**Review article**

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# Pediatric Kidney Transplantation

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Pediatric kidney transplantation is the best option since it can achieve near normal glomerular filtration rate, adequate fluid balance, and autonomic endocrine function of the kidney in end-stage kidney disease. However, pediatric kidney transplantation is difficult because children are developing and growing, management and complications of pediatric kidney transplantation are different from those of adults. This review covers the current status of pediatric kidney transplantation in Korea, key considerations that must be taken before kidney transplantation in children, and management strategy of immunosuppression and common complications.

**Key words:** Kidney transplantation, Child, End-stage kidney disease

## Introduction

Patients with end-stage kidney disease (ESKD) need renal replacement therapy. There are three modalities of hemodialysis, peritoneal dialysis, and kidney transplantation (KT). Among them, KT is the best option since it can achieve near normal glomerular filtration rate, adequate fluid balance, and autonomic endocrine function of the kidney[1]. In children, normal development and improvement of growth are possible with successful kidney transplant[2], along with better school performance[3,4]. Therefore, success of pediatric KT is a common goal for pediatric nephrologists[5]. Since children are developing and growing, management and complications of pediatric KT are different from those of adults. This review covers the current status of pediatric KT in Korea, key considerations that must be taken before KT in children, and management strategy of immunosuppression and common complications.

## Current status of pediatric kidney transplantation

The number of kidney transplants in Korea is increasing every year, reaching 2107 cases (807 deceased donor transplantation) as of 2018. However, the number of people waiting for kidney transplants is also increasing every year, and the average waiting period is 5.6 years in 2018, after registering on the waiting list for a deceased kidney donor[6]. Based on the Korean Network for Organ Sharing (KONOS) annual report of 2018, overall patient survivals at 1yr after KT were 98.65% for living donor KT and 95.15% for deceased donor KT; 5yr survivals were 96.47% and 91.65%, respectively. 10yr survivals

were >91.29% and >84.89%, respectively. Better survival of living donor KT over deceased donor KT is a universal finding; shorter cold-ischemia time (the gap between organ harvest and re-vascularization to the recipient's vascular system), better HLA mismatch, a shorter waiting time, and surgery of non-emergency setting in living donor KT might explain this difference.

In children, an average of 48.5 cases of KT have been performed annually for the last 10 years, 67.8 % living related KT and 32.2% cadaveric. Interestingly, the male to female ratio is 1.55:1 with male dominance[6]. Similar results are also reported by the North American Pediatric KT Research Association (NAPRTCS) with male to female ratio 1.45:1[7]. Such male dominance might come from higher prevalence in boys of congenital anomalies of kidney and urinary tract (CAKUT), including renal dysplasia, hypoplasia, aplasia and obstructive uropathy, the primary diagnoses of pediatric ESKD, comprising up to 25% of the causes of ESKD in children[7,8]. Overall survival rates of pediatric KT are not inferior to those of adults as shown at Table 1.

Waiting period of pediatric KT for children in Korea are expected to be shorter than that of adults. Since the donor kidney allocation policy was changed in October 2018, and now organs from a deceased donor under the age of 18 are distributed preferentially to children and adolescents. This policy change was influenced by Share 35 in the United States, which gives high priority to children when allocating young deceased donor's kidneys[9].

## Preparation of pediatric kidney transplantation

### 1. General evaluation

Clinically important differences of pediatric KT from adults are 1) causes of in children (affecting selection of donor, comorbidity and risk of relapse), 2) necessity of developing and growing (affecting the timing of transplantation and dosage of medications), and 3) immune status (often naïve to common infections). Therefore, it is necessary to take a detailed medical history including the patient's age and size, underlying disease of ESKD, past medical history, vaccination history, family history, and mental disorder. Physical examination, blood tests, and urine tests are performed to evaluate comorbidities including congenital anomalies, systemic diseases, infectious diseases, and status of the cardiovascular system. Furthermore, problems associated with chronic kidney disease including anemia, acidosis, metabolic bone disease, hypertension, and stunted growth need to be treated as much as possible before KT.

