Monitoring of post-vaccination anti-HBs titles vaccine in children and adolescents in the pre-dialysis of chronic kidney disease

Monitoramento dos títulos de anti-HBs pós-vacinal em crianças e adolescentes em fase pré-dialítica da doença renal crônica

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ABSTRACT

Introduction: Bacterial or viral diseases are one of the major causes of death in patients with chronic kidney disease (CKD). These patients show a quantitative reduction of levels of antibodies over time. Among the infectious diseases that affect CKD patients, stands out hepatitis B (HB). Immunization and control of antibodies levels against the hepatitis B surface antigen (anti-HBs) are ways to prevent the HB infection in this population. Patients with anti-HBs levels ≥ 10 IU/ml are considered adequate responders, whereas those with anti-HBs levels ≥ 100 IU/ml are considered excellent responders. **Objective:** To analyze the variation of the anti-HBs levels obtained after vaccination against HB in children and adolescents in the pre-dialysis stage of CKD. **Methods:** A retrospective cohort study on anti-HBs levels of children and adolescents in the pre-dialysis stage of CKD. Correlation between levels of anti-HBs titers and time since the vaccination were estimated. **Results:** From the total of 116 studied patients most of the studied patients were considered excellent responders, obtaining in the three anti-HBs titers percentages of 70.7%, 62.1% and 54.9% respectively. The anti-HBs titer levels showed a negative correlation with the time since vaccination (Kendall Tau-b = -0.16; p = 0.02). **Conclusion:** The majority of the studied population was vaccinated by PNI and showed excellent anti-HBs titer levels, even experiencing a progressive reduced response over the time.

Keywords: renal insufficiency, chronic; hepatitis B; immunization; pediatrics.

RESUMO

Introdução: As doenças infecciosas, bacterianas ou virais, são uma das principais causas de morte dos pacientes com doença renal crônica (DRC), que apresentam um decréscimo na duração da imunidade em comparação às pessoas saudáveis. Entre as doenças infecciosas que acometem os portadores de DRC, destaca-se a hepatite B (HB). A imunização e o controle dos níveis de anticorpos contra o antígeno da superfície da hepatite B (anti-HBs) são formas de evitar a contaminação da HB nessa população. Pacientes com o nível de anti-HBs ≥ 10 UI/ml são considerados adequados respondedores, enquanto aqueles com níveis de anti-HBs ≥ 100 UI/ml são considerados excelentes respondedores. **Objetivo:** Analisar a variação dos níveis de anti-HBs adquiridos após a vacinação contra a HB em crianças e adolescentes na fase pré-dialítica da DRC. **Métodos:** Estudo de coorte retrospectivo dos níveis de anti-HBs de crianças e adolescentes na fase pré-dialítica da DRC. **Resultados:** Dos 116 pacientes do estudo, a maior parte foi considerada respondedores excelentes, obtendo nas três titulagens percentuais de 70,7%, 62,1% e 54,9%, respectivamente. Os níveis de anti-HBs apresentaram uma correlação negativa com o tempo de vacinação (Kendall Tau-b = - 0,16; p = 0,02). **Conclusão:** Conclui-se que a maior parte da população do estudo apresenta níveis de anti-HBs excelentes, ocorrendo uma queda progressiva da titulagem ao longo do tempo.

Palavras-chave: insuficiência renal crônica; hepatite B; imunização; pediatria.

Introduction

Chronic Kidney Disease (CKD) is defined as the presence of abnormalities in kidney structure and/or function for more than three months, leading to a generally slow and progressive loss of renal excretory, regulatory, and endocrine capacities, which compromise other organs of the body.[1] It is accompanied by several immunological deficiencies, be they innate or acquired immunity. With the progression of renal disease, antibody production, immunoglobulins, and interleukin-2 secretion by T lymphocytes are reduced, leading patients to an increased risk of contracting potentially preventable diseases due to decreased vaccine response.[2,3]

Patients with CKD have a greater decrease in the duration of post-vaccinal immunity compared to healthy patients, with a quantitative decrease in protective antibodies over time. The reasons for the fall of these titrations are not clearly understood and may be related to age, nutritional status and low immune response, which, when present, result in the inhibition of many cellular functions such as neutrophil adhesion and antibody formation.[4,5]

Infectious diseases, whether bacterial or viral, are a major cause of death in patients with CKD, regardless of age. These include hepatitis B (HB), considered a serious public health problem in the world and in Brazil.[6] An essential part of the pre-dialytic treatment of CKD in children and adolescents, is the control of infectious diseases through immunization. Among priority immunizations, we highlight the one directed at the prevention of HB, since such patients, in addition to the immunodeficiency mentioned above, are potential candidates for hemodialysis, which makes them even more susceptible, because the parenteral route is the main form of contamination from the hepatitis B virus (HBV).[7]

Regarding protection against HB, the National Immunization Program (PNI), which defines immunization schedules throughout the national territory, in July 2012 instituted the pentavalent vaccine, which contains the triple cell combined with Haemophilus influenzae type b (Hib) and with the recombinant hepatitis B vaccine.

