

Hepatitis C in Hemodialysis Patients: Current Global Magnitude, Natural History, Diagnostic Difficulties, and Preventive Measures

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Key Words

Hepatitis C virus, prevalence · Hemodialysis · Renal failure, diagnosis · Epidemiology, HCV · Nosocomial transmission, HCV · Natural history, HCV · Prevention, HCV

Abstract

Hepatitis C virus (HCV) infection is a significant cause of morbidity and mortality in hemodialysis (HD) patients. The reported prevalence of HCV among the HD population has varied greatly from 1.9 to 84.6% in different countries in recent years. The length of time on HD is generally believed to be associated with HCV acquisition in HD subjects. Nevertheless, several recent reports failed to recognize any significant role of blood transfusion. Although there are some considerations about the accuracy of serologic testing in detecting HCV in HD patients, the accumulated data in this review suggest the false-negativity rate to be not more than 1.66% (153/9,220). Therefore, substituting virologic for serologic testing in the routine diagnosis of HCV infection in HD patients seems unreasonable. Several phylogenetic analyses of viral isolates suggested nosocomial patient-to-patient transmission of HCV among HD patients for which the main potential source is believed to be contaminated hands and articles. However, isolation of HCV-infected HD patients and use of dedicated machines are currently unjustified while strict adherence to universal precautions seems to be

enough to control disease spread in HD units. The present article is an update on epidemiological and clinical features of HCV in HD population.

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Introduction

Hepatitis C virus (HCV) infection is a major public health problem, with an estimated global prevalence of 3% occurring in about 170 million infected persons worldwide [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 healthcare workers, unprotected sexual contact, and vertical transmission [2, 3].

The relation between HCV infection and kidney disorders is well recognized. On one hand, hepatitis C infection has been associated with essential mixed cryoglobulinemia that may lead to membranoproliferative glomerulonephritis [4], but on the other hand, patients with renal disease are at an increased risk of acquiring HCV because of prolonged vascular access and the potential for exposure to infected patients and contaminated equipment. Hepati-

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tis C is the most common liver disease in renal dialysis patients while liver disease itself is a significant cause of morbidity and mortality in patients with end-stage renal disease (ESRD) treated by dialysis or transplantation [5].

The present article is an update on the current worldwide magnitude, diagnostic features, natural history, and preventive measures of HCV in HD populations mostly based on the accumulated evidence from 1999 to early 2007.

Methods

We identified eligible studies using a search up to May 2007 in MEDLINE (since 1966) and EMBASE (since 1980). The searches were run using several predefined combinations of the following keywords and MESH terms or their equivalents: renal failure, end-stage renal disease, hemodialysis, dialysis, hepatitis C, virology, epidemiology, prevalence, frequency, incidence, de novo infection, risk factor, transmission, nosocomial infection, diagnosis, serology, enzyme-linked immunosorbent assay, antibody, recombinant immunoblot assay, HCV RNA, quantitative test, qualitative test, genotype, polymerase chain reaction (PCR), HCV core antigen, phylogenetic analysis, liver tests, liver biopsy, immunity, histopathology, natural history, prevention, universal precautions, machine segregation, and isolation. Two of us (M.R. and S.M.H.M.) independently reviewed the final list of titles and abstracts identified by the search strategy to judge their eligibility. Full publications were obtained when articles were thought to be potentially relevant. Bibliographies of the included studies and review papers were screened to identify other relevant studies. To be included, a report should be published in full, in the English language using any format, in a journal or the Cochrane library. For the purpose of data gathering on the disease prevalence in different countries, unpublished presentations (abstracts) were also included. Final decision on inclusion was made by consensus.

To review the current global magnitude of the disease, only studies that had been published since 1999 were included. Furthermore, selected keywords were used to search Google and Alta Vista for unpublished presentations on the prevalence of the disease since 1999. However, studies that presented HCV status in a HD population and were selected considering criteria for another research purpose were excluded. The average HCV seroprevalence among HD patients of a country was calculated by accumulating data from all retrieved studies (since 1999) from that country (total number of seropositive cases of different studies/total number of patients of the same studies \times 100). By calculating the average frequencies of HCV among HD patients of those countries with available data, a global map of seroprevalence was prepared.

