Proposed Scope of Work for the Update to KDIGO Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease

Introduction

Kidney Disease: Improving Global Outcomes (KDIGO) is a not-for-profit organization established to develop and implement global clinical practice guidelines for patients with kidney disease. Since its inception in 2003, KDIGO has published nine guidelines, beginning with the KDIGO Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C (HCV) in Chronic Kidney Disease (CKD). This proposal is designed to briefly describe the rationale for updating this guideline, the scope or topics that the guideline intends to cover, and areas where systematic searches of the medical literature will yield pertinent evidence. We are now seeking comments concerning the proposed Scope of Work presented here and our intent is to ensure that feedback from potential stakeholders of this global guideline is duly considered before a formal systematic review of the literature is undertaken.

KDIGO HCV Guideline 2008

The KDIGO HCV guideline published in April 2008 was based on a literature search which included original articles and systematic reviews through January 2007. Additional articles were also identified by the Work Group (WG) through May 2007. The evidence review and data tables were compiled by the Evidence Review Team at Tufts Medical Center, Boston, Massachusetts, USA. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used for rating guideline recommendations though the nomenclature employed at the time was based on a 3-tier structure (i.e., strong, moderate, and weak). We expect this update will now utilize the current nomenclature adopted by KDIGO to denote the strength of the recommendation and the quality of the supporting evidence. Where applicable, ungraded statements will be issued for guidance based on common sense or where topics do not lend themselves to clinical trials or systematic review.
Background

Hepatitis C (HCV) infection remains a serious worldwide public health problem. Some 170–200 million individuals are chronically infected with HCV. These figures may very well underestimate the actual prevalence of HCV, which is implicated in 350,000–400,000 deaths every year.

HCV infection is both a cause and a complication of chronic kidney disease (CKD). As a cause of kidney disease, its most common presentation is immune-complex glomerular deposition resulting in membranoproliferative glomerulonephritis, although other forms of glomerular injury have been recognized.4

After the availability of diagnostic testing for HCV, it soon became apparent that patients with CKD requiring renal replacement therapy (RRT) had an extremely high prevalence of HCV, mostly as a result of contaminated blood transfusions and nosocomial transmission of HCV within dialysis units. Although improved screening of blood donors, widespread use of erythropoiesis-stimulating agents and measures to prevent nosocomial transmission have contributed to a decrease in the prevalence of HCV infection in hemodialysis (HD) patients over the last two decades, HCV infection remains a challenge in this population. Furthermore, nosocomial HCV transmission still occurs in HD units, albeit relatively infrequently in the Western world, but much more frequently in low-resource settings. Several studies have in addition reported that patients with kidney failure have a two- to four-fold likelihood of HCV seropositivity at the time of initiation of dialysis, compared to the general population. This problem is of considerable importance when one considers that there are currently over one million patients with end-stage renal disease (ESRD) globally. Apart from its contribution to the morbidity and mortality of CKD patients, HCV has also been implicated in CKD onset and accelerated progression of CKD to ESRD.5-7

The reported prevalence of pre-transplantation anti-HCV seropositivity among transplant recipients varies from 1 to 50%, reflecting local epidemiology. Pre-transplantation seropositivity is associated with an increased prevalence of post-transplantation morbidity and mortality due to progressive liver disease, de novo glomerular disease of the allograft, and post-transplantation diabetes mellitus. Another concern is the risk of HCV transmission by the transplanted organ, although this currently occurs much less frequently than in the past.

The 2008 KDIGO HCV in CKD Guideline undoubtedly contributed to an enhanced understanding and management of HCV by nephrologists and hepatologists regarding how best to screen for HCV depending on the setting, how to enforce prevention of HCV transmission in HD, and how best to manage HCV before and after kidney transplantation.

Over the last 6 years, major progress has been made in several key areas of HCV management and a full revision of the 2008 KDIGO Guideline is indicated, as outlined below for each section of the Guideline. In addition, the 2008 KDIGO Guideline did not employ the current KDIGO grading and nomenclature for rating its recommendations. Thus, a full revision is required not only in terms of content but to also adopt methods consistent with current KDIGO guidelines.
**Guideline 1: Detection and Evaluation of HCV in CKD**

Since 2008, several large cohort studies\(^6\) and meta-analyses\(^13,14\) have strengthened the suspected association between CKD and HCV infection. The merits of some newer tests (such as the HCV antigen and HCV core-specific antibodies) need to be reviewed.

