World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v7.i24.2503

World J Hepatol 2015 October 28; 7(24): 2503-2509
ISSN 1948-5182 (online)

TOPIC HIGHLIGHT

2015 Advances in Hepatitis B virus

Recent advances in vaccination of non-responders to standard dose hepatitis B virus vaccine

Saqib Walayat, Zohair Ahmed, Daniel Martin, Srinivas Puli, Michael Cashman, Sonu Dhillon

Saqib Walayat, Daniel Martin, Srinivas Puli, Michael Cashman, Sonu Dhillon, Department of Gastroenterology and Hepatology, University of Illinois Peoria, Campus, OSF Saint Francis Medical Center, Peoria, IL 61637, United States

Zohair Ahmed, Department of Internal Medicine, University of Illinois Peoria Campus, OSF Saint Francis Medical Center, Peoria, IL 61637, United States

Author contributions: Walayat S, Ahmed Z and Martin D reviewed the literature, drafted the manuscript and approved the final version of the article to be published; Dhillon S reviewed the literature, made critical revisions related to the content of the article and approved the final version of the article to be published; Puli S and Cashman M edited the article to be published.

Conflict-of-interest statement: No conflicting interest related to the manuscript submitted for publication.

Correspondence to: Sonu Dhillon, MD, Department of Gastroenterology and Hepatology, University of Illinois Peoria, Campus, OSF Saint Francis Medical Center, NE Glen Oak Ave, Peoria, IL 61637, United States. sonu.dhillon@osfhealthcare.org
Telephone: +1-630-2153157
Fax: +1-410-7835884

Received: April 25, 2015
Peer-review started: April 27, 2015
First decision: June 2, 2015
Revised: June 17, 2015
Accepted: August 25, 2015
Article in press: September 28, 2015
Published online: October 28, 2015

Abstract

Hepatitis B virus (HBV) infection is a global health problem. It is estimated there are more than 2 billion individuals exposed to the virus and 250 million are chronically infected. Hepatitis B is the cause of more than 600000 annual deaths due to cirrhosis and hepatocellular carcinoma. An effective vaccine exists and preventative initiatives center around universal vaccination especially in those at highest risk. Effective vaccination algorithms have led to a significant decline in the development of new infections and its devastating consequences. The vaccine is administered intramuscularly in three doses, with 95% showing long lasting serologic immunity. An additional fourth dose or a repeated higher dose three course regimen is given to those that fail to show immunity. Despite these additional regimens, some remain vulnerable to hepatitis B and are deemed non-responders. Individuals with chronic disease states such as kidney disease, liver disease, diabetes mellitus, as well as those with a genetic predisposition, and those on immunomodulation therapy, have the highest likelihood of non-response. Various strategies have been developed to elicit an immune response in these individuals. These include increased vaccination dose, intradermal administration, alternative adjuvants, alternative routes of administration, co-administration with other vaccines, and other novel therapies. These alternative strategies can show improved response and lasting immunity. In summary, HBV vaccination is a major advance of modern medicine and all individuals at risk should be sought and vaccinated with subsequent adequate titers demonstrated.

Key words: Hepatitis B vaccine; Non-responders; Intradermal vaccine; Adjuvants; Oral vaccine

Core tip: Hepatitis B is a major global pandemic. Hepatitis B vaccine has been very effective in eradicating the disease from the world. Despite its efficacy, the standard vaccine fails to produce an immune response in 5% of immunocompetent individuals as well as individuals with chronic diseases and immunosuppressed states. Different modalities have been used to produce an immune response in these non-responders. These include double dosing, more frequent dosing, intradermal vaccine, adjuvant vaccines and recombinant vaccine with variable efficacies. Despite these novel techniques there are still no official guidelines available to vaccinate non-responders.

Walayat S, Ahmed Z, Martin D, Puli S, Cashman M, Dhillon S. Recent advances in vaccination of non-responders to standard dose hepatitis B virus vaccine. *World J Hepatol* 2015; 7(24): 2503-2509 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i24/2503.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i24.2503

INTRODUCTION

Hepatitis B is a major contributor to the burden of infectious disease worldwide. Over 2 billion people have been exposed to the virus, which has resulted in nearly 350 million chronic carriers with 4 million new cases diagnosed yearly worldwide[1]. According to the CDC in United States alone, there were almost 18760 new infections in 2012, contributing to 2.2 million chronic carriers of hepatitis B[2,3]. Hepatitis B is the cause for nearly half of all cirrhosis diagnosis, 80% of hepatocellular carcinomas and 1 million deaths yearly worldwide. This places hepatitis B virus (HBV) infection second only to tobacco as a major carcinogen[1,4,5].

