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TOPIC HIGHLIGHT

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Factors affecting effectiveness of vaccination against hepatitis B virus in hemodialysis patients

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Core tip: The prevalence of hepatitis B virus (HBV) infection among the hemodialysis (HD) patients is still high. Although vaccination against HBV has became a necessity in this population, the seroprotection achieved in HD patients remains relatively low. In this review patient, HD procedure and vaccine-associated factors that affect the efficacy of HBV vaccination are analyzed. The alternative routes of HBV vaccine administration as well as new and more immunogenic vaccine formulations are discussed with a detailed view of the protocols that increase HBV vaccination efficacy.

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Abstract

Hepatitis B virus (HBV) is a major global health problem. Despite the success of the general measures against blood transmitted infections in hemodialysis (HD) units, the prevalence of HBV infection among the HD patients is still high. Thus vaccination against HBV is indicating in this population. However, compared with the general population the seroprotection achieved in HD patients remains relatively low, at about 70%. In this review patient, HD procedure and vaccine-associated factors that affect the efficacy of HBV vaccination are analyzed. Also alternative routes of HBV vaccine administration as well as new and more immunogenic vaccine formulations are discussed. However, besides scientific progress, vigilance of HD physicians and staff regarding the general measures against the transmission of blood borne infections and the vaccination against HBV is also required for reducing the prevalence of this viral infection.

HEPATITIS B AMONG HEMODIALYSIS PATIENTS

It is estimated that approximately 350 million people are chronic hepatitis B virus (HBV) carriers worldwide[1]. Consequently, most hemodialysis (HD) units treat chronic HBV carriers. Certainly the prevalence of HBV in HD is depended on its prevalence in the general population. For example, in western countries the prevalence of HBV across HD units ranges between 0.6% and 6.6%[2], its prevalence is higher in the Asia-Pacific region and ranges between 1.3% and 14.6%[3], and in China the pooled prevalence is 11.9%[4].

In HD patients, the risk of HBV infection is higher than in the general population, since the HD procedure per se favors the spread of blood borne infections. Thus the usual precautions for blood transmitted infections should be strictly applied for preventing intra-unit HBV spread. Blood could be present even on surfaces that otherwise seem very clean with the naked eye[5]. Patients should be isolated and hemodialyzed in separate machines[6], since HBV is found in high titers and is potentially infectious for more than 7 d in the environment. In comparison, hepatitis C virus (HCV) is less infectious and survives for a shorter period of time, while human immunodeficiency virus (HIV) is far less infectious and cannot survive in natural environment[7-9]. HBV-DNA is detected in high-flux HD ultrafiltrate but its contagiousness is unknown[10,11]. The risk of infection after contaminated needle stick exposure is about 6% if the patient is HBeAg negative and about 30% if the patient is hepatitis B e antigen (HBeAg) positive[12]. The general measures for preventing HBV spread in HD units decreased the incidence of new HBV infections in United States from 6.2% in 1974 to 1% by 1980, before the widespread use of vaccination[13]. Although in HBV high prevalence areas, prophylaxis with nucleoside analogues in seronegative patients undergoing HD seems reasonable; in our opinion such a strategy could lead to the development of resistance to such medicines. For instance 15% of patients develop resistance to lamivudine after one year of treatment and 30% after two years due to mutation of RNA-dependent HBV DNA polymerase[14-16].

Besides the features of the HD procedure per se and the high virulence of the HBV virus, the spread of this infection among the HD patients is also favored by the known acquired immunity disturbances that characterize this population[17]. After the initial HBV infection, 60% of HD patients become chronic carriers, while the respective percentage in the general population is only 5%[18-20]. Both innate and adaptive immunity contribute to HBV clearance after an acute infection[21,22]. Since both arms of the immune system are disturbed in HD patients[17,23], it is not surprising that there is a higher possibility to become chronic carriers after an initial HBV infection. For instance, the role of CD8+ T-cells in HBV clearance has been confirmed[24]. It is known that this T-cell subset is decreased both in number and in function in HD population[17,23]. The increased probability of chronic infection in the HD population enhances the pool of HBV carriers in HD units. Fortunately, HBV carriage does not significantly affect prognosis of HD patients. Although 30% of HBV carriers develop histologically confirmed chronic hepatitis, only 5% die from liver disease[25,26]. Obviously, the decreased survival in these patients mainly due to cardiovascular diseases and bacterial infections contribute to the above relative low percentage. However, because of the immunosuppressive treatment, life threatening exacerbations and increased rates of liver disease were reported in renal transplant recipients who were asymptomatic during HD[27-31].

