

Original article

Complications by age in primary pediatric renal transplant recipients

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Abstract. We asked whether pediatric renal transplant recipients, subgrouped by age, differed in the percentage and number of hospital readmissions and in the incidence of infectious complications post transplant. Between 1 August 1985 and 31 October 1993, a total of 164 patients <18 years of age underwent primary transplants, with cyclosporine-based immunosuppression, at the University of Minnesota. The percentage of readmissions ($P = NS$), the mean number of readmissions ($P = NS$), and the length of hospital stay during readmission ($P = NS$) did not differ significantly among age groups. The overall incidence of acute rejection was greater in those ≥ 2 years than those <2 years ($P = 0.002$), and in living donor recipients ≥ 2 years versus those <2 years ($P = 0.02$). The incidence of bacterial infection (<2 years, 87%; 2–5 years, 72%; 6–12 years, 51%; 13–17 years, 40%) was greater in younger recipients ($P = 0.0001$). The most common bacterial infection in recipients ≤ 5 years was *Clostridium difficile*-associated diarrhea; in those >5 years, urinary tract infection. The overall incidence of viral infection did not differ among groups ($P = NS$). The most common viral infection in recipients ≤ 5 years was varicella and those >5 years, cytomegalovirus infection. Risk factors for infection in the first 6 months post transplant included age <2 years and Solu-Medrol treatment for acute rejection. In conclusion, young recipients <2 years of age at the time of transplant are at a higher risk for bacterial infection post transplant.

Key words: Renal transplantation – Hospital readmissions – Infections

Introduction

Studies of pediatric renal transplantation have focused on graft and patient survival as well as on growth. Recent data

suggest that, overall, survival is improving. Some studies report poorer survival rates in infants and young children than in older children [1–4]; however, we and others have noted rates equivalent to those of older children and adults [5–8]. In this study, we asked whether pediatric renal transplant recipients, subgrouped by age, differed in the percentage and number of hospital readmissions and in the incidence of infectious complications post transplant.

Patients and methods

Between 1 August 1985 and 31 October 1993, a total of 164 patients <18 years of age (106 male, 58 female) underwent primary transplants at our center. We chose this time span because our cyclosporine (CSA) protocol was stable during this period. Of the 164 grafts, 130 were from living related donors (LRD), 33 cadaver donors (CAD), and 1 living unrelated donor. The term living donor (LD) was used to combine living unrelated donor and LRD groups. Recipients were subgrouped by age; the number in each age group was similar (<2 years, $n = 46$; 2–5 years, $n = 39$; 6–12 years, $n = 37$; 13–17 years, $n = 42$). The cause of end-stage renal disease (ESRD) was similar among groups; obstructive or reflux nephropathy was the most common, followed by congenital anomalies. The one exception to this pattern was in those 13–17 years, where glomerulonephritis was the most common cause of ESRD.

Recipient and donor evaluation and the immunosuppressive protocol have been described in detail [5]. In brief, all recipients underwent pretransplant blood transfusions (3 transfusions, $n = 107$; >3 transfusions, $n = 57$; random donor, $n = 158$; donor-specific, $n = 6$). In all, 162 recipients were on sequential immunosuppression: prednisone (started at 2 mg/kg per day orally, then tapered to 0.45 mg/kg per day at 1 month and 0.25 to 0.3 mg/kg per day at 1 year post transplant); azathioprine (5 mg/kg per day orally on the day of transplant, then tapered to a maintenance dose of 2–2.5 mg/kg per day over the 1st week post transplant); and antibody [Minnesota antilymphoblast globulin (MALG) or antithymocyte globulin] 20 mg/kg per day for the first 14 days post transplant [5]. If the serum creatinine level was less than 1.0 mg/dl, CSA began on posttransplant day 10–12 (5 mg/kg per day orally, then reduced by 1 mg/kg per month to a maintenance dose of 3 mg/kg per day).

One recipient whose ESRD was due to hemolytic uremic syndrome (HUS) took 14 days of prophylactic monoclonal antibody OKT3 instead of MALG. One recipient with HUS and 1 recipient who underwent donor-specific transfusions did not receive CSA. Prophyl-

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lactic antimicrobial therapy for all recipients included a one-time intravenous dose of a cephalosporin on induction in the operating room; maintenance oral nystatin for 6 months post transplant (100,000 units four times a day if <4 years old, 500,000 units four times a day if 4–12 years, and 1,000,000 units four times a day if >12 years); and trimethoprim-sulfamethoxazole (2 mg/kg per day of trimethoprim up to a maximum of 80 mg each day) given for the duration of graft function.

