Review Article

Viral hepatitis in hemodialysis: An update

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ABSTRACT

Hepatitis outbreaks in hemodialysis (HD) patients and staff were reported in the late 1960s, and a number of hepatotropic viruses transmitted by blood and other body fluids have been identified. Hepatitis B virus (HBV) was the first significant hepatotropic virus to be identified in HD centers. HBV infection has been effectively controlled by active vaccination, screening of blood donors, the use of erythropoietin and segregation of HBV carriers. Hepatitis delta virus is a defective virus that can only infect HBV-positive individuals. Hepatitis C virus (HCV) is the most significant cause of non-A, non-B hepatitis and is mainly transmitted by blood transfusion. The introduction in 1990 of routine screening of blood donors for HCV contributed significantly to the control of HCV transmission. An effective HCV vaccine remains an unsolved challenge; however, pegylation of interferon-alfa has made it possible to treat HCV-positive dialysis patients. Unexplained sporadic outbreaks of hepatitis by the mid-1990s prompted the discovery of hepatitis G virus, hepatitis GB virus C and the TT virus. The vigilant observation of guidelines on universal precaution and regular virologic testing are the cornerstones of the effective control of chronic hepatitis in the setting of HD. Major recent advances in the viral diagnosis technology and the development of new oral, direct-acting antiviral agents allow early diagnosis and better therapeutic response. The current update will review the recent developments, controversies and new treatment of viral hepatitis in HD patients.

Key words: DAAs, hemodialysis, hepatitis B, hepatitis C, occult HBV, viral hepatitis

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Access this article online

Website: www.intern-med.com

DOI: 10.1515/jtim-2015-0018

Quick Response Code:

INTRODUCTION

It is well known that patients undergoing dialysis treatment, and in particular hemodialysis (HD), are at increased risk for contracting viral infections. This is due to their underlying impaired cellular immunity, which increases their susceptibility to infection. In addition, the process of HD requires blood exposure to infectious materials through the extracorporeal circulation for a prolonged period. Moreover, HD patients may require blood transfusion, frequent hospitalizations and surgery, which increase opportunities for nosocomial infection exposure.[1] The most frequent viral infections encountered in HD units are hepatitis B (HBV), hepatitis C (HCV) and, to a lesser extent, human immunodeficiency virus infection (HIV).

After the identification of HCV in 1989 and HEV in 1990, there were still unexplained cases of posttransfusion and "community-acquired" hepatitis, implying that cryptogenic hepatitis and cirrhosis may be related to viruses other than hepatitis A, B, C, D or E. By the mid-1990s, between 3% and 4% of anti-HCV-negative patients on chronic HD had elevated serum aminotransferase levels with no apparent etiology.[2,3] In 1995-1996, Simons *et al.*[4] and Linnen *et al.*,[5] both from the United States, independently reported a group of putative agents that accounted for the unexplained non-A to non-E hepatitis. These viruses were named GB virus C (GBV-C) and hepatitis G virus (HGV). HGV was identified by molecular cloning with plasma from a patient originally identified by the CDC as having NANBH.[5] Nucleotide sequence and amino acid sequence alignment revealed homology between HGV and GBV-C of 86% and 95%, respectively; thus, it is likely that they represent different genotypes of the same virus.[6] The clinical significance

of GBV-C/HGV infection in humans remains to be established. Few data in patients on HD are available. After the identification of GBV-C/HGV in 1995-1996, it was thought that additional hepatotropic viruses might exist because GBV-C/HGV infection has not been consistently shown to induce liver disease.[7] In 1997, a novel virus associated with posttransfusion hepatitis was identified in three patients from Japan who developed serum aminotransferase elevation following transfusion and tested negative for all known hepatitis viruses.[8] The virus, referred to as TT virus (TTV) for the initials of the patient in whom it was originally isolated or mnemonically for "transfusion-transmitted virus," exhibited hepatotropism as its titers in serum correlated with the rise in hepatic transaminase levels of affected subjects. The epidemiology of TTV in the HD population is not well characterized. A relationship between TTV infection and hepatitis or liver disease has not been established. Hence, the exact clinical significance of TTV in the HD population remains to be determined.

In the current review, we will restrict our update to HBV and HCV only, and will discuss the most recent data of these viruses in HD.

HEPATITIS B VIRUS (HBV)

HBV infection is a substantial global health problem. It is estimated that more than two billion people worldwide have serological evidence of current or historical infection.[9] HBV is highly infectious compared with other blood-borne viruses: An untreated percutaneous exposure to an infected source carries a risk of seroconversion of up to 30%. By contrast, the risks for HCV and HIV are 1.8% and 0.31%, respectively.[10] Acute infection occasionally results in fulminant hepatitis, but more importantly can progress to a chronic state, where decompensation, cirrhosis and hepatocellular carcinoma (HCC) are all potential complications. HD, which requires access to the bloodstream, affords an opportunity for transmission of HBV between patients and between patients and staff. Viral hepatitis complicating HD has been recognized from the earliest days of this therapy. While the introduction of vaccination programs and stringent infection control measures have succeeded in limiting the spread of hepatitis infection within dialysis facilities, outbreaks continue to occur periodically and prevalence rates remain unacceptably high. As such, HBV infection remains an important issue in renal replacement therapy.

