Kidney Transplantation in Children Younger Than 1 Year Using Cyclosporine Immunosuppression

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Objective
The optimal age for transplantation in children with end-stage renal disease remains controversial. Supported by national data, many centers recommend dialysis until the child reaches a certain minimum age. The authors’ policy, however, has been to encourage living donor (LD) transplants for young children, with no minimum age restriction.

Methods
Between January 1, 1984, and December 31, 1996, the authors performed 248 kidney transplants in children younger than age 13 years, using cyclosporine as the primary immunosuppressive agent. Recipients were analyzed in three age groups: group 1, younger than age 1 year (n = 26); group 2, age 1 through 4 (n = 92); and group 3, age 5 through 13 (n = 130). Almost all recipients in group 1 underwent a primary LD transplant. Therefore, to compare results more meaningfully among the three age groups, only primary LD transplants were analyzed (group 1, n = 25; group 2, n = 59; group 3, n = 58).

Results
In primary LD transplants, no significant difference was noted among the age groups in 1- and 5-year patient or graft survival rates. To date, all 25 recipients from group 1 are alive and well; 19 still have a functional original graft. Causes of graft loss in the remaining six recipients were chronic rejection (n = 3), vascular thrombosis (n = 2), and recurrent disease (n = 1). The incidence of acute rejection in group 1 recipients was lower than in the two older groups. However, the incidence of delayed graft function was slightly higher in the youngest group than in the two older groups.

For recipients in group 1, growth (as measured by weight) improved significantly posttransplant: the mean standard deviation score rose from −2.8 pretransplant to −0.2 by age 5 and to +1.8 by age 10. The improvement in height was not as dramatic: the mean standard deviation score rose from −3.2 pretransplant to −1.6 by age 5 and to −1.4 by age 10.

Conclusions
Kidney transplantation in young children, including those younger than 1 year old, can achieve results comparable to those in older children. As long as an adult LD is available, the timing of the transplant should be based on renal function rather than age.

Transplantation is the preferred treatment for children with end-stage renal disease, providing not only freedom from dialysis but also the best opportunity for growth and development. Patient and graft survival rates have improved substantially and are now similar to those seen for adult recipients. Several factors are responsible for these improved results, the most important being superior immunosuppressive drugs. With the routine use of cyclosporine-based immunosuppressive protocols, pediatric kidney transplantation has flourished.

However, not all pediatric age groups have enjoyed the same excellent results. Several analyses have shown that patient and graft survival rates are inferior and the number of surgical complications is increased for infants and young children.1,2 Thus, many centers have adopted a policy of waiting until the child reaches a certain minimum age before proceeding to a transplant.3 During this waiting time, the child is maintained on dialysis if needed.
Our center has had extensive experience with young recipients; we have performed more than 700 pediatric kidney transplants since 1963. Based on a previous analysis of our data, our policy (since 1978) has been not to impose any minimum age. The previous analysis demonstrated comparable results with young children (including those younger than 1 year old) given two conditions: the use of an adult living donor (LD) and maintenance immunosuppression with cyclosporine. To verify the validity of our policy, we undertook this review. We examined our results with kidney transplants in recipients younger than 1 year old versus older children since we started to use cyclosporine as part of our routine maintenance immunosuppressive regimen.

### METHODS

Between January 1, 1984, and December 31, 1996, 248 children 13 years old or younger underwent a kidney transplant at the University of Minnesota. We obtained data on these recipients from their transplant charts and from our computerized data base. Information collected included age at transplant, sex, donor source, transplant number, initial graft function, rejection episodes, causes of graft loss and patient death, and complications. We analyzed recipients in three groups, based on their age at transplant: group 1, younger than 1 year (n = 26); group 2, 1 through 4 years (n = 92); and group 3, 5 through 13 years (n = 130). Because all the recipients in group 1 underwent primary transplants, all but one with an LD, we compared outcomes of primary LD transplants only. We used the following endpoints: patient and graft survival rates; incidence of acute and chronic rejection; incidence of delayed graft function, as defined by the need for posttransplant dialysis; and complication rates.

The surgical technique for pediatric kidney transplants has been detailed previously. The procedure differs slightly in infants because the kidney is placed intraperitoneally. In contrast, a retroperitoneal approach is used in children weighing more than 20 kg. With intraperitoneal placement, the abdomen is entered through a midline incision and the ascending colon is reflected medially. The distal aorta, vena cava, iliac arteries, and iliac veins are all mobilized. Proximal occlusion is achieved with a vascular clamp, distal occlusion with vessel loops (thought to be less traumatic). The arterial anastomosis is performed to the distal aorta, the venous anastomosis to the distal vena cava. Intravascular volume must be adequate before removal of the occluding clamps and reperfusion of the adult donor kidney, which may sequester a significant amount of the recipient’s blood volume. The ureter is implanted into the bladder using a standard Leadbetter-Politano technique. We often stent the ureteral anastomosis with a 5F or 8F Silastic feeding tube for the first 7 days posttransplant.

