobulinemia.” HCV has been implicated in the etiology of 80% to 90% of previously “idiopathic” mixed cryoglobulinemia cases.\(^7\)\(^,\)\(^8\) In general, HCV is associated with type II mixed
cryoglobulinemia (cryoglobulins consisting of polyclonal IgG and monoclonal IgM with rheumatoid factor activity), although it is also less frequently associated with type III mixed cryoglobulinemia (cryoglobulins consisting of polyclonal IgG and polyclonal IgM).

5.1: HCV-infected patients with a typical presentation of immune-complex proliferative glomerulonephritis can be managed without a confirmatory kidney biopsy. However, a biopsy may be indicated in certain clinical circumstances (Figure 3) (Not Graded).

5.2: We recommend that patients with HCV-associated glomerulonephritis receive antiviral therapy (IA).

5.2.1: We recommend that patients with HCV-associated glomerulonephritis, stable kidney function, and without nephrotic syndrome be treated with DAAs prior to other treatments (IC).

5.2.2: We recommend that patients with cryoglobulinemic flare or rapidly progressive glomerulonephritis be treated with both DAAs and immunosuppressive agents with or without plasma exchange (IC).

5.2.2.1: The decision whether to use immunosuppressive agents in patients with nephrotic syndrome should be individualized (Not Graded).

5.2.3: We recommend immunosuppressive therapy in patients with histologically active HCV-associated glomerulonephritis that does not respond to antiviral therapy, particularly those with cryoglobulinemic kidney disease (IB).

5.2.3.1: We recommend rituximab as the first-line immunosuppressive treatment (IC).
Figure 3. Indications for biopsy in patients with HCV and severe GN. Algorithm above assumes that patient with HCV and CKD is already receiving DAA treatment. Systemic signs of cryoglobulinemia include skin lesions such as purpura, arthralgias, and weakness. HCV, hepatitis C virus; GFR, glomerular filtration rate; GN, glomerulonephritis; IS, immunosuppression; RPGN, rapidly progressive glomerulonephritis; SVR, sustained virologic response.
RATIONALE

5.1:  **HCV-infected patients with a typical presentation of immune-complex proliferative GN can be managed without a confirmatory kidney biopsy. However, a biopsy may be indicated in certain clinical circumstances (Figure 3) (Not Graded).**

Clinical manifestations of glomerular disease in HCV-infected patients include the presence of proteinuria and/or microscopic hematuria, with or without a reduction in GFR. It remains unclear why only a minority of patients with HCV infection develop kidney abnormalities, although polymorphisms in several genes have been suggested as risk factors for onset of cryoglobulinemia.\(^{10-12}\) Glomerular disease associated with HCV infection has been described in the presence or absence of significant liver disease.\(^{13,14}\)

The indications for a kidney biopsy in patients with HCV infection and signs of glomerular disease are not markedly different from the usual indications prompting a kidney biopsy in other glomerular diseases.\(^{15}\) Kidney biopsy remains invaluable to assess the precise histological picture of the disease and the probability that the observed lesions are causally related to HCV infection. Other glomerular diseases (e.g., diabetic nephropathy) are not infrequently reported among patients with HCV infection.\(^{16}\) This may partly result from the fact that the incidence of diabetes is known to be greater in HCV-infected patients than in the general population.\(^{17,18}\) In addition, the histology will provide an assessment of the extent of active lesions that may be amenable to immunosuppressive treatment versus chronic lesions that are unlikely to respond to immunosuppression. Thus, some patients may be able to avoid immunosuppression in the presence of severe chronic lesions, as long as there is no extrarenal indication warranting immunosuppression.\(^{15}\)

As almost all patients with chronic HCV (with or without GN) should be treated with DAAs, a kidney biopsy may not change management in the majority of HCV patients with renal involvement. Most HCV-GN patients can be managed without a biopsy if there is strong suggestion of active GN based on typical clinical presentation (hematuria, proteinuria, slowly declining GFR). In a recent study by Ana Perez de Jose
et al., more than 50% of patients with HCV-mixed cryoglobulinemia with kidney involvement were treated with DAAs based on clinical presentation, without a kidney biopsy. Treatment with DAAs should not be delayed or postponed while waiting for a kidney biopsy. This is particularly true in patients with chronic liver disease who have a prohibitively high risk of bleeding after a kidney biopsy (e.g., due to severe thrombocytopenia, coagulopathy, concern for retroperitoneal varices etc.). However, if clinical signs of kidney disease (hematuria, eGFR, albuminuria) do not improve or at least stabilize despite achieving SVR, or if there is evidence of rapidly progressive disease, a kidney biopsy may be warranted to confirm the diagnosis prior to escalating the therapy.

A biopsy is therefore not a prerequisite for initiating DAAs for the treatment of HCV-associated GN; kidney biopsy should, however, be performed if immunosuppressive therapy is planned or an alternative diagnosis other than HCV-related GN is suspected (Figure 3). With such a strategy, the small but not insignificant risk of complications from a kidney biopsy may be avoided in most patients. Systematic reviews have found that after a kidney biopsy, the risk of bleeding to the extent of requiring transfusion is around 1%-1.5%; the need for interventions required to stop bleeding is around 0.3%; and the risk of death is approximately 0.06%.

The most common type of HCV-related GN on a kidney biopsy is immune complex-mediated MPGN, usually reflecting the presence of type II cryoglobulinemia. Distinctive histological features of cryoglobulinemic GN, especially in patients with progressive deterioration of kidney function, include intraglomerular deposits, which are commonly seen in a subendothelial location. Cryoglobulin deposits may sometimes occlude the capillary lumen (seen as eosinophilic intraluminal thrombi on light microscopy). Glomeruli may show prominent hypercellularity as a result of infiltration of glomerular capillaries by mononuclear and polymorphonuclear leukocytes. Glomeruli frequently show accentuation of lobulation of the tuft architecture with a combination of increased matrix and mesangial cells, capillary endothelial swelling, splitting of capillary basement membrane, and accumulation of eosinophilic material representing precipitated immune complexes or cryoglobulins. The glomerular basement membrane often exhibits
a double contour caused by the interposition of monocytes between the basement membrane and the endothelium. On electron microscopy, large subendothelial deposits are present. Vasculitis of small renal arteries is present in 30% of cases. Histological features of exudative or lobular MPGN are associated with the occurrence of nephrotic and/or nephritic syndromes, whereas mesangial proliferation and matrix expansion are prevalent in cases with intact kidney function and isolated proteinuria and/or microscopic hematuria.

Cases of HCV-associated MPGN without cryoglobulinemia have not infrequently been reported. In these patients, the clinical picture, histological features and laboratory data are indistinguishable from “classical” idiopathic immune complex-mediated MPGN. Both subendothelial and mesangial immune complexes can be identified by electron microscopy typically without a distinctive substructure. In both forms of HCV-associated GN, immunofluorescence commonly reveals deposition of IgM, IgG, and C3 in the mesangium and capillary walls.

PLA2R-negative membranous nephropathy is also observed in association with chronic HCV infection. Whether this is a true association is unclear. Other glomerular diseases that have been occasionally reported in chronic HCV infection are acute proliferative GN, focal segmental glomerulosclerosis, IgA nephropathy, thrombotic microangiopathy, rapidly progressive GN, fibrillary GN, and immunotactoid glomerulopathy. However, their pathogenic link with HCV remains even more uncertain than for membranous nephropathy.

The pathogenesis of glomerular disease associated with HCV infection involves immune-mediated damage (including effects from cryoglobulinemia) as well as direct effects of virus on renal tissue. It appears that HCV binds and penetrates into the renal parenchymal cells via the CD81 and SR-B1 receptors. HCV RNA has been found in mesangial cells, tubular epithelial cells, and endothelial cells of glomerular and tubular capillaries. The deposition of immune complexes containing HCV proteins in the glomerular basement membrane has been cited in the pathogenesis of HCV-associated membranous nephropathy. HCV-related granular protein deposits located in the mesangium have been observed in patients with HCV-related MPGN; they are probably
related to higher degrees of proteinuria. Viral antigens have been found by immunohistochemistry, in situ hybridization, and laser capture microdissection.

