PAPER

Transplantation of Adult Living Donor Kidneys Into Infants and Small Children

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Hypothesis: We hypothesized that improved outcomes following renal transplantation in high-risk infants and small children primarily are due to advances in immunosuppression and accurate diagnosis of rejection. Optimizing renal allograft perfusion is critical to achieving good early graft function and decreasing early graft loss.

Design: Twenty-eight consecutive recipients (weighing <20 kg) of adult living donor kidneys transplanted at our center from 1984 to 1999 were reviewed. Two groups were identified based on differing immunosuppression protocols and clinical surveillance. Actuarial graft and patient survival reported at 1, 3, and 5 years were compared for group 1 (1984-1991) and group 2 (1992-1999). Graft losses, categorized as immunologic or nonimmunologic, and the incidences of delayed graft function, vascular thrombosis, and rejection were compared.

Results: Graft and patient survival in group 1 (n=13) at 1, 3, and 5 years was 77% and 92%, 54% and 85%, and 54% and 85%, respectively. In group 2, all 15 patients are alive with functioning grafts to date. Immunologic graft loss occurred in 5 of 13 patients in group 1 who developed chronic rejection. Nonimmunologic causes (vascular thrombosis [2 patients]) and patient death [1]) resulted in early graft failure within 2 weeks in 3 of 13 patients in group 1. The overall incidences of delayed graft function (10.7%) and thrombosis (7.1%) were low and did not differ between groups. Percutaneous renal biopsy was used more frequently in group 2 to evaluate graft dysfunction and guide treatment.

Conclusions: We conclude that improved overall graft and patient survival in group 2 is owing to advances in immunosuppression and better treatment of rejection. Percutaneous renal biopsy allows prompt and accurate histological diagnosis of graft dysfunction. Surgical technique and aggressive fluid management aimed at maximizing renal allograft perfusion is critical in optimizing early graft function and decreasing vascular complications.

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ALTHOUGH GRAFT and patient survival has steadily improved in children undergoing renal transplantation with results similar to that of adults, outcomes in infants and small children continue to be inferior.[1,2] A high rate of early graft loss from vascular thrombosis,[3,4] acute tubular necrosis,[5,6] rejection,[7] and recipient death[8,9] has been reported in infant kidney transplant recipients. An increased incidence of short-term rejection, irreversible rejection,[7] and long-term rejection[5] have supported the concept that small children may be more immune responsive than older children and adults.[10] However, infant transplant recipients who maintain good graft function beyond 1 year have experienced the best reported long-term graft survival.[1]

Advances in medical and nutritional management of children with end-stage renal disease, improvements in intraoperative anesthetic and surgical management, and major advances in immunosuppression have led to increased overall survival of children undergoing kidney transplantation. The establishment of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) in 1987 to collect and analyze data on children undergoing kidney transplantation at centers in the United States and Canada has been instrumental in identifying risk factors and practice patterns that may contribute to decreased graft survival. The NAPRTCS has become the most complete database for pediatric renal transplant recipients, and its annual reports most closely represent the clinical practice and outcomes of children who receive kidney transplants.[5]

Since 1984, our surgical technique using central vascular anastomoses and a short renal vascular pedicle, and perioperative clinical management, including aggressive intravascular volume expansion, have focused on maximizing renal perfusion to decrease the risk of delayed graft function (DGF) and vascular thrombosis and to optimize early graft function. To improve long-term graft survival we have used immunosuppression protocols that include the most effective available therapies. Percutaneous renal biopsy has been increasingly used at

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PATIENTS AND METHODS

PATIENT POPULATION

One hundred thirty-three pediatric kidney transplantations have been performed at the Children's Hospital and Regional Medical Center, University of Washington, Seattle, from March 1, 1984, through December 31, 1999. Eighty-eight children (66%) were recipients of adult living donor (LD) kidneys; 45 (34%) received cadaveric donor kidneys. Twenty-eight (32%) of the 88 LD recipients were infants or small children weighing less than 20 kg. Overall, 33 patients weighed less than 20 kg, of whom 28 (85%) received LD kidney transplants. The medical records of these 28 LD kidney recipients were retrospectively reviewed.

Patient demographic data including age, weight, sex, and origin of renal disease were recorded. Pretransplantation dialysis requirement and mode of dialysis were noted. Transplantation data including site of vascular anastomoses, size of donor kidney (if available), cold ischemia time, and early graft function were noted. Immunosuppression was according to our protocol and is described below.