As a preparation of KT, vaccination history should be checked and the necessary vaccinations need to be done in advance, such as chicken pox, Haemophilus influenza type b (Hib), hepatitis B virus (HBV), and Influenza. Live vaccines are not safe in patients with chronic immunosuppression after transplantation, so vaccination prior to transplant is necessary[10]. Urological anomalies such as high grade vesicoureteral reflux or neurogenic bladder with small capacity might need to be intervened surgically before transplantation to improve the allograft outcome[11].

The small size of children might hinder the operation itself. Therefore, most pediatric transplant centers wait until the patients weigh more than 10kg. Improvement of surgical method might improve the allograft survival of young children[12]. Other comorbidities also need to be considered before transplantation, such as life-threatening/quality of life-limiting congenital anomalies or chronic

Table 1. Overall patient survival rates of pediatric kidney transplantation

| | Age* | 3 month | 1 year | 3 year | 5 year | 7 year | 9 year | 11 year |
|---|---|---|---|---|---|---|---|---|
| Deceased donor | Total | 97.66% | 96.15% | 93.84% | 91.65% | 89.67% | 87.32% | 84.89% |
| | 1–5 | 100% | 100% | 95.45% | 95.45% | 95.45% | 95.45% | 95.45% |
| | 6–10 | 96.83% | 96.83% | 95.22% | 95.22% | 95.22% | 92.90% | 92.90% |
| | 11–18 | 98.63% | 98.63% | 98.63% | 97.85% | 96.14% | 96.14% | 96.14% |
| Living donor | Total | 99.22% | 98.65% | 97.67% | 96.47% | 95.01% | 93.44% | 91.29% |
| | 1–5 | 95.00% | 95.00% | 95.00% | 91.04% | 91.04% | 91.04% | 91.04% |
| | 6–10 | 100% | 98.99% | 98.99% | 97.70% | 97.70% | 97.70% | 95.20% |
| | 11–18 | 99.72% | 99.72% | 99.72% | 99.38% | 99.38% | 99.38% | 99.38% |

*years.

infection including HBV or Human immunodeficiency virus (HIV). In the case of HBV infection, it has been a relative contraindication in the past because it can be reactivated due to the use of immunosuppressant and can lead to liver damage. However, along with the development of antiviral agents HBV infection is no longer a contraindication. HIV positivity is also no longer an absolute contraindication of KT, while the outcome of KTs in children with HIV infections are limited[13,14]. Per severe intellectual disabilities, the American Association of Transplant Physicians issued guidelines that cognitive impairment should not be considered a transplant contraindication in 1995[15].

### 2. Immunologic evaluation

Immunological evaluation before and after transplantation is necessary to minimize the risk of rejection, such as ABO type, human leukocyte antigen (HLA) type, and histocompatibility cross-matching. Previously, ABO blood type compatibility dictated the primary donor selection, but currently desensitization (remove ABO antibodies through plasma exchange and intravenous immunoglobulin (IVIG) and B lymphocytes through rituximab) enables ABO-mismatch KT[16,17].

Next, HLA typing important because it can predict rejection reactions depending on the degree of histocompatibility. Particularly, HLA type A, B (class I), and DR (class II) mismatching is associated with transplantation rejection. Therefore, when selection of donor is possible, it is important to choose a donor with a more number of matching HLA antigens, and it is particularly important to find a donor that matches at least one of the HLA-DR antigens [18]. There are three combinations of HLA conformance: HLA matched, haplo-matched, and mismatched. In the case of living related donor transplantation, HLA is haplo-matched between parents and children. Between siblings, there is a 25% probability of a perfect match, a 50% probability of a half match, and a 25% probability of a mismatch.

