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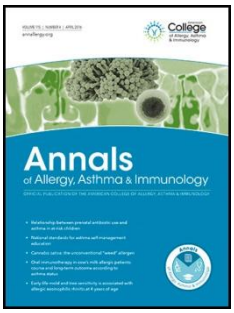

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Hepatitis B Vaccine Non-responders: Possible Mechanisms and Solutions

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Keywords: Hepatitis B, HBV, non-responder, hyporesponsiveness, innate immunity, adaptive immunity, vaccine

Abbreviations:

1. 1018 immunostimulatory DNA sequence: HEPLISAV™
2. Aluminum hydroxide: Alum
3. Antigen presenting cells: APC
4. B-cell receptor: BCR
5. CD40 ligand: CD40L
6. Celiac disease: CD
7. Dendritic cell: DC
8. **δ** inulin: Advax™
9. End stage renal disease: ESRD
10. Gluten-free diet: GFD
11. Granulocyte macrophage colony-stimulating factor: GM-CSF
12. Hepatitis B virus: HBV
13. Hepatitis B envelope specific antibody: anti-HBsAg
14. Hepatitis B surface antigen: HBsAg
15. Hepatitis C virus: HCV
16. Hepatocellular carcinoma: HCC
17. Highly active anti-retroviral therapy: HAART
18. Human immunodeficiency virus: HIV
19. Human papilloma virus: HPV
20. Immunoglobulin: Ig
21. Immunostimulatory DNA sequences: ISS
22. Inflammatory bowel disease: IBD
23. Interferon: IFN
24. Interleukin: IL
25. Intradermal: ID
26. Intramuscular: IM
27. Killer cell lectin-like receptor subfamily G member 1: KLRG1
28. Natural killer cells: NK cells
29. Natural killer T-cells: NKT cells
30. Programmed death-1: PD-1
31. Programmed death-1 ligand: PDL-1
32. Single nucleotide polymorphisms: SNPs

33. Suppressor of cytokine signaling-1: SOCS-1
34. T-cell receptor: TCR
35. T helper cell: Th
36. Toll-like receptor: TLR
37. Transforming growth factor: TGF
38. Tumor necrosis factor: TNF
39. Tumor necrosis factor- and Apo-L-related leukocyte-expressed ligand-1: TALL-1

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Abstract: Objective: Hepatitis B (HBV) is a viral illness that chronically infects 240 million people worldwide, leads to cirrhotic liver disease, and increases risk of hepatocellular carcinoma. The HBV vaccine has decreased HBV infection and along with human papilloma virus (HPV) vaccine are the only vaccines that prevent cancer. Despite the effectiveness of HBV vaccine, some populations do not develop protective responses. The risk groups for poor response include those with immunosuppression or dialysis-dependent, end-stage renal disease. Five percent of normal people do not respond. These subjects are deemed HBV "non-responders". Multiple strategies to improve the immunogenicity of the HBV vaccine are currently being pursued, including vaccine adjuvants, recombinant vaccines, and immune enhancement via up-regulation of dendritic cells.

Data Sources: PubMed was searched for peer-reviewed publications published from January 1980 to September 2017.

Study Selections: Studies retrieved for inclusion summarized potential mechanisms behind HBV vaccine non-responsiveness and potential solutions.

Results: The mechanisms behind HBV vaccine non-responsiveness vary between each subject population. There are many current and future strategies that may provide protective immunity against HBV in each of these populations.

Conclusion: This review will provide a background on the immunology of HBV infection, the possible immunologic mechanisms to explain HBV vaccine non-responsiveness, current research aimed at improving vaccine effectiveness, and possible future approaches for providing non-responders protection from HBV.

INTRODUCTION

Hepatitis B (HBV) is a viral illness that chronically infects up to 2.2 million people in the United States[1] and 240 million people worldwide[2]. Chronic infection may cause cirrhotic liver disease and hepatocellular carcinoma (HCC). HCC is the sixth most common cancer and second leading cause of cancer death worldwide[3]. Infected individuals are also at risk for fulminant hepatitis, which can be rapidly fatal[4]. The HBV vaccine has significantly reduced the incidence of HBV worldwide, and, along with the human papilloma virus (HPV) vaccine, are the only two vaccines to provide immunologic prevention of cancer[5]. However, the vaccine does not always stimulate protective immunity in subjects with human immunodeficiency virus (HIV), hepatitis C virus (HCV), celiac disease (CD), inflammatory bowel disease (ID), diabetes, and dialysis-dependent, end-stage renal disease (ESRD). Even healthy subjects are at risk for HBV vaccine non-responsiveness, possibly due to genetic predispositions[6–9]. This review summarizes the immune mechanisms associated with HBV infection, HBV vaccination and HBV vaccine non-responsiveness, as well as strategies to improve response to HBV vaccination.

