Kidney transplantation in infants and small children

Children make up a small part of the ESKD population. According to data published by the USRDS, in 2004 children accounted for about 1% of new ESKD patients and about 1.5% of all prevalent ESKD patients (1). The incidence rates for the pediatric ESKD population have been essentially stable since 1981. Among the pediatric group, ESKD is least common in the youngest age groups. The 2004 incidence rate reported for children aged 0–4 years was 10.8 per million population compared with 28.2 per million population for children aged 15–19 years and 119.1 per million population for adults aged 20–44 years (1). While dialysis remains an option for these patients once they develop the need for renal replacement therapy, for almost all pediatric patients with ESKD, renal transplantation has become the treatment of choice. Even when renal failure affects infants, i.e., during the first year of life, kidney transplantation should be considered the preferred treatment.

Children with ESKD should usually have a kidney transplant as soon as it is feasible, with the aim of avoiding the need for dialysis for any significant length of time. There are many advantages to performing transplants early or in a pre-emptive fashion early or in a pre-emptive fashion. The latter allows for minimizing the negative impact of uremia on physical and neurologic development in infants.

Abbreviations: CMV, cytomegalovirus; CNI, calcineurin inhibitors; DGF, delayed graft function; EBV, Epstein–Barr virus; ESKD, end stage kidney disease; HIV, human immunodeficiency virus; NAPRTCS, North American Pediatric Renal Transplant Cooperative Study; PTLD, post-transplant lymphoproliferative disorder; SDS, standard deviation scores; USRDS, United States Renal Data System.
Indications

Nephrotic syndrome (congenital, diffuse mesangial sclerosis) and ESKD (also termed chronic kidney disease stage 5) are the indications for pediatric kidney transplantation in infants and small children. Congenital disorders (aplasia/hypoplasia/dysplasia, structural abnormalities) account for most ESKD in infants and small children, and are more common in boys. According to the 2006 annual report of the NAPRTCS the five major known causes of pediatric ESKD are glomerulonephritis (18%), aplasia/hypoplasia/dysplasia (16%), obstructive uropathy (16%), focal segmental glomerulosclerosis (12%), and reflux nephropathy (5%) (2). The Pediatric Committee of the American Society of Transplantation published educational guidelines in 1998 on the indications for pediatric kidney transplantation (3). As growth and development are primary issues to consider in deciding transplantation strategies for infants and young children, the committee considered the following to be major indications for transplantation: (i) ESKD unresponsive to medical management, (ii) progressive growth failure despite adequate nutrition (including nasogastric/nasojejunal tube, or gastrostomy feedings) and correction of anemia, (iii) developmental delay, (iv) progressive renal osteodystrophy despite dietary phosphorus restriction, adequate use of phosphate binders, vitamin D supplementation, and correction of acidosis, and (v) failure to thrive (3).

The optimal age for kidney transplantation is controversial. At the University of Minnesota Medical Center, we do not have a set minimum age. Our preference is to avoid or minimize as much as possible the period of time that the child is exposed to dialysis. There are few contraindications to kidney transplantation in children. The Pediatric Committee of the American Society of Transplantation considers the following to be contraindications to kidney transplantation: (i) active malignancy or <12 months post-treatment for malignancy, (ii) HIV infection, (iii) positive current T-cell crossmatch, or (iv) history of active non-adherence with medical management by parents, caregivers, or patient (3).

Pretransplant evaluation

Because of the small number of infant kidney transplants performed each year in the USA, it is difficult for many centers to maintain the skills and have the expertise needed to perform such transplants. We have previously published our protocols for recipient evaluation and preparation in children (4, 5). A multi-disciplinary team of healthcare professionals should be involved in the evaluation and management process. Such a team often includes social workers, nurses, nutritionists, psychologists, neurologists, urologists, surgeons, dentists, physical therapists, speech therapists, and nephrologists.