5.2: We recommend that patients with HCV-associated glomerulonephritis receive antiviral therapy (1A).

5.2.1: We recommend that patients with HCV-associated glomerulonephritis, stable kidney function, and without nephrotic syndrome be treated with DAAs prior to other treatments (1C).

Randomized controlled trials (RCTs) are lacking to help establish evidence-based recommendations to treat glomerular lesions associated with HCV infection. Until this information is available, the treatment of HCV-associated GN should be driven by the severity of proteinuria and kidney failure. However with DAA therapy now available, all HCV-infected patients are candidates for antiviral therapy.

The development of kidney disease among patients with mixed cryoglobulinemia has particular importance because kidney involvement confers a poor prognosis. In view of the role of HCV in the pathogenesis of cryoglobulinemic GN, antiviral therapy has been used to cure HCV infection and ameliorate renal injury. The evidence regarding the impact of antiviral treatment of HCV-associated GN was, until recently, very limited and consisted mostly of anecdotal reports and small-sized observational studies.

With the arrival of DAAs, interferon-based regimens are now considered obsolete. These early antiviral studies nevertheless provided valuable insight into the etiological role of HCV in the pathogenesis of GN as well as information about the renal benefits of anti-HCV therapy.

An older systematic review of comparative studies of interferon versus immunosuppressive regimens for HCV-induced GN suggested some benefit of interferon to reduce proteinuria, but with a highly imprecise estimate: OR 1.92; 95% CI: 0.39–9.57. However, in a sensitivity analysis including only controlled trials using standard interferon doses, the odds ratio (OR) was 3.86 (95% CI: 1.44–10.3). Of note, in all patients with reduction in proteinuria, HCV RNA clearance was observed at the end of antiviral therapy.
A subsequent systematic review concluded that interferon-α therapy decreased proteinuria in HCV-positive CKD patients. At the end of antiviral therapy, the summary estimate of the mean decrease in proteinuria was 2.71 g/24 h (95% CI: 1.38–4.04). The decrease in proteinuria following antiviral therapy reflected HCV RNA clearance. Although serum creatinine did not significantly improve after interferon-α, stabilization of serum creatinine was achieved.

Given the remission of hematuria, proteinuria, and improvement of GFR in patients with HCV-associated GN after HCV RNA clearance by DAAs, antiviral therapy with DAA regimens should be considered the first-line treatment in patients without nephrotic syndrome and a relatively stable kidney function (Summary Tables 5.1-5.2 and Evidence Profile E). In addition, standard of care for proteinuric CKD should be implemented. This includes optimal BP control, frequently employing multidrug therapy including diuretics. Also, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be used to treat proteinuria.

Encouraging results have been obtained with interferon-free DAA regimens for HCV-associated GN; a small group of 7 patients with symptomatic mixed cryoglobulinemia and GN (5 had a biopsy-proven MPGN and 2 were diagnosed clinically) underwent SOF-based regimens (6 with SOF and simeprevir and 1 with SOF and RBV). Only 1 patient was receiving immunosuppression concurrent with antiviral therapy. All patients had improvement in eGFR and reduction in proteinuria. SVR was achieved in 6 out of 7 patients.

In another cohort of 44 consecutive patients with HCV-associated mixed cryoglobulinemia, 4 patients had renal involvement. Treatment with SOF-based DAA therapy appeared to be highly effective (SVR12, 100%) and safe with improvement in kidney disease parameters.

An updated literature review from 2018 to date identified 18 reports (94 unique patients). All patients underwent interferon-free, RBV-free antiviral therapy with DAAs for HCV-associated GN. The SVR rate ranged between 97% and 100%. Many patients achieved partial or complete clinical remission of kidney disease with DAAs (alone or in combination with immunosuppression). In addition, de novo HCV GN,
persistent HCV GN, or persistent serum cryoglobulins after successful therapy with DAAs was occasionally observed. It has been suggested that in a subset of patients, HCV-GN can persist despite achieving SVR likely due to residual B cell clones producing rheumatoid factor. Also, de novo HCV GN after rituximab was noted, and this was attributed to a flare-up of HCV induced by rituximab.

Of the 45,260 HCV RNA-positive patients treated with various DAA regimens (with/without RBV) (mean follow-up of 2.01 years) at the United States Department of Veterans Affairs, 41,711 (92.2%) obtained SVR. The fully adjusted hazard model showed that the incidence rate for GN after SVR was significantly reduced, adjusted hazards ratio (HR) 0.61; (95% CI: 0.41-0.90; \( P = 0.0126 \)).

These studies suggest that interferon-free (and almost always, RBV-free regimens) with DAAs offer excellent virological and clinical response in a difficult-to-treat condition such as HCV-associated mixed cryoglobulinemia with renal involvement or non-cryoglobulinemic HCV-associated GN. In fact, the SVR rates shown above are comparable to the SVR12 rates reported with similar regimens in other non-cryoglobulinemic real-world groups. However, larger and controlled studies are welcome to confirm these results.

Our systematic review supports the notion that DAAs have a beneficial impact on patient and kidney survival (Summary Table 5.1 and Evidence Profile E). In a multicenter study from Spain, 139 patients with HCV-mixed cryoglobulinemia (65 patients with biopsy proven HCV GN) were followed for a median duration of 138 months. Among 100 patients treated with unspecified DAAs, 4% died and 6% had doubling of serum creatinine or kidney failure. In contrast, among 15 untreated patients, two-thirds died and additional 20% had kidney loss. The HR for mortality was 0.12 (95% CI: 0.04-0.40) and for kidney loss 0.10 (95% CI: 0.04-0.33). Two studies of patients treated with DAAs supported the reduced death rate with 9% deaths at 6-48 months and 3% at 15 months.

Despite this impressive efficacy, antiviral treatment of HCV-associated GN has some limitations. The clinical benefit in patients who achieve SVR may occasionally be transient, and a dissociation between viral and renal responses can occur. Two
long-term (1- to 2-year) studies reported high rates of marked improvement of various cryoglobulinemia-related manifestations after SVR with DAAs, but confirmed that relapses of vasculitis may occasionally occur despite achieving SVR.\textsuperscript{61, 77}

\textbf{5.2.2: We recommend that patients with cryoglobulinemic flare or rapidly progressive glomerulonephritis be treated with both DAAs and immunosuppressive agents with or without plasma exchange (1C).}

\textbf{5.2.2.1: The decision whether to use immunosuppressive agents in patients with nephrotic syndrome should be individualized (Not Graded).}

Immunosuppressive agents have been administered to patients with serious, life-threatening complications of mixed cryoglobulinemia, such as MPGN, severe neuropathy, or extensive skin disease like ulcers or necrotic purpura. Rituximab, a chimeric monoclonal antibody, targets CD20, a surface antigen of B cells. It works by depleting, normal and pathogenic B cells and has recently been used with great success to suppress the synthesis of cryoglobulins. Cyclophosphamide too has been employed to reduce cryoglobulin synthesis; steroid pulses have been given to aggressively treat glomerular inflammation, and plasma exchange has been utilized to remove circulating cryoglobulins from the plasma and consequently reduce the deposition of immune complexes in the kidneys.