Vaccination against HBV started from the early 1980s. The first generation of vaccines consisted of HBV surface antigen (HBsAg) extracted from the plasma of HBV carriers[32]. Nowadays the second generation of vaccines are widely used and contain HBsAg produced by recombinant DNA technology from the yeast Saccharomyces cerevisiae[33]. Recombinant DNA technology offered also a more immunogenic third generation vaccine containing the pre-S1 and pre-S2 antigens of the viral envelope[34]. However the last vaccine is not in widespread use. Unfortunately, due to the impaired immune function of HD patients[17], response rates determined as anti-HBs titers higher than 10 IU/L are lower in HD patients than in the general population. The vaccine is administered intramuscularly (IM) in the deltoid muscle. Despite the recommended administration of double vaccine doses (40 mcg) along with an extra dose (at 0, 1, 2 and 6 mo) in HD patients, the response rate is about 70%, while the response rate in the general population is higher than 90%[35]. At this point it should be noted that although the cut-off point of the 10 IU/L for anti-HBs titer is recommended as a target, it has been confirmed that long lasting immune memory persists after vaccination even when anti-HBs titer drops at even lower levels. This has been demonstrated experimentally regarding the persistence of memory T and B cells[36]. In additional observational clinical studies showed that HBV vaccination may offer protection even in those vaccinated subjects with undetectable anti-HBs antibodies[37,38]. However, there are no available data for HD population.

Despite its lower efficacy than in the general population, vaccination against HBV is recommended for all seronegative HD patients since vaccinated patients have 70% less possibility to become HBV carriers[35,39]. All doses of the vaccine should be repeated in patients who have not responded 1-2 mo after complete first vaccination series[13]. Nevertheless, in individuals with initial anti-HBs levels higher than 10 IU/L due to successful response to vaccination or natural infection, but with present anti-HBs levels lower than 10 IU/L, only one dose is recommended[40,41].

Generally HBV vaccination does not offer long term protection in HD patients. A study showed that 3 years after successful vaccination only 41% of HD patients had detectable anti-HBs levels[42]. Post-vaccination testing every 6-12 mo is recommended with revaccination if required. Antibody titers decreased faster in vaccinated patients than in those with natural acquired immunity. Also an antibody titer above 100 IU/L following primary vaccination enhances the possibility of maintaining protective levels of antibodies after 1 year[40-45].

Identifying the factors that affect the effectiveness of vaccination against HBV in HD patients is of great importance in order to enhance the response rate and

constrain the prevalence of HBV carriage in HD units.

PATIENT-ASSOCIATED FACTORS THAT AFFECT HBV VACCINE EFFICACY

Acquired immunity disturbances in HD patients are many and diverse. They are caused by uremia per se, co-morbidities, the HD procedure, chronic renal failure complications and therapeutic interventions for their treatment[17]. As a consequence these patients are susceptible to both bacterial and viral infections[46,47]. Current data support that acquired immunity disturbances in HD patients concern mainly the T-lymphocytes and the antigen presenting cells. The required for an effective immune response interaction between antigen presenting cells and T-lymphocytes is impaired in HD patients[48], while defects have been detected in T-lymphocytes as well[49]. Disturbances of antigen presenting cells and T-cells have been related to the decreased efficacy of HBV vaccination in HD patients[50-54]. Also various other factors have been incriminated for the decreased response rate to HBV vaccination in HD patients, such as the increased levels of the immunosuppressive enzyme indoleamine 2,3-dioxygenase[55], or the deficiency of the immunomodulatory vitamin D[56]. However, many of the patient-associated factors that are known to affect the immune response have not been evaluated in the context of the response to HBV vaccination and remain to be elucidated.

Age of the HD patient at the time of vaccination plays significant role. A meta-analysis of 17 clinical trials (1800 patients) showed a clear association between older age and impaired immune response to HBV vaccine. The pooled relative risk of response among older HD patients was 0.74. This was detected even when older individuals were defined as being as 50 years old. Additional doses of vaccine did not appear to have an impact on relative risk of response by age[57]. Because the mean age of HD patients is relatively high, age could be considered as a non-modifiable factor that constrains the efficacy of vaccination against HBV.

