Standard Versus Augmented Dose of HBV Vaccine in Children Undergoing Hemodialysis: A Randomized Controlled Trial

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ABSTRACT

Background: Children with end stage renal disease (ESRD), particularly those who require hemodialysis (HD) are at high risk for hepatitis B virus (HBV) infection. Hemodialysis children have lower immune response to hepatitis B vaccine. Higher doses of the vaccine is one of multiple approaches have been used to improve immunogenicity in children on hemodialysis. The goals of this study were to compare rates of hepatitis B immune response following augmented (40 mcg) versus standard doses (20 mcg) of the hepatitis B vaccine in children receiving hemodialysis and to ascertain whether there are any variables influencing the immunological response to vaccination. **Methods:** This randomized control trail (RCT) included 70 hemodialysis children, randomly classified to receive recombinant HB vaccine with two different protocols: the augmented four dosing protocol and the standard three dosing protocol. Anti-HBs titers assessed one month after last vaccine dose. Predictive variables that can affect the immune response were assessed using multivariate analysis. **Results:** HD children who received augmented vaccine dosing had significantly higher seroprotection rate (94.3% had HBsAb>100 mIU/mL) than children who received standard vaccine dosing (77.1% had HBsAb > 100 mIU/mL) with significant difference (p= 0.028). Dose of HB vaccine (95.0% CI, 0.645; 6.685) and serum phosphorus (95.0% CI, -35.320;-2.611) are independent factors affecting the post vaccination titer. **Conclusion:** Augmented HB vaccine approach induced higher immune response in children on hemodialysis.

Keywords: Hepatitis B virus, vaccine, Dose, hemodialysis, children.

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INTRODUCTION

Cardiovascular illnesses and infections are the main causes of mortality and morbidity in pediatric end stage renal disease (ESRD), including those treated by dialysis or transplantation. [1]

Several multicenter surveys indicate that there is a low, yet noteworthy prevalence of HBV infection in dialysis facilities in developed countries. [2]On the other hand, developing-world dialysis centers continue to have significant prevalence and incidence rates of HBV. [3]

Due to blood components transfusions and contaminated dialysis milieu hemodialysis patients are at a higher risk of contracting HBV, which has a negative impact on their survival and quality of life. [4]

The hepatitis B vaccine is one of the key synergistic therapies discovered in the control of HBV, particularly in hemodialysis patients, according to the world health organization. [5] The HBV vaccine advised for chronic kidney disease (CKD) patients and medical personnel since 1982. [6]

It is widely established that after finishing the vaccine schedule, CKD patients have reduced antibody titers; also, anti-HBs titers decline exponentially with time**.** There is strong evidence in the medical literature that patients on maintenance dialysis who receive the full course of the recombinant HBV vaccination (four doses at 0, 1, 2, and 6 months, 20 mcg each dose by intramuscular method) have a seroprotection rate of roughly 50% to 60%. [7]

Age is one of the several clinical, demographic, and biochemical factors that have been suggested as a possible explanation for the low antibody response of HB vaccinations in progressive CKD. Gender, overweight, positive serologic status for HCV**,** history of blood transfusion, interleukin genotypes, ownership of the major histocompatibility complex haplotype HLA-B8, SCOI, DR3, and inadequate nutritional state, also considered of important factors affecting HB vaccination immunity. [8]

Large vaccine doses, extended courses, intradermal vaccine routes, and the use of adjuvants are only a few of the vaccination techniques that have been used to increase seroconversion rates to hepatitis B vaccine among predialysis patients. However, none of these is the most effective. [7]

According to current CDC recommendations, children receiving hemodialysis should receive a regular dose of the hepatitis B booster vaccine (5 mcg for ages 0 to 10 and 10 mcg for ages 11 to 19). The recommendations do, however, added that higher vaccine doses might induce more immunogenicity. [9]

The objectives of this study were to establish the rates of hepatitis B immune response following augmented and standard doses of the hepatitis B vaccine in dialysis children and to discover whether there are any variables influencing the immunological response to vaccination.

PATIENTS AND METHODS

a) Study Group

A randomized controlled study was carried out among 70 children at the Pediatrics hemodialysis center of Zagazig University Hospitals between October 2022 and March 2023. All children who are on regular hemodialysis, aged 3 to 18 years, and had a documented history of having the primary HBV vaccine as infants and whose HBs Ab (anti-HBs) titer was less than 50 IU/mL in our trial were enrolled in the study.