In patients with rapidly progressive kidney failure or acute cryoglobulinemic flare, control of disease by immunosuppressive agents, with or without plasma exchange (3 liters of plasma thrice weekly for 2–3 weeks), should be considered before or concurrently with the initiation of DAA therapy. Potential regimens include rituximab (375 mg/m\textsuperscript{2} weekly for 4 weeks, or two doses of 1 g given 14 days apart) with or without corticosteroids (see below), or cyclophosphamide (2 mg/kg/d, adjusted for eGFR, for 2–4 months) plus methylprednisolone pulses 0.5 to 1 g/d for 3 days. However, recent trials favor the use of rituximab with or without steroids compared to older immunosuppressive regimens like cyclophosphamide or azathioprine.\textsuperscript{78-80} Importantly, if rituximab is combined with plasma exchange, it should be given after a plasma-exchange session and several days before the next one. As per discretion of the treating clinician, immunosuppressive regimen alone or combined with DAA therapy is suggested as the
initial approach. In patients with nephrotic syndrome, immunosuppressive treatment in addition to DAAs should be considered in patients who have significant associated complications such as thromboembolic disease, severe hypoalbuminemia or anasarca etc.). Nephrotic range proteinuria (proteinuria > 3.5 g/day) alone does not warrant the use of immunosuppressive treatment as such patients can achieve remission of proteinuria after treatment with DAAs.19 Until the DAA era, combined therapy with corticosteroids and immunosuppressive agents (e.g., treatment using sequentially cyclophosphamide and azathioprine) was used while awaiting a response, if any, to interferon-based antiviral therapy. This approach was typically used because of the relatively poor prognosis of HCV-associated mixed cryoglobulinemia with GN with interferon-based treatment alone.35 However, given the much better prognosis with DAAs and/or rituximab, we strongly suggest that older immunosuppressive regimens should be used only if rituximab is unavailable or unaffordable.

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

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

Immunosuppressive therapies are typically reserved for patients with HCV-associated mixed cryoglobulinemia with severe disease manifestations, such as progressive glomerular disease. In addition to conventional immunosuppressants, which target inflammation at the glomerular level, encouraging results have been obtained with rituximab, a human-mouse chimeric monoclonal antibody that binds to the B-cell surface antigen CD20 and selectively targets B cells.78-83 Rituximab interferes with synthesis of cryoglobulins, monoclonal IgM, and renal deposition of immune complexes. An important pathogenetic feature of mixed cryoglobulinemia (including cryoglobulinemic GN) is chronic stimulation of B lymphocytes by HCV and widespread autoantibody synthesis related to HCV-induced lowering of cell activation threshold.
Two RCTs have demonstrated the superiority of rituximab monotherapy as compared with conventional immunosuppressive therapy (i.e., corticosteroids, azathioprine, cyclophosphamide, methotrexate, and plasma exchange) for the treatment of HCV-associated cryoglobulinemic vasculitis in patients who failed or were not eligible for interferon therapy. However, importantly, only a minority of the included patients had renal involvement. Rituximab was well tolerated and was effective in 71% to 83% of patients with HCV-associated cryoglobulinemic vasculitis. Frequent relapses may occur after finishing treatment with rituximab when B cells re-emerge in the peripheral blood; in addition, repeated rituximab infusions may expose patients to opportunistic infections.

In a recent prospective, single-center study, rituximab was administered to 31 patients (27 anti-HCV positive) with mixed cryoglobulinemia (type II in 29 individuals and type III in 2) and diffuse MPGN (n = 16 cases), peripheral neuropathy (n = 26 cases) and severe skin ulcers (n = 7 cases). Five patients were also given three pulses of 500 mg of methylprednisolone. No further immunosuppressive or antiviral agents were given. Complete remission of pre-treatment active manifestations was observed in all patients with purpuric lesions and non-healing vasculitic ulcers, and in 80% of the peripheral neuropathies. 16 patients with cryoglobulinemic nephropathy (diffuse MPGN and mixed cryoglobulinemia) who were HCV antibody positive received rituximab at a dose of 375 mg/m², according to a “4 + 2” protocol (days 1, 8, 15, and 22 plus one dose 1 and 2 months later). Safety and efficacy of rituximab was evaluated over a long-term follow-up (mean: 72.5 months). A significant improvement of cryoglobulinemic GN was found, starting from the second month after rituximab (serum creatinine from 2.1 ± 1.7 mg/dl [186 ± 150 μmol/l] to 1.5 ± 1.6 mg/dl [133 ± 141 μmol/l], P < 0.05; and 24-hour proteinuria from 2.3 ± 2.1 to 0.9 ± 1.9 g/24 hr, P < 0.05). Two months after the initial rituximab treatment, a marked amelioration in serum complement C4 and cryocrit was recorded. No clinically relevant side effects were recorded. Re-induction with rituximab was carried out in 9 (out of 31 patients) who relapsed after a mean of 31.1 (12-54) months, again with beneficial effects. Six patients died (median of 55 months) after their rituximab cycle, due to cardiovascular events (mean age of 75.3 years). The probability
of being disease-activity free after a single course of rituximab was 65% at 5 years, and 50% at 5 years after a second course following relapse.

A point of caution is important to note that rituximab, which selectively targets B cells, has been associated with severe infectious complications including exceptionally, reactivation of HCV, but more frequently, HBV. The risk of reactivation of HBV infection has been added to the existing “Black Box” warning on the rituximab label by the Food and Drug Administration (FDA) in 2013. Severe bacterial infections after rituximab therapy have been observed in kidney transplant recipients and in the non-transplant setting. Admittedly, these complications were mostly observed in patients receiving multiple immunosuppressive agents. Infectious episodes have been frequently reported in a susceptible patient subgroup (age > 70 years, GFR < 60 ml/min per 1.73 m², and concomitant high-dose corticosteroids) and were fatal in some patients. Fatal cholestatic liver disease due to HCV reactivation after a single dose of rituximab has been also observed after kidney transplant.

In addition to conventional or selective immunosuppressive agents, additional immunosuppressive agents such as MMF may deserve further evaluation. Preliminary evidence suggests that MMF can be effective for maintaining remission of HCV-associated cryoglobulinemic GN.

In summary, patients with mild or moderate forms of HCV-associated GN with stable kidney function and without nephrotic syndrome should be managed first with a DAA regimen. Patients with severe cryoglobulinemia or severe glomerular disease induced by HCV (i.e., nephrotic syndrome with associated complications or rapidly progressive GN) should be treated with immunosuppressive agents (preferably with rituximab as the first-line agent) and/or plasma exchange in addition to DAA therapies. Patients with HCV-associated GN who do not respond to, or are intolerant of, antiviral treatment should also be treated with immunosuppressive agents. Clinical indicators that HCV-associated GN is responding to treatment with antiviral therapy would include improvement in hematuria, degree of proteinuria and stabilization (or improvement) in GFR. Therefore, in all cases, achievement of SVR after DAA treatment, changes in kidney function, evolution of proteinuria and hematuria, and side effects from antiviral
therapy must be carefully monitored. Finally, the standard of care of proteinuric CKD should be implemented. This includes optimal blood pressure control, frequently employing multidrug therapy including diuretics. In addition, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers should be used to treat proteinuria.

RESEARCH RECOMMENDATIONS

- Occult HCV infection (detectable HCV RNA in peripheral blood mononuclear cells and/or in serum after centrifugation) could be involved in the pathogenesis of glomerular disease among patients negative for HCV RNA. We need large-sized studies with appropriate technology to assess the relationship between occult HCV and glomerular disease.

- The efficacy and safety of DAA therapies and/or immunosuppressive agents for the treatment of HCV-associated GN should be confirmed in large controlled clinical studies with longer follow-up.

- The antiviral approach to the treatment of HCV-associated GN has improved with the introduction of interferon-free and RBV-free regimens. Typically, patients with HCV-associated GN receive a high number of concomitant drugs, including cytotoxic agents. The potential risk resulting from drug–drug interactions should be studied in patients with HCV-induced GN.

- The role of immunosuppressive agents in the management of aggressive HCV-associated GN (i.e., severe nephrotic syndrome, rapidly progressive decline of GFR) needs to be further clarified in light of ultra-short DAA treatment courses.

