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Assessment of Immune Response to Pneumococcal Conjugate Vaccine in Hemodialysis Children after One Year

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ABSTRACT

Background: Pediatric patients with impaired immune systems, including those with chronic renal failure, should receive pneumococcal vaccinations which have a great role in prevention of chest infections.

Objective: The aim of the current work was to evaluate immune response for Pneumococcal Conjugate Vaccine 13 (PCV13) in Hemodialysis (HD) children after 3 months 1 year and 2 years of vaccination.

Patients and methods: Thirty-six children and adolescent on regular HD were included in this trial. All patients were not previously vaccinated by PCV13. We had determined pneumococcal immunoglobulin (IgG) antibodies 3 months, 1 year and 2 years after vaccination by PCV13. This study was carried out in Dialysis Nephrology Unit at Zagazig University Hospital of Children.

Results: As regard frequency of chest infection after PCV13, there was a statistically significant decrease in frequency for patients who developed chest infections after PCV vaccinations from 75% to 16.7%. Chest infections and antibody titers were statistically linked at three months, one year, and two years. The best cutoff of serum antibody titer at 2 years≥0.03825 for prediction of absence of infection with area under curve 0.917, sensitivity 90%, specificity 83.3%, positive predictive value 96.4% and negative predictive value 62.5% and accuracy 91.7% ($p<0.05$).

Conclusion: It is possible for patients with end-stage renal disease (ESRD) and dialysis to produce enough antibodies against the PCV13 vaccine to reduce their risk of developing chest infections. Adequate protective concentration of antibody post PCV13 which is higher than 0.35ug/ml was maintained for most of cases at 1 year.

Keywords: Pneumococcal Conjugate Vaccine, Hemodialysis.

INTRODUCTION

Bacterial Streptococcus pneumoniae infection is the cause of pneumonia, bacterial hemorrhage, meningitis as well as otitis media [(1)].

Pneumococcal infection is more common in people who are on dialysis because of advanced renal impairment [(2)].

Dialysis patients are 10 to 16 times more likely to die of pneumonia than the general population. Pneumococcal strains that are resistant to numerous antibiotics have exacerbated this problem. Pneumococcal illness has become a major concern for this population of individuals because of this [(3)].

Pneumococcal infection can be prevented with two vaccinations [(4)]. One vaccination is required. Because children under the age of 2 are more susceptible to a variety of serious diseases, including pneumonia, bacterial meningitis, and bacterial meningitis, the pneumococcal conjugate vaccination (PCV13) is essential. In some cases, older children may additionally require PCV13 treatment [(5)].

The second vaccine is now available for use. Children two years of age and older should be vaccinated with the pneumococcal polysaccharide vaccine (PPSV23). Pneumococcal disease is prevented with this vaccine [(6, 7)].

Strict guidelines have been put in place for people with chronic renal illness to receive a pneumococcal immunization. Vaccination and revaccination, on the other hand, have varying effects, and the appropriateness of vaccination is up for debate [(8)].

PPSV23 and PCV13 vaccines differ greatly in their construction. Capsular polysaccharide antigens are included in PPSV23. T-cell-independent antibodies are elicited in response to certain antigens. Immunoglobulins produced increase phagocytic cell activity and cause pneumococcus death. Polysaccharides from the capsular polysaccharides are conjugated with a protein carrier to form PCV13. Adding the protein to PCV13 activates a T-cell-dependent immunological response, which results in the creation of antibodies and the possibility for immune memory [(9, 10)].

Dialysis patients have a compromised immune system, which raises the risk of serious infections. In dialysis patients, pneumococcal illness is prevalent, with S. pneumonia accounting for more than half of all reported cases of pneumonia [(11)]. For patients with chronic kidney disease, the risk of pneumococcal infection is higher for those who do not establish a sufficient immune response to PPSV23 [(12)].

Antigen presentation, T-cell-mediated immune response, and immunological memory are all impaired in patients with ESRD, which has a negative impact on their overall health [(11, 13)]. As a result, vaccination hypo responsiveness is a real possibility for these people. According to research, patients on dialysis have a lower immune response to PPSV23 than healthy individuals. Furthermore, within one year of immunization with PPSV23, patients with end-stage renal disease (ESRD) show a rapid reduction in anti-pneumococcal IgG levels [(14)].

This study's purpose was to evaluate immune

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response for PCV13 in Hemodialysis (HD) children after 3 months 1 year and 2 years of vaccination.

