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# Long-Term Outcome In Children With Kidney Transplant: A Review

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**Abstract**

Kidney transplantation is a preferred treatment for end-stage renal disease in children. The purpose of this article is to review the factors affecting the long- term outcome of renal allograft and patient survival. We also would like to emphasize the impact of kidney transplantation in childhood on long-term psycho-social and economic outcome in these patients.

**Keywords:** long-term outcome, kidney transplantation, children

## Introduction

End-stage renal disease (ESRD) is a rare condition in children. In comparison with the adult population where, according to the ERA-EDTA Registry, the average incidence of ESRD is 117-121 per million population, the incidence of ESRD in children is 7-9 per million age-related population [1]. There is also an important difference between the adult and children populations regarding the etiology of ESRD. The most common cause of ESRD in adults is diabetes mellitus type 2, whereas in children congenital anomalies of the kidneys and urinary tract are the most common cause of ESRD [1]. The preferred renal replacement therapy in children with ESRD is kidney transplantation, because it improves growth, increases life expectancy, and provides for a better quality of life [2-4]. Despite all the advantages of kidney transplantation in children, there are also multiple factors which affect patient and renal allograft survival. Kidney transplantation also has an important effect on long-term psycho-social and economic status in pediatric patients [5].

## Patient survival

Compared with adults, the patient survival rate in pediatric transplant recipients is longer [6,7]. The life span of children who received a renal allograft is also longer in comparison with those who underwent dialysis [8] or were placed on a waiting list for renal transplantation [9]. However, the relative risk of death after transplantation is still assessed as 12.7 times higher compared to the age-related general population [10]. The patient survival rate varies between 89% and 98% at 3 years, 84% and 97% at 5 years, 68% and 94% at 10 years, and 54% and 86% at 20 years [10-17]. In one study the patient survival rate was 81% after 25 years [18]. There were no differences in patient survival by donor source (living versus deceased donor) [19].

The major causes of death after transplantation are cardiovascular disease (CVD), infection, and malignancy [13,20,21]. The main causes of cardiovascular deaths are heart failure and arrhythmias [22]. With the purpose to at least partially prevent CVD, a healthy lifestyle and weight control should be encouraged among patients with renal transplants and their families. Additionally, anemia correction, arterial hypertension and hyperlipidemia treatment are also recommended. As a consequence of immunosuppressive therapy, sepsis due to bacterial infections and CMV infections are most common [20]. Compared with the general population, the risk of malignancy is 10 times more common than expected for age. Non-Hodgkin lymphoma represents the majority of cases and is a cause of death in children with kidney transplants [20]. EBV-driven PTLD is also an important cause of morbidity and mortality in pediatric renal transplant recipients. Reduction of the dose of immunosuppressive drugs is a common first-line practice [23,24]. Non-adherence to therapy or treatment withdrawal and obesity are also indicated as contributing to death in children with kidney transplants [10,25].

## Renal allograft survival

In recent decades, kidney transplant survival has markedly improved particularly in the immediate post-operative period as the result of refinements in surgical techniques, optimization of immunosuppressive protocols, introduction of new immunosuppressive drugs, and improvements in patient care [26]. The overall renal graft survival rates varies between 82% and 84% at 3 years, 74% and 87% at 5 years, 56 % and 68 % at 10 years, 45% in 53% at 15 years, 25% and 54% at 20 years, and 31% at 25 years [10,11,13,14,18,27,28]. Despite impro-

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vements in graft survival, there are many factors affecting long-term renal allograft survival.

***Effect of donor type*-**According to literature, living donor transplantation offers an advantage in renal allograft survival as compared to deceased donor transplantation [29-32]. Despite the advantages of living donation, there are settings where a deceased donor is preferred, such as in patients with focal segmental glomerulosclerosis, hemolytic uremic syndrome, or primary hyperoxaluria [33].

