July 24, 2019

Cynthia Mulrow, MD, MSc, MACP
Senior Deputy Editor
Annals of Internal Medicine

Re: Manuscript M19-1539: "Prevention, Diagnosis, Evaluation and Treatment of Hepatitis C in Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2018 Clinical Practice Guideline."

Dear Dr. Mulrow:

Many thanks for the opportunity to submit a revision of the manuscript. We have carefully considered the comments of your reviewers and altered the manuscript accordingly. Our response to the comments is detailed below in RED and the changes within the updated manuscript are fully tracked. A clean copy of the manuscript with the edits accepted is also enclosed. We hope the revisions have satisfactorily addressed all the issues raised.

Kind regards,
Drs. Craig Gordon, Michel Jadoul and Paul Martin on behalf of the authors

General comments from the Editor

1. Reviewers made several constructive comments requesting clarifications and more discussion. We think that addressing those comments will improve the value of the synopsis for our readers but we advise keeping the synopsis length brief. We suggest that you consider deleting the section on HCV transmission in hemodialysis units (chapter 3) to accommodate responses to reviewers' suggestions, as we believe that section is the least relevant to our readership. (Of note this would entail deletion of some material in the discussion also (lines 452-458) and deletion and renumbering of references.)

We agree with removing chapter 3 and as well as any related comments and accompanying references.

2. Add a sentence or two that tells readers the general topic matter of the recommendations that are not covered in the synopsis (line 102).

We agree with this suggestion and added some additional text highlighting the general areas of recommendations not included in this review (p. 5-6).

3. Clarify in the section that addresses screening (section 1) whether you are recommending one-time only screening and whether there are particular circumstances in which repeat screening might be considered or important.

We added a sentence that the recommendation is for one-time screening except in circumstances of ongoing risk of infection (p. 8).

4. Add comment to the discussion regarding any major studies relevant to the synopsis recommendations that were published since completion of the searches for evidence that were done to underpin the guideline.

Two important studies have been published since the evidence search. 1) Sise ME, Kidney International 2019 is the first study to show a statistically significant association between DAA treatment and slower rate of CKD progression. We added some discussion of this important study on p. 9 (top, ref 14). 2. Molnar, et al, Am J of Transpl was also just published and is the largest cohort of HCV positive donor kidney transplantation to HCV negative recipients (n=53) and adds to the evidence base describing the impact of this practice. We included this study on p. 18 (ref 51).

Reviewer Comments

Reviewer # 1:

Manuscript: Synopsis of KDIGO 2018 Guideline on Hepatitis C in CKD

COMMENTS FOR AUTHORS

Principal point of the synopsis is stated by the authors: to focus "on 38 key recommendations pertinent to prevention, diagnosis, treatment and management of HCV in adult CKD populations" summarized in the updated clinical practice guideline developed and published previously in 2018 by the KDIGO work group assembled for this purpose.

The complete 2018 updated guideline is, as appropriate, much more lengthy (with additional recommendations and supporting documentation, materials, and citations) than the synopsis. For context, authors state:

"The overall objective for the guideline is to inform the management of HCV including the use of DAA agents in adults with CKD. The target audience of the guideline includes nephrologists, transplant physicians, hepatologists, infectious disease specialists, primary care physicians, and other practitioners caring for adults with HCV and CKD worldwide. … The updated guideline included 66 recommendations."

This review is mostly limited to the submitted manuscript synopsis although I read the 2018 updated guideline in its entirety (and more closely than when it was first issued last year). My understanding is that the synopsis is intended to be simply that (a clinically useful and informative summary of the full 2018 updated guideline) without additional commentary, perspective, or editorial bias. It is my impression that the synopsis authors achieved their task.

A few of my critical comments (below) related to a specific topic, issue, or subject addressed by the full 2018 updated guideline are included for framing of specific suggestions of focus that I think would be useful to improve the clarity or clinical context of the synopsis for some of those clinicians less familiar with the field or who do not encounter such patients on a regular basis.

Major Strengths

Conceptualization and design: The authors provide sufficient and appropriate amount of information in the Abstract and the synopsis to inform the reader of the background (extent of HCV in the CKD population), rationale (last HCV Guideline was 2008), and current clinical context (advent of highly effective DAA agents for HCV therapy) for an update at this time.

Methods: The specific approach and parameters for the literature search and review are well described as is the application of GRADE standards for appraisal of the quality of the evidence and rating the strength of the recommendations. The clinical content is current (the May 2017 literature search updated in July 2018). The articles that I have read in the peer reviewed published literature since that time would only serve to support the findings of previous studies and would not alter the recommendations in the 2018 updated guideline (or synopsis).

Analysis of research and presentation

The synopsis is appropriately and clearly organized for the most part along the sections of specific CKD patient sub-populations in the full 2018 updated guideline. The presentation is clear with judicious incorporation of explanatory tables, charts and flow chart diagrams from the updated guideline. The recommendations are highlighted in bold-face for ease of use and reference followed by explanatory summaries within each section. The recommendations themselves are sound (as expected from the well researched and developed guideline itself).

Major weaknesses: none

Minor weaknesses: the two minor weaknesses (below) are related to the organization and discussion of clinical management of solid organ transplant patients with CKD and HCV infection, both the content and its organization/presentation within the synopsis (and fully appreciating that this ties directly back to the 2018 updated guideline itself).

Minor weakness 1: suggest consolidate in a single section the recommendations and explanatory material related to the recommendations in sections 2 and 4 that address clinical management of HCV in kidney transplant candidates and recipients. The 2018 updated guideline and synopsis manuscript presents this material in two separate sections with some redundancy. Section 2 contains recommendations for specific DAA agents for HCV treatment in kidney transplant recipients and strategies to optimize timing of kidney transplant in ESRD patients with HCV. Section 4 further expands these recommendations to include considerations of donor type, HCV genotype, extent of hepatic fibrosis, and use of HCV donors in noninfected

kidney recipients. Although the authors obviously cannot alter the 2018 updated guideline itself, presenting this information in a single section would be more convenient for the synopsis readers and somewhat less awkward having to refer back from section 4 to section 2.

Although we cannot reorganize the guideline statements given they reflect the organization of the original 2018 KDIGO guideline, we recognize the reviewer's point. Since one of the general comments from the Editor was to delete Chapter 3, fortuitously the treatment discussions can now flow naturally from Chapter 2 (CKD patients including transplant recipients) to Chapter 4 (management of patients before/after kidney transplantation). We have since also inserted chapter labels that better map to the sections of the original guideline. We hope this will improve the organization of this summary. Additionally, we also added text to chapter 4 (p. 15) to cross reference that specifics of HCV treatment in kidney transplant recipients is covered in chapter 2.

Minor weakness 2: suggest consider a brief paragraph in the Discussion section to provide some practical clinical "precautionary" considerations to the fragility of clinical immunosuppression management in solid organ transplant recipients (both kidney recipients and non-renal organ recipients with minor impairments in renal function).

We appreciate the suggestion of the reviewer but are concerned that this may be beyond the scope of this manuscript. We agree that this commentary is important to emphasize and have done so on p. 13.

Although early evidence suggests nearly all DAA agents can be used with near impunity in patients on common transplant immunosuppression drugs, and most of these are FDA approved and safe in patients with GFR > 30 ml/min per 1.73 m^2, the clinical experience with numbers of actual organ transplant recipients treated with DAA agents is still relatively small. Two recent publications (that appeared too late for inclusion in the 2018 updated guideline or synopsis manuscript) confirm this observation:
"Eradication of HCV infection with the direct-acting antiviral therapy in renal allograft recipients (Review Article), C Armando et at, BioMed Research International, Volume 2019, Article ID 4674560, 8 pages, at: https://www.hindawi.com/journals/bmri/2019/4674560/

"Efficacy and tolerability of direct-acting antiviral agents for hepatitis C virus infection in kidney transplant recipients", N Suna et al, Transplantation: July 2018, Volume 102, Issue pS909 at: https://journals.lww.com/transplantjournal/Abstract/2018/07001/Efficacy_and_Tolerability_of_Direct_Acting.1486.aspx

The majority of kidney transplant recipients and non-renal organ transplant recipients exhibit long term GFR < 60 ml/min per 1.73 m^2 (categories G3a and G3b) post-transplant (citations below). The transplanted kidney of course functions in isolation as a solitary kidney and often experiences initial perioperative physiologic insults related to the deceased donor multi-organ procurement procedure in addition to prolonged cold static storage times ranging up to 40 hours. Impairments of renal function in non-renal organ transplant recipients (most notably heart and liver) can result from major intraoperative hemodynamic changes and (for heart recipients) cardiac bypass pump. Of course, all solid organ transplant recipients are subject to long recognized and well described adverse effects of calcineurin inhibitors on renal function.

Limited documentation of the extent of renal function impairment in solid organ transplant recipients is available at:

"Long-term graft function changes in kidney transplant recipients" R Marcen et al, NDT Plus, 2010 Jun; 3(Suppl 2): ii2–ii8 at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2875040/

"Understanding trends in kidney function 1 year after kidney transplant in the United States" Y Huang et al, JASN August 2017, 28 (8) 2498-2510 cited at: https://jasn.asnjournals.org/content/28/8/2498

"Chronic kidney disease after nonrenal solid-organ transplantation" R Bloom and P Reese, JASN December 2007, 18 (12) 3031-3041 at: https://jasn.asnjournals.org/content/18/12/3031

We agree with the reviewer's above points that depending on timing of DAA treatment following transplant as well as the type (deceased donor vs. live donor) of transplant (in addition to numerous other factors) have significant impact on eGFR and accordingly on the choice of DAA regimen. As the reviewer correctly highlights, this is particularly challenging in patients with an eGFR approximately 30 ml/min, below which sofosbuvir is not FDA approved. The recent development of new regimens (notably glecaprevir/pibrentasvir) has made this a bit easier but the evidence base for the efficacy of this regimen is somewhat limited (as is the evidence behind elbasvir/grazoprevir in transplant recipients). We have attempted to further clarify on this issue with additional text on p. 13.

Although both the 2018 updated guideline and the submitted synopsis manuscript recommend coordination by the treating clinician (regardless of medical field) with the transplant center (and nephrologist and hepatologist as appropriate) in the clinical management of these diverse subsets of CKD transplant recipients with HCV, it might be prudent to add a focused paragraph in the Discussion section for emphasis and effect regarding a heightened awareness for any

sudden decline in allograft function (whether kidney or other organ allografts) when initiating HCV therapy concomitant with chronic immunosuppression drugs (especially calcineurin inhibitors). An undetected drop in calcineurin inhibitor blood level can precipitate irreversible acute rejection in short order even in the long term organ transplant recipient. Similarly, an undetected bump up in calcineruin inhibitor blood level can further degrade renal function. Until more extensive experience is available for reassurance of safety of DAA agents with the transplanted kidney functioning in the common GFR range of 30-60 ml/min per 1.73 m^2, close monitoring of the kidney allograft function should be the order of the day while these patients are undergoing DAA agent therapy.

We agree this point requires emphasis and added additional text to highlight this important concept although we did so not in the discussion as suggested by the reviewer but instead in Chapter 2 where the guideline statement about this was included (p. 13). We thank the reviewer for highlighting this oversight in our text.

Although most transplant physicians remain accessible for urgent access to their non-transplant colleagues regarding specific patients, navigating the modern "mega-medical center" system to reach that "last cyber-mile" might be somewhat daunting for some outside the loop (usually limited to "intensivist/hospitalist/ER" insiders) with more established connections. It would behoove clinicians (non-transplant physicians and non-physician extenders alike) to be proactive in their interaction, coordination, and connectivity with key transplant center staff. Likewise for the transplant physicians in their proactive outreach to their referring community clinicians.

We entirely agree with this point. In fact, this is why we opted for the phrase "transplant center" instead of "transplant team" (see query of reviewer 4) to emphasize the multidisciplinary collaboration required for these patients and that the burden should not fall on any particular specialist.

Reviewer #2:

I find this article extremely useful for internists, nephrologists, family doctors and hepatologists. The points I am citing below are not necessarily any flaws but mere omissions which could prove this article even more useful.

Line 84-85. Can the authors clarify what are the actual rates of viral eradication in CKD populations infected with HCV?

