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REVIEW

Pediatric kidney transplantation: a review

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Abstract: Pediatric kidney transplantation is the preferred treatment for children with end-stage renal disease. The most common indications for transplantation in children are renal developmental anomalies, obstructive uropathy, and focal segmental glomerulosclerosis. Living donor kidney transplants are often performed pre-emptively and offer excellent graft function. Policy changes in deceased-donor kidney allocation have increased the proportion of such transplants in pediatric recipients. Adequate pretransplant workup along with evaluation of urologic abnormalities is imperative in achieving good outcomes. Overall, patient and graft outcomes after kidney transplantation have improved, with five-year deceased donor and living donor graft survivals of 78.8% and 84.3%, respectively. Improvements in induction and maintenance immunosuppression have contributed to the gradual improvement in outcomes. Unique challenges in pediatric recipients include increased graft thrombosis, adverse growth, and abnormal development relating to immunosuppression, increased rejection due to nonadherence, increased susceptibility to opportunistic infections, and post-transplant malignancy. This review focuses on the current practices and outcomes in pediatric kidney transplantation in North America. We discuss the indications for transplantation, the evaluation process, some key surgical and immunologic considerations, and the common risk factors for graft dysfunction.

Keywords: pediatric kidney transplantation, end-stage renal disease, dialysis, organ donors, immunosuppression

Introduction

The first successful pediatric kidney transplantation was reported in 1966.[1] Since then, the outcomes have steadily improved and kidney transplantation is now the preferred treatment modality for children with end-stage renal disease (ESRD). In the USA, approximately 800 kidney transplants are performed per year in children under the age of 18 years.[2] Pediatric kidney transplantation is generally performed in specialized centers due to complex technical, metabolic, immunologic, and physiologic factors. This involves a multidisciplinary team comprising transplant surgeons, anesthetists, pediatric nephrologists, and urologists who are supported by psychologists, pediatric nurses, and social workers.

This review focuses on the current practices and outcomes in pediatric kidney transplantation in North America. We will discuss the indications for transplantation, describe the evaluation process, highlight the key surgical and immunologic considerations, and review the common risk factors for graft dysfunction.

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ESRD in children

The incidence of ESRD in the United States increases progressively with age, ie, 14 per million population for ages 0–19 years, 115 for ages 20–44 years, 606 for ages 45–64 years, 1435 for ages 65–74 years, and 1686 for ages 75 years and over.[3] The etiology of ESRD in children is most often developmental renal anomalies, which include aplastic, hypoplastic, and dysplastic kidneys, obstructive uropathies (posterior urethral valves), focal segmental glomerular sclerosis, reflux nephropathy, and polycystic kidney disease (Table 1). The most common causes of renal failure in adults, ie, glomerular disease, hypertension, and diabetes, are rare in children.

Both hemodialysis and peritoneal dialysis are used as renal replacement therapy in children with ESRD. Hemodialysis is challenging in younger children due to difficulties with vascular access and low circulating volumes. Available data suggest that, compared with hemodialysis, peritoneal dialysis allows better growth and development and improved quality of life and is more cost-effective.[3] Data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry, a collaborative with 131 contributing centers, report a higher percentage of children on peritoneal dialysis prior to transplantation (39%) as compared with hemodialysis (29%).[2] The 5-year patient survival after renal transplantation in children is 91.7% compared with 78.6% with hemodialysis and 80.6% with peritoneal dialysis. Due to superior outcomes after kidney transplantation, most children with ESRD are referred for transplantation, in contrast with adults where only 16% of the dialysis population is listed for transplantation. Additionally, a majority of centers proceed with transplantation in the presence of residual renal function if there is growth cessation. Graft survival for such pre-emptively performed living and cadaver donor kidney transplants is superior to transplantation in dialysis-dependent children. As a result of improved graft survival and potential problems with dialysis access, a pre-emptive transplant is planned close to the time of initiation of dialysis in children with favorable growth.

