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Dialysis and Renal Transplantation in Children

MC ***CHIU,*** KC ***TSE,*** WM ***LAI***

Abstract

With dialysis and renal transplantation as long-term renal replacement therapy (RRT), the prognosis of end-stage renal failure in children has been completely changed as compared with 20 years ago. Either dialysis or tranplantation should be considered when glomerular filtration rate (GRF) is reduced to 10-15 ml/min/1.73m^2 BSA in the presence of growth failure and significant symptoms. For dialysing small children, peritoneal dialysis is the preferred mode; and automated peritoneal dialysis (APD) is better than continuous ambulatory peritoneal dialysis (CAPD) in that it allows a better quality of life and sees to the different requirements of dialysis. Adequate dialysis is correlated with less morbidities and mortalities, and thus is important in long term dialysis. Nowadays, chronic dialysis in infants has a high success rate, which justifies its implementation even in end-stage renal failure neonates, unless there are significant non-renal co-morbidities of the brain, heart or lung. Haemdialysis is an option of RRT especially for bigger children and adolescents. The main problem is vascular access. Thrombosis and stenosis are complications not uncommonly encountered when patients have been put on haemodialysis for some years. Renal transplantation is the best modality of RRT and can be successfully done in small children, depending on expertise and centres. With the use of potent immunosuppressants, rejections are few and good long-term results can be achieved. The experience and results of the RRT programme of the Paediatric Nephrology Centre at Princess Margaret Hospital are discussed. Since 1996, all children requiring peritoneal dialysis were put on automated peritoneal dialsysis (APD), and there were 24 of them altogether. Dialysis adequacy exceeded the recommended targets, and the peritonitis rate was recorded to be very low, 1 in 87.5 patient-months. There were 15 patients on long-term haemodialysis, and either permanent central catheter or arteriovenous fistula (AVF) had been used as the vascular access. The main problems were blockage, thrombosis and stenosis in small children. Renal transplantation was done in 19 children with 20 kidney grafts, 13 from cadaver donors and 7 from living donors. One child had a second transplant. For cadaveric transplants, the graft survival rates at 1 and 3 years were 92% and 81%; and for living transplants, the graft survival rates at 1 and 3 years were 100%. These results compared favourably with those reported by the North American Pediatric Renal Tranplant Co-operative Study (NAPRTCS). Such results could only be achieved through re-organization of services to allow accumulation of patients and expertise.

Key words Haemodialysis; Peritoneal dialysis; Renal replacement therapy; Renal transplant

Department of Paediatrics & Adolescent Medicine, Princess Margaret Hospital, Lai Chi Kok, Kowloon, Hong Kong, China

MC **CHIU** （趙孟準） *MBBS, FHKAM(Paed), FRCP(Lond, Edin, Glasg)*
KC **TSE** （謝紀超） *MBBS, FHKAM(Paed), MRCP(UK)*
WM **LAI** （賴偉明） *MBBS, FHKAM(Paed), MRCP(UK)*

Correspondence to: Dr MC **CHIU**

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Introduction

Dialysis and renal transplantation (RT) has completely changed the outlook of children with end-stage renal disease (ESRD). While 20 to 30 years ago, these children had no hope of living, now with successful long term dialysis and renal transplantation as means of renal replacement therapy

(RRT), they may be able to lead a life of reasonable quality. Prolonged dialysis with many complications can be frustrating and a burden to the family; however, those having a successful transplant are able to lead a nearly normal life. It is a lifelong therapy aiming not only at sustaining life but also to permit a worthwhile quality of living, with the ultimate aim of an enjoyable and satisfying adulthood.[1]

Renal Replacement Therapy (RRT)

