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Hepatitis C among Hemodialysis Patients: A Review on Epidemiologic, Diagnostic, and Therapeutic Features

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Hepatitis C virus (HCV) is a major public health problem and is the most common liver disease among hemodialysis (HD) patients. The seroprevalence of HCV infection among HD ranged from 1.9% to 80% in reports published since 1999. The main risk factor for HCV acquisition in HD patients seems the length of time on HD. Phylogenetic analysis of HCV viral isolates has suggested nosocomial patient-to-patient transmission of HCV infection among HD patients. Lack of strict adherence to universal precautions by staff and sharing of articles such as multidose drugs might be the main mode of nosocomial HCV spread among HD patients. Currently, there are several dilemmas on the management of these patients: should HCV-RNA testing be included in the routine screening of HD population for HCV infection?; does periodic serum alanine aminotransferase testing have a role in screening HD patients for HCV infection?; can dialysis really 'save' the liver of HCV-infected HD patients?; should HCV-infected subjects be isolated and dialyzed by segregated machines?; is there any difference in treating HD and non-HD HCV-infected subjects? This article gathers the present evidence to address these issues and to demonstrate the current worldwide magnitude of HCV in HD population.

Keywords: **Hepatitis C Virus, Hemodialysis, Genotype**

Introduction

Hepatitis C virus (HCV), infecting about 170 million persons worldwide, is a major public health problem [(1)]. An estimated 5-20% of HCV-infected patients have or will develop cirrhosis, 1-4% of whom will annually develop hepatocellular carcinoma. Well-known risk factors for HCV transmission include injection drug use, blood product transfusion, organ transplantation, chronic hemodialysis (HD), occupational exposure among health care workers, unprotected sexual contact, and vertical transmission [(2, 3)].

The relation between HCV infection and kidney disorders is well recognized. Hepatitis C infection has been associated with essential mixed cryoglobulinemia that may lead to membranoproliferative glomerulonephritis [(4)]. On the other hand, patients with renal disease have been at increased risk of acquiring HCV because of prolonged vascular access as well as the potential for exposure to infected patients and contaminated

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equipment. Liver disease is a significant cause of morbidity and mortality in patients with end-stage renal disease (ESRD) treated by dialysis or transplantation and hepatitis C is the most common liver disease in renal dialysis patients [5]. This article is an update on the current worldwide magnitude of HCV in ESRD patients under HD, the diagnostic features, natural history, preventive measures, and current therapeutic advances in this particular population.

Historical Aspects and Virology

In 1974, Prince *et al.* [6] firstly reported non-A, non-B viral hepatitis. Fifteen years later, Choo *et al.* [7] discovered and described HCV. HCV is a small RNA virus that is included in the Flaviviridae family and has been recently classified as the sole member of the Hepacivirus genus [8]. HCV isolates are classified into 6 major genotypes and more than 50 subtypes [9].

HCV Global Epidemiologic Features in HD Population

The prevalence of HCV infection varies greatly among various populations of patients on HD from different geographic regions. In a review of so far published data in 1999, Wreghitt [10] described HCV prevalence among HD population ranging from 4% in the UK to 71% in Kuwait. Some investigators suggested a decline in HCV prevalence among HD patients in recent years, mostly attributable to strict adherence to universal precautions and with [11-17] or without [18, 19] observing isolation measures.

The reported anti-HCV positivity since 1999 ranged from 1.9% in the Slovenian 2001 annual report [20] to 80% in Senegal [21]. The HCV seroprevalence in HD population was 59% in Bosnia and Herzegovina [22], 6.8% in Belgium [11], 16.3% in France [23], 6.1% in Germany [24], 10-29% in Greece [25-27], 22.5-32.1% in Italy [28, 29], 75% in Moldavia [30], 3.4% in the Netherlands [31], 11% in Sweden [32], 7-23.3% in the USA [33-37], 20.5% in Libya [38], 80% in Senegal [21], 23.7% in Sudan [39], 19-41.7% in Tunisia [40, 41], 8.4-43.2% in Brazil [42, 43], 6.7% in Mexico [44], 59.3% in Peru [45], and 3.5% in Puerto Rico [46].

