

# 10 Years' Experience of Paediatric Kidney Transplantation at a Paediatric Nephrology Center

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## Abstract

Successful renal transplantation is the best renal replacement therapy for children with end stage renal disease. In the present study, we reviewed our experience with renal transplanted children currently managed in our Department. There were 20 transplants done in 19 Chinese children from 4/1992 to 2/2002. The most common cause of renal failure was renal dysplasia (27%) followed by focal segmental glomerulosclerosis (FSGS) (16%). Seven allografts came from living donors and 13 were from cadaveric donors. Three children underwent pre-emptive transplantation. The mean waiting time for local cadaveric kidney was  $4.4 \pm 2.3$  years. Mean age at transplantation was  $15.3 \pm 4.5$  years and the mean duration of follow-up was  $2.4 \pm 2.4$  years. Immunosuppressive protocol consisted mainly of triple therapy with prednisolone, azathioprine/mycophenolate mofetil, and neoral/FK506. Lamivudine was used in 5 children with chronic HBV infection with no flare-up of the infection at the last follow-up and with good tolerance of the drug. There was no case of CMV infection. Acute rejection occurred in 5 allografts (25%); and chronic rejection occurred in 4 allografts (20%). There were 3 graft loss (15%) due to resistant acute rejection, chronic rejection and recurrence of the original renal disease respectively. Actuarial graft survival rate at 1 year and 3 years post-transplantation were 100% for living donor kidney and those for cadaveric donor kidney at 1 year and 3 years were 92.3% and 83.1% respectively. The mean GFR was  $71.8 \pm 17.2$  ml/min/1.73 m<sup>2</sup>. Actuarial patient survival rate was 100%. Most of them were able to go back to school or be employed. In conclusion, good short-term graft survival rate and excellent patient survival rate had been achieved with kidney transplantation in children in our Center. Chronic allograft nephropathy and recurrence of the original renal disease remained the major problems to long-term graft survival. Lamivudine might make transplantation feasible in those chronic HBV infected ESRD patients.

**Key words** Paediatric renal transplantation

## Introduction

Children suffering from end stage renal disease (ESRD) need to have renal replacement therapy to sustain life. Kidney transplantation is the best therapy for these children

for it provides the best rehabilitation potential in respect to growth, development and quality of life without putting the child on the trial of dialysis.<sup>1</sup> With the advances in transplantation immunology and introduction of better immunosuppressive agents, kidney transplantation is more successful although long-term issues such as chronic rejection/chronic allograft nephropathy, recurrence of original renal disease, and malignancy remain obstacles to long-term success. In this review, results of kidney transplantation in children in our Center are reported.

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## Patients and Methods

Records of all children with kidney transplantation, carried out within the period of 4/1992 to 2/2002 and

currently followed up in our center, are reviewed.

Immunosuppressive protocol consisted mainly of triple therapy with steroid, azathioprine/mycophenolate mofetil (MMF), and neoral/FK506. Pulse methylprednisolone, 30 mg/kg iv (max. 1 gm), was given preoperatively. Postoperatively, pulse methylprednisolone 10 mg/kg/day would be continued for 1 to 2 days and to be followed by oral prednisolone 2 mg/kg/day (max. 80 mg) for 1 week with gradual reduction to 0.5 mg/kg/day at week 5 and 0.15 mg/kg/day at month 7 and thereafter. Intravenous cyclosporin A was administered at 3.5 mg/kg preoperatively and then daily postoperatively until oral route could be used at a dose of 5 mg/kg/dose bd targeted at a trough level (ug/L) (measured by monoclonal antibody Tdx method) of 240-320 at 0-1wk; 200-320 at 2-4wks; 160-240 at 2-3 mths; 80-160 at 4-6 mths; and 80-120 at 7th mths onwards. For children less than 6 years old, thrice daily dose was used instead of twice daily dose. Azathioprine was given 2 mg/kg intravenous preoperatively and maintained at the same dose daily per orally. MMF was given 600 mg/m<sup>2</sup> preoperatively and then at the same dose bd after oral intake was tolerated. MMF at 300 mg/m<sup>2</sup>/dose bd was prescribed when it was used with FK506.<sup>2</sup> All of them received steroid treatment. Eight were put on azathioprine and 11 were given MMF. MMF was used in all cases of chronic HBV infection. Neoral was used in 17 children and FK506 was used in 3 others (in 2 as continuing therapy instead of cyclosporin and in 1 adolescent girl to replace cyclosporin for its much less cosmetic side effects i.e. hirsutism and gum hypertrophy). Five received anti-T cell therapy (3 ATG & 2 zenapax) – for second graft, delayed graft function due to acute tubular necrosis, and transplantation in Mainland China.