Co-morbidities are common among HD patients. Diabetes mellitus is the leading cause of end-stage renal disease in developed world[58]. A meta-analysis of 12 studies (1002 patients) showed a significant decrease in response rates among the diabetic *vs* nondiabetic HD patients (pooled OR = 0.52)[59]. Thus diabetes mellitus is another well recognized non-modifiable patient-associated factor that limits the efficacy of vaccination against HBV.

Malnutrition is common among HD patients and inflammation plays a significant role. The term malnutrition inflammation atherosclerosis syndrome is also in use[60]. A meta-analysis of 7 studies, involving 15152 patients with chronic kidney disease, most of them on HD, showed an increased risk (pooled RR = 1.63) of impaired serologic response to HBV vaccine among patients having poor nutritional status[61]. Although not evaluated yet, measures to constrain inflammation and/or to improve the nutritional status of malnourished HD patients may improve the efficacy of vaccination against HBV.

HCV carriage state does not affect immune response to HBV vaccine in HD patients[62]. Surprisingly in a study performed in HIV infected HD patients, the response rate to HBV vaccination was the same with a group of randomly selected non-HIV infected HD patients. Seventy percent of the HIV infected responders maintained protective titers 6 mo after vaccination[63].

Interestingly, it has been confirmed that the earlier the vaccination against HBV in the course of chronic kidney diseases, the greater the response rate. Consequently, vaccination should be performed as soon as possible in the course of chronic renal failure, before patient reaches HD, since response is associated with the degree of renal function[64].

DIALYSIS ASSOCIATED FACTORS THAT AFFECT HBV VACCINE EFFICACY

There are two available modes of dialysis for patients with end-stage renal disease, the HD and the peritoneal dialysis (PD). The risk for HBV infection for patients in peritoneal dialysis is far less since nowadays this method is performed at home. A meta-analysis of 14 clinical trials (1211 patients) showed that there is no significant link between dialysis mode and response to HBV vaccine[65]. However, the decay rate of anti-HBs titers in the PD patients is faster than that in the HD group[43]. Malnutrition and increased protein loss due to PD could be responsible for the last observation since the anti-HBV titer was inversely to serum albumin[43].

Pre-activation of antigen presenting cells and the consequent inflammation have been incriminated for impaired adaptive immunity in HD patients. Uremic toxins, use of less biocompatible dialysis membranes and contamination of the dialysate, all have been implicated[17]. High-flux HD is performed with more biocompatible dialyzers and also offers better removal of middle molecular weight uremic toxins. A study of 1480 HD patients showed that the rate of seroconversion to HBV vaccine was significantly higher in patients receiving HD with high-flux membranes than in patients receiving HD with low-flux membranes. Also anti-HBs antibody titers were higher with the high-flux membranes[66]. Hence it is likely that high-flux HD offers benefits regarding response to HBV vaccine. The role of other interventions, such as the use of ultra-pure dialysate, remains to be elucidated.

Many HD patients receive medications for the complications of chronic kidney disease. Recombinant Human erythropoietin (rHuEpo) is used for treating anemia and also has contributed significantly to decreased prevalence of HBV in HD units by limiting the need for blood transfusions. Initially, it was thought that rHuEpo improves the response to HBV vaccine[67]. This response was shown to be dose dependent but blunted if intravenous iron was administered during the vaccination period[68]. However, a meta-analysis of 11 studies, but with

a relatively small number of patients, failed to detect any benefit by rHuEpo treatment regarding the response to HBV vaccine[69]. Therefore the role of rHuEpo treatment in the responsiveness to HBV vaccine remains to be elucidated.

Vitamin D receptors activators are used for the treatment of secondary hyperparathyreodism. They also have known immunomodulatory properties and suppress inflammation[70-72]. Also vitamin D deficiency is associated with poor response to active hepatitis B immunization in patients with chronic kidney disease[56]. However, neither 1α,25-diydroxyvitamin-D3 nor paricalcitol administration have been proved advantageous regarding the response to HBV vaccine in HD patients[73,74].