Epidemiology of HBV

Hepatitis B is a blood-borne virus. Modes of infection include perinatal and through percutaneous or mucosal exposure to infected blood or body fluids.[11] There are considered to be more than 350 million people worldwide with chronic hepatitis B (CHB) infection.[12] More than 75% of these live in the Asia-Pacific region, with high numbers also residing in Africa and the Amazon basin. In areas of high endemicity, the lifetime infection rate is above 50%, and more than 8% of the population are chronic carriers.[13] Infection in such regions is typically acquired in childhood, either horizontally from other children or perinatally from maternal carriers. By contrast, parenteral transmission is common in Australia, and fewer than 2% of the population are chronic HBV carriers. HCC is the sixth most common cancer worldwide, and half of all cases are caused by HBV.[14] HBV is the second most important carcinogen after cigarette smoke.

In dialysis units, both patient-to-patient and patient-to-staff transmission of the virus have been recognized since the 1960s. Before the advent of vaccination, some success in limiting the spread of HBV was achieved by dialyzing seropositive patients separately from those who were seronegative. This followed the publication in the UK of the Rosenheim Report in 1972,[15] which set out a code of practice for reducing transmission of hepatitis among dialysis patients. In 1977, guidelines were published in the USA to reduce HBV infection in dialysis units.[16] The incidence of new hepatitis B infections in US dialysis patients subsequently fell from 6.2% in 1974 to 1% by 1980.[17] Testing of a vaccine began in the 1970s, and this came into widespread clinical use from the early 1980s.[18,19] This further reduced the risk of HBV infection in the dialysis setting.

Nevertheless, although rates of new infection are now low,[20] hepatitis B continues to exist in dialysis populations. Prevalence rates tend to be dependent on baseline population rates. An analysis of data from the Dialysis Outcomes and Practice Patterns Study showed an HBV prevalence of 0-6.6% across dialysis facilities in Western Europe, Japan and the USA.[21] In contrast, a registry study of Asia-Pacific countries found that the prevalence of hepatitis B surface antigen (HBsAg) positivity ranged between 1.3% and 14.6%.[22] Reports from much smaller cohorts elsewhere have indicated HBsAg positivity rates of 13.3% in Turkey and 2.4-10% in Brazil.[23-25] In the middle East, the prevalence of HBV was reported as 11.8% in Saudi patients, 3.7% in Bahrainis[26] and 2.2% in our HD unit in the UAE (no published data)

In addition to being at increased risk of infection, it has been demonstrated that HD patients are more likely to become chronic carriers of HBV than members of the general population.[27]

Occult hepatitis B

Recently, with advanced HBV diagnostic tools, emerged the problem of occult HBV infection (OBI). OBI is defined

as the presence of HBV-DNA without detectable HBsAg with or without hepatitis B core antibody (anti-HBc) or hepatitis B surface antibody (anti-HBs). Sensitivity and specificity improvement of polymerase chain reaction (PCR) methods with a detection limit of <10 IU/mL for HBV-DNA led to the identification of an increasing number of individuals carrying HBV-DNA as the only marker of HBV infection.[28,29]

OBI harbors potential risk of HBV transmission through HD, blood transfusion and organ transplantation,[30] and causes the progression of liver fibrosis and the development of HCC. It may also become reactivated when an immunosuppressive status occurs.[31]

OBI is defined as persistent detectable HBV-DNA in the serum or liver while HBsAg is undetectable in patients with serological markers of previous infection (anti-HBc and/or anti-HBs positive) or in patients without serological markers (anti-HBc and/or anti-HBs negative). In general, about 20% of OBI individuals are negative for all serological markers and 80% are positive for serological markers of previous infection.[30]

It is reported that the prevalence of OBI is parallel with the prevalence of apparent HBV infection in that region.[32-38] For example, OBI prevalence varies between 7% and 19% among blood donors in endemic regions, where 70-90% of the population are exposed to HBV, whereas in Western countries (where the HBV exposure is about 5%), the frequency of OBI ranged between 0% and 9%.[38]

A number of explanations for the persistence of HBV-DNA in HBsAg-negative samples have been proposed, including integration of HBV-DNA into the host's chromosomes,[39] genetic variations in the S gene[40-42] and the presence of immune complexes in which HBsAg may be hidden.[43,44] Occult hepatitis B may also be due to the window period following acute HBV infection, poor laboratory detection of HBsAg due to low level of HBs antigenemia, underlying HCV or hepatitis delta virus co-infection, immunosuppression or other host factors.[32,45]

The clinical implications of occult HBV infection involve different clinical aspects. OBI harbors the potential risk of HBV transmission through HD, blood transfusion and organ transplantation. It can cause cryptogenic liver disease, acute exacerbation of CHB or even fulminant hepatitis, poor response to antiviral treatment and development of HCC.[46] In other words, OBI patients are at risk for progression of liver disease, transmitting infection to others or early death as a result of the complications of the disease.[28]