Glomerular filtration rate (GFR) was calculated according to Schwartz formula. Cytomegalovirus (CMV) prophylaxis with gancyclovir and acyclovir was used when the recipient was CMV IgG antibody negative and the donor was CMV IgG antibody positive. Lamivudine was used when the child was HBsAg positive. Cotrimoxazole was routinely given for 6 months for *Pneumocystis carinii* prophylaxis.

**Definitions:** 1) Preemptive transplantation – transplantation without prior dialysis, 2) Acute rejection – the decision to treat unless the diagnosis is not supported by subsequent biopsy, 3) Chronic rejection (chronic allograft nephropathy) – slow insidious progressive deterioration of renal function with the exclusion of other causes of kidney dysfunction with or without biopsy; and hypertension and proteinuria are usually present,<sup>3</sup> 4) Delayed graft function –

use of dialysis in the first week after transplantation, 5) Hypertension – use of anti-hypertensive drugs to control blood pressure, 6) Significant proteinuria – spot urine protein/creatinine ratio of >0.2 mg/mg.

## Results

### Patient Characteristics

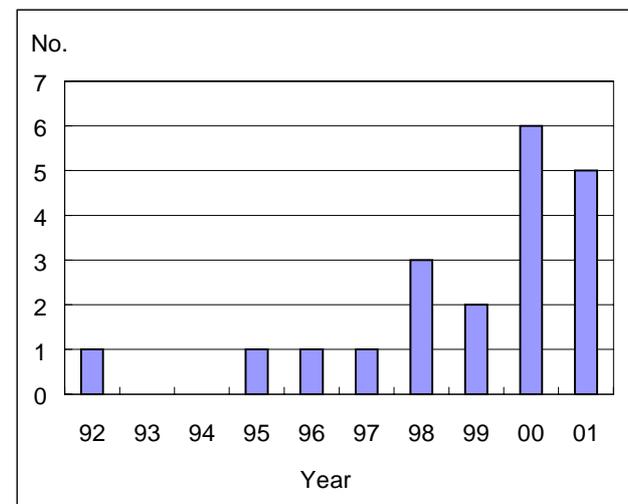
There were 19 Chinese children (14 males, 5 females) transplanted with 20 kidneys from 4/1992 to 2/2002 (Figure 1). There were an increasing number of transplants done in the recent few years.

The mean waiting time for the whole group was 2.4±2.5 years. For the 7 local cadaveric kidney recipients, the mean waiting time was 4.4±2.3 years (range: 3.0-8.9 years). There were 3 pre-emptive transplantations (15%).

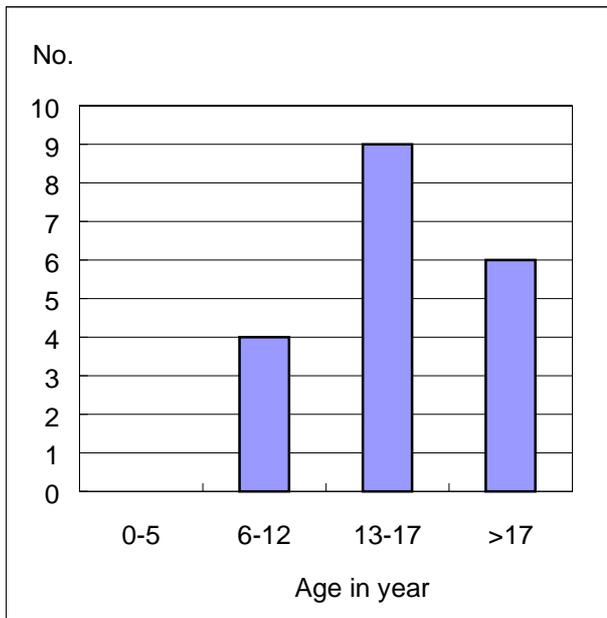
The mean age at transplantation was 15.3±4.5 years (range: 6.7-22.0 years) (Figure 2). None was transplanted at less than 5 years of age.