Historical Perspectives and Virology

Non-A, non-B hepatitis was first reported by Prince et al. [6] in 1974. Fifteen years later, Choo et al. [7] discovered and described HCV. HCV is a small double-shelled

RNA virus that is included in the *Flaviviridae* family and has recently been classified as the sole member of the genus *Hepacivirus* [8]. HCV has structural (core, E1, and E2) and nonstructural (from NS2 to NS5) components and its isolates are classified into 6 major genotypes and more than 50 subtypes [9].

HCV Global Magnitude in HD Population

The prevalence of HCV infection varies greatly among patients on HD from different geographic regions. In a review of so far published data in 1999, Wreghitt [10] described a range from 4% in the UK to 71% in Kuwait for HCV prevalence among a HD population. Some investigators suggested a decline in HCV prevalence among HD patients in recent years mostly attributable to strict adherence to universal precautions, with [11–17] or even without [18, 19] observing isolation measures. Since 1999, the reported anti-HCV seropositivity ranged from 1.9% in the Slovenian 2001 annual report [20] to 84.6% in Saudi Arabia [21]. Tables 1–3 summarize the details of published reports since 1999 on HCV prevalence in Asian (table 1), US and European (table 2), and African and non-US American (table 3) HD patients. Reports of high (>40%) HCV seroprevalence in HD patients were from Brazil [73], Peru [76], Bosnia and Herzegovina [42], Senegal [63], Syria [38], Tunisia [66], Pakistan [33], Saudi Arabia [21], Iran [27], and Moldavia [51]. However, reports from these countries were not congruent. For example, in a single-center study from northern Iran in 2002, a high seroprevalence rate of 55.9% was reported [27]. Nonetheless, a recent report from 45 centers in Tehran, the capital city, reported a relatively low rate of 8.1% [24]. The same contrast exists in reports from several other countries (tables 1–3). Moreover, the HCV seroprevalence rates among the HD population do not seem to represent those of normal blood donors [78]. Therefore, one can assume that a lack of strict adherence to universal precautions in some centers is the main reason for presented extreme figures. Especially centers located in poor-resource regions may be vulnerable to poor implementation of hygienic precautions. Of note, it seems that most of the reported high HCV seroprevalence records were not obtained in multicenter studies and cannot accurately represent the HCV seroprevalence rate among HD patients of a country.

Figure 1 depicts a global map of HCV seroprevalence among HD patients based on the pooled data published since 1999 and gathered in this review. However, the rates

Table 1. Hepatitis C prevalence among Asian HD patients

Country	Author(s)	Ref. year	Number of HD centers	HCV seropositivity, +/total	EIA generation	HCV RNA, +/total tested	RNA detection method	HCV RNA (+), anti-HCV Ab (-), n/total
Bahrain	Almawi et al. [22]	2004	NA	NA	NA	6/81 (7.4%)	RT-nested-PCR	NA
India	Reddy et al. [23]	2006	1	15/111 (13.5%)	3rd	21/111 (18.9%)	RT-PCR	6/111 (5.4%)
Iran	Hosseini-Moghaddam et al. [24]	2006	45	155/1,914 (8.1%)	3rd	6/155 ^a	RT-PCR	NA
Iran	Amiri et al. [25]	2005	7	80/298 (24.8%)	2nd	NA	NA	NA
Iran	Alavian et al. [26]	2003	26	111/838 (13.2%)	3rd	NA	NA	NA
Iran	Ansari et al. [27]	2002	1	52/93 (55.9%)	2nd	NA	NA	NA
Japan	Kumagai et al. [28]	2005	75	NA	NA	242/1,882 (12.9%)	Nested-PCR	NA
Japan	Goodkin et al. [29]	2003	61	NA/2,169 (13.4%)	NA	NA	NA	NA
Japan	Furusyo et al. [30]	2001	1	100/269 (37.2%)	2nd	88/269 (32.7%)	RT-PCR	0/269 (0%)
Japan	Iwasaki et al. [31]	2000	1	34/142 (23.9%)	1st or 2nd	38/142 (26.8%)	RT-nested-PCR	8/142 (5.6%)
Jordan	Bdour [32]	2002	6	98/283 (34.6%)	3rd	30/98 ^a	RT-nested-PCR	NA
Pakistan	Gul et al. [33]	2003	1	34/50 (68.0%)	NA	NA	NA	NA
Saudi Arabia	Hussein et al. [34]	2007	1	34/180 (18.9%)	3rd	NA	RT-PCR	5/180 (2.8%)
Saudi Arabia	Almawi et al. [22]	2004	NA	NA	NA	5/34 (14.7%)	RT-nested-PCR	NA
Saudi Arabia	Shaheen et al. [35]	2003	4	295/408 (72.3%)	2nd	NA	NA	NA
Saudi Arabia	Saxena et al. [36]	2003	1	81/146 (41.3%)	2nd	NA	NA	NA
Saudi Arabia	Omar et al. [21]	2003	NA	126/149 (84.6%)	NA	NA	NA	NA
Saudi Arabia	Al-Shohaib et al. [37]	2003	3	73/139 (52.5%)	NA	NA	NA	NA
Syria	Othman et al. [38]	2001	2	68/139 (48.9%)	3rd	NA	NA	NA
Turkey	Ocak et al. [39]	2006	3	34/267 (12.7%)	2nd	27/34 ^a	RT-PCR	NA
Turkey	Olut et al. [40]	2005	9	83/437 (19.0%)	2nd	38/61 ^a	RT-PCR	NA
Turkey	Harmankaya et al. [41]	2002	1	8/168 (4.7%)	2nd or 3rd	NA	NA	NA