PATIENTS AND METHODS

This cross-sectional trial study included a total of 36 children and adolescent on regular HD, attending at Pediatric Nephrology Unit, Children Hospital, Zagazig University. This study was conducted over a period of one year from February 2020 and January 2021.

Inclusion Criteria: Age ranged 2-8 years, both sexes. All children included in the study were end stage renal failure on regular HD, and before the research, no one had been vaccinated by PCV13 against pneumococcal disease.

Exclusion Criteria: Previous vaccinated HD children and adolescents by pneumococcal conjugate vaccine before time of study, patients with neutropenia, and present or recent (Less than 3 month) Immunosuppressive medicine, such as corticosteroid therapy.

***Ethical Consideration*:**

An approval of the study was obtained from Zagazig University Academic and Ethical Committee (ZU-IRB#7801). Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

All study groups underwent the following:

1. History taking: Full history was collected and special care for renal history onset, course and management plan with hemodialysis and family history taken

2. Clinical examination: General examinations, with weight, BMI, and height assessment.

3. Laboratory investigations: Complete blood count (CBC), and serum levels of albumin, urea, creatinine, calcium, phosphorus, iron, ferritin and PTH were determined.

Specific investigation: Assess serum antibody titer for PCV13 after 3 months, 1 year and 2 years.

Immunization procedures:

All the study patients (n=36) undergoing hemodialysis had taken the pneumococcal conjugate vaccine. For those who were not immune to the thirteen pneumococcal serotypes in the pneumococcal conjugate vaccine (Prevenar; Wyeth Madison, NJ), a single 0.5 ml intramuscular injection of the vaccine was given (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) of which the diphtheria protein was a conjugation

Assessment of Antibody response:

For testing the efficacy of pneumococcal conjugated vaccinations in babies, the World Health Organization (WHO) recommends a concentration of 0.35 μg/ml [(15)].

Antibody generation following vaccination was determined by the WHO's criteria as equal or higher than 0.35 μg/ml for each vaccine serotype and by at least four-fold rise in the baseline concentration of IgG for each vaccine serotype [(16, 17)]. "Sufficient" antibody production was defined in our study as a post-vaccination antibody production of 0.35 μg/ml or greater, which we categorized as "adequate" in our study.

A 2-fold increase in antibody concentration and a postvaccination absolute concentration of at least 1 g/ml were used to identify a vaccine serotype response [(18)].

All patients were monitored for a period of 12 months after their first discharge. Each and every one of the vaccinated participants made it through the trial without missing a beat. According to the nature and distribution of the factors tested, the results were evaluated.

Statistical analysis

The IBM SPSS software programme version 20.0 was used. The range (minimum and maximum), mean, standard deviation, median, and interquartile range were used to characterize quantitative data (IQR). In order to determine the significance of the acquired results, a 5-percent threshold was used. It was a Chi-square test. For categorical variables, chi-square correction for more than 20% of cells with anticipated count less than 5 was required, Student t-test: to calculate the quantities of data of normal distribution and to compare between two studied groups. P value < 0.05 was considered significant.

RESULTS

Female predominant represented by 52.8% of the study patients. Age ranged from 5 to 18 years with mean 13.194 years. Weight ranged from 15 to 46 kg with mean 32.042 kg. Height ranged from 98 to 160 cm with mean 132.44 cm. BMI ranged from 13.23 to 23.46 kg/m^2 with mean 17.754±2.354 (**Table 1).**

Table (1): demographic data

	Variable	N=36	%
Gender:	**Female**	19	52.8
	Male	17	47.2
Age (year):	**Mean ± SD**	13.194 ± 3.293	
	Range	5 – 18	
Weight (kg):	**Mean ± SD**	32.042 ± 9.366	
	Range	15 – 46	
Height (cm):	**Mean ± SD**	132.44 ± 17.606	
	Range	98 – 160	
BMI (kg/m^2)	**Mean ± SD**	17.754 ± 2.354	
	Range	13.23 – 23.46	

There was statistically significant decrease in antibody titer over time. The difference is significant on comparing antibody titer at each two points of time (Table 2).

Table (2): Antibody titers over time among the studied patients:

Time	**Antibody titer**		**P**
	Median	**Range**	
At 3 months	7.915 µg/ml	2.99 – 9.72	<0.001**
At 1 year	3.334 µg/ml	0.093 – 6.18	<0.001**
At 2 years	0.24 µg/ml	0.013 – 0.85	<0.001**
P (Fr)	<0.001**		

There was statistically significant association between presence of chest infections and antibody titer at 3 month, 1 and 2 years (Table 3).