Most were transplanted in or after 1998, and the mean duration of follow-up was 2.4±2.4 years (range: 0.3-9.8 years) (Figure 3). Three grafts had been followed up for more than 4 years with 1 for nearly 10 years.

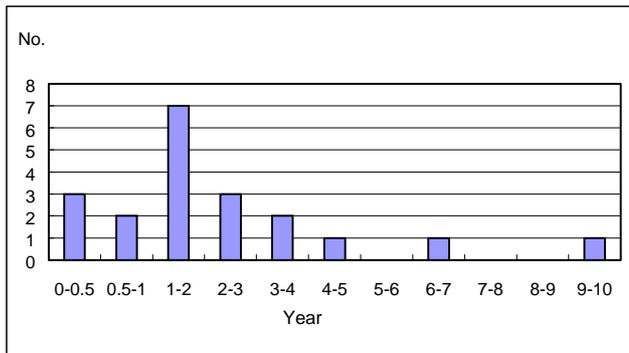
The most common cause of renal failure was renal dysplasia in 5 (27%) followed by focal segmental glomerulosclerosis in 3 (16%), IgA nephropathy in 2 (11%), and chronic glomerulonephritis (GN) in 2 (11%); and 1 (5%) each for hereditary nephritis, juvenile nephropathosis, Drash syndrome, reflux nephropathy, endocapillary proliferative glomerulonephritis,



**Figure 1** Number of kidney transplantation per year.



**Figure 2** Age at transplantation (for the first graft).



**Figure 3** Duration of follow-up.

membranous glomerulonephritis and renal veinous thrombosis.

**Graft Source**

Seven grafts (35%) were from living donors (4 from mother, 1 from father, 1 from sister and 1 from brother in law); and 13 grafts (65%) were from cadaveric donors of which 7 were from local donors. The mean local waiting time was 4.4±2.3 years (range: 3.0-8.9 years).

**Infection**

Eight children suffered from *urinary tract infection* after transplantation despite prophylactic co-trimoxazole therapy. Most were due to *E. coli*. There were 3 cases of

Herpes zoster, 1 case of Herpes simplex and 2 cases of Pneumonia. There was no case of pneumocystis carinii.

*CMV prophylaxis* was required in 4 children. So far, there was no CMV infection. Lamivudine, 100 mg QD, was given to 4 children with *chronic hepatitis B virus infection* just before transplantation and to 1 child five years after transplantation. Four were HBeAg positive. All had normal liver function before transplantation. Mild elevation of liver transaminase occurred in 3 children post-transplantation, which was later reverted to normal. Mean duration of lamivudine treatment was 14 months (range: 3 mths-27 mths); and the liver function was normal at the last follow-up in all of them.

**Surgical Complications**

There were 4 surgical complications. One ureteric leakage necessitated repair. Two hematomas required blood transfusion and exploration. One lymphocele resolved on conservative management.

**Acute Rejection (AR)**

Fifteen grafts (75%) were free from any acute rejection (AR). Five grafts (25%) had 8 AR episodes and all 5 grafts had their first AR episode within first 3 months post-transplantation. Two AR episodes had full response to pulse methyl-prednisolone (PMP) treatment; 4 had partial response and 2 were resistant. For the 2 resistant cases, 1 ended in graft loss despite OKT3 treatment and the child had to return to chronic haemodialysis and received his 2<sup>nd</sup> transplant 3 years later. One OKT3 resistant case was salvaged by FK506 and now was enjoying normal renal function.

**Chronic Rejection (CR)**

Four grafts had chronic rejection. One had multiple episodes of AR, 2 had 1 episode of AR and 1 had no AR but suffered from delayed graft function. One ended in graft loss 4 year 11 months after transplantation. Serum creatinine for the other 3 were 192, 201 and 248 umol/L. All were hypertensive requiring anti-hypertensive drug treatment; and were proteinuric.