Children who have used immunosuppressive medications in the past, as well as those with immunosuppressive illnesses unrelated to ESRD, a history of HBV infection, and those who have had repeated HBV booster shots since receiving the initial immunization, were all excluded.

b) Study Design

The study carried out through two phases

First phase: A complete history was taken from all participants by either them or their caregivers. It included age, sex, length of dialysis, and the primary causes of CKD. Then Body mass index (BMI) in Kg/m2 calculated using anthropometric measurements of dry weight and height together with a thorough clinical examination.

Second phase: Patients randomly assigned into two groups using stratified block randomization.

Group I (experimental group) received the commercial Hepatitis B vaccination Engerix-B (GlaxoSmithKline) with an augmented protocol (40 mcg), four double intramuscular doses, two 1.0 mL mono-doses at 0, 1, 2, and three months.

Group II (control group) given the standard dose

(20 mcg) in three doses of 1.0mL vaccine vials at 0, 1, and 2 months. The deltoid muscle received the injections of the vaccinations.

Anti-HBs titers were measured one month following the last dose of vaccine.

c) Blood Sampling, Biochemical and immunological assays

Blood samples were collected under complete aseptic and were divided into plain for sera collection and into EDTA containing tube for total blood count (CBC). Colorimetric assays (Spin react, Santa Coloma, Spain) were used to measure biochemical assays such as liver enzymes, serum albumin levels, blood urea nitrogen and creatinine. Ferritin levels were also estimated.

Parathyroid hormone (PTH) concentration was measured by a quantitative enzyme-linked immunosorbent assay (ELISA) kit (Abcam com., USA). Evaluation of HCV-Ab was done by ELISA.

Serum HBsAb concentration were estimated by a quantitative sandwich ELISA kit (AccuDiag™-HBsAb USA) according to the manufacturer's instructions. Except for the blank samples, 50 µL of all standard ones was pipetted into the wells. Then, 50 µL of the streptavidin–horseradish peroxidase (HRP) conjugate was added into each well except the blank sample and mixed. Incubation of the plate was done for 60 minutes at 37 °C and washed 5 times with a diluted wash buffer. 50 µl of chromogen a solution and 50 µl of chromogen B solution were added to each well containing blank and incubated for 15 minutes at 37°C in the dark. The enzymatic reaction between the chromogen solution and the HRP conjugate turned blue in standard wells (except 0 IU/mL) and anti-HBs positive sample wells in the standard curve. Finally, 50 µl of stop solution was added to each well and mixed. The blue solution turned yellow when the reaction was complete. The absorbance of the resulting product assessed colorimetrically at 450 nm. The absorbance was proportional to HBsAb concentration. Non/low responders and high-level responders were defined as anti-HBs ≤ 100 IU/mL and > 100 IU/mL, respectively. [10]

d) Data analysis

SPSS (Statistical Package for the Social Sciences) version 26 was used for data analysis. Means and standard deviations were used to characterize quantitative variables. When necessary, Monte Carlo tests and the chi square test were used to compare categorical variables and to describe them using their absolute frequencies. The chi square for trend testing was employed for ordinal binary data. To validate assumptions for use in parametric tests, Kolmogorov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests were utilized. Independent sample t tests (for normally distributed data) and Mann Whitney tests (for non-normally distributed data) were used to compare quantitative data between two groups. Wilcoxon signed rank test was utilized to compare changes in the same variable between two points in time within one group. The Kruskal Wallis test was used to compare quantitative non-normally distributed data between more than two groups. The strength and connection of the correlation between two continuous, non-normally distributed variables were measured using the Spearman rank correlation coefficient..The measurement of related independent factors for the dependent factor and the prediction of the value of a variable based on value of another variable were done using linear regression analysis. P 0.05 was used as set the statistical significance level. If $p \leq 0.001$, a highly significant difference was evident.

ETHICAL APPROVAL:

The approval for the study was obtained from the pediatrics departments of Zagazig University after approval of the Ethical Committee of Zagazig University (ZU-IRB #10017) and informed written consent was obtained in every case from their legal guardians. The study was concordant with the code of ethics for human studies "Declaration of Helsinki".

