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Pediatric kidney transplantation: An overview

Reza F. Saidi, MD, FICS, FACS (**corresponding author*): *Assistant Professor of Surgery, Division of Organ Transplantation, Department of Surgery, Alpert Medical School of Brown University, 593 Eddy Street, Providence, RI 02903.*
reza_saidi@brown.edu

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Abstract

Kidney Transplantation in children is the treatment of choice to treat end stage renal disease. Improvements in immunosuppressive management have dramatically reduced the risk of early acute rejection and graft loss, however the long term results in terms of graft survival and morbidity still require search for new immunosuppressive regimens. Reducing of side effects are the challenges for improving the outcome of pediatric transplantation. This review will discuss the current trends and outcomes of the kidney transplantation in children.

Keywords: Pediatric kidney transplantation, Immunosuppressive managements, Outcomes

Introduction

Kidney Transplantation is not only considered as the last resort therapy but also as a treatment of choice for children with end-stage-renal disease (ESRD) and many patients with end-stage organ damage (ESRD). Recipient-mediated acute or chronic immune response is the main challenge after transplant surgery. Non-specific suppression of the host immune system is currently the only method used to prevent organ rejection. Lifelong immunosuppression (IS) will cause significant side effects such as infections, malignancies, chronic kidney disease, hypertension, and diabetes (1). These issues are more relevant in children who have a longer life expectancy and so may receive a longer period on immunosuppressive medications. Efforts to minimize or completely withdraw IS would improve the quality of life and long-term outcome of pediatric kidney transplant recipients (2).

Current status of pediatric kidney transplantation (PKT)

There are currently 1741 pediatric patients on the waiting list for solid organ transplantation in the United States, including 836 for kidney and 465 for liver transplantation. More than 40,000 children have undergone transplantation in the United States, comprising 7.4% of all transplantations. Infants (less than one year old) represent 16% of all pediatric transplant patients. The biggest challenge in organ transplantation is organ shortage. Since 2004, the number of living donors has decreased (3). Decrease in the number of living donors may be due to loss of income during post-operative recovery and expenses which may not be paid by insurance companies (3). Interestingly, the number of organ transplantation in children in the United States has increased about 50% from 1988 to 2011 (OPTN). The number of deceased donor organs available for organ transplantation (Tx) has decreased in recent years (4).

Indications and surgical considerations

The most common primary causes of ESRD in children are congenital or inherited disorders such as renal dysplasia, obstructive uropathies, or reflux nephropathy in young children and acquired glomerular diseases such as focal segmental glomerulosclerosis and lupus nephritis in older children (1).

The kidney can be placed in retroperitoneal or intraperitoneal space, but it depends on the size of the child or the allograft itself. The arterial anastomosis is done to iliac artery (common, external or internal iliac artery) or aorta. The venous anastomosis is done to iliac vein (common or external iliac vein) or inferior vena cava. In children abnormal bladder function may cause ESRD such as posterior urethral valve. An open vesicostomy may be kept in place for many months after transplantation. Children with small bladder capacity may benefit from a bladder augmentation using segments of ileum, stomach, or appendix to

Table 1. Common side effects of immunosuppressants.

Medication	Side effects
Anti-CD25 receptor antibodies (basiliximab, daclizumab)	Anaphylaxis, allergic reaction
Anti-CD52 monoclonal antibody (alemtuzumab)	T-cell depletion, which increases the risk of infection, in particular CMV reactivation
Anti-thymocyte globulin (ATG)	Lymphopenia, Serum sickness, anaphylactic reaction, shock, bronchospasm
Corticosteroids	Cushinoid appearance, fluid retention, diabetes mellitus, hypertension, growth impairment, hyperlipidemia, osteopenia, impairment in wound healing, Failure to thrive
Calcineurin inhibitors (CNI)	Nephrotoxicity, neurotoxicity, hypertension, hyperlipidemia and hyperkalemia, diabetes mellitus, increased bone resorption, hirsutism, gingival hyperplasia, hearing impairment and cholestatic syndrome
Azathioprine	Hepatic nodular hyperplasia, portal sclerosis, myelosuppression
Mycophenolate	GI disturbance, myelosuppression

create a permanent cutaneous conduit that enables the child to be continent and to have clean, intermittent catheterization. Pediatric patients with obstructive uropathy have a higher rate of urinary tract infection after transplantation which needs lifelong antimicrobial prophylaxis.