- Numerous questions regarding the use of rituximab in HCV-positive GN remain. Rituximab has been administered in HCV GN patients for whom DAAs failed to induce clinical remission; alternatively, rituximab has been given as add-on to DAAs. In this vein, what is the optimal timing and dosing of periodic rituximab infusions for relapsers? The role of rituximab as first-line or rescue therapy needs to be defined further.
Severe infections after rituximab therapy frequently occur in patients who are older than 50 years, have kidney disease, and report concomitant use of high-dose corticosteroids. Future studies should delineate how best to avoid infections associated with immunosuppression regimens.
SUPPLEMENTAL DATA

Summary Table 5.1: HCV-associated GN DAA treatment, categorical outcomes

Summary Table 5.2: HCV-associated GN DAA treatment, continuous outcomes

Evidence Profile E: Chapter 5. Management of HCV-associated glomerulonephritis
REFERENCES


Outcomes of Patients With Hepatitis C Virus-Associated Cryoglobulinemia Treated With

cryoglobulinemia vasculitis treatment: From interferon-based to direct-acting antivirals
era. *Liver Int* 2017; **37**: 1805-1813.

44. Emery JS, Kuczynski M, La D, et al. Efficacy and Safety of Direct Acting Antivirals for
the Treatment of Mixed Cryoglobulinemia. *Am J Gastroenterol* 2017; **112**: 1298-1308.

45. Gragnani L, Piluso A, Urraro T, et al. Virological and Clinical Response to Interferon-
Free Regimens in Patients with HCV-Related Mixed Cryoglobulinemia: Preliminary
Results of a Prospective Pilot Study. *Curr Drug Targets* 2017; **18**: 772-785.

therapy with direct-acting antivirals for hepatitis C virus-associated mixed

47. Lauletta G, Russi S, Pavone F, et al. Direct-acting antiviral agents in the therapy of

antiviral agents (DAAs) therapy for HCV-related mixed cryoglobulinaemia: a multicentre

Treatment of HCV-Associated Cryoglobulinemia Vasculitis. *Gastroenterology* 2017;
**153**: 49-52 e45.


METHODS FOR GUIDELINE DEVELOPMENT

Aim

The overall aim of this project was to update a portion of the KDIGO clinical practice guideline (CPG) for the management of patients with CKD and HCV infection. The guideline consists of recommendation statements, rationale text, and a summary of systematically generated evidence on relevant pre-defined clinical topics. The general guideline development method is described below.

Overview of process

The development process for the KDIGO 2022 CPG Update for the Prevention, Diagnosis, Evaluation and Treatment of Hepatitis C in CKD included the following steps:

- Appointing Work Group members and the evidence review team (ERT)
- Discussing process, methods, and results
- Developing and refining topics for updating and systematic evidence review
- Identifying populations, interventions or predictors, and outcomes of interest, and other study eligibility criteria
- Developing and implementing literature search update strategies
- Screening abstracts and retrieving full-text articles on the basis of pre-defined eligibility criteria
- Creating data extraction forms
- Standardizing quality assessment methodology
- Extracting data and performing critical appraisal of the literature
- Grading the methodology and outcomes in individual studies
- Tabulating data from individual studies into summary tables
- Grading quality of evidence for each outcome across studies, and assessing the overall quality of evidence across outcomes with the aid of evidence profiles
- Updating recommendation statements based on the current evidence and other considerations
- Determining the strength of recommendations on the basis of the quality of evidence and other considerations
Finalizing guideline recommendations and supporting text
Proffering the guideline draft for public review in February 2022
Editing the guideline based on review feedback
Publishing the final version of the guideline

The overall process for conducting the systematic reviews and developing the CPG follow international standards, including those from the Institute of Medicine.1, 2

The Work Group Co-Chairs and the ERT met regularly (approximately every 2 weeks) to review the guideline development process, determine the specific CPG topics and recommendations to be updated, determine the specific topics to have updated systematic reviews, determine study eligibility criteria, assess progress of the review, discuss systematic review findings, evaluate the evidence base, and review draft updated recommendations and rationale text. The Work Group, ERT, and KDIGO staff also intermittently met with Work Group members to discuss the update process, review the updated evidence, and discuss updated recommendations and rationale text.

**Commissioning of Work Group and ERT**

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

**Defining scope and topics**

The Work Group Co-Chairs and the ERT defined the overall scope and goals of the guideline update and drafted a preliminary list of topics and key clinical questions. The list of research and recommendation topics for update was based on the original KDIGO guideline on HCV,3 and the 2018 update.4 The current ERT was also the ERT for both prior CPGs (for the original 2008 CPG, the ERT was based at Tufts Medical Center in Boston, Massachusetts, USA). The Work Group and ERT further developed and refined each topic and its eligibility criteria, literature search strategies, and data extraction forms (Table 2).
Table 2. Systematic review topics and screening criteria

**Chapter 2: Treatment of HCV Infection in Patients with CKD**

| Population | CKD G4-G5ND (or equivalent) with HCV infection  
| CKD G5D with HCV infection  
| CKD G1T-G5T (any category of kidney function except dialysis) with HCV infection  
| Included only results data for clearly identifiable population categories* |
| Interventions | Any DAA regimen, including combination regimens  
| Within single-group studies, we included only results data for clearly identifiable DAA regimens†  
| Allowed multiple (non-parsable) DAA regimens for kidney function, graft, and mortality outcomes |
| Comparator | Other regimen, no treatment, no comparator (single-group studies) |
| Outcomes | SVR (≥12 week), serious AE attributable to DAA, DAA discontinuation due to AE, death, change in CKD category, QoL, eGFR (CKD G4-G5ND, CKD G1T-G5T), proteinuria (CKD G4-G5ND, CKD G1T-G5T), acute rejection (CKD G1T-G5T), graft loss (CKD G1T-G5T) |
| Study design | RCT, nonrandomized comparative studies, single group studies; prospective or retrospective.  
| Published, peer-reviewed, or presented at AASLD, APASL, EASL, ERA-EDTA, or ASN 2019 & 2020 conferences |
| Minimum duration of follow-up | 12 weeks post-treatment: SVR, kidney/graft measures and outcomes  
| End of treatment: AEs  
| 6 mo post-treatment: Death |
| Minimum N of Subjects | ≥10 (within each specified population and DAA regimen*) |
| Publication dates | All ‡ |

**Chapter 4: Management of Patients with before and after Kidney Transplantation**

| Population | Graft recipient HCV negative & graft donor HCV positive (by NAT) |
| Interventions | Any DAA regimen, including combination regimens |
| Comparator | Other regimen, no treatment, no comparator (single-group studies) |
| Outcome | SVR (≥12 week), serious AE attributable to DAA, DAA discontinuation due to AE, death, QoL, acute rejection, delayed graft function, graft loss, graft eGFR, liver damage/failure, time on waitlist (comparative studies only, vs. D−/R−) |
| Design | RCT, nonrandomized comparative studies, single group studies; prospective or retrospective.  
| Published, peer-reviewed, or presented at AASLD, APASL, EASL, ERA-EDTA, or ASN 2019 & 2020 conferences |
| Minimum duration of follow-up | 12 weeks post-treatment  
<p>| End of treatment: AEs |
| Minimum N of Subjects | ≥10 |
| Publication dates | All ‡ |</p>
<table>
<thead>
<tr>
<th>Population</th>
<th>HCV-associated glomerular disease §</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Any DAA regimen</td>
</tr>
<tr>
<td></td>
<td>Any CKD treatment (e.g., corticosteroids, immunosuppressive agents)</td>
</tr>
<tr>
<td>Comparator</td>
<td>Other regimen, no treatment, no comparator (single-group studies)</td>
</tr>
<tr>
<td>Outcome</td>
<td>SVR (≥12 week), serious AE attributable to DAA, DAA discontinuation due to AE, death, change in CKD category or change in kidney function, cryoglobulinemia, QoL, eGFR, proteinuria, cryocrit, complement levels</td>
</tr>
<tr>
<td>Design</td>
<td>RCT, nonrandomized comparative studies, single group studies; prospective or retrospective. Published, peer-reviewed, or presented at AASLD, APASL, EASL, ERA-EDTA, or ASN 2019 &amp; 2020 conferences</td>
</tr>
<tr>
<td>Minimum duration of follow-up</td>
<td>12 weeks post-treatment</td>
</tr>
<tr>
<td>End of treatment: AEs</td>
<td></td>
</tr>
<tr>
<td>Minimum N of subjects</td>
<td>≥10</td>
</tr>
<tr>
<td>Publication dates</td>
<td>All ‡</td>
</tr>
</tbody>
</table>

AASLD, American Association for the Study of Liver Diseases; AE, adverse event; APASL, Asian Pacific Association for the Study of the Liver; ASN, American Society of Nephrology; CKD, chronic kidney disease; D, dialysis; DAA, direct acting antiviral; EASL, European Association for the Study of the Liver; eGFR, estimated glomerular filtration rate; ERA-EDTA, European Renal Association-European Dialysis and Transplant Association; HCV, hepatitis C virus; NAT, nucleic acid test; ND, non-dialysis; QoL, quality of life; RCT, randomized controlled trial; SVR: sustained viral response.