RESULTS

This study included 70 patients; 35 patients within group I received four doses of 40 mcg HB vaccine while group II received three doses of 20 mcg .

Baseline data of the studied groups were studied and there is statistically non-significant difference between both groups as regard age, gender, hepatitis C, disease onset, underlying etiology, or laboratory data. Larger percentage within both groups were males (65.7% and 51.4% within group I and II respectively). About 29% and 23% within group I and II respectively

had positive hepatitis C. similarly larger percentage within each group had nephrotic syndrome (31.4% within group I and 25.7% within group II) followed by obstructive uropathy (25.7% within group I and 17.1% within group II). (table 1)

Table 1. Comparison between the studied groups regarding baseline data

Parameter	Group I	Group II	Test	p
Male sex n (%)	23 (65.7%)	18 (51.4%)	1.472	0.225
Positive HCV	10 (28.6%)	8 (22.9%)	0.299	0.584
Age (y)	13.83 ± 3.55$^{\infty}$	12.01 ± 4.09$^{\infty}$	1.98	0.052
Height (m)	1.27 ± 0.19$^{\infty}$	1.21 ± 0.27$^{\infty}$	1.158	0.252
Weight (kg)	33 (19.5 – 41) $^{¥}$	34 (18.5 – 41) $^{¥}$	-0.294	0.769
BMI (kg/m^2)	19 (16 – 21) $^{¥}$	19 (14 – 23) $^{¥}$	-0.194	0.846
Duration of dialysis(y)	4(1.88 – 7.25) $^{¥}$	4(0.75 – 9) $^{¥}$	-0.072	0.942
Hemoglobin (g/dl)	10.07 ± 1.26$^{\infty}$	9.62 ± 0.65$^{\infty}$	1.874	0.065
TLC (10^{*3}/ul)	7.0 ± 2.17$^{\infty}$	7.43 ± 1.84$^{\infty}$	-0.902	0.37
Platelet count (10^{*3}/ul)	249.4 ± 80.16$^{\infty}$	249.51 ± 85.66$^{\infty}$	-0.006	0.995
CRP (mg/dl)	3.6 (0.7 – 8.1) $^{¥}$	4.24 (1.1 – 8.4) $^{¥}$	-1.142	0.253
BUN (mg/dl)	50.2 (42 – 57) $^{¥}$	49.5 (40.5 – 64.5) $^{¥}$	-0.135	0.893
Creatinine (mg/dl)	6.63 ±1.66$^{\infty}$	7.4 ± 1.83$^{\infty}$	-1.842	0.07
Calcium (mg/dl)	7.92 ± 1.34$^{\infty}$	8.04 ± 1.27$^{\infty}$	-0.385	0.701
Phosphorus (mg/dl)	6.26 ± 1.54$^{\infty}$	7.02 ± 2.12$^{\infty}$	-1.723	0.089
PTH(pg/mL)	287 (78.2 – 763.9) $^{¥}$	448 (86 – 1030) $^{¥}$	-1.334	0.182
Ferritin (ng/ml**)**	778 (720 – 860) $^{¥}$	1101 (645.2 – 1655) $^{¥}$	-1.71	0.087
Vitamin D (ng/ml**)**	22 (10 – 27) $^{¥}$	18.4 (11 – 23.7) $^{¥}$	-1.472	0.141
Etiology:				
Nephrotic syndrome	11 (31.4%)	9 (25.7%)		
HUS	3 (8.6%)	2 (5.7%)		
Atrophy	4 (11.4%)	8 (22.9%)	MC	0.343
Idiopathic	0 (0%)	4 (11.4%)		
Neurogenic bladder	3 (8.6%)	3 (8.6%)		
Obstructive uropathy	9 (25.7%)	6 (17.1%)		
Uretero-renal reflux	2 (5.7%)	0 (0%)		

Ns all parameters $^{¥}$data is represented as median and interquartile range and compared using Mann Whitney test $^{\infty}$data is represented as mean and standard deviation and compared using independent sample t test data is represented as frequency and percentage and compared using chi square test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant MC Monte Carlo test

Antibody titer was comparable between both groups before vaccination while after vaccination, The group received dose 40 mcg had significantly higher antibody titer (median 413.72 within group I versus 343.12 within group II). Two patient within group I (5.7%) had titer less than 100 IU/mL versus eight patients (22.8%) within group II while 33 patients within group I (94.3%) had titer more than 100 IU/mL versus 27 patients (77.1%) within group II. (Table 2)