Changes in our postsurgical immunosuppressive protocols over the last 30 years have also been detailed previously. Since the introduction and routine use of cyclosporine in 1984, our protocols in pediatric patients have not changed significantly. Immediately after the transplant, they receive azathioprine (5 mg/kg tapered to 2.5 mg/kg/day by posttransplant day 7), prednisone (2 mg/kg tapered to 0.5 mg/kg/day at 1 month, then to a maintenance dose of 0.25 mg/kg/day at 1 year posttransplant), and a polyclonal antilymphocyte preparation—previously Minnesota antilymphocyte globulin (MALG) and now antithymocyte globulin (ATG) (10 to 20 mg/kg/day for 14 days). Initially cyclosporine was not added until postsurgical day 10 to 12 (2.5 mg/kg twice a day). However, noting a high incidence of rejection with this sequential immunosuppressive protocol, we began introducing cyclosporine earlier (usually by post-surgical day 5), especially in the face of good graft function. Currently, cyclosporine levels (by high-performance liquid chromatography) are measured frequently and the dosage is adjusted to maintain a serum level of 150 to 200 ng/dl during the first 6 months posttransplant and 100 to 125 ng/dl after that. All suspected rejection episodes are confirmed with a biopsy and treated by recycling the prednisone taper and by administering an antilymphocyte preparation (MALG, ATG, or OKT3) for 10 to 14 days.

Minimum follow-up for patients included in this analysis was 12 months. Patient and graft survival rates were computed using Kaplan–Meier survival methods and compared among the age groups using a generalized Wilcoxon test. The incidence of both acute and chronic rejection was calculated. Other comparisons were made using the Student’s t test or a chi square test.
For recipients younger than 1 year at the time of transplant, we obtained data on growth (height and weight) by retrospective chart review. These data were converted to standard deviation scores (SDS) according to the following formula, based on previously published normal values for American children:

$$SDS = \frac{\text{patient value} - \text{mean value}}{\text{standard deviation}}$$

We calculated mean SDS at various times posttransplant and plotted them on a graph of time posttransplant versus age.

**RESULTS**

Of our 248 pediatric transplants, 26 were in children younger than 1 year (Table 1). On average, we performed two or three transplants per year in this youngest age group (Fig. 1). Our total represents roughly 30% of all U.S. transplants in recipients of this age (Table 2). Of our 26 transplants, all were primary and all but one were LD. Our two older pediatric groups involved more retransplants and cadaver transplants. Therefore, to compare results more meaningfully among the age groups, we analyzed only primary LD transplants (group 1, n = 25; group 2, n = 59; group 3, n = 58) (see Table 1).

Causes of renal failure in the 25 recipients in group 1 were obstructive uropathy (n = 10), congenital hypoplasia (n = 4), congenital nephrotic syndrome (n = 4), cortical necrosis (n = 2), polycystic disease (n = 1), oxalosis (n = 1), and unknown or other (n = 3).

To date, all 25 recipients from group 1 are alive and well. Patient survival at 5 years was not significantly different among the age groups (Fig. 2). Of these 25 recipients, 19 (76%) still have a functional original graft. Graft survival at 5 years was 86% in group 1, 82% in group 2, and 84% in group 3 (p = NS) (Fig. 3).

The incidence of acute rejection was significantly lower in group 1 than in the older groups (Fig. 4). One year after the transplant, the incidence of acute rejection was 16% in group 1, 51% in group 2 (p < 0.05), and 59% in group 3 (p = 0.04). Of the 25 recipients in group 1, 5 have had a single episode of acute rejection to date—4 early (<6 months posttransplant) and 1 later (>1 year posttransplant). All episodes were reversed with antilymphocyte therapy (used as primary treatment for rejection episodes in our

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**Table 2. PEDIATRIC KIDNEY TRANSPLANTS: REGISTRY (NAPRTCS) VS. U OF M (1987–1995)**

<table>
<thead>
<tr>
<th></th>
<th>&lt;1 Year Old (%)</th>
<th>1–4 Years Old (%)</th>
<th>5–13 Years Old (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S.</td>
<td>60</td>
<td>767</td>
<td>2171</td>
<td>2998</td>
</tr>
<tr>
<td>U of M</td>
<td>18</td>
<td>70</td>
<td>167</td>
<td>265</td>
</tr>
<tr>
<td>% U of M</td>
<td>30.0</td>
<td>9.1</td>
<td>7.7</td>
<td>8.5</td>
</tr>
</tbody>
</table>

NAPRTCS = North American Pediatric Renal Transplant Cooperative Study. U of M = University of Minnesota.
pediatric recipients). Similarly, the incidence of biopsy-proven chronic rejection was lower in group 1 than in the older groups (Fig. 5). At 5 years posttransplant, the incidence of chronic rejection was 16% in group 1, 37% in group 2 (p < 0.05), and 38% in group 3 (p < 0.05).

