Published in final edited form as:

Pediatr Clin North Am. 2019 February ; 66(1): 269–280. doi:10.1016/j.pcl.2018.09.008.

Long-term Outcomes of Kidney Transplantation in Children

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Keywords

Pediatric; Kidney Transplantation; Outcomes

Kidney transplantation in children

The most common causes of end-stage renal disease (ESRD) in children are congenital, cystic, and hereditary diseases, which combined account for 38% of incident cases.¹ The most common disorders in this category are congenital obstructive uropathies (9.5%) and renal hypoplasia/dysplasia (10%). Primary glomerular disease is the second-most common etiology accounting for 25% of new cases, predominantly due to focal segmental glomerulosclerosis (FSGS). Secondary glomerulonephritis and vasculitis account for 12% of new cases, of which lupus nephritis is the most common. The underlying etiology of ESRD also varies by age of presentation (Figure 1A). As expected, congenital/hereditary/cystic disorders are the most common underlying cause of ESRD amongst the youngest age groups, while primary and secondary glomerular diseases are the leading cause among adolescents.¹

Kidney transplantation is the preferred treatment for ESRD in children and confers improved survival, skeletal growth, health-related quality of life, and neuropsychological development compared to dialysis.¹

Timing of Transplant

Transplantation is initially considered when renal replacement therapy is imminent. Due to increased risk of graft loss and mortality in very young children, most pediatric centers perform kidney transplantation once children achieve a weight above 10–15 kg, which is typically around the age of 2 years. The underlying etiology for kidney failure, the rapidity of decline in kidney function, and the age and size of the patient determine whether an individual can receive a pre-emptive kidney transplant without preceding dialysis, which

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Disclosure Statement: The authors have no financial interests or conflicts of interest to disclose.

may provide a graft survival advantage.² On average, 30% of pediatric kidney transplant recipients in the U.S. receive pre-emptive transplant, and an additional 24% receive dialysis treatment for less than 1 year prior to transplant.³

Donor Source

Patients can receive kidney transplants from living or deceased donors. Historically, living-related donor transplants were more common in children than deceased-donor transplants. This was likely driven by parents' understanding of the benefit of living donation for their child such as superior long-term graft survival (see Figure 1B) and ability to schedule the procedure.^{4,5} However, the rate of living donor transplants in children has been declining since 2002, with only 34% of pediatric recipients in 2015 receiving living donor kidney transplants compared to 50% in 2004.

The transplant community has consistently supported timely access to deceased-donor kidney grafts for pediatric candidates with an allocation system that has historically emphasized younger donors and shorter waiting times over human leukocyte antigen (HLA) matching. As a result, the absolute number and proportion of deceased-donor kidney transplants in pediatric recipients has been steadily increasing over the past 20 years accompanied by a decrease in the absolute number of living-donor transplants.⁶ It is unclear at this time if the trend in fewer living donor transplants is a direct consequence of policy change or due to increasing prevalence of co-morbidities in parents that preclude them from donating (e.g. obesity and diabetes).⁷

Patient Survival

The success of kidney transplantation in children with ESRD now results in 10-year patient survival of 90–95%. Therefore, the long-term management of these patients is focused on maintaining quality of life and minimizing long-term side effects of immunosuppression. Optimal management of pediatric kidney transplant recipients includes preventing rejection and infection, identifying and reducing the cardiovascular and metabolic effects of long-term immunosuppressive therapy, supporting normal growth and development, and managing a smooth transition into adulthood (Figure 2).