We determined infections by reviewing data maintained on a microcomputer, using a database management program (Dataease). These data were originally collected by a staff review of medical records and outpatient transplant charts. Readmissions to hospitals other than the University of Minnesota were included. Bacterial infections were diagnosed by culture. Viral infections were diagnosed by culture results, rapid antigen detection tests, changes in viral serology, cerebral spinal fluid cellular and biochemical abnormalities, and in 1 recipient, at autopsy. *Pneumocystis carinii* infection was diagnosed by cytology. Sinusitis and pneumonia were diagnosed by X-ray. Rejection was diagnosed by allograft biopsy. Mean lengths of follow-up were 4.6 ± 2.6 years (\pm SD) (<2 years), 4.6 ± 2.5 years (2–5 years), 4.6 ± 2.3 years (6–12 years), and 4.6 ± 2.5 years (13–17 years) and did not differ significantly among age groups. Six patients (3.7%) were lost to follow-up during the study period.

Statistical analyses included the chi-squared test, analysis of variance, and Duncan's multiple range test where applicable. The Cox proportional hazards model was used to analyze for risk factors associated with infection in the first 6 months post transplant. Risk factors evaluated included cytomegalovirus (CMV) status of the donor (D) and recipient (R) pre transplant (D-R-, D-R+, D+R-, D+R+), antibody treatment for rejection in the first 6 months, Solu-Medrol administration for rejection in the first 6 months, number of rejection episodes, donor source (CAD, LD), and age at transplant. A forward stepwise selection procedure was implemented; risk factors were considered significant if the *P* value to enter the model was <0.05. Actuarial patient and graft survival rates were computed using Kaplan-Meier survival methods; comparisons were made using Gehan's test. All values are expressed as mean plus or minus standard deviation. A *P* value ≤ 0.05 was considered statistically significant.

Results

Actuarial graft and patient survival rates did not differ significantly among groups at 1, 3, or 5 years post transplant (*P* = NS). Graft survival rates at 1, 3, and 5 years were 87%, 79%, and 72% for recipients <2 years; 84%, 81%, and 81% for those 2 to 5 years; 89%, 83%, and 78% for those 6–12 years; and 88%, 76%, and 68% for those 13–17 years (Fig. 1). Patient survival rates at 1, 3, and 5 years were 98%, 95%, and 95% for recipients <2 years; 100%, 100%, and 100% for those 2–5 years; 100%, 97%, and 97% for those 6–12 years; and 98%, 98%, and 98% for those 13–17 years. When evaluated by donor source, patient and graft survival rates did not differ significantly among age groups (*P* = NS).

Initial length of hospital stay

The mean initial length of hospital stay was 28 ± 20 days in recipients <2 years, 23 ± 13 days in those 2–5 years, 18 ± 3 days in those 6–12 years, and 16 ± 4 days in those 13–17 years. It was shorter in all recipients ≥ 2 years than those <2 years (*P* < 0.0001) and in those 13–17 years versus those 2–5 years (*P* = 0.05). The two most common causes of prolonged initial hospital stay (>16 days) in

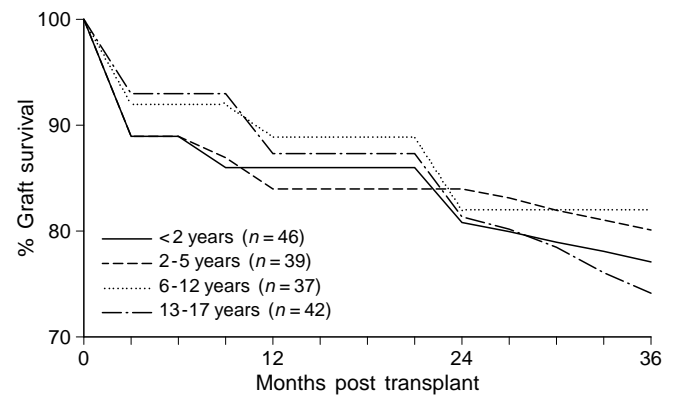


Fig. 1. Actuarial graft survival in 164 recipients, by age at transplant

Table 1. Primary cause and number of hospital readmissions by age

Cause	Age at transplant (years)			
	<2 (n = 46)	2–5 (n = 39)	6–12 (n = 37)	13–17 (n = 42)
Rejection	32	46	51	59
Infection	40	25	33	33
Transient creatinine level elevation	14	4	10	11
Urological problems ^a	1	12	12	6
Other ^b	18	12	30	26

