

## Management of hepatitis C virus infection in hemodialysis patients

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### Abstract

The prevalence of hepatitis C virus (HCV) infection in patients on maintenance hemodialysis (MHD) is relatively higher than those without MHD. Chronic HCV infection detrimentally affects the life quality and expectancy, leads to renal transplant rejection, and increases the mortality of MHD patients. With the application of erythropoietin to improve uremic anemia and avoid blood transfusion, the new HCV infections during MHD in recent years are mainly caused by the lack of stringent universal precautions. Strict implementation of universal precautions for HCV transmission has led to markedly decreased HCV infections in many hemodialysis units, but physicians still should be alert for the anti-HCV negative HCV infection and occult HCV infection in MHD patients. Standard interferon alpha and pegylated interferon alpha monotherapies at a reduced dose are

currently the main treatment strategies for MHD patients with active HCV replication, but how to increase the sustained virological response and decrease the side effects is the key problem. IFN $\alpha$ -free treatments with two or three direct-acting antivirals without ribavirin in MHD patients are waiting for future investigations.

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**Key words:** Hemodialysis; Hepatitis C virus; Epidemiology; Risk factors; Prophylaxis; Treatment

**Core tip:** The new hepatitis C virus (HCV) infections during maintenance hemodialysis (MHD) in recent years are mainly caused by the lack of stringent universal precautions. Strict implementation of universal precautions for HCV transmission has led to markedly decreased HCV infections in many hemodialysis units, but the anti-HCV negative HCV infection and occult HCV infection in MHD patients still should be noted. How to increase the sustained virological response and decrease the side effects is the key problem for the currently recommended interferon alpha-based antiviral therapy in MHD patients. Interferon alpha-free treatments with two or three direct-acting antivirals without ribavirin in MHD patients are waiting for future investigations.

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### INTRODUCTION

Hepatitis C virus (HCV) infection is a major public health problem worldwide which can lead to chronic hepatitis

C, liver cirrhosis and hepatocellular carcinoma (HCC)<sup>[1,2]</sup>. Prevalence of HCV infection is markedly higher in patients on maintenance hemodialysis (MHD)<sup>[3-7]</sup>. Chronic HCV infection detrimentally affects the life quality, decreases life expectancy, leads to renal transplant rejection, and increases the mortality of MHD patients suffering from chronic kidney failure<sup>[1,5,6]</sup>. Moreover, HCV infection has been shown to increase the prevalence of renal insufficiency, defined by serum creatinine  $\geq 1.5$  mg/dL; the mechanisms may include the direct HCV-related renal injury and HCV-related cirrhosis with subsequent renal impairment<sup>[7]</sup>, and this will be harmful for patients who receive renal transplantation. The rates of HCV infection in MHD patients vary markedly among different countries and hospitals. Multiple factors are associated with the high risk of HCV transmission in MHD patients<sup>[3]</sup>. Standard interferon alpha (ST-IFN $\alpha$ ) and pegylated IFN $\alpha$  (PEG-IFN $\alpha$ ) are currently the main treatment strategies for HCV infection in MHD patients, and the key problems are how to increase the sustained virological response (SVR), control the side effects and minimize the dropout rates<sup>[1,2,8-10]</sup>. This review summarizes the advancement in understanding the prevalence, risk factors, monitoring strategy, and more importantly, prophylaxis and treatment of HCV infection in MHD patients.

## EPIDEMIOLOGY

HCV infection in hemodialysis patients varies by patients' behavioral and cultural differences, geographic location, socioeconomic aspects, community exposure factors, number of patients per hemodialyzer and rigorous use of the strictest biosafety standards<sup>[4,11]</sup>, with the reported prevalence ranging from 1.9% to 90% (Table 1)<sup>[3]</sup>. Generally, new cases of HCV infection related to hemodialysis are more frequent in regions that have a higher prevalence of serum anti-HCV, and HCV genotypes in hemodialysis patients are usually in accordance with those found in non-hemodialysis patients; but some HCV genotypes that are rare in the general population may be more prevalent in hemodialysis patients because of the nosocomial person-to-person transmission in the hemodialysis unit<sup>[4]</sup>. For instance, a higher prevalence of HCV genotype 2b has been found in hemodialysis populations in southern Brazil, a genotype rarely occurring in Brazil, where the 1a, 1b, or 3a are more common<sup>[4]</sup>.