We advocate early referral to the potential transplant center. It is hoped that evaluation, planning, and management can be performed prior to the need for dialysis. Early evaluation provides the best opportunity to intensify nutrition, as adequate nutrition is important to adequately handle the stress associated with surgery. Early evaluation also provides opportunity to treat renal osteodystrophy, correct bladder outlet obstruction such as that caused by posterior urethral valves, correct acidosis and anemia, educate the family about kidney transplantation, and select an appropriate donor.

Table 1 lists the evaluation protocol used for children at the University of Minnesota (5). Children should be examined for evidence of active infection, such as otitis media, dental caries, pneumonia, urinary tract infection, and tuberculosis exposure. Patients should be screened for viral infections such as HIV, CMV, EBV, and hepatitis B and C. Both the CMV and EBV viruses can be transmitted by the transplanted kidney to a CMV or EBV naive recipient. The latter is especially important, as EBV seronegativity at the time of kidney transplant is a major risk factor for the development of EBV-associated PTLD and lymphoma (6). Data from the USRDS and United Network of Organ Sharing databases show age <20 (6) and <18 years (7) to be risk factors for the post-transplant development of PTLD.

Routine childhood immunizations should be administered before transplant. Patients should also be immunized against pathogens known to be associated with an increased incidence of infection post-transplant, such as hepatitis B, pneumococcus, Hemophilus influenza, and varicella (8). The varicella vaccine can be administered in patients who are at least 12 months of age and who have not had prior varicella zoster infection. A tuberculin skin test with controls should be placed before transplant. Attention to potential causes of infection post-transplant is an important issue because infection is a major cause of mortality and morbidity in children post-transplant. Infection is now the major cause of hospitalization in children post-transplant, surpassing post-transplant hospitalization for allograft rejection (9). In addition, pediatric kidney transplant patients have a higher cumulative
incidence of hospitalization for infection (47.7%) over the first three-years post-transplant compared with adult kidney transplant patients (39.8%) (10). The native kidneys themselves may represent a significant risk for post-transplant infections, especially in the setting of grade IV reflux and chronic pyelonephritis. This is usually an indication for bilateral nephrectomy, either before or at the time of transplant.

Infants and small children should be evaluated for hypercoagulability as the risk of vascular thrombosis of the allograft is increased in children <2 years of age (11). According to the 2006 NAPRTCS annual report, vascular thrombosis accounts for 10.5% of all graft failures in pediatric kidney transplant patients and is the third most common known cause of graft failure in children (2). However, even in the presence of documented thrombophilias, excellent outcomes can be achieved with good surgical technique and the use of post-operative anticoagulation (12). Nephrotic syndrome represents a unique hypercoagulable condition in these patients. Persistent proteinuria pretransplant in these patients should be treated with bilateral nephrectomy and then support on dialysis until the protein levels have normalized, and the patient is no longer hypercoagulable.

It is also important to document patency of the aorta and inferior vena cava prior to surgery as these vessels are used for anastomoses in infants and small children. Additional studies to perform as part of the pretransplant evaluation include a voiding cystourethrogram to evaluate bladder adequacy and urethral patency and, if needed, cystoscopy to evaluate bladder function.

### Operative care

The technical challenges of transplants in infants may well be greater compared with transplantation in older children. Some use this as an argument to maintain the young patient on dialysis until he or she reaches some predetermined age or weight. While short-term dialysis may be useful in select situations, these young patients can be very challenging to maintain on chronic long-term dialysis. Given their small total circulating volume, hemodialysis can be difficult to perform. Vascular access may also be difficult to maintain, with potential complications of thrombosis and infections. Peritoneal dialysis may also be associated with potential problems, including the risk for recurrent infectious episodes. All of the advantages of a transplant (vs. dialysis) that are cited for older children also apply for infants.