HD = Hemodialysis; HCV = hepatitis C virus; EIA = enzyme immunoassay; Ab = antibody; NA = data not available; RT = reverse transcriptase; PCR = polymerase chain reaction.

^a HCV RNA testing was done only in seropositive patients.

from most of the countries were obtained from accumulated available evidence; most of them were not vast multicenter studies with accurate sampling. Therefore, the suggested rates of this map may not accurately represent the whole country and thus should be cautiously interpreted.

Those 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 [79], 0.5% in Tunisia [65], 0.5% in the Netherlands [52], 0.83% in Italy [50], 1.38% [80] and 2.1% [81] in the USA, 0.33% [28], 2.59% [30], and 3.1% in Japan [82], 3.7% [72] and 5.5% [69] in Brazil, and 6.2% in Greece [46].

Risk Factors for HCV Transmission in Renal Failure Patients

Almost all recent surveys have congruently suggested the length of time on HD as a risk factor for HCV seropositivity [25–27, 32, 34, 37, 42–44, 46, 51, 52, 55, 58, 64, 67, 71, 73, 82]. A relatively large study in Brazil demonstrated that patients on HD for more than 3 years had a

13.6-fold greater risk of HCV positivity compared to subjects with less than 1 year HD treatment [73]. Historically, the number of blood transfusions received was consistently reported in the literature to be associated with an 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 [25, 35, 37, 38, 43, 46, 52, 53, 58, 64, 67]. Indeed, erythropoietin prescription from the late 1980s onwards reduced the HD patients' need for blood transfusion. Furthermore, the introduction of nucleic acid amplification testing for the screening of blood donors has markedly reduced the risk of HCV transmission through blood product transfusion. The current risk of transfusion-associated hepatitis C is approximately 1 in 2 million [83] or even lower [84]. A history of organ transplantation [25, 43, 46, 52], older age [64, 65, 85], younger age [55], dialysis in multiple centers [24, 48, 64, 73], hepatitis B infection [43, 82], human immunodeficiency virus infection [65, 81], and diabetes mellitus [36, 39] are other factors that have been suggested to be associated with HCV positivity by some investigators.