Then, we need to know if the recipient has antibodies against the donor HLA (donor specific antibody, DSA) or HLA in general (panel reactive antibody, PRA). In PRA, the serum of the recipient is reacted with a panel consisting of dozens of lymphocytes with known HLA information, to assess whether the recipient is sensitized to HLA. These days, flow cytometry method is used for PRA testing. The result of PRA is reported as % and median fluorescent intensity (MFI). % means the portion of HLA pools of the panel that recipient's serum reacted (had antibodies against) and MFI roughly means the amounts of antibodies. From PRA, you can identify HLAs the recipient was sensitized against. If a certain donor (candidate) has the respective HLA, then the recipient has DSA. When recipient has high PRA or DSA, desensitization using IVIG, plasma exchange, and rituximab is also available[19].

Cross-matching determines the presence of antibodies through direct reaction of donor cells and recipient's serum. Complement dependent cytotoxicity (CDC), CDC-AHG (addition of anti-human globulin (AHG) to enhance the reaction), and flow cytometric crossmatch (FCXM, using fluorescence to assess the attachment of antibodies from recipient to donor HLA) are the methods used. Luminex Array method using beads containing HLAs has also been used in the recent years[20]. If the recipient has DSA, donor cells are killed at CDC or CDC-AHG, and reported as (+), meaning that if transplantation of this donor-recipient pair is proceeded, hyper-acute rejection would occur. Therefore, cross-match (-) should be confirmed before kidney transplantation to avoid hyper-acute rejection.

## Immunosuppressive treatment

Graft and patient survival rate KT in pediatric patients have improved since 2000s due to the development of potent immunosuppressant[21]. To avoid rejection of allograft, use of immunosuppressants, induction and maintenance, is imperative. It is a principle to initiate immunosuppressants concurrently with transplantation and maintain it for a lifetime, as long as the transplanted kidney is functioning[22].

Induction therapy is to prevent acute rejection by using a strong immunosuppressant at the beginning of the transplant to eliminate total T cells (anti-thymoglobulin, ATG) or activated T cells (IL-2 receptor Ab or anti CD25 monoclonal Ab, Basilixmab). Induction therapy can improve the survival rate of transplants by reducing acute rejection[23], but it is associated with higher risk of infections and tumors.

Maintenance therapy is to prevent long-term rejection while minimizing the side effects of immunosuppressant. Steroids, calcineurin inhibitor (CNI), and antiproliferative

agents such as azathioprine, mycophenolate mofetil or sirolimus are commonly used for treatment. Each agent has its own side effects, therefore monitoring of the side effects and timely management of them are necessary. Particularly, long-term administration of steroids can cause growth stunting, diabetes, hypertension, hyperlipidemia, and osteoporosis, thus steroids are often tapered and discontinued (~40%)[24]. In general, there are two kinds of approach for steroid minimization. One is complete steroid avoidance or early steroid withdrawal (<7 days post-transplantation) along with very potent induction agents such as ATG or alemtuzumab (anti CD52 antibody eradicating total lymphocytes). The other is late steroid withdrawal (> 6mo–1 year post-transplantation). Outcomes of these steroid minimization protocols are fair, but infection (the former approach) and rejection might complicate the post-transplant course.

CNIs may cause hypertension, diabetes, hypomagnesemia, and hair loss (tacrolimus) or hairiness (cyclosporine). They have narrow therapeutic window, so trough level should be monitored. Therapeutic drug monitoring is also used to monitor drug compliance. Especially in adolescents, trough levels often fluctuate, probably because of more common non-adherence and rapid growth. Therefore, more frequent monitoring and adjustment are necessary.

## Post-transplant monitoring

After transplantation, allograft kidney function, complications of transplantations, and side effects of immunosuppressants should be monitored regularly by measuring renal function, DSA, and virus titers.

### 1. Thrombosis

Thrombosis in pediatric transplant patients is an important complication, the third cause of transplant failure[25-29]. Once it occurs, it is often not reversible, therefore early diagnosis and prevention are paramount. When pain, oliguria, azotemia, or thrombocytopenia occurs after transplantation, thrombosis should be suspected. The rapid diagnosis can be made through ultrasound, and early thrombectomy might rescue the graft. For prevention, prophylactic use of anticoagulants such as heparin, aspirin is possible.