**Recurrence of the Original Renal Disease**

Recurrence occurred in 2 children with FSGS. One recurred soon after transplantation with nephrotic syndrome and resulted in graft loss 1.1 year after transplantation. The other recurred 5 months after transplantation with mildly impaired renal function 1.6 years after transplantation. Both were resistant to aggressive immunosuppressive therapy and plasma exchange.

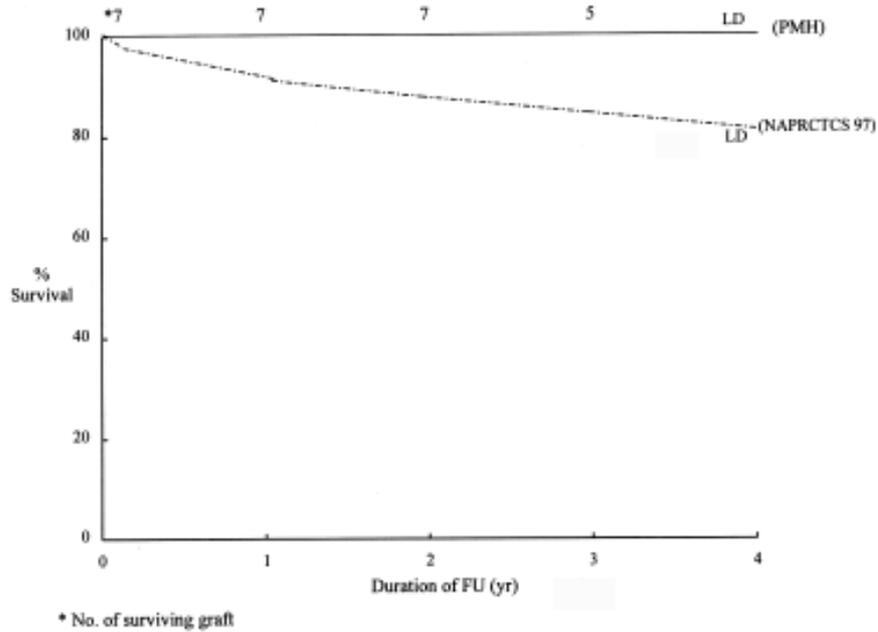
**Post-transplant Lymphoproliferative Disease (PTLD)**

One child suffered from PTLT 4.6 years after transplantation. He presented with persistent cough and multiple chest shadows on CXR. Because he was at a late stage of CR (Scr about 600 umol/L), he had all immuno-suppressive drugs withdrawn and was treated with 2 weeks' of a interferon and oral acyclovir.<sup>4</sup> His PTLT was under control with regression of lesions.

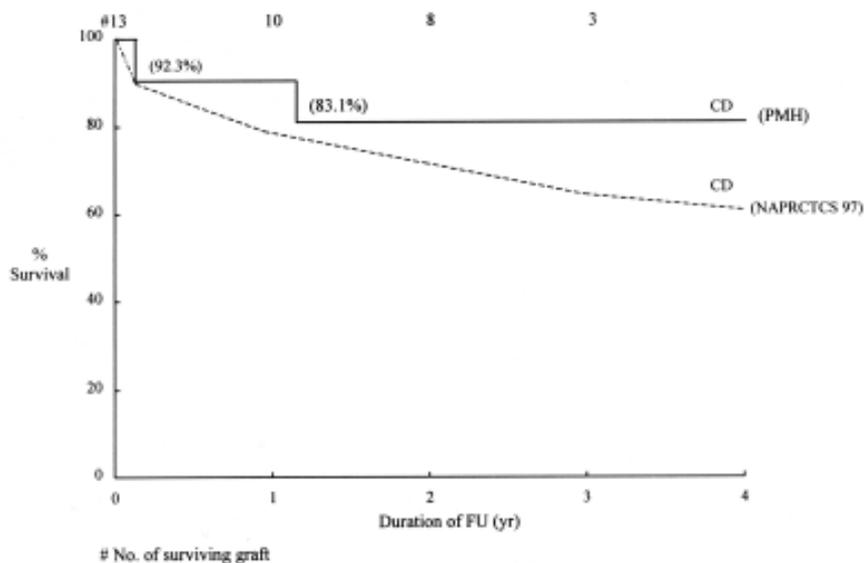
**Graft Outcome**

There were 3 graft loss (15%) caused by 1 resistant AR, 1 recurrence of FSGS, and 1 CR & PTLT. The 1-year and 3-year actuarial graft survival rate were 100% for living donor kidneys (Figure 4) and those for cadaveric donor kidneys were 92.3% and 83.1% respectively (Figure 5).