SURGICAL MANAGEMENT

Donor nephrectomy and recipient transplantation operations were performed simultaneously in adjoining operating rooms by independent surgical teams. The donor nephrectomy was done through a flank approach and a brisk diuresis (100-200 mL/h) was induced using aggressive intravascular volume expansion with crystalloid and albumin colloid solutions. A combination of mannitol and furosemide was occasionally used, and some donors were systemically heparinized prior to cross-clamping the renal vessels.

Recipient hemodynamic monitoring included central venous pressure (CVP) through an internal jugular vein or subclavian vein catheter. Initial CVP measurements ranged from 0 to 5 mm Hg, and aggressive intravenous crystalloid and colloid fluids were given to achieve a CVP of 16 to 20 mm Hg by the time of vascular unclamping. A few of the patients had radial arterial catheters to help with blood pressure management. Some patients required transfusion of packed red blood cells for dilutional anemia or plasma for coagulopathy. Many patients required ventilatory assistance postoperatively for 1 to 2 days.

A Foley catheter was sterilely inserted and the bladder irrigated with antibiotic solution. Special care was taken to avoid overdistension and injury to the small defunctionalized bladders in anuric recipients. Peritoneal dialysis catheters, if present, were accessed to drain the peritoneum and then excluded from the sterile field. A curvilinear suprainguinal incision extended to the flank was made and an extraperitoneal dissection performed. The inferior vena cava (IVC), aorta, and common iliac vessels were dissected, ligating all lymphatics. Vascular anastomoses were performed to the distal aorta or proximal common iliac artery in all patients, and venous anastomoses to the IVC. The donor renal vascular pedicle was shortened to allow the transplanted kidney to lie comfortably in the retroperitoneal space and to prevent kinking or excess tension on the vessels as they pass across the psoas. Ureteroneocystostomy was performed using a Ledbetter-Politano technique early in our experience or, as needed, for small contracted bladders; an extravesical ureteroneocystostomy (Gregoire-Liche) was done in the remainder of the patients.

Immediate postoperative radionuclide scans were performed in all patients to assess renal graft perfusion and excretion and to detect ureteral obstruction or leakage. Doppler ultrasounds were performed within 24 hours to provide a baseline examination and to assess renal arterial flow characteristics which may herald inflow problems. Postoperative fluid management consisted of aggressive volume replacement of urine output (milliliter per milliliter) for the first 24 hours, and progressively transitioning the replacement fluids to a maintenance infusion rate over the next several days after transplantation. The CVP was monitored continuously during the period of urine replacement. Oliguria was managed by volume expansion with colloid (5% albumin or blood products) and judicious use of diuretics (mannitol and/or furosemide) to promote urine output.

IMMUNOSUPPRESSION MANAGEMENT

Significant advances in immunosuppression have been made during the time course of this study and our immunosuppression protocol has evolved to incorporate many of those changes. All patients received cyclosporine-based triple-drug maintenance immunosuppression, azathioprine or mycophenolate mofetil (Cellcept [MMF]; Roche Pharmaceuticals, Nutley, NJ), and steroids. Starting in 1984, cyclosporine (Sandimmune; Sandoz Pharmaceutical Corp, Hanover, NJ) was initiated at 12 mg/kg per day early post-transplantation when the recipient demonstrated good

our center, and is now routinely employed to establish the cause and to guide treatment of graft dysfunction. This study reviewed the effect of our management approach on patient and graft survival and on the development of significant complications in infants and small children who underwent renal transplantation during 2 distinct eras of immunosuppression and clinical surveillance.

RESULTS

Characteristics of the 13 children in group 1 and the 15 in group 2 are compared in **Table 1**. Follow-up was at least 6 months in all patients and was naturally longer in group 1 (mean follow-up ± SD, 95.4 ± 13.6 months vs 27.1 ± 4.3 months). The mother was most often the kidney donor in both groups, though 2 children in group 2 received LD kidneys from unrelated female donors. A higher proportion of boys with congenital obstructive uropathy due to posterior urethral valves was observed in group 2 compared with group 1, though the overall frequencies of pediatric renal diagnoses were similar to that of the NAPRTCS[5] database (**Table 2**). Calculated mean volumes of the donor kidneys were approximately 300 mL, which represented approximately 22 mL/kg recipient circulating blood volume, were no different between groups.

