



## Kidney Transplantation in Children: Post-Transplantation Challenges and Management - Single Center Experience

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### Abstract

**Aim:** Understanding the aspects of transplantation immunology is essential for the personalized management of pediatric renal graft recipients. Kidney graft rejection represents an inflammatory reaction that occurs after transplantation, which is characterized by a cellular and humoral attack on the graft. Therefore, in order to optimize the medical approach of transplanted children, it is important to assess the immunological risk to which the child is exposed after transplantation. This work shows our experience in pediatric kidney transplantation.

**Methods:** We analyzed retrospectively data from kidney transplanted children, between 2014-2018 in Fundeni Clinical Institute, Bucharest. Data collection included age of the patient, the pathology that required a kidney transplant, blood group testing, immunosuppression regimen, HLA genotyping, anti-HLA antibodies, virology screen and cross matching. Donor type was also analyzed.

**Results:** During the study period the transplant was performed from 23 living related donors and 4 cadaveric donors. Of the 26 haploidentical patients, there were 20 males and 6 females. The mean age at transplantation was 12 years. The most common diagnosis was congenital anomalies of the kidney and urinary tract in 53.85% of patients. More than half of the patients were on dialysis before transplantation, and only 30.77% received preemptive renal transplantation. From 26 children, five had an episode of acute or chronic rejection. And of these 5 children with an episode of acute or chronic rejection, 3 were younger children and two older children. There was a statistically significant difference in acute rejection between the 5-year-old and over-5-year-old patients ( $p=0.001$ ). Acute rejection was more common in 5-year-olds. Regarding the type of donor (related donor versus cadaveric donor) no statistically significant difference was found in terms of rejection. Instead, there were statistical differences between the types of donor in terms of the rate of post-transplant complications. Surgical complications were more common in cadaveric donor transplantation than in related donor transplantation ( $p=0.0001$ ). Detection of anti-HLA antibodies was performed at the time of registration on the waiting list and then after transplantation every three months. All the patients had negative antibodies to class I and class II throughout the follow-up period post-transplantation. No patients died during the follow-up period. Cross-match tests were negative for all patients.

**Conclusion:** Improved HLA matching between donor and recipient, the absence of anti HLA antibodies and preemptive kidney transplantation are essential factors for long-term good quality life of kidney transplanted children.

**Keywords:** Kidney transplantation; Pediatrics; Transplantation immunology

### Introduction

ESKD is a devastating disease with many long-term consequences especially for pediatric patients [1]. Children compared with adults, are at higher risk to develop cardiovascular complications, bone diseases which lead to growth retardation and a significantly reduced quality of life [2]. According to "PREDATORR" study which was conducted in 2013 by the Romanian Society of Nephrology, approximately 7% of Romanians are affected by chronic kidney disease and a small proportion of the total number of cases are in children. Also, a study from North America showed that pediatric patients represent less than 2% of the total ESKD cases worldwide [3,4].

The best therapeutic approach for this particular group of patients is kidney transplantation.

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Over the past few decades, better immunosuppressive regimens, but also better HLA-matched donors have tremendously improved the life span of transplant recipients [5]. However, improving the long-term management after solid organ transplantation in children remains a challenge. The main challenge in kidney transplantation, in younger children, remains graft rejection because immune reactivity is different between younger children and older children. Studies have shown that children aged five and under have an increased number of CD2+, CD3+ and CD4+ T lymphocytes when compared with teenagers. Younger children also have higher than expected functional indices of cellular immune function [6]. These peculiarities of children as well as the fact that the most living-related transplants are only one HLA haplotype matched lead to an increased risk of graft rejection.

Our study aims to show our experience in pediatric kidney transplantation and to find future ways to improve the results after transplant procedures.

## Materials and Methods

### Patient selection

We conducted a retrospective study of 26 patients of which 22 patients who underwent kidney transplant from a related donor and 4 patients who underwent a kidney transplant from an unrelated donor between 2013-2019 in Bucharest, at Fundeni Clinical Institute.

