Pretransplant Screening and Management of HCV Infection

MAJOR LONG-TERM COMPLICATIONS OF CHRONIC HCV INFECTION

- Liver fibrosis
- Cirrhosis
- Portal hypertension
- Hepatocellular carcinoma
- Liver failure

RECOMMENDATIONS (SEE ALGORITHM 1)

All kidney transplant candidates should be evaluated for HCV infection (strong evidence* G.4.1.1).

- In low-prevalence settings, initial testing with EIA and follow-up of positive EIA with NAT should be considered (moderate evidence G.4.1.1).
- In high-prevalence settings, initial testing with NAT should be considered (moderate evidence G.4.1.1).

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

- Pretransplant liver biopsy for HCV-infected candidates can help determine the severity of hepatic injury, along with prognosis and management.
- A decision for biopsy should be based on a positive NAT, due to the poor sensitivity of HCV antibody testing in patients with kidney failure.

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

HCV-infected candidates without diabetes should have an oral glucose tolerance test during evaluation.

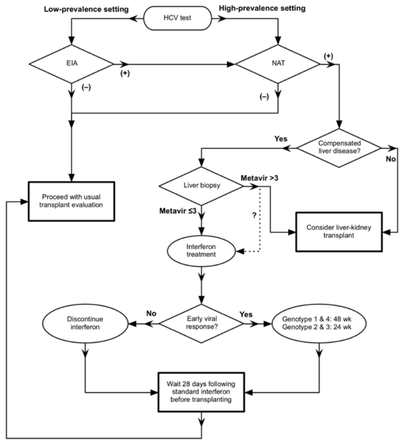
It is suggested that HCV-infected kidney transplant candidates be considered for treatment with standard IFN before transplantation (weak evidence G.4.1.5).

- Achieving SVR before transplantation reduces the risk of hepatic and extra-hepatic complications of viremia after transplantation (e.g. NODAT, GN).
  - SVR is defined as RNA clearance 6 months after completion of antiviral treatment.
- IFN can be discontinued if an early virologic response is not obtained within 12 weeks of initiating treatment.
  - Patients should not receive a kidney transplant while receiving IFN; therefore avoid exposure of the allograft to IFN by waiting at least 28 days after terminating or completing IFN therapy before proceeding with transplantation.
- As it will not be known whether the patient has received SVR until 6 months after completion of therapy, it is recommended that these patients only receive a kidney from an HCV negative donor during this period of time.

Absence of IFN therapy before transplantation has been associated with increased risk for CAN.

*See table: Levels of Strength of Recommendations.

Algorithm 1: Pretransplant Screening and Management of HCV Infection



Early viral response patients have a >2 log decrease in viral titer.

ABBREVIATIONS: *EIA, enzyme immunoassay; HCV, hepatitis C virus; IFN, interferon; NAT, nucleic acid test.*

Management of Wait-listed Transplant Candidates

It is suggested that patients on a kidney transplant waiting list be evaluated for HCV infection (see algorithm 2) (weak evidence G.4.1.6).

RECOMMENDATIONS

Place HCV-infected patients not previously known to be viremic on hold status, pending full evaluation of the severity of their liver disease.

At least annually, use NAT to confirm durability of the SVR in patients who received antiviral treatment prior to waitlisting and obtaining SVR.

- If NAT becomes positive, put the patient on hold status and fully evaluate their liver disease.

For HCV-infected patients who had prior evaluation with liver biopsy, but either failed or refused antiviral treatment, repeat liver biopsy:

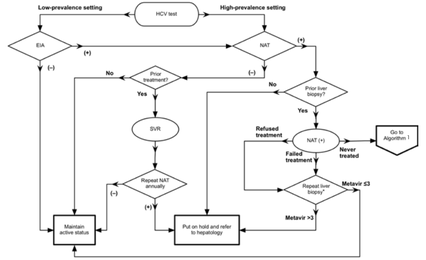
- Every 3 years in patients with Metavir Stage 3, or
- Every 5 years for patients with Metavir Stage 1 or 2, and
- Refer to a hepatologist to assess clinical stability of liver disease.

HISTORIC SCORING SYSTEMS OF LIVER FIBROSIS

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

P-C, portal-central; P-P, portal-portal.
(https://www.aasld.org/eweb/docs/hepatitisc.pdf)

Algorithm 2: Management of Wait-listed Transplant Candidates



*For Metavir 1 and 2, liver biopsy is recommended every 5 years; for Metavir 3, liver biopsy is recommended every 3 years.

