The Outcome of 304 Primary Renal Transplants in Children (1968–1985)

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Of 304 children who received primary renal transplants at the University of Minnesota between January 1, 1968, and December 31, 1985, 48 (16%) were under the age of 24 months, 60 (20%) were 2–5 years old, and 196 (64%) were 6–17 years old at transplantation. Currently, 254 (84%) are alive at 2 months to 18 years following their first transplants, 77% with functioning grafts (188 first, 45 retransplants) and 7% on dialysis. Overall, patient and graft survival were not significantly different from the primary graft outcome of nondiabetic adults. The actuarial primary graft function rates at 1, 5, and 10 years were 100, 100, and 90% in 16 HLA-identical sibling kidneys; 84, 64, and 52% in 210 mismatched related kidneys; and 72, 54, and 47% in 78 cadaver kidneys ($p < 0.002$). The 1-year patient survival and primary graft function rates in 44 mismatched related recipients under the age of 24 months were 92 and 88%. The use of deliberate, pretransplant random blood transfusion since 1979 has been associated with a decreased rejection rate. Primary graft function of mismatched related kidneys in children receiving standard immunosuppression has significantly improved from 78% at 1 year in the pretransfusion era to 91% ($p < 0.01$) in the transfusion era. The overall primary cadaver graft function rate, however, did not improve in the transfusion era. Whether cyclosporine use will improve the cadaver renal allograft function in very young recipients remains to be established. However, with the use of related donors, even very young children can be transplanted safely and with excellent results.

TWENTY YEARS AGO the outlook for the child with end-stage renal disease (ESRD) was grim.[1] As recently as 1970, some physicians expressed the view that it would be kinder to both the parents and the child to let the child die rather than to prolong their suffering by unproven methods such as dialysis or renal transplantation.[2] Despite these early and difficult years, in the past 2 decades, we have established and built an aggressive pediatric hemodialysis and renal transplant program at the University of Minnesota.[3–7] The first pediatric renal transplant was performed in 1963, and by 1968 standardized surgical techniques for renal transplantation and immunosuppression, consisting of antilymphoblast globulin (ALG), azathioprine, and prednisone were adopted.[3,5]

From January 1, 1968, to December 31, 1985, 315 children between the ages of 6 months and 17 years received 380 renal transplants (304 first transplants, 76 retransplants) at the University of Minnesota (Fig. 1). We analyze the results of the 304 children who received primary renal transplants to examine their long-term outcome and causes of primary graft failures and deaths. We evaluated whether the recipient's ages at transplantation or the various immunosuppressive regimens used had an impact on graft function and patient survival. The outcome of retransplantation in children has been the subject of a recent report and will not be presented here.[7]

Materials and Methods

Patients

Forty-eight (16%) of the 304 children were under 24 months of age (0.5–1 yr) at the time of transplantation, 60 (20%) were between 2 and 5 years, and 196 (64%) were between 6 and 17 years of age. Sixteen received kidneys from HLA-identical siblings, 210 from HLA-mismatched relatives, and 78 from cadaver donors.

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The leading cause of renal failure (Fig. 2) in older children (6–17 years) was glomerulonephritis. For children transplanted before their second birthday, the primary cause was congenital hypoplasia–dysplasia, and between 2 and 5 years of age it was congenital nephrotic syndrome (Fig. 2). Forty-one children received renal transplantation for diseases, which can recur following transplant (20 with steroid-resistant nephrotic syndrome and focal segmental glomerulosclerosis, FSGS; 9 with hemolytic–uremic syndrome, HUS; 7 with type I hyperoxaluria, oxalosis; 3 with dense intramembranous deposit disease; and 2 with Wilms' tumor). Causes of ESRD, shown as the "other" category in Figure 2, included interstitial nephritis (2), IgA nephropathy (1), Wegner's granulomatosis (1), congenital renal tubular acidosis (1), and various congenital syndromes associated with nephropathies—Epstein (2), Cockayne (1), Drash (1), Jeune–Dwarf (2), and Senior (1).

Excluded from this study were two children who received combined kidney and liver transplants for alpha-1 antitrypsin deficienty and three children under 6 months of age, who were transplanted between 1968 and 1973.[3,4]

Recipient and Donor Selection

Our criteria for accepting children for transplantation are quite liberal.[8] Important relative or absolute contraindications to transplantation included active infection, active autoimmune disease (*e.g.*, active systemic lupus erythematosus, high levels of antiglomerular basement membrane antibodies), ABO incompatibility between recipient and donor, malignancy that cannot be brought under control, and debilitating, irreversible brain injury. Recipients with extrarenal congenital abnormalities such as coarctation of the aorta and anal agenesis have been accepted for transplantation after appropriate surgical treatment. All potential recipients undergo a thorough evaluation by a multidisciplinary team of pediatric nephrologists, surgeons, neurologists, psychologists, and social workers. Hepatitis B and pneumococcal vaccines are currently given prior to transplantation. Children with primary oxalosis are evaluated and managed, as described by Scheinman et al.[9]

The assessment of living related, ABO compatible, potential donors has previously been described.[8,10] Living donors with hypertesion were not used. Tissue typing and cross-matching techniques were performed, as previously described.[8] When cadaveric kidneys were used, an effort was generally made towards HLA-A,B matching, although HLA-A,B mismatched kidneys were regularly used. No attempt was made to match the recipient and donor at the HLA-D locus. However, transplantation was performed only when cross-matches were negative to the recipient's past and current sera.