HBV is up to a 100 times more transmissible than human immunodeficiency virus (HIV). This is largely secondary to the fact that it is abundantly found in body fluids, can survive up to seven days on fomites, and most infected carriers are asymptomatic and unaware of their disease[1,3]. As such, development of an effective vaccine and successful vaccination is a major achievement of modern medicine and has the potential to eradicate this infection from humankind.

HBV is an enveloped double stranded DNA virus belonging to the Hepadna family of viruses[6]. Humans are the only known natural host of this virus and the liver is the only organ where it is known to replicate[7]. In developing countries the vast majority of infections are transmitted vertically, of whom nearly 90% develop chronic hepatitis[3,8]. The principle mode of transmission in adults is *via* intravenous (IV) drug use and sexual contact and the vast majority of these cases will clear the virus spontaneously with few if any overt symptoms and only < 5% develop chronic hepatitis[8,9].

In the United States, IV drug use is the major mode of transmission. While the prevalence of chronic HBV infection (HBSAg +ve) is only about 0.5% in general population, it increases to approximately 50% among IV drug users who have been using for at least 1 year and over 90% if injecting drugs for more than 10 years[1,10,11].

Hepatitis B vaccine has been a major breakthrough in the global effort to eradicate the virus. The vaccine is made from the yeast saccharomyces cervisiae and is composed of physiochemically purified non-glycosylated molecule of HepBsAg which is adherent to aluminum hydroxide and preserved with thiamersol[12]. It is highly immunogenic, and dramatically reduces morbidity and mortality related to hepatitis B. For example, the introduction of screening in expectant mothers and subsequent vaccination programs has led to an 80% decline in the incidence of HBV infection between 1987-2004, from 10.7 to 2.1 per 100000[13]. Similarly, in Taiwan, where the prevalence of HBV was inordinately high; introduction of universal HBV in newborns has decreased the rate of hepatocellular cancer by 75%, with the incidence rate declining from 0.70 in 1981-1986 to 0.36 in 1990-1994/100000 children (ages 6-9) and a 68% decline in infant mortality from fulminant hepatitis[14]. The World Health Organization (WHO) now recommends universal vaccination of all neonates and adolescents as well as adults who have not been previously vaccinated[1].

PATHOPHYSIOLOGY

HBV vaccine consists of the highly immunogenic surface antigen (HepBsAg) protein. When administered, it interacts with antigen presenting cells present in the blood (HepBsAg specific B cells) where it is lysed and processed. This epitope coupled with an major histocompatibility complex (MHC)-Ⅱ molecule on the cell surface is then presented to TH-2 cells. The TH-2 cells, when activated, stimulate the differentiation of B-cells to plasma cells. These cells then release hepatitis B surface antibodies (HepBsAb) in large quantities as well as induce development of memory B and T cells. These memory cells then play an important role in long-term protection[15]. Immunogenicity is generally known to last approximately 10-31 years after a primary vaccination, with the duration and degree of immune response depending on the age, body mass index, sex, and smoking status at the time of initial inoculation series[16,17].

It is not entirely clear why the persistence of immunity, as defined by titers of HepBsAb greater than 10 mIU/mL, may last for several decades after a single round of vaccination. One possible explanation of constant antibody response over prolonged periods might be the persistence of antigen on the follicular dendritic cells which may keep up-regulating the B and T cells. Another possibility may be the initial antigen dose. The higher the dose administered initially, the greater the B-cell response. This increases the proportion of

memory B-cells, resulting in longer lasting immunity[18].

VACCINE ADMINISTRATION

The vaccine is typically administered as a 10 mg intramuscular (IM) dose in three doses at 0, 1, and 6 mo. Successful vaccination is documented by an antibody response of more than 10 mIU/mL and is achieved in about 95% of the immune-competent population. A fourth dose can be administered in immunocompromised or individuals at greater risk of exposure to the virus[8]. In high-risk patients the antibody response should be rechecked 1-3 mo after completion of the series and if the antibody titer is less than 10 mIU/mL then the series (40 mg) should be repeated again and the antibody titers should also be rechecked. This usually results in a response in fifty to sixty percent of the non-responder subgroup of patients[8,19]. Those who do not respond to the standard regimen as well as the additional booster or repeated course regimen are labeled as true non-responders[18]. While avoidance of high-risk behavior and prevention of exposure to blood and body fluids remains universally advocated for non-responders, these patients should be monitored for any acute changes in their liver enzymes and aggressively treated if infection is confirmed.

NON-RESPONDERS

Despite the high efficacy of the HBV vaccine, nearly 5% of immunocompetent individuals fail to respond to the primary HBV series. The reason for this non-response is not clear, however certain populations are at high risk including those with genetic predisposition, chronic disease, and immunomodulatory medications. Some interesting observations have been made in these populations. There may be a genetic predisposition for non-response. The human leukocyte antigen (HLA) along with MHC-Ⅱ plays an important role in presentation of the viral peptides to CD-4 T-helper cells and subjects who fail to respond may have a defect in the antigen presentation or the stimulation of T-helper cells. Studies have shown that patients who are homozygous for HLA DRB1*0301, HLA-B8, SC01, DR-3, HLAB44, FC-31, DR-7 have an increased predisposition to non-responsiveness[20,21]. Patients with advanced age, chronic diseases, immune defects or on immunomodulatory medications have a blunted immune response.