**Guideline 2: Treatment of HCV Infection in CKD**

Over the last 6 years, dozens of large randomized controlled trials (RCTs) have been published with impressive improvement in sustained virologic response (SVR) rates possible with oral direct-acting antivirals (DAAs).\(^15-23\) These results may well be used in managing patients with CKD GFR categories 1, 2, and perhaps, 3a who were not excluded from most trials. The applicability of the registration RCT results to people with advanced stages of CKD (i.e., GFR categories 3b, 4, 5, dialysis) and kidney transplant recipients awaits confirmation. Findings from ongoing HCV RCTs\(^24-26\) in CKD or transplant populations will be monitored and appraised as relevant data become available.

In addition some DAAs undergo renal elimination raising concern about their safety and tolerability. In addition patients with advanced chronic kidney typically have additional comorbidities requiring multiple medications with potential for drug-drug interactions. This is also a challenge in renal transplant recipients who are maintenance medications such as calcineurin inhibitors.\(^27-34\)

The advances in treating HCV infection in the general population (i.e., higher SVR rates—close to 100%—and shorter regimens) will expand the spectrum of patients with HCV for whom treatment would or should be offered. Previous interferon-based regimens were contraindicated after kidney transplantation due to concerns about precipitating graft dysfunction and are poorly tolerated in dialysis patients, which likely account partly for the very low treatment rates of HCV in dialysis patients over the last decade.\(^35\)

The optimal follow-up of patients for HCV-related complications (including cirrhosis, hepatocellular carcinoma) has recently also been debated,\(^36-39\) and this topic should be revisited in the context of CKD management.

**Guideline 3: Preventing HCV Transmission in HD Units**

There have been some RCTs of interventions to further reduce nosocomial infection rates in intensive care units and other settings by improving hand hygiene, a key prevention of HCV transmission during HD.\(^40\) However, observational studies have recently highlighted that hand hygiene and related practices are at best suboptimal, even in some Western HD units.\(^41-44\) In the United States, the prevalence of HCV infection among patients in HD centers was about five times higher than the general population and of the 13 HCV outbreaks reported in 2008-2011, five occurred in outpatient dialysis clinics.\(^45\) Thus, the incidence and prevalence rate of HCV infection in the HD population remains high, probably even more so in developing countries.\(^46,47\) Nevertheless we believe that our strong recommendations mandating adoption of robust
infection-control procedures will remain pertinent and as such we anticipate the main guideline statements in this section likely will not undergo major changes.

Guideline 4: Management of HCV-Infected Patients before and after Kidney Transplantation
Until recently a liver biopsy was considered mandatory prior to HCV treatment, especially in patients with CKD given the toxicity of interferon and ribavirin-based therapy. In recent years, non-invasive algorithms such as AST to platelet ratio index (APRI), FibroTest, and imaging techniques such as vibration-controlled transient elastography with FibroScan have been used with increasing confidence to assess disease severity and to facilitate treatment decisions and follow-up in the general population with HCV. Such tools have also been used in some series of patients with late-stage CKD, those on dialysis, and potential candidates for kidney transplantation. Considerations detailed under the section about Guideline 2 about the use of new treatment regimens for pre- and post-kidney transplantation patients are also particularly relevant here.

The improvement of anti-HCV regimens may also lessen the need for combined liver-kidney transplantation. An emerging issue is whether treatment of HCV infection is wise in all renal transplant candidates as cure of infection removes the option of receiving a renal graft from an HCV infected donor. Furthermore the conventional wisdom has been that combined liver/kidney transplant is indicated in a renal transplant candidate with cirrhosis. However more recent experience suggests that cirrhotic patients with portal pressures < 10 mmHg may be acceptable candidates for isolated renal transplant. This will become increasingly feasible as SVR becomes commonplace in HCV treated renal transplant candidates.

Until relatively recently, kidney transplantation was not even considered in patients infected by human immunodeficiency virus (HIV), but with the availability of highly active anti-retroviral therapy, kidney transplantation is now feasible for these patients. However, new questions have emerged regarding the management of the patients with HIV-HCV co-infection. Recent studies have shown that HCV infection is associated with worse outcomes in kidney transplant recipients with and without HIV infection; thus, the role of DAA treatments in these patient populations merits a closer review.