*Results data for mixed populations (e.g., CKD G4-G5 D & ND, CKD G3-G5ND) were omitted. To the extent possible, we parsed data for the specific populations of interest from the reported data. However, we allowed up to 10% of participants to be in a different CKD category. If SVR12 was 100% or 0% had serious AEs (as examples) across populations, we included these results for the specific populations of interest (if we could determine the number of patients analyzed within each specific population of interest).

†To the extent possible, we parsed data for the specific DAA regimens from the reported data. However, we allowed up to 10% of participants to have a different DAA regimen.

‡We re-screened all studies included for guideline chapters 2, 4, 5 from both the 2008 KDIGO HCV CPG and the 2018 CPG update. We conducted a de novo literature search update from January 1, 2016 through December 20, 2020, supplemented with studies known to the Work Group through May 2021.

§We also included studies of patients with HCV-associated cryoglobulinemia of whom at least 10 had glomerular disease.
Establishing the process for guideline development

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

Formulating questions of interest

Questions of interest were formulated according to the PICOS criteria (Population, Intervention, Comparator, Outcome, Study design). Details of the PICOS criteria are presented in Table 2.

Ranking of outcomes

The Work Group ranked outcomes of interest on the basis of their importance for informing clinical decision making (Table 3).

Table 3. Hierarchy of outcomes

<table>
<thead>
<tr>
<th>Hierarchy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical importance</td>
<td>Death, graft loss, ESKD</td>
</tr>
<tr>
<td>High importance</td>
<td>SVR12, treatment discontinuation due to adverse events, serious adverse events attributable to DAA, change in CKD category (or SCr doubling and including incident dialysis), quality of life, allograft eGFR, fibrosing cholestatic hepatitis, cryoglobulinemia complete remission</td>
</tr>
<tr>
<td>Moderate importance</td>
<td>Delayed graft function, acute rejection, eGFR (native kidney), proteinuria, cryocrit, complement</td>
</tr>
</tbody>
</table>

CKD, chronic kidney disease; DAA, direct acting antiviral; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HCV, hepatitis C virus; SCr, serum creatinine; SVR, sustained virologic response

Literature searches and article selection

The literature search strategies from the 2018 KDIGO HCV CPG were reviewed and replicated for the update, with minor revisions. The original systematic search strategies were developed by the ERT with input from the Work Group Co-Chairs. Modules were created for kidney disease, HCV, and study designs. Searches were conducted in Medline, Embase, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. For topics covered in the 2018 KDIGO HCV CPG, searches were limited to 2016 and later to capture new evidence. The full literature search strategies are provided in Appendix 1. In addition, the ERT searched for existing relevant systematic reviews. The final searches were conducted in December 2020 [the search will be updated during public review of the draft]. The search yield was also supplemented by focused searches for DAAs, HCV, and cryoglobulinemia in
conference abstracts from the 2019 and 2020 American Society of Nephrology (ASN), American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), European Renal Association-European Dialysis and Transplant Association (ERA-EDTA), and Asian Pacific Association for the Study of the Liver (APASL) meetings. The Work Group provided additional articles for screening through May 2021.

For selection of studies, all members of the ERT screened the abstracts in duplicate using an open-source online screening program, Abstrackr (http://abstrackr.cebm.brown.edu/). To establish relevance and consensus among reviewers, the entire team screened and achieved consensus on a series of initial batches of 100 abstracts. A total of 1946 citations from the databases were screened, in addition to conference abstracts, studies included in the 2008 and 2018 KDIGO HCV CPGs, and articles suggested by Work Group members (Figure 4). Potentially relevant articles (or abstracts) were retrieved in full text and re-screened in duplicate for eligibility. In total, 486 articles were selected for consideration for inclusion, of which 112 articles met eligibility criteria (this search will be updated during public review of the draft).

**Data extraction**

Data extraction was performed by one ERT member. Extracted data from each study was reviewed by another ERT member to confirm accuracy. The ERT designed a form to capture data on design, methodology, eligibility criteria, study participant characteristics, interventions, comparators, outcomes, and results of individual studies. Methodology and outcomes were also systematically assessed for risk of bias (see the section on risk of bias assessment below). Data were extracted into the online repository SRDR+ (Systematic Review Data Repository-Plus). The data are available for review at http://srdrplus.ahrq.gov/.

**Summary tables**

Summary tables were developed for each reviewed topic. Summary Tables report study descriptions and results for each study. For Chapter 2, the Summary Tables are organized by specific DAA regimen, with summary results across studies for each regimen. The Summary Table for Chapter 4 organizes studies first by study design (prospective with a protocol, followed by retrospective), then alphabetically by first author. For Chapter 5, studies are presented in alphabetical order by first author.
For each study, the Summary Tables include regimen, study identifier, study country, treatment duration, HCV GT data, pretreatment liver cirrhosis data, and results data. For SVR12 results, we include whether analyses were conducted as intention-to-treat (ITT, including if all participants were analyzed) or other approach. For all results, we include footnotes describing caveats, explanations for missing participants; for selected outcomes (e.g., serious adverse events, death), we included reported data about details such as nature of serious adverse event or cause of death).

For all outcomes, we report either meta-analyzed, pooled, or descriptive summaries of outcomes across studies.
Work Group members reviewed and confirmed all summary table data and quality assessments. Final summary tables will be available at www.kdigo.org.

**Evidence profiles**

Evidence profiles were constructed to assess the quality and record quality grades and descriptions of effect (or association) for each outcome across studies, as well as the quality of overall evidence and description of net benefits or harms of the intervention or comparator across all outcomes. The Evidence Profiles aim to make the evidence synthesis process transparent. Decisions in the Evidence Profiles were based on data from the primary studies listed in corresponding Summary Tables and on judgments of the ERT and Work Group. Each Evidence Profile was initially constructed by the ERT and then reviewed, edited, and approved by the Work Group. The work products created by the ERT for summarizing the evidence base are listed in Table 4, together with the number of included studies.

<table>
<thead>
<tr>
<th>Topics</th>
<th>Summary Table</th>
<th>Included Studies, n</th>
<th>Evidence Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ch 2. HCV treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.1. DAA, CKD G4-G5ND</td>
<td>+</td>
<td>20</td>
<td>+</td>
</tr>
<tr>
<td>2.1. DAA, CKD G5D</td>
<td>+</td>
<td>61</td>
<td>+</td>
</tr>
<tr>
<td>2.1. DAA, KTR</td>
<td>+</td>
<td>25</td>
<td>+</td>
</tr>
<tr>
<td>Ch 4. Kidney transplantation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1. DAA treatment in D+/R- KTR</td>
<td>+</td>
<td>14</td>
<td>+</td>
</tr>
<tr>
<td>Ch 5. HCV-associated glomerulonephritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.2. HCV-associated glomerulonephritis management</td>
<td>+</td>
<td>4</td>
<td>+</td>
</tr>
</tbody>
</table>

CKD, chronic kidney disease; D, dialysis; D+, donor hepatitis C positive; DAA, direct acting antiviral; HCV, hepatitis C virus; KTR, kidney transplantation recipients; ND, non-dialysis; R-, recipient hepatitis C negative

**Grading of quality of evidence for outcomes of individual studies**

Studies were assessed for risk of bias and methodological quality concerns. We used the Cochrane Risk of Bias tool\(^5\) to evaluate RCTs (that evaluated comparisons of interest). The tool asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. However, no eligible studies were evaluated as RCTs.

