What does Hepatitis C mean to me as a CKD Patient?

Clinical Practice Guidelines for the Prevention, Diagnosis, Evaluation and Treatment of Hepatitis C in CKD

Introduction

Worldwide, about 170 million people are infected by the hepatitis C virus (HCV). Infection is much more common in patients with chronic kidney disease (CKD) than in the general population. One reason for this is that infection with HCV can cause kidney disease. Another reason is that the virus is transmitted through contact with blood and can be passed between patients in dialysis units if the correct hygienic precautions are not followed. Before it was possible to screen for HCV, many CKD patients were infected through blood transfusions.

Hepatitis C is one of a family of viruses that cause inflammation of the liver. Initial infection with HCV is usually so mild that people affected do not seek medical attention. Some people are able to completely clear the virus from their blood, but more than half of those infected with HCV become chronic carriers of the disease. The main long-term complications of chronic infection with HCV are liver failure caused by scarring (fibrosis or cirrhosis) and liver cancer.

The guidance on how to diagnose, prevent and manage HCV in CKD patients was the first global guideline in nephrology. It was prepared by an international working group with a range of expertise with the help of a team based at Tufts University (Boston, USA) who specialise in searching through medical publications for evidence on which guidelines can be based. The draft guidelines were reviewed by interested organisations and individuals before being finalised and published in 2008.

The complete KDIGO guideline in English can be downloaded free-of-charge from the KDIGO website (www.kdigo.org). Summaries are also available in Arabic, Chinese, French, Italian, Japanese, Russian, Spanish, and Turkish. The European Best Practice (ERBP) Advisory Board endorsed and commented on the KDIGO guideline in 2009 and you can access their full report at http://ndt.oxfordjournals.org/content/24/3/719.full

Strength of recommendations

The nature and history of guidelines are explained in the opening paragraphs of the introduction to this paper and the implications for the strength of the recommendation are discussed in Appendix A.

In the guideline on hepatitis C, the recommendations were graded as **strong**, **moderate**, or **weak**. The wording of the recommendation used gives an indication of the strength.

- A strong recommendation will say that something ***should*** be done. In most cases this is how you would like to be treated.

- A moderately strong recommendation will say that an action should ***be considered.*** You can think of this recommendation as being suitable for most patients, but circumstances may make you choose other options.
- When a recommendation only ***suggests*** doing something, it is weak. In this case other options can be just as valid

Most doctors would be expected to advise you to follow a **strong** recommendation, if the intervention is available and appropriate for you. If the recommendation is **moderate** or **weak**, your doctor is expected to give more consideration to your individual circumstances and discuss alternatives with you.

1. **Detection and evaluation of HCV in CKD**

Guideline 1 ***suggests*** that all CKD patients are tested for HCV. This is because HCV has been associated with some types of kidney disease and also allows early treatment to be considered. Doctors may decide not to test for HCV in new patients if they have been diagnosed with a kidney disease that is not linked to HCV.

The guideline goes on to say that patients ***should*** be tested for HCV if they are candidates for a kidney transplant or if they are receiving haemodialysis (HD). It is essential to know if a patient who may receive a transplant is HCV-infected because it affects the way that donated kidneys are allocated. If the patient is to be given treatment to clear HCV, this is best carried out before the transplant takes place so this is another reason for testing these patients.

Patients ***should*** be tested when they start HD or when they transfer from another HD unit. This should form part of the dialysis unit's infection control procedures. If your unit follows the recommendations in guideline 3 (below), there should be no cross-infection between patients. If a patient is found to be HCV-infected, the staff need to know if the infection occurred before or after the patient started HD in your unit so they can take appropriate action.

There are two types of test for HCV. The simpler 'EIA' test (**E**nzyme-linked **I**mmunosorbant **A**ssay) looks for antibodies that the body produces to fight off the virus while 'NAT' (**N**ucleic **A**cid **T**est) looks for the virus itself. NAT is more complicated and expensive but it is more accurate and it gives information about how infectious the patient is. The guideline recommends that units where there are few or no HCV-infected patients ***should consider*** using the EIA test routinely and only test with NAT if the EIA test is positive. Units where HCV infection is more common ***should consider*** using NAT as the first test for new patients. NAT is also the most appropriate test for new patients with a high risk of HCV infection such as drug users who may have shared needles. This strategy is intended to minimise the number of false-positive and false-negative tests.