In one study of patients more than 60 years old, only 32 of 70 (45.7%) patients developed anti-HBs antibodies[22]. In another study of 106 patients more than 59 years old, only 60% of the subjects had an antibody titer greater than 10 mIU/mL at 7 mo post vaccination[23].

In patients with HIV, the seroconversion rate varies from 18%-72% depending on the immune status of the patient. In patients not receiving HAART therapy, the rate of immune response can vary from 30%-50% while in those receiving HAART the response increases to 60%-70% and is directly proportional to the CD-4 count and inversely proportional to the viral load[19,24,25].

Patients with chronic liver diseases also have a blunted response. In a study done by Mattos *et al*[26], patients with hepatitis C infection who were vaccinated showed only a 55% seroconversion rate. Out of these patients, only 37% had a robust response (Seroconversion was defined as an antibody level greater than 10 mIU/mL while robust response defined as antibody titers > 100 mIU/mL). Interestingly, patients with genotype 1 had a worse response then other genotypes. Additionally, immune response to vaccination was inversely related to advanced liver disease as measured by the MELD score[27,28].

In a study done by Agarwal *et al*[29], evaluating response rates to HBV vaccine in mild (creatinine 1.5 to 3.0 mg/dL), moderate (creatinine 3.0 to 6.0 mg/dL) and severe (creatinine > 6.0 mg/dL) chronic kidney disease, the seroconversion rates after 3 doses of 40 μg HBV vaccine were 87.5%, 66.6% and 35.7%; respectively. Rates improved significantly after a 4th dose was administered to 100%, 77% and 36.4%, respectively. Multiple studies have demonstrated patients with low glomerular filtration rate, higher creatinine (late stage kidney disease), diabetes, and old age are less likely to seroconvert[28].

STRATEGIES TO VACCINATE PATIENTS WHO DO NOT RESPOND TO STANDARD THERAPY

Increased dose

Considerable data exists on increased dose vaccination as well as accelerated frequency to elicit an immune response in high-risk individuals. Bonazzi *et al*[30] showed 68% response rate with double dosing (40 μg IM) at 0, 1 and 6 mo in pre-transplant patients. Forty-one percent of their patients had a robust response with an anti-HBs level > 1000 IU/mL. In another study, Wiedmann *et al*[31] showed a seroconversion rate of 80% in patients with chronic hepatitis C who had not responded to a primary vaccine just after giving a single (40 μg) high dose booster. Ramzan and colleagues also showed that higher dose and shorter interval (40 μg/mo for 3 mo) produced seroconversion in 72% of the patients with chronic liver disease as compared to 92% response in controls. Response was lower in cirrhotics as compared to non-cirrhotics (54% *vs* 80%) but after an additional booster dose of 80 mg, response increased to 74% and 88%, respectively[32].

INTRADERMAL ADMINISTRATION OF THE VACCINE

Multiple studies have exploited the fact that a large number of antigen presenting dendritic cells reside in the skin, specifically the dermis. These cells then activate the immunogenic cells in the corresponding lymph

node where they drain. This presentation of antigen into the dermis enhances the potential for activation of the immune cascade and development of protective antibodies[33-35].

Rahman *et al*[36] compared the efficacy of intradermal vaccine and showed that it resulted in a significantly higher immune response as compared to IM form. Both T and B cell response were higher with intradermal form as compared to IM form, suggesting that the intradermal presentation of the antigen to Langerhans cells in the dermis might result in trapping of the antigen in the skin resulting in a more robust and more sustained humoral and cell mediated response.

Forty-two chronic liver disease patients who had not responded to standard 40 mg three doses and booster doses were treated by Dhillon *et al*[37] using 40 mg intradermally (20 μg in each arm) for a maximum of three doses and seroconversion was seen in 29 (69%) of the 42 patients in their study with 15 (51%) of the patients developing a robust response.

In patients on hemodialysis who were primarily non responsive to standard dosing of hepatitis B vaccine, Barraclough *et al*[38] showed seroconversion rate of 79% in intradermal *vs* 40% in IM when a weekly 5 μg dose was injected intradermally for 8 wk as compared to 40 μg IM dose at 1 and 8 wk. The response in the intradermal group was more robust than IM group with titers being 239 IU/L *vs* 78 IU/L respectively[38].

No significant complications have been reported with intradermal vaccination in the studies mentioned above. Discoloration, itching, and nodule formation at the site of injection were the most commonly noted side effects and typically resolved spontaneously. The intradermal vaccine requires a certain skill set for proper inoculation in the dermis and its enhanced effectiveness. This coupled with general lack of knowledge regarding its efficacy has led to its limited adoption in non-responders[39].