METHODS

PubMed was searched for peer-reviewed publications published from January 1980 to September 2017 focusing on the immunology of HBV infection and HBV vaccination, potential mechanisms contributing to HBV vaccine hypo- or non-responsiveness, and current and future methods for increasing HBV vaccine immunogenicity.

HEPATITIS B VIRUS AND HUMAN IMMUNE RESPONSE BACKGROUND

Most adults clear HBV after acute infection via HBV-mediated activation of natural killer (NK) cells, which produce interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and granulocyte

macrophage colony-stimulating factor (GM-CSF). HBV also activates natural killer T (NKT) cells via antigens presented by CD1 molecules. Activated NKT then secrete IFN-γ and interleukin (IL)-4. NKT cells are in high numbers in the liver and destroy HBV infected cells through the Fas/Fas-ligand and perforin pathways. HBV replication is typically suppressed by IFN-α by dendritic cells (DCs) and infected hepatocytes. In addition, antigen presenting cells (APCs) lead to T-cell activation, initiation of anti-HBsAg antibody production, and induction of memory T- and B-cells[10]. Evidence suggests that these anti-HBV immunoglobulin (Ig) G antibodies can persist for up to ten years[11].

There are several mechanisms that dampen the immune response to natural HBV infection. HBV has the incompletely understood capability to escape innate immune detection and thus prevent secretion of IFN-α. For unclear reasons, subjects with acute HBV infection often have high levels of IL-10, which suppresses the lytic activity of NK and NKT cells. HBV infection also induces activation of T-cells during its incubation period, but this activation is often delayed. This delay occurs because the liver filters a number of microbes and antigens from the intestine, inducing an immune tolerant cellular milieu and suppressed $CD4^+$, $CD8^+$, and T-memory cell responses. This weakened response does not always lead to chronic HBV but may impair HBV clearance. Chronic HBV also leads to dendritic cell malfunction, which may resolve with HBV treatment and perhaps result in bolstering of the adaptive immune response[10,12].

HEPATITIS B VACCINE BACKGROUND

In children, the HBV vaccine is normally administered intramuscularly (IM) at birth and 2, and 6 months of age, while adults requiring vaccination receive a three dose series at monthly intervals[13]. The HBV vaccine consists of recombinant hepatitis B surface antigen (HBsAg), an aluminum hydroxide (alum) adjuvant, and a virus-like particle. The alum adjuvant induces

humoral immunity by promoting production of HBV envelope-specific antibody (anti-HBsAg) through T-helper (Th_2) cell stimulation and production of IL-4. However, alum does not augment T-cell responses as effectively as other adjuvants, thus newer more immunogenic adjuvants are currently being researched[14]. Anti-HBsAg titers are used to assess the adequacy of the humoral immune response to the HBV vaccine[15].

IMPAIRED HEPATITIS B VACCINE IMMUNE RESPONDERS

A response to the HBV vaccine is defined as the production of an anti-HBsAg level ≥ 10 IU/L with >100 IU/L accepted as a protective titer. IU is an arbitrary antibody unit defined by a chemiluminescent, in vitro antibody assay. If confirmation of immune response is necessary, the titer is checked 1 to 2 months after completing a vaccination series. The Center for Disease Control and Prevention does not recommend routine post-vaccination titers except for infants born to mothers with HBV, immunocompromised individuals, healthcare workers and sex partners of persons with chronic HBV. HBV non-responders or hyporesponders are subjects who fail to produce an anti-HBsAg titer ≥ 10 IU/L or between 10 – 99 IU/L, respectively, after undergoing two HBV vaccine series of 3 immunizations. Five to ten percent of immunocompetent subjects meet non-responder criteria[6]. Non-responsiveness is a concern in general but especially for health care professionals, given that the World Health Organization reports an annual incidence of 66,000 global cases of HBV transmission due to needle-stick injuries[16]. Other vulnerable populations include subjects with HIV, HCV, ESRD receiving dialysis, diabetes, obesity[17,18], celiac disease, and inflammatory bowel disease, some elderly subjects and those with certain genetic risk factors. Primary immunologic mechanisms to explain immune impaired immune response in at risk populations will be summarized below, while additional mechanisms are in Tables 1 and 2.