For non-randomized, observational comparative studies (that evaluated comparisons of interest), we used pertinent questions from the Cochrane Risk of Bias tool pertaining to outcome assessor blinding, incomplete outcome data (i.e., missing data and dropouts), and selective reporting. We also used selected questions from the Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool.\(^6\) Specifically, for comparative studies we evaluated whether evaluated cohorts were comparable, and whether potential confounders were accounted for.
For all studies, including single group (non-comparative) studies, we determined whether analyses were intention-to-treat (or otherwise included all participants) or were per-protocol (or other incomplete assessment), whether selection of participants into the study based on participant characteristics observed after the start of intervention, selective reporting, whether there was clear reporting without discrepancies, clear eligibility criteria, adequately described interventions (including dosages and treatment duration), and adequate outcome definition. For studies that reported harms, we assessed whether pre-defined or standard definitions of adverse events were used. For all studies, we also captured whether there were other potential biases or methodological problems of note. Where quality issues may have pertained only to some reported outcomes, this was noted.

For each study, assessment of quality was done by one of the reviewers, then confirmed by another, with discrepancies discussed in conference (Table 5).

Table 5. Classification of study quality

<table>
<thead>
<tr>
<th>Quality Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good quality</td>
<td>Low risk of bias and no obvious reporting errors; complete reporting of data. Must be prospective.</td>
</tr>
<tr>
<td>Fair quality</td>
<td>Moderate risk of bias, but problems with study or paper are unlikely to cause major bias.</td>
</tr>
<tr>
<td>Poor quality</td>
<td>High risk of bias or cannot rule out possible significant biases. Poor methods, incomplete data, reporting errors.</td>
</tr>
</tbody>
</table>

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

A structured approach, based on Grading of Recommendations, Assessment, Development and Evaluation (GRADE)\textsuperscript{7,8} and facilitated by the use of evidence profiles, was used to grade the quality of the overall evidence and the strength of recommendations. For each topic, the discussion on grading of the quality of the evidence was led by the ERT, and the discussion regarding the strength of the recommendations was led by the Work Group Co-Chairs. The “strength of a recommendation” indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm. The “quality of a body of evidence” refers to the extent to which our confidence in an estimate of effect is sufficient to support a particular recommendation.\textsuperscript{9}

Grading the quality of evidence for each outcome across studies

Following GRADE, the quality of a body of evidence pertaining to a particular outcome of interest was initially categorized on the basis of study design. For each outcome, the potential grade for the quality of evidence for each intervention-outcome pair started at “high” but was then lowered if there were serious limitations to the methodological quality of the aggregate of studies, if there were important inconsistencies in the results across studies, if there was uncertainty about the directness of evidence (including limited applicability of the findings to the population of interest),
if the data were imprecise or based on sparse studies, or if there was thought to be a high likelihood of reporting bias. The final grade for the quality of the evidence for an intervention-outcome pair could be one of the following 4 grades: “high”, “moderate”, “low”, or “very low” (Table 6).
Table 6. GRADE system for grading quality of evidence

<table>
<thead>
<tr>
<th>Step 1: Starting grade for quality of evidence based on study design</th>
<th>Step 2: Reduce grade</th>
<th>Step 3: Raise grade</th>
<th>Final grade for quality of evidence and definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter 2&lt;sup&gt;a&lt;/sup&gt;: All study designs = High</td>
<td>Study quality</td>
<td>Strength of association&lt;sup&gt;d&lt;/sup&gt;</td>
<td>High = Further research is unlikely to change confidence in the estimate of the effect</td>
</tr>
<tr>
<td>Chapters 4 and 5: Randomized trials = High</td>
<td>Consistency</td>
<td>Other</td>
<td>Moderate = Further research is likely to have an important impact on confidence in the estimate of effect, and may change the estimate</td>
</tr>
<tr>
<td>Observational study = Low</td>
<td>Directness</td>
<td></td>
<td>Low = Further research is very likely to have an important impact on confidence in the estimate, and may change the estimate</td>
</tr>
<tr>
<td>Any other evidence = Very Low</td>
<td>Other</td>
<td></td>
<td>Very Low = Any estimate of effect is very uncertain</td>
</tr>
<tr>
<td>Study quality</td>
<td>−1 level if serious limitations</td>
<td>+1 level if strong association&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>−2 levels if very serious limitations</td>
<td>+2 levels if very strong association&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consistency</td>
<td>−1 level if important inconsistency</td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Directness</td>
<td>−1 level if some uncertainty</td>
<td>+1 level if evidence of a dose–response gradient</td>
<td></td>
</tr>
<tr>
<td>−2 levels if major uncertainty</td>
<td>+1 level if all residual plausible confounders would have reduced the observed effect&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Reduce to Very Low if sparse&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduce to Very Low if imprecise&lt;sup&gt;c&lt;/sup&gt;</td>
<td>−1 level if high probability of reporting bias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a Since it is well-established that non-DAA treatment is ineffective to achieve SVR12, the review for Chapter 2 relied on primarily noncomparative, single group studies. In contrast with the standard GRADE system, we considered that all study designs could provide high quality evidence (Step 1). We did not consider confounders or strength of association as possible factors that may increase the grade since these are not relevant concepts for single group studies.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b Sparse if only one study (N&lt;100 per study group)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c Imprecise if there is a low event rate (0 or 1 event) in either study group. For comparative studies, imprecise if 95% confidence interval spans both 0.5 and 2.0. For single group studies, imprecise if in our judgment, the 95% confidence intervals of incidence estimates spanned across categories of rare, uncommon, common, or frequent.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d Omitted from consideration for Chapter 2, since association analyses and confounding are not relevant for noncomparative studies.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e Strong evidence of association is defined as &quot;significant relative risk of &gt;2 (&lt;0.5)&quot; based on consistent evidence from two or more observational studies with no major threats to validity. Very strong evidence of association is defined as &quot;significant relative risk of &gt; 5 (&lt; 0.2)&quot; based on consistent evidence from two or more observational studies with no major threats to validity.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GRADE, Grading of Recommendations Assessment, Development and Evaluation
Grading the overall quality of evidence

The quality of the overall body of evidence was then determined on the basis of the quality grades for all outcomes of interest, taking into account explicit judgments about the relative importance of each outcome. The resulting 4 final categories for the quality of overall evidence were “A”, “B”, “C”, or “D” (Table 7).

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

Assessment of the net health benefit across all important clinical outcomes

The net health benefit was determined on the basis of the anticipated balance of benefits and harms across all clinically important outcomes (Table 8). The assessment of net benefit also involved the judgment of the Work Group and the ERT.

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

Developing the recommendations

Draft recommendation statements were developed by the Work Group. The health benefits, side effects, and risks associated with each recommendation were considered when formulating the guideline, as well as information on patient preferences when available. Recommendation statements were revised in a multistep process during video-conference meetings and by subsequent drafts by e-mail. Relevant recommendations from AASLD/IDSA and EASL guidelines on management of HCV
were also reviewed. The final draft was sent for external public review. Based on feedback, it was further revised by the Work Group Co-Chairs and members. All Work Group members provided feedback on initial and final drafts of the recommendation statements and guideline text and approved the final version of the guideline.

**Grading the strength of the recommendations**

The strength of a recommendation is graded as level 1 or level 2. Table 9 shows the KDIGO nomenclature for grading the strength of a recommendation and the implications of each level for patients, clinicians, and policy makers. Recommendations can be for or against doing something. Each recommendation includes an explicit link between the quality of the available evidence and the strength of that recommendation. However, as elaborated on Table 10, the strength of a recommendation is determined not only by the quality of the evidence but also by other, often complex judgments, regarding the size of the net medical benefit (potential risks vs. benefit), values, and preferences, and costs. Formal decision analyses including cost analysis were not conducted.