We used various variables for each patient gender, age of the patient on the day of the transplant, the cause of chronic kidney disease, HLA genotyping for class I and class II alleles, donor type (related, unrelated), presence of acute rejection, history of dialysis, blood group, blood transfusions, infection disease screening. Using Hippocrates, our hospital information program, their post-transplant evolution was monitored for a year checking for post-transplant complications, acute or chronic rejection and transplant-related mortality up until January 2020. This work was approved by Fundeni Clinical Institute Ethical Committee.

### Sample collection

We used blood samples which were taken into vacutainer tubes with anticoagulant EDTA for transplant tests and also samples of blood were taken into vacutainer tubes with anticoagulant heparin for serological analysis. HLA-DNA isolation and HLA genotyping for kidney transplant recipients Firstly, the DNA must be extracted and purified from the blood sample. For DNA extraction we used QIAamp DNA Blood Mini kit (Qiagen, Hilden, Germany) following the instructions provided by the manufacturers. HLA genotyping for class I and class II alleles was performed by Polymerase Chain Reaction - Sequence Specific Primers (PCR-SSP) using the HLA-Ready Gene kit (Inno-Train, Germany).

For interpretation we used Ready Gene Online software. The anti-HLA antibodies screening was performed using a LAB Scan 3D analyzer (Luminex Corporation, Texas, USA). We used LAB Screen Mixed kit (One Lambda, CA, USA).

The tests were carried out according to the manufacturer instructions and the results were analyzed using One Lambda software. Cross match tests also were performed by Luminex Technology.

### Statistical analysis

Statistical analysis was carried out on Microsoft Excel 2013 to record all the data from Hippocrates. Event times were calculated from

the date of transplant. All graphs and percentages were calculated using Microsoft Excel. The p values were calculated following a paired student T-test. A p-value less than 0.05 was considered statistically significant.

Acute graft rejection was defined as an increase in serum creatinine level after exclusion of other causes of graft dysfunction, accompanied by sudden decline in glomerular filtration rate and kidney allograft biopsy demonstrating the presence of antibodies and/or T cell lymphocytes. Acute rejection can occur at any time after kidney transplantation.

Chronic graft rejection was defined by serum creatinine level >1.5 mg/dl for children between 5 and 10 years and a creatinine level >2 mg/dl for children above 10 years of age, associated with characteristic features on kidney allograft biopsy due to antibody-mediated or T cell-mediated changes. Chronic rejection occurs months to years after transplantation. Return to dialysis or retransplantation was considered graft failure.

### Ethics statement

All legal representatives of the children analyzed provided their written informed consent to participate in this study, according to ethical principles express in the Helsinki Declaration, and the study was approved by the Commission of Bioethics at Fundeni Clinical Institute, Romania.

## Results

Our study group consisted of 26 pediatric patients who received a kidney transplant between 2014-2018 at Fundeni Clinical Institute (Bucharest, Romania). Among the patients aged between 5 and 16 years twenty of them were boys (76%) and six were girls (23%) with a mean age of 12 years. The youngest patient who underwent transplantation was 5 years old and the oldest 16 years old. The majority of kidney allografts came from parents (22) and only a few (4) were from cadaveric donors. The most common causes of End Stage Renal Disease (ESRD) for patients who received kidney transplantation were Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) in 53% of patients followed by focal segmental glomerular sclerosis (23%), and other glomerular disease (23%). Table 1 summarizes the characteristics of our pediatric patients.

More than half of the patients (69.23%) were on dialysis before transplantation procedure. Only eight (30.77%) children from our centre had the chance of preemptive transplantation. Among the children treated by dialysis the median length of time from the beginning of the dialysis until receiving a kidney graft was 19.77 months.

From our group of patients, 3 children received blood transfusions before transplant procedure. All the patients had a negative cross match tests and also negative antibodies to class I and class II throughout the follow-up period post-transplantation. Within this population there were 4 (15.38%) cases of acute rejection, 1 (3.84%) case of chronic rejection and none of them had graft failure.