One crucial factor for a successful outcome in infants is proper donor selection. Using an adult-sized kidney (as opposed to a kidney from a pediatric donor) is preferable, because it provides the infant recipient with a large renal mass, and is less surgically complex. Our preference is to almost exclusively use living donors. In previous analyses, we have shown the superior results with living donors vs. deceased donors with transplants in this age group (13). In a recent multivariate analysis of the NAPRTC data, recipient age <2 years was a significant risk factor for graft loss (2). However, this finding was true only with deceased donor kidneys. In an analysis of living donor transplants only, recipient age was not a significant risk factor.
The growth of laparoscopic donor nephrectomy has offered an attractive option for potential donors. The most recent adult literature does not suggest any significant difference in recipient outcomes with regard to laparoscopic vs. open donor nephrectomy (14). However, one recent analysis of the U.S. national data suggests that there may be a higher incidence of DGF and acute rejection in young recipients (0–5 years old) of laparoscopic vs open donor kidneys (15). This is of concern and needs further detailed exam to insure that this earlier report does not represent a “learning curve” effect. At our center, we now routinely use the laparoscopic approach for all living donors, and have not seen an increase in the incidence of DGF, or acute rejection in infants or older pediatric recipients.

With regard to the recipient operation, an intraperitoneal approach is generally preferred (Fig. 1). This approach with complete mobilization of the right colon, provides adequate space in which to fit a large adult kidney (Fig. 2). Additionally, recipients often require removal of the native kidneys, which can be performed easily via the intraperitoneal approach. The most common indication for bilateral nephrectomies in these patients is vesicoureteral reflux with significant dilatation of the collecting system, which is a risk factor for chronic infections after transplant. Infants with underlying nephrotic syndrome should usually undergo nephrectomy six wk pretransplant, thus allowing for nutritionally recovery and resolution of the hypercoagulable stage associated with severe proteinuria. Some centers advocate a retroperitoneal approach to placement of the kidney, even for these small recipients. Advantages cited include a lower risk of bowel complications and the possibility of future peritoneal dialysis (16). Graft compression may be concern with this approach, especially when using a large adult kidney.

The actual surgical technique for kidney implantation does not differ significantly from older children or adults. The distal aorta and inferior vena cava are generally used for inflow and outflow with end-to-side anastomosis to the donor renal artery and vein. The ureter is then implanted into the bladder by any of a number of different techniques, with or without a stent.

One concern with transplantation of adult-sized kidneys into infants was that infants were simply too small and could not provide the blood flow required to sustain the large kidney. It has been shown that aortic flow in infants increases post-transplant. However, during the surgery it is very important to maintain maximal intravascular volume. This is especially true around the...
time of reperfusion, when the adult kidney may sequester a significant proportion of the infant’s circulating blood volume.

Use of living donors minimizes the risk of DGF, which is more common in younger recipients. With careful attention to surgical detail and perioperative care, the incidence of DGF can be minimized. To maximize inflow to the kidney, we preferentially use the abdominal aorta in infant recipients. Central venous pressure monitoring ensures an adequate cardiac filling volume throughout the operation, especially important before unclamping and reperfusing the new kidney. A large proportion of the infant’s circulating volume can be diverted to the adult-sized kidney. Therefore, to minimize hemodynamic instability, it is best to raise the central venous pressure before reperfusion, generally to between 10 and 15 mmHg. Our preference is to use colloid solutions for this including blood, if the hemoglobin is low.

Immunosuppression

Immunosuppression protocols for infants are generally similar to those used for older children. There are some data to suggest that rejection may be higher in the infant recipient (17, 18), suggesting that these patients may be at higher immunologic risks. At the University of Minnesota, we have actually seen the opposite, with a lower incidence of acute rejection in infants vs. older children or adolescents (13). This lower incidence of rejection in this age group is in fact supported by the most recent analysis of the NAPRTCS data, demonstrating a lower incidence of acute rejection in patients <2 years old vs. the other age groups (2).

CNI have allowed for significant improvements in results, and all centers use a CNI as part of maintenance immunosuppression for these patients. Both tacrolimus and cyclosporine are used and there is very limited data comparing the two agents in this patient population. There is concern regarding the long-term use of either CNI and the potential for nephrotoxicity, but at present, there is very limited experience with calcineurin-free protocols in this group of recipients. There is some experience with steroid-free protocols in infants, and there is hope regarding the beneficial effects of such protocols on growth in infants (19). Future progress will, hopefully, be in the areas of steroid-avoidance and calcineurin minimization protocols for these recipients.

