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Vaccination of children with chronic kidney disease in pre- and posttransplantation periods

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The article is dedicated to an extremely important issue of pediatric nephrology and pediatric transplantology – vaccination of children with chronic kidney disease for prevention of vaccine-manageable infections. Commonplace and often mild (in healthy children) viral and bacterial infections in the patients on immunosuppressive therapy may cause development of life-threatening conditions and loss of a transplant in children with transplanted kidneys. There are no common vaccination protocols for such children neither in Russia nor in any other country. Moreover, it is presumed that vaccination should not take place in children with chronic renal diseases, especially in the stage of renal failure; however, in many cases it is unreasonable. The authors present personal experience of children's vaccination before and after kidney transplantation.
Keywords: *chronic kidney disease, infections, prevention, vaccination, transplantation, children.*

INTRODUCTION

Candidates for transplantation and recipients of transplanted organs are part of the group of high risk of infectious complications, primarily due to immunosuppressive therapy. Vaccination may prevent development of these diseases and reduce replication and dissemination of dangerous microbes. That is why specific vaccination, including pneumococci, influenza viruses, hepatitis B, pertussis, tetanus-diphtheria, hemophilic bacilli and poliomyelitis, is recommended for this category of patients. In extraordinary cases, vaccination against hepatitis A, tick-borne encephalitis and other infections is indicated.

Chickenpox is a highly contagious disease in children, usually with a favorable outcome. However, it may be accompanied by severe complications in the children undergoing immunosuppression. Although the use of antiviral drugs has slightly reduced severity of chickenpox, chickenpox mortality remains even in this population of patients [1].

Prevention of development of systemic viral and bacterial infections is the primary task of pediatric nephrology, which is in charge of children in the terminal stage of chronic kidney disease (CKD), who later undergo kidney allotransplantation using long-term immunosuppression. This review concentrates on the following aspects:

- risk of development of vaccine-controlled diseases;
- immunogenicity and clinical efficacy of available vaccines;
- introduction of immunization protocols.

It ought to be mentioned that doctors have no common opinion on efficacy, safety and protocols of administering several vaccines in this population of patients. As long as immunosuppressive therapy features several protocols, several questions arise.

1. What is the effect of immunosuppression on duration of the pre-transplantation vaccination performed both in the early and terminal disease stages?
2. Are the vaccinations performed both in early and late post-transplantation periods effective?

3. What are the side effects of live and inactivated vaccines in patients in the setting of immunosuppression; what is their effect on the transplanted kidney function?

However, the main question is, whether the vaccination may or may not cause graft rejection and, therefore, loss of a transplanted kidney [2-5]? That is why this work was aimed at studying, whether the vaccination increases the graft rejection rate in children.

PATIENTS AND METHODS

We started performing vaccination at the renal transplantation department of the FSBI Petrovskiy RSCS in 2010. We performed 78 vaccine injections to 46 children (patients) from September 2010 to February 2011; 26 patients received 1 injection, whereas 20 patients received 60 vaccinations in tote. Number of vaccinations per child – 2-5. Age of children at the time of vaccination was 2-18 years (11.2±5.04 years of age on the average).

It is commonly accepted all over the world that the optimal period for vaccination is before the transplantation: not only because introduction of a vaccine to recipients of allotransplanted organs is fraught with rejection development [6, 7], but also due to the common opinion that aggressive immunosuppression in post-transplantation period hinders vaccinal action.

Only 7 of the observed patients were vaccinated before kidney transplantation (group I). This group involved patients of 2-17 years of age (9.0±6.6 years of age on the average), 3 girls and 4 boys. The vaccination was performed 0.2-12 months before the transplantation (2.78±3.95 months on the average). 2 patients underwent vaccination twice with intervals of 7 and 14 days between injections.

26 patients (group II) underwent singular vaccination in the post-transplantation period 0.8-144 months after the transplantation (36.42±33.76 months on the average). Age of the children was 2-18 years (11.77±5.00 years of age on the average); 17 boys, 9 girls.

14 patients underwent multiple vaccination (group III); number of vaccine injections varied from 2 to 6 (3.44±1.39 on the average). Age of the patients was 2-17 years (9.54±4.98 years of age on the average); 7 boys, 7 girls. The range of the administered vaccines was the same as in the patients of groups I and II.