HIV/AIDS

HIV subjects are at risk for HBV given immunosuppression and similar routes of transmission. Co-infected subjects are at greater risk for severe HBV-related cirrhosis, HCC, and worsening of HIV infection[19]. Therefore, prevention of co-infection with successful HBV vaccination can decrease morbidity and mortality in this population[20]. However, compared to the 90-95% HBV vaccine effectiveness in immunocompetent subjects, only 20-70% of HIV infected subjects develop protective anti-HBsAg titers. This decreased antibody response is likely related to HIV-induced low CD4 counts and reduced CD40 ligand (CD40L) on $CD4^+$ T-cells. $CD4^+$ T-cells are essential for effective antibody production via stimulation of B-cell mediated immunoglobulin (Ig) isotype-switching following CD40L binding to CD40 on B cells. HIV reduces $CD4^+$ T-cells and $CD4^+$ memory T-cells and suppresses production of new lymphocytes. The CD4 number required to produce protective anti-HBsAg titers ranges from 150-500 cells/mm^3 [19].

Duration of highly active anti-retroviral therapy (HAART) positively correlates to HBV vaccine response, with longer treatment courses corresponding to higher anti-HBsAg titers. HAART reverses constitutive innate immune activation, which allows replenishment of functional naïve and memory $CD4^+$ T-cells, and NKT cells[19].

Hepatitis C

Only 40-60% of chronic HCV-infected subjects respond to the HBV vaccine, with fibrosis-predominant HCV cirrhotics having the poorest vaccine response[21,22]. Chronic HCV infection leads to immune senescence and immune exhaustion. Moorman et. al. studied HBV vaccine response in chronic HCV infection and the role of programed death-1 (PD-1) receptor. PD-1 is a negative-regulatory receptor on activated T- and B-cells that induces an inhibitory

signal through the TCR and B-cell receptor (BCR) signaling pathways after binding to PD-1 ligand (PDL-1). HCV-infected HBV vaccine non-responders had higher levels of PD-1, which attenuated T-cell stimulation and induced T-cell depletion. This was reversed by inhibiting PDL-1 on T- and B-cells[23]. Another mechanism which suppresses HBV response in HCV is the killer cell lectin-like receptor subfamily G member 1 (KLRG1). Shi et. al. examined KLRG1, which is upregulated on NK and T-cells in subjects with chronic HCV and suppresses T-cell proliferation and IL-2 secretion[21]. Finally, HCV also causes activated B-cells to create Igs incapable of recognizing and destroying HBV, theoretically via upregulation of tumor necrosis factor- and Apo-L-related leukocyte-expressed ligand-1 (TALL-1) and inhibition of suppressor of cytokine signaling-1 (SOCS-1)[24,25]. Other potential mechanisms are summarized in Table 1.

End stage renal disease and dialysis

Hemodialysis subjects are at a greater risk for exposure to HBV due to HBV's ability to remain infectious for seven days or more on dialysis tubing. They also have depressed adaptive immune responses. The HBV vaccine has decreased HBV prevalence amongst dialysis subjects, but this population's response rate to the vaccine is 50 – 70%, and only approximately 40% maintain protective titers 3 years after initial vaccination[26]

Uremia impairs T-cell and APC production and interaction[27]. Toxins and increased prostaglandin E_2 and methylguanidine in uremia decrease T-cell generation, which is partially corrected after dialysis. In vitro, culturing $CD4^+$ T-cells from dialysis-dependent and normal subjects in uremic serum reduced TCR expression by almost 50%, which correlated with HBV vaccine hyporesponsiveness[28]. Activated monocytes from subjects with ESRD have reduced MHC II expression. Decreased levels of both TCRs and MHC II contribute to impaired adaptive immunity and HBV vaccine hyporesponsiveness[29]. Finally, DCs, which differentiate from

monocytes and act as APCs, are decreased in number and function in dialysis-dependent non-responders. These DCs also have decreased expression of HLA and CD83 molecules, which decrease their APC efficacy and attenuate T-memory cell production[30].