Table 1 describes the results of reports from Asian countries since 2000 on HCV seroprevalence among HD patients. The studies that prospectively followed HD patients for their HCV status presented an annual incidence rate of de novo HCV infection of 0.4% in France [47], 0.5% in Tunisia [47], 0.5% in the Netherlands [31], 0.83% in Italy [28], 1.38% [48] and 2.1% [49] in the USA, 0.33% [50], 2.59% [51], and 3.1% in Japan [52], 3.7% [53] and 5.5% in Brazil [54], and 6.2% in Greece [27].

Table 1. Reports on HCV seroprevalence among HD patients in Asian countries (2000-2007).

Study	Country	Year	HD centers enrolled	HCV seropositivity/ Patients (%)
Hosseini-Moghaddam *et al.* [64]	Iran	2006	45	155/1914 (8.1)
Amiri *et al.* [55]	Iran	2005	7	80/298 (24.8)
Alavian *et al.* [56]	Iran	2003	26	111/838 (13.2)
Ansar *et al.* [57]	Iran	2002	1	52/93 (55.9)
Furusyo *et al.* [51]	Japan	2001	1	100/269 (37.2)
Iwasaki *et al.* [93]	Japan	2000	1	34/142 (23.9)
Bdour *et al.* [58]	Jordan	2002	6	98/283 (34.6)
Hussein *et al.* [59]	Saudi Arabia	2007	1	34/180 (18.9)
Al-Shohaib *et al.* [60]	Saudi Arabia	2003	3	73/139 (52.5)
Othman *et al.* [62]	Syria	2001	2	68/139 (48.9)
Ocak *et al.* [65]	Turkey	2006	3	34/267 (12.7)
Harmankaya *et al.* [102]	Turkey	2002	1	8/168 (4.7)

Almost all recent surveys on the subject have congruently suggested the length of time on HD as a risk factor for HCV seropositivity [22-24, 27, 30, 31, 35, 37, 39, 42, 43, 52, 55-61]. Historically, the number of blood transfusions received was consistently reported in the literature to be associated with increased prevalence of HCV positive dialysis patients [10]. However, several recent reports could not recognize blood transfusion as an independent risk factor in HCV spread among HD subjects [23, 27, 31, 35, 39, 55, 60-63]. Indeed, erythropoietin prescription from the late 1980s onward reduced the HD patients' need to blood transfusion. Furthermore, introduction of sensitive tests for the screening of blood donors has markedly reduced the risk of HCV transmission through blood product transfusion. These two main reasons may explain recent findings on the lack of association between blood transfusion and HCV infection. History of organ transplantation [23, 27, 31, 55], older age [17, 39, 48], younger age [37], dialysis in multiple centers [29, 39, 43, 64], the HD unit [54], hepatitis B infection [23, 52], human immunodeficiency virus infection [48, 52], and diabetes mellitus [17, 65] were other factors that were suggested by some studies to be associated with HCV positivity.

Diagnostic Features

In non-HD population, HCV antibody testing by an enzyme-linked immunosorbent assay (ELISA) is generally used as a screening tool and recombinant immunoblot assay (RIBA) is considered as a confirmatory test because of its high specificity [66-68]. Viral-based testing is widely accepted as the gold standard in HCV detection. HCV-RNA testing is essential for confirmation of active HCV infection and for monitoring of antiviral therapy. Both qualitative and quantitative tests for HCV-RNA have been developed recently; although, the sensitivities of quantitative tests are lower than qualitative PCR assays [69-71].

Routine serological testing for HCV infection among HD patients is currently recommended [72, 73]. Current recommendations of Centers for Disease Control and Prevention (CDC) for HCV screening in HD patients include anti-HCV and serum alanine aminotransferase (ALT) testing on admission, monthly ALT, and semiannual anti-HCV [72, 73]. However, the cost-effectiveness of such an approach is under debate. Saab *et al.* [69] demonstrated that serological-based screening (anti-HCV testing) is less costly and more effective than biochemical-based screening (ALT plus anti-HCV testing) in the diagnosis of *de novo* HCV infection in HD subjects. In comparison to healthy individuals, serum aminotransferase levels are depressed in patients with chronic renal failure (CRF) not requiring dialysis and aspartate aminotransferase (AST) and ALT activity are even lower in dialysis than predialysis patients with CRF [74]. A newly elevated aminotransferase level was found to be neither sensitive nor positively predictive for chronic HCV infection [36]. However, Fabrizi *et al.* [49] found that ALT level rose into the abnormal range in newly HCV-infected HD patients and thus suggested the need to monitor chronic HD patients by serial ALT testing.