IMPROVED IMMUNOGENICITY

Much research has focused on improving the immunogenicity by adding pre-S1, pre-S2 particle or nucleocapsids containing core antigen (HBcAg) to the S-protein to enhance efficacy of the vaccine. There are several reports citing an increase response in non-responders by using this technique[40-43]. In a study done by Zuckerman *et al*[43] on 100 non-responsive health care workers to standard vaccine who failed to seroconvert after 3 doses plus booster vaccine; a single dose of the triple S recombinant produced seroconversion in 69 patients. Similarly, seroconversion rates of 65% and 71% were reported after a 3rd and 4th dose of recombinant pre-S1 and pre-S2 containing hepatitis B vaccine; in 17 non-responders with underlying chronic renal failure[44].

USE OF ADJUVANTS

Currently, the HBV vaccine uses aluminum as an adjuvant to enhance immune response. Other more immunogenic compounds have been identified. 3-deacylatedmonophosphoryl lipid A (3D-MPL) combined with aluminum has shown to produce more immunogenicity then aluminum alone in unresponsive subjects, with immune response seen in up to 98% of the patients one month after receiving three doses[45]. Another polysaccharide adjuvant, Delta inulin: Advax™, has shown to enhance immunogenicity (strong CD-4 And CD-8 T cell response) with a robust response in pre-clinical trials on mice and pigs when compared with the traditional aluminum based vaccine[46].

OTHER NOVEL THERAPIES

Phase 3 clinical trials are underway for HEPLISAV-B™, a toll like receptor (TLR) agent in which HepBsAg is combined with immunostimulatory TLR 9 agonist to enhance response on a 2 dose regimen over 1 mo compared to the current 6 mo 3 dose regimen. It has shown earlier and higher seroconversion rates than the standard vaccine in those at risk for blunted or non-response. In 218 subjects that were divided in two groups (179 HEPLISAV B and 39 Energix B) the sero-protection rates at 12 and 52 wk post immunization for HEPLISAV B was 79% and 82% respectively as compared to 61% and 11% in the standard vaccine group[47].

ALTERNATIVE MECHANISM

Akbar and colleagues compared antibody production between HepBsAg and HepBcAg pulsed dendritic cells from spleen and liver of HBV infected transgenic mice. They showed while the surface antigen stimulated cells resulted in production of only surface antibodies, core antigen stimulated cells produced both core and surface antibodies with higher titers ($P < 0.05$). Thus, the use of core antigen is yet another fertile area of research in the development of the next generation of vaccines against HBV[48].

ROUTES OF ADMINISTRATION

While intramuscular and intradermal administration have been commonly used and extensively studied, other routes are also being actively sought.

NASAL VACCINE

A nasal based vaccine, Nasvac, which is a combination of HBV surface and core antigen has shown good efficacy in healthy as well as chronic HepB carriers possibly by stimulating naive human B cells[49]. In Phase 1 trials of NASVAC, a mixture of 50 mcg of HBsAg and HBcAg were administered *via* nasal spray to healthy adults (age 18-45) in five doses at 0, 7, 15, 30 and 60 d. It showed anti-HBc seroconversion in 100% of patients as early as day 30 with anti-HBs titers > 10 IU/L in 75% of the patients at day 90 with no major side effects[50].

ORAL VACCINE

A once daily Oral preparation, V-5 Immunitor™, has shown efficacy both in development of protective antibody as well as normalization of liver function tests in chronically infected individuals. When administered to ten patients with chronic hepatitis B, it resulted in normalization of liver enzymes in 100% of the patients (112.4 to 44.4 U/L for aspartate aminotransferase and 118.8 to 46.1 U/L for alanine aminotransferase) while half of the patients became HBsAg negative at the end of one month[51]. The preventative and therapeutic potential for such a compound would be a major breakthrough in the study of this infection.

COMBINATION VACCINES

Another technique employs both HepBcAg and HepBsAg to elicit humoral/cell mediated response which could be employed in controlling infection *via* CD-8 T cells as well as antibody production by stimulating memory B-cells. Vaccine development trials are underway which would stimulate both humoral and cellular immunity and help in controlling infection *via* CD-8 T cells as well as stimulating memory cells in producing antibodies. A novel vaccine consisting of HepBsAg and HepBcAg on a saponin-based ISCOMATRIX™ adjuvant has proven to be effective. In mice with chronic HBV infection it produces HBsAg specific and HBcAg specific CD-8 T-cells as well as stimulates plasma cells to produce high titers of antibodies against both antigens[52]. These early trials are encouraging but more clinical trials are needed in humans to document efficacy in the future. In another study, Cardell *et al*[53] gave three doses of IM combined hep A, hep B vaccine (TWIN-RIX) to 44 patients, who had been previously non-responsive to 4 doses of intradermal vaccine. Approximately 95% (42 patients) showed an immune titer > 10 mIU/mL, with 35 of these patients developing an antibody titer of > 100 mIU/mL. This suggests hepatitis A antigen may act as an adjuvant and enhance immune response globally.