Table (3): Relation between level of antibody titer over time and occurrence of chest infection after vaccination:

Antibody titer	**Chest infection**		**Test**	
	No	**Yes**	**Z**	**P**
	Median (range)	**Median (range)**		
At 3 month	8.21 (3.12 – 9.72)	4.585 (2.99 – 5.24)	-2.463	0.014*
At one year	3.955 (0.093 – 6.18)	1.32 (0.792 – 1.83)	-2.462	0.014*
At 2 years	2.66 (0.013 –0.85)	0.029 (0.013 – 0.052)	-3.184	0.001**
P	0.001**	0.002*		

There was statistically significant association between cause of renal failure and antibody titer at 3 months. On LSD comparison, the difference is significant between glomerular cause and each of unexplained RF, obstructive uropathy and nephritis. Also, the difference was significant between unexplained RF and each of glomerular, congenital causes and nephritis. Also, the difference was significant between obstructive uropathy and each of glomerular, congenital causes and nephritis. Also, the difference was significant between congenital causes and each of unexplained RF, congenital causes and nephritis. Also, the difference was significant between nephritis group and each other group (Table 4).

Table (4): Relation between cause and antibody titer at 3 months, among the studied patients:

	Antibody titer at 3 months		**Test**	
	Mean ± SD	**Range**	F	p
Glomerular	4.14 ± 0.79	2.99 – 5.24	47.661	<0.001**
Unexplained	8.91 ± 0.57	8.12 – 9.72		
Obstructive uropathy	9.06 ± 0.35	8.21 – 9.73		
Congenital	5.22 ± 2.84	3.21 – 7.22		
Interstitial	6.93 ± 1.38	5.21 – 8.21		

There is statistically significant association between cause of renal failure and antibody titer at 1 years. On LSD comparison, the difference is significant between each two groups, There was statistically significant association between cause of renal failure and antibody titer at 2 years. On pairwise comparison, the difference was significant only between glomerular cause and each unexplained RF and those with obstructive uropathy (Table 5).

Table (5): Relation between cause and antibody titer at 1, 2 years among the studied patients.

	Antibody titer at 1 year		Test	
	Mean ± SD	Range	F	p
Glomerular	1.04 ± 0.46	0.09 – 1.83	62.704	<0.001**
Unexplained	5.76 ± 0.34	5.21 – 6.18		
Obstructive uropathy	4.62 ± 1	3.25 – 5.92		
Congenital	2.25 ± 1.36	1.29 – 3.21		
Interstitial	3.77 ± 0.67	3.21 – 4.93		
	Antibody titer at 2 year		**Test**	
	Median	**Range**	**KW**	**P**
Glomerular	0.037	0.09 – 1.83	25.683	<0.001**
Unexplained	0.32	0.12 – 0.46		
Obstructive uropathy	0.362	0.26 – 0.85		
Congenital	0.22	0.19 – 0.25		
Interstitial	0.253	0.03 – 0.31		

There was significant negative correlation between antibody titer at 1 year and TLC. There was non-significant correlation between antibody titer at 1 year and the other studied laboratory parameters, there was statistically significant positive correlation between antibody titer after two years and weight and significant negative correlation between it and frequency of dialysis. On the other hand, there was non-significant correlation between antibody titer and any of other studied parameters (Table 6).

Table (6): Correlation between antibody titer at 1 year and laboratory data of the studied patients, Correlation between antibody titer at 2 years and some clinical data of the studied patients

Variable	Antibody titer at 1 year	
	r	P
Hemoglobin (g/dL)	**-0.273**	**0.108**
TLC (10^3/mm^3)	**-0.366**	**0.028***
Platelet count (10^3/mm^3)	**-0.066**	**0.704**
Serum albumin (g/dL)	**0.108**	**0.532**
Serum urea (mg/dL)	**0.1**	**0.561**
Serum creatinine (mg/dL)	**0.212**	**0.214**
Serum calcium (mg/dL)	**0.098**	**0.569**
Serum phosphate	**-0.018**	**0.917**
Serum iron (mcg/dL)	**-0.283**	**0.094**
Serum ferritin (ng/mL)	**-0.305**	**0.07**
Parathyroid hormone (pg/mL)	**-0.178**	**0.299**
	Antibody titer at 2 years	
	r	**P**
Age (year)	**0.293**	**0.116**
Weight (kg)	**0.417**	**0.022***
Height (cm)	**0.282**	**0.132**
BMI	**0.189**	**0.317**
Onset of dialysis	**0.011**	**0.955**
Frequency of dialysis	**-0.469**	**0.009***
Size of filter	**0.242**	**0.198**
Duration of session	**-0.053**	**0.782**