A dilemma exists on the value of serology since some investigators reported a high rate of false-negative serologic testing [25, 34]. However, the current literature reflects conflicting results in the topic since the frequency of HCV-RNA positive, anti-HCV negative HD patients ranged from 0-12% of all studied HD subjects from several recent reports [25, 26]. A study in India presented a high proportion of HCV-RNA positive, anti-HCV negative subjects (30/124; 24.2%) among the studied CRF population treated with HD or renal transplantation [75].

The immunocompromised state of HD patients is usually regarded as an explanation for their deficient antibody response to HCV virus [5, 73]. On the other hand, the reported figures for false-negative serology in some studies might be an overestimate because follow-up samples to detect possible antibody seroconversions were not obtained on these patients [73]. A relatively large study in 562 HD patients showed that the median numbers of days that the HCV-RNA assay detected HCV infection earlier than anti-HCV testing was 246 and 154 days for the second and third generation ELISA, respectively [27]. Considering the results of large studies showing only 5/1323 (0.38%) [23], 24/2777 (0.8%) [24], and 2/2286 (0.1%) [31] and some [26, 33, 42, 51, 76] without any false-negative serology, routine testing for HCV-RNA to diagnose HCV infection in the HD patients seems unjustified. Congruently, the latest CDC guideline does not recommend the use of reverse transcriptase polymerase chain reaction (RT-PCR) for HCV-RNA detection as the primary test for routine screening. Nonetheless, RT-PCR should still be considered as a confirmatory test when the patient tests positive for anti-HCV or if ALT levels are persistently abnormal in those who are anti-HCV negative in the absence of another etiology [73]. It is also noteworthy that a single negative anti-HCV test cannot rule out HCV infection in HD population because of the potential latency between infection and seroconversion as well as possible lower sensitivity of ELISA in HD patients as discussed above.

Recent advance in diagnosing early HCV infection is made by detecting the HCV core antigen (HCVcAg) that is present during the early stage of infection when anti-HCV seroconversion has not established. The strong point of this technique is the relative ease of performing ELISA for HCVcAg than assays for HCV-RNA based on gene technology. Additionally, HCVcAg testing permits the detection of an HCV infection about 1.5 months earlier than the HCV antibody screening tests and an average of only 2 days later than quantitative HCV-RNA detection in individual specimens [77]. In relation to the results obtained with the amplicor HCV monitor test, Fabrizi *et al.* [74] calculated the efficacy of HCVcAg ELISA to be 95.9%, with a sensitivity of 92.7%, a specificity of 97.4%, and positive and negative predictive values of 94.7% and 96.5%, respectively. In one study [40], there were no HCV-RNA positive patients who tested negative in both HCVcAg and anti-HCV antibody. HCVcAg ELISA would be useful in screening asymptomatic HCV carriers or *de novo* infection in HD patients. Combination of anti-HCV antibody and HCVcAg ELISA assays

would add the sensitivity of the screening program. Since the concentrations of HCV core Ag and HCV-RNA levels are significantly correlated [40, 74, 78], a further presented advantage of HCVcAg detection could be its role as a reliable marker of HCV replication in anti-HCV positive patients. Thus, it could help in the diagnosis of active HCV infection in anti-HCV positive therapy-naïve individuals, especially in poor-resource settings [40, 74].

Natural History of HCV in HD Patients

Evaluating the natural history of HCV infection among HD patients faces great controversy because the onset is rarely recognized; the course of HCV is usually indolent and extends over decades rather than years; and HD patients may actually die from various co-morbid conditions before the long-term consequences of HCV infection establishes. Severity of histological changes and HCV-RNA levels were not associated in several series [79-83] and ALT level alone could not predict the extent of the liver damage of HD patients with HCV viremia. HCV-infected HD patients may develop liver damage despite normal ALT levels [79, 84]. Therefore, liver biopsy is the only accurate means of assessing the severity of the hepatitis C infection. The frequency of bridging hepatic fibrosis or cirrhosis ranged from 5% to 32% in various series of HCV-infected HD patients [85].