Table 1 Common causes of end-stage renal disease in the pediatric population

Etiology	%
Aplasia/hypoplasia/dysplasia	15.8
Obstructive uropathy	15.3
Focal segmental glomerulosclerosis	11.7
Reflux nephropathy	5.2
Polycystic disease	3.0
Chronic glomerulonephritis	3.2
Medullary cystic disease	2.7
Hemolytic uremic syndrome	2.6
Prune belly	2.5
Congenital nephrotic syndrome	2.6
Familial nephritis	2.3
Cystinosis	2.1
Pyelo/interstitial nephritis	1.7

The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) 2010.[2]

Indications for transplantation

In 2010, the NAPRTCS registry reported 11,603 renal transplants in 10,632 patients. Kidney transplantation was most commonly performed for aplastic/hypoplastic/dysplastic kidneys (15.8%), followed by obstructive uropathy (15.3%) and focal segmental glomerulosclerosis (11.7%, Table 1).[2] Absolute contraindications to transplantation include active infections, recent or uncontrollable malignancy, ABO incompatibility, positive lymphocytotoxic cross-match, progressive neurologic disorders, and multiorgan failure. Relative contraindications to transplantation include a history of malignancy, including Wilm's tumor, human immunodeficiency virus infection, hepatitis B or C virus, age younger than 6 months, severe mental retardation, and likelihood of nonadherence.[4,5] Isolated mild mental retardation is not considered an absolute contraindication because substantial cognitive improvement can be seen routinely in pediatric patients.

Combined liver-kidney transplantation

In certain circumstances, combined liver and kidney transplantation may be necessary. Analysis of the United Network for Organ Sharing data registry reveals that 6.0% of all combined liver-kidney transplants performed in the United States between 1998 and 2006 were performed in children.[6] The most common indications were type 1 primary hyperoxaluria, autosomal recessive polycystic kidney disease, and primary liver disease with irreversible kidney injury. Other indications included congenital congestive heart failure due to Caroli disease, metabolic diseases of the kidney for which liver transplantation addressed the enzyme deficiency (methylmalonic acidemia, atypical hemolytic uremic syndrome), and metabolic diseases affecting both organs (alpha-1 antitrypsin deficiency, tyrosinemia).[7] Several series have reported excellent outcomes, with more favorable outcomes in children who have been on dialysis for less than 5 years and who are in good overall condition.[8–10] When comparing simultaneous and sequential liver-kidney transplants, simultaneous transplants appear to be associated with improved short-term and long-term renal allograft function.[11]

Donor source

Living donors

Pre-emptive kidney transplantation from living donors has the best outcomes in children. About one third of pediatric living donor transplants are performed pre-emptively in the USA. Parents are the living donors for approximately three quarters of the children, and nearly two thirds of the children who receive living donor kidneys are Caucasian males. A majority of transplant recipients (39%) are in the age group of 13–17 years followed by 6–12 years (33%).[2,12] There has been a gradual increase in the number of unrelated living donors from three per year in 1987–1995 to 16 per year presently.[2]

Adult deceased donors

In October 2005, the Organ Procurement and Transplant Network implemented a new allocation policy in the USA (known as Share-35) that preferentially allocates kidneys from deceased donors aged younger than 35 years to pediatric recipients. In this schema, only adult recipients with zero-antigen mismatches, multiorgan recipients, highly sensitized recipients, and prior living donors supersede pediatric recipients.[13,14] This has served to decrease the wait times for children and to maximize the life of the allograft.[14,15] Expanded criteria deceased donors are not used for transplantation in children.[16] Since Share-35, there has been a shift away from living donor transplants towards a predominance of deceased donor transplants, whereby the proportion of living donor allografts in pediatric transplantation has decreased from 62% in 2002 to 51% in 2010.[2] A recent analysis of the Organ Procurement and Transplant Network database involving 18,461 Share 35-kidneys transplanted into pediatric recipients showed that recipient age affects allograft survival. Best survival occurs in children aged <12 years, whereas adolescents (13–17 years) and young adults (18–25 years) do not derive optimal benefit.[15] In another analysis of the United States Renal Data System, Share-35 seems to have attenuated racial disparities in the time to transplantation and the probability of children receiving a deceased donor kidney transplant, with Hispanics experiencing the greatest improvements.[13] The long-term effect of this policy change remains to be seen.