For the 17 surviving grafts, mean serum creatinine (Scr) was 125.0±46.3 umol/L (range: 248-73 umol/L); and mean



**Figure 4** Actuarial graft survival rate for living donor (LD) kidneys.



**Figure 5** Actuarial graft survival rate for cadaveric donor (CD) kidneys.

calculated GFR was  $71.8 \pm 17.2$  ml/min/1.73 m<sup>2</sup> (<50 ml/min/1.73 m<sup>2</sup> in 1 child; 50-75 ml/min/1.73 m<sup>2</sup> in 8 children; & >75 ml/min/1.73 m<sup>2</sup> in 8 children). Nine children had hypertension requiring anti-hypertensive treatment; and 3 of them had CR. Thirteen children did not have any proteinuria or hematuria. One child with recurrence of FSGS had nephrotic syndrome; 3 children with CR had significant proteinuria.

### **Patient Survival**

Patient survival rate was 100% in these 10 years. Thirteen of them were back to school and 2 were having gainful employment.

### **Discussion**

Successful renal transplantation is the best therapy for children with ESRD for it provides the best rehabilitation potential although long-term maintenance immunosuppressive drug therapy is necessary.<sup>1,5</sup>

In our center, the first transplantation was carried out in early 1992. In the recent years, more transplants were carried out. The number of transplantation was up to 5-6 per year in the recent 2 years. At present, the total number of children transplanted represented 47.6% of the total ESRD children currently under our care. With a bigger case volume, better results in patient outcome would be expected.<sup>6</sup>

In our series, the most common renal diseases requiring transplantation was renal dysplasia (bilateral/unilateral) (27%) followed by FSGS (16%). These findings are comparable to other reports except that there was no case of obstructive uropathy transplanted up till now.<sup>3</sup> In contrast, the common causes of ESRD in adults are diabetes mellitus and hypertension (>70%).

Our number of living donor transplants represented 35% of cases as compared to 40.2% in North America Pediatric Renal Transplant Cooperative Study (NAPRTCS) 97 Annual Report.<sup>7</sup> Five were from parental source (80% mother, 20% father). We have relatively low contribution from fathers, as compared to 44% of parental donor in the same Annual Report.

The mean waiting time for local cadaveric transplantation of 4.4 years was relatively long (as compared to that of 1.4 year in USA),<sup>8</sup> due to an increasing discrepancy in demand of kidneys for transplantation and the availability of cadaveric kidney from donation. "The lack of knowledge of the wishes of the deceased" was found to be the major reason in objecting donation in Hong Kong.<sup>9</sup> During the

waiting period, patients have to undergo long-term maintenance dialysis (3.0 years longer than those in USA). This might explain for the 6 cases of transplantation in China.

In recent years, MMF was used more often instead of AZA as part of the triple immunosuppressive protocol for its effect in reducing acute rejection rate. In the present review, it appeared that those on MMF had fewer AR episodes (9.1%) than those on AZA (50%). Such findings were also the experience of others – MMF reduced AR rate to about half of that when AZA was used.<sup>10</sup>

Both FK506 (tacrolimus) and neoral were calcineurin inhibitors and the former was found to be more potent than the latter.<sup>11</sup> For that reason, one case of resistant AR was successively reversed and one could be maintained with a very low dose of prednisolone (5 mg QOD). Because hirsutism and gum hypertrophy are not seen with FK506 therapy, such advantages make this drug more preferable to neoral by an adolescent girl. However, because of its potency, one has to be careful about infective complications and its alleged potential risk of malignancy with its long-term use.