Several studies reported the disease activity in HCV-infected HD patients to be mild to moderate and usually milder than non-HD subjects [80, 81, 86-88]. There are several explanations for this phenomenon including the altered immunologic state of the ESRD patients under HD, the relatively low HCV viral load in the HD population with HCV infection [89] probably secondary to the clearance of HCV RNA by the dialysate and/or the entrapment of HCV-RNA particles onto the membrane surface of dialyzers, marked and prolonged hepatocyte growth factor (HGF) release in HD compared to non-HD HCV-infected subjects [86] regarding the suggested acceleration in the liver regeneration by exogenous HGF administration in animal studies, and marked endogenous interferon (IFN) alpha increment after HD using both cellulosic and synthetic membranes [90] which can contribute to reduction in HCV viremia. The issue deserves further studies in larger series of patients before the actual role of dialysis in "saving" liver from hepatitis can be confirmed.

Several well-designed prospective studies aimed to address the natural history of HCV infection in HD population including the patients' survival. In an important multi-centric prospective study from Japan, Nakayama *et al.* [91] followed up 1470 HD patients (276 positive anti-HCV patients) from 16 dialysis centers for an average of 6 years. Mortality was significantly higher in the anti-HCV-positive than -negative subjects (33% versus 23%). Hepatocellular carcinoma (5.5% versus 0.0%) and liver cirrhosis (8.8% versus 0.4%) were significantly more frequent causes of death in anti-HCV-positive than -negative patients. They presented anti-HCV positivity as a risk factor for death with an adjusted relative risk of 1.57 (95% CI: 1.23-2.00). In another study based on a US national database of 13664 HD patients, Kalantar-Zadeh *et al.* [37] reported a significant 1.25 (95% CI: 1.12 to 1.39) mortality hazard ratio for HCV infection. Fabrizi *et al.* [92] performed a meta-analysis and introduced the summary estimate for relative risk of HCV infection on mortality in HD patients to be 1.57 (95% CI: 1.33-1.86), a rate close to that of Nakayama *et al.* [91] probably because they enrolled this large study in their meta-analysis. Since the frequency of hepatocellular carcinoma and liver cirrhosis as causes of death was significantly higher among anti-HCV-positive than -negative HD patients in all enrolled surveys, the investigators of this meta-analysis suggested that the increased mortality in anti-HCV-positive patients was at least partially related to chronic liver disease with its attendant complications.

HCV Nosocomial Transmission and Preventive Strategies

Nosocomial patient-to-patient transmission of HCV infection among HD patients is suggested by several investigators who performed phylogenetic analysis of HCV viral isolates [31, 32, 47, 48, 76, 93-98]. Lack of strict adherence to universal precautions by staff and sharing of articles such as multidose drugs might be the main mode of nosocomial HCV spread among HD patients [48, 93, 97-101]. Although some studies found that nosocomial spread of HCV declined when HCV infected patients were treated in dedicated HD units [12-17, 102, 103], other investigators could control nosocomial spread of HCV among HD patients by strict application of hygienic precautions without isolation of HCV-infected subjects or machine segregation [18, 100, 104]. Indeed, the presented efficacy of isolation might be simply due to the prevented sharing of articles between patients and might reflect a better implementation of other hygienic precautions.

Thereupon, in the absence of more convincing evidence, isolation of HCV-infected dialysis patients and use of dedicated machines are currently unjustified [73, 105]. Strict adherence to universal precautions seems to be enough to control disease spread in HD units. CDC recommends especial precautions to be observed in dialysis units including the wearing and changing of gloves and water-proof gowns between patients, systematic decontamination of the equipment, circuit, and surfaces after each patient treatment, no sharing of instruments (e.g., tourniquets) or medications (e.g., multiuse vials of heparin) among patients, and the assignment of patients to specific HD units [73].

