Kidney Transplantation in Children and Adolescents

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ABSTRACT
Worldwide, specific pediatric allocation schemes successfully try to minimize waiting time for children with end-stage renal disease (ESRD). The article is a review of current issues in pediatric kidney transplantation. The procedure is the treatment of choice for children and adolescents with ESRD, with 1- and 3-year graft survival rates of 95% and 90% and recipient survival after 5 and 10 years of 95% and 90%. Preoperative surgery is often necessary to minimize negative effects of congenital anomalies. No minimum age exists for pediatric transplantation, but most often the recipient body weight is ideally above 10 to 15 kg. Technical concepts should include extravesical anastomosis, stenting of the ureter, and potentially intraperitoneal placement of the graft. Immunosuppression has constantly improved. The aim is a tailored regimen to reduce side effects and improve compliance, which necessitates intense counseling of the child and the parents prior to, during, and after transplantation as many adolescents lose their graft due to noncompliance. Intense follow-up must also exclude infections, especially with herpes and polyoma viruses. For the future, age matching may be only one promising concept to improve results. As only a small number of children require the procedure in each country, multinational studies should be initiated to optimize outcomes in children and adolescents.

THE PREVALENCE OF end-stage renal disease (ESRD) in children is four to six per million.1-3 Affected children suffer not only from effects of the underlying disease but also from many other associated conditions, such as nutritional deficits, cardiovascular problems, osteoporosis, and lack of growth development. Hemodialysis (HD) and peritoneal dialysis (PD) are well-established renal replacement therapies but must be judged as bridging methods, as they are less beneficial than a kidney transplantation. Besides technical difficulties (shunt obstruction, peritonitis) HD and PD have a strong negative impact on the social (eg, school attendance) and family life of the child as well as the parents.5,6 Transplantation is the best option for treating pediatric ESRD. However, one must be aware that children are not simply “small adults,” there are specific pediatric issues in children and adolescents.

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PEDIATRIC RENAL CARE

About 170,000 pediatricians work in the 42 European countries, including 850 pediatric nephrologists. There is wide variation in the number of pediatric nephrologists available with 1.1 per 1 million children in Denmark and 8.8 in Germany. Some countries (Iceland, Estonia, Luxembourg) have no pediatric nephrologists. Transplantation in pediatric recipients is performed by more than half of the European pediatric centers: 87% of those in European Union (EU) countries but about 30% in non-EU countries. Interestingly, “pediatric” is defined differently; in Great Britain, Ireland, and the United States, an age below 18 years is the threshold; it is below 16 years in France and the Eurotransplant community; and below 15 years in Italy and Spain. Despite these differences, almost all countries have special programs for ESRD children and adolescents to expedite the procedure and keep waiting time short. In the Eurotransplant community, waiting time is about 1 year and preemptive operations are possible.8

UNDERLYING DISEASE IN CHILDHOOD ESRD

In contrast to adult ESRD patients, about 40% of children suffer from congenital conditions, such as aplasia/dysplasia of the kidneys, obstructive uropathy, or cystic disease. Glomerulosclerosis causes about 25% of pediatric ESRD with focal sclerosing glomerulonephritis (FSGS) accounting for half of these cases. Hemolytic uremic syndrome (HUS) is also a cause of ESRD in childhood and adolescence (8%), with yet incompletely understood disease-specific implications. Age distribution in pediatric ESRD is about 40% between 10 and 15 years, and 15%, 20% and 25% for the age groups below 2 years, 2 to 5 years, and 6 to 9 years.1-3