Determinants of Graft Survival

In general, the estimated half-life for transplanted kidneys in children is 12–15 years, therefore children with ESRD often require more than one kidney transplant in their lifetime. The adolescent age group (11–17 years), which accounts for >50% of the pediatric kidney transplant waiting list, has worse 5-year graft survival compared to pediatric recipients under age 11 years (Figure 1C).³ Overall, living donor transplants have improved long-term outcomes compared to deceased donor transplants with 10-year graft loss of 38% versus 52%, respectively (Figure 1B).³ Long-term graft survival is affected by a number of factors including the quality of the donated kidney (e.g. living vs deceased donor, number of HLA mismatches, delayed graft function, donor age and size), the presence of pre-existing HLA antibodies (pre-sensitization), recipient race/ethnicity, recipient age (e.g. adolescence),

as well as subsequent graft injury from recurrence of primary disease (e.g. FSGS), allograft infections, and acute or chronic rejection episodes.⁸

Rejection

Children with kidney transplants require life-long immunosuppressive therapy to prevent rejection of the allograft. The most common medication regimen in the U.S. includes the combination of corticosteroid (e.g. prednisone), a calcineurin inhibitor (or CNI, most commonly tacrolimus), and an anti-metabolite such as mycophenolate mofetil (MMF). Cyclosporine and azathioprine are less commonly used for maintenance immunosuppression. Some centers offer steroid-sparing, or CNI-sparing regimens as well.

With modern immunosuppressive therapy, rates of acute rejection episodes within the first 12-months for pediatric kidney transplant in the U.S. are reported at 11%.³ Chronic allograft rejection, however, is a leading cause of graft loss in children. Late and multiple episodes of acute rejection are associated with worse long-term allograft survival. Therefore, early identification and treatment of acute rejection are paramount to improve long-term outcomes.

The diagnosis of acute rejection is not always straightforward in pediatric kidney transplant recipients. Small children who have adult-sized allografts have a large renal reserve relative to their muscle mass. Therefore, significant renal injury may occur with little to no change in the serum creatinine. Children with acute rejection can present with low-grade fever and mild hypertension, but can also be asymptomatic. Therefore, most transplant centers follow serum creatinine closely with serial laboratory testing to establish baseline kidney function in order to detect early changes graft function. Some centers also perform surveillance biopsies to detect and treat subclinical rejection.

Suspected nonadherence contributes to approximately 44% of graft losses and 23% of late acute rejection episodes reported in the literature for adolescent kidney transplant recipients.⁹ Pre-transplant patterns of medication and dialysis treatment adherence may predict post-transplant behavior. Social, behavioral, and psychiatric interventions should be initiated prior to transplant and maintained post-transplant for those patients with identified or anticipated issues with non-adherence.

Infection and Immunity

While modern immunosuppression regimens have reduced the rate of acute rejection, infectious complications have become more frequent.^{10–12} In particular, pediatric transplant recipients are at risk for developing virus-related complications due to immunological naiveté at the time of transplantation and primary infection under immunosuppressive therapy.

Common Viral Illnesses

Children with kidney transplants often have more severe and prolonged illness from even common viral pathogens (e.g. RSV, influenza, adenovirus) secondary to their immunocompromised status. Therefore, pediatric transplant recipients are recommended to

receive annual influenza vaccination and to remain up-to-date on all other non-live viral vaccine schedules, including those for the prevention of human papilloma virus (HPV), meningococcal, and pneumococcal diseases. Care-givers and close household contacts should also be fully immunized and there are no restrictions for these otherwise healthy contacts to receive live-attenuated vaccines.

Diarrheal illness in children with kidney transplants requires special attention, since graft injury can occur even with mild dehydration, and diarrhea often significantly alters the metabolism and absorption of immunosuppressant medications. Therefore, children with kidney transplants presenting with vomiting and/or diarrhea require prompt medical evaluation including laboratory testing to assess kidney function and drug levels, and often the administration of IV fluids. Finally, should diarrhea persist, testing for opportunistic pathogens such as *Giardia*, microsporidia, and *cryptosporidium* should be considered.

Latent Viruses

Transplant recipients are routinely monitored for the re-activation or primary infection of the latent viruses, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and BK polyoma virus (BKV) using detection of viral nucleic acid in plasma (viremia). Roughly half of children are serologically naïve to CMV or EBV at the time of transplant. The combination of a CMV or EBV-positive donor with a serologically naïve pediatric recipient represents the highest risk for infection and disease post-transplant. Early detection of viremia and intervention with antiviral medications and/or reduced immunosuppression are the cornerstones of management for these viruses post-transplant.