Kidney allograft allocation for pediatric kidney transplantation

The allocation of kidneys from deceased donors involves a complex algorithm that includes the degree of anti-HLA sensitization, the need for multiple donor organs, the blood-group match, the relative HLA match, and the waiting time. Children make up a small fraction of persons awaiting kidney transplantation (approximately 2%). Allocation policies regarding organ transplants have preferentially allocated higher-quality kidneys from deceased donors to children in relatively prompt fashion, with resultant mean waiting times as short as 3 months in some regions. In general potential children waiting for PKT get priority for young donors age 35 or younger, known as Share 35 policy (5). However, such policies have led to a decline in the donation of kidneys from living donors and to a greater proportion of poorly HLA-matched kidney transplants from deceased donors in children.

Chronic IS therapy after PKT

The current limitations of continuous immunosuppressive therapy are their side effects, high cost, and the high incidence of non-adherence, particularly among adolescents.

There are various studies that estimate the consequences of post-transplant non-specific IS in children. These complications fall into two broad categories: direct tissue or organ toxicity, or non-specific IS action (i.e., infection and malignancy). A detailed description of these complications is shown in Table 1.

Insurance coverage for long-term IS medication is a considerable problem. Over 70% of kidney transplant programs report that their patients have serious problems of paying for their medication costs (6). On average, the annual cost of IS is 10,000–15,000$ in the United States (6). Furthermore, more than 68% of all programs report deaths and graft loss because of cost related IS non-adherence.

Although drug payment issues are more significant in adults than children in the United States, the costs of medication and post-transplant care do still pose many challenges for families of children who have undergone PKT. Time away from work for caregivers may also be a significant financial stressor for these families. Tx may affect behavior, cognitive development, and the mental health of solid organ transplant patients. Both patients and caregivers have an increased risk of developing psychiatric disorders such as depression, PTSD, and other anxiety disorders (7). Adolescents have the worst patient and graft survival, mainly as a result of non-adherence, although other developmental issues (including immune responsiveness) may play an important role in graft outcomes (8). Education about the potential risks of non-adherence is challenging in this group. Less complex medical regimens and medications with less side effects and improved cosmetic appearance can potentially aid in promoting adherence (7-19). Achieving the state of tolerance, however, seems to be the best possible solution to overcome adolescent non-adherence.

Side effects of immunosuppresion

The current IS regimens led to decrease in acute rejection to 10% or less (11). There are various studies estimating the consequences of post-transplantation non-specific immunosuppression, either by side effect of immunosuppression or as a complication of a defect in body's defense mechanism.

The type and dosage of most immunosuppressive agents after transplantation have been changed during past decades (5,6). For example while usages of cyclosporine and azathoprine have decreased from 1995 to 2005, usage of mycophenolate and tacrolimus have increased. In 2005, 92% of post-transplant patients received tacrolimus (1,2,5,6).

Immunosuppressive therapy can be divided into induction and maintenance therapy. Table 1 shows some of the medications that more commonly used for post-transplantation immunosuppression along with their most common side effects (3,7).

Two groups of medications that are well-known to cause direct side effects but yet are the backbone of all immunosuppression therapies, are calcineurin inhibitors (CNI) and corticosteroids. However, current efforts are minimizing their adverse effects by close drug monitoring and multiple drug combination; we cannot fully inhibit their side effects (7).

Corticosteroids put the patients under the risk of developing a wide range of medical problems from poor wound healing, susceptibility to infections, cardiovascular risk factors such as hypertension (by up regulating of α_1 receptors), and hyperlipidemia to growth retardation and even changing of appearance (6-8).

CNI are associated with renal toxicity both in renal and non-renal transplantation (8-10). Rate of renal dysfunction in pediatric recipients of non-renal transplantation is about 55% (6-10), 3%–6% of whom may develop ESRD (7,13). Neurotoxicity, hypertension, hyperlipidemia, diabetes mellitus, and hyperkalemia are other side effects of CNIs (7).

Half of pediatric kidney recipients also have hyperlipidemia (7). Neurological disorders affect approximately 20% of kidney transplant recipients (7); risk of developing *de novo* malignancies are 3–5 times higher than normal population (7). The risk of developing post-transplant lymphoproliferative disorder (PTLD), which has close relation with Epstein-Barr virus (EBV) infection, is found to be higher in children comparing to adults as it is more likely that they be EBV-seronegative at the time of transplantation (7). Most pediatric patients receive transplantation at an age when they have naïve immune system and are seronegative for many viruses including EBV and herpes simplex virus (HSV). CMV infection, BK virus nephropathy and *Pneumocystis carinii* pneumonia (PCP) are among other complications. In general, infection, as the main cause of hospitalization after kidney transplantation, is related to immunosuppression (7,8).