Group 1 patient and graft survival measured 92% and 78% at 1 year, and 85% and 54% at 3 years and 5 years, respectively. All patients in group 2 are presently alive with functioning grafts. Three early graft losses occurred in group

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urine output and had a decrease in serum creatinine levels to less than 221 mmol/L (2.5 mg/dL). Target cyclosporine trough levels, measured by high-power liquid chromatography, were 150 to 200 ng/mL for weeks 1 through 3. A progressive tapering of the dosage was followed over the first 6 months to result in daily dose of 4 to 6 mg/kg and a corresponding cyclosporine trough level of 80 ng/dL. In 1989, target cyclosporine levels were increased to approximately 50 to 100 ng/dL at all time points of the protocol tapering. Neoral (Novartis Pharmaceuticals, Basel, Switzerland), a microemulsion formulation of cyclosporine, was introduced in 1993 and replaced Sandimmune as primary maintenance therapy in our protocol.

Azathioprine was initiated preoperatively at 3 mg/kg per day and continued daily after transplantation at 2 to 3 mg/kg per day in patients who underwent transplantation between 1984 and 1994; dosage adjustments were made for leukopenia. In 1995, MMF was introduced for clinical use and replaced azathiorpine in our protocol. The MMF dose was 1.2 g/m^2 per day. Dose reductions were made for toxic effects of infection, leukopenia, and gastrointestinal intolerance.

Steroid dosing included intravenous methylprednisolone starting preoperatively at 3 mg/kg per day and tapering to 1 mg/kg per day by posttransplantation day 7. The daily dose was gradually tapered over 6 to 9 months to a dose of 0.15 mg/kg per day, which was continued indefinitely.

Cytolytic induction therapy was used in 8 of 28 patients. Minnesota antilymphoblast globulin (MALG) at 15 mg/kg per dose was used from 1984 to 1992. After that time, OKT3 (Ortho Pharmaceutical Corp, Raritan, NJ) at 5 mg/d or antithymocyte globulin (15-20 mg/kg per day) were given daily for 7 to 14 days depending on recovery of renal function. Intravenous cyclosporine was used for induction therapy in some patients. More recently, 3 patients received induction therapy using an anti-interleukin 2–receptor antagonist followed by early introduction of cyclosporine.

Biopsy-proven rejection episodes were treated with pulse methylprednisolone therapy. Cytolytic therapy using OKT3 or antithymocyte globulin was used for steroid-resistant rejection. Several recipients who underwent transplantation between 1984 and 1991 were treated with steroid pulse therapy for presumed rejection without renal biopsy. Since 1992, ultrasound-guided percutaneous renal biopsies have been routinely performed to evaluate allograft dysfunction. Indications for biopsy include elevation of the serum creatinine level, unexplained persistenthypertension or fever, and proteinuria. Intravenous sedation or general anesthesia was used in all patients undergoing renal biopsy to minimize patient anxiety, discomfort, and motion. Starting in 1995, tacrolimus (FK506) (Fujisawa Pharmaceuticals Co Ltd, Osaka, Japan) was used as rescue immunosuppression therapy for patients who had developed chronic rejection or recurrent acute rejection while receiving cyclosporine.

Recognizing that immunosuppression management has evolved significantly from 1984 through 1999 and was not entirely uniform for either patient population, 2 broad eras of immunosuppression management were identified. Group 1 includes all recipients of LD kidney transplants from 1984 through 1991. Patients in group 1 all received Sandimmune, azathiorpine, and steroids for maintenance immunosuppression; some patients received MALG induction. Patients in group 2 received an LD kidney transplant from 1992 through 1999. All patients in group 2 received Neoral, MMF, and steroids. Induction therapy included OKT3, antithymocyte globulin, or interleukin 2–receptor antagonist; none received MALG. All patients in group 2 received vigilant surveillance of graft function with routine use of percutaneous renal biopsy for prompt diagnosis of allograft dysfunction. The clinical care and immunosuppression management of these 2 groups are significantly different to identify 2 distinct eras for comparison: a historical era (group 1) and current clinical practice era (group 2).

MAIN OUTCOME MEASURES

Actuarial graft and patient survival were calculated for each group and reported at 1, 3, and 5 years. Significant posttransplantation events including DGF and vascular thrombosis were recorded and compared. The DGF was defined as the requirement for dialysis during the first week after transplantation. Graft losses were categorized as immunologic or nonimmunologic. Biopsy-proven rejection episodes occurring in the first 6 months, the number of rejection episodes, and time to first rejection were compared between groups.

STATISTICAL ANALYSIS

Actuarial survival statistics were compared using Kaplan-Meier lifetable analysis. To compare proportions of categorical variables, Fisher exact test was used, because of the small frequencies observed. Continuous data were compared using nonparametric Wilcoxon–Mann-Whitney test. Statistical significance was defined at $P<.05$.