Before, chronic active HBV infection was usually contraindicated in kidney transplantation because of its propensity to deteriorate and progress to active and fulminant hepatitis and cirrhosis after transplantation.<sup>12,13</sup> With the availability of lamivudine, a potent inhibitor of HBV replication, kidney transplantation might be feasible to be carried out in children with chronic HBV infection.<sup>14</sup> In our group, 4 children with chronic HBV infection and 1 child with suspected re-activation of chronic HBV infection were put on lamivudine therapy. There was no significant flare-up of HBV infection after transplantation and the drug was well tolerated. However, the long-term outcome of such treatment is not yet known and the development of resistance is a genuine risk.<sup>15</sup>

Acute rejection (AR) episodes occurred in 5 grafts (25%) and most were reverted with pulse methylprednisolone treatment; and 15 grafts were AR free. Such rejection rate was low as compared with more than 40% frequently quoted.<sup>16</sup> One child had 4 AR episodes which depicted the typical pattern of progressive decrease in responsiveness to methylprednisolone treatment; and now suffered from chronic rejection and was also hypertensive and proteinuric. One other child gradually developed CR. The prevention of AR is important in long-term graft survival.<sup>17</sup>

Chronic rejection (CR) is the most important factor affecting long-term graft survival. Four of our transplanted children suffered from CR and one had resulted in graft

loss. The other 3 were hypertensive and proteinuric. MMF was found to be useful in treating CR<sup>18,19</sup> and its use in 1 of the CR cases was followed by stabilization and improvement of renal function. However, good control of blood pressure, proteinuria and hyperlipidemia are important aspects of management as well.<sup>20</sup>

Recurrence of the original renal disease is a troublesome condition and focal segmental glomerulosclerosis is the most common one to recur.<sup>7</sup> Its recurrence rate was 20-30% for first graft and 70-80% for subsequent grafts, with a high rate of graft loss (50%).<sup>21</sup> In the current review, 2 out of 3 cases of FSGS recurred and 1 out of 2 recurrences ended in graft loss despite aggressive treatment. The importance of counseling parents about the prognosis in this group of unfortunate children needs to be stressed. At present, there is no promising therapy for recurrence although there were reports of encouraging results being associated with the use of plasma exchange, high dose cyclosporin A, and cyclophosphamide.<sup>22,23</sup>

Common causes of graft loss include chronic rejection (29.8%), acute rejection (18.3%), vascular thrombosis (12.4%), recurrence of primary renal disease (5.7%) and non-compliance 2.6%.<sup>7</sup> Graft loss in the current review occurred in 3 kidney grafts (15%) due to chronic rejection, acute rejection and recurrence of the original renal disease respectively. That we had not encountered vascular thrombosis might be because we had not transplanted very young children. As reported, drug non-compliance had been noted to be a problem in transplanted adolescents, which resulted in graft loss of up to 5-10%.<sup>24</sup> With the continuous effort of education and monitoring, non-compliance had not been found to be a cause for graft loss in the present study.

Our longest surviving graft had been transplanted for nearly 10 years and the majority of transplants were carried out in the recent 3 to 4 years. The 1 and 3 year actuarial graft survival rate in our current review were 100% and 100% for living donors and 92.3% and 83.1% for cadaveric donors respectively. Our results appeared to be better than those reported by NAPRTCS 97, which showed a survival rate of 91% and 85% for living donors and 81% and 70% for cadaveric donors at 1 and 3 years respectively. One of the main reasons would be that we had not transplanted children less than 5 years old. For those with functioning grafts, only 1 graft had GFR below 50 ml/min/1.73 m<sup>2</sup> and all other were above 50 ml/min/1.73 m<sup>2</sup>. Such results are encouraging. About 55% children had hypertension which was mostly related to the use of steroid and cyclosporin A. Thirteen out of 17 functioning grafts did not have

proteinuria or hematuria and should have a good prognosis. So far, there is no mortality and most of the patients were able to resume their normal social life.

## Conclusion

In conclusion, good short-term graft survival rate and excellent patient survival rate had been achieved with kidney transplantation in children in our Center. Chronic rejection and recurrence of the original renal disease remained the major problems of long-term graft survival. Lamivudine might make transplantation feasible in those chronic HBV infected ESRD patients.

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