

# Hepatitis B Vaccination in Patients with Chronic Kidney Disease

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## ABSTRACT

Hepatitis B infection is a serious global health problem. Chronic kidney disease patients with hepatitis B infections are associated with high rates of mortality and morbidity. The problems with vaccinating hemodialysis patients are that they have been shown to have lower seroconversion rates, lower peak antibodies, and antibody decline faster than in healthy persons. Patients with chronic kidney disease should be vaccinated as early as possible. Four double doses of vaccination are recommended. Anti-HBs should be monitored every 12 months in vaccinated hemodialysis patients. Additional strategies to improve seroconversion rates are third generation hepatitis B vaccine, combined hepatitis B and hepatitis A vaccine, intradermal injection, and adjuvants.

**Keywords:** Hepatitis B vaccinations, chronic kidney disease, adjuvants

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## INTRODUCTION

Hepatitis B infection is a serious global health problem. About 350 million people worldwide are chronic hepatitis B infection<sup>1</sup> who are at increased risk of developing cirrhosis and hepatocellular carcinoma. An estimated 75% of people with chronic hepatitis B live in the Asia-Pacific region.<sup>2</sup>

Hemodialysis patients are at risk of acquiring hepatitis B virus due to increased exposure to blood products, shared hemodialysis equipment, frequent breaching of skin, and immunodeficiency. Data from recent reports demonstrate that the rate of new hepatitis B infections in hemodialysis

patients is low (0-7%), but extant. Hepatitis B outbreaks continue to occur in hemodialysis units. The prevalence rates of hepatitis B infection in hemodialysis patients depend on baseline population rate which ranges from 0-6.6% in Western Europe, Japan, and the USA and 1.3-14.6% in the Asia-Pacific region<sup>3</sup>. Hemodialysis patients are more likely to be chronic carriers. Chronic kidney disease (CKD) with hepatitis B infection is associated with high rates of mortality and morbidity<sup>4</sup>. Centers for Disease Control and Prevention (CDC) recommends how to control hepatitis B transmission in hemodialysis patients including vaccination<sup>5</sup>. Problems of vaccination in hemodialysis patients are lower seroconversion rate, lower peak antibody, and faster antibody decline than normal population. The best seroconversion rate in hemodialysis patients is less than 85%. Proposed mechanisms include decreased immunoglobulin production, decreased IL-2 secretion by

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T lymphocyte, and impaired macrophage function. Multiple factors influence seroconversion rate including age, sex, body weight, CKD. Staging, nutritional status mainly low serum albumin concentration, diabetes mellitus, coinfection with hepatitis C virus or Human immunodeficiency virus (HIV), history of blood or blood products transfusion, and major histocompatibility complex (MHC).<sup>2,3,6-15</sup> The failure to complete a full course of hepatitis B vaccination also decreases seroconversion rate. Chronic kidney disease stage 3-5D patients deficient in vitamin D have lower seroconversion rate.<sup>16</sup>

### How to improve seroconversion rate

Agawal *et al*, demonstrated that seroconversion rate decreases if renal failure progresses. In that study,<sup>17</sup> Engerix B 40 mcg was given at 0, 1, and 2 months (3-dose group) or 0, 1, 2, and 6 months (4-dose group). Seroconversion rates among patients with mild (creatinine 1.5-3 mg/dL), moderate (creatinine 3-6 mg/dL) and severe (creatinine more than 6 mg/dL) were 87.5%, 66.6%, and 35.7% in the 3-dose group, respectively. In the 4-dose group, seroconversion rate was 100%, 77% and 36%, respectively.<sup>17</sup> Grzegorzewska *et al*, showed that level of glomerular filtration rate (GFR) was the independent predictor of seroconversion rate in multivariate analysis.<sup>7</sup> Mohammed *et al*, also found that more advanced chronic kidney disease had less seroconversion rate. Seroconversion rates were 44.3% in hemodialysis patients who received 4 doses (0, 1, 2, and 6 months) and 89.7% in patients with chronic kidney disease stage 3-4 who received 3 doses (0, 1, 6, months) of 40 mcg hepatitis B vaccine.<sup>8</sup> After 4 doses of 40 mcg, seroconversion was only 36% in renal allograft recipients on immunosuppressants and 86% in predialysis patients. Patients with end stage renal disease should be vaccinated during the pre-transplant period.<sup>7</sup> Four doses of 40 mcg give a higher response rate than 3 doses of 40 mcg.<sup>17,18</sup> CDC recommends giving double dose and additional dose of vaccine (Recombivax 40 mcg at 0, 1, and 6 months or Engerix B 40 mcg at 0, 1, 2, and 6 months) for hemodialysis patients. Deltoid muscle is the preferred injection site. Seroconversion rate

in patients with end stage renal disease (ESRD) vaccinated with 4 doses of 40 mcg was 60-90.5%.<sup>11</sup> In hemodialysis patients, seroconversion rate was 69% after 4 doses 40 mcg of vaccine (0, 1, 2, and 6 months) and if the last dose was injected at 12 months seroconversion was 76%.<sup>19</sup> Chow *et al*, compared seroconversion rates after 3 doses of 80 mcg with 3 doses of 40 mcg in peritoneal dialysis patients. Seroconversion rates 3 months after vaccination was not significantly different (62.2% and 78.6%,  $p=0.11$ ).<sup>20</sup>