INDICATIONS/CONTRAINDICATIONS

The indication for pediatric renal transplantation is ESRD. Absolute contraindications are “active” malignancies and a positive crossmatch with the current donor, even though boundaries are currently pushed by specific immunosuppressive agents.1,9 In patients with a Wilms tumor, there must be a disease-free interval of at least 2 years. HIV disease is still considered a contraindication by most investigators. Indispensable prerequisites are the existence of a low pressure reservoir (leak point pressure < 40 mm Hg, detrusor pressure < 100 mm Hg) and the elimination of obstructive pathologies like posterior urethral valves. Some children (bladder exstrophy, prune belly) require extensive surgery, such as formation of a conduit or bladder augmentation.5 There is no minimum age for pediatric kidney recipients but mostly transplantation is not performed before the age of 2 years. As weight seems to be crucial and as it increases with age, graft and patient survival improve with age as well. Most authors prefer a weight above 15 to 20 kg,10,11 but renal transplantation has been successfully performed below 1 year of age and below 9 kg.1,12 Age matching influences graft survival. Besides, a gross size mismatch may cause difficulties placing the kidney and closing the abdomen; due to hypoperfusion of an adult donor kidney in a pediatric recipient, about 25% of the functional renal mass may be lost within 6 months. Furthermore, moderate cardiovascular risk exists in size mismatching, as fluid and catecholamine demand is elevated. Pape et al13 showed that donor kidneys from donors < 16 years have the ability to grow with the pediatric recipient and that glomerular filtration rate of younger donor kidneys is stable or even increases over time, whereas it decreases in adult kidneys transplanted into pediatric recipients.13,15 As a consequence of the specific abilities and demands of young kidneys as well as of young recipients, some authors demand a “young for young” program similar to the Eurotransplant Senior Program, where kidneys from donors > 65 years are allocated to recipients > 65 years.14 Regarding the timing of transplantation, preemptive cases were found to show improved graft survival only in the premycophenolate era (before 1995) and only for deceased donor organs.2 Fewer acute rejections in pediatric recipients of deceased donor kidneys have been described when it is performed before dialysis becomes necessary.2

SURGICAL ASPECTS

Anesthesia requirements are intraoperative monitoring of central venous pressure, (noninvasive) arterial pressure, and oxygenization; intraoperative fluid substitution should be 60–80 mL/kg per hour. Postoperative recovery is faster when epidural analgesia is used rather than on-demand intravenous medication.16 The preferred graft site is extra-peritoneal. Not only peritoneal dialysis can thus be maintained if necessary but intraoperative gastrointestinal complications are avoided and postoperative gastrointestinal adhesions and obstructions minimized.17,18 Vessel anastomosis should be performed with absorbable monofil material (polydioxanone) in order to promote growth of the anastomoses and prevent stenosis.19 For ureteral anastomosis, most authors prefer the extravesical approach using the Lich-Gregoir technique or a modification of this technique because it reduces the risk of ureteral stenosis and shortens operative time. The advantage of the intravesical antirefluxive technique according to Politano-Leadbetter is that it facilitates ureterorenoscopic handling in case of ureteral stenosis, but this technique produces more stenoses itself. Performing ureter-ureterostomy in nonrefluxing recipients is believed to render better blood supply to the ureter and prevent reflux into the transplanted kidney. This technique makes it either necessary to remove the recipient’s own kidney for an end-to-end anastomosis or perform an end-to-side anastomosis with the recipient’s own kidney left in place. With ureter-ureterostomy techniques, stricture rates of up to 7% have been reported, making these techniques rather not to be performed as the first choice.20,21 Ureteral stenting should be obligatory not only in uretero-ureteral anastomoses, but also when uretero-
vesical techniques are used, as urinary leakage is reduced. Infectious complications can be successfully avoided by applying antibiotic prophylaxis as long as the stent is in the ureter. We use an 8 Ch tube in the transplant ureter, passing it through the bladder contralateral to the implantation site and to the suprapubic area. The tube and the hole in the bladder are secured with a Z-suture in the urothelium and the bladder muscle with absorbable Vicryl. Thus, the child needs no further anesthesia for removal of the ureteral stent on days 10 to 12. Furthermore, the amount of urine produced by the transplant can be easily measured.