## RISK FACTORS

Currently, it is still unclear how MHD patients become HCV-infected. Nevertheless, both intradialysis (number of blood transfusions, duration and mode of dialysis, prevalence of HCV in the hemodialysis unit, breakdown of standard infection control practices) and extra dialysis (high risk of lifestyle behaviour) variables have been identified.

First, many of these patients had severe uremic anemia needing blood transfusion, which is the most important route of HCV transmission<sup>[3,7]</sup>. Thus, it was

**Table 1** Prevalence of anti-hepatitis C virus seropositivity in hemodialysis patients

Country/region	Prevalence	Investigators and year of publication
Slovenia	1.9%	Buturović-Ponikvar <sup>[12]</sup> , 2001
Netherlands	3.4%	Schneeberger <i>et al</i> <sup>[13]</sup> , 1999
Puerto Rico	3.5%	López-Navedo <i>et al</i> <sup>[14]</sup> , 1999
United Kingdom	4.0%	Wreghitt <sup>[15]</sup> , 1999
Germany	6.1%	Hinrichsen <i>et al</i> <sup>[16]</sup> , 2002
Mexico	6.7%	Méndez-Sánchez <i>et al</i> <sup>[17]</sup> , 2004
Belgium	6.8%	Jadoul <i>et al</i> <sup>[18]</sup> , 2004
United States	7%-23.3%	Kalantar-Zadeh <i>et al</i> <sup>[5]</sup> , 2007 Kalantar-Zadeh <i>et al</i> <sup>[19]</sup> , 2005 Sivapalasingam <i>et al</i> <sup>[20]</sup> , 2002 Kelley <i>et al</i> <sup>[21]</sup> , 2002 Saab <i>et al</i> <sup>[22]</sup> , 2001
Brazil	6%-90%	da Silva <i>et al</i> <sup>[4]</sup> , 2013 Mello Lde <i>et al</i> <sup>[23]</sup> , 2007 Lopes <i>et al</i> <sup>[24]</sup> , 2006 Albuquerque <i>et al</i> <sup>[25]</sup> , 2005 Carneiro <i>et al</i> <sup>[26]</sup> , 2001
China Maintain	7.01%-37.34%	Ren <i>et al</i> <sup>[27]</sup> , 2011 Qi <i>et al</i> <sup>[28]</sup> , 2003
Greece	10%-29%	Garinis <i>et al</i> <sup>[29]</sup> , 1999 Rigopoulou <i>et al</i> <sup>[30]</sup> , 2005 Sypsa <i>et al</i> <sup>[31]</sup> , 2005
Sweden	11.0%	Almroth <i>et al</i> <sup>[32]</sup> , 2002
Iran	13.2%	Alavian <i>et al</i> <sup>[33]</sup> , 2003
France	16.3%	Salama <i>et al</i> <sup>[34]</sup> , 2000
Tunisia	19%-41.7%	Bouzgarrou <i>et al</i> <sup>[35]</sup> , 2005 Ayed <i>et al</i> <sup>[36]</sup> , 2003
Libya	20.5%	Daw <i>et al</i> <sup>[37]</sup> , 2002
Italy	22.5%-32.1%	Petrosillo <i>et al</i> <sup>[38]</sup> , 2001 Lombardi <i>et al</i> <sup>[39]</sup> , 1999
Sudan	23.7%	El-Amin <i>et al</i> <sup>[40]</sup> , 2007
Vietnam	26.6%	Dunford <i>et al</i> <sup>[7]</sup> , 2012
Bosnia and Herzegovina	59.0%	Ahmetagić <i>et al</i> <sup>[41]</sup> , 2006
Peru	59.3%	Sanchez <i>et al</i> <sup>[42]</sup> , 2000
Kuwait	71.0%	Wreghitt <sup>[15]</sup> , 1999
Moldavia	75.0%	Covic <i>et al</i> <sup>[43]</sup> , 1999
Senegal	80.0%	Diouf <i>et al</i> <sup>[44]</sup> , 2000