The incidence of delayed graft function was higher in group 1 than in the older groups: 12% in group 1, 6% in group 2 (p = NS), and 0.8% in group 3 (p < 0.05).

Six grafts were lost in group 1. Causes included technical failure (n = 2), chronic rejection (n = 3), and disease recurrence (n = 1). Causes of graft loss in the older groups are shown in Table 3. Other surgical complications in group 1 included relaparotomies for small bowel obstruction (n = 2), hematuria requiring cystoscopy (n = 1), and urine leak treated with stenting (n = 1). Infectious complications were common in this age group; within the first 6 months post-transplant, four recipients were treated for a respiratory infection, two for a urinary tract infection, and three for *Clostridium difficile* colitis.

Growth, as measured by height and weight, is presented in Figures 6 and 7 for group 1. Weight improved significantly after the transplant: the mean SDS rose from -2.8 pretransplant to -0.2 by age 5 and to +1.8 by age 10. The improvement in height was not as dramatic: the mean SDS rose from -3.2 pretransplant to -1.6 by age 5 and to -1.4 by age 10.

**DISCUSSION**

Although transplantation is the treatment of choice for the pediatric patient with end-stage renal disease, its application in the young recipient has not been as widely accepted. According to multivariate analysis from the North American Pediatric Renal Transplant Cooperative Study, the strongest risk factor for graft failure is recipient age younger than 2 years. Given this, some centers have adopted a policy of waiting until the child reaches a specific minimum age; during this time, the infant is usually maintained on dialysis. Based on our extensive experience with pediatric transplants, however, we think that the timing of transplant should be based on individual patient need rather than age.

Since January 1, 1984, we have transplanted close to 250 recipients ages 0 to 13. This represents nearly 10% of the

**Table 3. CAUSES OF GRAFT LOSS FOR DIFFERENT AGE GROUPS**

<table>
<thead>
<tr>
<th>Causes of Graft Loss</th>
<th>&lt;1 Year Old (%)</th>
<th>1-4 Years Old (%)</th>
<th>5-13 Years Old (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute rejection</td>
<td>0</td>
<td>2 (3.4)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Chronic rejection</td>
<td>3 (12)</td>
<td>6 (10.2)</td>
<td>7 (12.1)</td>
</tr>
<tr>
<td>Death with function</td>
<td>0</td>
<td>2 (3.4)</td>
<td>0</td>
</tr>
<tr>
<td>Recurrence</td>
<td>1 (4)</td>
<td>0</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Technical problems</td>
<td>2 (8)</td>
<td>1 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Discontinuation of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>1 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>12</td>
<td>10</td>
</tr>
</tbody>
</table>

* Performed at the University of Minnesota, 1984-1996.
Kidney Transplantation in Children Younger Than 1

Figure 7. Growth in weight, group 1 (<1 y.o.)

total number of transplants performed in children 13 years or younger in the United States. Of the total number of transplants performed nationally in recipients younger than 1 year, almost one third were performed at our center. Given our large volume of pediatric renal transplants, we have in place an experienced team of surgeons, pediatric nephrologists, anesthesiologists, radiologists, nurses, social workers, and others. Our team members are knowledgeable about the complete care of these challenging patients.

Based on previous analyses of our own data and data from other centers, we have three main recommendations for ensuring a successful outcome in young recipients:

1. Use an adult-sized kidney as opposed to a kidney from a pediatric donor.
2. Use an LD; even an unrelated LD kidney is preferred to a cadaver organ. Since 1984, we have performed only one cadaver kidney transplant in a recipient younger than 1 year, for an infant with oxalosis who received a combined liver-kidney transplant.
3. Use antilymphocyte induction, followed by triple immunosuppression for maintenance, including an agent such as cyclosporine.

If these three recommendations are followed, we think that young recipients can enjoy the same degree of success seen in older children. Our retrospective study specifically compared outcomes among three pediatric age groups. We found no significant differences in patient and graft survival rates between the groups. Specifically, all recipients younger than 1 year are currently alive and well; graft survival in this group was 92% at 1 year and 87% at 5 years.

