Pediatric Kidney Transplantation

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KEYWORDS

• Kidney transplantation • Pediatric • Evaluation • Outcomes

Kidney transplantation in pediatric patients has become a routinely successful procedure, with 1- and 5-year patient survival rates of 98% and 94%, and 1- and 5-year graft survival rates of 93% to 95% and 77% to 85% (the range takes into account differences between living and deceased donors). These good outcomes represent the cumulative effect of improvements in pre- and posttransplant patient care, operative techniques, immunosuppression, and infection prophylaxis, diagnosis, and treatment. This article provides a brief historical overview, discusses the indications for transplantation, describes the evaluation process for the recipient and the potential donor, outlines the operative details, reviews the various causes of and risk factors for graft dysfunction, and analyzes outcomes.

HISTORICAL NOTES

Pediatric kidney transplantation, like transplantation in general, is relatively young. Fifty years ago end-stage renal disease (ESRD) was a terminal illness, as neither dialysis nor transplantation were available. The first successful transplant took place in 1954 with an adult recipient and an identical twin donor; immunosuppression had not yet been developed (**Table 1**). The first immunosuppressive agent, azathioprine, was a failed anticancer agent found to be effective in dogs and then used with steroids in the first clinical experiences in the early 1960s. Unfortunately, early success rates for 1-year graft survival were in the 50% to 70% range, depending on the type of donor, and the high steroid dosages were associated with important and common side effects.

The advent of a failed antifungal agent, cyclosporine, in the late 1970s and early 1980s, transformed the field of transplantation, improving outcomes in kidney transplantation to 75% to 85% 1-year graft survival, and making routinely successful nonrenal abdominal and thoracic transplantation possible. The late 1980s and 1990s saw

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Table 1
Selected historical landmarks

	Adult	Pediatric
First identical twin transplant	1954	1959
Azathioprine/prednisone	1962	1962
Cyclosporine	1978	1982
Tacrolimus	1989	1989
Mycophenolate mofetil		
Sirolimus		
OKT3	1982	1987
Thymoglobulin	1997	1997
IL2 receptor antagonist	1997	1997
Alemtuzumab	1998	2005

the introduction of the currently used immunosuppressive agents including tacrolimus, mycophenolate mofetil (MMF), and more effective antibody induction agents. See the article by Dr Feng elsewhere in this issue for further explanation of immunosuppression.

Progress in pediatric kidney transplantation generally kept pace with that seen in adults, with some lag time related to technical issues and the slower introduction of newer immunosuppressive agents. Not surprisingly, clinical trials took place in adults before being conducted in children, as is true in most of medicine. In general, however, current progress in and outcomes of pediatric kidney transplantation are similar to those seen in adults.

Incidence and Trends in Pediatric Transplantation

Of the 1781 pediatric patients waitlisted for an organ transplant in the United States, 791 are awaiting a kidney transplant. To date, 10,762 renal transplants have been reported by the North American Pediatric Renal Transplant Cooperative Society (NAPRTCS) https://web.emmes.com/study/ped/registry for 9854 pediatric patients in North America. The United Network of Organ Sharing (UNOS) http://www.unos.org/ maintains a system of pediatric priority in kidney transplantation assigning additional points to recipients less than 11 years old waitlisted for a kidney from a deceased donor. In 2005, a revised allocation policy (Share 35) conferring preferential allocation of allografts from young deceased donors (<35 years old) to pediatric patients less than 18 years old was implemented (Organ Procurement and Transplant Network: Policies at http://www.optn.org/PoliciesandBylaws2/policies/). This policy change resulted in an overall increase in the mean number of pediatric kidney transplants per quarter from 188 to 211 ($P = .07$) with a reduction in the wait time after listing. The mean wait time for a deceased donor kidney before the rule change was 350 days compared with 119 days after the rule change ($P = .04$). The policy change also resulted in an increase in the number of HLA-mismatched allografts and more deceased donor transplants.[1] A reasonable question, given the historically longer half-lives with living donor kidneys compared with deceased donor kidneys, is whether the unanticipated consequence of the change in allocation (ie, an increased proportion of deceased donor kidney transplants in children) will lead to a higher rate of retransplantation in the future. However, the follow-up is too short for any meaningful data to have become available to answer this question, and, in any event, there is substantial selectivity in choosing deceased donor kidneys for children.