In addition to reducing immunocyte numbers, ESRD reduces function of T-cells. Cytokine imbalances suppress adaptive immunity in dialysis subjects. Decreased levels of IL-2 made by T-cells impairs differentiation of $CD4^+$ T-cells to Th_1 and Th_2 cells. Deficiency of Th_2 cells causes B-cell dysfunction and attenuates antibody production[28]. Subjects with higher CD4:CD8 ratios have better responses to the HBV vaccine[31]. There are conflicting results regarding the over- or under-production of IL-10 in dialysis subjects. One study reported HBV vaccine hyporesponsiveness in dialysis subjects with genetic polymorphisms causing deficient IL-10 production and subsequent upregulation of TNF-α and IL-6. However, excess IL-10 can impair adaptive immunity through decreased MHC-II production and preferential differentiation of $CD4^+$ T-cells into T-regulatory (Treg) cells[32]. Increased production of Treg cells contributes to HBV vaccine hyporesponsiveness, even in healthy subjects[33]. Dialysis does not correct these cytokine imbalances[28].

Diabetes

Comorbid type 2 diabetes in subjects with ESRD has been linked to hyporesponsiveness[34]. However, subjects with type 1 and 2 diabetes with normal renal function may be non-responders as well. Mormile et. al. proposed that non-responders may have undiagnosed type 1 diabetes since HBV vaccine non-responsiveness and type 1 diabetes mellitus are associated with the HLA-DQ and HLA-DR haplotypes DQ2, DQ3, DR3, and DR4, as well as HLA-DRB1. These HLA haplotypes may impair MHC II HBV antigen presentation and

suppressed T-cell responses. Thus, non-responders with this genotype may develop type 1 diabetes and may require more vigilant monitoring[35].

Celiac disease and inflammatory bowel disease

CD subjects have high rates of HBV vaccine hyporesponsiveness, with response rates ranging from 54% to 78%[36,37]. CD is associated with a 90 – 95% incidence of the HLA-DQ2 haplotype, which has been linked to HBV vaccine non-responsiveness[38]. Competitive binding to HLA-DQ2 occurs between gliadin peptides and HBsAg, thus if an abundance of gliadin saturates the HLA-DQ2 molecules and prevents vaccine HBsAg binding, the resulting T-cell activation and B-cell antibody production may be impaired. Decreased anti-HBsAg titers occur in children eating gluten who subsequently were diagnosed with CD, as well as in CD-diagnosed subjects who were non-adherent to gluten free diets (GFDs). Those who were initially non-responders but were then adherent to a GFD and re-vaccinated had response rates similar to healthy subjects[39].

IBD subjects are at greater risk of contracting HBV due to blood transfusions and repeated colonoscopies. They are also at risk of contracting or reactivating HBV when started on immunosuppressants. To compound this problem, their HBV vaccine response rates are as low as 26 – 39%[40,41]. IBD has been linked to decreased adaptive immune responses due to genetic polymorphisms of HLA, IL2RA, IL-10 and IL-23 and their respective receptors[42]. Other potentially immunosuppressive factors include anti-TNF-α therapy, corticosteroid treatment, and hypoalbuminemia[43]. The association between non-responsiveness and anti-TNF-α therapy is debated[44,45]. Corticosteroid therapy decreases TNF-α and IFN-γ production, which impairs T-cell activation[46], while hypoalbuminemia impairs T-cell maturation and interaction with HBsAg[43]. It has been suggested that these subjects should receive the HBV vaccine at the time of IBD diagnosis, during disease remission, or prior to initiation of immunosuppressive therapy[41].

Advanced age

Age contributes to decreased adaptive immune responses due to immune senescence. Reduction of thymic size with age decreases T-cell production and impairs differentiation to $CD4^+$ T-cells, $CD8^+$ T-cells, and memory T-cells. Progressive loss of CD28 molecules on T-cells contributes to T-cell anergy and apoptosis. Decreased $CD4^+$ T-cells impairs germinal center activation, which results in attenuated antibody production. Co-stimulation of B-cells and antibody production is also inhibited due to loss of CD86 on B-cells. Deficiency of the adhesion molecule, CD62L, that occurs with aging also contributes to senescence since it is required for migration of undifferentiated T-cells and memory T-cells into lymph nodes. Suppressed CD62L impairs T-cell activation of B-cells and subsequent antibody formation[47].

Genetics

HLA and IL genetic polymorphisms affect HBV vaccine responsiveness both positively and negatively. Previously the associations with HLA-DQ and HLA-DR haplotypes DQ2, DQ3, DR3, and DR4 and HLA-DRB1 were discussed as being related to impaired HBV vaccine response. In contrast, HLA-A11 is associated with an increase in HBV vaccine response in type 1 diabetes[48]. Multiple genetic studies examining responders and non-responders in the Chinese Han, Taiwanese, and Japanese populations have identified several single nucleotide polymorphisms (SNPs) related to increased and decreased HBV vaccine protective titers[6,9,49,50]. These findings are summarized in Table 1. Although the SNP relationships with immune response are complex, insight into these associations and underlying mechanisms may aid in understanding HBV vaccine hyporesponsiveness in healthy subjects.