Occult HBV infection in HD patients

HD patients are at a high risk of acquiring parenterally transmitted infections, not only because of the large number of received blood transfusions, the invasive procedures that they undergo, low response to HBV vaccination and duration on dialysis but also because of their immunosuppressed state.[30] Some studies found that time on dialysis was significantly greater in anti-HBc positive than negative HD patients.[47] Other scholars found that HD duration was not significantly different in patients with and without occult HBV infection.[30,48,49]

HBV vaccination seems to go along with the emergence and/or selection of immune-escape HBV mutants that enable viral persistence in spite of adequate antibody titers. These HBsAg escape mutants harbor single or double point mutations that may significantly alter the immunological characteristics of HbsAg.[50]

There is evidence that the sera of 40% of high-risk groups such as HD patients had isolated anti-HBC as the only marker of HBV infection, which may contain HBV-DNA, and at least some of them are infected with surface mutants.[51] Variants of HBV surface antigen proteins may have a potential impact on immunization against this important infection and on public health.[41] The prevalence of OBI in renal dialysis patients ranges between 0% and 58% in published reports.[47,52-54]

In our experience, we have recently (2014) screened all our HD patients for hepatitis serology. The total number of (HD) patients screened was 270 and the total number of control healthy group subjects (blood donors) was 1422. Six (2.2%) HD patients were HBsAg positive and 3 (0.2%) ($P = 0.000$) subjects of the control were HbsAg positive. Sixty-six (25%) of the HD patients were HBsAg negative with HBcAb positivity compared with 35 (2.5%) of the control group ($P = 0.000$). HBV DNA was detected in one (1.5%) of the HD HBcAb positive patients compared with none in the control and other HD groups. HCVAb positivity was found in 26 (9.6%) of the HD patients and 2 (0.14%) of the control group ($P = 0.000$) subjects. Nine (35%) of the HCV positive patients had HBcAb positivity; none of them had HBV DNA detected (none published data). Dumaidi *et al.* in the West Bank, Palestine have reported a prevalence of 12.5% of OBI in HD patients, with 35% of them being HBcAb positve.[55] In Egypt, Abu Al Makarem *et al.* found an OBI prevalence of 4.1% among their HD patients, while 20% of them were HBcAb positive.[56]

In a study involving subjects from Turkey, OBI was found in 2.7% of HD patients. Isolated anti-HBc positivity was more frequent in patients with occult hepatitis B than in those without (40% vs. 5.5%). None of the patients with HCV had occult hepatitis B.[57] In another study in Turkey in 50 chronic HD patients with negative HbsAg and positive

anti-HCV, none of them revealed HBV-DNA in serum by the PCR method.[44]

Motta *et al*.[58] studied serum samples from 100 HBsAg-negative HD patients for the presence of HBV-DNA. HBV-DNA was detected in 15% of the samples. They did not find any significant differences in HCV status, sex, age, duration of dialysis, alanine aminotransferase (ALT) levels or HBV serological markers between patients with or without occult HBV infection.

In a study in Iranian HD patients with isolated anti-HBc, the HBV-DNA was detectable in 50% of these patients. This survey showed that occult HBV infection was common in HD patients with isolated anti-HBc, and detection of isolated anti-HBc could reflect unrecognized OBI in HD patients. The majority of these infections are associated with low viral loads.[30]

In an investigation on the prevalence of OBI in continuous ambulatory peritoneal dialysis (CAPD) and HD patients, 16.9% of HD patients and 9.8% of CAPD patients were HBV-DNA positive. Anti-HCV was negative and AST and ALT levels were normal in all of the HBV-DNA positive patients. They concluded that the prevalence of the occult HBV may be common in CAPD patients as in HD patients, and HCV positivity is not a contributing factor to occult HBV infection in dialysis patients.[59]

OBI and HCV infection

HCV infection suppresses the replication of HBV and also the expression of HBV surface proteins *in vitro* and *in vivo*.[60,61] Therefore, HbsAg synthesis may be downregulated by coinfection with HCV.[60,62] The presence of OBI in patients with chronic hepatitis C infection was frequently reported,[63-65] and suggested a coincidence for HBV and HCV infection and mentioned a possible role for OBI in the chronic HCV-related liver disease.[63]

Several studies have been conducted to assess the prevalence of OBI in HD patients with chronic HCV infection, and all reported dissimilar rates of HBV-DNA positivity, ranging from 0% to 36% in these patients.[48,49,54,66] On the other hand, although HCV is known to inhibit HBV replication and thus may lead to the absence of detectable HBsAg in serum, some studies did not show any association between HCV and OBI. Motta *et al*.[58] indicated that the prevalence of OBI is not associated with the presence of anti-HCV antibodies in HD patients, and their findings are in agreement with the Kanbay study.[48]