<table>
<thead>
<tr>
<th>Grade*</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
</tr>
<tr>
<td><strong>Level 1 ‘Strong’</strong></td>
<td></td>
</tr>
<tr>
<td>“We recommend”</td>
<td>Most people in your situation would want the recommended course of action and only a small proportion would not.</td>
</tr>
<tr>
<td><strong>Level 2 ‘Weak’</strong></td>
<td></td>
</tr>
<tr>
<td>“We suggest”</td>
<td>The majority of people in your situation would want the recommended course of action, but many would not.</td>
</tr>
</tbody>
</table>

*The additional category “Not Graded” was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements. They should not be interpreted as being weaker recommendations than Level 1 or 2 recommendations.*
Table 10. Determinants of strength of recommendation

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

**Ungraded statements**

This category was designed to allow the Work Group to issue general advice. Although this category has now been replaced with “Practice Points” in recent KDIGO guidelines published after 2019, KDIGO decided to maintain this category of ungraded statements for the sake of consistency with the remaining Chapters 1 and 3 from the 2018 guideline which are still current and integral to the entire CPG for the prevention, diagnosis, evaluation, and treatment of patients with HCV and CKD.4

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

This grading scheme, with 2 levels for the strength of a recommendation together with four levels of grading the quality of the evidence, as well as the option of an ungraded statement for general guidance, was adopted by the KDIGO Board in December 2008. The Work Group took on the primary role of writing the recommendations and rationale statements and retained final responsibility for the content of the guideline statements and the accompanying narrative. The ERT reviewed
draft recommendations and grades for consistency with the conclusions of the evidence review.

**Format for guideline recommendations**

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

**Limitations of approach**

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

**Review of guideline development process**

The Conference on Guideline Standardization (COGS) checklist has been developed to assess the quality of the methodological process for systematic review and guideline development. Table 11 shows the criteria that correspond to the COGS checklist and how each one is addressed in this guideline.
<table>
<thead>
<tr>
<th>Topic</th>
<th>Description</th>
<th>Discussed in 2022 KDIGO HCV in CKD CPG Update</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Overview material</td>
<td>Provide a structured abstract that includes the guideline’s release date, status (original, revised, updated), and print and electronic sources.</td>
<td>See Abstract and Methods for Guideline Development.</td>
</tr>
<tr>
<td>2. Focus</td>
<td>Describe the primary disease/condition and intervention/service/technology that the guideline addresses. Indicate any alternative preventative, diagnostic or therapeutic interventions that were considered during development.</td>
<td>Management of HCV in terms of treatment, monitoring, and prevention in adults with CKD, including both dialysis and transplant populations.</td>
</tr>
<tr>
<td>3. Goal</td>
<td>Describe the goal that following the guideline is expected to achieve, including the rationale for development of a guideline on this topic.</td>
<td>This CPG is intended to assist the practitioner caring for patients with CKD and HCV and to prevent transmission, resolve the infection, and prevent adverse outcomes such as deaths, graft loss, and progression to kidney failure while optimizing patients’ quality of life.</td>
</tr>
<tr>
<td>4. User/setting</td>
<td>Describe the intended users of the guideline (e.g., provider types, patients) and the settings in which the guideline is intended to be used.</td>
<td>Target audience is practicing nephrologists and other health care providers for adults with CKD and HCV infection.</td>
</tr>
<tr>
<td>5. Target population</td>
<td>Describe the patient population eligible for guideline recommendations and list any exclusion criteria.</td>
<td>Adults with CKD (including those on dialysis therapy and kidney transplant recipients) and HCV infection.</td>
</tr>
<tr>
<td>6. Developer</td>
<td>Identify the organization(s) responsible for guideline development and the names/credentials/potential conflicts of interest of individuals involved in the guideline’s development.</td>
<td>Organization: KDIGO Names/credentials/potential conflicts of interest of individuals involved in the guideline’s development will be disclosed in the final guideline publication.</td>
</tr>
<tr>
<td>7. Funding source/sponsor</td>
<td>Identify the funding source/sponsor and describe its role in developing and/or reporting the guideline. Disclose potential conflict of interest.</td>
<td>This guideline is funded by KDIGO. Financial disclosures of Work Group members will be available in the final guideline publication.</td>
</tr>
<tr>
<td>8. Evidence collection</td>
<td>Describe the methods used to search the scientific literature, including the range of dates and databases searched, and criteria applied to filter the retrieved evidence.</td>
<td>Topics were triaged either to a) systematic review, b) systematic search followed by narrative summary, or c) narrative summary. For systematic reviews, we searched PubMed, Embase, Cochrane Central Registry for trials, and Cochrane database of systematic reviews. Screening criteria for this and other topics are outlined in the Methods for Guideline Development chapter. The search was updated through December 2020 and supplemented by articles identified by Work Group members through May 2021. We also searched for pertinent existing guidelines and systematic reviews.</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>9. Recommendation grading criteria</td>
<td>Describe the criteria used to rate the quality of evidence that supports the recommendations and the system for describing the strength of the recommendations. Recommendation strength communicates the importance of adherence to a recommendation and is based on both the quality of the evidence and the magnitude of anticipated benefits and harms.</td>
<td>Quality of individual studies was graded in a 3-tiered grading system (see Table 5). Quality of evidence and strength of recommendations were graded following the GRADE approach (Tables 6, 7, and 9). The Work Group could provide general guidance in ungraded statements.</td>
</tr>
<tr>
<td>10. Method for synthesizing evidence</td>
<td>Describe how evidence was used to create recommendations, e.g., evidence tables, meta-analysis, decision analysis.</td>
<td>For systematic review topics, summary tables and evidence profiles were generated. For recommendations on interventions, the steps outlined by GRADE were followed.</td>
</tr>
<tr>
<td>11. Prerelease review</td>
<td>Describe how the guideline developer reviewed and/or tested the guidelines prior to release.</td>
<td>The guideline undergoes an external public review in February 2022. Public review comments were compiled and fed back to the Work Group, which considered comments in its revision of the guideline.</td>
</tr>
<tr>
<td>12. Update plan</td>
<td>State whether or not there is a plan to update the guideline and, if applicable, an expiration date for this version of the guideline.</td>
<td>The requirement for an update will be assessed periodically from the publication date or earlier if important new evidence becomes available in the interim. Such evidence might, for example, lead to changes to the recommendations or may modify information provided on the balance between benefits and harms of a particular therapeutic intervention.</td>
</tr>
</tbody>
</table>
### 13. Definitions
Define unfamiliar terms and those critical to correct application of the guideline that might be subject to misinterpretation. See Abbreviations and Acronyms.

### 14. Recommendations and rationale
State the recommended action precisely and the specific circumstances under which to perform it. Justify each recommendation by describing the linkage between the recommendation and its supporting evidence. Indicate the quality of evidence and the recommendation strength, based on the criteria described in Topic 9. Each guideline chapter contains recommendations for the management of HCV in CKD patients. Each recommendation builds on a supporting rationale with evidence tables if available. The strength of the recommendation and the quality of evidence are provided in parenthesis within each recommendation.

### 15. Potential benefits and harms
Describe anticipated benefits and potential risks associated with implementation of guideline recommendations. The benefits and harm for each comparison of interventions are provided in summary tables and summarized in evidence profiles. The estimated balance between potential benefits and harm was considered when formulating the recommendations.

### 16. Patient preferences
Describe the role of patient preferences when a recommendation involves a substantial element of personal choice or values. Recommendations that are level 2 or "discretionary," indicating a greater need to help each patient arrive at a management decision consistent with her or his values and preferences.

### 17. Algorithm
Provide (when appropriate) a graphical description of the stages and decisions in clinical care described by the guideline. Algorithms were developed where applicable (see Chapters 4 and 5).