ABBREVIATIONS: *EIA, enzyme immunoassay; HCV, hepatitis C virus; NAT, nucleic acid test; SVR, sustained virologic response.*

Use of Kidneys from HCV-Infected Donors

All kidney donors should be tested for HCV infection (weak evidence G.4.2.1).

- Testing with both EIA and NAT (if NAT is available) is suggested (weak evidence G.4.2.1).
- Using NAT is the optimal way to distinguish kidney donors who have active viremia from those who have acquired immunity after a previous infection. Antibody testing does not make this distinction. Where NAT is unavailable, use EIA.

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

- Balance the risks of HCV transmission compared to the benefits of being transplanted instead of remaining on dialysis.
- Pulsatile pump perfusion techniques during donor organ procurement may reduce the viral load in the donor kidney and thus potentially reduce viral transmission.
- Involve potential recipients in the treatment decision through discussion of risks and benefits of an organ from an HCV-infected donor.

The risks and effects of superinfection with an HCV genotype from the donor that is different from the genotype of the HCV-infected recipient are unknown.

LIVING KIDNEY DONORS

Living donors should be tested for HCV infection using NAT.

Exclude HCV-infected persons from donating because of:

- Transmission risk
- Association of HCV with risk for extrahepatic complications such as glomerulopathies and diabetes mellitus.

Immunosuppression Therapy for HCV-Infected Recipients

By virtue of their mechanisms of action in preventing rejection, immunosuppressive (IS) therapies have the potential for permissive effects on HCV kinetics after transplantation. As a result, IS agents could impact viral replication, progressive liver disease, extrahepatic manifestations, and patient and graft outcomes after kidney transplantation in HCV-infected recipients.

Recent data indicate that pretransplant SVR is well sustained after transplantation despite intense immunosuppressive therapy.

At the present time, it is not clear that the impact of immunosuppression on outcomes in liver transplant patients with HCV infection can be extrapolated to HCV-infected kidney transplant recipients. Therefore carefully weigh the safety and efficacy of each IS agent against the potential impact on HCV-related hepatic and extrahepatic complications.

Hepatic dysfunction may diminish drug clearance and affect blood levels of some IS agents (e.g., cyclosporin and tacrolimus).

MANAGEMENT OF IS THERAPY

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

Tailor the regimen for the lowest possible maintenance doses that provide effective immunosuppression.

COMPLICATIONS ASSOCIATED WITH IS THERAPY

- Infection
- Malignancy
- Hypertension
- Hyperlipidemia
- New-Onset Diabetes

LEVELS OF STRENGTH OF RECOMMENDATIONS

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

ABBREVIATIONS AND ACRONYMS

ACEI	Angiotensin-converting enzyme inhibitor(s)
ADA	American Diabetes Association
ARB	Angiotensin receptor blocker(s)
CAN	Chronic allograft nephropathy
EIA	Enzyme immunoassay
GN	Glomerulonephritis
IS	Immunosuppression
HCV	Hepatitis C virus
KDIGO	Kidney Disease: Improving Global Outcomes
MGN	Membranous glomerulonephritis
MPGN	Membranoproliferative glomerulonephritis
NAT	Nucleic acid test(ing)
NODAT	New-onset diabetes after transplantation
RR	Relative risk
SVR	Sustained virologic response

Management of HCV-Related Complications in Kidney Transplant Recipients (GUIDELINE 4.4)

FOCUS EFFORTS ON:

- Ongoing monitoring of liver function
- Selective and cautious use of IFN
- Prevention, detection and treatment of extrahepatic complications

RECOMMENDATIONS

LIVER DISEASE

- Check liver enzymes monthly for the first 6 months post-transplant and every 3 months thereafter.
  - Promptly refer patients with clinically worsening liver enzymes to a hepatologist.
- A post-transplant liver biopsy is not necessary, unless:
  - There is evidence of worsening liver disease, or
  - As part of an investigational protocol.
- Screen patients with cirrhosis for hepatocellular carcinoma on an annual basis using liver ultrasound and α-fetoprotein level.
- Perform a full evaluation at least annually after month 6 post-transplant.

Avoid IFN therapy, except where the benefits of attenuating liver injury (e.g., fibrosing cholestatic hepatitis, life-threatening vasculitis) clearly outweigh the substantial risk of allograft dysfunction or loss.