In pediatric kidney transplantation the most frequent living related transplants are only one-haplotype matched.

This incomplete HLA matching increases the risk of graft rejection and graft failure. The more HLA alleles we match the more survival rate we have. In addition we have noticed a better quality of life after kidney transplantation in the children best HLA matched.

**Table 1:** Patients Characteristics based on related vs. unrelated kidney transplant (N=26).

	Living Related Donor Transplant (n=22)	Cadaveric Donor Transplant (n=4)	Total n (%)
<b>Age at transplant (years)</b>			
≥ 5	4	1	5 (19.23%)
<5	18	3	21 (80.76%)
Average Age	12.19	11.25	
<b>Sex</b>			
Male/Female	16/6	4/0	76.92/23.07%
<b>Diagnosis</b>			
Congenital Anomalies of the Kidney and Urinary Tract (CAKUT)	13	1	14 (53.84%)
Nephrotic Syndrome	5	1	6 (23.07%)
Chronic glomerulonephritis	4	2	6 (23.07%)
HLA haploidentical matched patients	22	4	26 (100%)
<b>Anti-HLA antibodies detection</b>			
<b>Class I</b>			
-	21	4	25 (96.15%)
+	1	0	1 (3.84%)
<b>Class II</b>			
-	21	4	25 (96.15%)
+	1	0	1 (3.84%)
<b>Crossmatch test</b>			
-	22	4	26 (100%)
+	0	0	
<b>Year of Transplant</b>			
2014	3	0	3 (11.53%)
2015	3	3	6 (23.07%)
2016	6	1	7 (27.92%)
2017	4	0	4 (15.38%)
2018	6	0	6 (23.07%)
<b>Transfusions</b>			
yes	3	0	3 (11.53%)
no	19	4	23 (88.46%)
<b>Dialysis</b>			
Hemodialysis	14	4	18 (69.23%)
Preemptive	8	0	8 (30.76%)
<b>Induction</b>			
IL-2-R (Simulect)	22	4	26 (100%)
<b>Initial immunosuppressive</b>			
TPM	22	4	26 (100%)
Growth retardation	6	3	9 (34.61%)

n: number of cases; IL-2-R: Interleukin Receptor blocker; TPM: Tacrolimus, Prednisolone and Mycophenolate; HLA: Human Leucocyte Antigen

HLA A, B, C, DRB1, DPB1 and DQB1 alleles were available for all patients (n=26). It was observed that the most common alleles were represented by HLA A\*02 (26.92%), HLA B\*35 (25%) and HLA DRB\*11 (36.53%).

And also the most frequent haplotype in this group of patients

**Table 2:** Complications of kidney transplantation: Living related donor transplant vs. cadaveric donor transplant.

	Living related donor transplant (n=22)	Cadaveric donor transplant (n=4)	P value*
Recurrent Urinary Tract Infection	10 (45%)	2 (50%)	0.87
Surgical complications	0	2 (50%)	0.0001
Vascular thrombosis	1 (4.5%)	0	0.67
High blood pressure	5 (22%)	2 (50%)	0.27
Other viral infections	2 (9.09%)	0	0.54
CMV	3 (13.63%)	0	0.45
BKV	9 (40%)	2 (50%)	0.74
EBV	1 (4.5%)	0	0.67

\*Significance was set at a P value <0.05; CMV: Cytomegalovirus; BKV: BK Virus; EBV: Epstein-Barr Virus; n: number of cases

**Table 3:** Post-transplantation outcomes in young vs. older children in HLA haploidentical matched kidney transplant.

Outcome	Young Children (n=5)	Older Children (n=21)	P value*
Acute rejection	3 (60%)	1 (4.7%)	0.001
Chronic rejection	0	1 (4.7%)	0.635

\*Significance was set at a P value <0.05

**Table 4:** Post-transplantation outcomes in living related donor transplant vs. cadaveric donor transplant.

Outcome	Living Related Donor Transplant (n=22)	Cadaveric Donor Transplant (n=4)	P value*
Acute rejection	4 (18.18%)	1 (25%)	
Chronic rejection	1 (25%)	0	0.185

\*Significance was set at a P value <0.05

was represented by HLA A\*02-B\*18-DRB1\*11.