^a Urinary incontinence, ureteral obstruction, renal stones, vesicoureteral reflux

^b Lymphocele, chest pain, hypertension, cyclosporine toxicity, serum sickness, return to dialysis, central catheter removal, dehydration, hernia repair, bowel perforation or obstruction, anemia, ascites, unexplained fever, abdominal pain, electrolyte imbalance, central line placement, splenic rupture, acute tubular necrosis, dilatation of stenosed renal artery, hematuria, hip pinning, protocol biopsy, nonhealing gastrostomy site, seizures, double vision, psychological problems, constipation, unexplained illness

recipients <2 years were infection (*n* = 7) and acute renal dysfunction plus infection and/or rejection (*n* = 6).

Hospital readmissions

The percentage of hospital readmissions post transplant was high (<2 years, 65%; 2–5 years, 69%; 6–12 years, 78%; 13–17 years, 79%), but did not differ significantly among age groups (*P* = NS). The mean number of readmissions varied (<2 years, 2.6 ± 4.4 ; 2–5 years, 2.2 ± 2.4 ; 6–12 years, 3.7 ± 3.4 ; 13–17 years, 3.4 ± 3.4), but did not differ significantly among age groups (*P* = NS). The mean number of hospital days during readmissions (<2 years, 20 ± 31 ; 2–5 years, 18 ± 23 ; 6–12 years, 29 ± 36 ; 13–17 years, 15 ± 28) did not differ significantly among age groups (*P* = NS).

Biopsy-proven acute rejection was the most common reason for readmission (40% of readmissions). Recipients were readmitted for suspected rejection when the serum creatinine level rose >25% above baseline, fever remained unexplained >5 days, or hypertension worsened [9].

Table 2. Infections during the initial hospital stay

Type of infection	Age at transplant (years)			
	<2 (n = 31)	2–5 (n = 10)	6–12 (n = 6)	13–17 (n = 1)
Bacterial				
<i>Clostridium difficile</i> diarrhea	13	3	1	
Urinary tract	12	1	1	1
Peritoneal	9	1		
Bacteremia	5	2	1	
Central line	2	3	1	1
Otitis media	2			
Sinusitis	1			
Pneumonia	1	1		
Wound	1			
Viral				
Cytomegalovirus		1	1	
Meningitis	3			
Respiratory syncytial	1	1		
Rotavirus	1			
Herpes simplex			1	
Echovirus	1			
Parasitic				
<i>Pneumocystis carinii</i>	1			

Throughout the study period, the incidence of acute rejection remained greater in recipients ≥ 2 years than those < 2 years ($P = 0.002$), and in LRD recipients ≥ 2 years than those < 2 years ($P = 0.02$). Other common reasons for readmission were infection (28%), transient unexplained creatinine elevation (8%), and urological problems (6%) (Table 1). A full 18% of readmissions were due to isolated reasons (i.e., return to dialysis, seizures, dehydration, unexplained fever, blood pressure control) (Table 1).

Infections post transplant

The incidence of bacterial or viral infections was 89% in recipients < 2 years, 79% in those 2–5 years, 59% in those 6–12 years, and 52% in those 13–17 years. Younger recipients were more likely to develop an infection post transplant ($P = 0.0005$). The incidence of bacterial infections (< 2 years, 87%; 2–5 years, 72%; 6–12 years, 51%; 13–17 years, 40%) was greater in younger recipients ($P = 0.0001$). The incidence of viral infections (< 2 years, 38%; 2–5 years, 28%; 6–12 years, 32%; 13–17 years, 36%) did not differ significantly among age groups ($P = \text{NS}$).