highly possible that some of the hemodialysis patients got HCV infection through this way, especially in regions with poor socioeconomic conditions, where the qualified medical staff and equipments available to treat MHD patients were very limited. In the past two decades, the sensitivity and specificity of laboratory tests for detection of HCV have improved greatly, leading to the more stringent screening of blood donors and the marked decline of new HCV infections<sup>[6,45,46]</sup>. On the other hand, the availability of erythropoietin has reduced the need of blood transfusion in hemodialysis patients. Accordingly, the risk of HCV infection through blood transfusion in hemodialysis patients has decreased significantly in many countries<sup>[45]</sup>.

Second, new HCV infections can occur in patients who lack the risk factors of blood transfusion, intravenous drug use, high-risk sexual activity, or exposure to known HCV-positive persons. It is believed that these patients were infected by HCV during the course of hemodialysis<sup>[47]</sup>. Phylogenetic analysis of HCV isolates implies that many HCV infections during hemodialysis

are surely the result of nosocomial patient-to-patient transmission<sup>[45,47-50]</sup>. The infection risk usually increases with the prevalence of HCV, and the number and length of hemodialysis exposure in corresponding hemodialysis units<sup>[4,5,31,40]</sup>. Recently, da Silva *et al.*<sup>[4]</sup> reported that HCV-infected patients had been on hemodialysis for 91.9 mo, more prolonged than HCV-negative patients ( $P = 0.001$ ). Another investigation showed that the prevalence of HCV infection at admission in a New York City hemodialysis unit was 18%, far higher than the 1.6% in the United States population overall. During 2001-2008, nine patients treated in this unit were found to have seroconversion from anti-HCV negative to positive. Of them the sources for four HCV infections were identified phylogenetically and epidemiologically as four other patients in the unit. The epidemiologic and site investigations showed that the hemodialysis unit had inadequate HCV infection surveillance and patient follow-up, inadequate cleaning and disinfection practices, failing to wear or change gloves or perform hand hygiene between contacted patients, lack of a separate clean area for medication storage and preparation, and short turnover periods between patient treatments<sup>[47]</sup>. Accordingly, it is suspected that the way for HCV transmission in these patients may be direct percutaneous exposure to infectious blood because of inadequate infection control<sup>[1]</sup>. On the contrary, the use of dedicated hemodialyzer specially prepared for each patient and the strict implementation of hygienic precautions against HCV transmission could markedly decrease the incidence of nosocomial HCV infection in hemodialysis patients<sup>[45]</sup>.

## MONITORING

Monitoring serum anti-HCV by enzyme-linked immunosorbent assay or enzyme immunoassay every three to six months is essential to identify HCV seroconversion<sup>[45,47]</sup>. Sometimes the recombinant immunoblot assay for anti-HCV should be added to confirm the positivity of anti-HCV<sup>[47]</sup>. Of note is that the anti-HCV tests may fail to detect HCV infection in 1.66%<sup>[45]</sup> to 7.2%<sup>[46]</sup> of MHD patients, because the immunocompromised status of these patients prevents them from having detectable anti-HCV antibodies<sup>[1]</sup>. So it is necessary to detect HCV core antigen by chemiluminescent assay or HCV RNA by polymerase chain reaction (PCR) in anti-HCV negative patients who are at high risk of HCV transmission<sup>[6,46]</sup>. If HCV RNA is positive, it is necessary to quantitate and genotype the HCV RNA further to provide important information for phylogenetic analysis of HCV isolates and selection of treatment strategy in MHD patients<sup>[45,50]</sup>. In addition, serum alanine aminotransferase (ALT) and other liver-associated biochemical tests, alpha fetoprotein and ultrasonic scan of the liver should also be conducted regularly.