Table 2. Hepatitis C prevalence among US and European HD patients

Country	Author(s)	Ref. year	Number of HD centers	HCV seropositivity, +/total	EIA generation	HCV RNA, +/total tested	RNA detection method	HCV RNA (+), anti-HCV Ab (-), n/total
Bosnia and Herzegovina	Ahmetagic et al. [42]	2006	NA	99/168 (58.9%)	3rd	NA	NA	NA
Belgium	Jadoul et al. [11]	2004	15	116/1,710 (6.8%)	3rd	NA	NA	NA
France	Salama et al. [43]	2000	25	216/1,323 (16.3%)	3rd	157/1,323 (11.9%)	RT-PCR	5/1,323 (0.4%)
Germany	Hinrichsen et al. [44]	2002	43	171/2,786 (6.1%)	3rd	111/2,777 (4.0%)	RT-PCR	24/2,777 (0.8%)
Greece	Rigopoulou et al. [45]	2005	5	88/366 (24.0%)	3rd	116/366 (31.7%)	TMA	44/366 (12.0%)
Greece	Sypsa et al. [46]	2005	5	163/562 (29.0%)	2nd	110/163 ^a	NA	NA
Greece	Garinis et al. [47]	1999	NA	16/161 (9.9%)	3rd	16/161 (9.9%)	RT-PCR	0/161 (0%)
Italy	Petrosillo et al. [48]	2001	58	1,177/2,739 (32.1%)	3rd	NA	NA	NA
Italy	Campo et al. [49]	2000	1	26/78 (33.3%)	2nd	15/26 ^a	Nested-PCR	NA
Italy	Lombardi et al. [50]	1999	225	2,274/10,097 (22.5%)	NA	NA	NA	NA
Moldavia	Covic et al. [51]	1999	3	111/148 (75.0%)	3rd	NA	NA	NA
Netherlands	Schneeberger et al. [52]	2000	35	76/2,286 (3.3%)	2nd	59/2,286 (2.6%)	RT-PCR	2/2,286 (0.1%)
Slovenia	Buturovic-Ponikvar et al. [20]	2003	17	21/1,125 (1.9%)	NA	NA	NA	NA
Spain	Lopez-Alcorocho et al. [53]	2001	1	NA	NA	2/45 (4.4%)	Nested-PCR	NA
Sweden	Almroth et al. [54]	2002	1	4/37 (10.8%)	3rd	3/4 ^a	Nested-PCR	NA
USA	Kalantar-Zadeh et al. [55]	2007	580	1,590/13,664 (11.6%)	3rd	NA	NA	NA
USA	Kalantar-Zadeh et al. [56]	2005	8	29/314 (9.2%)	2nd	47/314 (15.0%)	TMA	22/314 (7.0%)
USA	Goodkin et al. [29]	2003	142	NA/3,856 (7.4%)	NA	NA	NA	NA
USA	Kelley et al. [57]	2002	1	22/258 (8.5%)	2nd	19/258 (7.4%)	RT-PCR	0/258 (0%)
USA	Sivapalasingam et al. [58]	2002	1	53/227 (23.3%)	2nd	NA	NA	NA
USA	Sullivan et al. [59]	2001	6	132/670 (19.7%)	2nd	115/132 ^a	RT-PCR	0/45 (0%)
USA	Saab et al. [60]	2001	39	172/2,440 (7.0%)	3rd	NA	NA	NA

HD = Hemodialysis; HCV = hepatitis C virus; EIA = enzyme immunoassay; Ab = antibody; NA = data not available; RT = reverse transcriptase; PCR = polymerase chain reaction; TMA = transcription-mediated amplification.

^a HCV RNA testing was done only in seropositive patients.

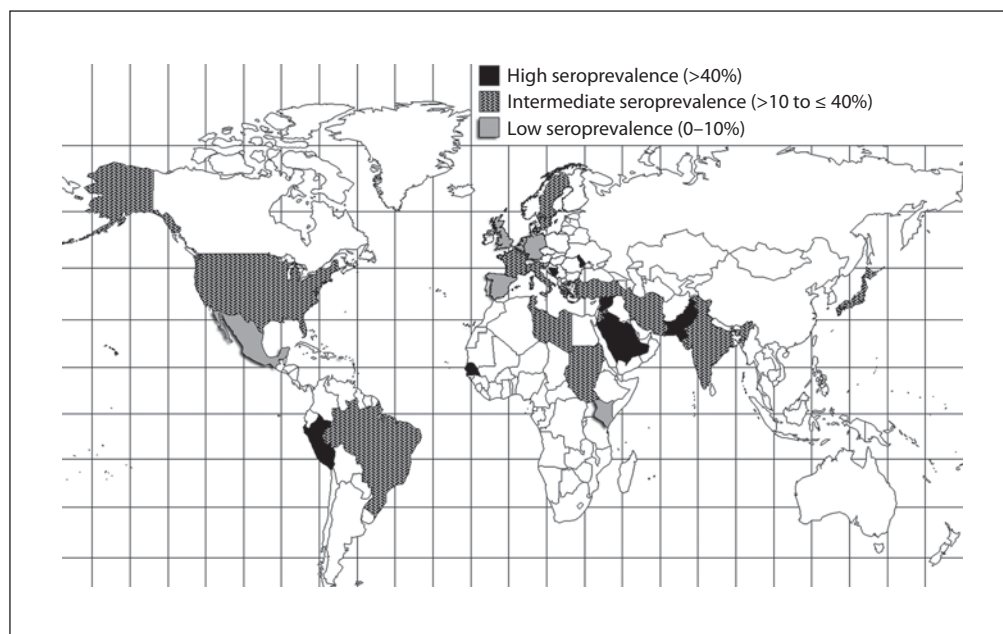


Fig. 1. A global map of hepatitis C seroprevalence among hemodialysis patients based on the pooled data published since 1999 (presented in tables 1–3). Data were not available for the unshaded countries.