We appreciate the excellent suggestion and changed “high” to “greater than 95%” (p. 5).

Line 146-147. Can we mention the actual prevalence of HCV in CKD and the general population?

We added prevalence estimates from incident dialysis patients and CDC estimates from the general US population on p. 8.

Line 189. Can we mention the rate of false negative EIA tests in dialysis population?

We opted to not include this in the manuscript as it’s an extremely complicated issue that depends on the pre-test probability of HCV in each dialysis unit (essentially the unit-specific prevalence of HCV). The prevalence of HCV in HD units varies substantially across and within nations from very low rates in some countries to rates higher than 50% in others. The rates vary even within a single nation (for instance, urban, underserved US populations or regions with high rates of IV narcotics injections versus other US populations). The higher the prevalence of HCV within any individual HD unit, the higher the likelihood that a negative EIA test is a false negative result. We added a phrase emphasizing the role of monitoring liver biochemical tests to detect acute HCV infection in HD due to the delayed seroconversion to EIA positivity that can occur in this population after acute HCV (p. 9).

Line 373-378. It will be better to document actual mortality rates.

We appreciate the reviewer’s comment. Unfortunately, the actual mortality rates are not well described in the cited studies but can be extrapolated from a figure in Bloom AJKD 2005, which demonstrated an approximately 80% 8-year survival for HCV-infected kidney transplant recipients compared with 55-60% 8-year survival for HCV+ patients who remained on the waiting list. The focus of this and the other cited studies are on statistically significant lower HR or RR of mortality in HCV+ patients who are transplanted versus HCV+ patients who remain on waiting list.

Cost of HCV treatment remains to be identified and may be a barrier for implementation.

We agree with the reviewer but cost-effectiveness analysis was beyond the scope of this synopsis and the actual guideline itself, but is certainly a critical issue that should be further studied. This further underscores the importance for additional cost effectiveness research as stated in our Conclusion (p. 18).

Reviewer #3:

Below are my suggestions for your manuscript:

1. Suggest to sectionalize this synopsis according to 5 different chapters as in complete version for readers to follow

We agree with this suggestion, which was also suggested by reviewer #4, and we made this change.

2. Please make appropriate reference to table 1 – seems to be this table is related to recommendations relating to the detection and evaluation of HCV in CKD

We appreciate the reviewer's recognition of this important oversight and have corrected this (p. 8) as well as other absence of callouts to tables/figures throughout the manuscript.

3. Suggest to include 2.1.1 recommendation at "Treatment in CKD G1-G5 and G5D" section from complete version –i.e. 2.1.1: We recommend an interferon-free regimen (1A).

We added the statement back to emphasize this important point (p. 10). Explanatory text already existed in the document (p. 10-11) so we did not enhance this point in the rationale.

4. Please make appropriate reference to figure 1 in the text– seems to be this is related to recommendation 2.4.1

Inserted on p. 11 as noted in response to query #2, above.

5. Please make appropriate reference to figure 2 in the text
Inserted on p. 12, 13 as noted in response to query #2, above.

Reviewer #4:
This is a timely and much needed update to most recent KDIGO Guideline on HCV in CKD published in 2008. There have been significant advances in HCV therapy since that time that specifically affect patients with CKD. Overall the Guideline is organized, clearly written and well referenced. There are a few areas where clarifications would strengthen the Guideline, and they are detailed below by section.

1. Abstract
-Overall concise, clear and well organized
-Line 73-would consider a different word than "public" when describing the review process, as this implies lay people had input in the process.

Thanks for the recommendation. We accordingly changed the word "public" to "stakeholder".

2. Introduction

Line 90-the authors' inclusion of primary care physicians among the target audience of the guideline is important.

We agree with the reviewer.

Line 102- it would be helpful to very briefly describe the content of the 28 recommendations that are not included in this synopsis. The authors state that the 38 recommendations included are relevant to clinical practice, but it would be nice to know what we are missing by not seeing those 28.

We agree and added text to highlight this point on pages 4 and 5-6.

Line 116- please specify which existing guidelines were reviewed. The AASLD/IDSA HCV guidelines are cited, but it's unclear whether these are the only other guidelines reviewed, or whether there were others. If these were the only guidelines reviewed, I would name them in the text.

We agree. We spelled out and added references to highlight several of the other guidelines that were reviewed including the European Association for the Study of Liver guidelines, among others (p. 6).

Line 122- research question 6 is a bit confusing—do these three topics (CKD progression, graft loss and mortality) all apply to kidney transplant? If not, the topics seem disparate to be grouped together.

We agree with the reviewer than combining these into a single question is confusing and thus separated into 2 distinct questions, first on CKD progression and the second on graft loss and mortality in kidney transplantation (p. 7, top).

The authors might consider including a supplemental figure that helps readers understand the relationship between the 5 chapters and 6 research questions, outlining which research questions stem from which chapters. It would also be helpful to link these to the major headings in the guidelines. As a reader, it required several readings to get straight how the chapters, research topics and guidelines headings related to each other in an overall framework, so being able to visualize this would add clarity.

We agree with the reviewer and listed the chapter headings in parentheses next to each of the 5 systematic review topics in Appendix 3.

Line 132- similar to the comment from the abstract, consider replacing “public” with a different word.

Changed as above on p. 6.

3. Recommendations
General: Similar to comment above, since the major topic headings correspond to the 5 chapters, it would be helpful to number them to better link them to the main chapter content areas. The sub sections are well outlined and this would create consistency for the main headings as well.

We agree with this suggestion, which was also suggested by reviewer #3, and we made this change.

RECOMMENDATIONS RELATING TO THE DETECTION AND EVALUATION OF HCV IN CKD

Line 137- this section only addresses detection, not evaluation, so I would consider removing "evaluation" from the title. Also, since the following section uses the term "testing" as opposed to "detection," would choose one term and use it in both titles for consistency. Finally, minor point but this is the only major heading that uses "relating to"—all others use "related to."

We appreciate the very careful review and have changed to "related to". We opted to not remove the word "evaluation" or change "detection" to "testing" to maintain consistency with terminology used in the full KDIGO guideline document.

Line 143- While the description of HCV testing using immunoassay (EIA) and nucleic acid testing (NAT) is correct, most readers will be more familiar with the terminology used in clinical practice, ie anti-HCV (or HCV antibody) and HCV RNA. The HCV guidelines (hcvguidelines.org) use this terminology. It would be helpful to link these more familiar terms to the technical terms here where they are first mentioned, and then subsequently use the more familiar terms throughout the rest of the Guideline.

We agree with the reviewer that HCV RNA may be more familiar than NAT but both the original (2008) and current (2018) KDIGO HCV guidelines used the phrase NAT intentionally in anticipation that the terminology of testing may evolve, so instead of changing throughout, we just emphasized that NAT is synonymous with HCV RNA and EIA with anti-HCV (p. 9-10).

Line 146- specify what the prevalence of HCV is among CKD patients vs. the general population so readers can compare

We added some information on the prevalence of EIA (HCV antibody) positivity for incident dialysis patients to contrast the difference between these estimates and those of the general population (p. 8)

Line 147- the authors explain that HCV is a risk for faster CKD progression, and it would be helpful here to also highlight that HCV is a cause of several kidney diseases.

We added text highlighting the association of HCV and glomerulonephritis but hesitate to overstate the claim as the association of HCV and faster CKD progression seems independent of whether there is overt evidence of glomerulonephritis (p. 8).

Line 150- consider re-ordering this list of risk factors, placing “ever required HD” first given the focus of these guidelines. I would also suggest placing the baby boomer screening recommendation (line 152) ahead of all the other risk factors listed as this reflects the order that the risk factors are outlined in Table 1.

We re-ordered the list of risk factors as the reviewer suggests.

Line 157- The CDC recently discussed at a public meeting its plans to recommend universal one time HCV screening for all Americans in the coming months. This recommendation takes into account cost effectiveness analysis, so these studies may not be necessary. It would also be helpful for the authors to present data on the percentage of CKD patients who fall within the 1945-1965 birth cohort. If there is significant overlap, which seems likely, many CKD patients are already captured in the baby boomer screening recommendations.

We are unable to comment on whether CDC plans to recommend one-time screening for all Americans but we agree with the reviewer that cost-effectiveness might be less pertinent given the existing recommendation for the 1945-1965 birth cohort to be screened. Thus, we have modified our sentence to focus on assessment of clinical benefit for this population rather than on cost-effectiveness (p. 8). A recent publication (Eckman MH, Clinical Gastroenterology and Hepatology 2019) used a Markov model to evaluate cost effectiveness of universal screening; like the reviewer, we are very curious to see if this becomes a future practice.

RECOMMENDATIONS RELATED TO HCV TESTING IN END-STAGE KIDNEY DISEASE PATIENTS

Line 174- clarify that the high prevalence of HCV in HD populations is related to both HCV causing CKD and nosocomial transmission of HCV in HD units

We added text to highlight this important point (p. 9).

Line 175- please define DOPPS

Done. Thank you for noticing this omission which we have now clarified (p. 8).

Line 180- the recommendation for HCV testing in kidney transplant recipients could use a statement supporting why this is the case.

We thank the reviewer for noticing this oversight, which we agree would not be intuitive to the entire readership of the Annals of Internal Medicine (see line 9-10). Thank you.

Line 183- I suggest adding a statement about the benefit of reflex HCV RNA testing as a means of simplifying the testing process.

We added a brief phrase to the text to address this suggestion (p. 10). Thank you.

RECOMMENDATIONS RELATED TO TREATMENT OF HCV INFECTION IN PATIENTS WITH CKD

Line 198- recommendation 2.1.2-consider re-ordering the factors that inform antiviral therapy choice as follows: prior treatment history, genotype, stage of hepatic fibrosis, viral load, GFR, transplant candidacy, comorbidities and drug-drug interactions. This more closely mirrors the hcvguidelines.org treatment decision tree and the thought process HCV treaters use in choosing an antiviral regimen.

Although we appreciate the suggestion, we prefer to keep in the present order, which mirrors the actual guideline recommendation from the original KDIGO guideline.

Line 205- the authors should add that NS5B-containing regimens should also be avoided in patients with GFR <30.

We agree that this important point and added text on p. 11 (bottom) which is taken from later in the manuscript in the section on DAAs in kidney transplantation, where sofosbuvir is used frequently due to the higher GFRs generally in these populations.

Line 208-for consistency would use the term “DAAs” throughout instead of “DAA agents” which is used here but not later in the text.

We made this change throughout.

Line 219- I would argue that we have passed the period of rapid evolution of evidence regarding DAA treatment in CKD populations, as there have been no new DAAs approved since glecaprevir/pibrentasvir in 2017.

Although we agree that the period of new FDA approved DAAs is likely nearing or at its end, we believe the field does continue to evolve rapidly with regard to treatment in CKD populations, including the HCV positive to negative transplant with immediate DAA treatment as well as recent data on HCV treatment as a potential mechanism to slow CKD progression (Sise, KI 2019). So, although new agents may not be developed, the field is still evolving as far as

identifying new patient populations who might benefit from treatment as well as shorter treatment durations, among other anticipated changes.

Line 234- I was confused as to why elbasvir/grazoprevir was not included in Table 2 when the text reads that "patients with GFR< 30 should be treated with the regimens outlined above," one of which is elbasvir/grazoprevir.

The reviewer may have been searching for elbasvir/grazoprevir in the table where we listed the agents in reverse order, grazoprevir/elbasvir. The table was reproduced from the KDIGO guideline itself and we prefer to maintain the order of the agents as we did in the guideline.

Line 273- consider using "transplant team" instead of "transplant center."

We kept the "center" nomenclature as this was used in the actual guideline statement. Please refer above in our response to last comment from reviewer 1 for our rationale in choosing this terminology.

Line 275- consider replacing "benefit from" with "experience."

We maintained the phrase "benefit from" to highlight that this may be a strategically advantageous choice for the HCV infected kidney transplant candidate.

Line 285- In the article cited, I believe all cases of HBV reactivation reported occurred during rather than following DAA treatment, so I would change this in the text.