Pediatric deceased donors

Kidneys from pediatric deceased donors, particularly those younger than five years, have traditionally not been used for pediatric recipients due to higher rates of graft thrombosis and technical failures.[17] En bloc transplantation of pediatric kidneys into pediatric recipients has been reported, with fewer complications compared with single pediatric kidney transplantation.[18] However, a majority of pediatric donor kidneys continue to be transplanted into adult recipients either en bloc or as single pediatric kidneys, and have outcomes comparable with those in living donor kidney transplantation and standard criteria deceased donor transplantation, respectively.[19,20]

Recipient workup

The pretransplant evaluation of pediatric recipients includes a thorough history and physical examination, with comprehensive laboratory studies, chest radiography, and electrocardiography as the initial steps. Urinalysis and urine culture, 24-hour urine collection, and occasional native renal biopsies are also routinely obtained. Cardiac, pulmonary, dental, and other evaluations may be required depending upon comorbidities. Potential recipients should be screened for human immunodeficiency virus, hepatitis B and C, cytomegalovirus, Epstein-Barr virus, varicella, and tuberculosis. Children should receive all age-appropriate immunizations, including hepatitis A and B, varicella, pneumococcal, meningococcal, and human papilloma virus vaccinations.[21] Vaccination protocols may have regional variations worldwide, based on local disease patterns and practices. Social service and psychosocial evaluation are particularly important because noncompliance, especially in teenagers, is an important source of graft loss and patient death after transplantation.

Children may undergo a hypercoagulability workup that includes anticardiolipin antibodies, levels of factor VIII and homocysteine, activity of protein S, C, and anti-thrombin III, and mutations in prothrombin, factor V Leiden, and methyltetrahydrofolate reductase genes. Children with vascular access issues, previous intra-abdominal procedures like bilateral nephrectomy, or hypercoagulable states like nephrotic syndrome, or thrombosis of the major intra-abdominal vessels like the inferior vena cava must be carefully evaluated. Such patients may benefit from preoperative magnetic resonance angiography to demonstrate collateral venous channels draining the lower extremities and pelvis. This assists in selection of an appropriately sized donor kidney that may be accommodated to the smaller collateral vessels in the abdomen.[22,23]

Approximately 20% of pediatric recipients may need unilateral or bilateral native nephrectomy prior to transplantation. Native nephrectomy prior to transplantation can reduce the risk of graft hypoperfusion by improving serum protein levels and the post-transplant fluid intake in select children.[24]

The common indications for pretransplantation native nephrectomy are listed in Table 2.[25]

Pretransplant desensitization is considered for highly sensitized children with panel reactive antibodies over 80%.[26,27] While less frequent than in adults, the risk factors for high panel reactive antibodies in pediatric recipients are similar, and include repeat transplants and history of multiple blood transfusions. The desensitization strategies in children mirror those in adults and include high-dose immunoglobulin with or without rituximab.[28,29]

Urologic complexities

Pediatric urologic evaluation is valuable in patients with a history of lower urinary tract dysfunction (LUTD) such as posterior urethral valves, reflux, or other congenital problems. Historically, such patients were denied transplantation due to inferior graft survival, but it is now possible to have transplant outcomes that are comparable with those in the non-LUTD population.[30–32] However, there are also reports of worse graft survival rates in recipients with LUTD.[33,34]

The optimal management of pediatric patients with ESRD and LUTD is unclear.[35] The mainstay of most protocols is a thorough pretransplant assessment of bladder urodynamics to quantify hostile bladders based on estimates of bladder capacity, compliance, and voiding pressures. When the native bladder is deemed unsuitable, there are three categories of possible intervention, including drainage procedures, augmentation, and urinary diversion. Patients with compromised bladder drainage and for whom intermittent catheterization per urethra is unsuitable or has failed, the fashioning of a Mitrofanoff channel from the appendix or small intestine (Monti-Mitrofanoff) creates an alternative route for catheterization to achieve adequate drainage of the native or augmented bladder.[36] The augmentation procedures include ureterocystoplasty (preferable), enterocystoplasty, and gastrocystoplasty.[37–39] Urinary diversion may be continent or incontinent, and is restricted to patients with complex anomalies. Strict adherence to a clean intermittent catheterization regimen and use of low-dose prophylactic antibiotics is recommended to reduce the risk of postoperative urinary tract infections.[40] Many centers prefer living donor kidney transplantation in children with LUTD in order to improve preoperative and intraoperative coordination with urologic teams.