Sixty-two percent of patients with chronic kidney disease had a significant fall in anti-HBs titer and 26% lost detectable antibodies 3-36 months after vaccination.<sup>21</sup> In dialysis patients, protective antibody is present in 47% and 68% of patients at 3 years and 5 years after vaccination, respectively.<sup>22</sup> Undetectable anti-HBs were found in 41% of responsive patients at 3 years.<sup>23</sup> Anti-HBs should be monitored every 12 months in vaccinated hemodialysis patients. If the titer is lower than 10 IUs, single booster 40 mcg should be given.<sup>5</sup> Response to booster dose was favorable in patients with chronic kidney disease.

Anti-HBs more than 10 IUs is usually considered to be protective, but in some patients it may not protect against hepatitis B infection. Experts have suggested that protective anti-HBs titer in hemodialysis patients should be over 50 IUs and over 200 IUs in some patients.<sup>7</sup>

Hemodialysis patients who are unresponsive to the primary course should be revaccinated with three additional doses 1-2 months after the first course. Retest for response is advised.

Cost effectiveness of hepatitis B vaccination in hemodialysis patients depends on the prevalence of hepatitis B in the population at risk.<sup>21</sup> CDC stated that cost of vaccination is mitigated by the reduced need for surveillance of antigen and antibody status.

### Other strategies to improve seroconversion rate

#### Third generation hepatitis B vaccine

First generation hepatitis B vaccine consists of inactivate HBs antigen extracted from hepatitis B carriers. Merck and Pasteur institute simultaneously produced it and it was approved by the American FDA in 1981. Second generation

hepatitis B vaccines are recombinant non-infectious subunits vaccines containing HBs antigen that are produced by the yeast *Saccharomyces cerevisiae*. There are two formulations: Engerix B and Recombivax HB. Seroconversion rate in normal population is over 95%. Recently, a third generation hepatitis B vaccine contains the pre-S1 and pre-S2 antigens. These antigens are more immunogenic than HBs antigen in the second generation vaccines. It has limited availability. Pre-S2/S GenHevac B (5 doses of 20 mcg) has been compared to the plasma-derived vaccine in predialysis patients. Seroconversion rates were 71% and 59%, respectively.<sup>24</sup> Bio-Hep-B (3 doses of 10 mcg) has seroconversion in 86% of non-responsive ESRD patients.<sup>25</sup>

### **Hepatitis B and Hepatitis A combined vaccine**

Hepatitis B and Hepatitis A combined vaccine has a statistically different seroconversion as compared to hepatitis B vaccine.<sup>8</sup>

### **Intradermal injection**

Skin is thought to be a more immunogenic site for vaccination than muscle. Dendritic cells in the dermis present antigens and stimulate both innate and adaptive immune responses.

Ashraf *et al*, compared seroconversion of 4 mcg intradermal injection with 40 mcg intramuscular injection of Engerix B at 0, 1, 2, and 6 months in hemodialysis patients. At the third month, seroconversion rates were 40.4% and 60.9%, respectively. However, seroconversion rate at 7 months was similar (68%).<sup>26</sup> Charest *et al*, found that intradermal injection group (5 mcg every 2 weeks) had a higher seroconversion rate than intramuscular injection group (40 mcg at 0, 1, 2, and 6 months) (97.6% and 90.5%).<sup>27</sup> Morais *et al*, showed that protective antibody titer was 82% after 16 intradermal injections of 0.1 mL of hepatitis B vaccine over an 8-week period. At 12 months, persistent protective titer was only 58.7%.<sup>28</sup> Barraclough *et al*, conducted the largest study of intradermal injection in nonresponsive hemodialysis patients. Intradermal injection (weekly for 8 weeks) improved seroconversion rates (79% in intradermal group and 40% in intramuscular group), and has greater peak anti-

body titers with protective antibody titres which persisted for similar duration.<sup>29</sup> Meta-analysis showed that intradermal injection induced higher seroconversion rate at the end of vaccination, but there was no significant difference in long term follow up.<sup>30</sup>

### **Adjuvants**

Adjuvants are thought to improve immune responses by causing depot formation at the injection site, increasing interaction between immunogens and macrophages and improving antigen presentation to T cells<sup>2</sup>. Many adjuvants used for improving Hepatitis B vaccination efficacy in CKD patients have been reported.