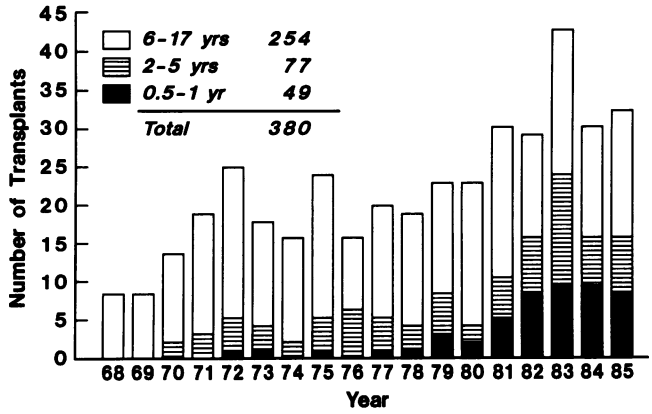


FIG. 1. The number of transplants performed in children each year and their ages at transplantation between January 1, 1968, and December 31, 1985, at the University of Minnesota. During this period, 315 children received 304 primary transplants and 76 second or multiple transplants. 0.5–1 yr represents children 6 to 23 months of age.

Operative Techniques

The surgical techniques and perioperative management, especially of small children, have previously been described in detail.[10,11] In brief, meticulous intraoperative monitoring of core temperature with a rectal probe, central

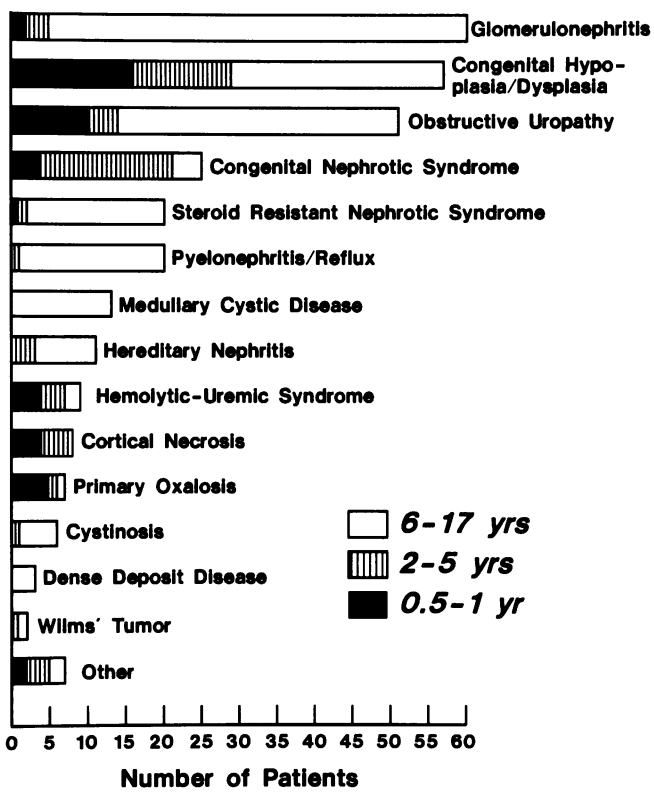


FIG. 2. The etiology of end-stage renal disease (ESRD) and the ages at transplantation in 304 pediatric recipients of primary renal allografts. 0.5–1 yr represents children 6 to 23 months of age.

venous pressure through a central line or a Hickman catheter, and accurate monitoring of arterial blood pressure and posttransplant urine output are mandatory. It is prudent to raise the central venous pressure to 12–18 cm H_2O just prior to releasing the vascular clamps to compensate for the volume required to perfuse the transplanted kidney.

In recipients weighing over 17 kg, the extraperitoneal operative approach is used for either a pediatric cadaver kidney or an adult donor kidney. In children weighing less than 17 kg, adult kidneys are transplanted through a transperitoneal midline incision; the cecum is mobilized, and the aorta and vena cava are dissected free. The donor renal vein is anastomosed to the side of the recipient's distal inferior vena cava or common iliac vein, and the donor renal artery is anastomosed to the side of the aorta or the common iliac artery. The donor ureter is implanted into the bladder using the Leadbetter–Politano ureteroneocystostomy technique.[10]

Unilateral or bilateral nephrectomies are performed when indicated. Right atrial Silastic® or Hickman catheters placed in infants before operation for dialysis access have greatly facilitated their perioperative dialysis management.[12–14]

Immunosuppression Protocols

Apart from the introduction of deliberate pretransplant random blood transfusions in 1979, the immunosuppression protocol used in most children between January 1968 and June 1984 was fairly standard.[7,8,10] In brief, azathioprine (5 mg/kg/day) was begun on the day of transplantation and tapered to a maintenance dose of 2.5 mg/kg/day; prednisone was started at 2 mg/kg/day and tapered to a maintenance dose of 0.25–0.3 mg/kg/day by 1 year after transplantation. Minnesota antilymphoblast globulin (ALG) was given for the first 14 postoperative days at 30 mg/kg/day, and methylprednisolone was given at 20 mg/kg for the first 3 postoperative days. The 16 children who recieved kidneys from HLA-identical siblings received a lower dose of ALG at 20 mg/kg/day and a lower dose of prednisone starting at 1 mg/kg/day. Acute rejection episodes were generally documented by percutaneous biopsy and treated by increasing the oral prednisone dose back to 2 mg/kg/day, followed by a tapering schedule. A 10-day course of ALG at 20 mg/kg/day was often added to treat first injection episodes. An identical immunosuppressive schedule was generally followed in retransplantation, but, more recently, several children received fractionated total lymphoid irradiation or cyclosporine (CSA).[7] The protocols for these regimens have previously been described.[15,16] Transplant nephrectomy was not routinely performed unless the patient developed graft tenderness, toxic systemic symptoms, hyperacute rejection, severe hypertension, or unless the graft was removed to expedite the management of infection. When the initial graft was not removed, low dose immunosuppression was usually continued until the patient was retransplanted.[7]

Splenectomy was routinely performed in almost all patients prior to 1984. Because of the increased risk of overwhelming sepsis following splenectomy[17–19] and our failure to document the long-term beneficial effect of splenectomy on graft function,[20] the practice of routine pretransplant splenectomy was abandoned in June 1984. Following transplantation, all children receive daily oral trimethoprim–sulfamethoxazole to prevent *Pneumocystis carinii,* Nocardia, Listeria, and Legionella infections. Splenectomized children are also placed on daily phenoxymethyl penicillin to minimize the risk of overwhelming, postsplenectomy sepsis.[21] Oral nystatin is always prescribed during the immediate posttransplant period and during treatment of rejection to minimize the risk of opportunistic fungal infection.