We thank the reviewer for the careful review and made the suggested change (p. 14, top)

Line 286- HBV DNA testing is not necessary unless indicated based on the results of the other HBV serologic tests mentioned, ie HBV sAg positive. From hcvguidelines.org, "all patients initiating HCV DAA therapy should be assessed for HBV coinfection with HBsAg testing, and for prior infection with anti-HBs and anti-HBc testing. HBV vaccination is recommended for all susceptible individuals. A test for HBV DNA should be obtained prior to DAA therapy in patients who are HBsAg positive."

We added text to reflect that HBV DNA testing occurs based on the results of the antibody testing (p. 14).

Also, a comment here on the prevalence of HBV infection in CKD patients would strengthen this section. Is there a higher prevalence of HBV in CKD populations that makes this testing especially important?

Although little data exists on HBV prevalence in CKD patients, it is likely higher than in the general population, as data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) suggests mean HBV prevalence in HD units is 3.0% (Burdick RA, Kidney International 2003), and likely higher in developing nations that were not part of DOPPS. Although there is potentially transmission of HBV within HD units, this higher prevalence likely represents a higher HBV prevalence in CKD. We added text on p. 14 and cited the Burdick paper (ref 29) to emphasize this important point.

RECOMMENDATIONS RELATED TO PREVENTING HCV TRANSMISSION IN HEMODIALYSIS UNITS
Line 330- it's unclear why isolation of HBV-infected patients makes isolation of HCV-infected patients impractical. Please provide further clarification.

As per recommendations from the Editors, we are removing the section on Chapter 3. However, the issue here is practicality. It would require the dialysis unit to divide into 4 sections of different sizes based on HBV and HCV status and would not solve the issue of transmission of different genotypes.

Line 337- consider reframing this discussion to state that a joint strategy of DAA treatment plus optimizing infection control practices would be a sound approach. These should be complementary rather than either-or strategies.

We agree with the reviewer that this would be the optimal strategy but as noted above this section will be removed from the manuscript.

RECOMMENDATIONS RELATED TO THE MANAGEMENT OF HCV-INFECTED PATIENTS BEFORE AND AFTER KIDNEY TRANSPLANTATION

Line 379- again change "transplant center" to "transplant team."

We did not make the change to this terminology for reason cited above.

Line 385-a transition sentence prior to the sentence starting, “The first descriptions…” that introduces the concept of HCV positive donors->HCV negative recipients would improve the flow here.

We agree and made edits in this area of the manuscript.

RECOMMENDATIONS RELATED TO THE DIAGNOSIS AND MANAGEMENT OF KIDNEY DISEASES ASSOCIATED WITH HCV INFECTION

Line 415-please provide more information about the studies mentioned. “These studies” are referenced but not introduced.

We agree with the reviewer and edited this section accordingly (p. 16).

4. Discussion

The first paragraph is an excellent summary that conveys the positive developments in the field of HCV in CKD. Overall the discussion is well organized and clear.

Line 467- the topic of equitable distribution of a limited resource is a packed one that feels too weighty to introduce without an associated discussion, which is outside the scope of this Guideline. I would suggest removing this sentence and stating that HCV positive donor to HCV negative recipients is a new field that warrants further investigation.

We agree with the reviewer and edited this section accordingly (p. 18).

Line 471- reiterating an earlier point, identifying HCV in CKD patients may soon not be an issue if universal screening for all adults becomes the new guideline. Also, the meaning of equitable access to DAA treatment is unclear. Does this refer to access to DAAs by insured vs. uninsured patients, or treatment restrictions imposed by payors based on fibrosis, sobriety or provider type? More specifics here would be helpful.

We agree with the reviewer if universal screening becomes the new standard, this will impact this recommendation. However, we did not edit the manuscript as this is not current standard of care. With regard to the equitable access, we feel all of the suggested explanations of the reviewer were what we had in mind, but felt it was better to keep the statement vague for the purposes of this manuscript.

TABLES AND FIGURES

Table 2-It's unclear why elbasvir/grazoprevir is not included here

We apologize for the confusion that occurred from decisions about nomenclature (i.e., grazoprevir/elbasvir) made during the guideline development process, which led to the confusion.

Figure 1-conventional naming for DAAs including fixed dose combinations of two drugs uses "/" not "-" so grazoprevir-elbasvir should be grazoprevir/elbasvir (and is usually elbasvir/grazoprevir). This format is consistent with Table 2.

We have amended both figures 1 and 2 to reflect the "/" convention to be consistent with Table 2.

Figure 2- It's unclear why elbasvir/grazoprevir is not included under the left branch, box below genotypes 1,4.

Although we agree with the reviewer that this regimen potentially has a role in kidney transplant recipients, the supporting evidence base of studies of elbasvir/grazoprevir in kidney transplant recipients is quite small, with only one study of treatment following HCV positive to negative transplant describing the use of the regimen in kidney transplant recipients. Most studies identified in our systematic review were of sofosbuvir-based regimens or of glecaprveir/pibrentasvir.

Production Editor Comments

Text

• If any of the tables or figures are reproduced from a published source, we will need written permission from the copyright holder in order the publish them.

KDIGO is the copyright holder for all of the figures and tables used in this guideline synopsis.

• On a separate page after the text, please include current postal addresses (including institution name; not e-mail addresses) for all authors.

Completed.

References

• Reference citations in the text should be in regular font, within punctuation, and in parentheses. For example:

The first clinical practice guideline published by Kidney Disease: Improving Global Outcomes (KDIGO) was the 2008 guideline for the Prevention, Diagnosis, Evaluation and Treatment of Hepatitis C virus (HCV) in patients with chronic kidney disease (CKD) (1, 2).

We edited our reference citations to comply with the style of the journal.

Tables

• Please ensure that all abbreviations used in the tables are defined in the table footnotes (including those already defined in the text).

• Please use the following footnote symbols in the following order: *, †, ‡, §, ||, ¶, **, ††, ‡‡, and so on (left to right, top to bottom, starting with the table title). Please do not use letters or numbers. Please make sure that every note has a corresponding footnote symbol (symbols for general notes applying to the entire table can be placed at the end of the table title).

• Table 2 has been provided as a picture. Please provide a Word table that can be copyedited.
Done.

Permissions
• People who are acknowledged by name must provide written permission to be acknowledged. Please provide letters of permission from David C. Wheeler and Wolfgang C. Winkelmayer. A short, informal e-mail from each person would be sufficient.

Their permissions have been provided.

Electronic Manuscript Submission

• When submitting your revisions, please submit a Word file for the manuscript, a separate Word file containing all tables (including appendix tables), and individual files for each figure. Please place the figure legends at the end of the manuscript file.

Done.

Prevention, Diagnosis, Evaluation and Treatment of Hepatitis C in Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2018 Clinical Practice Guideline

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Abstract

Description: The Kidney Disease: Improving Global Outcomes (KDIGO) 2018 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation and Treatment of Hepatitis C in Chronic Kidney Disease (CKD) is an extensive update of the prior (2008) hepatitis C virus (HCV) and CKD KDIGO guideline. This update reflects the major advances since the introduction of direct acting antivirals (DAAs) in the management of HCV in the CKD population.

Methods: The KDIGO HCV and CKD Guideline Development Work Group defined the scope of the Guideline, gathered evidence, determined topics for systematic review, and graded the quality of evidence previously summarized by an Evidence Review Team. Appraisal of the quality of the evidence and rating the strength of the recommendations followed the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. Searches of the English language literature were conducted through May 2017 and were supplemented with targeted searches for studies of DAA treatment and with abstracts from Nephrology, Hepatology and Transplantation conferences. A stakeholder review process involving numerous stakeholders, subject matter experts, and industry and national organizations informed final modification of the guideline.

Recommendations: The updated guideline included 66 recommendations. This synopsis focus is on 32 key recommendations pertinent to prevention, diagnosis, treatment and management of HCV in adult CKD populations.

Introduction

The first Clinical Practice Guideline published by Kidney Disease: Improving Global Outcomes (KDIGO) was the 2008 guideline for the Prevention, Diagnosis, Evaluation and Treatment of Hepatitis C virus (HCV) in patients with Chronic Kidney Disease (CKD) (1, 2). In the subsequent 10 years, the development of direct acting antiviral (DAAs) allowing a greater than 95% rate of viral eradication in CKD populations infected with HCV prompted KDIGO to update the 2008 Clinical Practice Guideline (3, 4).

The overall objective for the guideline is to inform the management of HCV including the use of DAAs in adults with CKD. The target audience of the guideline includes nephrologists, transplant physicians, hepatologists, infectious disease specialists, primary care physicians, and other practitioners caring for adults with HCV and CKD worldwide. As with the original 2008 HCV and CKD guideline, recommendations are divided into 5 chapters, 1) Detection and evaluation of HCV in CKD; 2) Treatment of HCV infection in patients with CKD; 3) Preventing HCV transmission in hemodialysis units; 4) Management of HCV-infected patients before and after kidney transplantation; 5) Diagnosis and management of kidney diseases associated with HCV infection.

Within the Guideline, recommendations for clinical practice, implementation and future research are highlighted. The Guideline sought to provide comprehensive guidance encompassing all aspects of managing HCV in CKD populations (Appendix Figure 1) and considers implementation across international settings where HCV and CKD are encountered. The complete version is available at www.kdigo.org and includes 66 recommendations. This synopsis focuses on 32 key

recommendations relevant to the clinical practice regarding HCV in CKD patients. The major topics of the remaining 34 recommendations relate to preventing HCV transmission in hemodialysis units, CKD testing in HCV infected patients, performance characteristics of non-invasive tests of hepatic fibrosis, and decisions about combined liver-kidney versus kidney transplantation alone.

GUIDELINE DEVELOPMENT PROCESS, EVIDENCE GRADING, AND STAKEHOLDER CONSULTATION

The Work Group consisted of an international group of clinicians and researchers, including nephrologists, hepatologists, virologists, a representative from the Centers for Disease Control and Prevention (CDC) and a professional evidence review team. The Work Group formulated the scope of the Guideline and graded evidence on the basis of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) (5) system as per KDIGO's usual practice (**Appendix Tables 1** and **2**, available at www.annals.org).

Briefly, the process involved reviewing the 2008 KDIGO Guideline on HCV and CKD, other existing guidelines (American Association for the Study of Liver Diseases/ Infectious Diseases Society of America (AASLD/IDSA), European Association for the Study of the Liver (EASL), Japanese Society for Dialysis Therapy) on HCV that had sections related to CKD (6-8), and subsequently developing research questions for each of the chapters. Based on specific research questions identified by the Work Group, the evidence review team conducted systematic reviews on seven topics: 1) HCV treatment in CKD populations (Chapters 2, 4 and 5); 2) Pre-transplantation noninvasive testing for hepatic fibrosis (Chapter 1); 3) Outcome of isolation of HCV infected patients in hemodialysis units (Chapter 3); 4) Outcomes with early versus late

kidney transplantation for HCV infected patients on the wait list (Chapter 4); 5) Transplantation of HCV infected kidney transplant candidates with HCV-positive donors (Chapter 4); 6) Predictors of CKD progression associated with HCV (Chapter 1); 7) Relationships between HCV and graft loss and mortality in kidney transplant recipients (Chapter 4). The search parameters are presented in **Appendix Table 3**. The formal literature search identified 125 eligible studies that were summarized and assessed for quality using the GRADE methodology (5). The Work Group then developed guideline statements rated as strong (level 1) or weak (level 2) based on the strength of evidence from the systematic review as well as other evidence from non-CKD populations. Following GRADE, the strength of the evidence supporting each guideline statement was rated from high to very low (A to D). Guidelines statements providing general guidance and therefore not based on systematic evidence review were labeled "non-graded."

The Guideline statements and supporting text subsequently underwent external stakeholder review by individuals and organizations worldwide with expertise in the field. The final document incorporated comments and suggestions from the external review where appropriate.