STRATEGIES TO INCREASE VACCINE EFFECTIVENESS

The current HBV vaccine is effective, but the alum adjuvant is not optimal for cellular and humoral response in the aforementioned at-risk populations. Strategies to improve vaccine efficacy include revaccination or increased vaccine dose, alternate routes of vaccination, improved adjuvants, vaccines with superior immunogenicity, and co-administration of medications with vaccination. Additional approaches are summarized in Table 3.

Repeat vaccination or Increased vaccine dose

Repeat vaccination with the same dose, usually increases rates of seroconversions in 83 – 87.5% of healthy non-responders[51,52]. Revaccination is variably effective in HIV non-responders[19]. ESRD and dialysis dependent non-responders also have improved seroconversion rates after repeat vaccination, but anti-HBsAg antibodies have a reduced half-life. The hyporesponsiveness of CD usually can be overcome with repeat vaccination, with a secondary response rate of 97.3%[53]. However, re-vaccination of individuals with IBD leads to a more modest increase in response rates ranging from 60 – 75%, significantly lower than the normal population[42].

Increased vaccination dose with 40 µg HBV vaccine (double the usual dose) has also been studied. HCV non-responders achieve a protective response rate of 80% after a single double-dose booster[5]. The effectiveness of the double-dose HBV vaccine in HIV is debated[54], but some investigators recommend double-dosed vaccination in initial non-responders and double-dosed boosters in those with persistent non-responsiveness[19]. A study evaluating the immunogenicity of 60 µg HBV vaccine (three times the usual dose) in hemodialysis patients reported favorable results[55].

Vaccination route

The current HBV vaccine is administered IM, but skeletal muscle injection does not always provide optimal immune responses. Intradermal (ID) HBV vaccines may enhance immunity. ID vaccination stimulates both humoral and cellular immune responses by directly activating DCs, which then promote $CD4^+$ and $CD8^+$ T-cell activation and production of IL-6, IL-12, and TNF-α. $CD4^+$ cells subsequently promote B-cell maturation and antibody production[48].

Improved response rates occur in adult HIV non-responders after ID repeat HBV vaccination (77% vs 65%), but no statistically significant differences were noted between the ID and IM double-dose vaccines. Comparable response rates following the IM and ID vaccines occur in HIV children (92.3% vs 90.2 % respectively)[48,56].

Hemodialysis and ESRD non-responders developed increased response rates with repeat ID vaccination vs IM re-vaccination (79 – 100% vs 40 – 48% respectively). The anti-HBsAg titers in the ID vaccine subjects also persisted longer than those of the IM vaccine. ID vaccination is also more cost-effective given responses with lower doses and fewer administrations[48].

Vaccine adjuvants

Numerous alternative adjuvants for the HBV vaccine have been evaluated, and several are superior to alum. The most promising are **δ** inulin (Advax™) and immunostimulatory DNA sequences (ISS).

Advax™ is a polysaccharide that enhances cellular immune responses in a variety of vaccines, including the HBV vaccine[57]. Animal studies and phase 1 human clinical trials demonstrate its safety and effectiveness. Saade et. al. reported that, in comparison with the alum-based HBV vaccine, Advax™-based HBV vaccination induced higher levels of $CD4^+$ and $CD8^+$

T-cells in mice and guinea pigs, with subsequent upregulation and earlier onset of Th_1 and Th_2 HBV-specific responses[58].

ISS bind to TLR-9 on human immune cells, which results in upregulation of Th_1 responses, enhanced B-cell function, reduced B-cell apoptosis, and promotion of Ig class switching. 1018 ISS (HEPLISAV™) in particular has proven to be safe and effective in human phase 1, phase 2, and phase 3 clinical trials. HEPLISAV™ also induced early and sustained levels of anti-HBsAg in ESRD and dialysis subjects, with a seroprotection rate ranging from 50 – 71% depending on the vaccine dose[59,60]. Although more research evaluating their efficacy and safety must be conducted, the number of potential new adjuvants is encouraging.