On June 20, 1984, a prospective nonrandomized trial was begun comparing the results of donor-specific transfusion (DST) with a protocol consisting of standard immunosuppression plus low dose CSA. Only children with two or more acceptable mismatched related donors are considered for DST. This criteria was arbitrarily established so that the child sensitized to one donor by DST can still be transplanted without delay, if an alternate related donor is available. Instead of receiving random blood transfusions, children on the DST protocol receive three transfusions from the potential donor (3 ml/kg of packed cells) given over 2 weeks on days 0, 7, and 14. Azathioprine is given (2 mg/kg/day) beginning 1 week prior to the first transfusion and continued until transplantation, which is usually 4–6 weeks following the last transfusion. Following transplantation, the children receive standard immunosuppression, identical to the protocol previously described, except that the dose of azathioprine is maintained at 2 mg/kg/day.

Recipients of mismatched related kidneys who are not on the DST protocol and recipients of cadaver kidneys are given standard immunosuppression plus low dose CSA.[22] These patients are started on oral CSA at 6 mg/kg/day on the 10–12th postoperative day, at a time when the patients all had good renal function (creatinine below 1.0 mg/kg). Then every 30 days, the CSA dosage is reduced by 1 mg/kg until the patient is weaned entirely from the drug or until an episode of rejection occurs. If rejection is suspected, the patient undergoes percutaneous transplant biopsy to confirm the diagnosis. When rejection is demonstrated, the dose of CSA is increased 1–2 mg/kg and the patient is treated with additional steroids. Trough CSA levels are determined by whole blood HPLC.[23] We compared the pediatric transplant experience with the results of 493 nondiabetic adults who received primary renal

transplants during the same 18-year period. The immunosuppression used in adults was the same as in children, but cyclosprine was used in most adults transplanted since 1981.[16,24]

Data Analysis

All 304 children were studied 2 months to 18 years following their primary renal transplants. All deaths, including patients who died after returning to maintenance dialysis, are included in the analysis. Graft failures are defined as the return of the patient to dialysis, transplant nephrectomy, or patient death, even if the graft was functioning at the time of death. Actuarial graft and patient survival rates were obtained by life table analysis, and Gehan's test was used for statistical comparison.[25]

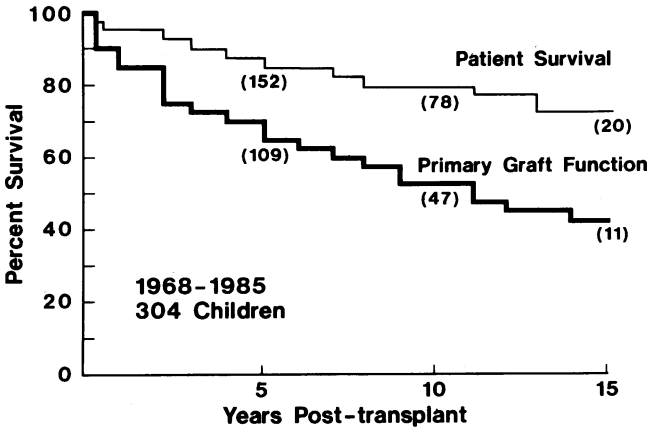


FIG. 3. Combined actuarial primary graft function and patient survival in 304 children. The number of patients at risk at the various time intervals is shown.

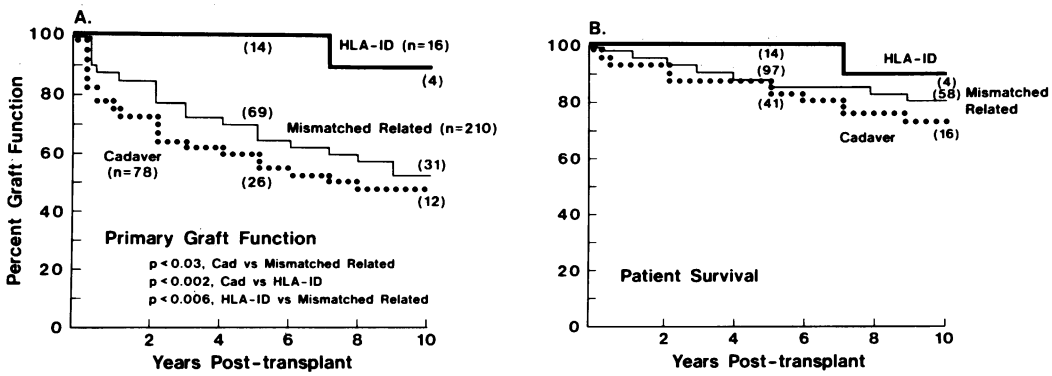
Results

Primary graft function rates in the 304 children at 5, 10, and 15 years were 64, 53, and 43%, and patient survival rates were 85, 79, and 74 (Fig. 3). Children who received HLA-identical sibling kidneys achieved, by far, the best results. Primary graft function and patient survial rates were 100, 100, and 90% at 1, 5, and 10 years, respectively (Figs. 4A and B). Children with mismatched related kidneys had a significantly better primary graft function than children who received cadaver kidneys ($p < 0.03$). The 1-, 5-, and 10-year primary graft function rates were 84, 64, and 52% for mismatched related kidneys, and 72, 54,and 47% for cadaver kidneys (Fig. 4A). Patient survival for recipients of cadaver kidneys and mismatched related kidneys was not significantly different. Patient survival rates at 1, 5, and 10 years for mismatched related and cadaver kidneys were 95, 85, and 81%, and 95, 84, and 73%, respectively (Fig. 4B).