- The ERBP Advisory Board agreed that NAT is a more accurate test than EIA, but it is expensive and units where HCV infection is more common are usually in regions where funding for dialysis is low. They suggest that doctors in these units decide which test to use for new patients based on their understanding of the tests and their resources.

The guideline says that units ***should consider*** routinely testing HD patients who are HCV-negative every 6–12 months with the simpler EIA test, even if there is nothing to suggest that the patient has been infected. However, any patient with an abnormally high level of a liver enzyme called ALT (Alanine transaminase) which can be a sign of infection ***should*** be tested at once with NAT. Testing with NAT ***should*** also be carried out for all potentially affected patients if cross-infection is found to have occurred within a dialysis unit.

2. Treatment of HCV infection in patients with CKD

Evaluation of HCV-infected patients for antiviral treatment: Guideline 2.1 ***suggests*** that doctors should evaluate all CKD patients with HCV infection to see if they will benefit from antiviral treatment. The current treatment does have side effects and it is not always successful, especially in HCV with 'genotype' 1 and 4. (A genotype is the genetic make-up of a cell. organism or individual). If you are being assessed for treatment, you may have to have a biopsy in which a small piece of your liver is removed to see how much scar tissue it contains.

The complications of HCV usually take decades to appear. Together with the potential risks of treatment, this means that you are most likely to benefit from treatment if you are hoping, and are suitable, for a kidney transplant; or if you are young and expecting to spend many years on dialysis.

Antiviral therapy reduces the risk for developing diabetes or HCV-related kidney disease after transplantation. It should be carried out before the transplant as antiviral therapy carried out after transplantation frequently leads to rejection of the transplanted kidney. The guideline ***suggests*** that therapy is initiated after transplantation, only where the consequences of not treating the HCV are life-threatening and where the patient accepts that they may have to go back onto dialysis should the transplanted kidney be rejected.

If you are infected with HCV and anti-viral treatment is considered to be in your best interest, the guideline ***suggests*** that it can be started as early as 12 weeks after the initial infection if you have not been able to clear the virus. NAT is used to see if you have been able to fight off the infection in which case you won't need anti-viral treatment.

- The ERBP Advisory Board agreed that treatment should be mainly considered for younger patients. They emphasise the need for doctors to discuss the treatment and side effects carefully with the patient, particularly if they are infected with genotype 1 which is more difficult to clear.

Basing HCV treatment on CKD Stage: The severity of CKD is measured using the 'glomerular filtration rate' (GFR). This is the volume of fluid filtered by the kidney every minute with a correction for body size. A young person with healthy kidneys will have a GFR of around 120 ml/min/1.73m^2.

Guideline 2.2 ***suggests*** that patients with CKD Stages 1 and 2 (GFR > 60 ml/min/1.73m^2) who are suitable for treatment should receive the same antiviral drugs as the general population. This is currently a combination of 'pegylated' interferon and ribavirin for 6 to 12 months.

Interferons (IFNs) are naturally-occurring proteins that activate the immune system and interfere with the reproduction (replication) of viruses. Pegylated IFN has a polymer attached that enables it to stay in the body for longer by reducing the normal excretion via the kidneys. Ribavarin also interferes with viral replication. The mechanism by which ribavarin works is not known, but it has been shown to make IFN treatment more effective. One of the side-effects of ribavarin is anaemia caused by damage to red blood cells, so the guideline suggests adjusting the dose while monitoring and treating the patient for anaemia.

For patients with CKD Stages 3 and 4 (GFR 15 to 60 ml/min/1.73m^2) who are suitable for antiviral treatment, the guideline ***suggests*** using pegylated IFN alone as the side effects of combined therapy are expected to get worse as renal function declines. Anaemia caused by ribavarin can be particularly dangerous so it has to be used with caution and only if ribavarin levels in the blood can be monitored and any resultant anaemia can be treated. Lower doses of pegylated IFN are recommended for patients with CKD Stage 3 and 4.

Patients with CKD Stage 5 (GFR < 15 ml/min/1.73m^2) who are not yet on dialysis can also be treated with pegylated IFN as described for patients with CKD Stages 3 and 4. For those who have started dialysis, the guideline ***suggests*** using standard IFN at a reduced dose because excretion via the kidneys is reduced. Ribavarin is not recommended for use in dialysis patients, but if a decision is made to use ribavarin, it should be with the same caution as for Stage 3 and 4 patients.

In the absence of evidence, the guideline ***suggests*** using the treatment recommended for dialysis patients in patients with transplants for whom the benefits of antiviral treatment outweigh the risks.