CHAPTER 1: RECOMMENDATIONS RELATED TO THE DETECTION AND EVALUATION OF HCV IN CKD

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

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

The prevalence of HCV is higher among CKD patients than in the general population with around 5% of incident dialysis patients testing positive by EIA (9), substantially higher than the estimated 1% HCV prevalence in the general population in the US (10). Recent studies have implicated HCV infection as an independent risk factor for faster rates of CKD progression (11), in part related to the association of HCV with several glomerulonephritides but likely also independent of this connection. The AASLD/IDSA guidelines and CDC recommend one time HCV testing for the 1945-1965 birth cohort due to a higher prevalence of HCV in this group (6, 12). Additionally, the AASLD/IDSA and CDC recommend HCV testing for high risk patients including those who have ever required long-term hemodialysis (HD), engaged in injection or intranasal drug use, solid organ transplant recipients prior to July 1992, HIV infected individuals, and persons who were ever incarcerated, among others (6) (**Table 1**). The recommendation to screen all patients for HCV at the time of initial CKD evaluation incorporates these guideline recommendations, the higher prevalence of HCV among CKD patients, and the more rapid CKD progression seen in HCV-infected CKD patients compared with uninfected patients (13). Future studies should determine the degree of clinical benefit of this strategy of HCV testing in CKD patients. Repeat HCV testing is prudent for patients with ongoing possible exposure to HCV including ongoing drug use, chronic hemodialysis, among others. Decisions about the benefit of HCV screening in CKD patients may be impacted by a recent report describing slower GFR decline following

successful HCV-treatment in patients with eGFR < 60ml/min/1.73 m^2 than the rate of decline preceding treatment (14).

RECOMMENDATIONS RELATED TO HCV TESTING IN END-STAGE KIDNEY DISEASE PATIENTS

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

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

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

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

The prevalence of HCV in the HD population exceeds that of the general population with approximately 10% of patients in recent Dialysis Outcomes and Practice Patterns Study (DOPPS) analyses testing positive by enzyme immunoassay (EIA), also known as anti-HCV or HCV antibody (9, 15). This occurs as a result both of the high prevalence of HCV on initiation of dialysis (9) as well as nosocomial transmission within HD units. HCV testing prior to initiation of in-center HD (including when transitioning from other dialysis modalities) and upon transfer between HD facilities provides the opportunity to identify patients potentially exposed to HCV at the prior facility. Acute HCV infection in HD units is identified through monitoring for increases above baseline for liver biochemical tests, which can suggest acute HCV and prompt testing for HCV viremia several months before EIA testing becomes positive. The recommendation for HCV testing in patients treated with peritoneal dialysis or home HD is based on limited evidence but nevertheless is a prudent approach. HCV testing is recommended in kidney transplant candidates

to determine who is at risk of progressive hepatic disease, who might benefit from an HCV-infected donor kidney and to select the optimal HCV treatment strategies for transplant candidates.

NAT testing confirms active HCV infection (HCV RNA positivity or viremia) but EIA testing, followed by NAT for EIA-positive patients, ideally via reflex testing, is a reasonable approach with adequate sensitivity and specificity in immunocompetent patients. However, NAT is the most appropriate first-line test for immunocompromised kidney transplant recipients and possibly for patients undergoing hemodialysis due to concerns about delayed seroconversion in acute HCV (window period). The prevalence and incidence of HCV in individual HD units informs the choice between EIA or NAT as the risk of false negative EIA tests rises with increasing HCV prevalence (closely associated with incidence) in the dialysis population (1).

CHAPTER 2: RECOMMENDATIONS RELATED TO TREATMENT OF HCV INFECTION IN PATIENTS WITH CKD

Treatment in CKD G1-G5 and G5D

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

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

2.1.2: We recommend that the choice of specific regimen be based on HCV genotype (and subtype), viral load, prior treatment history, drug-drug interactions, glomerular filtration rate (GFR), stage of hepatic fibrosis, kidney and liver transplant candidacy, and comorbidities (*1A*).

2.2: We recommend that patients with GFR ≥ 30 ml/min/1.73 m^2 (CKD G1-G3b) be treated with any licensed direct-acting antiviral (DAA)-based regimen (*1A*).

2.3: Patients with GFR < 30 ml/min/1.73 m^2 (CKD G4-G5D) should be treated with a ribavirin-free DAA-based regimen.

The development of DAAs has changed the approach to HCV treatment in CKD patients compared with the 2008 Guideline. Interferon treatment is no longer recommended due to high

rates of adverse events with modest sustained virologic response (SVR) rates of 37-41% (16, 17). Moreover, interferon is contraindicated in kidney transplant recipients due to a high risk of acute rejection and allograft loss (18). DAAs achieve SVR rates of 90-100% with few adverse events including in patients with CKD G4-G5, patients with end-stage kidney disease (ESKD), and kidney transplant recipients (19-22). All CKD patients should be evaluated for treatment with the choice of DAA regimen determined by HCV genotype, viral load, prior treatment history, GFR, stage of hepatic fibrosis, kidney and liver transplant candidacy and after considering drug-drug interactions. Figure 1 presents a treatment algorithm based on CKD stage and HCV genotype.

The evidence base regarding DAA treatment in CKD populations is rapidly evolving, requiring professional organizations to update frequently recommendations regarding choice of antiviral regimens. Clinicians should refer to www.HCVguidelines.org, a useful resource that is updated frequently to reflect new evidence (6). Key studies in CKD populations include C-SURFER, a randomized controlled trial (RCT) of immediate versus delayed treatment with a 12 week course of elbasvir/grazoprevir in 224 patients with HCV genotype 1 and CKD G4-G5 (76% ESKD) (22). SVR was 94% in immediately treated patients and 98% in those randomized to deferred treatment (19). No patients discontinued treatment due to of adverse events. Similarly, the pangenotypic regimen of 12 weeks of glecaprevir/pibrentasvir resulted in a 98% SVR rate in 104 patients with CKD G4-G5 (82% ESKD) (21). Four subjects discontinued treatment but three of these achieved SVR. Although studies exist reporting the use of sofosbuvir-based regimens in CKD G4-G5 and ESKD, sofosbuvir is renally excreted and is not FDA-approved for use in patients with GFR < 30 ml/min/1.73 m^2.

Based on extrapolation of data from multiple studies in non-CKD populations (which likely included some patients with CKD G1-G3b) (23, 24), CKD patients with GFR ≥ 30 ml/min/1.73 m^2 can be treated with any licensed DAA regimen. Patients with GFR < 30 ml/min/1.73 m^2 should be treated with the specific regimens outlined above (**Table 2**).

HCV treatment in kidney transplant recipients

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

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

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

2.4.3: We recommend avoiding treatment with interferon (*1A*).

2.4.4: We recommend pre-treatment assessment for drug-drug interactions between the DAA-based regimen and other concomitant medications including immunosuppressive drugs in kidney transplant recipients (*1A*).

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

DAA treatment studies in kidney transplant recipients have generally included patients with GFR ≥ 30 ml/min/1.73 m^2 and as a result have included sofosbuvir-based regimens. Treatment with DAAs in kidney transplant recipients have resulted in SVR rates exceeding 95%. Colombo et al. reported an SVR of 100% following treatment with sofosbuvir and ledipasvir in 114 kidney transplant recipients, with only 1% discontinuing treatment due to adverse events (20). A study combining kidney and liver transplant recipients demonstrated an overall SVR of 98% following treatment with glecaprevir and pibrentasvir, with all 20 kidney transplant recipients achieving SVR (25).

For kidney transplant recipients, the selection of DAA regimen should reflect HCV genotype, viral load, prior treatment history, GFR, and stage of hepatic fibrosis, and particularly should consider drug-drug interactions between DAA and other medications, notably calcineurin inhibitors.

Information on drug-drug interactions is available on https://www.hep-druginteractions.org/,which is updated frequently based on new data. Clinicians treating HCV-infected kidney transplant recipients should have heightened awareness for changes in allograft function particularly in those treated with calcineurin inhibitors as increased or decreased plasma levels have been described due to drug-drug interactions with DAA. HCV treatment in kidney transplant recipients should follow the algorithm in **Figure 2** and with the specific regimens outlined in **Table 2**. Although early evidence suggests most DAAs can be used safely in patients on transplant immunosuppressive agents, and most are FDA-approved in patients with GFR > 30 ml/min per 1.73 m2, the clinical experience with DAAs in organ transplant recipients remains relatively small and careful attention to treatment in this population is prudent.

Timing of treatment in kidney transplant candidates

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

As a result of the universally high SVR rates in all CKD populations, decisions about optimal timing of treatment in transplant candidates should include the transplant center (26). HCV-infected kidney transplant candidates willing to accept a kidney from an HCV-infected donor may benefit from a shorter waitlist time if they remain untreated until following transplantation from an HCV-positive donor, a graft that might otherwise be discarded (27). However, kidney transplant candidates with compensated cirrhosis from HCV should be considered for pre-transplant treatment to induce regression of fibrosis post-SVR to allow kidney alone transplantation.

2.5: All treatment candidates should undergo testing for HBV infection prior to therapy (*Not Graded*).

Assessment for unrecognized hepatitis B virus (HBV) infection prior to DAA treatment is recommended because of recent reports of fulminant HBV reactivation during DAA treatment (28). The prevalence of HBV in HD facilities sampled by DOPPS was 3.0% (29), suggesting that the prevalence in CKD patients likely exceeds that of the general population. Testing should include HBsAg, HBsAb, HBcAb and, when required by test results, HBV DNA.

CHAPTER 4: RECOMMENDATIONS RELATED TO THE MANAGEMENT OF HCV-INFECTED PATIENTS BEFORE AND AFTER KIDNEY TRANSPLANTATION

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

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

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

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

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

4.2 Use of kidneys from HCV-infected donors

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

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

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

HCV infection is not a contraindication to kidney transplantation. The mortality rates are significantly lower in HCV-infected kidney transplant recipients than in HCV-infected patients on the transplantation waiting list (30-32). Nevertheless, HCV-infected kidney transplant recipients have had increased mortality (33, 34), allograft loss (35, 36), and post-transplant diabetes (37-39) and glomerulonephritis (40, 41) than non-infected patients, so DAA treatment is critical with individualization of the decision of pre- versus post-transplant treatment to maximize the benefit to each patient (26). Incorporating the judgment of the transplant center and other specialists in these complex decisions is critical. Specific details of evidence-based DAA treatment regimens, timing of treatment, and the importance of monitoring GFR and calcineurin inhibitor levels during and following treatment are discussed earlier (Chapter 2, section 2.4).

HCV-infected kidney donors

Potential deceased donors require HCV testing using both EIA and NAT to determine if viremia is present. HCV-infected deceased donor kidneys should be directed to recipients with positive NAT. Modifying this practice is the development of research protocols describing kidney transplantation from NAT positive donors to HCV negative recipients with immediate DAA treatment, which report 100% SVR rate with good short-term allograft outcomes (42, 43). This practice may become more widespread in the future but for now should be restricted to

investigational settings, although this statement may require revision as new evidence accrues. HCV-infected potential living kidney donors should receive DAA treatment and upon achieving SVR should be re-evaluated to ensure they remain appropriate kidney donors.

CHAPTER 5: RECOMMENDATIONS RELATED TO THE DIAGNOSIS AND MANAGEMENT OF KIDNEY DISEASES ASSOCIATED WITH HCV INFECTION

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

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

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

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

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

The role of DAAs in the management of HCV-associated glomerulonephritis (GN) including HCV-associated mixed cryoglobulinemia and membranoproliferative GN has become clearer in recent years. SVR rates have ranged from 74-83% in studies of DAAs for HCV-associated GN with low rates of adverse events (44-46). Importantly, DAA treatment leads to diminished proteinuria, increased GFR, and quality of life but studies have been limited to patients with stable GFR and without rapidly progressive glomerulonephritis, cryoglobulinemic vasculitis or nephrotic range proteinuria. In these more urgent scenarios, immunosuppressive therapy should be administered concomitantly with DAA and plasma exchange should be considered. Among immunosuppressive agents, rituximab is the best-studied agent for HCV-related GN (47, 48). Prior

to the initiation of rituximab, patients should be assessed for HBV infection to avoid fulminant hepatitis resulting from HBV reactivation.