An analysis of the demographics of the pediatric transplants performed in the last decade, from the NAPRTCS database, reveals that approximately 20% of transplants are performed in young recipients less than 6 years old, and approximately 25% of primary transplants are performed preemptively. Thus, most pediatric kidney transplantation recipients are teenagers. For deceased donor transplantation, compared with adults, pediatric patients receive more poorly matched kidneys than adults, as only 5% of pediatric patients receive HLA antigen mismatched kidneys compared with almost 14% of adult recipients. This situation is probably a function of preferential allocation of kidneys from donors less than 35 years of age to children, without regard to HLA matching.

INDICATIONS FOR LISTING

The causes of ESRD in pediatric patients are different from those seen in adult patients. The important causes of ESRD in pediatric patients (**Table 2**) include obstructive uropathy secondary to posterior urethral valves; renal dysplasia; glomular diseases, such as focal segmental glomerulosclerosis (FSGS), hemolytic uremic syndrome (HUS), and membranoproliferative glomerulonephritis Type II (MPGN Type II); infantile polycystic kidney disease (PCK), and several less common diseases. In contrast to adults, where only 16% to 17% of the dialysis population is listed for transplant, most children with ESRD are referred for transplantation. The only circumstances in which a child would not be an appropriate candidate for renal transplantation would be in the setting of multiple medical issues and an overall poor prognosis for any meaningful recovery, untreated malignancy, or untreated infection. Isolated mild mental retardation is not per se a contraindication, and substantial intellectual catch-up can be seen routinely in pediatric patients.

RECIPIENT EVALUATION

In general, pediatric recipient evaluation is not that different from that used in adults. A thorough history and physical with routine comprehensive laboratory studies, chest radiograph and electrocardiogram are obvious starting points (**Box 1**). Urinalysis and urine culture, 24-hour urine collection, and occasional native renal biopsies are also routinely obtained. Pediatric urologic evaluation is performed as needed, particularly in patients with a history of posterior urethral valves, reflux, or other congenital

Table 2
Indications/causes of ESRD in pediatric patients

	Percent
Obstructive uropathy	16
Dysplasia	16
FSGS	11
Reflux	5
GN	3.5
Prune belly	3
HUS	3
MPGN	3
PCK	3
Other	36.5

Box 1
Recipient evaluation

History and physical

Chest radiograph

Electrocardiogram

Routine chemistries, liver function tests, Ca, Mg, P, cytomegalovirus, Epstein-Barr virus (EBV), human immunodeficiency virus

Urine analysis, culture, protein

Additional studies as indicated

Urologic studies: voiding cystourethrography, urodynamic studies, postvoid residual volumes, as needed

problems. Most pediatric patients are reasonable medical candidates for transplantation. Social service and psychosocial evaluation are a particularly important part of the evaluation process, and represent poorly understood aspects of the care of pediatric (and for the matter, adult) renal transplant patients. Noncompliance, especially in teenagers, is an important source of graft loss and patient death after transplantation.[2]

DONOR SELECTION

Living donation confers superior outcomes for pediatric recipients, limits wait times, allows for preemptive transplantation, and thus should be recommended for pediatric patients. Parents comprise 80% of living donors. An analysis of the UNOS data over a decade[3] showed that transplantation of a pediatric recipient, with an excellent quality adult-sized kidney, without acute tubular necrosis, conferred a distinct and significant survival advantage, particularly for the young infant recipient less than 6 years old. The projected graft half-lives after the first year in the young recipients of living donors was even better (26.3 and 29.3 years for children aged 0–2.5 years and 2.5–5 years, respectively) than the gold standard transplant category (23.3-year graft half-lives of HLA-identical adult sibling recipients aged 19 to 45 years). Deceased donor kidneys tend to be from younger adults or teenagers, and there is fairly routine and obvious cherry-picking for good quality donors for pediatric recipients.