Guideline 5: Diagnosis and Management of Kidney Diseases Associated with HCV Infection
The anticipated changes in this area relate to the impact of the newer HCV treatment regimens on HCV-related kidney disease. These include a multitude of antiviral drugs and monoclonal antibodies targeting various lymphocyte subpopulations (e.g., rituximab) and more recent agents with substantial efficacy against the HCV-related cryoglobulinemia manifestations.
The systematic review topics and eligibility criteria for the 2008 KDIGO Guideline are summarized in Table 30 of Guideline Appendix 2: Methods for Guideline Development (http://www.nature.com/ki/journal/v73/n109s/fig_tab/ki2008121t1.html#figure-title). As discussed above, some topic sections will require simple literature updating while others may necessitate revisions in the literature screening criteria (e.g., new populations of interest such as individuals with HCV-HIV co-infections; new diagnostic tests of interest such as core antigen assays, biomarkers such as APRI, FibroTest, FibroScan; new interventional agents of interest (see Table 1); new/modified outcome measures (e.g., from SVR 24 weeks to SVR 12 or shorter).
### Table 1: Potential Intervventional Agents of Interest

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<th>Direct-acting agents</th>
<th>Host-targeting agents (host target)</th>
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<tr>
<td>NS3/NS4A inhibitors</td>
<td>Telaprevir*</td>
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<td>Interferons (alpha 2a, 2b, peginterferon alpha 2a, 2b, IFNλ)</td>
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<td>Daclatasvir (BMS-790052)</td>
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<td>Boceprevir*</td>
<td>Ombitasvir (ABT-267)</td>
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<td>NS5A inhibitors</td>
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<td>NS5B inhibitors (nucleoside)</td>
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*Utilized with pegylated interferon and ribavirin for genotype 1

This is a preliminary list to assist the Evidence Review Team in defining the potential interventional agents of interest and is not meant to be exhaustive; further refinement will take place with input from the Work Group.

Modified from Fabrizi F et al.57
Potential New Key Clinical Questions

1. Management of the HCV-positive live donor: Can a subject with SVR after receiving anti-HCV treatment be a kidney donor for an HCV-negative recipient?58, 59
2. Can a cirrhotic patient who has been successfully treated for HCV undergo an isolated kidney transplant?
3. What is the role of transjugular liver biopsy in assessing liver disease in HCV patients with CKD (including dialysis patients and transplant recipients)?
4. Can recommendations be made regarding vaccinations in addition to HBV (e.g., hepatitis A virus)?60 Vaccination is indeed mandated for any patient with chronic HCV without CKD.
5. How do biochemical indices, such as APRI or ALT/platelet ratio, perform in the detection of significant fibrosis or cirrhosis compared to the gold standard, liver biopsy, for various CKD populations?
6. How reliable is transient elastography compared to the gold standard, liver biopsy, in the detection of significant fibrosis or cirrhosis for various CKD populations?
7. Does “occult HCV infection” (i.e., repeatedly no HCV RNA detected in serum but HCV still detected in peripheral blood mononuclear cells or hepatocytes) have implications in terms of management or prognosis for the CKD population?61
8. The 2008 KDIGO Guidelines defined SVR as a negative nucleic acid test (NAT) 6 months after treatment withdrawal. Should/could this interval be shortened with (some of) the new anti-HCV regimens?62-65
9. Pegylated interferon monotherapy in HCV dialysis patients has proved to be unsatisfactory in terms of efficacy and safety.66, 67 As such could low-dose ribavirin be given in conjunction with pegylated interferon for dialysis patients as some reports have reported higher SVR rates than achieved with IFN monotherapy?68-71
10. Which CKD patients with HCV should or should not be treated?
11. What is the impact of kidney function and RRT modality on the optimal dosing of drugs listed in Table 1?
12. What is the impact, if any, of the therapeutic agents listed in Table 1 on the pharmacodynamics and pharmacokinetics of drugs commonly used in various CKD populations (i.e., predialysis, dialysis, kidney transplant recipients) such as immunosuppressants, warfarin, antihypertensives, antidiabetic drugs, etc.?
13. Can an optimal decision strategy be delineated between pursuing for a HCV+ kidney donor, whose waiting time is typically substantially shorter, versus seeking for an HCV-donor after attaining SVR following anti-HCV treatment?
References


27. Consider drug pharmacokinetics when selecting the most suitable treatments for hepatitis C infection. Drugs Ther Perspect 2014; 30: 427-431.