***Age of donor and recipient*-**Grafts from pediatric donors show a superior long-term kidney function compared with grafts from adult donors, most likely due to their ability to adapt to a growing child. There is, however, a higher risk of graft loss in the recipients of very young donors, most likely due to surgical complications, graft thrombosis, and early rejection. Recipient age also has an important effect on graft survival because there is a higher rate of graft failure in the youngest and adolescent recipients. In recipients younger than 5 years, graft failure in the first 3 months post-transplant is mostly due to surgical difficulties. In adolescents, poor graft survival is usually the result of inadequate adherence to immunosuppression regimens. Additionally, the highest rate of graft failure occurred in the recipients of young donor grafts [34].

***Infections*-**have an important role in the morbidity of children with renal allografts, and can also lead to renal graft failure. Viruses are among the most common causes of opportunistic infections after transplantation. CMV infection is among the most common infections during that period, and is associated with increased morbidity and mortality. Antiviral prophylaxis may improve patient and allograft survival [35]. Infections with polyomavirus BK can also cause chronic renal allograft dysfunction with secondary rejection and have a poor prognosis [36].

***Acute rejection episodes***-are one of the most important negative predictors of renal allograft survival and among the most frequent complications of renal transplantation [27,37,38]. Acute rejection episodes may also increase the risk of chronic rejection and enhance the possibility of graft loss over time [39]. In order to prevent acute rejection episodes, it is important to have optimal HLA matching and to optimize immunosuppression regimens.

***Human leukocyte antigen (HLA) matching*-**HLA plays an important role in the cellular and humoral responses that determine the outcome of a kidney transplant. It is one of the most important modifiable factors for reducing the risk of renal allograft loss. Superior HLA matching improves renal allograft outcome [40]. Sensitized patients with panel reactive antibodies (PRA) above 40% have a poorer outcome [8]. Additionally, an association between positive post-transplant, donor-specific HLA antibodies (DSA) and subsequent rejection was found [41].

***Arterial hypertension*-**Hypertension after renal transplantation is common and its estimated prevalence in children ranges from 58% to 89% [42,43]. It is a predictor of poor long-term renal allograft function, regardless of the number of rejection episodes or transplant function at 1 year [44]. It is a significant and modifiable risk factor for CVD.

***Kidney and urinary tract anomalies with bladder dysfunction*-**Children with congenital anomalies of the kidneys and urinary tract with bladder dysfunction are even more prone to repeated urinary tract infections when on immunosuppressive therapy after kidney transplantation. Despite this, several studies have found no significant effect on renal allograft outcome [45,46]. Due to numerous urological complications, careful surveillance of lower urinary tract function is needed before renal transplantation. There is no need to correct vesicoureteral reflux before renal transplantation, unless it is causing symptoms or infections [47].

***Immunosuppressive therapy*-**is imperative in the reduction of immune-related injury to an immunological, non-identical renal allograft, and in the prevention of allograft rejection and functional failure. The conventional regimens nowadays include corticosteroid, calcineurin inhibitors, antimetabolite purine antagonists, and less routinely used mammalian target rapamycin inhibitors (mTORIs). According to NAPRTCS [12], the use of cyclosporine has significantly decreased, while the use of tacrolimus has increased over the same period. Also, the use of mycophenolate mophetil (MMF) exceeded the azathioprine prescription. The use of steroid sparing regimens is becoming increasingly more common [48].

MMF-based protocols improved long-term graft survival without any increase in side effects. Cumulative rejection-free survival was better in the MMF group compared to the azathioprine group [49]. It was also evidenced that tacrolimus was significantly more effective than cyclosporine in preventing acute rejection in pediatric renal recipients. Renal function and graft survival were also superior with tacrolimus [50].

***Delayed graft function (DGF)*-**is defined as the requirement for dialysis within the first seven days following renal transplantation. Several clinical factors related to donor, recipient and organ transplantation procedures could increase the risk of DGF. The factors that may increase the risk of DGF include long cold ischemia, drug nephrotoxicity, and surgical problems. DGF may decrease long-term graft function. The strategies to minimize DGF are: reduction of individual risk factors for DGF and specific pharmacologic strategies designed to prevent or treat ischemia and reperfusion injury [51].