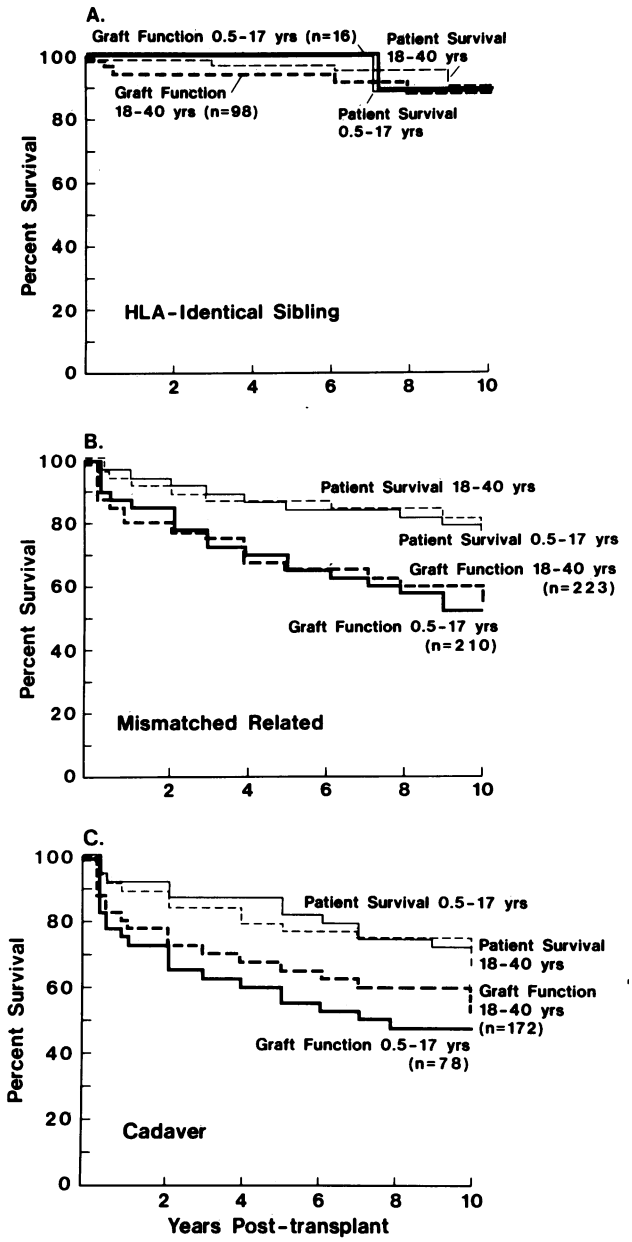
The results of 39 cadaver kidneys matched for two or more HLA-A,B antigens were compared with the outcome of 39 cadaver kidneys that were completely mismatched or matched for only one HLA-A,B antigen, in order to assess whether tissue matching affected primary cadaver graft outcome in children. Primary graft function at 1 and 5 years for 0–1 HLA-A,B antigen matched cadaver kidneys was 79 and 57%, compared with 66 and 51% for cadaver kidneys matched at 2–4 HLA-A,B antigens. These differences were not significant. Patient survival rates were essentially identical in both groups.

Comparing the Results in Children Versus *Nondiabetic Adults*

The primary graft function and patient survival rates of the 304 children were compared with 493 nondiabetic adults, ages 18–40 years, transplanted at the University of Minnesota between January 1, 1968, and December 31, 1985 (Fig. 5). This group of adults was chosen because their results probably represent the best in the adult transplant population. Living related transplants in children had essentially the same patient and graft function rates as in young, nondiabetic adults (Figs. 5A and B). Similarly, cadaver transplantation in children and adults has the same patient survival (Fig. 5C). However, adults with cadaver kidneys tended to have a slightly better primary graft function rate than children who received cadaver kidneys, although the differences were not significant (Fig. 5C). The primary graft function rates at 1 and 5 years



FIGS. 4A and B. Long-term primary graft function (*A*) and patient survival (*B*) in 16 children with HLA-identical sibling kidneys, 210 with HLA-mismatched related kidneys, and 78 children with cadaver kidneys. N represents the total number of patients in each group.



FIGS. 5A–C. Comparison in primary graft function and patient survival between children (0.5–17 years) and nondiabetic adults (18–40 years) by the source of donor kidneys: HLA-identical sibling (*A*), mismatched related (*B*), and cadaver (*C*).

were 78 and 66% in nondiabetic adults, compared with 72 and 54% in children.

Effect of the Child's Age at Transplantation

The data comparing the results of children transplanted under the age of 24 months (0.5–1 year) with children ages 2–5 years and 6–17 years were analyzed to determine the safety and outcome in transplanting very young children. The 1-year patient survival rate for children aged 0.5–1, 2–5, and 6–17 years were 92, 95, and 95% for mismatched related kidneys, and 100, 85, and 95% for cadaveric kidneys (Figs. 6B and D). The 1- and 5-year graft function rates in 44 mismatched related allografts in children under 24 months were 88 and 67% and were not significantly different from the results in older children (Fig. 6A). The number of children less than 2 years of age transplanted with cadaver kidneys was too small to analyze.