Table 2 Indications for pretransplantation native nephrectomy

Chronic renal parenchymal infection
Infected urolithiasis
Heavy proteinuria
Intractable hypertension
Polycystic disease
Acquired renal cystic disease
Infected reflux
Infected hydronephrosis

Surgical procedure

The surgical techniques for kidney transplantation in teenagers and in children weighing more than 30 kg are generally similar to those in adults, with retroperitoneal exposure and anastomosis to the external iliac artery and vein. In children weighing 20 kg or less, the renal vessels are anastomosed to the aorta and vena cava. In children weighing 20–30 kg, the common iliac artery and vena cava are frequently used for vascular anastomoses via a retroperitoneal or an intraperitoneal approach. Ureteral reimplantation is commonly performed using simple extravesical ureteroneocystostomy, but open antireflux techniques are also used.[41] Ureteral stents (7 French) are used and may be attached to the Foley urethral catheter or cystostomy tube so that they are simultaneously removed at the time of discontinuation of urinary catheter drainage.

Special consideration must be given to adult kidney transplants in small infants (Table 3).[42] Adult allografts can take up a significant percentage of their cardiac output, and appropriate fluid resuscitation is required to avoid low-flow states that could induce vascular thrombosis or acute tubular necrosis in the allograft.[43] At our center, a single low dose of heparin is administered intraoperatively before clamping the aorta and

Table 3 Technical tips to improve outcomes of adult-size kidney transplantation in small pediatric recipients

Ensure perfect lie of both the renal artery and renal vein without any redundancy to prevent kinking and subsequent thrombosis
Avoid hooking one renal vessel over the other, but provide a straight course for each renal vessel from the renal hilum to both the aorta and vena cava
Avoid any purse-stringing of the anastomosis with possible distortion of the small diameter aorta
In order to minimize metabolic acidosis, re-establish vena cava flow by moving clamp from cava to renal vein after completion of venous anastomosis
To reduce warm ischemia and to ensure an arterial anastomosis without haste, externally cool the kidney with ice-cold saline slush after release of the vena cava vascular clamps
Before wound closure, ensure that the upper pole of the adult kidney is not obstructing blood flow in the vena cava, which may lead to renal vein thrombosis
Understand the dynamics of the increased blood flow demand of the adult kidney on the small child and undertake fluid resuscitative measures to ensure renal perfusion
Intraoperative and postoperative anticoagulation to prevent vascular thrombosis

a single dose of intravenous mannitol is administered at the time of graft revascularization as prophylaxis against ischemic reperfusion injury. Postoperatively, aspirin therapy is used for anticoagulation. Fluid management in the early postoperative period is governed by the urine output, and half-normal saline with 20 mEq of sodium bicarbonate per liter is commonly used to replace urine output in the first 48 hours.

Immunosuppression

The use of newer immunosuppressive drugs has led to significant improvements in early outcomes of pediatric kidney transplants. However, the challenge of chronic rejection continues to limit long-term graft survival.