### 18. Implementation considerations
Describe anticipated barriers to application of the recommendations. Provide reference to any auxiliary documents for providers or patients that are intended to facilitate implementation. Suggest review criteria for measuring changes in care when the guideline is implemented. These recommendations are global. Local versions of the guideline are anticipated to facilitate implementation and appropriate care. Review criteria were not suggested because implementation with prioritization and development of review criteria have to proceed locally. Most recommendations are discretionary, requiring substantial discussion among stakeholders before they can be adopted as review criteria. The decision whether to convert any recommendations to review criteria will vary globally. Research recommendations were also outlined to address current gaps in the evidence base.
CKD, chronic kidney disease; CPG, clinical practice guideline; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HCV, hepatitis C virus; KDIGO, Kidney Disease: Improving Global Outcomes.
APPENDIX

Appendix 1: Online search strategies
APPENDIX 1: ONLINE SEARCH STRATEGIES

PubMed

Search 1


OR ((kidney OR renal) AND ("transplantation"[MESH] OR "allografts"[MESH] OR transplant OR allograft* OR graft*)) OR "kidneys, artificial"[MESH] OR renal OR nephron* OR kidney OR uremia OR hemodialysis OR haemodialysis OR haemodialysis OR dialysis OR hemofilr* OR haemofilr* OR hemofilr* OR haemofilr*) AND ("Hepatitis C"[MESH] OR hepatitis c OR hep c OR HCV) AND (telaprevir OR "telaprevir" [Supplementary Concept] OR boceprevir OR "N-(3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl)-3-(2-(((1,1-dimethylethyl)amino)carbonyl)amino)-3,3-dimethyl-1-oxobutyl)-6,6-dimethyl-3-azabicyclo(3.1.0)hexan-2-carboxamide" [Supplementary Concept] OR danoprevir OR "danoprevir" [Supplementary Concept] OR faldaprevir OR "N-((cyclopentyl)oxy)carboxyl)-3-methylvalyl-4-((8-bromo-7-methoxy-2-(2-(2-methylpropanoyl)amino)-1,3-thiazol-4-yl)oxy)-N-(1-carboxy-2-ethenylcyclopropyl)prolinamide" [Supplementary Concept] OR vaniprevir OR "MK-7009" [Supplementary Concept] OR sovaprevir OR ACH-1625 OR simeprevir OR "Simeprevir"[Mesh] OR asunaprevir OR "asunaprevir" [Supplementary Concept] OR paritaprevir OR "ABT-450" [Supplementary Concept] OR grazoprevir OR "MK-5172" [Supplementary Concept] OR vedroprevir OR "GS-9451" [Supplementary Concept] OR daclatasvir OR "daclatasvir" [Supplementary Concept] OR ombitasvir OR "ABT-267" [Supplementary Concept] OR ledipasvir OR "ledipasvir" [Supplementary Concept] OR velpatasvir OR "velpatasvir" [Supplementary Concept] OR voxilaprevir OR "voxilaprevir" [Supplementary Concept] OR "direct acting antiviral" OR "direct-acting antiviral" OR DAA OR ribavirin OR "Ribavirin"[Mesh] OR peginterferon alfa-2b" [Supplementary Concept] OR pegylated interferon OR "peginterferon alfa-2b" [Supplementary Concept] OR pegylated IFN)
Search 2

Search 1 OR Search 2

AND

Date limits: 2016-present

Cochrane/Embase

Search 1
("kidney glomerulus" OR "Kidney Diseases" OR "kidney function tests" OR "renal replacement therapy" OR "kidney transplantation" OR ((kidney OR renal) AND ("transplantation" OR transplant OR allograft OR allograft* OR graft*)) OR renal OR nephron* OR kidney OR uremia OR uraemia OR hemodialysis OR hemodialysis OR haemodialysis OR haemodialysis OR dialysis OR hemofiltr* OR haemofiltr* OR hemofiltr*) AND (hepatitis c OR hep c OR HCV) AND (telaprevir OR danoprevir OR faldaprevir OR vaniprevir OR sovaprevir OR simeprevir OR paritaprevir OR grazoprevir OR vedroprevir OR daclatasvir OR ombitasvir OR ledipasvir OR samatasvir OR elbasvir OR sofosbuvir OR mericitabine OR valpicipatabine OR setrobuvir OR tegobuvir OR filibuvir OR dasabuvir OR deleobuvir OR beclabuvir OR glecaprevir OR pibrentasvir OR velpatasvir OR voxilaprevir OR "direct acting antiviral" OR "direct-acting antiviral" OR DAA OR ribavirin OR interferon OR IFN OR pegylated interferon OR pegylated IFN)

Search 2
(glmorulonephritis OR glomerulopathy OR "Nephrotic Syndrome" OR glomerulonephritis* OR membranous nephropathy OR IGA nephropathy OR immunoglobulin A nephropathy OR IGAN OR rapidly progressive glomerulonephr* OR RPGN OR "focal sclerosing glomerulopathy" OR FSGS OR glomerulosclerosis OR Berger's disease OR Bergers OR focal segmental glomerulo* OR Goodpasture OR Nephritis OR "Schoenlein-Henoch" OR ("Antineutrophil Cytoplasmic Antibodies" AND "vasculitis") OR (ANCA AND vasculitis) OR Nephrosis OR "Minimal change nephropathy" OR "minimal change disease" OR "churg-strauss syndrome" OR "Granulomatosis with Polyangiitis" OR "Lupus nephritis" OR "renal vasculitis" OR amyloidosis OR cryoglobulinemia) AND (hepatitis c OR hep c OR HCV)

Search 1 OR Search 2

Date limits: 2016-present
REFERENCES


WORK GROUP FINANCIAL DISCLOSURES

*denotes monies paid to institution

Michel Jadoul, MD (Work Group Co-Chair)
Consultancy: Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, FMC Asia Pacific, Mundipharma, and Vifor FMC
Grants / Grants Pending: Amgen* and AstraZeneca*
Speaker Bureaus: Astellas, AstraZeneca, Mundipharma, and Vifor FMC

Paul Martin, MD (Work Group Co-Chair)
Consultancy: AbbVie
Grants / Grants Pending: AbbVie* and Gilead*
Development of Educational Presentations: SC Liver Research Consortium

Ahmed A. Awan, MD, FACP
Reported no relevant financial relationships

Marina C. Berenguer, MD
Consultancy: AbbVie, Deep Genomics, Intercept, Natera, and Orphalan
Grants / Grants Pending: Gilead, Intercept
Speaker Bureaus: AbbVie, Astellas, Chiesi, Deep Genomics, Gilead, Intercept, Novartis and Orphalan

Annette Bruchfeld, MD, PhD
Consultancy: AstraZeneca* and Chemocentryx*
Advisory Board: AstraZeneca* and Bayer*
Speaker Bureaus: AbbVie, MSD/Merck and Vifor*

Fabrizio Fabrizi, MD
Reported no relevant financial relationships

David S. Goldberg, MD
Grants / Grants Pending: AbbVie and Gilead*
Development of Educational Presentations: Pfizer
Jidong Jia, MD, PhD
Grants / Grants Pending: BMS* and Gilead*
Speaker Bureaus: Gilead

Nassim Kamar, MD, PhD
Advisory Board and Speaker Bureaus: Astellas, AstraZeneca, Biotest, CSL Behring, Chiesi, ExeVir, GSK, Hansa, MSD, Novartis, Sandoz, Sanofi, and Takeda

Rosmawati Mohamed, MD, MRCP, MIntMed, MBBS
Reported no relevant financial relationships

Mário Guimarães Pessôa, MD, PhD
Board Member: Gilead
Consultancy: Gilead and Myralis
Speaker Bureaus: Gilead

Stanislas Pol, MD, PhD
Consultancy: Bristol Myers Squibb, Gilead, Janssen, MSD, and Roche
Speaker Bureaus: AbbVie, Biotest, LFB, and Shionogi
Grants / Grants Pending: Bristol Myers Squibb, Gilead, MSD and Roche

Meghan E. Sise, MD, MS
Consultancy: Bioporto, Gilead, Mallinckrodt, Traverese
Grants / Grants Pending: AbbVie*, Angion*, EMD-Serono*, Gilead*, and Merck*