The following medicines were used for vaccination:

1. Fluarix (SmithKline Beecham, Belgium) *against influenza*; inactivated.
2. Vaxigrip (Sanofi Pasteur, France) against influenza; inactivated.
3. Havrix-720 for children (GlaxoSmithKline, Belgium) against hepatitis A; inactivated hepatitis A virus.
4. Engerix (GlaxoSmithKline, LLC, Russia) against hepatitis B; inactivated.
5. Pentaxim (Sanofi Pasteur, France) *against diphtheria, pertussis, poliomyelitis, hemophilia infection and tetanus for children over 6 months of age*; inactivated.
6. Pneumo 23 (Sanofi Pasteur, France) *against pneumococcal infection for children over 2 years of age*; inactivated.
7. Prevenar (WYETH WHITEHALL, USA) *against pneumococcal infection for children under 2 years of age*; conjugated, inactivated.
8. Cervarix (GlaxoSmithKline, Belgium) *against human papillomavirus infection*.
9. FSME-IMMUN Inject (Baxter, Austria) *against tick-borne encephalitis*.
10. Gardasil (Merck Sharp & Dohme Inc., USA) *against human papillomavirus*.
11. Hiberix (GlaxoSmithKline Biological, Belgium) *against the Haemophilus influenzae type b infection*.

RESULTS

Patients undergoing vaccination in the pre-transplantation period (group I)

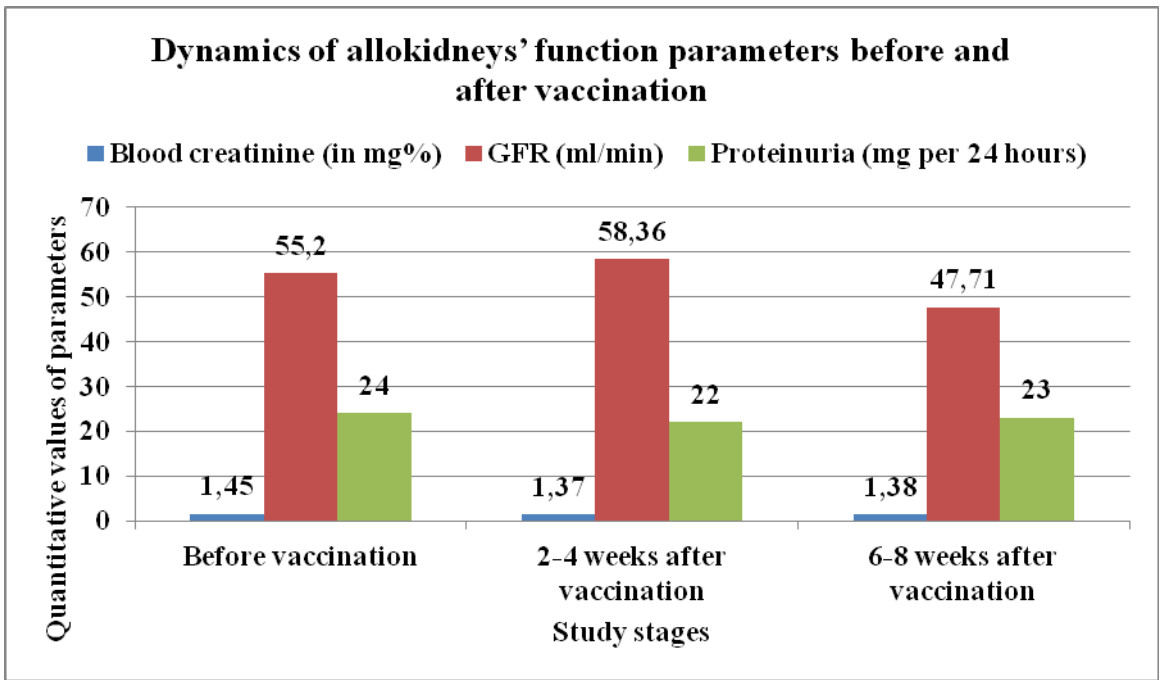
One patient received an anti-influenza vaccine; after 7 days – Pentaxim and Pneumo 23; another patient received 3 hepatitis B serum injections; after 2 weeks – Pneumo 23. Four patients