Induction immunosuppression

In 2009, about 45% of all pediatric kidney transplant recipients received some form of induction immunosuppression therapy. Lymphocyte-depleting agents such as antithymocyte globulin were used in up to 22% of recipients for a median duration of five days.[2] While antithymocyte globulin continues to be a standard part of many adult induction regimens, interleukin (IL)-2 inhibitors are more commonly used in pediatric recipients. There has been a gradual increase in the use of monoclonal IL-2 receptor antagonists, mirroring a decrease in the use of OKT3 due to its more severe systemic effects and higher risk of post-transplant lymphoproliferative disease (PTLD).[2,12] Extended induction with anti-IL-2 receptor antibody (daclizumab) has been studied in steroid avoidance protocols. Induction with alemtuzumab and antithymocyte globulin is also being used in steroid withdrawal and immunosuppression minimization protocols. While daclizumab is no longer available, another IL-2 inhibitor, basiliximab, has been shown to be safe and is associated with decreased rates of acute rejection in some studies.[44,45] Pape et al reported a 3-year single-center experience in 48 children who received an immunosuppressive regimen of induction therapy with basiliximab along with cyclosporine and prednisolone and compared it with a similar cohort without basiliximab. They found a 2.5-fold decrease in acute rejection rates with no serious adverse events.[46,47] However, a subsequent randomized multicenter European trial showed that, at 2-year follow-up, basiliximab showed no rejection, malignancy, or cardiovascular protection effect among low-immunologic risk pediatric patients on a maintenance regimen of tacrolimus, azathioprine, and steroids.[48] These differences suggest that the immunologic risk of the recipient and composition of the maintenance regimen are important factors to consider when using induction therapy.

Maintenance immunosuppression

Calcineurin inhibitors are the cornerstone of maintenance immunosuppression at most centers. In 2009, tacrolimus was the dominant calcineurin inhibitor and used in 74% of pediatric kidney transplants in the United States, whereas cyclosporine was used in less than 2% of recipients.[2] Tacrolimus binds specifically to FK-506 binding protein and inhibits T-cell activation genes for IL-2, while the cyclosporine microemulsion inhibits calcineurin, a T-cell activating enzyme.[49] Tacrolimus has been shown to be superior to cyclosporine in preventing rejection in adults and children in randomized trials.[50–53] While effective at preventing rejections, calcineurin inhibitors have been associated with nephrotoxicity cause by interstitial fibrosis and tubular atrophy. Strategies to avoid interstitial fibrosis and tubular atrophy include avoidance or withdrawal of calcineurin inhibitors. Harmon et al undertook a trial of calcineurin inhibitor avoidance after living donor pediatric kidney transplantation.[54] Their regimen included induction with monoclonal IL2-inhibitor antibody, prednisone, mycophenolate mofetil, and sirolimus. Their series was associated with six-month and 12-month rejection rates of 21.8% and 31.5%, respectively, so complete calcineurin inhibitor avoidance is now rarely pursued. Weintraub et al used calcineurin inhibitor withdrawal in 17 children with renal allograft injury due to calcineurin inhibitor nephrotoxicity by substituting with sirolimus and mycophenolate mofetil.[55] Although they achieved improvement in renal function, 41% of patients experienced an episode of acute rejection. While early calcineurin inhibitor avoidance is associated with higher rates of early acute rejection, late calcineurin inhibitor switch to sirolimus has been associated with a greater risk of decline in graft function with proteinuria.[54,55] For this reason, minimization of the calcineurin inhibitor dose, rather than avoidance or withdrawal, is the generally practiced approach for children. In addition to calcineurin inhibitors, maintenance regimens in children also commonly include an antimetabolite. Azathioprine was used in 49% of transplants in 1996, but its use had decreased to 2.5% in 2009 in favor of the less toxic agent, mycophenolate mofetil.[12] Currently, a maintenance regimen consisting of tacrolimus, mycophenolate mofetil, and prednisone is used in 55%–63% of all pediatric kidney transplants in the United States.[2]

Steroid-free immunosuppression

The deleterious effects of steroids on statutory growth, glucose regulation, and hyperlipidemia have been well documented. Given the unique growth needs and relative lifespan after

transplantation in children, the impact of steroids is magnified in this population. Multiple centers have found that steroid avoidance or withdrawal is associated with increased catchup growth, fewer adverse cardiovascular effects, and a lower incidence of post-transplant diabetes mellitus, without any increase in rates of graft failure or acute rejection.[26,56–64] Benfield et al prospectively evaluated a regimen of steroid withdrawal at 6 months post-transplant after induction therapy with anti-CD25 monoclonal antibody and maintenance with sirolimus and calcineurin inhibitors. Compared with regimens using continued low-dose steroids, steroid withdrawal was associated with increases in standard height velocity and no difference in the rate of acute rejection.[58]