Therapeutic Aspects

Treatment of HCV-infected non-uremic patients aims at slowing down the disease progression as well as preventing the hepatic and extrahepatic complications [3, 106]. Several outcome measures are used to evaluate response to treatment: sustained virologic response (SVR), the index of HCV eradication, is achieved when HCV-RNA is not detected in serum at the end of treatment and 6 months later by a sensitive test; end of treatment response (ETR) is the continued undetectable virus at completion of treatment; and early virologic response (EVR) is a 2-log drop or loss of HCV-RNA, 12 weeks into therapy.

Since 1991 when IFN-α was approved for use in the treatment of HCV infection, several therapeutic advances have been achieved. Thereafter, experiencing combination therapy with ribavirin and IFN was a major breakthrough that improved the SVR rate to as high as 43% [107]. The current optimal HCV treatment also includes IFN-based regimens together with antiviral therapy [3, 108]. However, introduction of a new formulation of IFN, namely pegylated IFN (peginterferon) (PEG-IFN) was another major advance in HCV treatment. Pegylation is the binding of the inert polyethylene glycol moiety to IFN molecule that decreases renal clearance despite retained biological activity and makes once-weekly administration of the drug possible [109]. Two different PEG-IFN formulations are available now, namely PEG-IFN α-2a (Pegasys) and PEG-IFN α-2b (Peg-Intron). PEG-IFN, when used in combination with ribavirin, conferred a relatively high SVR rate of 54% using PEG-IFN α-2b [110] and 56% using PEG-IFN α-2a [111]. Since SVR for genotype 2 or 3 infection was similar among patients treated for 24 versus 48 weeks, 24 weeks of treatment is usually considered sufficient to treat HCV infection with genotype 2 or 3 [111]. In contrast, the 48-week regimen should be used for those infected with HCV genotype 1 because HCV infection with this genotype was found to be the strongest negative predictor of response to PEG-IFN α and ribavirin [110, 112]. The goals of therapy in HCV-infected HD patients are not different from those of non-HD ones, as were described above. Importantly, the pre-transplant period in a HCV-infected HD patient should be considered as the 'golden' time for HCV treatment in this population. The main reason is that at present there is no safe and efficient therapy for HCV infection after kidney transplantation [113-115].

Similar to immunocompetent patients, IFN-based treatment for chronic hepatitis C is the mainstay therapy in HD population. Two meta-analyses showed that IFN monotherapy was even more effective in HD than non-uremic patients [116, 117], probably because of decreased IFN clearance rate in uremic patients [118]. Nonetheless, more adverse events in this population than non-uremic patients as well as marked estimated mean dropout rates of 17% [117] and 29.6% [116] were reported. Neurological (21%), flu-like (17%), and gastrointestinal (18%) symptoms were the most frequent side effects requiring interruption of treatment in a meta-analysis [117]. The gathered data in the current review shows that standard IFN α monotherapy in chronic HD patients have resulted in SVR rates ranged from 18.9% to 58.6% in different studies. The two meta-analyses estimated the overall mean of SVR rate to be 39% [117] and 33% [116]. Despite the initial promising SVR rates, not all HCV-positive HD patients should be treated with IFN because the risk-benefit ratio of administration of IFN is not well-known. It is reasonable to consider IFN therapy for all HCV-infected HD patients waiting for a kidney transplant because no post-transplant HCV relapse has occurred after successful pre-transplant IFN α therapy in several series [119-121]. IFN therapy for other HD patients should be justified according to their life expectancy, histologic severity of liver disease, and comorbidities. IFN α should be administered 3 million units, subcutaneously, trice weekly preferably for 48 weeks regardless of HCV genotype, because the 48-week regimen was associated with less relapses than the 24-week regimen [121, 122].

ESRD patients have reduced clearance of ribavirin, a drug with mainly renal metabolism. High ribavirin serum level poses a high risk of severe hemolytic anemia in ESRD patients, who are often

already anemic. Hence, ribavirin is contraindicated in HD subjects. However, Tan *et al.* [123] used combination IFN α-2b and low-dose ribavirin (200 mg/day) in five patients. Ribavirin was stopped permanently in two patients because of severe anemia. Safety and efficacy of this combination therapy should be studied in larger trials before any recommendation can be made.