SURGICAL COMPLICATIONS

Urinary obstruction (1% to 30%), urinary leakage (0.3% to 9%), and urolithiasis (1% to 11%) are the main urinary system complications. Lymphoceles, which may develop in 1% to 7%, should be operated on laparoscopically. Vascular complications such as thrombosis occur especially when the donor kidney is small, and are promoted by nephrotic syndrome or inherited coagulopathies. Arterial stenosis may develop in 1% to 6%. Some authors also observed a higher arterial stenosis rate among cyclosporine-treated recipients. Low-dose heparinization for the duration of the hospital stay is recommended. Irrespective whether complications are suspected, daily monitoring including Doppler ultrasound and serological parameters should be performed in the early phase after transplantation.

IMMUNOSUPPRESSION

Many changes in immunosuppressive management have occurred over the past decade. Today, induction therapy is performed most often by administration of interleukin-2 receptor antibodies (IL2ab), while antibodies like OKT 3 and antithymocyte globulin (ATG) are applied rarely. Also, azathioprine has proved to be inferior to mycophenolate mofetil. Both calcineurin inhibitors, cyclosporine (CsA) and Tacrolimus (Tac), are used. In the United States, Tac has almost replaced CsA even though some authors found an increased number of lymphoproliferative disorders when Tac was used in Epstein-Barr virus (EBV)-negative recipients of EBV-positive donor kidneys. Steroids are still routinely used. Side effects like diabetes mellitus and weight gain occur as in adult cases, but steroids also negatively affect longitudinal growth in children because they interfere with growth hormone and its receptors. Administration of growth hormones is therefore necessary but may increase the clinical symptoms is similar. Therefore, in doubtful cases, early biopsy is urgently recommended as opposing therapeutic strategies must be initiated (increase vs decrease of immunosuppression). As HUS is not yet fully understood and recurrence rate is extremely high, some authors strongly oppose living donor kidney transplantation in children with ESRD due to HUS. Pediatric transplant recipients experience a significant improvement in quality of life, which is severely impaired in ESRD children. One- and 3-year graft survival rates are about 95% and 90%; recipient survival after 5 and 10 years is about 95% and 90%. Graft and patient survival after living donor kidney transplants is better than after deceased donor organ transplants. However, only about 20% of kidneys in pediatric cases are from living donors in Europe, as opposed to about 40% in the United States. Studies on second or third procedures in young age patients also showed good outcomes for the graft and recipient, mostly depending on the era of immunosuppression. Thus, protocols reducing or avoiding steroids and calcineurin inhibitors (CNIs) are increasingly applied and mostly comprise induction therapy with an IL2ab in combination with an mTOR inhibitor (sirolimus/everolimus). Rejection therapy is usually performed as in adults with short steroid boosts and a switch of the CNI as the initial medication. For antibody-mediated rejection, several concepts exist and new agents are tested with a promising potential for the future. Multinational studies are urgently needed for a final appraisal of reduction protocols as the numbers of patients in each country is small. Noncompliance, which occurs in 5% to 50% of cases, must always be taken into consideration when graft function deteriorates. Adolescents are at the highest risk; here noncompliance accounts for more than 10% of graft failures. Delaying the procedure until the recipient is more mature is not an alternative, as the negative effects of a longer waiting time are much stronger than that of noncompliance. Although different monitoring options are available (blood level, electronic), thorough counseling and education of children and their parents, starting already in the pretransplant period, is crucial.