However, a Cochrane review of 30 randomized controlled trials evaluating steroid withdrawal or avoidance found that steroid-sparing regimens were associated with a higher risk of graft loss (relative risk 1.23, 95% confidence interval 1.00–1.52) and acute rejection (relative risk 1.27, 95% confidence interval 1.14–1.40).[16] In most studies, there is a reported failure rate of steroid-sparing therapy of about 10%, and the most frequent reasons for requiring conversion back to steroids is refractory acute rejection and recurrence of glomerulonephritis.[57] In conclusion, steroid-sparing regimens with induction antibody therapy and calcineurin inhibitor maintenance regimens appear to be safe in immunologically low-risk pediatric recipients.

Common post-transplant issues

Delayed graft function

Delayed graft function is defined as the need for dialysis in the first week after transplantation. In pediatric recipients, a delayed graft function rate of 5% and 15% has been observed after living and deceased donor transplantation, respectively.[2] The risk factors for delayed graft function include prolonged cold ischemia time (>24 hours), prolonged warm ischemia time, and perioperative hypotension. Extreme donor ages, ie, younger than 2 years and older than 50 years, are also associated with a higher risk of delayed graft function. The use of University of Wisconsin preservation solution has been associated with a lower rate of delayed graft function than Collins iced solution. The differential diagnosis of delayed graft function includes renal arterial or venous thrombosis, recurrent focal segmental glomerulosclerosis, hemolytic uremic syndrome, and urinary obstruction or leakage.

Acute rejection

Acute rejection typically occurs within 3 months of transplantation and has been classically characterized by fever, oliguria, hypertension, proteinuria, and graft tenderness.[65] With increased laboratory surveillance, asymptomatic increases in creatinine are currently the primary modality for screening rejection. Definitive diagnosis through biopsy and surveillance biopsy is gaining favor due to improved detection of acute and chronic rejection in pediatric transplantation.[66] Similar to adult renal transplantation, acute rejection is classified based on the Banff schema.

Early rejection is most often T-cell-mediated rejection and is characterized by acute tubulitis and interstitial inflammation. It is easier to treat than antibody-mediated rejection. Late acute rejection is most often due to nonadherence with immunosuppressive medications, and tends to present as an aggressive mixed infiltrate with elements of humoral rejection.[67] Antibody-mediated rejection is characterized histologically by a peritubular and glomerular neutrophilic and monocytic infiltrate, and deposition of complement C4d in peritubular capillaries. Antibody-mediated rejection is more common among highly sensitized patients, retransplants, and high-mismatch or ABO-incompatible donors.[4] Acute rejection is treated initially with intravenous steroids (methylprednisolone 10–15 mg/kg/day for three days). Antithymocyte globulin can be used for steroid-resistant or severe rejections (1.5 mg/kg/day for 5–7 days). For antibody-mediated rejection, intravenous immunoglobulin, rituximab, and plasmapheresis may be required.

In the NAPRTCS cohort, there was a 46% prevalence of at least one episode of acute rejection. Deceased donor kidney transplant recipients experienced more rejections than living donor recipients (51% versus 41%, respectively). Rejection episodes lead to graft loss in 5%–7% of recipients and there is successful reversal of rejection in 45%–52% of patients. Graft rejection is more common among African American recipients, children over 24 months of age, patients with one or two HLA-DR mismatches, and those who do not receive induction immunosuppression.[2]

Vascular thrombosis

The rate of vascular thrombosis in pediatric kidney transplant recipients ranges from 2% to 12% internationally and is about 7% in the United States.[68–70] Thrombosis-induced graft failure is seen in 1.9% of living donors and 3% of deceased donors.[2] Attempts to identify donor risk factors for vascular thrombosis have yielded mixed results.[69,71–73] Recipient risk factors include younger age and pre-existing hypercoagulability.[18,34,69,73–75] Duplex or color Doppler ultrasonography can be used reliably to evaluate and manage vascular thrombosis or stenosis.[76]