The RR of allograft loss from progressive HCV-associated glomerulopathy versus that from IFN-induced rejection is unknown.

HCV-ASSOCIATED GLOMERULOPATHY

- MPGN is commonly observed in the allograft of HCV-infected recipients. Therapy depends on cause of MPGN.
- Obtain baseline urine protein-to-creatinine ratio and urinalysis within the first 2 weeks after transplantation, or once stable kidney function is achieved.
- Test for proteinuria every 3–6 months for the first post-transplant year, then twice per year thereafter.
- An allograft biopsy with immunofluorescence and light and electron microscopy is suggested for patients with:
  - Urine protein/creatinine ratio >1, or
  - 24-h urine protein >1 g on two or more occasions
  - Microscopic hematuria without identifiable cause(s).
- Adjunct antiproteinuric therapy with agents that block the renin–angiotensin–aldosterone system should be used as tolerated.
  - Monitor kidney function, serum potassium, and hemoglobin during ACEI/ARB therapy, particularly if recipients have impaired kidney function.

DIABETES MELLITUS

- Both NODAT and HCV infection independently predict a higher mortality risk in kidney transplant recipients.
- Measure fasting blood glucose weekly during the first 3 months of the post-transplant period, then every other week for months 4–6, and then monthly for months 6–12.
- Measure fasting blood glucose and/or glycosylated hemoglobin at least annually, after the first post-transplant year.
- Diabetes diagnosis should be in line with current ADA criteria of a fasting blood glucose >125 mg per 100 ml (6.9 mmoll^{-1}) on 2 separate occasions.
- Risk of NODAT is especially high with tacrolimus use; conversion to a cyclosporine-based regimen should be considered for patients developing hyperglycemia.

KDIGO Disclaimer

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINES

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

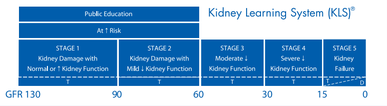
Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources and limitations unique to an institution or a type of practice. Every health care professional making use of these guidelines is responsible for evaluating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

SECTION II: DISCLOSURE

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

Specifically, all members of the Work Group are required to complete, sign and submit a disclosure and attestation form showing all such relationships that might be perceived as actual or perceived conflicts of interest. This document is updated annually and information is adjusted accordingly. All reported information is on file at the National Kidney Foundation.

A Curriculum for CKD Risk Reduction and Care



GFR = Glomerular Filtration Rate; T = Kidney Transplant; D = Dialysis

This reference tool was developed by the National Kidney Foundation's Kidney Learning System, which produces and disseminates public and professional educational materials for CKD risk reduction and care. More information is available at www.kdigo.org. The National Kidney Foundation manages KDIGO.

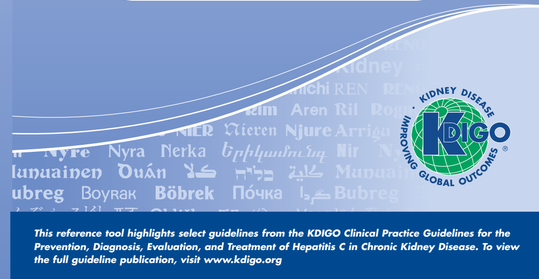
REFERENCE

Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int.* 2008; 73 (suppl 109):S1–S99.

KDIGO
30 East 33rd Street
New York, NY 10016
800.622.9010
212.889.2210
www.kdigo.org

Hepatitis C Management in Kidney Transplantation

- **The prevalence of HCV infection** among kidney transplant recipients ranges from 7%–40% with wide geographic and demographic variation.
- **HCV infection is not considered** a contraindication for kidney transplantation. Compared to remaining on dialysis, kidney transplantation confers a survival advantage to HCV-infected patients.
- **Patient and allograft survival** is worse in HCV-infected kidney transplant recipients compared with uninfected recipients.
- **Hepatic and extra-hepatic** post-transplant complications contribute to the inferior outcomes observed.
- **HCV infection is transmitted** by transplantation. Worldwide, the prevalence of HCV infection among deceased donors ranges from 1%–11%. Variation in transmission rates is multifactorial.



This reference tool highlights select guidelines from the KDIGO Clinical Practice Guidelines for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease. To view the full guideline publication, visit www.kdigo.org