### **Levamisole**

Initially, Levamisole has been use as an antihelmintic. It has been reported that Levamisole increases NK cells, and activates T cells by enhancing production of IL-1, IL-2, IL-18, and IL-12 or eliciting their synergistic effects<sup>2</sup>. Levamisole is metabolized by the liver and excreted by the kidney. No clearance by hemodialysis or peritoneal dialysis has been demonstrated. A meta-analysis has shown that Levamisole increased seroconversion in patients with ESRD undergoing dialysis<sup>31</sup>. In hemodialysis patients, Levamisole significantly improves immune response to hepatitis B vaccine<sup>32</sup>.

### **Tetanus-diphtheria (Td) vaccine**

Giving Td vaccine with first dose of vaccine gives better anti-HBs at 1 month, but this is not statistically significant. Anti-HBs titer at 6 months is not different<sup>33</sup>.

### **Thymopentin**

Thymopentin is a synergistic pentapeptide which promotes T cell maturation and responsiveness, enhances IL-2 production, and improves macrophage function. Meta-analysis has demonstrated that thymopentin does not increase seroconversion. In a subgroup analysis, higher thymopentin dose significantly improved seroconversion. However, studies with large numbers of patients are needed to make a definite conclusion<sup>34</sup>.

### **Granulocyte macrophage-colony stimulating**

### **factor (GM-CSF)**

GM-CSF has been shown to activate macrophage function, increase MHC class II antigen expression, enhance cell maturation and migration, and enhance memory cell generation via T and B cell activation. Administration of GM-CSF prior to primary or booster dose of hepatitis B vaccination may significantly increase seroconversion in hemodialysis patients<sup>35</sup>. A study in nonresponsive hemodialysis patients demonstrated that GM-CSF decreases the number of circulating dendritic cells and T-cell proliferation in antigen presentation<sup>36</sup>. Meta-analysis showed that GM-CSF provides a better immune response in ESRD patients<sup>37</sup>.

### **Erythropoietin (EPO)**

Recombinant human erythropoietin improves response to hepatitis B vaccination. Its response is correlated with the EPO dose during the vaccination period in ESRD patients without intravenous iron supplementation<sup>38</sup>. Meta-analysis has shown that EPO does not improve seroconversion in hemodialysis patients<sup>39</sup>.

### **Toll-like receptor 9 agonist adjuvant**

The toll-like receptor 9 agonist adjuvant (HBsAg-1018) HEPLISAV<sup>TM</sup> contains 20 mcg of recombinant HBs antigen and 3000 mcg of a synthetic phosphorothioate oligodeoxynucleotide, 1018. In a phase 3 study, it was found that three doses of HBsAg-1018 are noninferior to four doses of HBsAg-Eng. Janssen et al, compared HBsAg-1018 with HBsAg-Eng in CKD patients with or without diabetes mellitus (DM). In the HBsAg-1018 group, CKD patients with or without DM have similar seroconversion rates. In the HBsAg-Eng group, CKD patients with DM have significant lower seroconversion rate than CKD patients without DM. HBsAg-Eng is cheaper than Engerix B<sup>40</sup>.

### **Recombinant IFN- $\alpha$ 2b**

Recombinant IFN- $\alpha$ 2b enhances both T cell and antibody responses, augments the production of all subclasses of immunoglobulin, and induces long-term antibody production and immunological memory. In hemodialysis patients, recombinant

IFN- $\alpha$ 2b induced earlier and higher seroconversion in hemodialysis patients<sup>2</sup>.

### **HB-ASO<sub>4</sub> (FENDRIX)**

HB-ASO<sub>4</sub> consists of recombinant HBs antigen 3-O-desacyl-4 $\alpha$ -monophosphoryl lipid A. HB-ASO<sub>4</sub> elicited a faster, enhanced, and longer seroconversion in pre-hemodialysis and hemodialysis patients<sup>41</sup>. Studies in hemodialysis patients have shown higher response rate and slower decline of response rate than standard vaccines<sup>42</sup>. HB-ASO<sub>4</sub> induces high response rate in nonresponsive CKD patients<sup>43</sup>.

### **HB-ASO<sub>2</sub>**

HB-ASO<sub>2</sub> is extracted from the bark of the South American *Quillaja Saponaria* trees. HB-ASO<sub>2</sub> induced higher, more rapid and persistent seroconversion in pre-dialysis, peritoneal and hemodialysis patients as compared to HB-ASO<sub>4</sub><sup>44</sup>.

## **CONCLUSION**

Hepatitis B vaccination in patients with chronic kidney disease results in lower seroconversion rates, lower peak antibodies, and fast antibody decline. Four double doses of hepatitis B vaccine should be given as early as possible, possibly before dialysis. Anti-HBs should be monitored every 12 month in vaccinated haemodialysis patients. If antiHBs is less than 10 IUs, a booster dose should be administered. Intradermal injection may be more effective, but the optimal regimen remains undefined. The outcomes of some adjuvants are promising, but more clinical trials are required.

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