Prevention of HBV infection

Despite stringent measures, failures of infection control mechanisms leading to isolated outbreaks of HBV infection in HD centers were still reported in the 1980s and 1990s.[67] Further preventive strategies that have been developed over the past 25 years include the increased availability of disposable dialyzers, sophisticated machines with electronic fail-safe systems, the replacement of arteriovenous shunts with fistulae, durable synthetic grafts and cuffed indwelling venous catheters, the routine viral screening of blood donors and the launching of recombinant human erythropoietin in 1989 to substitute for or reduce the need for blood transfusions.[68] Guidelines on universal precautions had been initially recommended by the CDC in 1985 and updated in 1988.[68] These procedures are now standard practice and include hand-washing after touching blood or body fluid and the use of gowns and face shields when exposure is anticipated. Furthermore, two additional strategies represent important milestones in the prevention of HBV infection in the dialysis setting: Active vaccination and segregation of HBV carriers.

Hepatitis B vaccination

Hepatitis B vaccine: In the 1970s, Krugman observed that HBsAg was immunogenic and that anti-HBs antibodies were protective against hepatitis B.[69] A first-generation vaccine was subsequently developed, consisting of HBsAg extracted by plasmapheresis from HBV carriers and then inactivated.[70] This vaccine, manufactured by Merck, was approved by the Food and Drug Administration in 1981 and became widely available from July 1982. A similar vaccine was licensed at about the same time, produced by Institut Pasteur in France. Modern "second-generation" HBV vaccines are recombinant noninfectious subunit vaccines containing HbsAg.[71] These are produced by the yeast *Saccharomyces cerevisiae* using recombinant DNA technology. There are two such HBV vaccine formulations available, Engerix B and Recombivax HB.

A third-generation vaccine has been produced from a mammalian cell line, although it is not yet in widespread use. It contains the pre-S1 and pre-S2 antigens that are present on the viral envelope. These antigens are more immunogenic than the HBsAg present in second-generation vaccines.[72] In line with Krugman's earlier observations, efficacy studies have shown that at least 90% of subjects developing anti-HBs levels of 10 IU/L are protected from hepatitis B infection.[73] Safety data are comprehensive. A large prospective trial has shown the vaccine to be safe and well tolerated.[74]

Strategies to improve vaccination response: When the vaccine is used in immunocompetent individuals using a three-dose schedule, a 90-95% seroprotection rate is expected. Clearly, in vaccine recipients with renal failure, the rates are substantially lower. In an attempt to improve seroconversion rates, the following strategies were used:

1. Current recommendations state that dialysis patients should receive higher vaccine doses than individuals with normal renal function. As such, 40 μg of Recombivax HB at 0, 1 and 6 months or 40 μg of Engerix B at 0, 1, 2 and 6 months should be administered. The best reported response rates to these schedules are <85% achieving seroprotection.[75]
2. The likelihood of a seroconversion response to hepatitis B vaccine decreases as renal failure progresses. As a result, guidelines also recommended that patients with chronic kidney disease (CKD) be vaccinated as early as possible in the course of their renal disease.[76]
3. Use of vaccine adjuvants: The addition of granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-2 has not been consistently successful in improving response rates.[77,78] Alternatively, a more recent vaccine formulation (HBV-AS04) consisting of standard Engerix B, yeast-derived vaccine (YDV), with adjuvant 3-O-desacyl-40-monophosphoryl lipid A, has shown the ability to provide earlier and greater anti-HBs responses than the standard vaccine.[68] More importantly, a small follow-up study has shown that the rate of decline in seroprotectivity was slower for the HBV-AS04 vaccine.[79] As such, this is the most promising vaccine adjuvant to date. It was licensed for use in CKD patients in Europe in 2005.
4. Intradermal inoculation: Intradermal inoculation (repetitively every 2 weeks, 5 mg/dose) may elicit seroconversion in patients who failed conventional intramuscular regimens.[80,81] This newer regimen achieves a higher and almost complete seroconversion rate, although frequent boosters are necessary to maintain protective levels of anti-HBs. For these reasons, this regimen has not been widely adopted. The rationale for the superior efficacy of the intradermal vaccine stems from its immunogenic effect on epidermal Langerhans cells, which are less influenced by uremia than the antigen presenting celle (APC) of regional lymph nodes that the intramuscular vaccine has to depend upon.