DISCUSSION

The 2018 KDIGO Clinical Practice Guideline on HCV in CKD represents a major update to the original 2008 Guideline. Because of the efficacy of DAAs in CKD populations including CKD G4, G5 and G5D as well as in kidney transplant recipients, the approach to HCV management has evolved dramatically in the past 10 years. The ability to eradicate HCV with DAA treatment has influenced all chapters of the 2018 update. Moderately-sized prospective cohort studies and RCT in CKD G4, G5 as well as in HD patients and kidney transplant recipients have consistently revealed SVR rates of 90-100%. The results add to the evidence base supporting efficacy of DAA treatment in non-CKD patients and directly translate to the recommendation to evaluate treatment candidacy in all HCV-infected CKD patients. DAA-based treatment of HCV-associated glomerular disease is another area of rapid change with a shift in the focus from immunosuppression to HCV eradication as the first line management approach for most patients.

The potential to cure HCV also impacts the recommendations on testing for HCV. The CDC and AASLD/IDSA already recommend one-time HCV testing in the 1945-1965 birth cohort and in patients at high risk of acquiring HCV, which includes numerous risk factors common to CKD patients. Nephrologists generally recommend HCV testing in patients under evaluation for glomerular disease and additionally the yield of HCV testing in CKD patients is higher because of the increased prevalence of HCV in the CKD patient population. The growing evidence base supporting an association between HCV infection and faster CKD progression to ESKD also

supports the recommendation to test all patients at initial CKD evaluation. If future investigation replicates the early finding that DAA treatment may slow CKD progression (49), the imperative for HCV testing of all CKD patients would gain strength, as it would offer a novel avenue to slow CKD progression (50).

Finally, the efficacy of DAA in patients with advanced kidney disease including dialysis patients as well as among kidney transplant recipients has greatly affected the approach to HCV in kidney transplant candidates. Careful attention to strategies about timing of HCV treatment that maximize benefit to individual patients as well as those that improve the utilization of HCV-infected deceased donor kidneys are becoming increasingly important (27). The new development of transplantation of HCV-infected organs to HCV-uninfected individuals with immediate post-transplant DAA treatment may represent a major advance (42, 43, 51) but is a new field that warrants further investigation. Clinicians treating HCV-infected kidney transplant recipients should have heightened awareness for changes in allograft function particularly in those treated with calcineurin inhibitors. Until more extensive experience is available for reassurance of safety of DAAs with the transplanted kidney functioning in the common GFR range of 30-60 ml/min per 1.73 m2, close monitoring of the kidney allograft function should be employed while these patients are undergoing DAA therapy.

Future research in HCV and CKD will likely shift to implementation science, as well as cost effectiveness and decision analysis. What are the best approaches to identify HCV infected CKD patients? How do we ensure equitable access to DAA treatment? Does HCV treatment actually slow CKD progression? What is the optimal timing of HCV treatment in patients who may progress to ESKD? What are the cost implications of strategies designed to test all CKD patients

and to treat all HCV-infected individuals? The answers to these and other questions will likely guide the future of HCV management in CKD patients.

We are optimistic that the current KDIGO Guideline will increase the attention on the intersection between HCV and CKD as well as spur future investigation into new directions to improve the care of this patient population.

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Figure 1: Treatment scheme for chronic kidney disease (CKD) G1 to G5D

Caption: Recommendation grades (1-2) and strength of evidence (A-D) are provided for each recommended treatment regimen and hepatitis C virus (HCV) genotype. Sofosbuvir/velpatasvir-based regimens were not listed above since they were not formally reviewed by the Evidence Review Team at the time of guideline publication. However these regimens can be considered in patients with CKD G1-G3b given their availability in certain jurisdictions.
CKD G = chronic kidney disease, GFR category; DAA = direct-acting antiviral; GFR = glomerular filtration rate; NAT = nucleic acid testing.

Figure 2: Treatment scheme for kidney transplant recipients (KTRs).

Caption: Recommendation grade (1-2) and strength of evidence (A-D) are provided for each recommended treatment regimen and hepatitis C virus (HCV) genotype. Sofosbuvir/velpatasvir-based regimens were not listed above since they were not formally reviewed by the Evidence Review Team at the time of guideline publication. However these regimens can be considered in KTRs with GFR $\geq$ 30 ml/min/1.73 m^2 given their availability in certain jurisdictions.
CKD G = chronic kidney disease, GFR category; (suffix T denotes transplant recipient); NAT = nucleic acid testing. ‡Based on Reau *et al. (25).*

Appendix Figure 1: Prognosis of CKD, by categories of GFR and albuminuria.

CKD is defined as abnormalities of kidney structure or function that are present for >3 mo and have health implications. CKD is classified on the basis of cause, GFR category (G1 to G5), and albuminuria category (A1 to A3). Green means low risk (no CKD if no other markers of kidney disease), yellow means moderately increased risk, orange means high risk, and red means very high risk. The suffix “D” denotes dialysis (e.g., CKD G5D refers to a patient with CKD stage G5 who is receiving dialysis). (Reproduced with permission of Kidney Disease: Improving Global Outcomes) CKD = chronic kidney disease; GFR = glomerular filtration rate.

Prevention, Diagnosis, Evaluation and Treatment of Hepatitis C in Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2018 Clinical Practice Guideline

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Abstract

Description: The Kidney Disease: Improving Global Outcomes (KDIGO) 2018 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation and Treatment of Hepatitis C in Chronic Kidney Disease (CKD) is an extensive update of the prior (2008) hepatitis C virus (HCV) and CKD KDIGO guideline. This update reflects the major advances since the introduction of direct acting antivirals (DAAs) in the management of HCV in the CKD population.

Methods: The KDIGO HCV and CKD Guideline Development Work Group defined the scope of the Guideline, gathered evidence, determined topics for systematic review, and graded the quality of evidence previously summarized by an Evidence Review Team. Appraisal of the quality of the evidence and rating the strength of the recommendations followed the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. Searches of the English language literature were conducted through May 2017 and were supplemented with targeted searches for studies of DAA treatment and with abstracts from Nephrology, Hepatology and Transplantation conferences. A stakeholder review process involving numerous stakeholders, subject matter experts, and industry and national organizations informed final modification of the guideline.

Recommendations: The updated guideline included 66 recommendations. This synopsis focus is on 32 key recommendations pertinent to prevention, diagnosis, treatment and management of HCV in adult CKD populations.

Introduction

The first Clinical Practice Guideline published by Kidney Disease: Improving Global Outcomes (KDIGO) was the 2008 guideline for the Prevention, Diagnosis, Evaluation and Treatment of Hepatitis C virus (HCV) in patients with Chronic Kidney Disease (CKD) (1, 2). In the subsequent 10 years, the development of direct acting antiviral (DAAs) allowing a greater than 95% rate of viral eradication in CKD populations infected with HCV prompted KDIGO to update the 2008 Clinical Practice Guideline (3, 4).

The overall objective for the guideline is to inform the management of HCV including the use of DAAs in adults with CKD. The target audience of the guideline includes nephrologists, transplant physicians, hepatologists, infectious disease specialists, primary care physicians, and other practitioners caring for adults with HCV and CKD worldwide. As with the original 2008 HCV and CKD guideline, recommendations are divided into 5 chapters, 1) Detection and evaluation of HCV in CKD; 2) Treatment of HCV infection in patients with CKD; 3) Preventing HCV transmission in hemodialysis units; 4) Management of HCV-infected patients before and after kidney transplantation; 5) Diagnosis and management of kidney diseases associated with HCV infection.

Within the Guideline, recommendations for clinical practice, implementation and future research are highlighted. The Guideline sought to provide comprehensive guidance encompassing all aspects of managing HCV in CKD populations (Appendix Figure 1) and considers implementation across international settings where HCV and CKD are encountered. The complete version is available at www.kdigo.org and includes 66 recommendations. This synopsis focuses on 32 key

recommendations relevant to the clinical practice regarding HCV in CKD patients. The major topics of the remaining 34 recommendations relate to preventing HCV transmission in hemodialysis units, CKD testing in HCV infected patients, performance characteristics of non-invasive tests of hepatic fibrosis, and decisions about combined liver-kidney versus kidney transplantation alone.

GUIDELINE DEVELOPMENT PROCESS, EVIDENCE GRADING, AND STAKEHOLDER CONSULTATION

The Work Group consisted of an international group of clinicians and researchers, including nephrologists, hepatologists, virologists, a representative from the Centers for Disease Control and Prevention (CDC) and a professional evidence review team. The Work Group formulated the scope of the Guideline and graded evidence on the basis of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) (5) system as per KDIGO's usual practice (Appendix Tables 1 and 2, available at www.annals.org).

Briefly, the process involved reviewing the 2008 KDIGO Guideline on HCV and CKD, other existing guidelines (American Association for the Study of Liver Diseases/ Infectious Diseases Society of America (AASLD/IDSA), European Association for the Study of the Liver (EASL), Japanese Society for Dialysis Therapy) on HCV that had sections related to CKD (6-8), and subsequently developing research questions for each of the chapters. Based on specific research questions identified by the Work Group, the evidence review team conducted systematic reviews on seven topics: 1) HCV treatment in CKD populations (Chapters 2, 4 and 5); 2) Pre-transplantation noninvasive testing for hepatic fibrosis (Chapter 1); 3) Outcome of isolation of HCV infected patients in hemodialysis units (Chapter 3); 4) Outcomes with early versus late

kidney transplantation for HCV infected patients on the wait list (Chapter 4); 5) Transplantation of HCV infected kidney transplant candidates with HCV-positive donors (Chapter 4); 6) Predictors of CKD progression associated with HCV (Chapter 1); 7) Relationships between HCV and graft loss and mortality in kidney transplant recipients (Chapter 4). The search parameters are presented in Appendix Table 3. The formal literature search identified 125 eligible studies that were summarized and assessed for quality using the GRADE methodology (5). The Work Group then developed guideline statements rated as strong (level 1) or weak (level 2) based on the strength of evidence from the systematic review as well as other evidence from non-CKD populations. Following GRADE, the strength of the evidence supporting each guideline statement was rated from high to very low (A to D). Guidelines statements providing general guidance and therefore not based on systematic evidence review were labeled "non-graded."

The Guideline statements and supporting text subsequently underwent external stakeholder review by individuals and organizations worldwide with expertise in the field. The final document incorporated comments and suggestions from the external review where appropriate.

CHAPTER 1: RECOMMENDATIONS RELATED TO THE DETECTION AND EVALUATION OF HCV IN CKD

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

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

The prevalence of HCV is higher among CKD patients than in the general population with around 5% of incident dialysis patients testing positive by EIA (9), substantially higher than the estimated 1% HCV prevalence in the general population in the US (10). Recent studies have implicated HCV infection as an independent risk factor for faster rates of CKD progression (11), in part related to the association of HCV with several glomerulonephritides but likely also independent of this connection. The AASLD/IDSA guidelines and CDC recommend one time HCV testing for the 1945-1965 birth cohort due to a higher prevalence of HCV in this group (6, 12). Additionally, the AASLD/IDSA and CDC recommend HCV testing for high risk patients including those who have ever required long-term hemodialysis (HD), engaged in injection or intranasal drug use, solid organ transplant recipients prior to July 1992, HIV infected individuals, and persons who were ever incarcerated, among others (6) (Table 1). The recommendation to screen all patients for HCV at the time of initial CKD evaluation incorporates these guideline recommendations, the higher prevalence of HCV among CKD patients, and the more rapid CKD progression seen in HCV-infected CKD patients compared with uninfected patients (13). Future studies should determine the degree of clinical benefit of this strategy of HCV testing in CKD patients. Repeat HCV testing is prudent for patients with ongoing possible exposure to HCV including ongoing drug use, chronic hemodialysis, among others. Decisions about the benefit of HCV screening in CKD patients may be impacted by a recent report describing slower GFR decline following

successful HCV-treatment in patients with eGFR < 60ml/min/1.73 m^2 than the rate of decline preceding treatment (14).