In another study, hepatitis B vaccine was combined with HPV 16/18 and given to previously seronegative women. One month after the third dose, there was no difference in immune response in two groups (96.4% *vs* 96.9%). This confirms that co-administration of vaccine does not affect immunogenicity of either vaccine[54].

CONCLUSION

HBV is a global medical problem. While much morbidity and mortality is attributed to the disease, vaccination against this virus is both efficacious and readily available. Control of this infection *via* vaccination has markedly decreased the rates of new infection as well as hepatocellular cancer and chronic liver disease worldwide. Typically the vaccine shows a 95% response rate with durable and long-lasting immunity. Multiple novel methods have been developed to address those who do not respond to the regular vaccine schedule. Every effort should be made in high-risk populations (IV drug users, healthcare workers, patients with chronic diseases such as diabetes mellitus and chronic kidney disease) to vaccinate against this virus and the antibodies should be checked to ensure immunity. Both long-lasting immunity and therapeutic potential has been demonstrated with the various vaccines mentioned.

REFERENCES

1 **World Health Organization**. Hepatitis B. 2002. Available from: URL: http://apps.who.int/iris/handle/10665/67746
2 **Kowdley KV**, Wang CC, Welch S, Roberts H, Brosgart CL. Prevalence of chronic hepatitis B among foreign-born persons living in the United States by country of origin. *Hepatology* 2012; **56**: 422-433 [PMID: 22105832 DOI: 10.1002/hep.24804]
3 FAQs for Health Professionals: Hepatitis B. Available from: URL: http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm#overview
4 **Lavanchy D**. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepat* 2004; **11**: 97-107 [PMID: 14996343 DOI: 10.1046/j.1365-2893.2003.00487.x]
5 **Kane M**. Global programme for control of hepatitis B infection. *Vaccine* 1995; **13** Suppl 1: S47-S49 [PMID: 7571830 DOI: 10.1016/0264-410X(95)80050-N]
6 **Marion PL**, Robinson WS. Hepadna viruses: hepatitis B and related viruses. *Curr Top Microbiol Immunol* 1983; **105**: 99-121 [PMID: 6354611 DOI: 10.1007/9783-642-69159-1_2]
7 **Shepard CW**, Simard EP, Finelli L, Fiore AE, Bell BP. Hepatitis B virus infection: epidemiology and vaccination. *Epidemiol Rev* 2006; **28**: 112-125 [PMID: 16754644 DOI: 10.1093/epirev/mxj009]
8 **Poland GA**, Jacobson RM. Clinical practice: prevention of hepatitis B with the hepatitis B vaccine. *N Engl J Med* 2004; **351**: 2832-2838 [PMID: 15625334 DOI: 10.1056/NEJMcp041507]
9 **Hyams KC**. Risks of chronicity following acute hepatitis B virus infection: a review. *Clin Infect Dis* 1995; **20**: 992-1000 [PMID: 7795104 DOI: 10.1093/clinids/20.4.992]
10 **Levine OS**, Vlahov D, Koehler J, Cohn S, Spronk AM, Nelson KE. Seroepidemiology of hepatitis B virus in a population of injecting drug users. Association with drug injection patterns. *Am J Epidemiol* 1995; **142**: 331-341 [PMID: 7631637]
11 **McQuillan GM**, Coleman PJ, Kruszon-Moran D, Moyer LA, Lambert SB, Margolis HS. Prevalence of hepatitis B virus infection in the United States: the National Health and Nutrition Examination Surveys, 1976 through 1994. *Am J Public Health* 1999; **89**: 14-18 [PMID: 9987458]
12 **McAleer WJ**, Buynak EB, Maigetter RZ, Wampler DE, Miller WJ, Hilleman MR. Human hepatitis B vaccine from recombinant yeast. *Nature* 1984; **307**: 178-180 [PMID: 6318124]
13 **Kim WR**. Epidemiology of hepatitis B in the United States. *Hepatology* 2009; **49**: S28-S34 [PMID: 19399791 DOI: 10.1002/hep.22975]
14 **Chien YC**, Jan CF, Kuo HS, Chen CJ. Nationwide hepatitis B vaccination program in Taiwan: effectiveness in the 20 years after it was launched. *Epidemiol Rev* 2006; **28**: 126-135 [PMID: 16782778 DOI: 10.1093/epirev/mxj010]
15 **Vora KA**, Tumas-Brundage K, Manser T. Contrasting the in situ behavior of a memory B cell clone during primary and secondary immune responses. *J Immunol* 1999; **163**: 4315-4327 [PMID: 10510371]
16 **Bauer T**, Jilg W. Hepatitis B surface antigen-specific T and B cell memory in individuals who had lost protective antibodies after hepatitis B vaccination. *Vaccine* 2006; **24**: 572-577 [PMID: 16171909 DOI: 10.1016/j.vaccine.2005.08.058]
17 **Gara N**, Abdalla A, Rivera E, Zhao X, Werner JM, Liang TJ, Hoofnagle JH, Rehermann B, Ghany MG. Durability of antibody response against hepatitis B virus in healthcare workers vaccinated