The HB vaccination schedule was changed to four doses for children under 5 years of age, with the first dose of the monovalent vaccine against hepatitis B at birth in the first 12-24 hours and the remainder in vaccine form, combined pentavalent at two, four and six months. For patients older than 5 years, the three-dose regimen of the recombinant hepatitis B vaccine is adopted in the zero, one and six-month periods.[8]

In patients with immunological alterations, such as children and adolescents with CKD, there are different recommendations regarding dose and vaccination schedule for protection against HB.[9-11] According to the Special Immunobiological Reference Center (CRIE), four doses of the vaccine at twice the usual dose in the period of zero, one, two and six months.[10]

Due to the high efficacy of the vaccine in inducing protective titers, post-vaccinal serological testing is not routinely indicated for healthy people. The same does not occur with the individuals belonging to groups at risk, because in these groups it is important to run the serological evaluation of the levels of antibodies against the hepatitis B surface antigen (anti-HBs), and they will be considered protected when those levels of anti-HBs are ≥ 10 IU/ml.[10-12]

In patients with CKD, this evaluation should be performed two to three months after the end of the vaccination and repeated annually. Non-reactants, i.e. those with anti-HBs < 10 IU/ml, are indicated to repeat the four-dose vaccination schedule, with twice the dose normally administered. Those who remain with anti-HBs < 10 IU/ml after two complete vaccination schedules of four double doses of the vaccine against HB will be considered permanent non-responders and susceptible to the disease in case of exposure.[4,9-11]

Studies carried out with CKD patients demonstrate that titration of anti-HBs levels may vary over time, i.e., initially protected patients may present a decrease in anti-HBs levels and reach values considered insufficient to guarantee their seroprotection, making them - more susceptible to HBV.[13-15] Other studies also show that the duration of protection is related to the peak level of post-vaccination antibodies and that patients with CKD who have anti-HBs ≥ 100 IU/ml have better serum protection than those with anti-HBs between 10 and 99 IU/ml.[9,16]

In the interdisciplinary follow-up performed with children and adolescents in the pre-dialysis phase, in an outpatient clinic that is part of a university hospital, patients are regularly followed for the vaccines considered essential. The standard protocol controls vaccinations against hepatitis A and B, antipneumococcal 10 and 23, Haemophilus influenzae

b, chickenpox and influenza, almost all available in the basic PNI calendar and, if not, CRIE. In relation to the HBV vaccine, anti-HBs is titrated in patients admitted with the complete vaccination scheme, and those with anti-HBs ≥ 10 IU/ml are considered protected. Those not in this situation are considered unprotected and referred for further vaccination.

Studies performed with children and adolescents on dialysis demonstrate variations in levels of protection among patients. Those pre-immunized prior to the initiation of dialysis treatment remain longer protected and have higher titers - which influence protection duration.[14,15]

In the service in which the study patients are followed up, as the annual titres are made, it is observed that most of the patients are seroconverted, i.e., have anti-HBs levels ≥ 10 IU/ml, but it has variations of this titration over time. Knowing how anti-HBs levels behave in pre-dialytic patients becomes important for proposing measures that can help maintain high levels of protection against HB, especially at the time of referral for dialysis or transplantation.

This study aims to analyze the variation on anti-HBs levels acquired after vaccination against HB in children and adolescents in the pre-dialytic phase of CKD, and establish correlations with clinical parameters of the patients.

Methods

This is a retrospective cohort study on the post-vaccine development of anti-HBs levels in children and adolescents in the pre-dialytic phase of CKD.

The study was carried out in a pediatric nephrology clinic of a university hospital in Belo Horizonte, MG - Brazil. The children and adolescents are referred by professionals who work in the institution, other outpatient clinics and hospitals belonging to the public network of Belo Horizonte's metropolitan region and the country side of the state of Minas Gerais. The patients are followed by an interdisciplinary team made up of a pediatric nephrologist, a nurse, a nutritionist, a social worker and a psychologist. It is up to the nurse to follow the established protocol.