1 owing to nonimmunologic causes. Two (7.1%) of the 28 patients developed graft thrombosis resulting in graft loss within 2 weeks posttransplantation. One patient with aortic insufficiency and ischemic renal disease developed graft thrombosis on posttransplantation day 0. The second child experienced DGF and developed vascular thrombosis 2 weeks posttransplantation. This child was subsequently found to have circulating warm anti–donor antibody. The third graft loss occurred in a patient who suffered a hyperphosphatemic cardiac arrest in the immediate postoperative period. Overall, 3 (10.7%) of the 28 patients required dialysis in the first posttransplantation week for DGF, which was not different between groups. Significant posttransplantation events are compared in **Table 3**.

Beyond 1 year after transplantation, the incidence of graft loss due to immunologic causes (chronic rejection) was significantly higher in group 1 compared with group 2. Five recipients in group 1 developed graft failure 17 months to 11 years after kidney transplantation. Excluding the 3 group 1 patients with graft failure in the first 2 weeks, the incidence of biopsy-proven rejection occurring within 6 months was similar in both groups (30% vs 40%). Diagnostic percutaneous renal biopsy was obtained more frequently in group 2 compared with group 1 (8 of 15 patients vs 3 of 10 patients). Of the 5 group 1 recipients with graft failure from chronic rejection, 1 patient had developed fibrosis at the time of their first posttransplantation biopsy, 2 had had no biopsy specimen prior to transplantation nephrectomy and 2 had acute re-

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Table 1. Living Donor Kidney Transplant Recipient Characteristics*

Recipient Characteristics	Group 1 (n = 13)	Group 2 (n = 15)
Weight, mean ± SD, kg	15.9 ± 0.9	16.1 ± 0.7
Age, mean ± SD, y	3.6 ± 0.5	3.5 ± 0.4
Sex, M/F	6/7	11/4
Dialysis, HD/PD†	2/11	4/11
Donor M/F	2/10	5/10

*Statistically the groups showed no significant differences.
†HD indicates hemodialysis; PD, peritoneal dialysis.

Table 2. Cause of Renal Failure*

	No. (%) of Patients			
Type of ESRD	Group 1 (n = 13)	Group 2 (n = 15)	CHRMC 1984-1999	NAPRTCS,[7] %
Congenital obstructive	0 (0)	5 (33.3)	5 (17.8)	16.4
Dysplasia	2 (15.4)	2 (13.3)	4 (14.3)	16.0
Nephrotic syndrome	1 (7.7)	3 (20)	4 (14.3)	2.7
Immunologic disease	3 (23.0)	0 (0)	3 (10.7)	4.7
Cystic kidney disease	1 (7.7)	2 (13.3)	3 (10.7)	2.7
Ischemia	2 (15.4)	0 (0)	2 (7.1)	1.8
Reflux	0 (0)	2 (13.3)	2 (7.1)	5.6
Other	1 (7.7)	1 (6.6)	2 (7.1)	6.6
Oxalosis	1 (7.7)	0 (0)	1 (3.6)	0.7

*ESRD indicates end-stage renal disease; CHRMC, Children's Hospital and Regional Medical Center (Seattle, Wash); and NAPRTCS, North American Pediatric Renal Transplant Cooperative Study.

Table 3. Posttransplantation Events

	No. (%) of Patients		
Posttransplantation Events	Group 1 (n = 13)	Group 2 (n = 15)	*P*
DGF*	1 (7.7)	2 (13.3)	NS
Thrombosis	2 (15.4)	0 (0)	NS
Graft loss	8 (61.5)	0 (0)	.001
Immunologic	5 (38.5)	0 (0)	.03
Nonimmunologic	3 (23.0)	0 (0)	.17
Rejection in 6 mo	3 (30.0)†	6 (40.0)	NS
Time to first rejection, d	104	45	NS

*DGF indicates delayed graft function.
†Only 10 persons were included in this subgroup.

jection histologically. One patient in group 1 and 2 patients in group 2 were converted to tacrolimus for recurrent rejection. Two late graft losses (1 at 6 years, and 1 at 11 years) were related, at least in part, to patient noncompliance.