VACCINE ASSOCIATED FACTORS THAT AFFECT HBV VACCINE EFFICACY

As noted many of the HD patient-associated factors that affect HBV vaccine efficacy are not modifiable. Also HD procedure-associated factors that could affect adaptive immunity in HD patients are too many[17] and concurrent modification of all of them is difficult, although it is likely that high-fllux HD improves the response to HBV vaccine. For these reasons efforts are underway for the identification of conditions that could enhance the immunogenicity of the current vaccine or for the development of new more immunogenic HBV vaccine formulations.

Currently it is recommended for the HD patients the use of the second generation HBV vaccine IM in deltoid muscle but in the double dose of 40 mcg and with an extra dose compared with the general population. This protocol improved seroconvertion rate, which however remains low[35]. Increasing the dose of the vaccine to 80 mcg provided conflicted results in dialysis patients[4,75]. The intradermal (ID) route of administration has been also tested. The rational is the abundance of dendritic antigen presenting cells at this site of injection. A meta-analysis of 14 clinical trials (718 patients) showed that IM HBV vaccination is less likely to achieve seroprotection than ID vaccination (pooled OR = 0.454). However, this difference does not persist during follow up (6-60 mo) after completing the vaccine schedule[76]. Intradermal vaccination could be useful in HD patients failed to respond after two series of the recommended IM vaccine schedule. A study in non-responders to HBV vaccine HD patients showed that administration of 10 mcg of the vaccine ID weekly for 8 wk was superior to administration of 40 mcg of the vaccine IM at weeks 1 and 8 regarding seroconvertion (79% *vs* 40%), with a trend for longer seroprotection in responders[77].

Immunostimulants have also been tried in order to enhance the efficacy of HBV vaccination in HD patients. A meta-analysis of 4 studies (328 patients) showed that oral administration of levamisole, a drug that increases natural killer lymphocytes and activated T-lymphocytes, at a dose of 80 to 120 mg for 4 to 6 mo significantly increases seroconvertion (pooled OR = 2.432)[78]. Granulocyte macrophage-colony stimulating factor (GM-CSF), which enhances antigen presenting cell function, used with HBV vaccine is also beneficial. A meta-analysis of 7 studies (187 patients) showed a significant increase in response rates among study (GM-CSF plus HBV vaccine) versus control (HBV vaccine alone) patients (pooled OR = 4.63)[79]. Thymopentin (TP5), a synthetic pentapeptide that imitates the biologic activity of thymopoietin and promotes T-lymphocyte maturation and responsiveness was also used. A meta-analysis of 11 studies (272 patients) showed that there was benefit only in the subgroup of trials with the higher TP5 dose. The number of patients in the last subgroup of trials was too small for safe conclusions. Additionally TP5 is expensive[80]. Recombinant interferon-alpha-2b (IFN-α2b) was also used since it promotes both cellular and humoral immune response. Although the initial seroprotection rate was higher in patient received HBV vaccine plus 3×10^6 U of IFN-α2b no difference was detected 6 mo after the last vaccine dose[81].

A more immunologically focused, easier at administration and cost effective solution could be the development of new vaccines with adjuvants other than the aluminum hydroxide, which is generally used. Recent advances in immunology revealed that early innate immune signals shape subsequent adaptive responses and this has led to the design and development of more specific and focused adjuvants[82]. Such a vaccine is the HB-AS04, which has been licensed in Europe from 2005 for active immunization against HBV in patients with renal failure. HB-AS04 contains 20 mcg of recombinant HBsAg formulated with aluminum phosphate and monophosphoryl lipid (MPL), a purified, detoxified derivative of the lypopolysacharide of the bacterial wall of Salmonella minnesota[83]. Thus this vaccine is able to trigger the Toll-like receptor 4 (TLR4) of antigen presenting cells shaping a more effective subsequent adaptive immune response[84]. Compared to the four double dose schedule of the recombinant vaccine in patients with chronic renal failure, the HBV-AS04 vaccine was found to provide faster and higher initial response rates (78% *vs* 51%), which also lasts more. During the 42 mo of follow up fewer patients primed with HB-AS04 needed a booster dose (16.7% *vs* 42.9%)[85,86]. HB-AS02 vaccine does not contain aluminum. It is oil in water emulsion containing recombinant HBsAg (20 mcg) with MPL and QS1, a purified immunostimulant derived from the bark of South American Quillaja saponaria tree. Compared to the four doses of HB-AS04 vaccine, three doses at 0, 1 and 6 mo of HB-AS02 vaccine induce a more rapid seroprotection and higher anti-HBs antibody concentration[87]. After 36 mo 89.5% of subjects in HB-AS02 group and 72.6% of those in HB-AS04 group had anti-HBs concentrations higher than 10 IU/L. Anti-HBs antibody concentration was higher than 100 IU/L in 82.9% and in 35.5% respectively[88]. It should be noted that the overall reactogenecity of the HB-S04 vaccine was higher than in the non adjuvanted vaccine, although incidences of general symptoms