Patient dependency on lifelong non-specific immunosuppression is an unsolved problem after transplantation (7). Tolerance eliminates the complications of long-term immunosuppression use (12,13), which is a great challenge for pediatric transplant. It can also improve the patient's compliance which is the main problem in adolescents with chronic disease. Adolescents are particularly prone to non-compliance with their medical regimen as a result of developing sense of authority and poor judgment at this age.

Costs

Insurance coverage for long-term immunosuppression medication is a considerable problem. Over 70% of kidney transplant programs report that their patients have serious problems of paying for their medication costs (14). More than 68% of all programs report even deaths and graft loss because of cost-related immunosuppression non-adherence. However, these problems are more significant in adults than pediatrics, but even children and their families are potentially at risk of facing these problems (14). In average, the annual cost of immunosuppression is 10,000–15,000 US$.

Non-adherence

Daily usage of immunosuppression medications may affect the mental health of patients particularly adolescents and their families. Both of these groups are prone to developing psychiatry problems such as depression, post-traumatic stress disorders (PTSD) and other anxiety disorder (2,15). Adolescents have the worst outcome of graft survival mainly as a result of non-compliance (15). Education about the potential risk of non-adherence is challenging in this group. Less complex medical regimen, medication with less side effects and cosmetic change can potentially be more successful. Achieving the state of tolerance however seems to be the best possible solution to overcome adolescent non-adherence.

Outcomes after PKT

Allograft and patient survival: Kidney-allograft survival has improved tremendously over time in successive cohorts of pediatric recipients, regardless of whether the transplant was from a living or deceased donor. Such progress can be attributed to multiple factors refinements in pretransplantation preparation, enhanced surgical techniques, better choice of donors, more potent immunosuppressive medications, greater understanding of pediatric-specific pharmacokinetics, and use of evidence-based medication protocols. In addition, overall rates of acute rejection among children have declined; the acute-rejection rate at 1 year among recipients of allografts from living donors decreased from 55% in the late 1980s to 10 to 15% in the most recent cohorts. Although developing countries have lower rates of transplantation than developed countries, in addition to limited resources for acquiring the newer, more expensive immunosuppressive agents, they have had similar improvements (16).

Kidneys transplanted into children 5 years of age or younger have shown the most dramatic improvement. Unfortunately, adolescents now have the worst long-term graft survival among all pediatric-recipient age groups and represent the highest-risk recipients. Many reasons are postulated for this outcome, of which poor adherence to medication therapy is believed to be a major factor. The early mortality among pediatric kidney-transplant recipients is very low, and death results mostly from infection or cancer, whereas mortality after transplantation is much higher among adults, and deaths are largely due to cardiovascular disease.

Infections: Opportunistic viruses have emerged as great challenges to clinical management after kidney transplantation, probably related to the immunosuppressive regimens used currently, which are more potent than those used in the past. Since the mid-1990s, the incidence of the Epstein–Barr virus (EBV)–driven cancer known as post-transplantation lymphoproliferative disorder (PTLD) has dramatically increased, and BK virus has emerged as a new cause of infection (17). These two viruses typically infect people early in life, when they are immunocompetent, and cause mild disease but leave behind a pool of latent virus in the reticulothelium or urothelium. Since kidneys transplanted in children are usually from adult donors, there is an increased chance that a kidney from a seropositive donor (with latent virus) will be transplanted into a seronegative recipient. Thus, as compared with adults, children are at higher relative risk for severe disease from cytomegalovirus, EBV, or BK virus, with higher rates of complications, graft loss, and death.

Transplantation physicians typically reduce immunosuppression as a first response to each infection, with varied results. Ganciclovir is generally effective both as prophylaxis against and as treatment for cytomegalovirus infection, and antiviral prophylaxis have been associated with reduced rates of PTLD. For BK virus infection, no antiviral treatment strategies have been validated, although cidofovir and leflunomide have been used in both adults and children. Many pediatric kidney-transplantation centers perform serial monitoring for viruses with the use of a polymerase-chain-reaction (PCR) assay in the first 12 months after transplantation, in order to detect infections early.