From January 2007 to December 2014, the time selected for data collection, 153 patients were enrolled in the program. To participate in the study, the following inclusion criteria were defined: having 0 to 20 years; having been vaccinated against hepatitis B according to the scheme recommended by the PNI or CRIE; have negative hepatitis B antigen (HBsAg negative); have at least one measure of anti-HBs, being ≥ 10 IU/ml.

Exclusion criteria were defined as: patients under immunosuppression up to six months before or after any anti-HBs measurement and treatment of any infection for a period of two months before or after titration. Such exclusion is justified by the fact that immunosuppressive drugs and infectious diseases can lead to immune depression, directly interfering with the disease's vaccine response.[10] It is recommended that patients receiving high doses of immunosuppressants should wait three months after the end of treatment to be vaccinated and to obtain an effective vaccine response.[17]

After employing the criteria, 116 patients participated in the study. The losses were because two patients were taking immunosuppressants, 21 had anti-HBs < 10 IU/ml and 14 were over the age limit, in treatment of any infection or without previous vaccination against HBV.

The data collection was done by the researchers through consulting the patients' charts, which from 2007 onwards contained a sheet for recording and monitoring vaccines. An instrument for data collection was used, in which a pre-test was performed with part of the study population, and the necessary adjustments were made.

The instrument contained sociodemographic, clinical and hepatitis B vaccination data. Sociodemographic data refers to the timing of the first titration (T1), since at this time, all 116 patients were included. A second titration (T2) and a third titer (T3) were also collected with approximate interval of one year between them.

For the clinical evaluation, the Glomerular Filtration Rate (GFR) was calculated using the formula proposed by Schwartz *et al.*:[18] TFG = K x stature (cm)/plasma creatinine (mg/dl), where K is a constant, which varies according to patient's age. After this calculation, the CKD stage was classified according to the guidelines from the Kidney Disease Improving Global Outcomes (KDIGO) .[1] The hemoglobin level was assessed according to the age range of children and adolescents, following information from KDIGO and that of the National Kidney Foundation - Kidney Disease Outcomes Quality Initiative (K/DOQI).

The laboratory tests and the results of anti-HBs tests collected were those presented in the returns

to the outpatient clinic and the most recent ones available in the medical records, and no additional tests were necessary. Patients who had one, two and/or three titers were selected and anti-HBs levels were evaluated as those with titers between 10-100 IU/ml and excellent responders those with titers> 100 IU/ml.[15]

With respect to hemoglobin levels, patients with hemoglobin (Hb) < 11.0 g/dl, from 5 to 12 years old with Hb < 11.5 d/dl, 12 a 15 years Hb < 12 d/dl and for those over 15 years of age male Hb < 13 g/dl and female Hb < 12.0 g/dl.[19]

The data was analyzed using the Statistical Package for Social Science (SPSS), version 20.0. The study population was characterized by the distribution of frequencies by gender, age, syndrome diagnosis, CKD stage, time in the program, vaccines, anti-HBs levels, GFR and hemoglobin levels, being continuous and categorical variables.

The Kendall correlation was used to evaluate the existence of correlation between the anti-HBs variable with other variables: urea levels, GFR, time of vaccination and hemoglobin. This correlation was most indicated by the fact that the variables did not have normal distribution, in addition to having excessive draws. For the Kendall correlation coefficient (tau-b) values -1 to +1, the closer to zero, the less correlated the variables, and the closer to +1 (positive correlation) or -1 (Negative correlation), the more correlated the variables are with each other. In this study, a statistical significance level of 95% was considered.

The Bootstrap method was used to calculate the confidence intervals of the correlation coefficients. To do this, we calculated 1000 bootstrap replicates of the pilot sample and calculated the correlation coefficients in these 1000 re-samples, defining the 2.5 and 97.5 percentiles (upper and lower limits of a bootstrap confidence interval at the level of 95%).

The project was submitted to the Research Ethics Committee of the Federal University of Minas Gerais (COEP/UFMG) and approved under protocol No. 203.408. All the participants were clarified about the research objectives and signed the Informed Consent Term.

Results

Of the 116 patients studied, the majority was male (60.3%), aged between 10 and 19 years old (71.6%), the mean age was 12.94 years (SD = ± 5.24). The mean length of stay in the program was 6.57 years (SD = 4.42). The most common diagnoses were congenital kidney diseases (69.8%) and, with a lower percentage, glomerular diseases (9.5%), followed by cystic diseases (8.6%) and others (12.1%).