CMV disease can present as fever, elevated transaminases, diarrhea, and pneumonia. Morbidity and mortality from early disseminated CMV disease has dramatically improved with the use of surveillance testing and effective prophylaxis (e.g. valgancyclovir) in the highest risk recipients.

Primary EBV infection in children with kidney transplant can present similarly to healthy children (e.g. pharyngitis, fever, cervical lymphadenopathy, splenomegaly, mononucleosis syndrome). However, children receiving immunosuppression are at increased risk for developing post-transplant lymphoproliferative disease (PTLD) and lymphoma as consequences of EBV infection (see more under Malignancy below). There is no effective chemoprophylaxis for EBV infection.

BK virus is a polyomavirus that establishes a latent infection of the uroepithelium and is typically asymptomatic in the healthy host. In the transplant recipient, uncontrolled BK virus replication leads to infection of the kidney allograft (BK nephropathy) and can result in permanent damage and graft loss. BK virus infection (e.g. viremia) can occur early (within the first month) or late (several years) following kidney transplant in children. Definitive diagnosis of BK nephropathy (BKN) is obtained only by renal biopsy and the incidence in pediatric kidney transplant recipients is estimated to be 4–5%.^{13,14} Prospective monitoring for BK viremia with pre-emptive lowering of immunosuppression has been suggested as an effective approach.¹⁵

Urinary Tract Infection (UTI)

Urinary tract infection (UTI) is the most common infectious complication following kidney transplant in children, occurring in 15–33% of patients.^{10,16} Recurrent UTI has been associated with more rapid deterioration in graft function in children.^{16,17} Risk factors for febrile UTI include anatomical abnormalities, dysfunctional bladder, presence of foreign material (e.g. urinary catheter or stents), and baseline immunosuppression. Parenteral antibiotics are indicated for febrile UTI in pediatric transplant patients. Some children with recurrent UTI are treated with antibiotic prophylaxis, though the benefit of this approach needs to be weighed against the increased risk for bacterial resistance with prolonged antibiotic use.

Malignancy

Long-term use of immunosuppressive medications coupled with decades of remaining life expectancy place the pediatric transplant recipient at increased risk for the development of malignancy during their lifetime. The most common malignancy in childhood transplant recipients is viral-induced lymphoproliferative disease (or PTLN) with a cumulative incidence of 1.8% by 5 years. PTLN in children is often associated with EBV infection, and children who are immunologically naïve to EBV at the time of transplant are at highest risk of developing PTLN.³ EBV-related lymphoid hyperplasia may present as adenotonsillar hypertrophy, but can also affect the GI tract (chronic diarrhea) and kidney allograft. Central nervous system involvement is also described and can be fatal. Early recognition of PTLN via surveillance for significant EBV viremia and prompt detection of lymphadenopathy with appropriate intervention are essential. Chronic, low-grade EBV viremia in transplant recipients without development of PTLN is not uncommon, therefore serial monitoring and trending of viral load using consistent laboratory methods (e.g. whole blood versus plasma, consistent lab site) are required to detect changes in viral control when evaluating risk for PTLN.

There is limited data about long-term risk for non-lymphoproliferative malignancy in patients receiving kidney transplant during childhood. In a study of adult survivors of pediatric ESRD in The Netherlands, nearly 41% developed cancer after 30 years following transplant.¹⁸ Non-melanoma skin cancer was the most common form of malignancy and had very low mortality associated with it. Renal cell carcinoma of the native kidneys was the most common solid tumor reported during childhood following kidney transplant.¹⁹ Given the increased lifetime-risk for all cancers, pediatric transplant recipients should be counseled on avoiding additional risk factors for malignancy including excessive sun exposure (e.g. sunscreen use), alcohol consumption, and tobacco use.