The Effect of Era on Graft Outcome

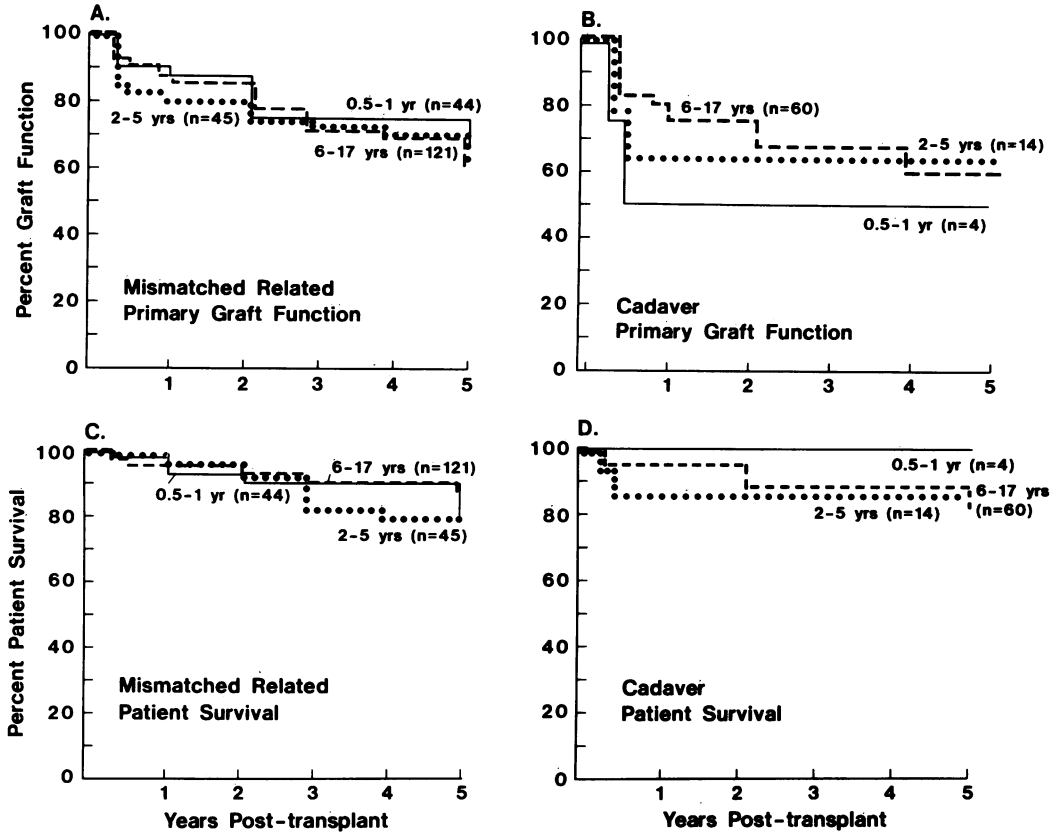
To better assess the current risk–benefit relationship of primary renal transplantation in children, we analyzed the results by eras. We compared the results of the most recent experiences using DST or low dose CSA (June 20, 1984–December 31, 1985; era 3) with the earlier experiences with standard immunosuppression either prior to the use of deliberate pretransplant random transfusion (January 1, 1968–July 31, 1979; era 1) or after the adoption of a transfusion policy (August 1, 1979–June 19, 1984; era 2).

Primary mismatched related graft function improved in both transfusion eras (eras 2 and 3) (Fig. 7A). The 1- and 5-year primary graft function rates in era 2 were 92 and 77%, compared with 78 and 56% in era 1 ($p < 0.01$). The 1-year graft function in era 3 was 89%, and none of the mismatched related recipients who received DST (14) or low dose CSA (14) lost their grafts because of rejection or infection. The incidence of sensitization following DST in 15 children was 7% (1/15). In all three eras, patient survival rates following mismatched related transplants were virtually identical. The 1-year patient survival rates were 93% in era 1, 95% in era 2, and 100% in era 3 (Fig. 7C).

A change in transfusion policy, however, did not improve the overall cadaver graft outcome in children on standard immunosuppression (Fig. 7B). The 1-year primary graft function rates for eras 1 and 2 were 73 and 70%, respectively, and patient survival rates were 95 and 97%. The recent experience (era 3) with low dose CSA, although limited to seven pediatric cadaver recipients (four children 1–5 years old and three children 10–11 years old), has been encouraging (Fig. 7B). Apart from one child who died from a technical complication on the first postoperative day, the other six children are alive with excellent graft function.

Causes of Primary Graft Failure

The causes of primary graft failure are shown in Table 1. Of the 304 primary renal allografts, 116 (38.2%) have lost function. Seventy-three (24%) were rejected, 16 (5.3%) patients developed recurrent disease, and 10 (3.3%) were lost due to nonseptic deaths in patients with functioning



FIGS. 6A–D. The effect of the age of the children at renal transplantation on graft function and patient survival in mismatched related (*A* and *C*) and cadaver primary allografts (*B* and *D*).

grafts. Only 18 (5.9%) of the 304 first renal allograft failed because of deaths from sepsis, technical failures, primary graft nonfunction, or due to the development of a viral associated lymphoma.[26] The natures of the eight technical failures were as follows: two had primary renal vascular thrombosis; two grafts were lost to complications associated with attempts to repair transplant renal artery stenoses by balloon angioplasty or surgery; three developed urinary leaks, one from an ileal bladder; and one patient died following an inadvertent enterotomy.