Occult HCV infection, defined as detectable HCV RNA in the liver or peripheral blood mononuclear cells (PBMCs) in the absence of both serum HCV RNA and

anti-HCV<sup>[51]</sup>, is a serious fact that might be ignored in hemodialysis patients. Barril *et al.*<sup>[51]</sup> reported that occult HCV infection, determined by the presence of genomic HCV RNA in PBMCs, was found in 45% of the 109 MHD patients, and 53% of these patients had ongoing HCV replication indicated by the presence of antigenomic HCV RNA. Patients with occult HCV infection had spent a significantly longer time on hemodialysis and had significantly higher mean ALT levels during the 6 mo before study entry. Accordingly, for patients with long time of hemodialysis and a relatively higher serum ALT level, the PBMCs or liver biopsy samples should be collected to detect HCV RNA to rule out occult HCV infection<sup>[51,52]</sup>.

## PROPHYLAXIS

There is no active vaccine to prevent MHD patients from HCV infection. It has been adopted by many medical centers to assign HCV-infected patients to dedicated hemodialysis machines in a dedicated room in order to separate HCV positive patients from the negative patients, and this has been considered to be able to decrease the risk of HCV transmission<sup>[53]</sup>. In those hemodialysis units with high HCV prevalence but without fulltime medical staff on HCV-infection control, this strategy may help decrease the risk of HCV transmission among patients<sup>[5]</sup>; but for hemodialysis units with strict universal precautions against HCV transmission, some specialists consider that the dedicated hemodialysis machine in a dedicated room for HCV-infected patients is somewhat unjustified and unnecessary<sup>[49,54]</sup>.

Universal precautions, especially stringent adherence of all necessary biosafety measures during hemodialysis, are considered to be the keystones to minimize HCV transmission related to hemodialysis and have maximized ideal prophylactic effects<sup>[45,47,53]</sup>. These measures include: (1) applying a disposable hemodialyzer to avoid sharing of a hemodialyzer; (2) systematic decontamination of the equipment and circuits after each patient's treatment; (3) avoiding sharing of medications, such as multiuse vials of heparin among patients; (4) avoiding sharing of instruments such as tourniquets; (5) preparing any medications in a separate area; (6) disinfecting hemodialysis station surfaces timely; (7) cleaning hands and changing gloves before contacting different patients; (8) periodic testing of all patients for anti-HCV and HCV RNA; and (9) systematic training of health workers in hemodialysis units.

## TREATMENT

HCV infection has a significant adverse effect on the health of persons with chronic kidney disease, leads to a higher mortality in MHD patients than non-infected MHD patients, and reduces the survival rates of patients who undergo kidney transplantation, as do their grafts. Moreover, HCV infection renders the patients at high risk of developing diabetes mellitus, membranous glomerulonephritis as well as fibrosing cholestatic hepatitis after

**Table 2** Current recommendations for antiviral treatment of hepatitis C virus infection in maintenance hemodialysis patients with kidney failure<sup>[1,54,56,57]</sup>

Drug	Dosage	Notes
ST-IFN $\alpha$ -2a	3 million units, three times a week	Usually 48 wk for HCV genotypes 1 and 4, and 24 wk for HCV genotypes 2 and 3, or receiving response-guided treatment
ST-IFN $\alpha$ -2b	3 million units, three times a week	
PEG-IFN $\alpha$ -2a	135 $\mu$ g, once a week	A more reduced dose, a longer interval between two injections, or temporary cessation of IFN $\alpha$ should be considered in patients with severe side effects such as dangerous bone marrow suppression
PEG-IFN $\alpha$ -2b	1 $\mu$ g/kg, once a week	
Ribavirin	200 mg, once a day, every other day, or thrice weekly after hemodialysis	Ribavirin is applied in combination with interferon, and should be prohibited if severe anemia or other adverse effects occurs

HCV: Hepatitis C virus; ST-IFN $\alpha$ : Standard interferon alpha; PEG-IFN $\alpha$ : Pegylated interferon alpha.

kidney transplantation<sup>[1]</sup>. Accordingly, patients with MHD who are infected with HCV should be treated if conditions permit, no matter whether they will receive kidney transplantation or not. On the other hand, occult HCV infection is usually persistent and can not be eradicated spontaneously. Though it seems to be less aggressive than chronic hepatitis C, occult HCV infection may also lead to liver cirrhosis and even HCC<sup>[52,55]</sup>. Accordingly, if occult HCV infection could be confirmed in MHD patients, the antiviral therapy should be given too<sup>[40]</sup>. Recommendations for the treatment of HCV infection in MHD patients with kidney failure are summarized in Table 2.