Table 2. Comparison between the studied groups before and after vaccination

Parameter	Group I		Group II		Z	p
Baseline AntiHBs Median (IQR)	0 (0 – 4.8)		0 (0 – 4.98)		-0.628	0.53
Post vaccination antiHBs Median (IQR)	413.72(350.18- 426.07)		343.12 (220.79 – 399.04)		-2.311	0.011*
P (Wx)	<0.001**		<0.001**			
AntiHBs titer 1 month after last vaccine	**Group I**		**Group II**		**F**	**p**
	(*n* = 35)	**%**	**(*n* = 35)**	**%**		
≤100 IU/mL	2	(5.7%)	8	(22.8%)		0.028*
>100 IU/mL	33	(94.3%)	27	(77.1%)		

Wx Wilcoxon signed rank test Z Mann Whitney test IQR interquartile range
F Fishers Exact Test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

There is statistically significant positive correlation between post-vaccination antibody titer and all of body mass index, and dose of vaccination, and there is significant negative correlation between it and serum phosphorus. The relationship between antibody titer and other investigated factors is not statistically significant. (Table 3)

Table 3. Correlation between post-vaccination antiHBs titers and the studied parameters

	R	**p**
Age (year)	0.202	0.093
Height (m)	0.002	0.984
Weight (kg)	0.167	0.167
BMI (kg/m^2)	0.385	0.001**
Hemoglobin (g/dl**)**	-0.001	0.995
TLC (10^{*3}/ul)	0.132	0.275
Platelet count (10^{*3}/ul)	-0.034	0.782
CRP (mg/dl)	-0.082	0.499
BUN (mg/dl)	-0.055	0.649
Creatinine (mg/dl)	0.065	0.594
Calcium (mg/dl)	0.031	0.796
Phosphorus (mg/dl)	-0.302	0.011*
PTH (pg/ml)	0.216	0.073
Ferritin (ng/ml)	0.119	0.328
Vitamin D (ng/ml)	0.22	0.67
Dose	0.328	0.006*
HCV	-0.115	0.343
Dialysis duration (year)	0.12	0.326
Gender	-0.152	0.21

r Spearman rank correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

There is statistically non-significant association between post-vaccination hepatitis B antibody titer and underlying etiology. (Table 4)

Table 4. Relation between post hepatitis vaccination antiHBs titers and underlying etiology

	Median	**IQR**	**Kw**	**P**
Nephrotic syndrome	390.42	334.27 – 419.9		
HUS	329.61	174.89 – 487.94		
Atrophy	340.21	71.86 – 417.92		
Idiopathic	399.04	154.38 – 399.04		
Neurogenic bladder	422.58	397.99 – 431.43		
Obstructive uropathy	367.12	317.72 – 454.5	**6.597**	**0.472**
Uretero-renal reflux	413.02	384.13 – 441.92		
Unknown	395.08	301.88 – 395.08		

IQR: Interquartile range. KW: Kruskal-Wallis test

On analyzing parameters that are correlated significantly with the post-vaccination antibody titer using linear regression, BMI (unstandardized β=3.13, p=0.054), vaccination dose (unstandardized β=3.665, p=0.018) and serum phosphorus (unstandardized β=-18.966, p=0.024) independently associated with it.

(Table 5)

Table 5. linear regression analysis of factors independently associated with post-vaccination antiHBs titer

	Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval	
	β	Std. Error	β	t	p	Lower	Upper
(Constant)	301.435	97.439		3.094	**0.003***	106.891	495.979
BMI	3.130	1.596	0.226	1.961	0.054	-0.057	6.316
Dose	3.665	1.513	0.277	2.423	**0.018***	0.645	6.685
Phosphorus	-18.966	8.191	-0.267	-2.315	**0.024***	-35.320	-2.611

*p<0.05 is statistically significant

DISCUSSION

Incomplete course of hepatitis B vaccine can affect immune response. Acute hepatitis B infection tends to be mildly symptomatic in hemodialysis patients, but still there is risk of progression to chronic hepatic disease and nosocomial transmission throughout dialysis units. [11]

The reason for the decline in the HBsAb titers is not well comprehended. Early dialysis initiation, advanced age, malnutrition, and a low initial antibody response have all been linked to a shorter duration of immunity. **[12, 13]**

The present study conducted a comparative study of the effectiveness of the high-dose versus standard-dose Hepatitis B virus vaccines among children with chronic kidney disease undergoing regular hemodialysis in the Pediatric Kidney Unit, Zagazig University Hospital for Children. Egypt.