The best cutoff of serum antibody titer at 1 year≥1.75 for prediction of absence of infection with area under curve 0.822, sensitivity 76.7%, specificity 83.3%, positive predictive value 95.8% and negative predictive value 41.7% and accuracy 77.8% ($p<0.05$). The best cutoff of serum antibody titer at 2 years ≥0.03825 for prediction of absence of infection with area under curve 0.917, sensitivity 90%, specificity 83.3%, positive predictive value 96.4% and negative predictive value 62.5% and accuracy 91.7% ($p<0.05$). (**Table 7, figure 1, 2)**

Table (7): Performance of serum antibody titer at 1, and 2 year in prediction of absence of chest infection among the studied patients

Performance of serum antibody titer at 1 year in prediction of absence of chest infection among the studied patients							
Cutoff	**AUC**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**	**P**
≥1.75	0.822	76.7	83.3	95.8	41.7	77.8	0.001**
Performance of serum antibody titer at 1 year in prediction of absence of chest infection among the studied patients							
Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	P
≥0.03825	0.917	90	83.3	96.4	62.5	91.7	0.001**

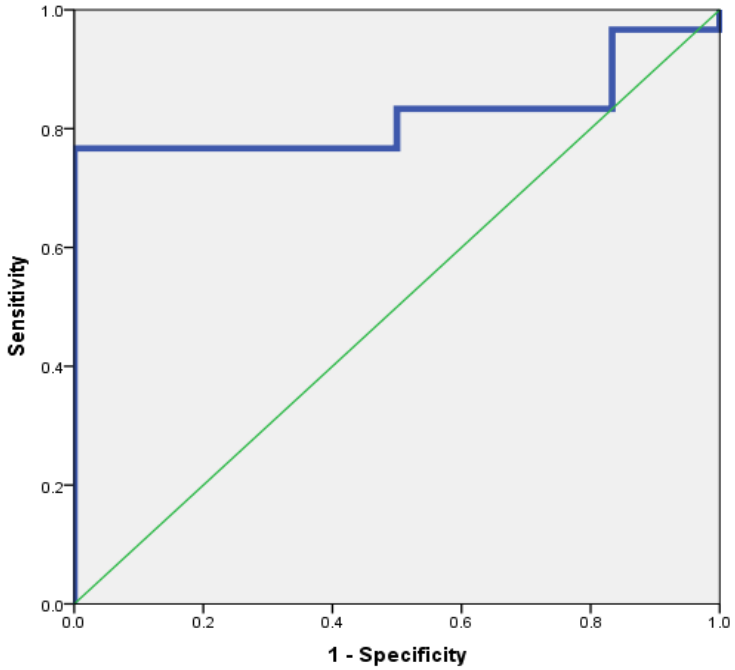

Figure (1): ROC curve showing performance of serum antibody titer at 1 year in prediction of absence of chest infection among the studied patients.

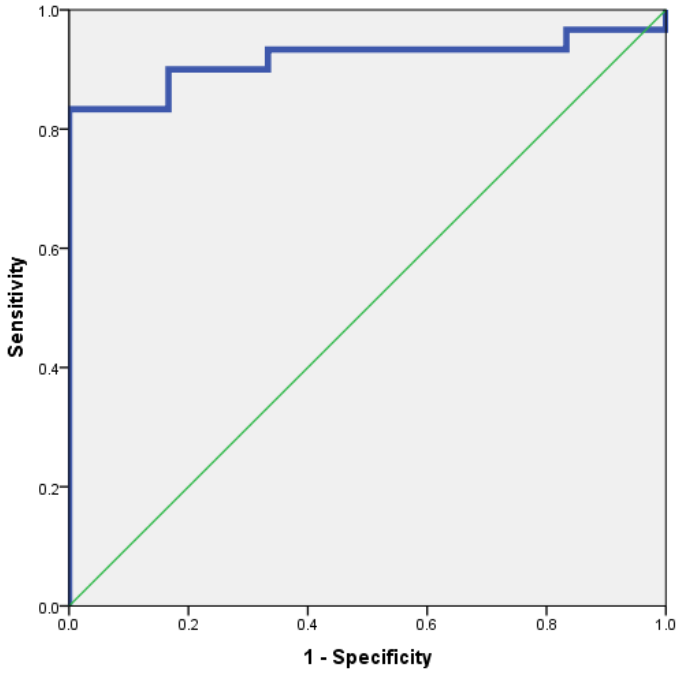

Figure (2): ROC curve showing performance of serum antibody titer at 2 years in prediction of absence of chest infection among the studied patients.