ST-IFN $\alpha$  and PEG-IFN $\alpha$  monotherapies are currently the main treatment strategies for MHD patients with active HCV RNA replication. For adult patients, ST-IFN $\alpha$ -2a or ST-IFN $\alpha$ -2b should be given at a reduced dose of 3 million units three times a week, and PEG-IFN $\alpha$ -2a or PEG-IFN $\alpha$ -2b should be given at a reduced dose of 135  $\mu$ g and 1  $\mu$ g/kg once a week, respectively<sup>[1]</sup>. If the patients still cannot endure the side effects even in the use of erythropoietin, granulocyte-macrophage colony stimulating factor, interleukin-11 or other symptomatic and supporting treatments, a more reduced dose of IFN $\alpha$  should be given, and/or the intervals between two injections should be prolonged, or the IFN $\alpha$  should be stopped temporarily. Generally, the recommended treatment duration of IFN $\alpha$  is based on the HCV genotypes, *i.e.*, 48 wk for HCV genotypes 1 and 4, and 24 wk for HCV genotypes 2 and 3<sup>[54]</sup>; but the response-guided treatment strategy should also be emphasized, *e.g.*, shorter treatment duration for patients achieving rapid virological response (defined as seronegativity of HCV RNA at week 4 of treatment) than those with early virological response (EVR, defined as a seronegative or at least a 2 log<sub>10</sub> decrease from baseline in the serum HCV RNA at week 12 of treatment), and early termination in those without an EVR<sup>[56]</sup>. Moreover, a shorter treatment duration of IFN $\alpha$  might be considered in patients with interleukin-28B (IL-28B) genotype rs12979860 CC or rs8099917 TT, but a longer treatment duration should be given in those with IL-28B genotype rs12979860 CT/TT or rs8099917 TG/GG<sup>[56]</sup>.

Though PEG-IFN $\alpha$  can be used and may be associated with improved SVR rates in MHD patients<sup>[57]</sup>, a group of experts in both kidney and liver disease recom-

mended ST-IFN $\alpha$  in preference to PEG-IFN $\alpha$  for the treatment of MHD patients with HCV infection<sup>[1]</sup>. The rationale for this recommendation is that ST-IFN $\alpha$  has appeared as effective as PEG-IFN $\alpha$  in MHD persons because its excretion is reduced in these patients, its adverse effects may be lower, and management of adverse effects is relatively easier than PEG-IFN $\alpha$ <sup>[1]</sup>.

Because ribavirin has the high risk of inducing or aggravating hemolytic anemia in uremic patients and can not be removed by hemodialysis, it should be prohibited or used at a markedly reduced daily dose with careful monitoring of anemia and other adverse effects in MHD patients<sup>[1,8-10]</sup>. If RBV is to be applied, it should be given at an individualized dosing of 200 mg once a day, or 200 mg every other day, or 200 mg thrice weekly after hemodialysis, and substantial hematopoietic support is essential<sup>[57]</sup>.