Table 3. Hepatitis C prevalence among African and non-US American HD patients

Country	Author(s)	Ref. year	Number of HD centers	HCV seropositivity, +/total	EIA generation	HCV RNA, +/total tested	RNA detection method	HCV RNA (+), anti-HCV Ab (-) n/total
Kenya	Otedo et al. [61]	2003	1	5/100 (5.0%)	NA	NA	NA	NA
Libya	Daw et al. [62]	2002	NA	41/200 (20.5%)	NA	NA	NA	NA
Senegal	Diouf et al. [63]	2000	1	12/15 (80.0%)	NA	NA	NA	NA
Sudan	El-Amin et al. [64]	2007	2	56/236 (23.7%)	3rd	NA	NA	NA
Tunisia	Hmaied et al. [65]	2006	10	NA/395 (20%)	3rd	NA	NA	NA
Tunisia	Bouzgarrou et al. [66]	2005	8	73/175 (41.7%)	3rd	69/175 (39.4%)	RT-PCR	3/175 (1.7%)
Tunisia	Ben Othman et al. [67]	2004	7	90/276 (32.6%)	3rd	71/276 (25.7%)	RT-PCR	NA
Tunisia	Ayed et al. [68]	2003	109	828/4,340 (19.1%)	2nd or 3rd	599/828 ^a	RT-PCR	NA
Brazil	Santos et al. [69]	2007	6	73/443 (16.9%)	3rd	NA	NA	NA
Brazil	Silva et al. [70]	2006	10	130/1,243 (10.5%)	3rd	92/125 ^a	Nested-PCR	NA
Brazil	Albuquerque et al. [71]	2005	1	21/250 (8.4%)	3rd	19/250 (7.6%)	RT-nested-PCR	0/250 (0%)
Brazil	Moreira et al. [72]	2003	2	33/281 (11.7%)	3rd	29/281 (10.3%)	RT-nested-PCR	6/281 (2.1%)
Brazil	Carneiro et al. [73]	2001	8	185/428 (43.2%)	3rd	131/428 (30.6%)	Nested-PCR	25/428 (5.8%)
Brazil	Carvalho et al. [74]	1999	1	29/74 (39.2%)	3rd	NA	NA	NA
Mexico	Mendez-Sanchez et al. [75]	2004	1	10/149 (6.7%)	3rd	8/149 (5.4%)	RT-PCR	3/149 (2.0%)
Peru	Sanchez et al. [76]	2000	NA	131/221 (59.3%)	2nd	NA	NA	NA
Puerto Rico	Lopez-Navedo et al. [77]	1999	NA	13/376 (3.5%)	NA	6/12 ^a	NA	NA

HD = Hemodialysis; HCV = hepatitis C virus; EIA = enzyme immunoassay; Ab = antibody; NA = data not available; RT = reverse transcriptase; PCR = polymerase chain reaction.

^a HCV RNA testing was done only in seropositive patients.

Diagnostic Features

Diagnosis in Non-HD Populations

In non-HD populations, HCV antibody testing is generally used for screening, and recombinant immunoblot assay is considered a confirmatory test because of its high specificity [86, 87]. Nonetheless, based on a guideline from the Centers for Disease Control and Prevention (CDC), the necessity for confirmatory tests can be limited to patients with low signal-to-cutoff ratios rather than all with positive ELISA results [88]. 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 antiviral therapy. Both qualitative and quantitative tests for HCV RNA have recently been developed although the sensitivities of quantitative tests are lower than the qualitative PCR assays [89–91].

HCV Diagnosis in HD Population and Its Obstacles

Routine serological testing for HCV infection among HD patients is currently recommended [92, 93]. The rationale is based on the following evidence: (a) HCV infection has a silent and subclinical course; (b) liver biochemical tests are poor indicators of HCV infection among HD patients; (c) HCV infection is more prevalent among HD patients than in the general population; (d) nosocomial transmission of HCV is a major problem in HD units,

and (e) early identification of HCV-infected patients is essential [94]. The current CDC recommendations for HCV screening in HD patients include testing for anti-HCV and serum alanine aminotransferase (ALT) on admission, ALT every month, and anti-HCV semiannually [92, 93]. Although the cost-effectiveness of such an approach is questioned [89, 95], Fabrizi et al. [81] followed a group of 120 HCV-negative HD patients and found that the ALT level rose into the abnormal range in HD patients at the onset of their HCV infection, and thus they suggested the need to monitor chronic HD patients by serial ALT testing.