COMMENT

Children younger than 6 years represent 2.4% of recipients of LD kidney transplants performed in the United States in 1997, according to the most recent United Network for Organ Sharing Annual Report.[2] Of the 5362 pediatric renal transplantations included in the 1997 NAPRTCS Annual Report, 53% used LD kidneys, and 21.3% of recipients were younger than 6 years.[5] Though not clearly specified in the NAPRTCS report, the percentage of LD kidney transplantations in children up to age 6 years may have been higher than 53%; as outcomes are particularly poor for cadaveric donor renal transplantations in this high-risk group, several active pediatric renal transplant centers have emphasized the importance of LD kidneys in infants and young children.[11,12] Our commitment to LD kidney transplantation in this high-risk group is evident in this study as 85% of children weighing less than 20 kg received LD kidney transplants and these small children represent 32% of our LD transplantation experience.

While outcomes following kidney transplantation in children have generally improved since 1984 and reported 1-year graft survival now approaches 90%,[1,5] 20% of children younger than 6 years included in NAPRTCS data have had graft loss. Chronic rejection (30%), acute rejection (18%), vascular thrombosis (12.4%), and death with a functioning graft (11.5%) account for most of the failed grafts.[5] In a review of pediatric transplantation data from United Network for Organ Sharing, Cecka et al[1] note poorer graft and patient survival (71% 1-year graft survival) for children younger than 3 years, with the worst outcomes (48% 1-year graft survival, 69% 1-year patient survival) seen in recipients younger than 1 year. Three quarters of graft losses occurred during the first month. Thrombosis (28%), rejection (22%), patient death (14%), and primary nonfunction (5%) were the most common causes. Short-term graft survival was inversely related to recipient age, with infants having 2.3 times higher risk of early graft failure compared with adults. Recipients who survived the first year with good renal allograft function, however, exhibited the best long-term graft survival with graft half-life of 18 years compared with adults (11 years) and adolescents (7 years).[1] One cannot therefore overstate the importance of optimizing early renal function after transplantation.

In the present study, 3 grafts in group 1 failed within the first month owing to nonimmunologic causes. Two kidneys were lost due to vascular thrombosis, 1 developing after a 2-week period of DGF. The third graft loss occurred as a result of patient death in the immediate postoperative period. Vascular thrombosis is perhaps the most devastating early complication after kidney transplantation. It most often occurs in the first 2 weeks after transplantation and is usually irreversible leading to early graft loss. A higher incidence of thrombosis has been observed in cadaveric donor transplantations compared with LD recipients, and in kidneys with prolonged cold ischemia time. Of LD kidney recipients, younger than 6 years was associated with an increased risk of graft thrombosis.[3] In a 1997 NAPRTCS review, Singh et al[4] noted that thrombosis accounted for 12.2% of index transplantation graft loss, and 19.2% of retransplantation graft failure.[13] Among LD recipients, young age was identified as an independent risk factor for thrombosis, with an incidence of 3.5% in children 2 years or younger. Salvage of thrombosed grafts have

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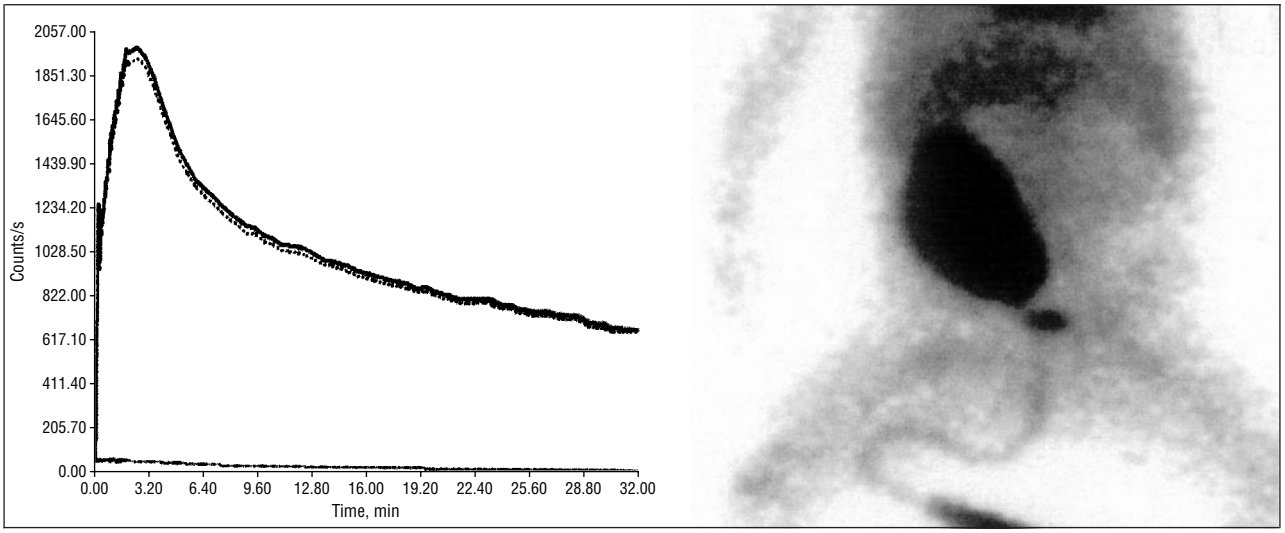