Table 1 Factors that decrease hepatitis B virus vaccination efficacy in hemodialysis patients

Factors that decrease HBV vaccination efficacy in HD patients
Patient - associated factors
Acquired immunity disturbances[17,50-55]
Age[57]
Diabetes mellitus[59]
Malnutrition[61]
Stage of chronic kidney disease[64]
Dialysis - associated factors
Peritoneal dialysis[43,65]
Low-flux HD[66]
No treatment with rHuEpo[67,68]
Vitamin D deficiency[56]

HBV: Hepatitis B virus; HD: Hemodialysis.

Table 2 Protocols that increase hepatitis B virus vaccination efficacy in hemodialysis patients

Protocols that increase HBV vaccination efficacy in HD patients
Second generation vaccine administration
Double dose and an extra dose of the 2nd generation HBV vaccine[35]
Intradermal route of the 2nd generation HBV vaccine[76,77]
Immunostimulants
Levamisole[78]
Granulocyte macrophage colony stimulating factor[79]
Thymopentin[80]
Recombinant interferon-α2b[81]
New Vaccines
Adjuvanted vaccines (HB-AS04, HB-AS02)[85-88]
3rd generation vaccine (pre-S1 and pre-S2 antigens)[89]

HBV: Hepatitis B virus; HD: Hemodialysis.

were similar. The higher local reactogenecity is related to the higher incidence of pain. However, occurrence of grade 3 pain is very low and similar in both groups[85,86]. Regarding the adjuvanted HB-S02 vaccine, it was found to be more reactogenic than HB-S04 vaccine. On the other hand, local and systemic reactions are mild to moderate in intensity and transient in nature[87,88].

Alternatively, third generation vaccines produced with recombinant DNA technology in mammalian cells and containing the pre-S1 and pre-S2 antigens of the viral envelope seems to be more immunogenic. Regarding its side effects, 15% of the subjects experience a local predominantly mild or moderate pain. General symptoms, including chills, dizziness, headaches and diarrhea are mild and transient[34]. A small study showed that such a vaccine induced seroprotection in 25 of the 29 non-responders to the classical second generation vaccine HD patients[89].

Tables 1 and 2 summarize the available data about factors that decrease HBV vaccination efficacy and protocols that increase HBV vaccination efficacy in HD patients.

CONCLUSION

HBV vaccine, along with the general measures against the transmission of blood borne infections, contributed to the decrease of HBV prevalence in HD units. Various patient, HD procedure and vaccine-associated factors affect the efficacy of vaccination against HBV. A modifiable patient-associated factor is the stage of chronic kidney disease. It is recommended to vaccinate patients as early as possible in the course of chronic kidney disease in order to achieve higher response rates. High-flux HD seems also to be beneficial regarding the response to HBV vaccine. The four double doses IM administration of the classical second generation recombinant vaccine is recommended for all HD patients. According to the available literature in case of no response after two series of the above vaccine schedule, ID administration of the classical vaccine, of a third generation vaccine or of the adjuvanted HB-AS04 vaccine could be considered as a solution. In our opinion the most convenient strategy is the administration of the more modern vaccines, and especially of the adjuvanted HB-AS04, already available in many countries. However, it is imperative that all HD patients should be vaccinated against HBV. It is impressive that in 2002 only 56% of HD patients in United States received at least three doses of the HBV vaccine[90]. Furthermore, recently in UK most HD units did not offer routine vaccination against HBV despite the fact that 15% of them experienced at least one recent seroconversion for HBV[91]. Consequently besides scientific progress, vigilance of HD physicians and clinical personnel regarding the general measures against the transmission of blood borne infections and the vaccination against HBV is also required for reducing the prevalence of this viral infection.

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