A dilemma exists on the value of serology because some investigators reported a high rate of false-negative serologic testing [45, 56]. The immunocompromised state of HD patients is usually regarded as an explanation for their deficient antibody response to HCV virus [5, 93]. Cellular immunity [96, 97] and systemic cytokine responses [98] altered in HD patients although a recent study showed that the limited virus-specific CD4+ T-cell proliferative response seen in HD patients is comparable to that of chronic HCV carriers without renal disease [99]. The frequency of HCV RNA-positive anti-HCV-negative HD patients ranged from 0 to 12% in all studied HD subjects in several recent reports gathered in this review (tables 1–3). A study from India presented a high proportion of HCV RNA-positive anti-HCV-negative

subjects (30/124; 24.2%) among the studied chronic renal failure (CRF) population treated with HD or renal transplantation [100]. The reasons for the divergence in reports may be due to many factors including the sensitivity of the tests used, the HCV genotypes in the infected patients, or the degree of immunological alterations in the population tested [57]. A relatively large study on 562 HD patients showed that the median number 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 generations of ELISA, respectively [46]. Another study calculated this lag to be 6.9 ± 4.1 months for the second generation of ELISA enrolling 22 patients [30]. Therefore, the reported figures for false-negative serology might be an overestimate because follow-up samples to detect possible seroconversions were not obtained [93]. Despite variation in the serological and virological methods used for HCV detection, the accumulated available data since 1999, presented in this review, show that among 9,220 HD patients tested both serologically and virologically, 153 (1.66%) subjects were HCV RNA-positive anti-HCV-negative (tables 1–3). Furthermore, large studies showed low false-negative rates of only 5/1,323 (0.38%) [43], 24/2,796 (0.86%) [44], and 2/2,286 (0.1%) [52] for serology. Other investigators reported a zero false-negative rate for serology [30, 47, 57, 59, 71]. Therefore, serological testing, preferably by the third generation of ELISA [47], seems to be enough for routine screening of HD patients. Congruently, the latest CDC guideline does not recommend HCV RNA detection as the primary test for routine screening. RT-PCR should still be considered a confirmatory test when the patient tests positive for anti-HCV or if ALT levels are persistently abnormal in patients who are anti-HCV-negative in the absence of another etiology [89]. Moreover, HCV-RNA should be considered as an important tool to diagnose HCV in HIV-infected patients with advanced immunosuppression (CD4 count of <100 cells/mm³) [101]. It is also noteworthy that a single negative anti-HCV test cannot rule out HCV infection in the HD population because of the potential latency between infection and seroconversion as well as the possible lower sensitivity of ELISA in HD patients as discussed above.

HCV Core Antigen: A New Diagnostic Feature

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 yet been 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 [102]. The efficacy of HCVcAg ELISA ranged from 81.9 [23] to 95.9% [103]. However, one should note that HCVcAg has low sensitivity for diagnosis of HCV infection in patients with low HCV viral loads (below $4.1 \log_{10}$ IU/ml) [66, 103]. In one study, there were no HCV RNA-positive patients who tested negative for both HCVcAg and anti-HCV antibody [66]. Thereupon, it is reasonable to assume that a combination of anti-HCV antibody and HCVcAg ELISA assays would add to the sensitivity of a screening program. Because the concentrations of HCVcAg and HCV RNA levels are significantly correlated [66, 103, 104], HCVcAg detection could also play a significant simple role as a reliable marker of HCV replication in anti-HCV-positive patients. HCVcAg testing could help in the diagnosis of active HCV infection in anti-HCV-positive therapy-naïve individuals, especially in poor-resource settings where virologic testing is not easily available or affordable [66, 103].

Natural History and Liver Histopathology in HCV-Infected 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 comorbid conditions before the long-term consequences of HCV infection have been established.