RECOMMENDATIONS RELATED TO HCV TESTING IN END-STAGE KIDNEY DISEASE PATIENTS

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

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

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

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

The prevalence of HCV in the HD population exceeds that of the general population with approximately 10% of patients in recent Dialysis Outcomes and Practice Patterns Study (DOPPS) analyses testing positive by enzyme immunoassay (EIA), also known as anti-HCV or HCV antibody (9, 15). This occurs as a result both of the high prevalence of HCV on initiation of dialysis (9) as well as nosocomial transmission within HD units. HCV testing prior to initiation of in-center HD (including when transitioning from other dialysis modalities) and upon transfer between HD facilities provides the opportunity to identify patients potentially exposed to HCV at the prior facility. Acute HCV infection in HD units is identified through monitoring for increases above baseline for liver biochemical tests, which can suggest acute HCV and prompt testing for HCV viremia several months before EIA testing becomes positive. The recommendation for HCV testing in patients treated with peritoneal dialysis or home HD is based on limited evidence but nevertheless is a prudent approach. HCV testing is recommended in kidney transplant candidates

to determine who is at risk of progressive hepatic disease, who might benefit from an HCV-infected donor kidney and to select the optimal HCV treatment strategies for transplant candidates.

NAT testing confirms active HCV infection (HCV RNA positivity or viremia) but EIA testing, followed by NAT for EIA-positive patients, ideally via reflex testing, is a reasonable approach with adequate sensitivity and specificity in immunocompetent patients. However, NAT is the most appropriate first-line test for immunocompromised kidney transplant recipients and possibly for patients undergoing hemodialysis due to concerns about delayed seroconversion in acute HCV (window period). The prevalence and incidence of HCV in individual HD units informs the choice between EIA or NAT as the risk of false negative EIA tests rises with increasing HCV prevalence (closely associated with incidence) in the dialysis population (1).

CHAPTER 2: RECOMMENDATIONS RELATED TO TREATMENT OF HCV INFECTION IN PATIENTS WITH CKD

Treatment in CKD G1-G5 and G5D

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

- **2.1.1: We recommend an interferon-free regimen (1A).**
- **2.1.2: We recommend that the choice of specific regimen be based on HCV genotype (and subtype), viral load, prior treatment history, drug-drug interactions, glomerular filtration rate (GFR), stage of hepatic fibrosis, kidney and liver transplant candidacy, and comorbidities (*1A*).**

2.2: We recommend that patients with GFR ≥ 30 ml/min/1.73 m^2 (CKD G1-G3b) be treated with any licensed direct-acting antiviral (DAA)-based regimen (*1A*).

2.3: Patients with GFR < 30 ml/min/1.73 m^2 (CKD G4-G5D) should be treated with a ribavirin-free DAA-based regimen.

The development of DAAs has changed the approach to HCV treatment in CKD patients compared with the 2008 Guideline. Interferon treatment is no longer recommended due to high

rates of adverse events with modest sustained virologic response (SVR) rates of 37-41% (16, 17). Moreover, interferon is contraindicated in kidney transplant recipients due to a high risk of acute rejection and allograft loss (18). DAAs achieve SVR rates of 90-100% with few adverse events including in patients with CKD G4-G5, patients with end-stage kidney disease (ESKD), and kidney transplant recipients (19-22). All CKD patients should be evaluated for treatment with the choice of DAA regimen determined by HCV genotype, viral load, prior treatment history, GFR, stage of hepatic fibrosis, kidney and liver transplant candidacy and after considering drug-drug interactions. Figure 1 presents a treatment algorithm based on CKD stage and HCV genotype.

The evidence base regarding DAA treatment in CKD populations is rapidly evolving, requiring professional organizations to update frequently recommendations regarding choice of antiviral regimens. Clinicians should refer to www.HCVguidelines.org, a useful resource that is updated frequently to reflect new evidence (6). Key studies in CKD populations include C-SURFER, a randomized controlled trial (RCT) of immediate versus delayed treatment with a 12 week course of elbasvir/grazoprevir in 224 patients with HCV genotype 1 and CKD G4-G5 (76% ESKD) (22). SVR was 94% in immediately treated patients and 98% in those randomized to deferred treatment (19). No patients discontinued treatment due to of adverse events. Similarly, the pangenotypic regimen of 12 weeks of glecaprevir/pibrentasvir resulted in a 98% SVR rate in 104 patients with CKD G4-G5 (82% ESKD) (21). Four subjects discontinued treatment but three of these achieved SVR. Although studies exist reporting the use of sofosbuvir-based regimens in CKD G4-G5 and ESKD, sofosbuvir is renally excreted and is not FDA-approved for use in patients with GFR < 30 ml/min/1.73 m^2.

Based on extrapolation of data from multiple studies in non-CKD populations (which likely included some patients with CKD G1-G3b) (23, 24), CKD patients with GFR ≥ 30 ml/min/1.73 m^2 can be treated with any licensed DAA regimen. Patients with GFR < 30 ml/min/1.73 m^2 should be treated with the specific regimens outlined above (Table 2).

HCV treatment in kidney transplant recipients

2.4: We recommend that all kidney transplant recipients infected with HCV be evaluated for treatment (*1A*).
- **2.4.1: We recommend treatment with a DAA-based regimen (*1A*).**
- **2.4.2: We recommend that the choice of regimen be based on HCV genotype (and subtype), viral load, prior treatment history, drug-drug interactions, GFR, stage of hepatic fibrosis, liver transplant candidacy, and comorbidities (*1A*).**
- **2.4.3: We recommend avoiding treatment with interferon (*1A*).**
- **2.4.4: We recommend pre-treatment assessment for drug-drug interactions between the DAA-based regimen and other concomitant medications including immunosuppressive drugs in kidney transplant recipients (*1A*).**
  - **2.4.4.1: We recommend that calcineurin inhibitor levels be monitored during and after DAA treatment (*1B*).**

DAA treatment studies in kidney transplant recipients have generally included patients with GFR ≥ 30 ml/min/1.73 m^2 and as a result have included sofosbuvir-based regimens. Treatment with DAAs in kidney transplant recipients have resulted in SVR rates exceeding 95%. Colombo et al. reported an SVR of 100% following treatment with sofosbuvir and ledipasvir in 114 kidney transplant recipients, with only 1% discontinuing treatment due to adverse events (20). A study combining kidney and liver transplant recipients demonstrated an overall SVR of 98% following treatment with glecaprevir and pibrentasvir, with all 20 kidney transplant recipients achieving SVR (25).

For kidney transplant recipients, the selection of DAA regimen should reflect HCV genotype, viral load, prior treatment history, GFR, and stage of hepatic fibrosis, and particularly should consider drug-drug interactions between DAA and other medications, notably calcineurin inhibitors.

Information on drug-drug interactions is available on https://www.hep-druginteractions.org/,which is updated frequently based on new data. Clinicians treating HCV-infected kidney transplant recipients should have heightened awareness for changes in allograft function particularly in those treated with calcineurin inhibitors as increased or decreased plasma levels have been described due to drug-drug interactions with DAA. HCV treatment in kidney transplant recipients should follow the algorithm in Figure 2 and with the specific regimens outlined in Table 2. Although early evidence suggests most DAAs can be used safely in patients on transplant immunosuppressive agents, and most are FDA-approved in patients with GFR > 30 ml/min per 1.73 m2, the clinical experience with DAAs in organ transplant recipients remains relatively small and careful attention to treatment in this population is prudent.

Timing of treatment in kidney transplant candidates

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

As a result of the universally high SVR rates in all CKD populations, decisions about optimal timing of treatment in transplant candidates should include the transplant center (26). HCV-infected kidney transplant candidates willing to accept a kidney from an HCV-infected donor may benefit from a shorter waitlist time if they remain untreated until following transplantation from an HCV-positive donor, a graft that might otherwise be discarded (27). However, kidney transplant candidates with compensated cirrhosis from HCV should be considered for pre-transplant treatment to induce regression of fibrosis post-SVR to allow kidney alone transplantation.

2.5: All treatment candidates should undergo testing for HBV infection prior to therapy (*Not Graded*).

Assessment for unrecognized hepatitis B virus (HBV) infection prior to DAA treatment is recommended because of recent reports of fulminant HBV reactivation during DAA treatment (28). The prevalence of HBV in HD facilities sampled by DOPPS was 3.0% (29), suggesting that the prevalence in CKD patients likely exceeds that of the general population. Testing should include HBsAg, HBsAb, HBcAb and, when required by test results, HBV DNA.

CHAPTER 4: RECOMMENDATIONS RELATED TO THE MANAGEMENT OF HCV-INFECTED PATIENTS BEFORE AND AFTER KIDNEY TRANSPLANTATION

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

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

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

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

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

4.2 Use of kidneys from HCV-infected donors

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

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

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

HCV infection is not a contraindication to kidney transplantation. The mortality rates are significantly lower in HCV-infected kidney transplant recipients than in HCV-infected patients on the transplantation waiting list (30-32). Nevertheless, HCV-infected kidney transplant recipients have had increased mortality (33, 34), allograft loss (35, 36), and post-transplant diabetes (37-39) and glomerulonephritis (40, 41) than non-infected patients, so DAA treatment is critical with individualization of the decision of pre- versus post-transplant treatment to maximize the benefit to each patient (26). Incorporating the judgment of the transplant center and other specialists in these complex decisions is critical. Specific details of evidence-based DAA treatment regimens, timing of treatment, and the importance of monitoring GFR and calcineurin inhibitor levels during and following treatment are discussed earlier (Chapter 2, section 2.4).

HCV-infected kidney donors

Potential deceased donors require HCV testing using both EIA and NAT to determine if viremia is present. HCV-infected deceased donor kidneys should be directed to recipients with positive NAT. Modifying this practice is the development of research protocols describing kidney transplantation from NAT positive donors to HCV negative recipients with immediate DAA treatment, which report 100% SVR rate with good short-term allograft outcomes (42, 43). This practice may become more widespread in the future but for now should be restricted to

investigational settings, although this statement may require revision as new evidence accrues. HCV-infected potential living kidney donors should receive DAA treatment and upon achieving SVR should be re-evaluated to ensure they remain appropriate kidney donors.

CHAPTER 5: RECOMMENDATIONS RELATED TO THE DIAGNOSIS AND MANAGEMENT OF KIDNEY DISEASES ASSOCIATED WITH HCV INFECTION

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

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

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

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

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

The role of DAAs in the management of HCV-associated glomerulonephritis (GN) including HCV-associated mixed cryoglobulinemia and membranoproliferative GN has become clearer in recent years. SVR rates have ranged from 74-83% in studies of DAAs for HCV-associated GN with low rates of adverse events (44-46). Importantly, DAA treatment leads to diminished proteinuria, increased GFR, and quality of life but studies have been limited to patients with stable GFR and without rapidly progressive glomerulonephritis, cryoglobulinemic vasculitis or nephrotic range proteinuria. In these more urgent scenarios, immunosuppressive therapy should be administered concomitantly with DAA and plasma exchange should be considered. Among immunosuppressive agents, rituximab is the best-studied agent for HCV-related GN (47, 48). Prior

to the initiation of rituximab, patients should be assessed for HBV infection to avoid fulminant hepatitis resulting from HBV reactivation.

DISCUSSION

The 2018 KDIGO Clinical Practice Guideline on HCV in CKD represents a major update to the original 2008 Guideline. Because of the efficacy of DAAs in CKD populations including CKD G4, G5 and G5D as well as in kidney transplant recipients, the approach to HCV management has evolved dramatically in the past 10 years. The ability to eradicate HCV with DAA treatment has influenced all chapters of the 2018 update. Moderately-sized prospective cohort studies and RCT in CKD G4, G5 as well as in HD patients and kidney transplant recipients have consistently revealed SVR rates of 90-100%. The results add to the evidence base supporting efficacy of DAA treatment in non-CKD patients and directly translate to the recommendation to evaluate treatment candidacy in all HCV-infected CKD patients. DAA-based treatment of HCV-associated glomerular disease is another area of rapid change with a shift in the focus from immunosuppression to HCV eradication as the first line management approach for most patients.

The potential to cure HCV also impacts the recommendations on testing for HCV. The CDC and AASLD/IDSA already recommend one-time HCV testing in the 1945-1965 birth cohort and in patients at high risk of acquiring HCV, which includes numerous risk factors common to CKD patients. Nephrologists generally recommend HCV testing in patients under evaluation for glomerular disease and additionally the yield of HCV testing in CKD patients is higher because of the increased prevalence of HCV in the CKD patient population. The growing evidence base supporting an association between HCV infection and faster CKD progression to ESKD also

supports the recommendation to test all patients at initial CKD evaluation. If future investigation replicates the early finding that DAA treatment may slow CKD progression (49), the imperative for HCV testing of all CKD patients would gain strength, as it would offer a novel avenue to slow CKD progression (50).