Among the 35 different baseline diagnoses, the most frequent was posterior urethral valve (19%), followed by neurogenic bladder and vesicoureteral reflux, both with 9.5%. The patients were classified in stage 3B (30.2%) and 4 (26.7%) of CKD[1]. Regarding the classification of anemia, according to KDIGO and K-DOQI parameters, 51.7% of the patients were anemic (Table 1).

We found that 57 patients (49.1%) received the HB vaccine at health posts by PNI. Another 24 (20.7%) were vaccinated at the CRIE program with referral performed after evaluation by the nurse. The remainder, a total of 35 patients (30.2%), did not record the dates of their vaccinations, and it was not possible to evaluate whether the vaccination occurred before or after admission to the outpatient clinic.

Regarding the number of anti-HBs titers per patient, all had at least one titer, 87 (75%) had two, and 51 (44%) had three titers. Table 2 shows the classification of anti-HBs levels by the stage of CKD in T1, T2 and T3. In all evaluated moments (T1, T2 and T3), most patients were considered excellent responders (anti-HBs > 100 IU/ml), obtaining percentages of 70.7%, 62.1% and 54.9% respectively.

It is possible to notice a decrease, even in small proportions, in the number of excellent responder patients at the three different moments of the evaluation (Figure 1).

When evaluating the evolution of the anti-HBs response over the three titers between the male and female genders (Table 3), it is possible to notice a decrease in the excellent response from the male patients, while there is practically a continuous maintenance of the excellent response and adequate treatment of female patients.

The Kendall correlation was analyzed at three times, in T1, T2 and T3 (Table 4). The results of this study are summarized in Table 1. In T1, anti-HBs levels showed a negative correlation with the time of vaccination, (tau-b = -0.158 and 95% CI = -0.2; -0.014), suggesting that at the level of

Table 1 Sociodemographic and clinical characteristics of the study population (n = 116)

Characteristics	N	%
Age range		
0 to 9 years	30	25.9
10 to 19 years	83	71.6
> 19 years	3	2.6
Gender		
Males	70	60.3
Females	46	39.7
Time in the program		
< 1 year	9	7.8
1 to 5 years	48	41.4
> 5 years	59	50.9
Syndrome diagnosis		
Congenital kidney diseases	81	69.8
Glomerular diseases	11	9.5
Cystic diseases	10	8.6
Others	14	12.1
CKD stage		
Stage 1	4	3.4
Stage 2	22	19.0
Stage 3A	18	15.5
Stage 3B	35	30.2
Stage 4	31	26.7
Stage 5	6	5.2
Hemoglobin levels		
Anemic	60	51.7
Non-anemic	56	48.3

CKD: Chronic kidney disease.

significance of 95% we reject the null correlation hypothesis, there being a negative correlation that is statistically significant. At T2, anti-HBs levels correlated positively with laboratory values of urea (tau-b = 0.219 and 95% CI = 0.063, 0.358). Regarding the other variables, GFR and hemoglobin levels, no statistically significant correlations were found.

Discussion

In the pre-dialytic phase of CKD, it is important to include the patient's vaccine control to prevent the occurrence of infectious diseases and the worsening of kidney damage caused by potentially preventable diseases through immunization. This study, carried out with patients in the pre-dialysis phase, contributed to the discussion of how to adequately address HBV immunization in this population.

Patients belonging to this study group are predominantly male and have congenital kidney diseases. Several other studies carried out with different populations, whether pediatric or adult patients, in a dialysis or conservative treatment, indicate the male gender and those with nephropathies as the groups with the highest prevalence of CKD.[14,15,20] In other studies conducted with the Same population, the same series was observed.[21-23]

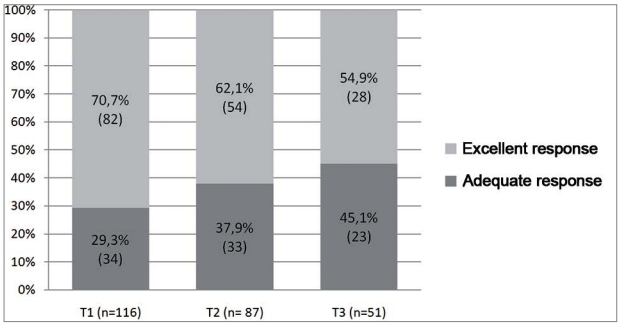
The age group affected by CKD is variable; however, in a study carried out with the children population, there is a predominance of children