The severity of histological changes and HCV RNA levels were not associated in several series [105–109] while the ALT level alone cannot predict the extent of liver damage in HD patients with HCV viremia. HCV-infected HD patients may develop liver damage despite normal ALT levels [105, 110]. Several studies [105–107, 109, 111], with the exception of one [108], suggested a lack of relationship between biochemical and histological findings in HCV-infected HD patients, indicating that liver biopsy is the only accurate means for assessing the severity of HCV infection. The degree of fibrosis on liver biopsy is generally believed to be an appropriate indicator for the progression of chronic liver disease in patients with normal kidney function [112]. Besides, the severity of pre-transplant liver disease has been reported to be an important predictor of ad-

verse post-transplant outcome in ESRD patients [113, 114]. Thus, including liver biopsy in the process of evaluating the HCV-infected renal transplant candidates can be recommended. Nonetheless, as there is a reluctance to perform liver biopsy in ESRD patients because of the abnormal platelet function secondary to uremia, transjugular rather than percutaneous liver biopsy can be encouraged regarding its efficacy with fewer complications [115]. The safety and risk-benefit ratio of the technique has to be assessed before any strong recommendation can be made.

The frequency of bridging hepatic fibrosis or cirrhosis ranged from 5 to 32% in various series of HCV-infected HD patients [116]. Several studies reported the disease activity in HCV-infected HD patients to be mild to moderate and usually milder than non-HD patients [106, 107, 117–119]. There are several explanations for less liver damage in HD than non-HD HCV-infected patients, including: (a) the altered immunologic state of the patients on HD; (b) a relatively low HCV viral load in the HD population with HCV infection [120] 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; (c) marked and prolonged hepatocyte growth factor release in HD compared to non-HD HCV-infected subjects [117] based on the suggested acceleration in liver regeneration by exogenous hepatocyte growth factor administration in animal studies, and (d) marked endogenous interferon- α increment after HD using both cellulosic and synthetic membranes [121], which may reduce HCV viremia.

Interestingly, liver damage was found to be less in dialysis than pre-dialysis CRF patients [105, 122]. Although the above-described mechanisms may contribute to the assumed 'preventive' role of HD in the hepatitis liver damage, the duration of infection but not the fibrosis progression rate (the ratio between fibrosis stage and duration of infection) was significantly higher in pre-dialysis than dialysis CRF patients in one series [122]. 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 the HD population, including the patient survival. In an important multicenter prospective study in Japan, Nakayama et al. [123] followed up 1,470 HD patients (276 [18.8%] anti-HCV-positive patients) from 16 dialysis centers for an average of 6 years: mortality was significantly higher in the anti-HCV-positive than negative HD subjects (33 vs. 23%); hepatocellular carcinoma (5.5 vs. 0.0%) and liver

cirrhosis (8.8 vs. 0.4%) were significantly more frequent causes of death in anti-HCV-positive than negative HD patients, and anti-HCV positivity was a risk factor for death with an adjusted relative risk of 1.57 (95% CI 1.23–2.00). Based on a US national database of 13,664 HD patients, Kalantar-Zadeh et al. [55] reported a significant mortality hazard ratio of 1.25 (95% CI 1.12–1.39) for HCV infection. The DOPPS study followed 16,720 HD patients in the USA, Europe, and Japan for 5 years and reported a significant relative risk of 1.17 for the association between anti-HCV positivity and mortality [29]. Fabrizi et al. [124] performed a meta-analysis of published data on the effect of HCV infection on mortality in HD patients. They incorporated three prospective [123, 125, 126] and one retrospective [127] studies with enough data on survival. Based on the pooling of study results, the presence of anti-HCV antibody was an independent and significant risk factor for death in patients on HD. The summary estimate for relative risk was 1.57 (95% CI 1.33–1.86). Because the frequencies of hepatocellular carcinoma and liver cirrhosis as causes of death were significantly higher among anti-HCV-positive than negative HD patients in all the enrolled surveys, the investigators of this meta-analysis suggested that the increased mortality in anti-HCV-positive HD patients was at least partially related to chronic liver disease with its attendant complications.