All patients received IL2-R blocker as induction agents before transplantation procedure. Maintenance immunosuppressant protocol for all children in our center means of tacrolimus, mycophenolate mofetil, and oral prednisolone given in a personalized approach.

The idea is to give less, but efficient doses of the immunosuppressive drug with the lowest possible side effects. One patient had BKV virus reactivation with increasing viremia, which is why we reduced immunosuppression and opted for switching from tacrolimus to cyclosporine and switching from mycophenolate to leflunomide. Tacrolimus blood level was maintained at 3.8 ng/ml to 10 ng/ml beyond 6 months for older children. For younger children (5 years old) we had to start with a higher tacrolimus dose to achieve the same immunosuppressive results. Regarding the type of donor (related donor versus the cadaveric donor) no statistically significant difference was found in terms of rejection.

Instead, there were statistical differences between the types of donor in terms of the rate of post-transplant complications. Surgical complications were more common in cadaveric donor transplantation than in related donor transplantation (p=0.0001) (Table 2).

Of the 26 children, five had an episode of acute or chronic rejection. And of these 5 children with an episode of acute or chronic rejection, 3 were younger children and two older children. There was a statistically significant difference in acute rejection between the 5-year-old and over-5-year-old patients (p=0.001). Acute rejection was more common in 5-year-olds (Table 3).

Regarding the type of donor there were no statistically significant differences in the rejection rate (Table 4).

## Discussion

End-stage kidney disease is a chronic condition with a high mortality and morbidity rate among pediatric patients [7]. In our group of children, the most common cause for end-stage kidney disease was congenital anomalies of the kidney and urinary tract in 53%. Also, a study from Japan showed that congenital anomalies of the kidney and urinary tract were reported to be the most frequent, followed by hereditary nephropathy and focal segmental glomerulosclerosis [8].

Children with a kidney transplant have a much better development and growth compared to children on dialysis [9].

Unfortunately, data from studies performed on adults are used for the management of the pediatric patient, thus not taking into account the characteristics of this group of patients [10]. Dialysis in children decreases the quality of life in this particular group of patients [11].

In our study group more than half of the patients were on dialysis before transplantation (69.93%) and the waiting time until they received a kidney graft was about 19.77 months. One of the most undesirable side effects of dialysis in children is growth retardation. A percentage of 34% suffered from growth retardation in the group we studied.

According to other studies, dialysis can negatively affect the overall mortality and morbidity. In addition, some studies have shown that patients with kidney transplant live longer compared with dialyzed patients [12].

Transplantation was used as initial therapy (preemptive renal transplantation) in 30.77 percent of the patients and all of these patients had a living related donor. Preemptive kidney transplantation, which is defined as transplantation prior to the initiation of dialysis, avoids the adverse effects associated with dialysis such as growth retardation, anemia, bone-mineral regulation, cardiovascular disease, and overall lifespan. Therefore, a kidney transplant is the treatment of choice for children with this disease [13].

For the proper development of the transplant program in children, we need to allocate appropriate kidney transplants for this group of patients. Most kidney grafts from cadaveric donors are allocated to adults and unfortunately, a low percentage of child benefit for a renal transplant. The majority of kidney grafts came from parents, because intrafamilial kidney transplantation is considered successful and thus we avoid the unwanted effects of dialysis [14].

For these reasons, in pediatric kidney transplantation the most living related transplants are only one HLA haplotype matched. The incomplete HLA matching but also the immune characteristics of children lead to an increased intensity of the immune response to HLA alleles over time and may be responsible for the high graft rejection rate.