Increased immunogenicity

Another approach to improve HBV vaccination response is enhanced immunogenicity via the use of HBV preS region of the hepatocyte binding domain. Pre-S1 and pre-S2 are components of the large protein of HBsAg that are vital to HBV infection. They are both significantly more immunostimulatory than the smaller protein in the current HBV vaccine. Antibodies against pre-S1 block HBV infection in chimpanzees. Thus, utilizing pre-S1 and pre-S2 could be used to create more effective preventative vaccines, as well as therapeutic vaccines for treatment of chronic HBV. These vaccines are created by fusing the pre-S1 and pre-S2 particles to either the S protein or the core protein. Studies show pre-S1 and pre-S2-based vaccines to be superior at upregulating humoral and cellular responses in responders, hyporesponders, and non-responders following the current S vaccine[61]. This is evidenced by increased anti-HBsAg titers, increased INF-**γ** secretion, and enhanced antigen-specific T-cell production[62].

Therapeutic supplementation

Concomitant therapies administered with the HBV vaccine may enhance the immune response. These medications include GM-CSF, levamisole, and praziquantel.

GM-CSF is a growth factor for myeloid cells made by T-cells, NK cells, mast cells, endothelial cells, fibroblasts and macrophages. GM-CSF is approved for neutropenia associated with cancer chemotherapy. GM-CSF may enhance vaccine responses and has been used as an adjuvant in HIV-infected subjects[63]. GM-CSF activates DCs and shifts $CD4^+$ T-cell activation to a Th_1 response. Improved HBV vaccine responses occur with GM-CSF co-administration in ESRD and subjects on dialysis[64].

Levamisole is an immunomodulatory drug used as an anti-helminthic agent. Levamisole has also been studied in therapeutic regimens for HBV infection due to its ability to enhance IFN production[65]. Zhang et. al. suggested mechanisms for enhanced HBV vaccine response with levamisole co-administration by demonstrating enhanced IFN-α, TNF-α, and DC activation. Levamisole also increased $CD4^+$ and $CD8^+$ T-cell activity and production and resulted in greater anti-HBsAg titers[66]. Enhanced HBV vaccine responses in ESRD and dialysis patients after co-administration of levamisole with HBV vaccine is reported[65]. Similar results have been reported in healthy individuals[67]. These effects, as well as DC activation, may be enhanced by the addition of cimetidine since it increases concentrations of many anti-helminthic medications[68,69].

Praziquantel is an anti-helminthic agent used for the treatment of parasites such as schistosoma, echinococca, liver flukes and tapeworms. Its mechanism(s) of action are multiple and include alternation of parasite membrane permeability and reduction of ova production. The enhancement of HBV vaccine response is associated with inhibition of TGF-**β**, TGF-**β**/Smad2,3 signaling, and Treg function. Praziquantel also enhances activation of $CD4^+$ and $CD8^+$ T-cells and increases IFN-γ, further enhancing response to the HBV vaccine[70]. The addition of

cimetidine to this regimen further enhances HBV vaccine response and could be a strategy to improve HBV vaccination response[71].

CONCLUSION

HBV infection is a chronic, debilitating infection with significant morbidity and mortality. The HBV vaccine is a major public health advancement that has limited the impact of HBV morbidity and mortality. However, the current HBV vaccine is not ideal as certain at risk populations, as well as a minority of healthy subjects, are vulnerable to infection despite completion of the 3 injection IM series. This is a particular problem for non- and hyporesponders in high risk populations, such as healthcare workers, those who live in endemic areas, and individuals who engage in unprotected sex with multiple partners or in intravenous drug use. Fortunately, immunologic understanding of the protective immune response to HBV has contributed to new approaches of enhancing the HBV vaccine efficacy. The best current strategy is to re-immunize hypo- or non-responders, with consideration for double-dose vaccination (up to 40 mcg for an adult dose) and for a 4-dose series. A 1inch needle should be used in adults with preference for the deltoid and avoidance of the gluteus to enhance the likelihood of IM administration. For children a needle of at least 5/8-inch length should be used in the lateral thigh. A third immunization series of vaccine minimally increases response, but some experts nevertheless recommend. Future improvement in HBV vaccination may include enhancement of adjuvants, ID administration, modified antigen components or co-administration of the vaccine with medications to enhance the immune response. A change in the route of administration from IM to ID would likely be the easiest modifiable strategy for practitioners and appears to hold the most promise for increased vaccine effectiveness. Better understanding of the normal and impaired immune response to HBV may facilitate the development of additional enhancements.