In immunocompetent patients, as discussed above, the current optimal treatment for HCV infection includes the combination of PEG-IFN and ribavirin. A pharmacokinetic study suggested the absorption, distribution, and body clearance of PEG-IFN α-2a were not significantly different in subjects with normal renal function versus renal failure, non-dialysis-dependent patients [124]. Although this pharmacokinetic study suggests that the use of PEG-IFN in HD population might be possible with comparable safety to non-uremic patients, one relatively large clinical study, treating 78 HCV-infected HD subjects with PEG-IFN α-2a (135 μg weekly), reported a high dropout frequency of 32% while 83% of patients experienced adverse events. The SVR was 14.1% in this study [125]. A randomized trial on either 1.0 or 0.5 μg/kg of PEG-IFN α-2b initially enrolled 16 patients but was terminated because of adverse events. After modification to the study design, the trial continued, yet 7/16 (44%) required discontinuation of therapy. Only 2 subjects in the 1.0 μg/kg (22%) and none in the 0.5 μg/kg groups showed SVR. Whereas these investigators could not find better results of PEG-IFN therapy compared to other reports from administration of IFN regimen, they observed poor tolerance and substantial side effects of the used pegylated formulation [126]. Nevertheless, Kokoglu *et al.* [127] administered PEG-IFN α-2a at a dose of 135 μg weekly for 48 weeks in 12 HCV-infected HD patients and reported no dropouts despite frequent side effects (anemia in 75%, fatigue in 58%, thrombocytopenia in 33%, and leucopenia in 33%). SVR rate was surprisingly as high as 75% (9/12) in this study. In another trial, Sporea *et al.* [128] observed SVR in 3/10 (30%) patients with 4/10 discontinued therapy, yet not because of severe PEG-IFN side effects in any subject. Other small trials observed SVR in 2/3 (66.6%) [129], and 2/6 (33.3%) [130] treated HCV-infected HD patients. Another retrospective study found ETR in 3/7 (42.8%) HD patients treated with PEG-IFN α-2a while the follow-up was insufficient to present SVR rate [131].

The combination of PEG-IFN α-2b and low dose ribavirin (200-400 mg/day initially) was used by Bruchfeld *et al.* [132] who reported a SVR rate of 50% (3/6), 1 death from cardiac arrest and discontinuation of treatment in 2 patients because of side effects. Despite some encouraging results obtained, since the treatment with ribavirin in this study was concentration controlled and thereby individualized and such a practice might not be easily applicable in a clinical setting, the same combination therapy cannot be recommended.

Currently, there is a clear lack of strong evidence on using PEG-IFN in HCV-infected HD patients because most of the so far published data on the topic incorporated small number of patients, were divergent in results, were not controlled, and did not compare the risk-benefit ratio of pegylated versus standard IFN formulations. Well-designed, large clinical trials are clearly required to improve our knowledge and suggest the best practice.

Summary

The prevalence of HCV infection varies greatly among various populations of patients on HD from different geographic regions. The reports since 1999 gathered in this review presented a range for HCV seroprevalence among HD patients from 1.9% in Slovenia to 80% in Senegal.

Whereas blood transfusions seems not to be a current risk factor for HCV infection in HD population, the length of time on HD was repeatedly introduced in recent reports as the major risk factor. Although the value of serology in detecting HCV infection in HD subjects is recently questioned, regarding the results of large studies, routine testing for HCV-RNA to screen HD patients for HCV infection seems unjustified. Performing ELISA for HCVcAg is a new advance in the diagnosis of HCV infection in HD patients that with its ease and low-cost in comparison to molecular studies would add the sensitivity of the screening program, especially in poor-resource settings. While mortality was found to be higher in HCV-infected than non-infected HD patients, this increment is at least partially related to chronic liver disease with its attendant complications. Since biochemical and virological testing cannot predict the extent of liver damage in HCV-infected HD persons, liver biopsy is the only accurate means of assessing the severity of the HCV infection. Strict adherence to universal precautions seems to be enough to control disease spread in HD units and isolation of HCV-infected HD patients and use of dedicated machines are currently unjustified. IFN-α monotherapy, 3 million units, subcutaneously, trice weekly for 48 weeks for all genotypes, offers a SVR rates ranged from 19% to 59% and is the only regimen that can currently be recommended.

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