Infection in the first 2 weeks post transplant (Table 2) resulted in a prolonged initial hospital stay and was more common in young recipients (< 2 years, $n = 31$; 2–5 years, $n = 10$; 6–12 years, $n = 6$; 13–17 years, $n = 1$). More than one infection developed in 21 recipients. The infections were largely bacterial (85%). *Clostridium difficile* diarrhea was the most common bacterial infection. It occurred mostly in recipients < 2 years with intraabdominal kidneys; they usually had fever and diarrhea between postoperative

Table 3. Number of recipients with the most common bacterial and viral infections

Type of infection	Age at transplant (years)			
	<2	2–5	6–12	13–17
<i>C. difficile</i> diarrhea	24	13	3	2
Urinary tract	18	11	10	8
Central line	11	7	1	4
Cytomegalovirus	2	4	2	9
Varicella	10	7	4	0
Herpes zoster	2	1	4	4

day 4 and 7. Two older recipients (10 years, 16 years) developed *C. difficile* diarrhea during the first 2 weeks post transplant. Urinary tract infection (UTI) was the second most common bacterial infection, occurring more frequently in recipients < 2 years. Bacteremia and line sepsis were more common in recipients < 5 years. Ten children had positive peritoneal fluid cultures. All but 1 of the recipients who had positive peritoneal cultures were on peritoneal dialysis pre transplant. Those on peritoneal dialysis were asymptomatic for infection at the time of transplant and had normal peritoneal fluid cell counts. Positive cultures were of peritoneal fluid obtained in the operative period. In all cases the peritoneal catheter was removed at the time of transplant. All recipients were successfully treated for infection without loss of life or graft.

Few viral infections occurred during the first 2 weeks post transplant (Table 2). Aseptic meningitis occurred in 3 recipients; the viral agents were never identified. Antiviral therapy was administered to 3 recipients who developed potentially life-threatening viral infections (1 case each of CMV, respiratory syncytial virus, and herpes virus). One recipient aged 17 months developed *Pneumocystis carinii* pneumonia 7 days post transplant, diagnosed by bronchoscopy of a right upper lobe infiltrate visible on chest X-ray. This child was successfully treated with aerosolized pentamidine and intravenous trimethoprim-sulfamethoxazole, while continuing post transplant immunosuppression.

Infection beyond the first 2 weeks post transplant. Between 1 and 6 months post transplant the incidence of infections in recipients < 2 years was 26% versus 29% in those 2–5 years, 30% in those 6–12 years, and 51% in those 13–17 years. The most common infection resulting in readmission during this time period was UTI associated with fever. *C. difficile* diarrhea was less common, occurring mostly in recipients < 5 years. However, 2 recipients > 6 years also developed *C. difficile* diarrhea. Line sepsis was rare.

Of all CMV infections, 87% occurred between 1 and 6 months post transplant. Of the 164 recipients, 17 (10%) developed CMV infection (Table 3). Of these 17 recipients, more in the 13- to 17-year age group had evidence of tissue invasion (positive CMV antigen, culture, or histology from blood, lung, gastrointestinal tract, or renal biopsy specimens) and took ganciclovir (< 2 years, 4%; 2–5 years, 10%; 6–12 years, 5%; 13–17 years, 21%) ($P = 0.04$). The donor/recipient CMV status in 15 of these 17 recipients was

as follows: D-/R- ($n = 1$), D-/R+ ($n = 2$), D+/R- ($n = 6$), and D+/R+ ($n = 6$).

In a proportional hazards model, risk factors for infection in the first 6 months were age at transplant (2–5 years vs. <2 years, odds ratio 0.41, $P = 0.075$; 6–12 years vs. <2 years, odds ratio 0.07, $P < 0.0001$; 13–17 years vs. <2 years, odds ratio 0.11, $P < 0.001$) and Solu-Medrol treatment for acute rejection (odds ratio 3.77, $P = 0.01$).

Beyond the first 6 months, the incidence of infections in recipients <2 years was 30% versus 31% in those 2–5 years, 53% in those 6–12 years, and 29% of those 13–17 years. The most common infection during this time period was UTI. The most common viral infection beyond the first 6 months post transplant was varicella. Varicella infection was more common in younger recipients [<2 years, 18% vs. 13–17 years, 0% ($P = 0.008$); 2–5 years, 13% vs. 13–17 years, 0% ($P = 0.045$)]. Varicella was most likely to occur beyond the 1st post transplant year. One recipient in the 6- to 12-year age group died from varicella sepsis 17 months post transplant.

Discussion

We previously reported that patient and graft survival rates in young children post transplant can be just as good as those achieved in older recipients [5]. We have fully reported elsewhere the outcome of acute rejection based on age at our center [10]. In this study, we report that recipients <2 years did not have a higher frequency of hospital readmissions for acute rejection and that infectious complications post transplant varied according to age.