Table 2 Anti-HBs levels classified by CKD stage in T1, T2 and T3

CKD Stage	T1				T2				T3			
	10 to 100 (n = 34)		> 100 (n = 82)		10 to 100 (n = 33)		> 100 (n = 54)		10 to 100 (n = 23)		> 100 (n = 28)	
	N	%	n	%	n	%	n	%	N	%	n	%
Stage 1	0	0%	4	3.4%	1	1.1%	4	4.6%	1	2%	3	5.9%
Stage 2	11	9.5%	11	9.5%	7	8.0%	6	6.9%	4	7.8%	3	5.9%
Stage 3A	4	3.4%	14	12.1%	5	5.7%	7	8.0%	3	5.9%	3	5.9%
Stage 3B	9	7.8%	26	22.4%	7	8.0%	13	14.9%	7	13.7%	7	13.7%
Stage 4	9	7.8%	22	19%	13	14.9%	14	16.1%	7	13.7%	4	7.8%
Stage 5	1	0.9%	5	4.3%	0	0%	10	11.5%	1	2%	8	15.7%
Total	34	29.3%	82	70.7%	33	37.9%	54	62.1%	23	45.1%	28	54.9%

T1 = titration at the first time period; T2 = titration at the second time period; T3 = titration at the third time period.

Figure 1. Relative frequency of the excellent and adequate response in the first, second and third titration assessments. T1 = titration 1; T2 = titration 2; T3 = titration 3.



in school or adolescent age group.[24] Similar data was found in this study, in which the majority had 10 to 19 years of age. In the adult population, age is one of the non-modifiable factors that interfere with seroconversion; Thus, more advanced ages are often associated with poorer vaccine response.[14,15,25]

Regarding CKD stage, we found that the patients in this study were concentrated in stages 3B and 4, and this was expected because they were patients in the predialysis phase.[1] The presence of patients in CKD stages 1 and 2 was justified by the fact that they came from other pediatric nephrology outpatient clinics of the same institution, and were unable to enter the primary health care network.

Patients who were admitted in the acute phase of CKD and who remained after stabilization were still in the outpatient clinic. Regarding hemoglobin levels, 51.7% of the population were anemic, being a CKD-related disorder. Anemia control is important for this population and studies have shown that patients with low hemoglobin levels have a lower immune response to vaccines.[26,27]

The Ministry of Health considers anemic those patients with Hb levels < 11 g/dL and recommends oral replacement of iron and/or erythropoietin in specific cases, such as the presence of chronic renal patients in stages 3 to 5 of the disease, Hb < 10 g/dL and with adequate iron reserves.[28]

In this study, the patients were mostly vaccinated by the PNI and, if they did not reach the levels expected for protection or had not been vaccinated, they were referred for vaccination by the CRIE. Most patients had an excellent response to anti-HBs levels, i.e. anti-HBs > 100 IU/ml. In all three evaluations of anti-HBs titers, there is a predominance of patients with such levels; however, over time, there is a moderate decline in these titers, increasing the number of patients with adequate response.

Table 3 Anti-HBs classification according to gender at T1, T2 and T3

	T1		T2		T3	
Gender	Male n (%)	Female n (%)	Male n (%)	Female n (%)	Male n (%)	Female n (%)
Adequate Response	21 (30%)	13 (28.3%)	23 (43.4%)	10 (29.4%)	17 (54.8%)	6 (30%)
Excellent Response	49 (70%)	33 (71.3%)	30 (56.6%)	24 (70.5%)	14 (45.1%)	14 (70%)
Total	70 (100%)	46 (100%)	53 (100%)	34 (100%)	31(100%)	20 (100%)

T1 = titration at the first time period; T2 = titration at the second time period; T3 = titration at the third time period.