DISCUSSION

Those on dialysis who have End-Stage Renal Disease (ESRD) have weakened immune systems, making them more vulnerable to serious infections. In dialysis patients, pneumococcal illness is prevalent, with S. pneumonia accounting for more than half of all reported cases of pneumonia **(2).**

Immunocompromised youngsters, such as those with chronic kidney illness, should receive the pneumococcal vaccine **(19, 20).**

Our study included 36 children and adolescents, 17 boys (47.2%) and 19 girls (52.8%). In contrary with many studies as **Fiest (21)** whose highest incidences are in males, and who relate that to the high incidence of congenital anomalies of the kidney and urinary tract in males. Also, **Ardissino *et al.* (22)** stated the male predominance even after eliminating patients with posterior urethral valves.

Our study's HD children had a median age of 13.19 years, ranging from 5 to 18 years old. The result was nearly agreed with Saran *et al.* (23) who reported that more children over the age of six had CKD than those under six. According to the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) cohort, the percentages in the age groups 0-1 years, 2-5, 6-12 and 12+ years were all 19%, 17%, 17% and 31% respectively.

Our study focused on the immunological responses to PCV13 in HD children approximately 5 to 18 years old. Our study showed all HD patients can mount adequate protective immunological response which measured by minimum or adequate antibody titer postvaccination higher than 0.35 μg/ml which maintained for most of children and adolescent over 1y. In agree with **WHO (19)** and **Siber *et al.* (15).**

PCV13 immunological response in children and adolescents with ESRD and on dialysis was evaluated in this study for the first time, and their ages ranged from 5 to 18 years old. A 7-valent conjugate pneumococcal vaccine produced antibody responses against at least one serotype in all patients 60 days postvaccination in the majority of the research **(20).**

Also, many studies were done for adult and elderly after either PCV13 or PPV23. Our study determined total level pneumococcal immunoglobulin (IgG) antibodies to 36 HD pediatric patients after single dose conjugated pneumococcal vaccine13.

Current study showed that HD children and adolescent can mount immunological responses to PCV13. Median level of total IgG at 3M were7.9 and ranged from 2.99-9.72ug/dl. Median level of total IgG at 1y were 3.33 and ranged from 0.093 to 6.18ugdl. There was a significant decrease in antibody titer over time from 3M to 1y.

At 12 months after immunization, we saw a significant drop in PCV13 antibody levels. Chronic renal disease patients have shown a similar decline in antibody concentrations after vaccination with PPSV23, which was verified by the researchers **(14)**.

Agree with **Mitra *et al.* (2)** however, in elderly ESRD patients, Antibody concentrations at 12 months postvaccination were 38 to 72 percent lower than they were at 2 months postvaccination, according to the geometric mean antibody concentrations. PCV13 immunization increases antibody responses to vaccine serotypes in individuals with end-stage renal disease (ESRD) and dialysis at 2 months after vaccination. The decrease in antibody levels 12 months after vaccination with a conjugate pneumococcal vaccine, on the other hand, is concerning.

Sharif *et al.* (11) and Kato *et al.* (13) Antibody concentrations in dialysis patients are rapidly declining for unknown causes. ESRD has been linked to a loss in immunological memory due to a disruption in the adaptive immune system. A portion of the serum antibody level may be gradually removed during dialysis, which could also contribute to the decrease in antibody levels.

Frequency of chest infection after PCV13 was significantly decreased in frequency of patients who developed chest infections after PCV vaccinations from 75% to 16.7%. Also, there was a significant association between presence of chest infections and antibody titer at 3 months, 1 and 2 years.

CONCLUSION

Patients with end stage renal disease (ESRD) and on dialysis can mount adequate antibody response to PCV13 that associated with decrease frequency of chest infection post vaccination. Adequate protective concentration of antibody post PCV13 which is higher than 0.35ug/ml was maintained for most of cases at 1 year.

Improvement of recurrent chest infection especially in the first year after vaccination. Total IgG titer was reduced after 1y post PCV13. Reduced antibody titer over time after immunization by PCV13.

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