Management of chronic HBV infection

The primary goal of treatment should be complete eradication of the virus. However, it is rarely achieved in real life due to the persistence of covalently closed circular DNA (ccc DNA), a replication intermediate of HBV, in the hepatic nuclei, which is difficult to be eradicated and is not targeted by the currently available anti-viral agents. Therefore, a pragmatic approach is to suppress HBV replication with anti-viral therapy in order to prevent the development of complications such as cirrhosis and HCC. In the event of advanced liver disease, liver transplantation should then be considered.[82] All the available therapies including interferon-a, nucleoside or nucleotide analogues are not ideal and each individual therapy is limited by its own efficacy, adverse effects, emergence of resistance and the cost of treatment. Studies have showed that satisfactory responses to current anti-viral therapies were observed only in patients with certain well-defined clinical characteristics; the decision to start is, therefore, relying on the demonstration of active viral replication (HBeAg and/or serum HBV DNA detectable by branched DNA or hybrid capture assays) and active liver disease (elevated serum ALT concentrations >1.5 times ULN and/or evidence of moderate/severe chronic hepatitis on liver biopsy).[83] Dialysis patients are used to having depressed baseline serum ALT levels, and their serum ALT levels could remain normal despite the presence of significant liver disease. The conventional cut-off value with serum ALT level >1.5 times ULN therefore might prove too high and not sensitive enough for the identification of HBV-infected dialysis patients with significant hepatic inflammation who otherwise warrant anti-viral treatment. As such, it has been suggested that if a dialysis patient with chronic HBV infection has otherwise unexplained elevation in serum ALT level persistently above 30 IU/L or 0.75 times ULN, or if the serum ALT level does not reach that level but there is clinical evidence of progressive liver disease, significant hepatic inflammation should be suspected and liver biopsy should be considered.[84]

Current treatment options for patients with CHB are interferons or antiviral therapy with nucleos(t)ide analogs (NAs) that target the viral polymerase.[85] The treatment of CHB in patients with CKD is based on nucleoside (lamivudine, telbivudine, entecavir) or nucleotide (adefovir, tenofovir) analogues (NAs). Entecavir and tenofovir represent the currently recommended first-line NAs for NA-naive CHB patients, while tenofovir is the NA of choice for CHB patients with resistance to nucleosides.[86] Table 1 and Figure 1 show the dose adjustment and the algorithm of use of NAs in CKD patients.[86]

HEPATITIS C (HCV)

HCV Epidemiology

Hepatitis C is a liver disease caused by the HCV, the virus that can cause both acute and chronic hepatitis infection

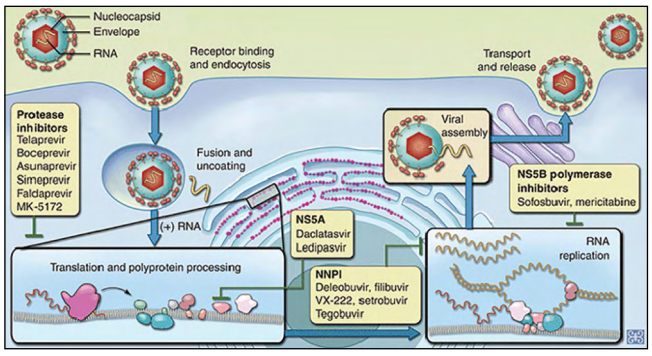

Figure 1: Mechanisms of action for direct-acting antivirals, currently in development. NNPI, nonnucleoside polymerase inhibitor (adapted from Reference 161)

Table 1: Dosage adjustments of nucleos(t)ide analogues according to creatinine clearance (CrCl) based on the approved special product characteristics (SPCs)

CrCl (mL/min)	Lamivudine	CrCl (mL/min)	Adefovir dipivoxil
≥50	100 mg daily	≥50	10 mg daily
30–49	100 mg loading dose – 50 mg daily	20–49	10 mg every 2nd day
15–29	100 mg loading dose – 25 mg daily	10–19	10 mg every 3rd day
5–14	35 mg loading dose – 15 mg daily	<10, no HD	–
5	<35 mg loading dose – 10 mg daily	HD[a]	10 mg once weekly
CrCl (mL/min)	**Entecavir**		
	NA-naive patients		**With lamivudine resistance[b]**
≥50	0.5 mg daily		1.0 mg daily
30–49	0.25 mg daily or 0.5 mg every 2nd day		0.5 mg daily
10–29	0.15 mg daily or 0.5 mg every 3rd day		0.3 mg daily or 0.5 mg every 2nd day
<10 or HD[a]	0.05 mg daily or 0.5 mg every 5th to 7th day		0.1 mg daily or 0.5 mg every 3rd day
CrCl (mL/min)	**Telbivudine**	**CrCl (mL/min)**	**Tenofovir DF**
≥50	600 mg daily	≥50	300 mg daily
30–49	400 mg daily or 600 mg every 2nd day	30–49	300 mg every 2nd day
<30, no HD	200 mg daily or 600 mg every 3rd day	10–29	300 mg every 3rd to 4th day
HD[a]	200 mg/24 h ή 600 mg/96 h	<10, no HD	–
		HD[a]	300 mg once weekly