OPERATIVE PROCEDURE/TRANSPLANT SURGERY

In teenagers and in children weighing more then 30 kg, the technical details associated with kidney transplantation are similar to those in adults, with retroperitoneal exposure of, and anastomosis to the external iliac artery and vein. In smaller children and infants, anastomosis to larger vessels is necessary. Infants weighing 10 kg or less generally undergo a midline laparotomy with vascular anastomosis at the level of the vena cava and the aorta. For children between 10 and 30 kg, there is some variability in approach, with the common iliac vessels usually being used, and surgeon preference dictating a retroperitoneal versus an intraperitoneal approach. For young children with previous intra-abdominal procedures or vascular access issues, thrombosis of the major intra-abdominal vessels must be carefully evaluated for selection of an appropriately sized donor organ that can be accommodated to small collateral vessels in the abdomen.[4,5]

Ureteral reimplantation is perhaps the most variable part of the transplant procedure. Simple extravesical ureteroneocystostomy is generally the most common variation, but formal open antireflux techniques are also used by some surgeons.[6] Pediatric patients with complex urologic issues may require more extensive pre- and peritransplant interventions, but this is beyond the scope of this article. Obviously, if the transplant surgeon is not a urologist, good planning and coordination among the different surgical members of the team is of great importance.

Important details of operative management include over hydration of the small recipient to ensure adequate perfusion. Adult kidneys in small infants can take up a huge percentage of the cardiac output, and appropriate volume loading is necessary to ensure a good perfusion pressure of the new kidney (generally a systolic blood pressure of 130 is adequate). Routine administration of mannitol 1 g/kg and furosemide 1 mg/kg during the performance of the vascular anastomoses is also useful to ensure prompt diuresis. Fluid management in the early postoperative period is governed by the urine output. Locally in Pittsburgh, the authors use a 1% glucose solution in half normal saline, to which 1 ampule of $NaHCO_3$ has been added, to replace the urine output. The authors replace 1 mL/1 mL for a urine output of 300 mL/h or less and 0.8 mL/1 mL for urine output greater than 300 mL/h.

Desensitization Strategies in Children

About 70% of children receiving a first transplant are unsensitized, but approximately 3% of children, mostly in the category of repeat transplants or blood transfusions, have prior allosensitization and thus have a panel reactive antibody (PRA) of more than 80%. Desensitizing patients to HLA antigens to allow for a negative cross match and transplantation is gaining momentum in adults and is now also being applied to children, so that children with long wait times on the sensitized lists can move toward successful transplantation. A recent open-label, phase 1/2, single-center study, building on a previous pilot trial (IG02; http://www.clinicaltrials.gov/, NCT00642655), provided encouraging results of desensitization in adults using the combination of high-dose immune globulin (IVIG) and rituximab, as the high rate of early rejection (50%) was reversible with excellent 1-year patient (100%) and graft survival (94%).[7] Other desensitization adaptations, applied primarily in adults, using low-dose IVIG, rituximab, and frequent plasmapheresis, with occasional splenectomy, have led to successful transplantation against a previously incompatible donor.[8,9] The recent reports of bortezomib for diminishing anti-HLA antibodies are encouraging for the additional use of this drug for desensitization strategies.[10] At Stanford University, the first pediatric randomized study for desensitization of highly sensitized pediatric recipients, testing the direct safety and efficacy of high-dose IVIG alone versus high-dose IVIG with rituximab, is actively enrolling highly sensitized pediatric patients.

GRAFT DYSFUNCTION

There are several causes of graft dysfunction, and they occur at different time points after transplantation. Initial delayed graft function (DGF), defined as the need for dialysis in the first week after transplantation, is related to ischemia-reperfusion injury. Deceased donor kidneys with long cold ischemia time (CITs) are at highest risk, and living donors kidneys with short CITs are at the lowest risk. Given the greater selectivity with which deceased donor kidneys are chosen for pediatric kidney transplantation, the incidence of DGF in pediatric patients should be low.

Rejection is another important source of graft dysfunction. Rejection can occur early after transplantation, and is called acute rejection (which can be further subdivided

into cellular or humoral), or it can occur late after transplantation, its nomenclature having evolved over time from chronic rejection, to chronic allograft nephropathy, to interstitial fibrosis/tubular atrophy. Rejection is a function of the immune system recognizing the transplanted organ as a foreign body and attempting to destroy it. It is a complex area of study and remains imperfectly understood. A variety of agents have been developed to prevent or treat rejection, and again this is discussed in a separate article in this issue.

Uniquely for the kidney, the most important immunosuppressive agents are nephrotoxic, and a great deal of graft loss can be associated with chronic nephrotoxicity related to immunosuppression, particularly the calcineurin inhibitors (CNIs) cyclosporine and tacrolimus. The CNIs can also cause renal failure of the native kidneys in nonrenal transplant patients. Acute graft dysfunction in kidney transplant patients related to elevated CNI levels is common and is generally reversible with dosage reduction.