Our initial length of hospital stay is a minimum of 16 days, in order to complete our induction protocol. Our study shows that young children are more likely to acquire a bacterial infection during their initial renal transplant hospitalization and are more likely to have a longer initial hospital stay. However, if the graft is not lost during this initial peritransplant period, the posttransplant course of young children will not likely differ from older children. Young children do not require more readmissions after the immediate posttransplant period, nor do they require longer stays with readmissions. Our data compare favorably with the 1993 annual report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS), which noted readmission of 59% of pediatric renal transplant recipients during the first 6 months post transplant [11]. The NAPRTCS report did not include data beyond the first 6 months or data stratified by age. In both our study and the NAPRTCS report, the most common reasons for readmission were treatment of rejection and infection.

For recipients <6 years in our study, the greatest incidence of infections was during the 1st month post transplant, with bacterial pathogens the most common cause. For those ≥ 6 years, the incidence of infections did not vary much with time; however, bacterial infections were usually more common at all time intervals post transplant. The one exception was in recipients 13–17 years at 1–3 months post transplant, when the incidence of bacterial and viral infections was the same.

Bacterial infections were as significant as viral infections as a cause of posttransplant morbidity. *C. difficile*-associated diarrhea was the major bacterial infection in our patient population. To assure adequate immunosuppression, we administered it intravenously to infants with *C. difficile* diarrhea during their active diarrheal phase. Most recipients responded within 7 days of starting oral metronidazole or vancomycin. The majority of *C. difficile* infections are acquired nosocomially, and antimicrobial therapy is the greatest risk factor [12]. Antibiotics were being administered in a percentage of the recipients who developed *C. difficile* diarrheal infections (<2 years, 28%; 2–5 years, 29%; >5 years, 17%). The antibiotics used were vancomycin, cephalosporins, and aminoglycosides. Recipients <2 years had a longer initial hospital stay than other age groups: a prolonged hospital stay has been reported to be a risk factor for *C. difficile* diarrhea [13]. Although not evaluated in this study, transient hypogammaglobulinemia of infancy (average patient age 18.8 months) has been associated with increased risk for *C. difficile* diarrhea [14]. Hypogammaglobulinemia has been reported in uremic infants undergoing peritoneal dialysis [15]; however, only 46% of those <2 years and 54% of those 2–5 years who developed *C. difficile* diarrhea were on peritoneal dialysis pre transplant. None of the recipients >5 years who developed *C. difficile* diarrhea were on peritoneal dialysis. Other putative risk factors for *C. difficile* diarrhea include use of immunosuppressive agents, environmental transmission by personnel caring for patients, and possibly intraabdominal graft placement in infants [12, 13, 16]. We have a high index of suspicion for *C. difficile* in recipients developing diarrhea.

UTIs were equally common among all our age groups. However, in the immediate posttransplant period, UTIs were more common in recipients <2 years. Our postoperative protocol generally resulted in removal of the Foley catheter on day 7 for recipients <2 years versus day 5 for older recipients: this difference in timing may partially account for the increased incidence of UTIs in recipients <2 years. All UTIs were initially treated with intravenous antibiotics in the peritransplant period. Our protocol for induction of immunosuppression included antibody therapy administered through a central line. Central line infections were equally common among the age groups during the initial hospital stay; either they were treated with intravenous antibiotics or the line was removed. Many of our small children were discharged from the hospital with their central lines still in place, to facilitate blood drawing; it was not uncommon for them to later develop central line infections.

Although young children in our study were more prone to bacterial infections, only one infection-related (varicella virus) death occurred – in a 13-year-old, at 17 months post transplant, who was not able to receive medical treatment in time. Varicella infection was seen in children who had not had chickenpox pre transplant and was more common after the 1st post transplant year. We currently recommend varicella vaccination pre transplant. We use zoster immune globulin prophylaxis for all exposures to this virus in children who lack immunity post transplant.

CMV was a major pathogen. As reported by others [17, 18], we more commonly saw it in our study in the first 3–6 months post transplant. Ganciclovir therapy for active CMV disease was associated with a lack of mortality in our study.

The overall incidence of infections in all age groups was greatest during the first 6 months post transplant, although infections continued to occur beyond the 1st year. The risk of bacterial or viral infections during the first 6 months post transplant was associated with young age and with Solu-Medrol treatment for rejection.

In conclusion, younger recipients do not have a greater number of hospital readmissions or longer hospital stays during readmissions than older children. Younger recipients are, however, at greater risk for bacterial infections post transplant. Infection-related morbidity remains a major complication of pediatric renal transplants in the CSA era, although fewer infection-related deaths are observed [19].

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