HD, haemodialysis; DF, disoproxil fumarate. [a]In patients undergoing HD, all agents should be given once weekly after an HD session. [b]In patients with prior lamivudine resistance, entecavir should be given 2 h before or 2 h after food. Adapted from Reference 86

ranging in severity from a mild illness lasting a few weeks to a serious, lifelong illness. The HCV is a blood-borne virus and the most common modes of infection are through unsafe injection practices; inadequate sterilization of medical equipment in some health-care settings; and unscreened blood and blood products. One hundred and thirty to 150 million people globally have chronic hepatitis C infection.[87] A significant number of those who are chronically infected will develop liver cirrhosis or liver cancer. Three hundred fifty thousand to 500,000 people die each year from hepatitis C-related liver diseases.[87] Antiviral treatment is successful in 50-90% of persons treated, depending on the treatment used, and has also been shown to reduce the development of liver cancer and cirrhosis.[88] There is currently no vaccine for hepatitis C; however, research in this area is ongoing.[87]

In the Middle East and Africa, prevalence is highest in Egypt (18%) due to public health campaigns against schistosomiasis in the second half of the last century.[88] Prevalence is approximately 1-2% in Syria and Saudi Arabia.[89] In Europe, HCV prevalence is approximately 1-2% in most countries, but ranges from the lowest prevalence of ≤0.5% in northern countries to the highest (≥3%) in Romania and the rural areas of Greece, Italy and Russia.[90]

Similarly, the distribution of HCV genotypes also varies according to geographical area, and is noteworthy because it is one of the most important predictors of response to anti-viral therapy. HCV genotypes 1, 2 and 3 are widely distributed among the world's population, but the lesser known genotypes tend to have a more focused geography and are associated with certain methods of transmission according to regional medical practices and public health standards. HCV genotype 4 is common in Africa and the Middle East.[91-98] HCV genotype 5 is found almost exclusively in South Africa and expatriates from that area, while HCV genotype 6 is found mostly in Southeast Asia, Southern China and immigrants from those regions.[99]

HCV infection in HD

Global magnitude of the problem

The prevalence of HCV infection varies greatly among patients on HD from different geographic regions.[100] Wreghitt[101] 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[102-107] or even without[108,109] observing isolation measures.

Since 1999, the reported anti-HCV seropositivity ranged from 1.9% in the Slovenian 2001 annual report[110] to 84.6% in Saudi Arabia.[111] Reports of high (>40%) HCV seroprevalence in HD patients were from Saudi Arabia,[111,112] Syria,[113] Pakistan,[114] Iran,[115] Tunisia,[116] Senegal,[117] Moldavia,[118] Bosnia and Herzegovina,[119] Brazil[120] and Peru.[121]

However, reports from these countries were not congruent. Moreover, the HCV seroprevalence rates among the HD population do not seem to represent those of normal blood donors.[122] Therefore, one can assume that a lack of strict adherence to universal precautions in some centers is the

main reason for the 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.[123]

Risk factors of HCV infection in CKD patients

Several factors are known to be associated with increased risk of HCV infection. Duration on HD is well recognized as a predisposing factor for HCV infection.[112,115,119,120] 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 with subjects with less than 1 year of HD treatment.[120] 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.[101] However, several recent reports could not recognize blood transfusion as an independent risk factor in HCV spread among HD subjects.[112,116,123] Other risk factors include older age,[124,125] dialysis in multiple centers,[120,124,126] a history of organ transplantation,[127-129] hepatitis B infection,[128,130] HIV infection[125,131] and diabetes mellitus.[132,133]

HCV Diagnosis in HD Population

Routine serological testing for HCV infection among HD patients is currently recommended.[134,135] The rational 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.[136]

The current CDC recommendations for HCV screening in HD patients include testing for anti-HCV and serum ALT on admission, ALT every month and anti-HCV semiannually.[134,135] A dilemma exists on the value of serology because some investigators reported a high rate of false-negative serologic testing.[137,138]

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.[139,140] 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 9220 HD patients tested both serologically and virologically, 153 (1.66%) subjects were HCV RNA-positive anti-HCV-negative.[139,140] Furthermore, large studies showed low false-negative rates of only 5/1323 (0.38%),[128] 24/2796 (0.86%)[141] and 2/2286 (0.1%)[127] for serology. Other investigators reported a zero false-negative rate for serology.[142-144] Therefore, serological testing, preferably by the third generation of enzyme-linked immunosorbent assay (ELISA),[47] seems to be enough for routine screening of HD patients.

HCV Core Antigen

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. 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.[145] The efficacy of HCVcAg ELISA ranged from 81.9%[146] to 95.9%.[147] The concentrations of HCVc Ag and HCV RNA levels are significantly correlated.[147,148]

HCV prevention in HD

Nosocomial transmission of HCV in HD units is well established.[126,128,144,149-151] 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.[151-155]

The CDC recommends that special precautions should be 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's treatment and no sharing of instruments (e.g., tourniquets, stethoscope, blood pressure cuff) or medications (e.g., multi-use vials of heparin) among patients.[156] The guidelines of the "Kidney Disease: Improving Global Outcomes" (KDIGO) in 2008 recommend, as well, the adherence to the universal measures to prevent the HCV transmission in HD units.[157]