Technical complications are fortunately uncommon after pediatric kidney transplantation, but do occur. They include arterial thrombosis or stenosis, venous thrombosis, ureteral leak, stenosis or reflux, and the development of fluid collections, including hematomas, seromas, or lymphoceles. Ultrasonography is a good screening test in the initial evaluation of these complications, with further diagnostic testing performed on an as-needed basis.

RISK FACTORS AND OUTCOMES

As stated at the outset, pediatric kidney transplantation at present is a generally successful procedure with high rates of short- and medium-term patient and graft survival. Different factors are associated with better or worse outcomes.

- Recipient age

The main effect of recipient age relates to poorer outcomes in teenagers, and this is largely related to noncompliance. Parenthetically, it is remarkable how little is known about compliance and how ineffective we are in preventing it. It is a dangerous problem and is associated with premature graft loss and death.

- Donor type

In general, living donor kidneys are associated with longer half-lives than deceased donor kidneys; this is almost assuredly related to better allograft quality and shorter CITs.

- DGF

DGF has remained an important risk factor for inferior graft survival throughout the history of kidney transplantation. There is also an association of DGF with acute rejection.

- Rejection

The effect of acute rejection has been somewhat controversial. Originally believed to be a negative prognostic factor, acute rejection has been subject to somewhat more nuanced analyses recently. Completely reversed acute rejection seems not to be associated with worse long-term outcomes. In addition, there are also registry data suggesting that a substantial reduction in the incidence of acute rejection has not led to improved long-term graft survival.

- Recipient race

Similar to registry data analyses in adults, African American race has been associated with more rejection and worse long-term outcomes. The reasons for this are not entirely clear.

- Recurrent disease

FSGS, MPGN Type II, and HUS all have the potential to recur in the transplanted kidney, but unpredictably. Our inability to predict or control these disease recurrences represents an important limitation of our understanding.

- Matching

There remains an advantage to O antigen mismatched kidneys from either deceased or living donors, but it is less clear that there are important differences at different levels of mismatching.

- Sensitization

As a group, sensitized patients have inferior outcomes after kidney transplantation, whether or not they have been subjected to trials of desensitization.

OUTCOMES AND LIMITATIONS

Although short- and medium-term outcomes have improved over the years, long-term (10 years) graft survival has not improved in 22 years. Chronic CNI toxicity and the side effects of immunosuppression, which can include diabetes, hypertension, and malignancy, have had important negative effects on graft survival, patient survival, and quality of life. The side effects of chronic corticosteroids have been particularly harmful to children, with an important effect on growth retardation. Thus, the field is still imperfect, and substantial progress remains to be made.

SPECIFIC AND INTEREST AREAS OF ACTIVE RESEARCH IN PEDIATRIC TRANSPLANTATION

Given the variations in the development of the immune response in the pediatric age group, the period of rapid linear growth in the child with age-dependent changes in drug pharmacokinetics and pharmacodynamics, and the clear discrepancy in size between the young recipient and the large adult-sized kidney, there are some specific issues that require further study in pediatric recipients of organ allografts. Some of these areas of interest are highlighted. Children, who are usually EBV naive, have a greater propensity for development of viral-driven lymphoproliferative disorders, which may differ in their prevalence under different immunosuppression protocols.[11] Understanding the development of viral and heterologous immunity in the young recipient, and its effect on skewing the immune response toward specific anergy or alloresponsiveness, is an important area of research. The molecular mechanisms that drive the extended survival of transplants from adult-sized kidney donors into infant recipients suggests the possibility of an accommodative response that requires further definition. Conversely, the rapid accrual of chronic tubular necrosis in kidneys of young pediatric recipients receiving adult-sized kidneys has highlighted the need for a better examination of the physiologic importance of vascular size discrepancy between the young recipient and the adult donor.[12,13] These issues, among others,

are peculiar to pediatric transplantation, and deserve greater definition and study, with the aim of improving clinical and graft outcomes for this group of patients.

SUMMARY

Renal transplantation in pediatric patients is a successful therapy, with excellent short- and medium-term patient and graft survival rates. Pediatric patients with ESRD are generally candidates for kidney transplantation, and the technical issues involved have largely been resolved. Several factors can lead to short- or long-term graft dysfunction or even graft loss. Despite reasonable short- and medium-term outcomes, many factors can compromise long-term outcomes.

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