Urologic complications

Urologic complications include urinary obstruction, urinary leak, vesicoureteral reflux, and urolithiasis. The incidence varies between 3% and 15%, and correlates with the presence of pretransplant obstructing uropathy or bladder dysfunction.[77–81] Recurrent urinary tract infections after transplantation may be an indicator of vesicoureteral reflux and can be confirmed by a voiding urethrocystogram.[82,83] Treatment to decrease the degree of vesicoureteral reflux consists of surgical lengthening of the submucosal bladder tunnel and this has not been found to affect graft survival negatively.[80,83]

Infectious complications

Infectious complications after transplantation are associated with a significant level of morbidity and mortality. During the first month after transplantation, urinary tract infections, wound infections, and pneumonias are common. Between one and 6 months after transplantation, fungal and viral infections including cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and varicella zoster, may be seen. After this critical period, the prevalence of infections appears to be similar to that in the general population.[21] In a review of the French registry, infections accounted for 33% of all mortality over a 70-month follow-up period.[84] A high index of suspicion and vigilance for infections prevalent in the community and their prompt treatment is required. Routine vaccinations are deferred until 6 months after transplant, except for influenza, which can be given after one month. Live vaccines are contraindicated after transplantation. Family members should be immunized with influenza vaccine annually.

Cytomegalovirus, Epstein-Barr virus, and BK virus may pose an increased threat in children undergoing transplantation. Cytomegalovirus disease was found to occur in 22% of all pediatric kidney recipients prior to routine prophylaxis.[21] Subclinical viremia is more prevalent in those with naivety at transplant, those aged younger than 5 years at transplant, and those on steroid-based immunosuppression. Cytomegalovirus viremia is associated with inferior graft function, an increase in acute rejections, hypertension, and graft loss.[85] Monitoring of cytomegalovirus viral loads for the detection of subclinical disease may improve renal allograft survival.[85–88] BK virus infection occurs in 4.6% of pediatric renal transplants in the USA, and BK virus nephropathy may lead to graft loss in up to 11% of patients.[89,90] Asymptomatic BK viruria is seen in 7% of healthy people and 28% of renal transplant recipients.[90–92]

Malignancy

In the NAPRTCS database, 2.4% of pediatric renal recipients experienced a malignancy. Over 50% of all malignancies in pediatric renal transplant recipients are PTLD.[2] Nonlymphoproliferative disorders include squamous cell carcinoma, Kaposi's sarcoma, melanoma, and other rare tumors.[93] The median time to develop PTLD and nonlymphoproliferative disorders is 12.7 and 17.0 months, respectively.[2] Epstein-Barr virus is a commonly identified etiologic agent, and donor positivity with recipient negativity (D+/R–) for Epstein-Barr virus serology at transplantation and use of induction immunosuppression is associated with higher rates of PTLD.[94,95–97] Several studies have argued for steroid withdrawal to reduce overall immunosuppression and thus lower the incidence of PTLD.[94,98] While no individual immunosuppressive agent may cause PTLD, a larger cumulative maintenance immunosuppressive dose increases the risk of PTLD. Recent studies have suggested that mTOR inhibitors like sirolimus may provide protection against PTLD through anti-Epstein-Barr virus activity.[99,100] Treatment for PTLD includes immunosuppression minimization and employing anti-CD 20 agents like rituximab.[101–104]

Noncompliance

The excellent outcomes seen in pediatric patients younger than 10 years of age are not observed in adolescent recipients. Noncompliance, especially in teenagers, is an important source of graft loss and recipient death after transplantation.[105] The transition to adult care that occurs during this vulnerable period of growth may be contributory.[106] In addition, the rejection episodes in this age group are more resistant to therapy.[107] Using the United Network for Organ Sharing database, the outcomes of 4125 deceased donor kidney transplants in recipients aged 5–35 years were compared with those of 6456 living donor kidney transplants. A significantly lower incidence of noncompliance was observed in young children (0.9%) compared with adolescents (2.2% in those aged 10–14 years; $P < 0.001$) and older teens (2.0% in those aged 15–20 years; $P < 0.001$).[108] Among African American recipients, 3.4% of grafts were lost due to noncompliance as a contributory cause of failure compared with 1.5% among other races.