Finally, the efficacy of DAA in patients with advanced kidney disease including dialysis patients as well as among kidney transplant recipients has greatly affected the approach to HCV in kidney transplant candidates. Careful attention to strategies about timing of HCV treatment that maximize benefit to individual patients as well as those that improve the utilization of HCV-infected deceased donor kidneys are becoming increasingly important (27). The new development of transplantation of HCV-infected organs to HCV-uninfected individuals with immediate post-transplant DAA treatment may represent a major advance (42, 43, 51) but is a new field that warrants further investigation. Clinicians treating HCV-infected kidney transplant recipients should have heightened awareness for changes in allograft function particularly in those treated with calcineurin inhibitors. Until more extensive experience is available for reassurance of safety of DAAs with the transplanted kidney functioning in the common GFR range of 30-60 ml/min per 1.73 m2, close monitoring of the kidney allograft function should be employed while these patients are undergoing DAA therapy.

Future research in HCV and CKD will likely shift to implementation science, as well as cost effectiveness and decision analysis. What are the best approaches to identify HCV infected CKD patients? How do we ensure equitable access to DAA treatment? Does HCV treatment actually slow CKD progression? What is the optimal timing of HCV treatment in patients who may progress to ESKD? What are the cost implications of strategies designed to test all CKD patients

and to treat all HCV-infected individuals? The answers to these and other questions will likely guide the future of HCV management in CKD patients.

We are optimistic that the current KDIGO Guideline will increase the attention on the intersection between HCV and CKD as well as spur future investigation into new directions to improve the care of this patient population.

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Figure 1: Treatment scheme for chronic kidney disease (CKD) G1 to G5D

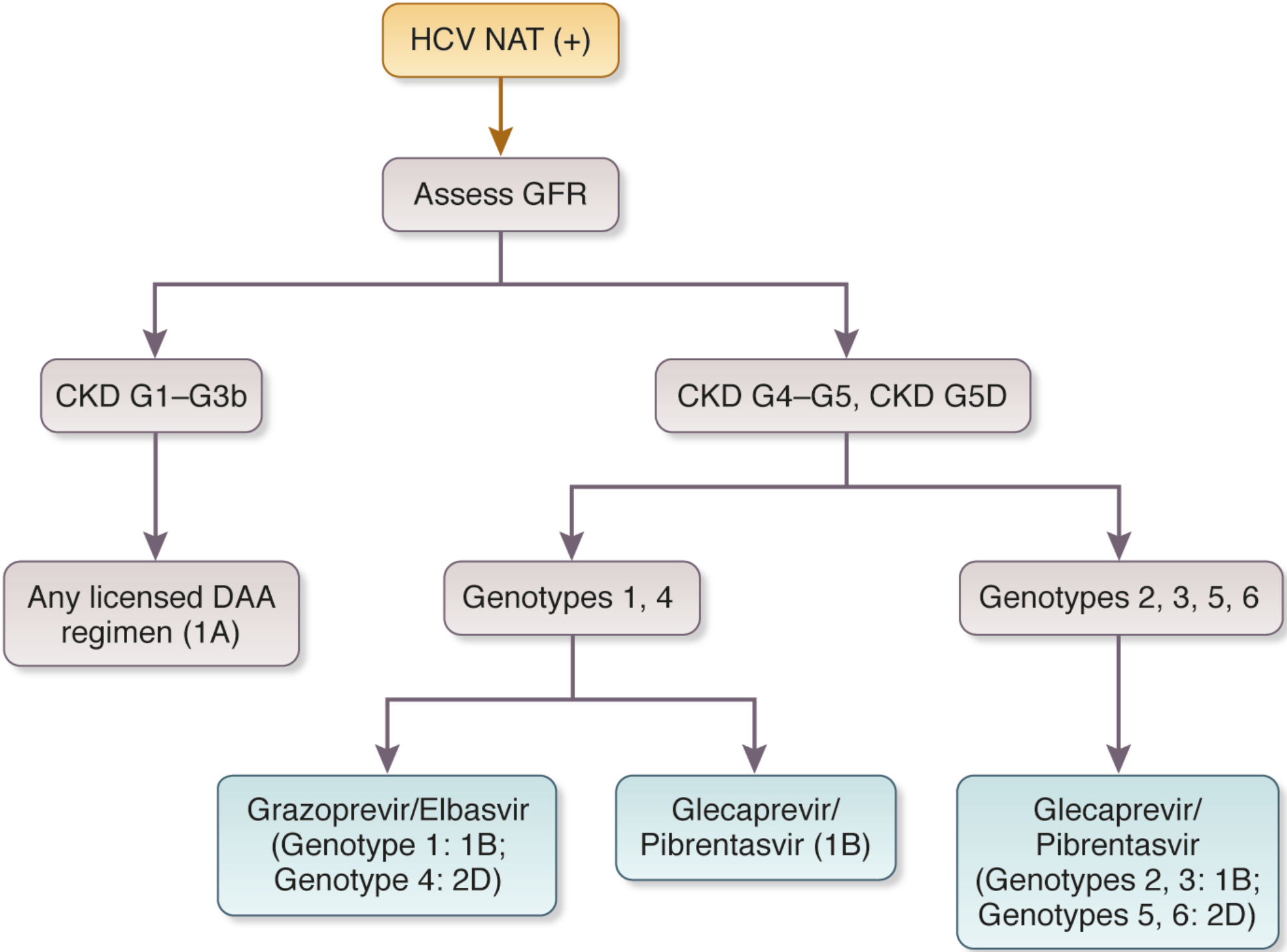
Caption: Recommendation grades (1-2) and strength of evidence (A-D) are provided for each recommended treatment regimen and hepatitis C virus (HCV) genotype. Sofosbuvir/velpatasvir-based regimens were not listed above since they were not formally reviewed by the Evidence Review Team at the time of guideline publication. However these regimens can be considered in patients with CKD G1-G3b given their availability in certain jurisdictions.
CKD G = chronic kidney disease, GFR category; DAA = direct-acting antiviral; GFR = glomerular filtration rate; NAT = nucleic acid testing.

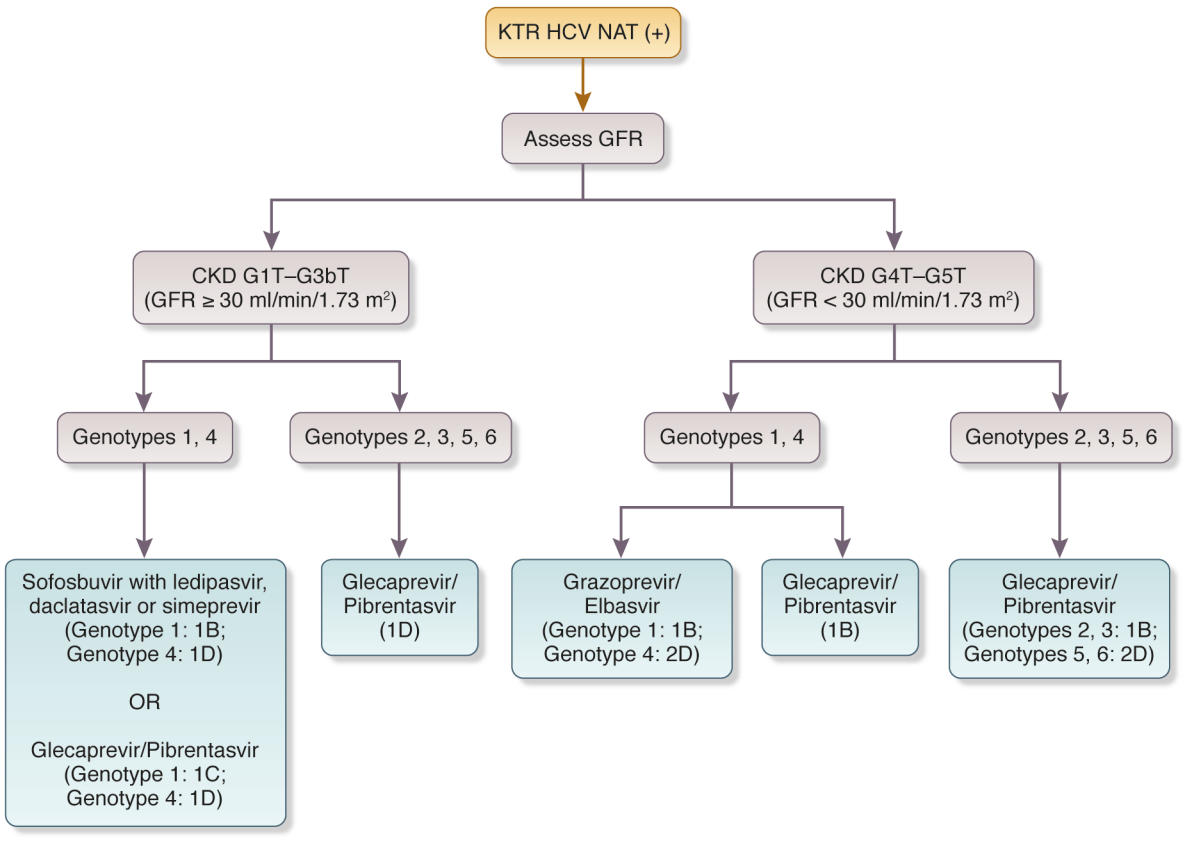
Figure 2: Treatment scheme for kidney transplant recipients (KTRs).

Caption: Recommendation grade (1-2) and strength of evidence (A-D) are provided for each recommended treatment regimen and hepatitis C virus (HCV) genotype. Sofosbuvir/velpatasvir-based regimens were not listed above since they were not formally reviewed by the Evidence Review Team at the time of guideline publication. However these regimens can be considered in KTRs with GFR $\geq$ 30 ml/min/1.73 m^2 given their availability in certain jurisdictions.
CKD G = chronic kidney disease, GFR category; (suffix T denotes transplant recipient); NAT = nucleic acid testing. ‡Based on Reau *et al. (25).*

Appendix Figure 1: Prognosis of CKD, by categories of GFR and albuminuria.

CKD is defined as abnormalities of kidney structure or function that are present for >3 mo and have health implications. CKD is classified on the basis of cause, GFR category (G1 to G5), and albuminuria category (A1 to A3). Green means low risk (no CKD if no other markers of kidney disease), yellow means moderately increased risk, orange means high risk, and red means very high risk. The suffix “D” denotes dialysis (e.g., CKD G5D refers to a patient with CKD stage G5 who is receiving dialysis). (Reproduced with permission of Kidney Disease: Improving Global Outcomes) CKD = chronic kidney disease; GFR = glomerular filtration rate.


HCV NAT (+)
Assess GFR
CKD G1–G3b
CKD G4–G5, CKD G5D
Any licensed DAA regimen (1A)
Genotypes 1, 4
Genotypes 2, 3, 5, 6
Grazoprevir/Elbasvir (Genotype 1: 1B; Genotype 4: 2D)
Glecaprevir/ Pibrentasvir (1B)
Glecaprevir/ Pibrentasvir (Genotypes 2, 3: 1B; Genotypes 5, 6: 2D)


KTR HCV NAT (+)
Assess GFR
CKD G1T–G3bT
(GFR ≥ 30 ml/min/1.73 m²)
CKD G4T–G5T
(GFR < 30 ml/min/1.73 m²)
Genotypes 1, 4
Genotypes 2, 3, 5, 6
Genotypes 1, 4
Genotypes 2, 3, 5, 6
Sofosbuvir with ledipasvir, daclatasvir or simeprevir
(Genotype 1: 1B;
Genotype 4: 1D)
OR
Glecaprevir/Pibrentasvir
(Genotype 1: 1C;
Genotype 4: 1D)
Glecaprevir/
Pibrentasvir
(1D)
Grazoprevir/
Elbasvir
(Genotype 1: 1B;
Genotype 4: 2D)
Glecaprevir/
Pibrentasvir
(1B)
Glecaprevir/
Pibrentasvir
(Genotypes 2, 3: 1B;
Genotypes 5, 6: 2D)

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

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

TABLES

Table 1: AASLD/IDSA guidelines for one-time HCV testing with focus on recommendations relevant to CKD populations*

• Patients born between 1945-1965 without regard to other risk factors
• Patients who have ever required long-term hemodialysis treatment
• Patients who received solid organ transplantation, particularly if prior to July 1992 or if patient informed that donor HCV positive
• Patients who have ever engaged in injection drug use
• Patients who have ever engaged in intranasal drug use
• Patients who have ever been incarcerated
• Patients with HIV infection
• Patients previously exposed to percutaneous/parenteral exposure including needle stick, sharp or mucosal exposure (health care providers)

*For complete listing, see: HCVguidelines.org.