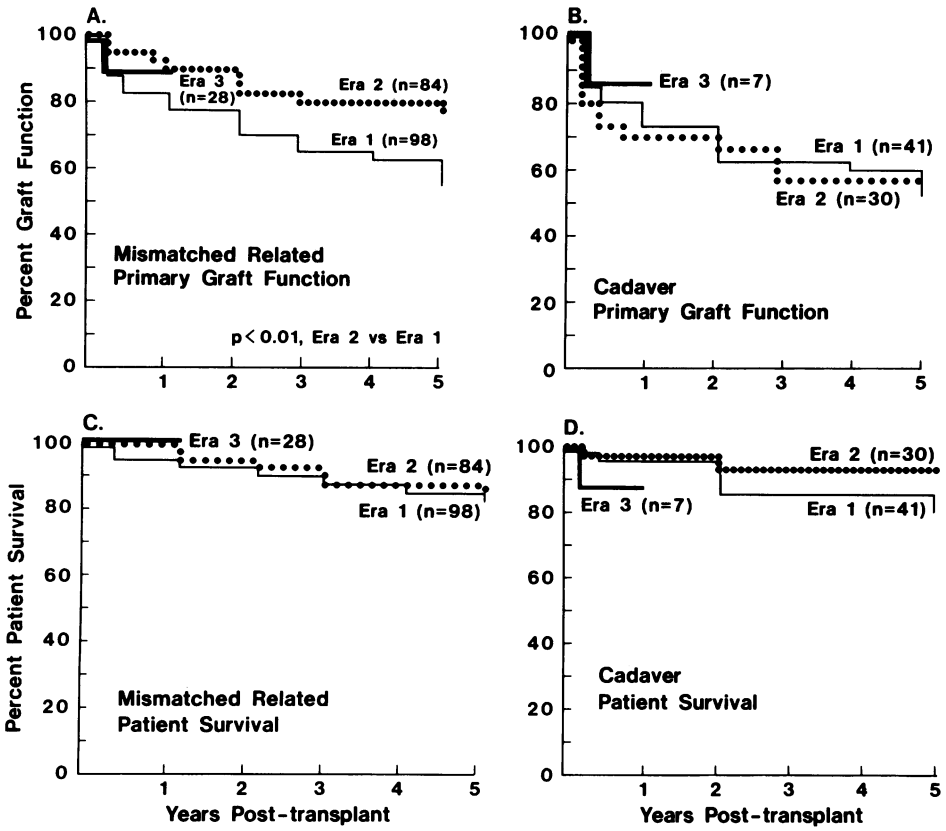
Recurrence of the primary disease was confirmed by biopsy samples taken from the allograft and was the second most common cause of graft loss. Children with primary oxalosis and dense intramembranous deposit disease (DIDD) had the highest incidence of graft loss from recurrence. Five out of seven primary grafts (71%) in children with primary oxalosis and two out of three grafts (67%) in children with DIDD failed because of recurrence. One child with DIDD has retained good graft function for 18 years, despite histologic evidence of recurrence. Six of the 20 children (30%) with focal segmental glomerulosclerosis and steroid resistant nephrotic syndrome and three out of nine children (33%) with hemolytic–uremic syndrome also lost their primary grafts because of recurrence. The two children whose native kidneys were removed because of Wilms' tumor died because of septic and technical complications, but recurrent tumor was found in both at autopsy.

Analysis of the causes of primary graft failures by era and interval shows that the improved survival of mismatched related allografts in era 2 was largely due to the marked reduction in the number of grafts lost to rejection (Table 2). In fact, recurrent disease has become the principal cause of failure in mismatched related primary allografts in the transfusion era. The causes of primary cadaver graft failures are shown in Table 3. Although overall cadaver graft function rates did not improve in era 2 (Fig. 7B), transfusion may have had a beneficial effect in lowering the incidence of loss of cadaver grafts to rejection (Table 3). In era 3, thus far, none of the mismatched related or cadaveric allografts in patients receiving either DST or low dose CSA have been lost to rejection.

Outcome of 304 Children

The outcome of 304 children studied 2 months to 18 years following their first kidney transplants is summarized in Table 4. Two hundred fifty-four patients (84%) are alive: 233 (77%) with functioning grafts (188 primary grafts and 45 retransplants), and 21 (7%) on maintenance dialysis following one or more transplant operations.

Fifty (16%) of the 304 children have died. Fourteen



FIGS. 7A–D. The effects of changes in immunosuppressive regimen and experiences gained with time on graft function and patient survival of mismatched related (*A* and *C*) and cadaver primary allografts (*B* and *D*). The data compare children who received ALG + azathioprine + prednisone without deliberate pretransplant random blood transfusion (January 1, 1968–July 31, 1979, or era 1), with children who received random blood transfusion (August 1, 1979–June 19, 1984, or era 2), and the most recent protocols of using either donor specific transfusion or low dose cyclosporine in addition to ALG + azathioprine + prednisone (June 20, 1984–December 31, 1985, or era 3).

(4.5%) died within the first 6 months following transplantation from septic and nonseptic complications—nine (3%) following the first transplant, and five following the second to fifth transplants. Four children died of uremia when, respecting the parents wishes, they were withdrawn from dialysis or not placed on dialysis after losing primary graft function (3 were children with primary oxalosis). Twelve died on maintenance dialysis (10 after losing their first grafts and 2 after failure of their retransplants) from the following causes: cardiac arrest due to hyperkalemia or aspiration, or some uncertain etiology (7); postsplenectomy overwhelming *Hemophilus influenzae* or *Escherichia coli* sepsis (2); cryptococcal and staphylococcal lung abscess (1); suicide (1); and hypertensive encephalopathy with intracerebral hemorrhage (1).

TABLE 1. *Causes of Primary Renal Allograft Failure in Children*

	N	(%)
1. Rejection (including 2 from noncompliance, 1 following withdrawal of therapy for cytomegalovirus infection)	73	(24)
2. Recurrent disease (6 steroid resistant nephrotic syndrome, 5 oxalosis, 3 hemolytic-uremic syndrome, 2 dense deposit disease)	16	(5.3)
3. Patient deaths		
(a) Sepsis (3 cytomegalovirus, 2 postsplenectomy overwhelming bacterial sepsis, 1 varicella, 1 virus associated lymphoproliferative disease)	7	(2.3)
(b) Nonseptic causes (3 traffic accidents, 1 heart block, 1 metabolic, 1 anesthetic accident, 1 pancreatitis, 1 intracerebral hemorrhage, 2 complications of exploratory laparotomy)	10	(3.3)
4. Technical failures (4 vascular, 3 urologic, 1 bowel perforation)	8	(2.6)
5. Primary nonfunction	2	(0.7)
Total	116/304	(38.2)

Twenty children (6.5%) died with functioning grafts (13 primary grafts and 7 retransplants) and their causes of death are shown in Table 5. Overwhelming pneumococcal or gram-negative sepsis after splenectomy, characterized by death within 72 hours of clinical presentation, occurred in four children and was the most common cause of death in children with functioning grafts (Table 5). Three children also died of Epstein–Barr virus associated lymphoproliferative disease, two of them after the use of total lymphoid irradiation for retransplantation.