as adults. *Clin Infect Dis* 2015; **60**: 505-513 [PMID: 25389254 DOI: 10.1093/cid/ciu867]
18 **Koff RS**. Immunogenicity of hepatitis B vaccines: implications of immune memory. *Vaccine* 2002; **20**: 3695-3701 [PMID: 12399197 DOI: 10.1016/S0264-410X(02)00405-X]
19 **Rubin LG**, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, Bousvaros A, Dhanireddy S, Sung L, Keyserling H, Kang I. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2014; **58**: e44-100 [PMID: 24311479 DOI: 10.1093/cid/cit684]
20 **Godkin A**, Davenport M, Hill AV. Molecular analysis of HLA class II associations with hepatitis B virus clearance and vaccine nonresponsiveness. *Hepatology* 2005; **41**: 1383-1390 [PMID: 15915462 DOI: 10.1002/hep.20716]
21 **Egea E**, Iglesias A, Salazar M, Morimoto C, Kruskall MS, Awdeh Z, Schlossman SF, Alper CA, Yunis EJ. The cellular basis for lack of antibody response to hepatitis B vaccine in humans. *J Exp Med* 1991; **173**: 531-538 [PMID: 1825504 DOI: 10.1084/jem.173.3.531]
22 **Denis F**, Mounier M, Hessel L, Michel JP, Gualde N, Dubois F, Barin F, Goudeau A. Hepatitis-B vaccination in the elderly. *J Infect Dis* 1984; **149**: 1019 [PMID: 6234369]
23 **de Rave S**, Heijtink RA, Bakker-Bendik M, Boot J, Schalm SW. Immunogenicity of standard and low dose vaccination using yeast-derived recombinant hepatitis B surface antigen in elderly volunteers. *Vaccine* 1994; **12**: 532-534 [PMID: 8036828 DOI: 10.1016/0264410X(94)90313-1]
24 **Overton ET**, Sungkanuparph S, Powderly WG, Seyfried W, Groger RK, Aberg JA. Undetectable plasma HIV RNA load predicts success after hepatitis B vaccination in HIV-infected persons. *Clin Infect Dis* 2005; **41**: 1045-1048 [PMID: 16142673 DOI: 10.1086/433180]
25 **Cruciani M**, Mengoli C, Serpelloni G, Lanza A, Gomma M, Nardi S, Rimondo C, Bricolo F, Consolaro S, Trevisan M, Bosco O. Serologic response to hepatitis B vaccine with high dose and increasing number of injections in HIV infected adult patients. *Vaccine* 2009; **27**: 17-22 [PMID: 18984022 DOI: 10.1016/j.vaccine.2008.10.040]
26 **Mattos AA**, Gomes EB, Tovo CV, Alexandre CO, Remião JO. Hepatitis B vaccine efficacy in patients with chronic liver disease by hepatitis C virus. *Arq Gastroenterol* 2004; **41**: 180-184 [PMID: 15678203]
27 **Gutierrez Domingo I**, Pascasio Acevedo JM, Alcalde Vargas A, Ramos Cuadra A, Ferrer Ríos MT, Sousa Martin JM, Sayago Mota M, Giráldez Gallego A, Suárez Artacho G. Response to vaccination against hepatitis B virus with a schedule of four 40-μg doses in cirrhotic patients evaluated for liver transplantation: factors associated with a response. *Transplant Proc* 2012; **44**: 1499-1501 [PMID: 22841195 DOI: 10.1016/j.transproceed.2012.05.071]
28 **DaRoza G**, Loewen A, Djurdjev O, Love J, Kempston C, Burnett S, Kiaii M, Taylor PA, Levin A. Stage of chronic kidney disease predicts seroconversion after hepatitis B immunization: earlier is better. *Am J Kidney Dis* 2003; **42**: 1184-1192 [PMID: 14655190 DOI: 10.1053/j.ajkd.2003.08.019]
29 **Agarwal SK**, Irshad M, Dash SC. Comparison of two schedules of hepatitis B vaccination in patients with mild, moderate and severe renal failure. *J Assoc Physicians India* 1999; **47**: 183-185 [PMID: 10999085]
30 **Bonazzi PR**, Bacchella T, Freitas AC, Osaki KT, Lopes MH, Freire MP, Machado MC, Abdala E. Double-dose hepatitis B vaccination in cirrhotic patients on a liver transplant waiting list. *Braz J Infect Dis* 2008; **12**: 306-309 [PMID: 19030730]
31 **Wiedmann M**, Liebert UG, Oesen U, Porst H, Wiese M, Schroeder S, Halm U, Mössner J, Berr F. Decreased immunogenicity of recombinant hepatitis B vaccine in chronic hepatitis C. *Hepatology* 2000; **31**: 230-234 [PMID: 10613751 DOI: 10.1002/hep.510310134]
32 **Idilman R**, De MN, Colantoni A, Nadir A, Van Thiel DH. The effect of high dose and short interval HBV vaccination in individuals with chronic hepatitis C. *Am J Gastroenterol* 2002; **97**: 435-439 [PMID: 11866284 DOI: 10.1111/j.15720241.2002.05482.x]