Table 4 Kendall correlation of the anti-HBs levels at T1, T2 and T3

	T1				T2				T3			
		IC 95%				IC 95%				IC 95%		
	tau-b	Inf	Sup	*p*-value	tau-b	Inf	Sup	*p*-value	tau-b	Inf	Sup	*p*-value
Urea	0.067	-0.068	0.192	0.291	0.219	0.063	0.358	0.010	0.147	-0.078	0.346	0.196
GFR	0.001	-0.132	0.132	0.985	-0.124	-0.300	0.055	0.145	-0.102	-0.301	0.124	0.368
Hb	0.032	-0.089	0.156	0.620	-0.056	-0.214	0.114	0.515	0.007	-0.210	0.251	0.949
Vac time	-0.158	-0.278	-0.014	0.025	0.022	-0.148	0.196	0.807	0.085	-0.128	0.305	0.473

T1 = titration at the first time period; T2 = titration at the second time period; T3 = titration at the third time period; CI = confidence interval; Inf = CI lower values; Sup = CI higher values; Tau = Kendall correlation coefficient; GFR = Glomerular filtration rate; Hb = hemoglobin; Temp = vac: vaccination time.

Although anti-HBs levels ≥ 10 IU/ml are considered protective, several authors propose as ideal an anti-HBs level ≥ 100 IU/ml in patients with CKD because seroprotection is more durable in these patients than in patients considered adequate responders[15] or poor responders (10 to 99 IU / ml).[16,20] The latter, although protected, are more susceptible to declining levels of antibodies over time.[20]

Some studies have reported male gender having decreased immunogenicity concerning the vaccine against HB, demonstrating that females respond better to vaccination, while males are less prone to seroconversion and develop poorer responses to the vaccine.[15,2]

Some studies associate the male gender to the decrease in immunogenicity of the vaccine against HB, demonstrating that females respond better to vaccination while males are less prone to seroconversion and develop a poor response to the vaccine.[15,20] In this study, they found that, despite the in male patients with excellent response throughout the three titrations, while females remained with the continuous and high percentage of this response.

When evaluating the correlation of anti-HBs levels with other variables, statistically significant results were found regarding the time variables of vaccination and urea levels. The time of vaccination showed a significant negative correlation with the level of the first titer, meaning that the titers of anti-HBs fall during the years after the end of the vaccination scheme.

Sheth *et al*.,[29] in a retrospective cohort study with 202 children in stage 5 of CKD, assessed the duration of HB vaccine immunity, noting the decline in anti-HBs levels over time. The authors concluded that protected children after initiation of dialysis had a rapid decline and a short immunity duration, compared to those who were vaccinated before or during predialysis.

DaRoza *et al*.[14] reinforced this result by stating that the earlier the patient with CKD is subjected to vaccination, the more susceptible the seroconversion will be. According to the literature,[12,13,15,16,20] there is a need to obtain protective titers of anti-HBs from patients before they become dialysis-dependent, to obtain more effective responses for protection against HBV.

These data reinforce the importance of annual control of patients' anti-HB levels, especially in the pre-dialysis phase, but also in the dialysis phase. With this strategy, it is possible to monitor the evolution of seroprotection of patients with CKD, ensuring an excellent or effective protection rate to keep them protected against HBV.

Regarding urea levels, a statistically significant positive correlation was observed, that is, with increasing laboratory levels of urea, the protective antibody titers also increased, which is surprising, since the urea increase can be due to worsening renal function, a factor that has been related to a worse vaccine response.[30]

No statistically significant correlation was found between GFR and anti-HBs levels, although a decrease in the number of excellent responders over time was observed. The study by DaRoza *et al*.[14] showed that the higher the GFR the better the seroconversion, and concludes that patients with CKD, prior to dialytic therapy, come close to the general population and have factors that predict the vaccine response in this population. It is still unclear whether the renal function stage is an independent predictor of seroconversion or serves as a marker for other factors, such as malnutrition and anemia, which may be responsible for a decreased immune response.[15]

This study, although it has contributed to the knowledge of how the anti-HBs levels in a population of children and adolescents with CKD behave, has limitations, such as sample size, the use of retrospective data, which led to a lack of data due to incomplete records, such as the absence of the vaccination date, besides the laboratory tests being held in different laboratories and the non-standardization of the time interval between patient titrations, as well as the absence of a control group.

Conclusion

We conclude that most children and adolescents with CKD in this study have excellent levels of anti-HBs, even with a progressive decrease of this titer over time. The importance of monitoring the patients' vaccination status from the pre-dialysis stage and the annual titration of the levels of protective antibodies is confirmed. In patients considered to be adequate responders and with low

GFR, continuous follow-up with titration is recommended to be held more frequently.

It is important to follow the patient from the pre-dialytic stage, keeping him/her in good clinical condition, which will contribute to a more adequate immune response and, consequently, a better protection against HB. Finally, we recommend that more studies on this topic should be carried out, searching for factors associated with the reduction of seroconversion in patients with CKD.

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