### 2. Allograft rejection

Allograft rejection can be classified as hyper-acute, acute, and chronic rejection according to the timing of occurrence, or cell mediated rejection and antibody mediated rejection according to the main factor. Hyperacute rejection by pre-formed antibodies against HLA or ABO practically no longer occurs with the development of immunologic evaluation. Acute rejection has also significantly decreased due to the potent immunosuppressants over the past 30 years[8,30]. However, it still occurs probably due to mixed immune responses, and is a major cause of allograft dysfunction, requiring early diagnosis and treatment. In acute rejection, most patients are asymptomatic, while fever, oliguria, and graft tenderness may present and indicate severe inflammation, probably from drug non-adherence. Confirmative diagnosis of rejection is obtained by allograft kidney biopsy, revealing interstitial infiltration by immune cells, tubulitis and vasculitis by T cells in cell mediated rejection. Especially, subendothelial infiltration of mononuclear cells are characteristic findings. Banff classification is used to describe the classification and severity of rejection[31,32]. Therapeutic options for treating acute cellular rejection include pulsed corticosteroids in children, and ATG for refractory rejection.

Antibody mediated rejection is associated production of DSA. It often accompanies proteinuria and azotemia, and characterized by DSA (+) and C4d deposition in capillaries on kidney biopsy. Intensifying immunosuppression, plasmapheresis, IVIG, and rituximab are treatment option, but antibody mediated rejection usually stems from insufficient immunosuppression such as inadequate dosage or drug non-adherence, and is often refractory.

### 3. Infection

While rejection rate decreased due to the development of new immunosuppressants risk of infection has increased. In particular, infection is the leading cause of death in pediatric kidney transplantation. Urinary tract infection is common during the first months after transplantation; Cytomegalovirus (CMV), Epstein virus (EBV), and BK virus reactivation occurs during 6 months' post-transplant period because of the strong immunosuppression. Children are often naïve to these common infection, and initial infection during immunosuppression or infection through

the allograft often cause severe diseases. CMV infection may present as allograft dysfunction, cytopenia, or CMV disease of lung, liver, or gastrointestinal tract, and can be treated with ganciclovir. EBV infection is notorious to be associated with post-transplant lymphoproliferative disease. BK virus infection causes allograft dysfunction, hydronephroureterosis, or hemorrhagic cystitis. Recipients without antibodies against those viruses are particularly vulnerable, and these infections can be life-or allograft-threatening. Therefore, regular monitoring of virus titer (monthly during first 6 months, then every 3 months during the first year, then yearly or when clinically suspected) is necessary. When virus infection is identified, immunosuppression should be modified, and prompt treatment should be ensued when available. Opportunistic infections such as herpes simplex virus, herpes zoster virus, and pneumonia are also common.

### 4. Recurrent disease after pediatric kidney transplantation

Recurrent glomerulonephritis in children with KT is one of the main causes of allograft loss. Especially, focal segmental glomerulosclerosis (FSGS), atypical hemolytic uremic syndrome (aHUS), and diseases such as membranoproliferative glomerulonephritis and primary hyperoxaluria are known to recur after transplantation. Therefore, when considering transplantation, possibility of recurrence should be discussed. On the other hand, FSGS due to genetic causes does not recur, and liver transplantation for aHUS due to complement factor H (or I) and primary hyperoxaluria can prevent recurrence. C5 antagonist is available to prevent recurrence of aHUS, as well.

### 5. Post-transplant lymphoproliferative disease and post-transplant diabetes

These diseases are also important complications of kidney transplantation requiring regular surveillance of EBV titer monitoring and Hb A1c measuring.

## Conclusion

The history of KT dates back to about 60 years before, however, pediatric KT in Korea has only been around for 40 years since the first case in 1979. The median survival rate of KT is about 15 years in the North American study, whereas in Korea, some of the first recipients still has functioning allograft, with median survival of current allograft kidney is expected to be longer than 20 years. The main task of the transplant team is to effectively prevent and treat complications that may occur after KT. Active organ donation is also important, as the waiting list is growing.

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## Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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