received singular vaccine injection (Vaxigrip, Pentaxim or Cervarix); one patient consequently received Pentaxim and Pneumo 23.
Undesirable reaction to administration of vaccines was observed only in 1 patient, who received Pentaxim and Pneumo 23: development of hyperthermia up to 37.5°C with chill. The aforementioned phenomena were arrested by administration of antihistamine drugs.
Puncture transplant biopsies were performed to 3 patients of this group after kidney transplantation. The response was the same in all cases: no rejection. As for the transplanted kidney's function, blood creatinine varied from 0.5 to 1.8 mg% (1.00±0.46 on the average), glomerular filtration rate – 22.4-148.8 ml/min (63.18±48.38 on the average). We may conclude that the transplanted kidney's function was satisfactory in all cases.
Few patients vaccinated in the pre-transplantation period do not allow us making fundamental conclusions; however, these cases helped to clearly show that the performed vaccination did not cause immune conflict of the donor organ and the recipient and did not negatively affect condition of the allotransplanted kidney.

Patients undergoing singular vaccination in the post-transplantation period (group II)

The following parameters were assessed in all patients before the vaccination: blood creatinine, glomerular filtration rate, daily proteinuria. These parameters were also assessed 2-4 and 6-8 weeks after the vaccination (pic. 1).

Pic. 1. Dynamics of allokidneys' function parameters before and after vaccination



Note. Hereinafter, GFR – glomerular filtration rate.

The picture shows that no negative dynamics of allotransplanted kidney's function was observed after the vaccination.
Moreover, comparative evaluation of transplant puncture biopsy (TPB) results was performed before and after the vaccination. Biopsies were performed in 16 patients before and after the vaccination, whereas the obtained result was examined by a morphologist. According to the morphologist, comparative evaluation of TPB results did not reveal negative dynamics before and after the vaccination: therefore, we may claim that the vaccination does not cause development of a rejection episode or negative effect on the transplanted kidney's function. Comparative evaluation data of transplant puncture biopsy results are given in tb. 1.

Table 1. Comparative evaluation of transplanted kidneys' puncture biopsy results before and after vaccination

TPB results before vaccination	**Quantitative Banff score**	**TPB results after vaccination**	**Quantitative Banff score**
Cicatrical deformities. CTN symptoms	0	No rejection	0
Norm	0	No symptoms of rejection	0
No rejection	0	No symptoms of rejection	0
Mild borderline changes	0	Chronic glomerulopathy	0
Mild borderline changes	0	Chronic glomerulopathy	0
Mild symptoms of acute rejection	1	No rejection	0
Acute rejection	1	Acute rejection	1
Initial CTN symptoms	0	Interstitial sclerosis	0
No rejection	0	Acute rejection (1a)	1
Borderline changes	0	No symptoms of rejection	0
No rejection	0	No rejection	0
Borderline changes	0	Arteriolohyalinosis, stage II	0
CTN	0	CTN	0
No rejection	0	No rejection	0
No rejection	0	Acute rejection (1a)	1
Borderline changes	0	No rejection	0
M±m	0.13±0.35	M±m	0.2±0.41

Note. TPB – transplant puncture biopsy, CTN – chronic transplant nephropathy.

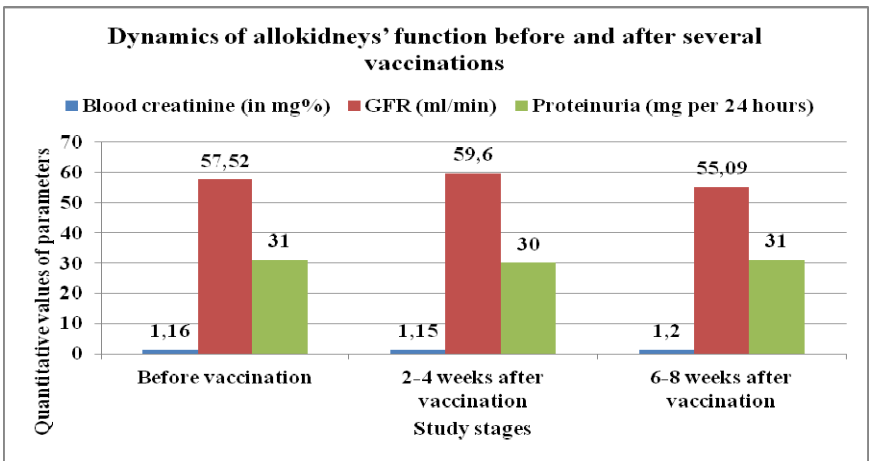
Banff evaluation of biopsy materials was quantitatively performed; intensity of the 10 morphological parameters was evaluated on a scale from 0 to 3. The sum of values of parameters (if more than 1.0) shows degree of process intensity – from 0 (norm) to 9-11 (acute rejection (2b)).