There was no statistically significant difference between the two groups for age, sex, hepatitis C, duration of dialysis, underlying etiology, or laboratory data. Both groups were predominantly male (65.7% and 51.4% within group I and II respectively). These results are consistent with those reported *by Misurac et al*. [14] Similarly, *Roozbeh et* al.**[15]** demonestrated that age, sex, and serum albumin concentration did not vary between hepatitis B vaccine responders and non-responders. In contrast to other studies proved the significant negative correlation between antibody titer and patient age. **[4, 16]**

Around 29% and 23% within group I and II respectively tested positive for hepatitis C. Similarly, a greater proportion of individuals in each group had nephrotic syndrome (31.4% within group I and 25.7% within group II) followed by obstructive uropathy (25.7% within group I and 17.1% within group II) (table 1)

In this research, the antibody concentration of an augmented vaccine dosage (40 mcg/dose) was contrasted with the standard three vaccine dosage (20 mcg/dose) in a group of 70 chronic haemodialysis children. Group 1 exhibited a marked increase in antibody levels (mean 413.72 in group I vs 343.12 in group II), with high level response in 94.3% in group I.

These findings are congruent with those of *Tong et al.***[17]** who conducted a randomized clinical study in which predialysis and hemodialysis cases were separated into two groups and dosed at 20 g and 40g at 0, 1, 2 and 6 months, attaining response in 91% versus 84%, respectively.

Siddiqui et al. [18] also evaluated the efficacy of four 40g doses of vaccine to three 20g doses of vaccine in 130 CKD patients and found that seroprotection was achieved in 68.7% and 57.7% of the cases, respectively.

Agarwal et al. [20] found that dialysis patients who did not seroconvert after three doses of therapy frequently did so after the fourth. They compared 2 regimens of HBV vaccine 40 µg in patients with all stages of CKD: 0, 1 and 2 months (3- dose group) versus 0, 1, 2 and 6 months (4-dose group). Seroconversion rates in patients with mild, moderate and severe CKD were 87.5%, 66.6%, and 35.7%, respectively, in the 3-dose group, and 100%, 77%, and 36% in the 4-dose group. They concluded that CKD patients at the earliest stage of the disease should be immunized with 40 ug of the vaccine and that four doses are preferable to three treatments.

According to Edey et al. [21], a 3-dose HBV vaccination regimen can result in a 90-95% seroprotection rate in immunocompetent persons; however, rates were lower in those with renal insufficiency. They proposed that dialysis

patients receive greater doses of the vaccine, such as 40ug at 0, 1, and 6 months or 40ug at 0, 1, 2, and 6 months to boost the immune response. Because of the low response rate to the HBV vaccination in HD patients, physicians are now using a higher dose (40 µg) and at more frequent intervals (0, 1, 2 and 6 months). In this study, there is significant positive correlation between post-vaccination antibody titers and BMI.

Misurac et al and Mulley found antagonizing results, as they didn't detect increase in immune response after increasing vaccine dose. [14, 22]

BMI significantly affects the rate of hepatitis B vaccine response in Belgium [23], China [24], and Turkey [25]. The low hepatitis B vaccine response rate in people with greater BMI may be related to the vaccine being distributed in fat rather than muscle, which limits absorption.

Young et al.[26] found that obese individuals (BMI $\geq 30 kg/m^2$) were considerably more likely than non-obese people (adjusted odds ratio 8.75; p=0.043) to not respond to 2 doses of recombinant hepatitis B vaccine, which was similar to our results. They also discovered no correlation between vaccination response and age. Obesity does not reduce response to initial HBV vaccination regimens, but has been suggested to shorten the lifetime of protective immunity. [27]

Studies by *Purvi et al*. [28] and *Kollathodi et al*. [29] discovered no link between BMI and non-response to hepatitis B vaccine.