The course of HCV infection after kidney transplantation and the impact of HCV on renal allograft recipients were addressed in some studies. In one recent retrospective study, HCV was reactivated in about half (19/43) of the anti-HCV-positive recipients at a mean time of 20.8 ± 5.7 months after transplantation, although patient and graft survival were not affected by HCV reactivation during a follow-up period of about 5 years [128]. Two retrospective studies suggested significantly lower graft and patient survival in HCV-infected than uninfected renal allograft recipients only after and not before 10 years post-transplantation [113, 129]. In a 9-year prospective study, Mahmoud et al. [130] found that HCV infection per se has no adverse effect on graft and patient survival. However, HCV-infected renal allograft recipients with abnormal liver function had inferior survival rates. Several other studies [131–135], with the exception of one [136], with shorter than 10-year follow-up periods reported no adverse impact of HCV infection on graft and/or patient survival. The promising results of the aforementioned studies suggest that for many patients, the benefits of renal transplantation outweigh its potential risks imposed by immunosuppression. Whereas anti-HCV-positive status alone is not a contradiction for renal

transplantation, advanced liver disease at the time of transplantation probably is [113, 114, 130]. Therefore, as mentioned earlier, liver biopsy should be an important element in assessing the suitability of kidney transplantation for HCV-infected ESRD patients. Importantly, the pre-transplant period in an HCV-infected HD patient should be considered as the 'golden' time for HCV treatment because with the interferon (IFN)-induced rejection and graft loss, there is no safe and efficient therapy for HCV after renal transplantation at present [137–139]. Moreover, those HCV-infected subjects that underwent kidney transplantation after HCV RNA clearance have shown no subsequent relapse despite immunosuppression [140]. Similar to immunocompetent patients, IFN-based treatment for chronic hepatitis C is the mainstay therapy in the HD population. However, ribavirin should be avoided in ESRD patients because reduced renal clearance results in severe hemolysis. Interestingly, two meta-analyses showed that IFN monotherapy was even more effective in HD than non-uremic patients [141, 142] probably because of a decreased IFN clearance rate in uremic patients. Nonetheless, the presented acceptable response to IFN- α treatment in HCV-infected HD subjects has been at the cost of more adverse events in this population than normal kidney subjects resulting in marked mean estimated dropout rates of 17 [142] and 29.6% [141]. Neurological (21%), flu-like (17%), and gastrointestinal (18%) symptoms were the most frequent side effects requiring interruption of treatment in a meta-analysis [142].

Evidence of Nosocomial Transmission and Preventive Strategies

Several recent studies [31, 52, 54, 59, 65, 79, 143–150] and one large study [44] reported nosocomial patient-to-patient transmission of HCV infection among HD patients performing phylogenetic analysis of HCV viral isolates. Although the potential sources of nosocomial transmission could be dialyzer reuse, internal contamination of HD monitors, and contaminated hands and articles, the two former mechanisms are almost unlikely [92, 93, 151, 152]. 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 [31, 65, 147, 149, 150, 152–154]. Although some studies found that nosocomial spread of HCV declined when HCV-infected patients were treated in dedicated HD units [12–17, 41, 155], other investigators could control nosocomial spread of HCV among HD pa-

tients by strict application of hygienic precautions without isolation of HCV-infected subjects or machine segregation [56, 152, 156]. Indeed, the presented efficacy of segregation policy and use of dedicated units for HCV-infected patients might be simply due to the prevention of article sharing between patients and might reflect a better implementation of other hygienic precautions. Thus, in the absence of more convincing evidence, isolation of HCV-infected dialysis patients and use of dedicated machines are currently unjustified [93, 157] and strict adherence to universal precautions seems to be enough to control disease spread in HD units. Moreover, CDC recommends that special precautions are observed in dialysis units, including wearing and changing of gloves and water-proof gowns between patients, systematic decontamination of the equipment circuit and surfaces after each patient treatment, and no sharing of instruments (e.g., tourniquets) or medications (e.g., multiuse vials of heparin) among patients [93]. Although the isolation of HCV-infected patients was not recommended, CDC encourages routine testing for ALT and anti-HCV and ensuring that appropriate precautions are being properly and consistently used [93]. The applicability of these recommendations in practice needs to be evaluated.

Conclusions

HCV infection is more prevalent among HD patients in the developing countries. HCV infection prominently increases the burden of disease in the HD population. The longer the patient is on HD, the more susceptible he/she is to HCV acquisition. HD patients should be routinely screened for HCV infection, preferably using serological methods. Liver biopsy in the evaluation of the HCV-infected renal transplant candidates should be considered, for which transjugular access may impose fewer complications. Whereas anti-HCV-positive status alone is not a contradiction for kidney transplant, advanced liver disease at the time of transplantation probably is. Strict adherence to universal precautions without isolating HCV-infected dialysis patients seems to be enough to control disease spread in HD units.

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