Statistical manipulation showed that the difference between values before and after the vaccination is uncertain ($t=0.52$; $p>0.1$) – another proof that singular post-transplantation vaccination does not cause rejection development.

Patients undergoing multiple vaccination in the post-transplantation period (group III)

Transplanted kidneys' function was assessed according to the same protocol as in the group II patients. Results of mathematical treatment are given in pic. 2.

Pic. 2. Results of mathematical treatment of allokidneys' function dynamics before and after several vaccinations



Effect of multiple vaccinations on the transplanted kidneys' function was assessed according to the same protocol as in the group II patients. The picture clearly demonstrates that no aggravation in the transplanted kidneys' function was observed throughout the study period. Therefore, we may conclude that multiple vaccinations do not aggravate the allotransplanted kidneys' function as well.

Transplant puncture biopsy was performed only in 6 out of 14 patients in the postvaccinal period. The results are given in tb. 2. Neither of the patients of this subgroup featured negative dynamics of allogeneic kidneys' morphology. Insufficient number of patients who underwent postvaccinal puncture biopsy does not allow us making a generalized conclusion for group III; however, it is important to observe that neither of these 6 patients featured negative dynamics of transplanted kidneys' morphology (see tb. 2).

Table 2. Comparative analysis of transplanted kidney's puncture biopsy results before and after vaccination

TPB results before vaccination	**Quantitative Banff score**	**TPB results after vaccination**	**Quantitative Banff score**
Focal stromal sclerosis	0	No rejection	0
Norm	0	No rejection	0
Norm	0	Extremely mild BC	0
No rejection	0	No rejection	0
Acute rejection (1a)	1	Initial CTN symptoms	0
Mild borderline changes	0	Mild borderline changes	0

Note. TPB – transplant puncture biopsy, BC – borderline changes, CTN – chronic transplantation nephropathy.

Therefore, we may conclude that multiple vaccinations do not cause aggravation of the transplanted kidneys' function in recipients of transplanted kidneys.

Vaccination protocol and side effects of vaccines

Our experience of vaccinating recipients of transplanted kidneys allows us to deem intramuscular mode of administration of vaccines optimal, excluding cases when the manufacturer recommends subcutaneous mode of administration. We did not always have an opportunity to observe the instructions when performing multiple vaccinations: in case the risk of development of an infectious disease was extremely high and the transplantation was to be performed urgently, vaccination was performed according to an accelerated scheme. The protocol was also not observed in those patients who underwent only one vaccination due to reasons beyond our control.

Like any bioactive drug, vaccines may cause various undesirable local and general reactions.