The correlation of a patient's post vaccination antibody titer with age was not significant in this study. However, a recent meta-analysis of 17 clinical trials found that older dialysis cases had a lower response to hepatitis B vaccination, possibly related to age-associated changes in immunological state. [30] This effect was not found in our study because our dialysis patient sample was younger than in other studies. [31]

Comparable to data from other sources, we did not find any correlation between gender and post-vaccination antibody titers. [28, 29, 32]

Roozbeh et al. [15] found no gender differences between responders and non-responders, consistent with this study. Some studies have reported an association between gender and titers <10 mIU/mL. Males are less responsive, but others indicate that females are. **[33]**

Albumin levels had no effect on hepatitis B antibody titers after vaccination in this study. These results agree with those reported by *Roozbeh et al.* [21]. *As* previously observed, the duration of HD before to immunization had no effect on vaccine response. **[40]**

However, Fernandez et al. [34] demonstrated that in hemodialysis patients, malnutrition negatively impacted HBV vaccination. In comparison to patients with serum albumin between 4.5 and 5g/dl (18.8%), those with serum albumin between 3 and 3.5g/dl had a higher non-response rate (87.5%). *Kara et al.***[39]**also showed that hemodialysis patients with serum albumin levels >3.5g/dl showed an excessive antibody response to hepatitis B vaccine.

There was no significant relationship between CRP level and post-vaccination antibody titer in the current study. This observation can be explained by the differential production of anti-inflammatory cytokines such interleukin-10 (IL-10), which results in improved B-cell activity in dialysis patients. Patients with increased IL-10 levels had lower uremia and chronic inflammation caused by dialysis, and they respond better to vaccinations.**[36]**

In this study, positive anti-HCV status had no effect on HBV vaccination in hemodialysis patients. This was previously reported by Taiwanese studies. **[38, 37]**

Contrary to an earlier finding that vitamin D deficiency is linked to a poor response to active HBV immunization in patients with CKD, this study found no significant correlation between vitamin D levels and post-vaccination antibody titer. **[39]** However, it has not been demonstrated that taking 1a, 25-Dihydroxyvitamin-D3 helps HD patients respond to the HBV vaccine. **[38]**

The cause of CKD was nephritic syndrome in 11 (31.4%) in group I and nine (25.7%) in group II of our patients. The underlying cause of CKD had no significant impact on the post-vaccination antibody titer. These results agree with those documented by *Al Saran et al.***[40]**

STUDY LIMITATIONS

Our results were limited by many factors. We assessed immunogenicity at one-month post vaccination but still long-term protection is

unknown. Also small sample size and single center study could affect reliability of our results. So further studies with longer follow up period might be needed.

CONCLUSIONS

HD children who received augmented vaccine dosing had significantly higher seroprotection rate than children who received standard vaccine dosing. Dose of HB vaccine and serum phosphorus are independent factors affecting the post vaccination titer. We recommend monitoring of antibody titers periodically and maintenance of antiHBs titer in a seroprotection level by higher doses of secondary vaccination.