The immunological characteristics of younger children are different from those of older children or adults.

Younger children have higher T and B cell counts and they also have increased ratio of CD4+ and CD8+ and increased blastogenic responses.

Our data suggest that children, but especially children under 5

years, may have a higher immune response, which has led to a higher number of episodes of acute rejection compared to older children. There was a statistically significant difference in acute rejection between the 5-year-old and over-5-year-old patients ( $p=0.001$ ). Acute rejection was more common in 5-year-olds. Regarding the type of donor (related donor vs. the cadaveric donor) no statistically significant difference was found in terms of rejection. We did not find any differences between the types of donors in terms of graft survival for one year post-transplantation follow-up.

Instead, there were statistical differences between the types of donor in terms of the rate of post-transplant complications. Surgical complications were more common in cadaveric donor transplantation than in related donor transplantation ( $p=0.0001$ ). The most common complications in children with renal transplantation were urinary tract infections, high blood pressure, and viral infections. The most common viral infections were due to the reactivation of the BKV virus. In our study group BKV viral infections were documented in 42.3% of pediatric patients. In terms of infection rate, there were no statistically significant differences between younger and older children and also between the types of donor.

Transplanted kidney is a continuous source of allogenicity that can induce rejection at any time after transplantation.

New discoveries in the field of immunology have provided many insights into mechanisms of alloimmune response and in the process of graft rejection [15]. Histocompatibility testing is an essential component for successful pediatric kidney transplantation. As a matter of fact immunological factors like HLA antibodies are the specific causes of worsening renal allograft function [16]. For a successful kidney transplant, along with HLA matching, anti-HLA antibodies are also detected in pediatric patients. Studies have shown that anti-HLA antibodies can be involved in acute graft rejection [17].

In our group of patients, the detection of anti-HLA antibodies was performed at the time of registration on the waiting list and then after transplantation every three months. All the patients had negative antibodies to class I and class II throughout the follow-up period post-transplantation. Also cross-match tests were negative for all patients.

Availability of living donor allografts, immunosuppression regimens and a better HLA matching between donor and recipient make the survival significantly improved.

The personalized of immunosuppressive protocols also contributed to a good quality of life of our patients. Studies have shown that in pediatric population it is needed a higher dose per kg bodyweight to achieve the same target blood concentration in young children compared with teenagers after kidney transplantation [18]. It is important to find the most appropriate immunosuppressive regimens in order to optimize kidney allograft survival in our pediatric patients by preventing the occurrence of acute rejection while limiting drug toxicities. Advances in solid organ transplantation have led to development of new immunosuppressant's to minimize the adverse effects in children [19]. Induction treatment consisted of administering IL-2-R blockers to all children before the transplant procedure. For all twenty-six patients, immunosuppressive medication consisted of tacrolimus, steroids and mycophenolate mofetil.

In our center children 5 years old started with a higher dose of tacrolimus to achieve the same immunosuppressive results as older



children. Thus younger children started with a dose of Tacrolimus of 22 mg per day and the older children with a dose of 8 mg per day to reach the same level of tacrolinemia. This aspect was demonstrated also in a paper published by G. Montini et al. [20] where it was shown that children under six years of age started with a 50% higher tacrolimus dose to achieve the same immunosuppressive results.

## Conclusion

Although our pediatric kidney transplant program is a young program it has good potential for development according to the needs. Transplanted kidney is a continuous source of allogenicity that can induce rejection at any time after transplantation. The immunological characteristics of children are different from those of adults. Children have higher T and B cell counts and they also have increased ratio of CD4+ and CD8+ and increased blastogenic responses.

Improved HLA matching between donor and recipient, the absence of anti HLA antibodies and preemptive kidney transplantation are essential factors for long-term good quality life of kidney transplanted children. In order to improve our kidney transplant program, we need to raise our cadaveric donor and perform high-resolution typing for donor and recipient.

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