33 **Sangaré L**, Manhart L, Zehrung D, Wang CC. Intradermal hepatitis B vaccination: a systematic review and meta-analysis. *Vaccine* 2009; **27**: 1777-1786 [PMID: 19200451 DOI: 10.1016/j.vaccine.2009.01.043]
34 **Jakob T**, Udey MC. Epidermal Langerhans cells: from neurons to nature's adjuvants. *Adv Dermatol* 1999; **14**: 209-258; discussion 259 [PMID: 10643500]
35 **Glenn GM**, Kenney RT, Hammond SA, Ellingsworth LR. Transcutaneous immunization and immunostimulant strategies. *Immunol Allergy Clin North Am* 2003; **23**: 787-813 [PMID: 14753392 DOI: 10.1016/S0889-8561(03)00094-8]
36 **Rahman F**, Dahmen A, Herzog-Hauff S, Böcher WO, Galle PR, Löhr HF. Cellular and humoral immune responses induced by intradermal or intramuscular vaccination with the major hepatitis B surface antigen. *Hepatology* 2000; **31**: 521-527 [PMID: 10655280]
37 **Dhillon S**, Moore C, Li SD, Aziz A, Kakar A, Dosanjh A, Beesla A, Murphy L, Van Thiel DH. Efficacy of high-dose intra-dermal hepatitis B virus vaccine in previous vaccination non-responders with chronic liver disease. *Dig Dis Sci* 2012; **57**: 215-220 [PMID: 22160636 DOI: 10.1007/s10620-011-1996-0]
38 **Barraclough KA**, Wiggins KJ, Hawley CM, van Eps CL, Mudge DW, Johnson DW, Whitby M, Carpenter S, Playford EG. Intradermal versus intramuscular hepatitis B vaccination in hemodialysis patients: a prospective open-label randomized controlled trial in nonresponders to primary vaccination. *Am J Kidney Dis* 2009; **54**: 95-103 [PMID: 19481320 DOI: 10.1053/j.ajkd.2009.03.010]
39 **Wahl M**, Hermodsson S. Intradermal, subcutaneous or intramuscular administration of hepatitis B vaccine: side effects and antibody response. *Scand J Infect Dis* 1987; **19**: 617-621 [PMID: 3441747]
40 **Hourvitz A**, Mosseri R, Solomon A, Yehezkelli Y, Atsmon J, Danon YL, Koren R, Shouval D. Reactogenicity and immunogenicity of a new recombinant hepatitis B vaccine containing Pre S antigens: a preliminary report. *J Viral Hepat* 1996; **3**: 37-42 [PMID: 8736239 DOI: 10.1111/j.13652893.1996.tb00079.x]
41 **Bertino JS**, Tirrell P, Greenberg RN, Keyserling HL, Poland GA, Gump D, Kumar ML, Ramsey K. A comparative trial of standard or high-dose S subunit recombinant hepatitis B vaccine versus a vaccine containing S subunit, pre-S1, and pre-S2 particles for revaccination of healthy adult nonresponders. *J Infect Dis* 1997; **175**: 678-681 [PMID: 9041342 DOI: 10.1093/infdis/175.3.678]
42 **Rendi-Wagner P**, Shouval D, Genton B, Lurie Y, Rümke H, Boland G, Cerny A, Heim M, Bach D, Schroeder M, Kollaritsch H. Comparative immunogenicity of a PreS/S hepatitis B vaccine in non- and low responders to conventional vaccine. *Vaccine* 2006; **24**: 2781-2789 [PMID: 16455169 DOI: 10.1016/j.vaccine.2006.01.007]
43 **Zuckerman JN**, Sabin C, Craig FM, Williams A, Zuckerman AJ. Immune response to a new hepatitis B vaccine in healthcare workers who had not responded to standard vaccine: randomised double blind dose-response study. *BMJ* 1997; **314**: 329-333 [PMID: 9040320 DOI: 10.1136/bmj.314.7077.329]
44 **Haubitz M**, Ehlerding G, Beigel A, Heuer U, Hemmerling AE, Thoma HA. Clinical experience with a new recombinant hepatitis-B vaccine in previous non-responders with chronic renal insufficiency. *Clin Nephrol* 1996; **45**: 180-182 [PMID: 8706359]
45 **Jacques P**, Moens G, Desombere I, Dewijngaert J, Leroux-Roels G, Wettendorff M, Thoelen S. The immunogenicity and reactogenicity profile of a candidate hepatitis B vaccine in an adult vaccine non-responder population. *Vaccine* 2002; **20**: 3644-3649 [PMID: 12399191 DOI: 10.1016/S0264-410X(02)00397-3]
46 **Saade F**, Honda-Okubo Y, Trec S, Petrovsky N. A novel hepatitis B vaccine containing Advax™, a polysaccharide adjuvant derived from delta inulin, induces robust humoral and cellular immunity with minimal reactogenicity in preclinical testing. *Vaccine* 2013; **31**: 1999-2007 [PMID: 23306367 DOI: 10.1016/j.vaccine.2012.12.077]
47 **Cooper C**, Mackie D. Hepatitis B surface antigen-1018 ISS adjuvant-containing vaccine: a review of HEPLISAV™ safety and efficacy. *Expert Rev Vaccines* 2011; **10**: 417-427 [PMID: 21506639 DOI: 10.1586/erv.10.162]