Although the strict adherence of universal precautions is considered the gold standard preventive tool in HD patients, the application of these universal precautions is not optimal in some circumstances, such as shortage of nursing staff,[155] high HCV +ve (prevalence >10%) and crowded units, and it is also due to inadequate infection control policies and procedures and/or a breakdown in infection control procedures.[158] These include inadequate isolation of infected patients, contamination of dialysis machines and/or improper sterilization and inadequately trained practicing staff on the value of hand washing, wearing sterile gowns, masks and gloves and proper disposal of contaminated linens and used disposables.[159]

Numerous measures have been taken to reduce the incidence and prevalence of viral hepatitis in HD units. However, isolation of dialysis patients and machines in separate rooms/halls, in order to prevent or reduce nosocomial transmission and sero-conversion of viral hepatitis in HD units, remains a controversial issue.[1]

Studies supporting isolation

In our personal experience in Medinah, Saudi Arabia, because of the high prevalence of HCV infection reaching 80% of our HD patients, we decided in 1996 to apply a complete isolation policy (separated rooms, machines and staff) of HCV-negative patients from HCV positive in addition to adherence to the universal precautions; in 2000, the prevalence of HCV-positive patients dropped to 40% and in 2006 this prevalence was 25%.[102] In our current experience in the UAE, the HCV isolation policy was applied in 1993, where the prevalence of HCV positivity was 40%, decreasing to 18.3% in 2002 and to 9.6% in 2014; we did not have any case of seroconversion during these 21 years (unpublished data).

Karkar *et al*. have reported a significant drop in the prevalence of HCV-positive patients from 57% to 29% after applying an isolation policy.[1] Mohamed *et al*. have reported similar results in decreasing the HCV-positive prevalence from 50% to 23% by the application of full isolation policy over a 5-year period from 2003 to 2008.[160] Hussein *et al*., by using a more advanced and sensitive diagnostic virologic test (HCV-RNA), reported that the prevalence of HCV positivity with complete isolation came down from 16.1% in 2005 to 6.5% in 2009, with zero seroconversion during this period.[161] Many other studies are supporting the isolation policy in reducing HCV transmission in HD patients.[162-166]

Problems with isolation

In spite of the tremendous value of HCV isolation application in controlling the epidemic of HCV infection in HD units, this policy has many drawbacks:

a. There is considerable difficulty in the recognition and isolation of HCV-infected patients in the early phase of the disease.[167]
b. There are many genotypes of HCV,[168] and the lack of cross-immunity between the different strains limits the usefulness of isolation. In addition, grouping of anti-HCV-positive patients together increases their exposure to various HCV strains and, in turn, might increase the risk of multiple infections.[169]
c. Unlike HBV, HCV is present in low concentrations in the serum and is probably destroyed within a few hours when the serum is stored at room temperature.[167] The risk of nosocomial transmission of HCV is thus expected to be lower than that of HBV. This is supported by the demonstration that the risk after accidental puncture with an infective needle is only 5-10% for transmission of HCV versus >30% for HBV.[170]
d. Isolation of anti-HCV-positive patients is cumbersome and, unlike HBV, requires four places for proper isolation, one each for: HBV and HCV positive, HBV positive and HCV negative, HBV negative and HCV positive and HBV and HCV negative patients. As a result of these problems and as an alternative to isolation, majority of HD units strictly adhere to "the universal infection control precautions." These precautions include cleaning and disinfecting instruments, machines and environmental surfaces that are routinely touched, avoiding sharing articles between patients, frequent hand washing and the systematic use of gloves.[171] However, the high prevalence of anti-HCV among HD patients in the developing countries calls for drastic measures to reduce this high prevalence. Therefore, it is advisable and more practical to isolate HD patients who are antiHCV negative in those units with a high prevalence of anti-HCV. Although the CDC recommends only strict adherence to the universal infection control precautions and does not recommend isolation, this may not be applicable in the developing countries wherein adherence to infection control precautions may not be feasible, as in the Western world, because of limited resources.[169]

Management of HCV infection

Treatment overview

Cumulative studies in the past two decades have shown that different genotypes respond differently to interferon (IFN)-based therapy, with genotypes 2 and 3 being the most easily cured and genotype 1 having the lowest cure rates with IFN-based regimens. With the approval of NS3/4 protease inhibitors (PIs) used in combination with pegylated IFN-alfa (PEG) and ribavirin (RBV; PEG+RBV), genotype 1b was found to have a higher barrier to resistance and thus was easier to cure than genotype 1a.[161] The genotypes have not been shown to differ in their progression to cirrhosis or in the development of liver cancer.[162]

The rate of cure of HCV was later found to be influenced by a genetic polymorphism near the interleukin 28B (IL28B) gene. Three polymorphisms exist: CC, TT and CT. Those patients with the CC genotype were found to have the greatest immune response and most favorable response to HCV treatment with PEG + RBV. TT genotype patients had the least favorable response and CT genotype patients had an intermediate response.[163]

Until 2011, the standard of care for the treatment of chronic HCV was PEG + RBV for 24-48 weeks, depending on HCV genotype. PEG and RBV represent nonspecific

antivirals, of which the mechanisms of action in treating HCV were poorly understood. Response to therapy is gauged by rapid virologic response (RVR), which is defined as an undetectable serum HCV RNA 4 weeks into treatment. When the HCV RNA remains undetectable from 4 weeks to 12 weeks of therapy, it is called an extended RVR (eRVR). Cure is defined by sustained virologic response (SVR), a persistently negative HCV RNA 12 (SVR12) or 24 weeks (SVR24) after the completion of therapy. Virologic relapse is the recurrence of quantifiable levels of HCV RNA after the completion of treatment.[164]

A greater understanding of the HCV has enabled efforts to improve the efficacy and tolerability of HCV treatment. Multiple direct-acting antivirals (DAAs) — medications targeted at specific processes within the HCV life cycle — have been and are being developed.