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REFERENCES

1. **Saran, R., Robinson, B., Abbott, K., Agodoa, L., Bragg-Gresham, J., Balkrishnan, R., et al.,** US renal data system 2018 annual data report: epidemiology of kidney disease in the United States. Am. J. Kidney Dis., 2019, 73, 1:A7–8.
2. **Garcia Agudo, R., Aoufi Rabih, S., Barril Cuadrado, G., Proy Vega, B., Arias Arias, A., Herruzo Gallego, J. A., et al.,** Spanish multicentre PIBHE study., Prevalence and immunization of chronic hepatitis B in haemodialysis patients in Spain., Nefrologia., 2016, 36, 126–32.
3. **Johnson, D. W., Dent, H., Yao, Q., Tranaeus, A., Huang, C. C., Han, D. S., et al.,** Frequencies of hepatitis B and C infections among haemodialysis and peritoneal dialysis patients in Asia-Pacific countries. analysis of registry data., Nephrol Dial Transplant., 2009, 24, 1598–603.
4. **Almueilo, S., H.,** Evaluation of Response to Hepatitis B Vaccination in Chronic Hemodialysis Patients., Saudi. J. Med Sci., 2017, 5,218-223.
5. **Nick, S., Anna, P., Christopher, M., et al.,** Cost-effectiveness of the controlled temperature chain for the hepatitis B virus birth dose vaccine in various global settings: a modelling study., Lancet Global Health., 2018, 6, 67–659.
6. **Finelli, L., Miller, J.T., Tokars, J.I., Alter MJ, Arduino MJ.** National surveillance of dialysis-associated diseases in the United States, 2002. Semin Dial. 2005, 18, 52-61
7. **Krueger, K. M., Ison, M. G., Ghossein, C., et al.,** Practical guide to vaccination in all stages of CKD, including patients treated by dialysis or kidney transplantation., Am. J. Kidney Dis. 2020, 75, 417–425.
8. **Fabrizi, F., Martin, P., Dixit, V., Bunnapradist, S., Dulai, G.,** Meta-analysis: the effect of age on the immunological response to hepatitis B vaccine in end-stage renal disease., Aliment Pharmacol Ther., 2004, 20, 1053–62
9. **Mast, E. E., Margolis, H. S., Fiore, A. E., Brink E. W., Goldstein, S. T., Wang, S. A., et al.,** A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: Immunization of infants, children, and adolescents. MMWR. Recomm. Rep., 2005, 54, 1–31
10. **Centers for Disease Control.** Guidelines for Vaccinating Kidney Dialysis Patients and Patients with Chronic Kidney Disease. Summary of ACIP Recommendations., 2012.
11. **Urbanek,** "Viral hepatitis infections in chronic kidney disease patients and renal transplant recipients," Kidney and Blood Pressure Research., 2012, 35, 454–467.
12. **Dinits-Pensy, M., Forrest, G. N., Cross, A. S.,** The use of vaccines in adult patients with renal disease., Am J Kidney Dis., 2005, 46, 997–1011.
13. **Tsouchnikas, I., Dounousi, E., Xanthopoulou K et al.** Loss of hepatitis B immunity in hemodialysis patients acquired

either naturally or after vaccination., Clin Nephrol., 2007, 68, 228–234.

14. **Misurac, J. M., Vandevoorde., R. G., Kallash., M., Iorember., FM., Luckritz KE., Rheault MN et al.,** Immunogenicity of augmented compared with standard dose hepatitis B vaccine in pediatric patients on dialysis: A midwest pediatric nephrology consortium study. Clinical Journal of the American Society of Nephrology., 2017, 12, 772-778.
15. **Roozbeh, J., Moini, M., Lankarani, K. B., Sagheb, M. M., Shahpoori, S., Bastani B.** Low dose intradermal versus high dose intramuscular hepatitis B vaccination in patients on chronic hemodialysis., ASAIO. J. 2005, 51, 242-5.
16. **Chow, K. M, Law, M. C, Leung, C. B, Szeto, C. C., Li, P. K.,** Antibody response to hepatitis B vaccine in end-stage renal disease patients. Nephron. Clin. Pract., 2006, 103, c89–c93
17. **Tong, N. K., Beran, J., Kee, S. A., et al.,** Immunogenicity and safety of an adjuvanted hepatitis B vaccine in pre-hemodialysis and hemodialysis patients., Kidney Int., 2005, 68, 2298.
18. **Siddiqui, S., Malik, A, Shukla I, et al.,** Seroprotection after hepatitis B vaccination in chronic kidney disease patients with modified schedule and dosage., J. Infect. Dev Ctries., 2010, 4,389.
19. **Rosman, A. S, Lieber, C. S.,** Improving the response to hepatitis B vaccine., Infect. Med., 1999, 16, 205-1810.
20. **Agarwal, S. K., Irshad, M., Dash, S. C.,** Comparison of two schedules of hepatitis B vaccination in patients with mild, moderate and severe renal failure., J. Assoc. Physicians India., 1999, 47, 183-5.
21. **Edey, M., Barraclough, K., Johnson, D. W.,** Review article: Hepatitis B and dialysis. Nephrology (Carlton)., 2010, 15, 137-45.
22. **Mulley, W. R., Le, S.T., Ives, K.E.,** Primary seroresponses to double-dose compared with standard-dose hepatitis B vaccination in patients with chronic kidney disease: a systematic review and meta-analysis., Nephrol Dial Transplant., 2017, 32, 136-143.
23. **Van Damme, P.,** Long-term protection after hepatitis B vaccine., J Infect Dis., 2016, 214,1-3.
24. **Yang, S., Ding, C., Cui, Y., Wu, J., Yu, C., Chen, P., et al.,** Prevalence and influencing factors of hepatitis B among a rural residential population in Zhejiang Province, China: A cross-sectional study., BMJ Open., 2017, 7, 014947.
25. **Asan, A., Demirhan, H., Sorkun, H. Ç., Özkan, S., Aydin, M., Akin, D., et al.,** Factors affecting responsiveness to hepatitis B immunization in dialysis patients., Int Urol Nephrol., 2017, 1-6.
26. **Young, K. M, Gray, C. M., Bekker, L. G.,** Is obesity a risk factor for vaccine non-responsiveness? PLoS One., 2013, e82779
27. **Morse, C. G, High, K. P.,** Nutrition, immunity and infection. In: Bennet JE, Dolin R, Blaser MJ (eds) Principles and practice of infectious diseases. Elsevier, Sounders, Philadelphia., 2015, 125–133
28. **Purvi, K., Rupal, P., Chirag, M.,** Hepatitis B immunization on status of health care personnel. Natl J Integr. Res. Med. 2018, 9,37-42
29. **Kollathodi, N., Moorkoth, A. P., George, K., Narayanan, M. P., Balakrishnan, S. M., LelithaBai, S. D.,** Hepatitis B vaccination-immune response and persistence of protection in susceptible population., J Acad Clin Microbiol., 2017, 19, 42-6.
30. **Vlassopoulos, D., Magana, P., Haji Yamakos., et al.,** Factors involved in low response to HBV vaccine in health and end-stage renal failure., Nephrol Dial Transplant., 1998, 13, A191.
31. **Dack,o C., Holly, J.,** The influence of nutritional status, dialysis adequacy, and residual renal function on the response to hepatitis B vacci- nation in peritoneal dialysis patients., Adv Perit Dial., 1996, 12, 315-7.
32. **Bwell, R. J., Neumann M, Baile, G. R.,** Factors associated with long term antibody production induced by hepatitis B vaccine in patients undergoing hemodialysis,. A retrospective cohort study., Pharmacotherapy., 2003, 23, 1558-63.