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603 **Table 1.** Susceptible populations to being hypo- or non-responders and the potential explanations

Susceptible Populations	Potential Mechanism		Results
HIV[19,20]	Decreased $CD4^+$ cells →	Attenuated CD8+ activation →	Suppressed protection against HBV replication
	Decreased CD40L →		Decreased Ig isotype switching
	HIV viremia →	Constitutive innate immune activation →	Attenuates T-cell dependent adaptive immune actions and induces immune senescence
	High viral loads →		B-cell dysfunction unrelated to impaired activation via $CD4^+$ T-cells
			Induces cytotoxic destruction of gp120 $CD4^+$ T-cells and $CD4^+$ T-cell apoptosis
HCV[21-25]	Increased inhibitory PD-1 receptors on T- and B cells →	Increased PDL-1 binding →	Decreased T-cell stimulation
	Increased KLRG1 on NK	Decreased T-cell proliferation →	$CD4^+$ dysfunction

	and T-cells →	Decreased IL-2 →		
		Increased cell cycle inhibitors (p16ink4a and p27kip1) →		
	Increased Tim-3 (T-cell fatigue marker) on monocytes →	Decreased IL-12 →	Increased IL-23 →	Increased differentiation of CD4+ to Th17 (contribute to monocyte non-responsiveness
				Induces production of dysfunctional Igs by B-cells (cannot recognize HBsAg)
ESRD & Dialysis[26-33]	Uremia →	Decreased T-cell production →		Impaired adaptive immunity
		Decreased MHC II on monocytes →		
		Decreased TCR expression →		
	Imbalance of adhesion molecules (decreased ICAM-1, increased LFA-1) →			Impaired T-cell response
	Decreased phosphorylation of ITAMs →			Decreased T-cell proliferation
	Decreased CD86 on APCs →	Decreased binding of APC CD80/CD36 to T-cell CD28 →		T-cell apoptosis/anergy
	Premature activation of monocytes →	Excessively high levels of IL-1β, IL-6, IL-12 →		Monocyte senescence and apoptosis in vitro

	Cellulose dialysis membranes →	Alternative complement pathway stimulation →	C5a upregulation →	Premature monocyte activation
	Premature activation of T- and B-cells →	Increased TNF-α secretion →		Early apoptosis of T- and B-cells
	Low-flux polysulfune dialysis →	Medium molecular weight uremic toxins are not removed →		Increased T-cell apoptosis
	Iron overload from frequent blood transfusions →			Compromised T-cell production
Diabetes[34-35]	Type I Diabetes Mellitus →	Decreased MHC II →		Decreased T-cell response
Obesity[17-18]	Decreased splenic CD4+ T-cells →			Impaired cell mediated immunity
	Decreased DC with CD83/CD86 →			Decreased T-cell activation
				Increased IL-10
Celiac Disease & IBD[36-46]	Gliadin saturation of HLA-DQ2 →	Prevents binding of vaccine HBsAg →		Decreased anti-HBsAg titers
	IBD →	HLA, IL-10, IL-23 →		Decreased adaptive immunity

	IBD therapy (corticosteroids and TNF-α inhibitors) →	Decreased TNF-α and IFN-γ →	Impaired T-cell activation
	Hypoalbuminemia →		Impaired T-cell maturation and interaction with HBsAg

Definition of abbreviations: HIV=Human Immunodeficiency Virus; Ig=immunoglobulin; NKT=Natural Killer T; PD-1=Programmed death-1; PDL-1=Programmed death ligand-1; KLRG1= killer cell lectin-like receptor subfamily G member 1; IL=Interleukin; Tim-3= T cell immunoglobulin mucin domain-3; HCV=Hepatitis C Virus; MHC II= major histocompatibility complex II; TCR= T-cell receptor; ICAM-1= intercellular adhesion molecule-1; LFA-1= lymphocyte function antigen-1; ITAM= TCR ζ-chain immunoreceptor tyrosine-based activation motif; APC=Antigen Presenting Cell; ESRD=End Stage Renal Disease; DC=Dendritic Cells; IBD=Inflammatory Bowel Disease; TNF= Tumor Necrosis Factor; IFN=Interferon; HBsAg=Hepatitis B surface Antigen

612 **Table 2.** Potential explanations for hypo- or non-responsiveness due to advanced age or genetics