Another viral-associated malignancy to consider in pediatric transplant patients is urogenital cancer associated with human papilloma virus (HPV). As such, all pediatric transplant recipients are encouraged to complete the full HPV vaccine series prior to sexual maturity.

Cardio-Metabolic Comorbidities

Children with ESRD have increased cardiovascular mortality relative to their peers accounting for nearly 40% of deaths among pediatric ESRD patients.^{20,21} Although kidney transplantation leads to a dramatic improvement in renal function and elimination of many traditional risk factors, cardiovascular disease still accounts for over one-third of deaths among patients who receive transplants prior to 21 years of age.

Hypertension

Hypertension is common in children post-transplant and is likely due to a combination of rapid weight-gain, medication side effects (e.g. CNI and steroids), and renal injury. An estimated 50–65% of pediatric kidney transplant recipients have hypertension at 1 year post-transplant.^{22–24} In addition to the concerns for long-term cardiovascular risk associated with uncontrolled hypertension, retrospective analyses of pediatric kidney transplant recipients suggest that systolic hypertension independently predicts poor long-term allograft survival.^{24,25}

Obesity

Obesity is an emerging challenge in renal transplant recipients, in parallel with the general pediatric population, leading to increased risk of surgical complications, hyperlipidemia, diabetes, and hypertension post-transplant.²⁶ Many children experience rapid weight gain following transplant, likely due to a combination of lifted dietary restrictions imposed during ESRD and appetite stimulation from corticosteroids used to prevent or treat rejection. Up to 50% of pediatric transplant recipients have been classified as obese or overweight in recent studies.^{27,28} Furthermore, obesity complicates hypertension management with approximately 80% of obese pediatric transplant recipients having poor control of hypertension at one year.²² Weight gain should be monitored closely following transplant to identify children early at risk for obesity, as increases in BMI in the first 6 months following transplant are likely to be persistent.²⁹

Hypercholesterolemia and hypertriglyceridemia are also common in children with kidney transplant likely due to a combination of drug side effects³⁰ (e.g. cyclosporine, mTOR inhibitors, glucocorticoids) and obesity.^{31,32} Therefore, semi-annual screening for hypercholesterolemia and hypertriglyceridemia is suggested.³³ Lifestyle modification including dietary changes and increased physical activity is typically preferred for young children with hyperlipidemia. While the use of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) is generally considered safe and effective in children over the age of 8 years, few data are available on long-term safety.³⁴ Omega-3 fatty acids have been reported to be effective at reducing LDL levels in young kidney transplant recipients in small case series.³⁵

Diabetes

Hyperglycemia and new-onset diabetes after transplant (NODAT) are serious and increasingly more common metabolic complications following kidney transplantation, with a reported incidence of 3–20% in pediatric recipients.^{36–38} NODAT is associated with

increased morbidity from cardiovascular complications, increased infection risk, and inferior allograft and patient survival following kidney transplantation.³⁷ The increased incidence of NODAT in the pediatric kidney transplant population has paralleled both the obesity epidemic in the general population and the increased use of calcineurin inhibitors (CNIs) for post-transplant immunosuppression.³⁹ Management should focus on prevention with close screening for early signs of glucose intolerance, tailoring of immunosuppressant regimen as appropriate, and promotion of lifestyle modifications. Pharmacologic intervention (e.g. insulin) is necessary to reduce complications of hyperglycemia and improve overall allograft and patient survival when lifestyle and medication modifications fail to achieve adequate glycemic control.