48 **Akbar SM**, Chen S, Al-Mahtab M, Abe M, Hiasa Y, Onji M. Strong and multi-antigen specific immunity by hepatitis B core antigen (HBcAg)-based vaccines in a murine model of chronic hepatitis B: HBcAg is a candidate for a therapeutic vaccine against hepatitis B virus. *Antiviral Res* 2012; **96**: 59-64 [PMID: 22884884 DOI: 10.1016/j.antiviral.2012.07.011]

49 **Lobaina Y**, Hardtke S, Wedemeyer H, Aguilar JC, Schlaphoff V. In vitro stimulation with HBV therapeutic vaccine candidate Nasvac activates B and T cells from chronic hepatitis B patients and healthy donors. *Mol Immunol* 2015; **63**: 320-327 [PMID: 25193323 DOI: 10.1016/j.molimm.2014.08.003]

50 **Betancourt AA**, Delgado CA, Estévez ZC, Martínez JC, Ríos GV, Aureoles-Roselló SR, Zaldívar RA, Guzmán MA, Baile NF, Reyes PA, Ruano LO, Fernández AC, Lobaina-Matos Y, Fernández AD, Madrazo AI, Martínez MI, Baños ML, Alvarez NP, Baldo MD, Mestre RE, Pérez MV, Martínez ME, Escobar DA, Guanche MJ, Cáceres LM, Betancourt RS, Rando EH, Nieto GE, González VL, Rubido JC. Phase I clinical trial in healthy adults of a nasal vaccine candidate containing recombinant hepatitis B surface and core antigens. *Int J Infect Dis* 2007; **11**: 394-401 [PMID: 17257877 DOI: 10.1016/j.ijid.2006.09.010]

51 **Batdelger D**, Dandii D, Jirathitikal V, Bourinbaia AS. Open label trial of therapeutic hepatitis B vaccine V-5 Immunitor (V5) delivered by oral route. *Lett Drug Des Discov* 2007; **4**: 540-544 [DOI: 10.2174/157018007782794545]

52 **Buchmann P**, Dembek C, Kuklick L, Jäger C, Tedjokusumo R, von Freyend MJ, Drebber U, Janowicz Z, Melber K, Protzer U. A novel therapeutic hepatitis B vaccine induces cellular and humoral immune responses and breaks tolerance in hepatitis B virus (HBV) transgenic mice. *Vaccine* 2013; **31**: 1197-1203 [PMID: 23306359 DOI: 10.1016/j.vaccine.2012.12.074]

53 **Cardell K**, Akerlind B, Sällberg M, Frydén A. Excellent response rate to a double dose of the combined hepatitis A and B vaccine in previous nonresponders to hepatitis B vaccine. *J Infect Dis* 2008; **198**: 299-304 [PMID: 18544037 DOI: 10.1086/589722]

54 **Leroux-Roels G**, Haelterman E, Maes C, Levy J, De Boever F, Licini L, David MP, Dobbelaere K, Descamps D. Randomized trial of the immunogenicity and safety of the Hepatitis B vaccine given in an accelerated schedule coadministered with the human papillomavirus type 16/18 AS04-adjuvanted cervical cancer vaccine. *Clin Vaccine Immunol* 2011; **18**: 1510-1518 [PMID: 21734063]

P- Reviewer: Tanaka Y **S- Editor**: Ma YJ
L- Editor: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com