OUTCOMES

Pediatric transplant recipients experience a significant improvement in quality of life, which is severely impaired in ESRD children. One- and 3-year graft survival rates are about 95% and 90%; recipient survival after 5 and 10 years is about 95% and 90%. Graft and patient survival after living donor kidney transplants is better than after deceased donor organ transplants. However, only about 20% of kidneys in pediatric cases are from living donors in Europe, as opposed to about 40% in the United States. Studies on second or third procedures in young age patients also showed good outcomes for the graft and recipient, mostly depending on the era of immunosuppression. Thus, protocols reducing or avoiding steroids and calcineurin inhibitors (CNIs) are increasingly applied and mostly comprise induction therapy with an IL2ab in combination with an mTOR inhibitor (sirolimus/everolimus). Rejection therapy is usually performed as in adults with short steroid boosts and a switch of the CNI as the initial medication. For antibody-mediated rejection, several concepts exist and new agents are tested with a promising potential for the future. Multinational studies are urgently needed for a final appraisal of reduction protocols as the numbers of patients in each country is small. Noncompliance, which occurs in 5% to 50% of cases, must always be taken into consideration when graft function deteriorates. Adolescents are at the highest risk; here noncompliance accounts for more than 10% of graft failures. Delaying the procedure until the recipient is more mature is not an alternative, as the negative effects of a longer waiting time are much stronger than that of noncompliance. Although different monitoring options are available (blood level, electronic), thorough counseling and education of children and their parents, starting already in the pretransplant period, is crucial.

INFECTIONS

Pediatric kidney recipients are at high risk for viral (re)infections. The therapeutic strategy, besides administration of antiviral agents in some cases, is to reduce...
immunosuppression in order to reconstitute the recipient’s immune response. Viruses of the herpes group represent the largest reservoir. Cytomegalovirus (CMV) reactivation or infection causes general symptoms and may lead to rejection of the kidney. Prophylaxis with gancyclovir or valacyclovir can be performed. EBV infection can induce infectious mononucleosis and promotes posttransplant lymphoproliferative disorder (PTLD) in 1% to 4% of pediatric recipients. PTLD is the most frequent malignancy (75% to 80%). Alarming, the share of pediatric recipients developing a malignant disease has increased more than threefold over the past 20 years, which may be due to intensified immunosuppression. No routine vaccination is available for CMV and EBV. Varicella virus may induce chicken pox with severe morbidity. Early vaccination is recommended for children awaiting kidney transplantation. Polyomavirus (BK, JC) infection is becoming more common, possibly due to intensified immunosuppressive strategies. As the associated nephropathy of the transplant can lead to graft loss, pediatric recipients should be screened with quantitative polymerase chain reaction for BK virus shedding. Usually, the virus is detected in urine before viremia develops. As in all viral infections after transplantation, reduction of immunosuppression is the main therapeutic approach, but therapy with leflunomide or cidofovir has been found to be effective as well.

EXPANDING THE DONOR POOL

Not all strategies used to increase the donor pool for adults are employed in children. No publication on crossover cases exists in pediatric recipients and only three case reports have been published on organs from non–heart-beating pediatric donors. ABO-incompatible cases from living donors have been performed mainly in Japan with encouraging results. Laparoscopic donor retrieval today accepted as a means to reduce donor fears and to thus increase the number of living kidney donors, has also been used to retrieve kidneys for pediatric recipients. While many single-center studies reported no disadvantage regarding organ function after this minimally invasive retrieval, Troppmann et al. in a UNOS study of almost 1000 pediatric recipients of laparoscopically retrieved living donor kidneys, found a higher share of delayed graft function compared to open donation techniques and identified laparoscopy as an independent risk factor for acute rejection, particularly in recipients below 5 years. The reasons for these results remain unclear, as immunosuppressive protocols were not compared and the results of the participating centers were not analyzed according to experience with laparoscopic kidney retrieval. Data from Troppmann’s own, experienced center showed no disadvantage of laparoscopic organ retrieval in pediatric cases.

CONCLUSIONS

In conclusion, kidney transplantation is the best therapy for pediatric ESRD and all efforts must be made to reduce waiting time for ESRD children. Surgical correction of anatomic abnormalities is frequently necessary prior to transplantation in children because of different etiologies of ESRD in children and adults. Recurrence rates of FSGS and HUS are high, which is why living donor transplantation is not generally recommended in these underlying diseases. Immunosuppression must be improved to prevent viral infection and to reduce noncompliance and consecutive graft loss. Optimal results can only be achieved if the specific requirements of kidney transplantation in children are taken into account rather than treating children and adolescents as “small adults,” which can best be assured by close cooperation of pediatric nephrologists, pediatric urologists, and pediatric surgeons.

REFERENCES