*Growth considerations***:** Children are in a state of active growth. Chronic kidney failure can lead to severe growth failure, often with associated loss of self-esteem. Children with kidney failure were once approximately 2.5 SD below the expected height for their age at the time of transplantation. Improved nutrition before transplantation and aggressive use of recombinant human growth hormone have reduced, although not eliminated, this height deficit. Renal transplantation generally improves linear growth but does not completely restore it (2). The greatest recovery in growth is seen in the youngest children, and the least is seen in adolescents. The use of glucocorticoid withdrawal or avoidance protocols and the administration of growth hormone after transplantation may further improve growth recovery.

In conclusion, PKT short and long-term results have been improving due to better pre- and post-operative care and long term management. However, the challenging problems such as chronic IS and cost still need practical solutions in future.

Conflicts of interest: None declared.

References

1. Shapiro R, Sarwal MM. Pediatric kidney transplantation. Pediatr Clin North [Am]. 2010;57:393-400.

2. Riley P, Marks SD, Desai DY, Mushtaq I, Koffman G, Mamode N. Challenges facing renal transplantation in pediatric patients with lower urinary tract dysfunction. Transplantation. 2010;89:1299-1307.

3. Saidi RF, Markmann JF, Jabbour N, Li Y, Shah S A, Cosimi AB, Bozorgzadeh A. The faltering solid organ donor pool in the United States (2001-2010).

World J Surg. 2012; 36: 2909–2913.

4. Horslen S, Barr ML, Christensen LL, Ettenger R, Magee JC. Pediatric transplantation in the United States, 1996-2005. Am J Transplant. 2007;7:1339-1358.

5. Moudgil A, Dharnidharka VR, Lamb KE, Meier-Kriesche HU. Best allograft survival from share-35 kidney donors occurs in middle-aged adults and young children-- an analysis of OPTN data. Transplantation. 2013; 95:319-325.

6. Saidi RF**,** Mirzakhani H, Hezaji K. Pediatric Transplantation and Tolerance. Pediatric Transplantation. 2014;18:435-45.

7. Tredger JM, Brown NW, Dhawan A. Immunosuppression in pediatric solid organ transplantation: Opportunities, risks, and management. Pediatr Transplant 2006: 10: 879–892.

8. Stuber ML. Psychiatric issues in pediatric organ transplantation. Child Adolesc Psychiatr Clin N Am. 2010; 19: 285–300.

9. Traum AZ, Ko DS, Kawai T. The potential for tolerance in pediatric renal transplantation. Curr Opin Organ Transplant. 2008; 13: 489–494.

10. Traum AZ, Kawai T, Vacanti JP, Sachs DH, Cosimi AB, Madsen JC. The need for tolerance in pediatric organ transplantation. Pediatrics. 2008;121: 1258–1260.

11. Solez K, Colvin RB, Racusen LC, Bonsib SM., Castro MC, Cavallo T. et al. Banff 07 classification of renal allograft pathology: updates and future directions. Am J Transplant. 2008;8:753-760.

12. Pearl JP, Preston E, Kirk AD. Tolerance: Is it achievable in pediatric solid organ transplantation? Pediatr Clin North Am. 2003; 50: 1261–1281.

13. Girlanda R, Kirk AD. Frontiers in nephrology: Immune tolerance to allografts in humans. J Am Soc Nephrol. 2007; 18: 2242–2251.

14. Evans RW, Applegate WH, Briscoe DM, Cohen DJ, Rorick, CC, Murphy BT, Madsen JC. Cost-related immunosuppressive medication non-adherence among kidney transplant recipients. Clin J Am Soc Nephrol. 2010;5: 2323–2328.

15. Dobbels F, Ruppar T, De Geest S, Decorte A, Van Damme-Lombaerts R, Fine RN. Adherence to the immunosuppressive regimen in pediatric kidney transplant recipients: a systematic review. Pediatr Transplant. 2010;14:603-613.

16. Scientific Registry of Transplant Recipients. 2014 Annual data report (http://srtr.transplant.hrsa.gov /annual_reports/2014/Default.aspx).

17. Dharnidharka VR, Martz KL, Stablein DM, Benfield MR. Improved survival with recent post-transplant lymphoproliferative disorder (PTLD) in children with kidney transplants. Am J Transplant. 2011;11:751-758.