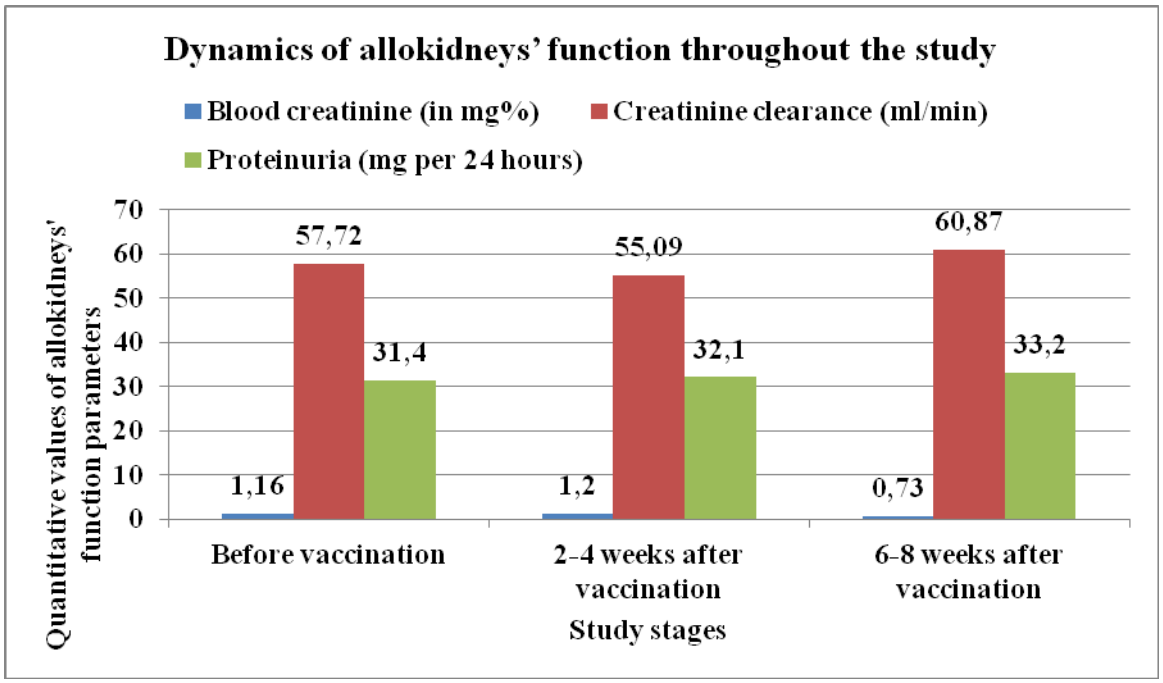
Out of local reactions in the children vaccinated after transplantation, we observed tenderness in the injection site, hyperemia and edema in 4 patients out of 46 (8.7%); hyperemia in the injection site – in 2 patients (4.35%); infiltrate in the vaccine injection site – in 1 patient (2.17%). General reactions were represented only by headache (in 2 patients; 4.35%).
Therefore, we may conclude that vaccination did not have severe consequences in our patients and may be considered safe.
For better visualization, information on the undesirable effects of vaccination is given in tb. 3.

Table 3. Undesirable reactions, which have developed after vaccination of transplantation candidates and recipients of allotransplanted kidneys

Name of a side effect	Number of patients (in %)
Tenderness in the injection site	4 (8.7)
Hyperemia in the injection site	2 (4.35)
Infiltrate in the injection site	1 (2.17)
Headache	2 (4.35)

Survival rate in the group of vaccinated patients
All the vaccinated patients were alive, all the allotransplanted kidneys functioned satisfactorily, no transplanted kidney was lost by the moment of writing of this article. Analysis of blood creatinine level, clearance and daily proteinuria is given in pic. 3.

Pic. 3. Analysis of blood creatinine level, glomerular clearance and daily proteinuria



Pic. 3 clearly shows that there was no aggravation in the allotransplanted kidneys' function throughout the postvaccinal period. Therefore, vaccination does not cause development of rejection of transplanted organs in the children – recipients of transplanted kidneys. It may have been caused by our using only imported vaccines. We chose to use imported vaccines as they do not contain polyoxidonium and interferon featuring intense immunostimulating effect.

CONCLUSION

Despite obviousness of safety and efficacy of vaccination for patients receiving immunosuppression, most vaccines are used insufficiently in this category of patients [8]. The following vaccination principles ought to be observed in recipients of transplanted organs:

- vaccination efficacy measured by determining antibody titer is usually lower than in healthy people;
- effective anti-infectious immunity may cease to exist earlier than in healthy people;
- safety profiles are modified and such specific complications as rejection and transplant dysfunction exist at least theoretically;
- live attenuated vaccines are usually contraindicated;
- immune reaction is better when vaccination was prescribed before the immunosuppressive therapy.

RESUME

1. Vaccination is indicated to recipients of transplanted organs.
2. Patients of this group ought to receive inactivated vaccines, as their undesirable reactions are minimal.

It is advisable to perform further clearly designed studies aimed at improvement of the existing protocols for this population involving more patients and establishing control groups with respect to vaccination time (before or after transplantation), compliance with the existing vaccination protocols (observation, accelerated mode, use of high doses), type (against pneumococcal infection, influenza, Hib etc.) and composition of vaccines (mono- or polycomponent).

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