Left, Immediate postoperative renal scan demonstrating excellent vascular flow with aortic or inferior vena cava anastomoses, complete renal perfusion, and prompt excretion of urine. Right, The large donor-recipient size discrepancy and small recipient bladder are also well illustrated.

been reported using surgical and thrombolytic therapies, though the likelihood of successful recovery of renal function remains low.[14] Acute tubular necrosis, rejection, and hypovolemia may predispose to vascular thrombosis. It is unclear if there is any difference in salvage rate between arterial and venous thromboses. To evaluate vascular flows, we have routinely used radionuclide renal scans immediately after transplantation (**Figure**), and ultrasound with Doppler flow analysis on postoperative day 1.

Three patients (10.7%) of the 28 in our series required dialysis within the first week for DGF. In the patient with oliguria after transplantation, initial efforts are directed at assuring adequate volume status. If volume resuscitation alone is not successful, then diuretics are administered to promote urine output. Ultrasound is obtained to rule out vascular thrombosis, or ureteral obstruction or leakage. In a recent report using NAPRTCS data, DGF was shown to be a major risk factor for graft failure after transplantation.[6] Though the incidence of DGF was higher in cadaveric donor recipients (19.1%), 5.6% of LD recipients developed DGF with significant decrease in graft survival. Two-year graft survival in LD recipients without DGF was 89.6%, as compared with 41.6% for those recipients with DGF. The relative risk for graft failure due to DGF was 6.02 in these LD recipients. In our series, 1 patient with DGF in group 1 developed early graft failure and has subsequently died. Delayed graft function and graft failure within 30 days have both been associated with increased mortality rate following transplantation in children.[8,9] The 2 patients who had DGF in group 2 recovered and continue to have good renal function 4 and 5 years after transplantation.

Key to the recovery of good early renal function after transplantation is optimizing renal perfusion. In this population of small recipients of adult-sized donor kidneys, there are size mismatch considerations as well as the absolute expansion of the intravascular compartment that occurs with reperfusion of the donor kidney. The normal-sized adult kidney repesented approximately 22 mL/kg recipient weight, or the equivalent of 25% of recipient blood volume in this study. In addition, renal perfusion pressure is lower in the recipient, where mean arterial pressure may normally be 50 to 70 mm Hg, as compared with 80 to 100 mm Hg in the adult donor. We have used central vascular anastomoses to the aorta or proximal common iliac artery and IVC to optimize renal perfusion. To avoid kinking of renal vessels, the vascular pedicle is shortened to assure a direct route to the aorta and IVC. These are fundamental techniques that have been well described by others. [11,15,16] Expansion of recipient intravascular volume is also critical to a prompt complete reperfusion of the donor kidney. We routinely set a target recipient CVP measurement of 16 to 20 mm Hg to expand the intravascular space and to increase perfusion pressure.[17] It is equally important, however, to establish a brisk diuresis in the donor prior to cross-clamping. Because the donor and recipient operations were performed simultaneously, ischemia times were minimized, usually less than 1 hour total. Postoperatively, continued aggressive fluid support is necessary to maintain intravascular volume output and adequate renal graft blood flow.[17]

While nonimmunologic or technical events are a significant cause of early graft loss following pediatric kidney transplantation, ongoing surveillance of renal function and the use of percutaneous kidney biopsy for diagnosis of renal dysfunction is critical for long-term graft survival. Early in our experience, percutaneous biopsy was not consistently used because of concerns about the risk of biopsy-related complications in the solitary transplanted kidney. Improvements in imaging and biopsy needles, however, have decreased procedural risks. As already noted, there was a significant size mismatch between the donor and recipient, and we have found that wide mobilization of the peritoneum to develop a retroperitoneal space allows easy and direct access to the aorta and IVC. Classically, these large adult kidneys have been placed intraperitoneally,[15,16] so as to avoid additional compression by the peritoneal contents that may contribute to the risk of vascular thrombosis. We have found the exposure excellent for vascular anastomoses, and believe that the peritoneum helps to maintain the kidney in a more stable position with a lower risk of unwanted twisting or