Advanced Age[47]	Decreased thymic size →	Decreased T-cell production
	Progressive loss of CD28 on T-cells →	T-cell apoptosis/anergy
	Decreased CD28 on B-cells →	Decreased co-stimulation of B-cells and antibody production
	Decreased CD62L →	Decreased T-cells migration into lymph nodes
		Impaired T-cell activation
Genetics[6,9,48-50]	HLA-DRB1 →	HBV vaccine non-responsiveness
	SNP rs477515 →	
	HLA-DRB1 SNP rs28366298 →	Enhanced HBV vaccine response
	HLA-DRB1 SNP rs3763316 →	
	HLA-DRB1 SNP rs13204672 →	
	HLA-DRB1 SNP rs7770370 →	
	Absence of HLA-A*02 →	HBV vaccine non-responders
	Absence of HLA-DB1*08 →	
	Presence of HLA-B*15 →	

	HLA-DPB1 05:01 allele →		HBV vaccine on-responsiveness
	HLA-DPB1 09:01 allele →		
	HLA-DPB1 allele 2:01:02 →		HBV vaccine protective titers
	HLA-DPB1 allele 2:02 →		
	HLA-DPB1 allele 3:01:01 →		
	HLA-DPB1 allele 4:01:01 →		
	HLA-DPB1 allele 14:01 →		
	Homozygotes for the HLA-DPB1 05:01 allele →		HBV vaccine non-responders, but slower decline of anti-HBsAg
	Celiac disease →	HLA-DQ2 →	Decreased response
		HLA-DQ8 →	
	Diabetes→	HLA-DQ2 →	Decreased response
		HLA-DQ3 →	
		HLA-DR3 →	
		HLA-DR4 →	
	Dialysis Dependent Subjects →	HLA-A1, HLA-B8, and HLA-DR3 →	Non-responsiveness
		Certain IL-10, IL-12, and IL-18 haplotypes →	

Definition of abbreviations: IL=Interleukin; HBsAg=Hepatitis B surface Antigen

614 Table 3. Strategies for Increasing Responses to Hepaitis B Vaccine

Potential Solutions	Considerations	Potential Results
Revaccination with the same dose (20µg)[19,42, 51-55]	Healthy non-responders →	83 – 87.5% increased seroconversion
	HIV →	Variable response
	ESRD →	Improved seroconversion rates, but anti-HBsAg antibodies have a reduced half life
	CD →	97.3% secondary response rate
	IBD →	60 – 75% response rate (only modest increase)
Increased vaccine dose (40µg)[5,19,54,55]	HCV →	80% response rate
	HIV →	Effectiveness debatable
Alternate routes of vaccination[48,56]	ID →	Stimulates humoral and cellular immune response
		More cost effective

			Local reaction infers response/immunity
			In HIV increased response from 65% IM to 77% ID in adults, comparable response in children (92.3% IM vs 90/2% ID)
			In ESRD increased response from 40 – 48% IM to 79 – 100% ID, and titers persisted longer
	Int ranasal or oral →	Increase mucosal Ag-specific IgA →	Additional line of defense against sexual transmission and improved response rates
Improved adjuvants[57-60]	**δ** inulin (AdvaxTM)		
	CpG oligoneucleotides		
	Immunostimulatory DNA sequences (ISS)		
Vaccines with superior immunogenicity[61,62]	Pre-S1 and Pre-S2 viral particles		More immunostimulatory
Co-administration of medications	Levamisole →		Increased DC activation
			Increased IFN-α and TNF-α

with vaccination[63-71]			Increased $CD4^+$ and $CD8^+$ activity
			Increased anti-HBsAg titers
			Enhanced HBV vaccine response in ESRD and dialysis dependent subjects
	Praziquantel →	Inhibits TGF-β and TGF-β/Smad2,3 →	Inhibits Tregs
		Increases IFN-γ →	Enhances vaccine response
		Increases CD4+ and CD8+ activation →	
	Cimetidine →	Suppresses Tregs and increases IFN-γ secretion by CD4+ →	Increased $CD8^+$ cytotoxicity
		Decreases IL-10 and TGF-β →	Attenuated Tregs
			Increases anti-HBs-Ag titers
		Increases Levamisole concentration →	Enhanced DC activation
		Increases Praziquantel concentration →	May augment therapeutic vaccination for chronic HBV

615 *Definition of abbreviations: ESRD=End stage renal disease; IBD=Inflammatory Bowel Disease; CD=Celiac Disease; CpG= 5'—C—phosphate—G—3';*

616 *HCV=Hepatitis C Virus; DC=Dendritic Cells; ID=Intradermal; IM=Intramuscular; HBsAg=Hepatitis B surface antigen*

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