Growth and development

Growth and development are unique considerations in pediatric transplantation. Statutory growth in children is frequently measured as the number of standard deviations (SD) below the mean height for age-matched

children (Z-score) and the height velocity. In children with chronic renal disease, every mg/dL increase in creatinine is associated with a 0.17 SD loss in height.[109] The mean height deficit in pediatric transplant recipients is −1.74 SD and this deficit persists through adulthood, with mean Z-scores of −1.40 for patients aged 19 years and older.[2] Prolonged duration of dialysis appears to be detrimental, with spontaneous increases in growth velocity noted after transplantation in children aged 9 years and younger.[110,111] Steroid-sparing immunosuppression has been shown to impact growth velocity and height positively.[63,112–114] Steroid withdrawal between 4–6 months in prepubertal recipients was associated with sustained catchup growth and attainment of an almost normal adult height of −0.5 SD below the normal mean. While there has been interest in the use of recombinant human growth hormone for pediatric recipients, it is not a standard practice at this time.[115]

Outcomes

There has been a gradual improvement in the patient and renal allograft outcomes in pediatric recipients. In the United States, one-year and 5-year graft survival for living donors has increased from 80.4% and 74.6%, respectively, in 1987–1990 to 96.5% and 84.3% in 2003–2010.[2] Over the same time period, deceased donor one-year and 5-year graft survival has improved from 75.1% and 54.8% to 95.1% and 78.0%, respectively. Factors that appear to be associated with inferior graft survival include black race, male gender, a previous transplant history, a history of more than five blood transfusions, HLA-mismatches, and lack of induction therapy.[2]

Of the 11603 pediatric kidney transplants in the NAPRTCS registry, there were 2920 graft failures (25.3%). The most common causes of graft failure were rejection, followed by death with functioning graft and primary disease recurrence (Table 4). Disease recurrence is a significant problem in pediatric transplantation, representing nearly 8% of all graft failures. Primary disease recurrence causing graft failure is higher in children with focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, or hemolytic-uremic syndrome. The retransplantation rate after graft failure in pediatric recipients is 7.6%, and recipients of two or more transplants have a 10% higher graft failure rate than recipients of an index transplant (34% versus 24%).[2] However, some single-center reports have not found any differences in long-term patient or graft survival, suggesting that retransplantation in children may be effective.[116]

Table 4 Causes of renal allograft failure in pediatric recipients

Chronic rejection	40.5%
Acute rejection	10.5%
Medication nonadherence	5.9%
Graft thrombosis	6.9%
Death with functioning graft	8.2%
Disease recurrence	7.8%
Focal segmental glomerulosclerosis	46.0%
Membranoproliferative glomerulonephritis	8.9%
Hemolytic-uremic syndrome	8.9%
Oxalosis	5.0%
Chronic glomerulonephritis	3.5%
Others	27.7%

The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) 2010.[2]

Conclusion

The ideal treatment of ESRD in pediatric patients is a functioning kidney transplant. Due to the acute shortage of deceased donor kidneys, transplantation from living related kidney donors is frequently performed. In the USA, specific allocation schemes have been formulated to increase the rates of deceased donor kidney transplantation in children and to improve their clinical outcomes by allocating kidneys from younger donors. Certain features are unique to pediatric patients with ESRD before transplantation, ie, the presence of underlying developmental renal disease, the benefits of peritoneal dialysis in young children, and growth issues. Adult donor kidneys can be used in children weighing 10 kg or more, while being aware of the higher risk of vascular thrombosis and using adequate perioperative hydration and anticoagulation. Urologic anomalies deserve timely intervention in pediatric recipients to achieve desired outcomes after transplantation. Noncompliance may lead to rejection and inferior graft outcomes in adolescent recipients who, therefore, deserve special attention. Viral infections (cytomegalovirus, Epstein-Barr virus) may pose serious problems, particularly in children who have not previously been exposed to these viruses. Other challenges include pyelonephritis in the graft and recurrence of underlying disease in the pediatric kidney transplant recipient. Long-term outcomes for patient and graft survival after kidney transplantation in children are excellent and provide a good quality of life.

Disclosure

The authors report no conflicts of interest in this work.

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