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shifting of the kidney that could lead to vascular compromise. As most patients have been receiving peritoneal dialysis before undergoing transplantation, their abdominal domain has been expanded, and the peritoneal layer is thicker and less apt to tear. The indwelling peritoneal dialysis catheter has been placed to gravity drainage to minimize retroperitoneal compression. Again, maintenance of adequate intravascular volume is critical to ensure good renal perfusion. We believe that 2 additional advantages of the extraperitoneal position are the ease and safety of percutaneous biopsy. Using ultrasound, a suitable biopsy site and path are selected without the risk of injury to overlying bowel, or a possibly shifting kidney. Potential biopsy-related complications (eg, bleeding or urine leakage) are contained in the retroperitoneum and clinically detectable at an early stage. The histological information provided by the biopsy allows accurate assessment of severity of rejection, and avoids unnecessary patient exposure to additional immunosuppression.

Coincident with increased use of renal biopsy in our clinical practice were the introduction of newer immunosuppressive agents and reports from the NAPRTCS database detailing the importance of cyclosporine levels[18] and the effect of immunosuppression practices on the short- and long-term graft survival.[7] Tejani and Sullivan[18] reported an increased rate of rejection and graft loss that corresponded to decreases in maintenance cyclosporine dose. The risk of graft loss was reduced 5% to 6% for each 1 mg/kg incremental increase in maintenance cyclosporine dose.[19] The availability of tacrolimus and MMF for rescue or primary immunosuppression has improved our ability to treat recurrent rejection episodes. Our immunosuppression protocol has evolved to incorporate several new agents, and our current practice is similar to that reported by Benfield et al[13] in a review of NAPRTCS data, where most pediatric renal transplantation centers report using prednisone (95%) and Neoral (81%) as maintenance immunosuppression. Thirty-six percent of centers reported routine use of MMF.

Despite these advances in immunosuppression, allograft rejection remains the leading cause of graft failure after transplantation.[1,5] The clinical importance of rejection is borne out in this study, as 5 of 8 graft losses that occurred were due to chronic rejection. Several of these patients had received additional steroid pulse therapy for presumed rejection; however, not all of these episodes were biopsy confirmed. In this study, histological diagnosis of acute rejection was established in 40% of LD recipients within the first year after transplantation. This compares favorably with a recent report by Tejani et al[7] citing a 49% rejection rate in year 1, and 19% late (after 1 year) rejection rate following LD transplantation. Though the incidences of histological acute rejection occurring during the first 6 months were similar in our 2 groups, the time to first rejection was shorter in group 2, reflecting our increasing use of percutaneous renal biopsy of graft dysfunction evaluation. As all rejection episodes in group 2 were biopsy proven, this is likely a more accurate representation of the true rejection incidence in this group. The finding of fibrosis and long-term rejection changes on the initial biopsy specimens of several group 1 patients also suggests that diagnostic renal biopsy was underused in that group. That all of the graft losses in group 1 occurred later than 1 year after transplantation highlights the importance of long-term vigilant graft surveillance. Earlier recognition and more accurate histological assessment of severity of rejection have allowed more appropriate use of immunosuppression therapy and, in our opinion, account for the increased success in treatment of rejection. We have not realized the same 8.7% incidence of irreversible rejection reported by Tejani et al[7] in their study from the NAPTRCS database. Despite this explanation, we remain cognizant of the shorter follow-up period in group 2, and that these patients remain at risk for the development of chronic rejection and require ongoing surveillance.

CONCLUSIONS

Excellent short-term and long-term outcomes can be achieved in pediatric renal transplantation in high-risk infants and small children using LD kidneys. Surgical management using aggressive intravascular volume support and central vascular anastomoses is critical to maximizing renal perfusion and achieving good early renal function. Decreases in early graft loss from DGF or thrombosis may alone result in approximately 20% improvement in long-term graft survival. Advances in immunosuppression and vigilant clinical surveillance including percutaneous renal biopsy, however, are primarily responsible for the improved overall graft survival in this study.

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DISCUSSION

Oscar Salvatierra, Jr, MD, Palo Alto, Calif: Dr Healey and his coworkers are to be especially congratulated for the outstanding results achieved in the second cohort of 15 recipients since 1992 that have 100% patient and graft survival. One cannot do any better than that. To place these results in perspective, one needs to recognize that infants and small children comprise the highest risk and most difficult subgroup of patients nationally undergoing kidney transplantation with the worst first-year graft survival of any other age group. I fully agree with the authors that living-related transplantation is the optimum therapy for small children with renal failure since an LD provides the best potential not only for good graft and patient survival but also for optimum rehabilitation. In contrast, transplantation of size-compatible pediatric cadaver kidneys into small children provides the worst results in the entire field of kidney transplantation.