The use of induction therapy is fairly common in infant recipients. Centers have reported on transplants without the use of induction therapy, but generally with higher rates of acute rejection. Analysis of national U.S. data has also shown the absence of induction therapy to be a risk factor for rejection. Therefore, at present, most centers would suggest that infants should receive some induction therapy followed by maintenance immunosuppression with a triple or double regimen involving a CNI. Our center’s preference has been to use induction therapy with a polyclonal antilymphocyte agent, though many centers utilize a humanized monoclonal antibody such as, dacluzimab or basiliximab. However, a recent publication suggests that induction therapy in infants is associated with a significantly increased risk for an infectious complication after transplant, especially in the youngest recipients, without a beneficial effect on graft survival (20).

Using modern immunosuppressive protocols, most centers report one-year acute rejection rates between 20% and 40%. While acute rejection often manifests with elevation of the serum creatinine, the degree of elevation may be minimal in infants because of the large renal mass. Other symptoms such as fever, proteinuria, or hypertension may signal the beginning of a rejection episode. Ultimately, a kidney biopsy is the best method for diagnosis, and should be performed whenever acute rejection is suspected.

Outcomes

According to the NAPRTCS data, graft survival rates are somewhat inferior in the youngest vs. the older age group recipients, though this was only statistically significant for deceased donor transplants. The reported five-year graft survival rates for recipients <2 years old was 82% for living donor transplants and 54.6% for deceased donor transplants (2). Data from the University of Minnesota for graft survival rates for recipients <1 year suggest that equivalent results to those seen in older recipients can be obtained with no impact of age of transplant on graft survival rates (21). The most recent analysis of this data is shown in Fig. 3 and Table 2, again demonstrating equivalent results in all age groups.

Benefit of early transplant

Early transplantation provides the best opportunity for survival and growth and development in infants and small children when compared with maintenance on chronic dialysis. Death rates are higher for children on chronic dialysis compared with rates for children that receive a successful kidney transplant. Data from the 2001 USRDS annual report show that by five years after the
Transplantation provides the best opportunity for linear growth in the infant and small child with ESKD. An NAPRTCS study evaluated longitudinal growth in 587 children with functioning kidney transplants for at least 54 months and who had pre- and post-transplant height measurements (23). Height SDS were determined for each patient using data from the National Center for Health Statistics. By SDS criteria, the majority of the children had growth retardation with a mean SD score of \(-2.41\). Catch-up growth was defined as a gain of 1 SD. Catch-up growth was seen only in those children with the greatest height deficit or in children age 0–1 years at transplant (24). Catch-up growth was seen in 47% of children aged 0–1 years, 44% of children aged 2–5 years, 19% of children aged 6–12 years, and 9% of those aged 13–17 years. This study showed that post-transplant improvement in linear growth is best in children transplanted before six years of age (24).

Uremia in infants is associated with the development of developmental delay and encephalopathy. Davis et al. (25) prospectively studied the outcome of kidney transplantation on neurologic development in 37 infants and small children transplanted at or before 30 months of age. A pediatric psychologist using either the Bayley Scales of Infant Development or the Stanford-Binet Intelligence Scale, Form L-M, performed all evaluations. Mental development scores were shown to improve an average of 12.6 points post-transplant in 33 patients with paired data. Eighteen patients had pretransplant scores consistent with developmental delay. After transplant 12/18 (67%) had scores that were in the range of normal mental development (25). This study suggests that the adverse effect of uremia on neurologic development can be mitigated by successful, early kidney transplantation.

**Summary**

In summary, infants can be transplanted with equivalent results to those seen in older recipients. With modern immunosuppression, proper donor selection, and careful attention to perioperative care, good outcomes can be obtained even in the youngest recipients. An experienced team, familiar with the care of these challenging patients, is also critical. An early transplant should be the treatment of choice for all pediatric patients with ESKD. A pre-emptive transplant is ideal, given the detrimental impact of prolonged dialysis on survival, growth, and neurologic development in these patients.
References