***Underlying primary disease and recurrence*-**The risk of disease recurrence becomes relatively high, with greater prevalence in children than adults. It increases patient morbidity and graft loss. The diseases that most commonly lead to recurrence are: focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, hemolytic uremic syndrome, and hyperoxaluria type

1 [52], where oxalate will continue to be deposited in the transplanted kidney, unless a liver transplant was performed at the same time. Congenital nephrotic syndrome (Finish type) and Alport syndrome can recur due to the development of antibodies to the "missing" proteins.

***Adherence (compliance)***-This is a difficult problem in all ages, particularly in adolescence. It is associated with increased episodes of acute and chronic rejection and graft loss of up to 71% [53]. The reasons for non-adherence in the adolescent period are mostly transition to adulthood, health care system, difficulties in patient-parent relationships, lack of parental supervision, cosmetic effects of medication, and poor knowledge. Not only failing to take medication, but also incorrect timing of medication intake and inappropriate drug dosage are signs of poor adherence. Multiple methods of assessing adherence are used, such as drug level assays, pill counting, and patient self-reporting [54]. Patients with kidney transplants are also exposed to a high drug and pill burden, which further increases the risk of non-adherence and adverse treatment effects, both of which influence graft survival. According to a Slovenian study, fifty percent of children have been receiving more than 10 different drugs daily, resulting in over 23 pills per day [55]. The daily drug and pill burden is high and can trigger non-adherence, which is why strategies to reduce drug and pill burden should be developed.

## Long-term psycho-social and economic outcome

The main goals of kidney transplantation in children are not only to increase life expectancy, but also to improve the social and professional components of life that importantly affect its quality. In pediatric transplant recipients, quality of life also depends on the primary diagnosis and on graft function.

***Educational level***-In a Slovenian study, 24% of patients with kidney transplants in childhood completed elementary school or have no education, and 76% of pediatric patients achieved a certain education level that can increase their chances of employment [27]. In a French study, the distribution of education levels was similar, but lower compared to the national averages [56]. It was found that renal transplant children have significantly worse scores on intelligence quotient tests compared to healthy individuals (86 vs 107). Lower maternal education level was also significantly associated with lower cognitive test scores. Additionally, children with renal allograft and comorbid conditions also had a significantly lower verbal ability and IQ score [57].
***Employment***-Some studies have shown a satisfactory level of employment. Between 54% and 86% patients were employed, which is similar to the general population [19,56,58]. In a Slovenian study, only 36% of patients were employed, which can partially be explained by the relatively high percentage of students (16%) who will apply for a job only after completing their education. According to different studies, the rate of unemployed patients was between 6.5% and 12.1% [18,27,58]. Additionally, the number of retired patients receiving a government pension and classified as non-employees was between 18.7 and 36% [27,56]. It has been confirmed that patients with childhood onset ESRD are unemployed more frequently than the age-matched population [59].
***Relationships***-According to different studies, 23% to 50% of patients were involved in a steady relationship or are married. It was also reported that between 12% and 27% of patients had children [27,56,58,59]. A significant correlation between education level, paid activity, marital life and independent housing was found [56].
***Quality of life***-Many studies confirm that the quality of life is reduced with chronic renal failure and dialysis, but is improved after renal transplantation. Transplant patients tend to score their quality of life higher than the controls, but parents rate their affected children more pessimistically, usually with regard to physical complaints, social functioning, and negative emotions [60]. The findings of a Slovenian study showed that a substantial number of patients (76%) meet with friends regularly, and 40% of them are regularly involved in sport activities. These data were in agreement with the fact than 60% of those patients expressed no particular worries regarding their health, and three quarters of them rated the quality of their life as excellent or good [27]. However, quality of life is also strongly correlated with illness associated variables and family relationships [60].

## Conclusion

Kidney transplantation is the preferred renal replacement treatment modality in children because it improves growth, prolongs life expectancy, and improves the quality of life. Nevertheless, there are multiple factors affecting the long-term outcome of renal allograft and patient survival in the pediatric population, among which acute rejection episodes and non-adherence are among the most important. Additionally, kidney transplantation in childhood has a significant impact on long-term psycho-social and economic outcome in adulthood.

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