Discussion

Although most children with ESRD can now be kept alive with maintenance dialysis, renal transplantation is

TABLE 2. *Causes of Primary Mismatched Related Allograft Failure in Children Analyzed by Era and Interval Following Transplantation*

	Era 1 (1/68–7/79) N = 98		Era 2 (8/79–6/19/84) N = 84		Era3 (6/20/84–12/85) N = 28	
Interval after transplant	≤1 yr	>1 yr	≤1 yr	>1 yr	≤1 yr	>1 yr
Rejection	20	25*	3†	1	0	0
Recurrent disease	1	3	2	5	2	0
Septic deaths						
Cytomegalovirus	1	0	0	0	0	0
Overwhelming postsplenectomy sepsis	0	0	1	0	0	0
Varicella	0	1	0	0	0	0
Virus associated lymphoproliferative disease	0	1	0	0	0	0
Nonseptic deaths						
Traffic accidents	0	1	0	1	0	0
Other causes***	0	3	0	2	0	0
Technical	2	—	1	—	1	—
Primary nonfunction	0	—	1	—	0	—
Total	24	34	8	9	3	0

* Two were from noncompliance.
† One from withdrawal of immunosuppression for cytomegalovirus infection.
*** Listed in Table 1.

the best long-term treatment and provides the child with the best chance for a normal life-style and the optimal potential for growth and development.[8,27–32]

Our results demonstrate that the long-term graft outcome and patient survival of primary renal transplantation in children is very good and is not significantly different from our experience with young nondiabetic adults between 18 and 40 years of age (Fig. 5). Primary graft function rates are comparable with the 10-year survival rates reported by two other pediatric centers. The group in San Francisco reported 10-year actuarial primary graft function of 55% in 60 HLA-identical and mismatched related kidneys and only 31% in 85 primary cadaver allografts.[33] On the other hand, the group from Toronto reported 10-year actuarial primary graft function of 59% in 78 cadaveric allografts in children.[34]

Children who received HLA-identical sibling kidneys had the best graft and patient survival (Fig. 4A). In fact, only one of 16 primary HLA-identical sibling allografts was lost; the recipient died in a traffic accident 7 years following transplantation. The primary graft outcome of mismatched related transplants in children was significantly better than cadaver kidneys. There was a trend, however, for both cadaver and mismatched related graft

TABLE 3. *Causes of Primary Cadaver Allograft Failure Analyzed by Era and Interval Following Transplantation*

	Era 1 (1/68–7/79) N = 41		Era 2 (8/79–6/19/84) N = 30		Era 3 (6/20/84–12/85) N = 7	
Interval after transplant	≤1 yr	>1 yr	≤1 yr	>1 yr	≤1 yr	>1 yr
Rejection	6	13	3	2	0	0
Recurrent disease	0	1	2	0	0	0
Septic deaths						
Cytomegalovirus	2	0	0	0	0	0
Overwhelming postsplenectomy sepsis	0	0	0	1	0	0
Nonseptic deaths						
Metabolic	0	0	1	0	0	0
Anesthetic accident	0	1	0	0	0	0
Technical	2	—	1	—	1	—
Primary nonfunction	0	—	1	—	0	—
Total	10	15	8	3	1	0

TABLE 4. *Outcome of 304 Children Receiving Primary Renal Allografts (1968–1985)*

	N	(%)	
Alive	254	(84)	
	233	(77)	Have functioning grafts (188 first, 45 retransplants)
	21	(7)	On dialysis (13 after 1st transplant, 8 after retransplants)
Deaths	50	(16)	
	16	(5)	Occurred in patients without graft function while on maintenance dialysis or following withdrawal from therapy (14 after 1st transplant, 2 after retransplant)
	20	(6.5)	Occurred in patients with functioning grafts
	14	(4.5)	Occurred within 6 months posttransplant following 9 first and 5 retransplants from septic and nonseptic complications (6 technical, 4 cytomegalovirus, 1 hypocalcemic cardiac arrest, 1 lymphoma, 1 bleeding gastric ulcer, 1 ruptured kidney from hyperacute rejection)

function to decline gradually with time (Fig. 4A), so that by 10 years after transplantation the overall graft function of mismatched related kidneys approached that of cadaver kidneys (Fig. 4A). Analysis of graft loss occurring more than 1 year following transplant (Tables 2 and 3) showed that chronic rejection largely accounted for the gradual decline in both mismatched related and cadaver graft survival in the pretransfusion era.

TABLE 5. *Causes of Death in 20 Children Who Died with Functioning Grafts (13 Primary Grafts, 7 Retransplants)*

Traffic accident	3
Lymphomas (2 following total lymphoid irradiation for retransplantation)	3
Infection	
Overwhelming postsplenectomy pneumococcal or gram-negative sepsis	4
Chickenpox	1
Fulminant hepatitis B	1
Heart block	1
Idiopathic chronic pulmonary fibrosis in a child with cystinosis	1
Intracerebral hemorrhage (bleeding diathesis)	1
Gastrointestinal causes	
Perforated left colon	1
Small bowel obstruction	1
Pancreatitis	1
Inadvertent enterotomy on abdominal exploration for abdominal pain	1
Anesthetic accident (inguinal hernia repair)	1
Total	20

Since the institution of random blood transfusion before transplantation (era 2), there has been a dramatic decrease in the rate of rejection of mismatched related grafts and, thus, a significant improvement in mismatched related primary graft function (Table 2, Fig. 7A). Only four of the 84 mismatched related transplants in era 2 were rejected (1.5–6.5 years following transplantation). Mismatched related graft outcome was also excellent in the 28 children who received either DST or low dose CSA in era 3. The 1-year graft function in era 3 was 89% and not a single graft has been lost to rejection 3 months to 1.5 years following transplantation (Table 2, Fig. 7A). In this center, recurrence of the original disease is the major cause of graft failure in children with mismatched related kidneys in the transfusion era (Table 2).