Growth and Development

Short Stature and Bone Health

Impaired linear growth in children with chronic kidney disease (CKD) is multifactorial and is mainly due to disturbances in the axis involving growth hormone (GH), insulin-like growth factor (IGF) and IGF-binding protein. Despite satisfactory renal function following transplant, spontaneous catch-up growth is often insufficient. Abnormalities in mineral metabolism including disturbances in serum calcium, phosphorus, parathyroid hormone (PTH), and vitamin D stores, are common in children following kidney transplant and increase the risk for growth delay and osteopenia or rickets.^{40–42}

Determinants of growth following transplant include age at the time of transplant, exposure to glucocorticoids, allograft function, and administration of recombinant human growth hormone (rhGH). Children under the age of 6 years have increased growth rates following transplant compared to older children.⁴³ The degree of growth stunting prior to transplant is also predictive of final adult height.⁴⁴ Therapy with rhGH is effective in improving the growth velocity and final adult height of children following kidney transplant.^{45,46} Finally, steroid-sparing immunosuppressive protocols have demonstrated improved linear growth for pre-pubertal children undergoing kidney transplant.⁴⁷

Bladder Function

Even children with non-urological causes of ESRD often have lower urinary tract symptoms following transplant including urinary urgency, bladder pain, incomplete bladder emptying, nighttime or daytime incontinence, and urinary tract infections.⁴⁸ Timed voiding and prevention or treatment of functional constipation are important in the management of incontinence and dysfunctional voiding. For those with congenital bladder outlet obstruction, intermittent catheterization is often still required to avoid graft damage and dysfunction.⁴⁹ Anticholinergic therapy and intermittent catheterization should be continued following transplantation as medical management of pre-existing neurogenic bladder.

Puberty

Onset of puberty is an important milestone during adolescence. The majority of children achieve normal puberty following transplant, but many may have a delayed onset and

shortened duration of pubertal growth spurt, which is predicted by delayed bone age compared to their chronological age.^{50,51}

Psychosocial Development

Transplant recipients are exposed to additional psychosocial stress related to their chronic illness. Developmental delay, issues with body image from drug side effects, difficulty interacting with peers, prolonged school absences, fastidious schedules required for immunosuppressant medication regimens, symptoms of post-traumatic stress, and family disruption due to financial burden or role strain may all exacerbate psychosocial difficulties in the pediatric transplant recipient. Collaboration with psychologists, psychiatrists, and social workers is important for the early identification and intensified treatment of high-risk individuals.

Children with emotional or psychiatric disorders often require additional mental health resources including psychiatric care before and after transplant. Acquisition of coping skills, problem solving skills, and behavior modification can improve a child's experience with the inherent complexity of dialysis or transplantation medical care. Pharmacotherapy for depression, bipolar disorder, and attention deficit hyperactivity disorder are important adjunctive therapies. Reduced clearance with impaired renal function, clearance by dialysis, and interference with the metabolism of immunosuppressive medications should be considered when selecting psychotropic medications in children with ESRD or transplant.

Children with ESRD during infancy can have significant developmental delay due to uremia. In the absence of structural brain abnormalities, psychomotor delay often improves following transplant, with many infants regaining normal developmental milestones.⁵² Lower IQ and learning disabilities are most common in children born prematurely and those who had multiple hypertensive crises and/or seizures prior to transplant.⁵³ Ongoing evaluation of neurocognitive abilities and appropriate support from school systems are needed to achieve optimal school performance following transplant.

Adolescence and Emerging Adulthood

Adolescence is an important transition period between childhood and adulthood characterized by a quest for independence and autonomy. This rapidly changing and volatile developmental period places adolescent transplant recipients at increased risk for medication non-adherence, acute rejection episodes, and graft loss. Furthermore, it may be difficult for teenagers to accept the cosmetic side effects of immunosuppressant medications such as weight gain, Cushingoid facial features, acne, and gingival hypertrophy. The accompanying psychological stress and impact on self-image for teenagers can provide a dangerous disincentive to adhere to immunosuppressant medications. Medical management of this population can be challenging and benefits from specialized, multi-disciplinary approaches to improve outcomes.