- The ERBP Advisory Board agree with the recommended treatment agents but point out treatment is best carried out in collaboration with dedicated, experienced centres and with very close monitoring.

Monitoring the response to HCV treatment in CKD patients: Guideline 2.3 ***suggests*** using SVR, the 'sustained viral response', to see if the antiviral treatment has worked. SVR is achieved if testing with NAT six months after completing treatment shows the virus has been completely cleared from the blood.

If you have been treated for HCV,, the guideline ***suggests*** that your unit checks if you are free of the virus once a year using NAT (or every 6 months if you are on HD). It is especially important to check for relapse if you are hoping for a transplant in case you need another course of treatment before transplantation. The higher frequency recommended for HD patients is for reasons of infection control. The guideline recommends treating patients who have relapsed for at least a year.

Whether or not they have responded to treatment, the guideline says that all patients with HCV ***should*** be followed for complications associated with HCV. A 6-monthly follow-up is ***suggested*** for patients with evidence of cirrhosis, and an annual follow-up for those without cirrhosis.

3. Preventing HCV transmission in haemodialysis units

Guideline 3 says that HD units ***should*** ensure their staff apply the strict infection control procedures necessary to prevent of blood-borne viruses (including HCV) being transferred from one patient to another. These procedures ***should*** include hygienic precautions that effectively prevent the transfer of blood between patients, either directly or via contaminated equipment or surfaces.

These procedures are not complicated or expensive. Staff must wash their hands or use an antiseptic alcohol gel rub before and after contact with a patient or equipment at the dialysis station. Gloves that have been worn when caring for a patient, or touching equipment that may be contaminated with blood, must be removed before leaving the dialysis station. Patients should also clean their hands when arriving at or leaving their dialysis station if they are able to.

Items that are used more than once, such as tourniquets or blood pressure cuffs, should be disinfected between patients or dedicated to a single patient. After each session, all surfaces at the dialysis station from the dialysis machine to the TV controller, should be wiped with a disinfectant. Any visible blood should be cleaned up with bleach or an equivalent disinfectant.

- The ERBP Advisory Board noted that the KDIGO guideline on hygienic precautions did not cover peritoneal dialysis. ERBP AB recommends that hands should be washed before and after, and gloves worn during, any manipulation of material contaminated with spent dialysate. Contaminated surfaces should be cleaned with a 1% bleach solution. Spent fluid should be kept in closed drainage bags or in open contained dosed with bleach and, when possible, disposed of in a drain (e.g. a toilet) that is not connected to surfaces used for food or washing (i.e. not a sink)

If the infection control procedures are strictly followed, cross-infection can be prevented without the need to segregate ('isolate') patients. Units where infection with hepatitis C is quite common often have separate rooms for HCV-infected and HCV-negative patients. The guideline ***suggests*** that even when HCV-infected patients are isolated, the infection control procedures still need to be enforced to protect patients from undetected viral or bacterial infections.

In units where very few patients are HCV-infected, isolation can mean that patients have to dialyse in locations or on shifts that are not convenient for them. This should not be necessary if the infection control procedures described above are properly enforced.

A common practice in units with few HCV-infected patients has been to dialyse infected patients with dedicated 'HCV' machines. Guideline 3 does not recommend this practice as the evidence indicates that the main route of transmission is via the staff (e.g. through poor hand washing). If dialysis units have to introduce isolation because they are unable to enforce infection control procedures, they need to ensure the staff do not move between HCV-infected and uninfected patients.

- The ERBP Advisory Board noted agrees that staff should apply strict hygienic precautions at all times. If HCV-infected patients are isolated as an additional measure to prevent

transmission in units where HCV is common, this should not lead to the staff being less vigilant.

The guideline ***suggests*** using regular audits where someone observes the staff while they work to ensure that the recommended infection control procedures are being followed. Staff should not object if a dialysis patient or their carer asks if they have washed their hands.

4. Management of HCV infected patients before and after kidney transplantation

Evaluation and management of kidney transplant candidates: Guideline 4.1 says that all patients who are candidates for a kidney transplant ***should*** be tested for HCV infection using EIA or NAT (as described in guideline 1). Most patients who are HCV-infected can still be listed for a transplant as, like other patients, they are expected to live longer with a transplant than on dialysis.

The immunosuppressive therapy required after a transplant can allow the virus to replicate more rapidly which could accelerate liver damage. The guideline ***suggests*** that HCV-infected patients undergo a liver biopsy before they have a transplant. The biopsy is to identify patients who may have problems after transplantation as well as those who really need a combined liver and kidney transplant.