Table 2: HCV treatment regimens in patients with CKD and kidney transplant recipients*

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

Caption: Duration of therapy for all above regimens is usually 12 weeks but readers should consult Association for the Study of Liver Diseases (AASLD) or European Association for the Study of the Liver guidelines for latest guidance. *We recommend that CKD patients with glomerular filtration rates (GFRs) ≥ 30 ml/min per 1.73 m^2 (CKD G1–G3b) be treated with any licensed DAA regimen. Sofosbuvir/velpatasvir-based regimens were not listed above since they were not formally reviewed by the Evidence Review Team at the time of guideline publication. However these regimens can be considered in patients with GFR ≥ 30 ml/min/1.73 m^2 given their availability in certain jurisdictions. †There is little

published evidence to guide treatment regimens in KTRs with GFR < 30 ml/min per 1.73 m^2 (CKD G4T–G5T). Regimens in KTRs should be selected to avoid drug–drug interactions, particularly with calcineurin inhibitors. ‡Based on Reau *et al. (25)*. §As suggested in AASLD guidelines (https://www.hcvguidelines.org/).
CKD G = chronic kidney disease (GFR category); HD = hemodialysis; n/a = no data or evidence available; PD = peritoneal dialysis.

Appendix Table 1: GRADE Criteria Used for Grading the Strength of a Recommendation*

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

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

Appendix Table 2: GRADE Criteria Used for Grading the Overall Quality of Evidence

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

Appendix Table 3. Research Questions Addressing the Systematic Update of Selected Recommendations

Predictor analyses (Chapter 1: Recommendations related to the detection and evaluation of HCV in CKD)	
Population	Predictors of CKD progression: any (including general population) *except* CKD G5D (dialysis); HCV as predictor: kidney transplant recipients
Predictor	HCV-infection (untreated), other predictors of CKD progression (if HCV-infected)
Outcome	CKD progression (change in GFR, SCr doubling, ESKD), proteinuria, patient mortality, graft loss, delayed graft function, kidney pathology (HCV-associated GN)
Design	Longitudinal, multivariable analyses; HCV-associated GN: any (except autopsy studies)
Minimum duration of follow-up	Any
Minimum *N* of subjects	≥ 100
Publication dates	Predictors of CKD progression: any; HCV as predictor: ≥ 2008 (plus studies in 2008 KDIGO CPG)
Hepatitis C treatment (Chapter 2: Recommendations related to treatment of HCV infection in patients with CKD and Chapter 5: Recommendations related to the diagnosis and management of kidney diseases associated with HCV infection)	
Population	CKD G3a–5 (including dialysis and transplant) or equivalent; HCV infection
Intervention	DAA (except 1st generation: telaprevir, boceprevir), pegylated interferon ± ribavirin, immunosuppression including induction (in combination with DAA or as treatment of HCV-associated GN)
Comparator	Active or control or none (single-arm studies)
Outcome	Categorical: all-cause mortality, SVR (preferably 24-wk), hepatocellular carcinoma, graft loss, NODAT, QoL, adverse events (including treatment discontinuation), pharmacokinetics/dynamics Continuous (HCV-associated GN only): kidney function, proteinuria
Study design	RCT, nonrandomized comparative studies, single-group studies; prospective (all topics) or retrospective (immunosuppression or GN topics only). Interferon in dialysis: RCT only.
Minimum duration of follow-up	HCV treatment studies: 12 weeks post-treatment; Other topics: no minimum
Minimum *N* of subjects	≥ 10; Immunosuppression topic: any, including case reports
Publication dates	All: ≥ 2008 (plus studies in 2008 KDIGO CPG); interferon and dialysis topic: Cochrane review[350] and ≥ 2012

Liver testing (Chapter 4: Recommendations related to the management of HCV-infected patients before and after kidney transplantation)	
Population	Tests for cirrhosis: CKD (all stages); pre-transplant biopsy: CKD G4–G5 pre-transplantation (or equivalent)
Intervention/comparator	Noninvasive liver testing, including upper endoscopy (for varices), liver biopsy
Outcome	Noninvasive test performance characteristics, change in management strategy, patient mortality, graft loss
Design	Any
Minimum *N* of subjects	Noninvasive testing: *N* ≥ 10, pre-transplant biopsy: *N* ≥ 5
Publication dates	Any
~~**Dialysis isolation**~~	
~~Population~~	~~Hemodialysis (patients or units)~~
~~Intervention~~	~~Isolation, quarantine, etc.~~
~~Comparator~~	~~No isolation, less stringent standard~~
~~Outcome~~	~~HCV transmission~~
~~Design~~	~~Any~~
~~Minimum duration of follow-up~~	~~None~~
~~Minimum *N* of subjects~~	~~*N* ≥ 30 patients~~
~~Publication dates~~	~~≥ 2008 (plus studies in 2008 KDIGO CPG)~~
Early versus late transplantation (Chapter 4: Recommendations related to the management of HCV-infected patients before and after kidney transplantation)	
Population	HCV-infected transplantation candidates
Intervention	Transplantation (“now”)
Comparator	Remaining on wait-list or awaiting HCV-negative status
Outcome	Patient mortality, graft loss
Design	Any, multivariable analysis
Minimum duration of follow-up	None

Commented [MC1]: The text for this section has since been deleted as per reviewer’s suggestion

Minimum *N* of subjects	*N* ≥ 100
Publication dates	≥ 2008 (plus studies in 2008 KDIGO CPG)

TABLES

Table 1: AASLD/IDSA guidelines for one-time HCV testing with focus on recommendations relevant to CKD populations*

• Patients born between 1945-1965 without regard to other risk factors • Patients who have ever required long-term hemodialysis treatment • Patients who received solid organ transplantation, particularly if prior to July 1992 or if patient informed that donor HCV positive • Patients who have ever engaged in injection drug use • Patients who have ever engaged in intranasal drug use • Patients who have ever been incarcerated • Patients with HIV infection • Patients previously exposed to percutaneous/parenteral exposure including needle stick, sharp or mucosal exposure (health care providers)

*For complete listing, see: HCVguidelines.org.

Table 2: HCV treatment regimens in patients with CKD and kidney transplant recipients*

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

Caption: Duration of therapy for all above regimens is usually 12 weeks but readers should consult Association for the Study of Liver Diseases (AASLD) or European Association for the Study of the Liver guidelines for latest guidance. *We recommend that CKD patients with glomerular filtration rates (GFRs) ≥ 30 ml/min per 1.73 m^2 (CKD G1–G3b) be treated with any licensed DAA regimen. Sofosbuvir/velpatasvir-based regimens were not listed above since they were not formally reviewed by the Evidence Review Team at the time of guideline publication. However these regimens can be considered in patients with GFR ≥ 30 ml/min/1.73 m^2 given their availability in certain jurisdictions. †There is little

published evidence to guide treatment regimens in KTRs with GFR < 30 ml/min per 1.73 m^2 (CKD G4T–G5T). Regimens in KTRs should be selected to avoid drug–drug interactions, particularly with calcineurin inhibitors. [‡]Based on Reau *et al. (25)*. [§]As suggested in AASLD guidelines (https://www.hcvguidelines.org/).
CKD G = chronic kidney disease (GFR category); HD = hemodialysis; n/a = no data or evidence available; PD = peritoneal dialysis.

Appendix Table 1: GRADE Criteria Used for Grading the Strength of a Recommendation*

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

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

Appendix Table 2: GRADE Criteria Used for Grading the Overall Quality of Evidence

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

Appendix Table 3. Research Questions Addressing the Systematic Update of Selected Recommendations

Predictor analyses (Chapter 1: Recommendations related to the detection and evaluation of HCV in CKD)	
Population	Predictors of CKD progression: any (including general population) *except* CKD G5D (dialysis); HCV as predictor: kidney transplant recipients
Predictor	HCV-infection (untreated), other predictors of CKD progression (if HCV-infected)
Outcome	CKD progression (change in GFR, SCr doubling, ESKD), proteinuria, patient mortality, graft loss, delayed graft function, kidney pathology (HCV-associated GN)
Design	Longitudinal, multivariable analyses; HCV-associated GN: any (except autopsy studies)
Minimum duration of follow-up	Any
Minimum *N* of subjects	≥ 100
Publication dates	Predictors of CKD progression: any; HCV as predictor: ≥ 2008 (plus studies in 2008 KDIGO CPG)
Hepatitis C treatment (Chapter 2: Recommendations related to treatment of HCV infection in patients with CKD and Chapter 5: Recommendations related to the diagnosis and management of kidney diseases associated with HCV infection)	
Population	CKD G3a–5 (including dialysis and transplant) or equivalent; HCV infection
Intervention	DAA (except 1st generation: telaprevir, boceprevir), pegylated interferon ± ribavirin, immunosuppression including induction (in combination with DAA or as treatment of HCV-associated GN)
Comparator	Active or control or none (single-arm studies)
Outcome	Categorical: all-cause mortality, SVR (preferably 24-wk), hepatocellular carcinoma, graft loss, NODAT, QoL, adverse events (including treatment discontinuation), pharmacokinetics/dynamics Continuous (HCV-associated GN only): kidney function, proteinuria
Study design	RCT, nonrandomized comparative studies, single-group studies; prospective (all topics) or retrospective (immunosuppression or GN topics only). Interferon in dialysis: RCT only.
Minimum duration of follow-up	HCV treatment studies: 12 weeks post-treatment; Other topics: no minimum
Minimum *N* of subjects	≥ 10; Immunosuppression topic: any, including case reports
Publication dates	All: ≥ 2008 (plus studies in 2008 KDIGO CPG); interferon and dialysis topic: Cochrane review[350] and ≥ 2012

Liver testing (Chapter 4: Recommendations related to the management of HCV-infected patients before and after kidney transplantation)	
Population	Tests for cirrhosis: CKD (all stages); pre-transplant biopsy: CKD G4–G5 pre-transplantation (or equivalent)
Intervention/comparator	Noninvasive liver testing, including upper endoscopy (for varices), liver biopsy
Outcome	Noninvasive test performance characteristics, change in management strategy, patient mortality, graft loss
Design	Any
Minimum *N* of subjects	Noninvasive testing: $N \geq 10$, pre-transplant biopsy: $N \geq 5$
Publication dates	Any
Early versus late transplantation (Chapter 4: Recommendations related to the management of HCV-infected patients before and after kidney transplantation)	
Population	HCV-infected transplantation candidates
Intervention	Transplantation (“now”)
Comparator	Remaining on wait-list or awaiting HCV-negative status
Outcome	Patient mortality, graft loss
Design	Any, multivariable analysis
Minimum duration of follow-up	None
Minimum *N* of subjects	$N \geq 100$
Publication dates	≥ 2008 (plus studies in 2008 KDIGO CPG)

HCV-infected donors (Chapter 4: Recommendations related to the management of HCV-infected patients before and after kidney transplantation)	
Population	HCV-infected kidney transplant recipients
Intervention	HCV-infected donors
Comparator	HCV-negative donors
Outcome	Patient mortality, graft loss
Design	Longitudinal comparative, multivariable analysis
Minimum duration of follow-up	None
Minimum *N* of subjects	*N* ≥ 100
Publication dates	Any

CKD = chronic kidney disease; DAA = direct-acting antiviral; ESKD = end-stage kidney disease; GFR = glomerular filtration rate; GN = glomerulonephritis; HCV = hepatitis C virus; NODAT = new-onset diabetes after transplantation; QoL = quality of life; RCT = randomized controlled trial; SCr = serum creatinine; SVR = sustained virologic response.