Sexuality-related issues including prevention of sexually transmitted diseases and family planning also need to be addressed with teenage transplant patients. Adolescent female transplant recipients have successfully become pregnant while receiving cyclosporine or tacrolimus. The effect of contraception on the metabolism of immunosuppressant

medications needs to be considered when counseling adolescent girls about pregnancy prevention. In addition, the teratogenic potential of immunosuppressant medications (notably MMF) and antihypertensive medications (e.g. ACE inhibitors) should be explained to the adolescent female and her family.

Transition to Adult Healthcare Delivery

The term, emerging adulthood, is used to define the interval of 18 to 25 years of age when young adults appear physically mature, yet brain maturation has not yet completed. This age group is at increased risk for graft failure likely due to a combination of age-related risk behavior and the processes involved in transitioning from pediatric-based to adult-based health care delivery systems.⁵⁴ The identification of strategies to facilitate safe transition to adult healthcare delivery systems and improve outcomes for adolescent transplant recipients has become a priority for the pediatric transplant community.^{54–56}

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Synopsis:

Kidney transplantation is the preferred treatment for end-stage renal disease (ESRD) in children and confers improved survival, skeletal growth, health-related quality of life, and neuropsychological development compared to dialysis. Kidney transplantation in children with ESRD results in 10-year patient survival exceeding 90%. Therefore, the long-term management of these patients is focused on maintaining quality of life and minimizing long-term side effects of immunosuppression. Optimal management of pediatric kidney transplant recipients includes preventing rejection and infection, identifying and reducing the cardiovascular and metabolic effects of long-term immunosuppressive therapy, supporting normal growth and development, and managing a smooth transition into adulthood.

Key Points:

- Patient survival is excellent following kidney transplantation in children (90–95% at 10-years)
- Long-term kidney transplant outcomes are dependent on excellent adherence to follow-up and immunosuppressive regimens
- Adolescent and young adult recipients have the highest risk for graft loss at 5-years
- Life-long immunosuppression increases the risk for infections and malignancies in children with kidney transplant
- Weight gain and immunosuppressive medications increase the risk for cardio-metabolic complications (hypertension, dyslipidemia, and diabetes)

Long-term Outcomes of Pediatric Kidney Transplant

Figure 1. Epidemiology of pediatric kidney transplantation in the U.S.

(A) Causes of end-stage renal disease (ESRD) requiring dialysis or kidney transplant for children in the U.S. broken down by age group. C/H/C, congenital/hereditary/cystic disorders; GN, glomerulonephritis; CAKUT, Congenital anomalies of the kidney and urinary tract. Data from the United States Renal Data System (USRDS) 2017 Annual Data Report: Epidemiology of Kidney Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive Kidney Diseases. (B) Recipients of living donor kidney transplant have superior graft survival compared to recipients of deceased donor transplant. Kidney graft survival at 3, 5, and 10 years is plotted by donor source and year transplanted. LD, Living Donor; DD, Deceased Donor. (C) Kidney graft survival by recipient age and donor source. Graft survival over 5 years is plotted for pediatric recipients <11 years and those age 11–17 years transplanted in the U.S. between 2006 and 2010.

Data (B and C) from Hart A, Smith JM, Skeans MA, et al. OPTN/SRTR 2015 Annual Data Report: Kidney. Am J Transplant. 2017;17 Suppl 1:21–116.

Figure 2. Long-term outcomes of pediatric kidney transplant.

Issues facing pediatric kidney transplant recipients include those pertaining directly to the health of the allograft (e.g. rejection, recurrence), immune deficiency due to medications (e.g. viral infections, malignancy), growth and development in the context of organ failure (e.g. bone disease, transition to adulthood with chronic medical condition), and cardio-metabolic co-morbidities from immunosuppression (e.g. obesity, hypertension). Optimal care of the pediatric kidney transplant recipient addresses these issues in a multi-disciplinary fashion. CKD, chronic kidney disease; CMV, cytomegalovirus; EBV, Epstein Barr virus; BKV, BK polyoma virus; UTI, urinary tract infection; NODAT, new-onset diabetes after transplant.