The tremendous size discrepancy incurred with transplantation of a LD adult-sized kidney into a small child presents a number of potential pitfalls. The technical challenges of finding proper placement for the adult-sized kidney and the anastomosis of the adult-size renal artery and renal vein to an infant or a small child's aorta and vena cava demand absolute preciseness. It is because of these difficulties that nationally 34% of LD grafts lost in infant recipients less than 2 years of age are lost early after transplantation for technical reasons with graft thrombosis leading the way at 24%. In the 2- to 5-year age group, there is also a high thrombosis rate accounting for 16% of graft loss.

With these considerations in mind, the Seattle group is to be applauded for not only their masterful technical skills but also their medical management of these infants and small children. With regards to medical management, I very much agree with the authors' intra- and postoperative aggressive fluid management to maintain optimum recipient intravascular volume. The importance of an aggressive fluid management approach can best be appreciated by recognizing that we are transplanting adult-sized kidneys with a large blood flow demand into infants and small children with small blood volumes, small hearts, and small blood vessels. We, therefore, agree with the authors that there is really little leeway for even the slightest hypotension with these infant recipients. Anything less than an aggressive fluid approach can result in a low flow state that would predispose to acute tubular necrosis, primary graft nonfunction, and worst of all, graft thrombosis.

I would very much be interested in knowing if the Seattle team utilizes supplemental nasogastric or gastrostomy tube feedings long-term postoperatively and for how long. When we performed our hemodynamic studies in infant recipients of adult-sized allografts, we demonstrated that an adult-sized kidney transplanted into an infant cannot achieve, even with maximum optimization of intravascular volume, more than two thirds of the blood flow present in this kidney prior to its removal from the living donor. Based on these studies, we have become more aggressive in continuing active hydration measures up to a year following transplantation. This has already resulted in a 50% improvement in GFR [glomerular filtration rate] at 1 year after transplantation.

As I read this article, I could not find major differences between our approach at Stanford University and that of the Seattle group with one exception, and that relates to the use of cyclosporine in the immunosuppressive protocol. We tend to go a little higher with our initial target trough blood levels of cyclosporine to approximately 350 to 400 ng/mL for the first 4 weeks following transplantation. And this in part may account for the lower incidence of acute rejection that we have seen.

The goal to obtain 100% graft survival in infants and small children is not unachievable as can be seen from the Seattle group's second cohort of patients. It also appears obvious to me from our own experience that the only way one can achieve these results is to have a closely integrated and experienced team of pediatric surgeons, pediatric nephrologists, pediatric anesthesiologists, and pediatric intensivists. The results of the Seattle and Stanford programs are a tribute to this integrated effort. I would greatly appreciate Dr Tapper's comments.

Dr Tapper: I want to thank the program committee for putting us on before Dr Salvatierra's paper, the title of which is "100% Survival." Dr Salvatierra has continually been the leader in pediatric transplantation. Two years ago he showed tiny incisions for doing a transplant, and tomorrow I think we will see a truly outstanding series. I really appreciate his continued teaching and also his support.

He asked basically 2 questions. One was related to long-term follow-up, and the other one was related to integrated efforts. With regards to long-term follow-up, in all of these children we have placed gastrostomy tubes at the same time that we place peritoneal dialysis catheters, and we continued the gastrostomy feedings. Now, as always, when you are working with Oscar, you always learn something, even today. I note that he is following up the children for about 1 year. We have not followed up the children that long. We have increased their intake volume to 2 to 2.5 L/d, but based on what his comments were I think we should begin to make certain that they continue to have this high volume further out. The other thing that I noticed was that, not to steal any of their thunder but our rejection episodes are a little higher than that at Stanford and it may be that they run their cyclosporin levels higher than we do and that is something that Pat and I need to look at.

With regard to an integrated effort, this is the only way surgeons can credibly run a major program. The second author on this article is Ruth McDonald. She is a transplantation physician; she is a nephrologist, and we work very closely with the intensivists in the intensive care unit. It gives us an opportunity for the surgical residents to learn how to do the pediatric anastomoses, the vascular procedure, the urologic reconstruction, and then work with a nephrologist and an intensivist in taking care of these patients. I do not think we could do the long-term follow-up and use the modern antirejection agents without having a major integrated effort.

Once again, I would like to thank Dr Salvatierra. It's an opportunity for me to thank Drs Lim and Blaisdell who taught me vascular surgery and Drs Salvatierra who taught me renal transplantation.

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