Era 2, defined by the use of pretransplant transfusion, was not associated with an improvement in the overall cadaver graft outcome of children receiving standard immunosuppression (Fig. 7B), but, since fewer cadaver allografts were lost to rejection (Table 3), the transfusion strategy may have been helpful. In addition, matching between the recipient and donor at the HLA-A or B locus did not influence the primary cadaver graft function in this series of 78 cadaver transplants in children.

Recently, we have designed an immunosuppressive protocol using low dose CSA combined with standard immunosuppression. This new protocol is based on our current adult regimen, which has achieved a 89% 1-year cadaver graft function.[24] Our results, although preliminary, are encouraging. Apart from the patient who died of a technical complication, the other sick cadaver allografts have excellent function at 3 months to 1.3 years.

Recurrence of the original disease in the transplanted kidney has become the leading cause of graft failure in children receiving mismatched related kidneys in the transfusion era (Table 2). These include primary oxalosis, dense intramembranous deposit disease, HUS, and FSGS with steroid resistant nephrotic syndrome. The long-term outcome of dialysis treatment when primary oxalosis is the cause of renal failure, however, is particularly grim.[9,35] Based on earlier reports that long-term graft function is possible, we have transplanted seven children with this disease.[9,36–38] Five of seven primary grafts were lost to recurrence, and three of the children have died following withdrawal from further treatment. However, four children are currently alive and well: two with functioning primary grafts at 3 and 5 years, and two with successful retransplants. Nonetheless, it should be clearly understood that the management of children with renal failure from oxalosis is extremely complex and difficult.

Dense intramembranous deposit disease (or type II membranoproliferative glomerulonephritis) invariably recurs in the transplanted kidney, but it was said that this seldom leads to graft failure.[39,40] In contrast, two thirds of the primary grafts in our patients with this disease have been lost to recurrence.[40]

The true incidence of recurrence following transplantation in children with HUS is unknown,[41,42] but, in nine children receiving primary allografts, three (33%) were lost to recurrent HUS. Although CSA has been reported to cause glomerular capillary thrombosis and even an HUS-like syndrome,[43,44] none of these nine received CSA. Currently, all HUS patients receive antiplatelet agents shortly after transplantation to minimize the risk of recurrence, but the effectiveness of this form of therapy has not been proven.

In the present study, the incidence of graft failure from recurrent FSGS in children with steroid resistant nephrotic syndrome following transplantation is 30% (6/20), which is similar to the 20% (5/24) reported by Habib et al.[45] In two recent reviews, Striegel et al.[46] and Hebert et al.[41] describe the clinicohistologic findings of these children with recurrent HUS and FSGS at the University of Minnesota.

Our results show that renal transplantation can be performed safely in children. Within the first 6 months following the first transplant, only 3% of the children have died from septic and nonseptic causes, compared with 5% who died on dialysis or following withdrawal from dialysis, and 6.5% who died with functioning grafts from a variety of causes, including traffic accidents. Postsplenectomy overwhelming sepsis accounted for six deaths (2%) and was a major cause of late deaths in young kidney recipients who were often otherwise healthy. In all cases, the clinical presentation characterized by acute death within 72 hours of symptoms was similar to the cases reported by Cerilli et al.[17] and McEnery et al.[18] The ages of the children ranged from 3 to 11 years. Pneumococcus was cultured in three children, *H. influenzae* in one, *E. coli* in one, and an unidentified gram-negative organism was found in the cerebrospinal fluid in one child. In view of the high risk of exposing the children to overwhelming septic death and because splenectomy did not improve long-term graft function,[20] we have abandoned the practice of routine pretransplant splenectomy. Furthermore, all the children who have been splenectomized should receive pneumococcal vaccination and daily oral phenoxymethyl penicillin in addition to trimethoprin–sulfamethoxazole for life, to minimize the potential for overwhelming sepsis. Although the effectiveness of chemoprophylaxis has not been proven in the postsplenectomized transplant population, noncompliance or temporarily withholding the antibiotics for other reasons seems to have contributed to several of the septic deaths. In fact, there were no deaths from overwhelming bacterial sepsis in any of our patients who were receiving both antibiotics.

This study confirms our earlier reports that young children, and even infants under the age of 1 year, can be transplanted safely, and graft outcome of living-related transplants in young children is extremely good.[20,51,52] This contradicts repeated reports that renal transplantation in children under 5 years of age, and especially those under 24 months, results in lower patient and graft survivals.[47–50]

Our 1-year patient survival and primary graft function rates in 44 children between the ages of 6 and 24 months, who received primary mismatched related allografts, were 92 and 88% (Figs. 6A and C). Growth following transplantation in very young children is also encouraging. In a study of the growth pattern in six boys under the age of 1 year,[53] we found that the mean increment in the height standard deviation score, 2–7 years following transplantation, was +1.4, and all had normal head circumference (five were microcephalic before transplantation).

In conclusion, renal transplantation in infants and children is at least as successful as in nondiabetic young adults. As immunosuppression has become increasingly sophisticated, renal losses from rejection have diminished. As a conseqeunce, recurrence of original disease has become relatively much more important in influencing graft outcome. One positive note for children, as transplant candidates, is the dominance of nonrecurrent diseases as causes of renal failure. Nonetheless, fundamental research in disease pathogenesis appears to be a vital next frontier.

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