Moreover, our recipients younger than 1 year actually had a significantly lower incidence of acute rejection than did the two older groups. Only 20% of these recipients had experienced an episode of acute rejection by 1 year posttransplant, and there were no graft losses secondary to acute rejection. The exact reason for the lower incidence of acute rejection is not clear; other studies have suggested that children, especially young ones, have an enhanced alloimmune response. We have previously shown that there is no increase in the incidence of acute rejection or an inability to reverse rejection episodes in younger recipients. It is possible that mild rejection episodes may not be as obvious in the younger recipients because of the presence of an adult kidney and the proportionally larger renal mass. The incidence of chronic rejection was also lower in our youngest group, most likely a reflection of the lower incidence of acute rejection. In our population, the most significant risk factor for chronic rejection is previous acute rejection.

Although our youngest recipients had a lower incidence of both acute and chronic rejection, they had a higher incidence of delayed graft function and graft loss secondary to vascular thrombosis. These two findings are both probably related to the smaller size of blood vessels and lower cardiac outputs in these recipients. With careful attention to surgical detail and perioperative care, these complications can be minimized. To maximize inflow to the kidney, we preferentially use the recipient’s abdominal aorta. It is important to ensure an adequate filling volume throughout the surgical procedure, using continuous central venous pressure monitoring. Such young recipients have a small circulating blood volume, a large portion of which can be sequestered by the reperfused adult donor kidney. Third-space losses, bleeding, and intraoperative vapor can also contribute to significant hypovolemia. To minimize hemodynamic instability when the clamps are removed, it is best to raise the central venous pressure before reperfusioning the kidney. These precautions have helped us to achieve a lower incidence of nontechnical graft thrombosis in young recipients than reported in other series. Nevertheless, the incidence remains higher than in older age groups. Some authors have recommended the use of intravenous heparin for the first few days posttransplant to decrease the incidence of graft thrombosis, however, we have not routinely used postsurgical anticoagulation.

Infectious complications were unfortunately common in our youngest recipients. In a previous multivariate analysis we showed that significant risk factors for infections in the first 6 months after the transplant were age younger than 2 years and prednisone treatment for acute rejection. All infectious episodes, however, were effectively treated. Because we have not noted a significant difference in overall results among the age groups, our approach has been to minimize dialysis therapy in light of its inherent complications, difficulties for the family, and expense. Our main concern is that dialysis therapy does not significantly arrest the growth failure and developmental delay that develops in these children secondary to uremia. Growth after a successful transplant is better than that seen with dialysis—not only physical growth, as measured by height and weight, but also neurologic growth, as measured by head circumference and formal assessment of cognitive development. As illustrated in Figures 6 and 7, our recipients
younger than 1 year demonstrated significant “catch-up” in growth immediately after the transplant, with growth velocities greater than those seen in normal infants of the same age. As the parent of one such recipient wrote: “Before the transplant he couldn’t walk, he wouldn’t eat—when you are in renal failure you have no appetite. He was fed through a tube. But after the transplant it was a whole new world—he blossomed, he grew, and he thrilled. After the transplant he was eating regular food.”

With long-term follow-up, our young recipients had significantly greater improvement in weight than in height. At age 10, most were 1 to 2 SDS above the national mean for weight but 1 SDS below it for height. Most likely this growth pattern is a side effect of long-term immunosuppression, probably prednisone. Major advances in immunosuppression, notably the introduction of cyclosporine, have in large part fueled the success of transplants in young recipients previously regarded as being at high risk.10 Our current regimen of induction with a polyclonal antilymphocyte agent (initially MALG and now ATG) and then maintenance with cyclosporine, azathioprine, and prednisone has led to a low incidence of acute rejection and a high graft survival rate. Nevertheless, the long-term morbidity of agents such as prednisone is significant. Recently there has been considerable interest in steroid-sparing protocols using newer agents such as tacrolimus or mycophenolate mofetil,26 which may allow for a significant decrease in or even elimination of long-term steroid use.

CONCLUSIONS

Our study confirms that equivalent results can be obtained in young pediatric recipients. With modern cyclosporine-based immunosuppression, good outcomes can be obtained even in recipients younger than 1 year. Every effort must be made to use an adult, LD kidney. An experienced team, familiar with the care of these challenging patients, is also critical. An early transplant is the treatment of choice for all pediatric patients with end-stage renal disease. The precise timing should be based on the recipient’s need, not age.

References


Discussion

DR. MARSHALL SCHWARTZ (Wilmington, Delaware): This series of renal transplants in children reported by Dr. Najarian and