33. **OSHA Factsheet.,** Hepatitis B Vaccination Prevention. Available from: https://www.osha.gov/OshDoc/data_BloodborneFacts/bbfact05. pdf. [Last accessed on 2019 Jul 18]
34. **Fernandez, E., Betriu, M. A, Gomez, R., et al.,** Response to the hepatitis B virus vaccine in hemodialysis patients: influence of malnutrition and its importance as a risk factor for morbidity and mortality., Nephrol Dial Transplan., 1996, 1 1,1 559-1563.
35. **Kara, 1., Yilmaz, M., Suner, A, et al.,** The evaluation of immune responses that occur after HBV infection and HBV vaccination in hemodialysis patients., Vaccine. 2004., 22, 3963-3967.
36. **Girndt, M., Kohler, H., Schiedhelm-Weick, E., et al.,** Production of intereukin6, tumor necrosis factor_ and interleukin-1O in vitro correlates with the clinical immune defect in chronic hemodialysis patients., Kidney tnt., 1995, 47, 559-565.
37. **Majdan, M., Polz, M., Ksiazek, A., et al.** The response to the hepatitis B virus vaccine in patients undergoing hemodialysis and peritoneal dialysis-personal experience., Przegl Lek. 1995, 52, 307-310.
38. **Tele, S. A., Martins, R. M., Lops, C. L., dos Santos Carneiro, M. A., Souza, K. P., Yoshida, C. F.,** Immunogenicity of a recombinant hepatitis B vaccine in hemodialysis patients and stuff., Eur. J. Epidemiol., 2001, 17, 145-9.
39. **Zitt, E., Sprenger-Mähr, H., Knoll, F., Neyer, U., Lhotta, K.,** Vitamin D deficiency is associated with poor response to active hepatitis B immunisation in patients with chronic kidney disease., Vaccine 2012, 30, 931-935
40. **Al Saran, K., Sabry, A., Al Halawany, Z., et al.,** Factors affecting response to hepatitis B vaccine among hemodialysis patients in a large Saudi Hemodialysis Center., Saudi J Kidney Dis Transpl., 2014, 25, 85–191.