In a meta-analysis made by Gordon *et al*<sup>[9]</sup> in 2009, which included 428 patients from 20 prospective studies from 1966 to February 2009, IFN $\alpha$  treatment for at least six months against chronic HCV infection in MHD patients was shown to result in a high overall SVR of 45%. Both univariate and multivariate regression analyses demonstrated that the higher SVR was related to the following factors: (1) three million units or higher dosage of IFN $\alpha$ , three times weekly; (2) completion of treatment for at least six months; (3) lower baseline HCV RNA; (4) female gender; and (5) early virological negativity<sup>[9]</sup>. In a later meta-analysis by Alavian *et al*<sup>[8]</sup> published in 2010, 491 MHD patients from 21 studies of ST-IFN $\alpha$  and 279 MHD patients from 12 studies of PEG-IFN $\alpha$  were meta-analyzed. The pooled SVR for ST-IFN $\alpha$  and PEG-IFN $\alpha$  monotherapy in random effects model were 39.1% and 39.3%, respectively. Pooled dropout rates were 22.6% and 29.7%, respectively. Only age less than 40 years was significantly associated with SVR. HCV RNA level, HCV genotype, ALT pattern, female gender, duration of infection, liver fibrosis stage, and treatment duration were not associated with SVR<sup>[8]</sup>. These conclusions are conflicting with that of Gordon *et al*<sup>[9]</sup>. Accordingly, the factors associated with the SVR are worthy of further investigations.

Tolerance to initial IFN $\alpha$  monotherapy was lower in MHD than in non uremic patients with chronic HCV infection. The most frequent side effects requiring interruption of treatment were severe flu-like symptoms, bone marrow suppression, neurological and gastrointestinal

discomfort. However, about 40% of MHD patients with HCV infection have been successfully treated with IFN $\alpha$  monotherapy. Further studies are warranted to define whether longer duration of IFN $\alpha$  monotherapy will have a better SVR on IFN $\alpha$  for chronic hepatitis C in MHD population<sup>[10]</sup>.

Telaprevir and boceprevir are HCV protease inhibitors (PIs) developed in recent years. No significant impact of renal dysfunction on telaprevir or boceprevir exposure was found in patients with end-stage renal disease<sup>[58]</sup>, suggested that both drugs might be used to treat HCV infection in this setting<sup>[57]</sup>. A recent study that included 36 treatment-naïve HCV genotype 1 infected MHD patients showed that telaprevir-containing triple therapy had superior efficacy than PEG-IFN $\alpha$ /RBV dual therapy, but was accompanied with anemia more frequently and severely<sup>[57]</sup>. Generally speaking, in consideration of added severe side effects and drug-drug interactions, triple or quadruple combinations based on IFN $\alpha$ /RBV therapy with one or two PIs are believed not very suitable for MHD patients with HCV infection. On the other hand, several IFN $\alpha$ -free clinical studies combining two or three new direct antiviral agents without RBV are now under investigation in HCV-infected patients without renal dysfunction<sup>[2]</sup>. This will bring new hopes to increase SVR with decreased side effects not only for HCV-infected patients without MHD, but also for patients with MHD.

## CONCLUSION

MHD patients without initial HCV infection may be infected by HCV through blood transfusion or negligence of universal precautions during hemodialysis. The application of erythropoietin has decreased the necessity of blood transfusion for uremic anemia greatly, and the improved detection tests of anti-HCV, HCV core antigen and HCV RNA have minimized the risk of HCV transmission through blood transfusion. Accordingly, the new HCV infections during MHD in recent years are mainly caused by the lack of standard universal precautions. Construction of detailed surveillance systems and implementation of stringent universal precautions for HCV transmission have led to a markedly decreased prevalence of HCV infection in many hemodialysis units<sup>[16]</sup>, and the effectiveness of different preventive strategies for HCV infection in hemodialysis units should be further investigated and clarified. The occult HCV infection in MHD patients should be paid more attention, and detection of HCV RNA by PCR from PBMCs or liver biopsy is necessary for MHD patients with unexplainable elevated serum ALT or liver cirrhosis. Currently, ST-IFN $\alpha$  and PEG-IFN $\alpha$  monotherapies at a reduced dose are the main treatment strategies for MHD patients with active HCV replication, and the SVRs are up to 40% or so. The emphases of future study for the treatment of HCV infection in MHD patients include how to increase the SVR, how the genetic factors such as polymorphisms of *IL-28B* gene will affect the SVR, how to optimize the

treatment duration, how to conquer the side effects of IFN $\alpha$ , and whether IFN $\alpha$ -free treatments with two or three DAAs without RBV are effective and practical for HCV eradication in MHD patients<sup>[2]</sup>.

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