DAAs are molecules that target specific nonstructural proteins within the HCV, which results in disruption of viral replication and infection. There are four classes of DAAs, which are defined by their mechanism of action and by their therapeutic target. The four classes are PIs (NS3/4A inhibitors), NS5B nucleoside polymerase inhibitors (NPIs), NS5B nonnucleoside polymerase inhibitors (NNPIs) and NS5A inhibitors.[165] Members of these different groups of DAAs and their mechanism of action are illustrated in Figure 1.

Treatment of HCV in HD patients

At present, therapy for hepatitis C in patients with end-stage renal disease is controversial and should be considered only in patients waiting for renal transplantation, those with significant liver disease and minimal comorbid conditions that may affect survival and in patients with acute hepatitis C. The therapeutic regimen varies with the severity of the kidney disease. Persons with creatinine clearance of more than 60 mL/min can be treated like those patients without kidney disease. Ribavirin (RBV) is cleared by the kidneys; therefore, HD patients have been treated with peg-IFN-α mono-therapy.[166] Because peg-IFN-α 2a is cleared through the liver and peg-IFN-α2b primarily through the kidneys, [265] there could be a theoretical accumulation of peg-IFN-α 2b when used in HD, although HD does not appear to affect clearance.[167,168] Even though this has not been formally compared, no obvious differences are observed clinically. Most experts support the cautious use of peg-IFN-α, adjusting the dose to the level of renal dysfunction.

Although the current practice is to administer the full dose of peg-IFN-α, the recommended starting doses for this group are peg-IFN-α 2b at 1 μg /kg subcutaneously once weekly or peg-IFN-α 2a 135 μg subcutaneously once weekly. In the absence of RBV, SVR rates are substantially lower and careful patient selection and side-effect management are important. Most studies used a 6-month posttherapy SVR as the end point for successful therapy. Overall, 40% of HCV-treated patients had an SVR, including 31% for genotype 1, a rate greater than that reported for IFN monotherapy.[169]

However, the use of peg-IFN and RBV in dialysis patients is hampered by fairly common side-effects. Combination treatment with peg-IFN-α and RBV might be considered by experienced physicians and used with caution in those with creatinine clearance below 50 mL/min,[170] with individualized RBV dosing of 200-800 mg/day and titrating the dose based on creatinine clearance and hemoglobin level decline during the first few weeks of therapy. These patients may need substantial hematopoietic support, as suggested by few preliminary studies.

The use of new DAAs, telaprevir and boceprevir, which are HCV protease inhibitors (PIs), showed no significant impact of renal dysfunction when these medications were used in patients with end-stage renal disease,[171] suggesting that both drugs might be used to treat HCV infection in this setting.[172] A recent study that included 36 treatment-naive HCV genotype 1 HD patients showed that telaprevir-containing triple therapy had superior efficacy than PEG-IFNα/RBV dual therapy, but was accompanied with more frequent and severe anemia.[172] Generally speaking, in consideration of added severe side-effects and drug-drug interactions, triple or quadruple combinations based on IFNα/RBV therapy with one or two PIs are believed not very suitable for HD patients with HCV infection. On the other hand, several IFNα-free clinical studies combining two or three new direct antiviral agents without RBV are now under investigation in HCV-infected patients without renal impairment.[173] This will bring new hopes to increase SVR with decreased side-effects for HCV-infected HD patients as well.

CONCLUSION

Viral hepatitis continues to be a significant health problem in HD patients, in particular in the developing countries with limited resources. New diagnostic tools allow early diagnosis and better control of hepatitis in the dialysis units. Optimizing the HBV vaccination in predialysis care, the strict adherence to the universal precaution measures, segregation of HBV-positive patients in an isolated area and use of the modern therapies are the mainstay in controlling HBV infection in HD units. The issue is more complicated for HCV in the absence of specific vaccine, the nosocomial transmission of the virus, the controversy of isolation and the bad tolerance for the current available treatment. However, the recent development of DAA

medications for HCV, the hard work to produce an anti-HCV vaccine and the strong emphasis on the adherence to the universal infection control precautions will give the hope for the cure and the control of HCV infection in this population of patients.

Conflicts of Interest

None declared.

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How to cite this article: Bernieh B. Viral hepatitis in hemodialysis: An update. J Transl Intern Med 2015;3:93-105