The guideline ***suggests*** that HCV-infected kidney transplant candidates are considered for treatment with standard IFN before transplantation (see guideline 2). As IFN works by stimulating the immune system, the transplant should not be done until at least 28 days after therapy to allow the IFN to be cleared from the body.

Guideline 1 recommends testing HCV-negative patients for new infection every 6-12 months. If a patient on the transplant list is found to be newly infected, guideline 4.1 ***suggests*** that they are suspended until their liver disease has been evaluated. The same advice is given for patients who relapse after having had antiviral therapy to clear the virus. For patients who have failed or refused antiviral treatment, guideline 4.1 ***suggests*** repeated the liver biopsy every 3 to 5 years while they are on the transplant list.

4.2 Use of kidneys from HCV-infected donors: As HCV can be transmitted from an infected donor to an uninfected recipient, guideline 4.2 says that all kidney donors ***should*** be tested for HCV infection using both EIA and NAT (if NAT is available). It ***suggests*** that kidneys from HCV-infected donors are only transplanted into HCV-infected recipients who have active infection (measured using NAT).

In practice, living donors who are HCV-infected will not be accepted because of the risk to the donor. To keep waiting times down, the kidneys of HCV-infected deceased donors are used for HCV-infected recipients and it has been shown that the recipients of these kidneys live longer than they would have done on dialysis.

4.3 Use of maintenance immunosuppressive regimens: As the most appropriate regime of immunosuppressive drugs for HCV-infected kidney transplant recipients has not been identified, guideline 4.3 ***suggests*** that all the currently available regimes can be considered. Most

immunosuppressive agents will increase replication of the virus so the lowest possible doses should be used and the patient should be checked for complications as described in guideline 4.4.

4.4 Management of HCV-related complications in kidney transplant recipients: HCV infected kidney transplant patients are at risk of worsening liver disease as well as developing 'NODAT' (new onset diabetes after transplantation) and glomerular disease (see guideline 5) in the new kidney. To ensure that these problems are picked up quickly, guideline 4.4 ***suggests*** checking liver enzyme levels (monthly for 6 months and then quarterly), fasting blood sugar (weekly for 3 months, fortnightly for months 4-6, monthly for months 6-12 then annually) and protein in the urine (every 3 to 6 months).

An annual ultrasound to check for liver cancer is recommended for patients whose liver biopsy showed cirrhosis, but there is no reason for patients to undergo liver biopsies after the transplant unless there is evidence that they have worsening liver disease. Antiviral treatment is not recommended unless the benefit (preventing liver failure) outweighs the risk of losing the transplanted kidney.

If significant levels of protein are found in the urine on two occasions, guideline 4.4 ***suggests*** carrying out a biopsy of the new kidney to look for glomerular disease. However, the IFN-based treatment that would be considered for glomerular disease associated with HCV infection (see guideline 5) is not recommended after transplantation.

5. Diagnosis and management of kidney diseases associated with HCV infection

Guideline 5 ***suggests*** that patients infected with HCV who are not on dialysis should be tested at least once a year for blood and protein in the urine and for changes in GFR. This is to check for 'glomerulo-nephritis' (GN) associated with HCV infection. GN is inflammation of the kidney caused by damage to the tiny structures (called 'glomeruli') that filter fluid containing toxins from the blood. The fluid is concentrated to make urine.

In HCV-associated GN, the body's immune system attacks the glomeruli and disrupts the filtration so that red blood cells and proteins, which are normally held back, can pass into the urine. There are several types of GN associated with HCV, the most common one being membranoproliferative glomerulonephritis (MPGN). The guideline ***suggests*** that HCV-infected patients with clinical evidence of GN (e.g. significant amounts of protein in the urine) undergo a kidney biopsy to identify which type of GN they have.

HCV infection is also associated with 'cryoglobulins' in the blood. Cryoglobulins are 'immunoglobulins' (antibodies) produced by the immune system to fight disease. They clump together in the cold and dissolve again on warming. Cryoglobulins can cause clots and 'vasculitis' (inflammation of blood vessels) which can lead to damage in the organs receiving blood from the affected vessels, such as the skin or kidneys.

The guideline ***suggests*** considering using antiviral treatment for patients with HCV-associated glomerular diseases, particularly MPGN, as described in guideline 2.2, and immunosuppressive agents for patients with diseases caused by cryoglobulins.