Initiation of Dialysis

When glomerular filtration rate (GFR) is reduced to less than 30 ml/min/1.73m^2 BSA or so, increasing adverse effects of chronic renal failure begin to appear, which include acidosis, fluid and electrolyte disturbances, growth failure, anaemia, and renal osteodystrophy. These can be managed conservatively by diet and drugs. However, when GFR is further reduced to below 10 ml/min/m^2 BSA, these complications and other major complications e.g. cardiomyopathy, encephalopathy and neuropathy will begin to appear and become difficult to manage, and renal replacement therapy (RRT) like dialysis or renal transplant need to be instituted. In fact, for optimal care, such measures should be considered when GFR is between 10-15 ml/min/1.73m^2 BSA unless the child remains asymptomatic and growth is well maintained.[2] According to the Kidney Diseases Outcome Quality Initiatives (K/DOQI) Guidelines 2000 Update, in order to avoid morbidities and for better outcomes, when Kt / V urea falls below 2.0, some form of dialysis should be considered.[3] Such parameters will be further discussed under 'dialysis adequacy'.

Mode of Peritoneal Dialysis

Dialysis can be either peritoneal dialysis (PD) or haemodialysis (HD). The former is usually more preferable in children because of its easy delivery, as vascular access can be difficult to maintain in small children. Generally speaking for those below 20 kg of weight, PD is the mode of choice.[4] Long term home peritoneal dialysis started in late 70s as Continuous Ambulatory Peritoneal Dialysis (CAPD), which was done manually. In recent years, peritoneal dialysis can also be done by using a PD machine in the night time while the child is asleep, keeping the child free from dialysis in the daytime – Night Intermittent PD (NIPD). If dialysis is not adequate, dialysate can be left in the abdomen during daytime – Continuous Cyclic PD (CCPD). Both NIPD and CCPD can be called Automated PD, as they involve the use of an automatic machine to do the dialysis. CAPD requires 3-4 exchanges to be done during daytime, which can be disruptive of normal daily life, making schooling difficult and keeping parents away from work. Thus, APD becomes the mode of choice for PD if resources allow. In North America, more than 70% of PD patients are using such mode.[5] Tidal PD is a special way in further enhancing dialysis in APD by leaving in the abdomen a certain fixed amount of dialysate during each cycle of dialysis (see Figure 1). However the total amount of dialysate used is much more by this mode of dialysis; and thus it is more costly and should only be considered when dialysis cannot be made adequate by other means. For those who have difficulties in doing home dialysis, intermittent PD can be done for them in the hospital twice a week; however only those having reasonable amount of residual urine can be maintained on such mode of dialysis.

Peritoneal Equilibration Test (PET)

The test is a means of assessing transport capacity of the peritoneum, including solute transport and ultrafiltration. A night dwell of 2.5% dialysate is left in the abdomen, and in the next morning after draining and refilling of 1100 ml/m^2 of dialysate, the blood and dialysate level of creatinine and glucose are measured at 0 hour, 2 hours and 4 hours. Patients are divided into high transporter, high average, low average and low transporters according to the rate of changes (transport) of creatinine and glucose in the dialysate as calculated from kinetic data of D:P and D:Do ratios.[6,7] It serves as a guide to decide on the mode and prescription of dialysis most suitable for individual patient. For example, NIPD is more suitable for high transporters and CCPD/CAPD for low average transporters.

Adequacy of Peritoneal Dialysis

There is much discussion of dialysis adequacy in recent years, which is believed to be related to better outcomes and less mortalities. It can be assessed by weekly creatinine clearances and Kt/V urea. The former is the sum of the weekly clearances of creatinine by PD and residual urine. Kt/V urea is the total weekly urea nitrogen clearance normalized to urea volume of distribution of the body (V). According to K/DOQI Guidelines 2000, the recommendations for weekly creatinine clearance in CAPD, CCPD and NIPD are ≥60 L, ≥63 L, and ≥66 L/1.73m^2 BSA respectively, whereas for Kt/V urea, they are ≥2.0, ≥2.1 and ≥2.2 respectively (Table 1).[8] These parameters serve as guides for adjustment of dialysis regimens to achieve

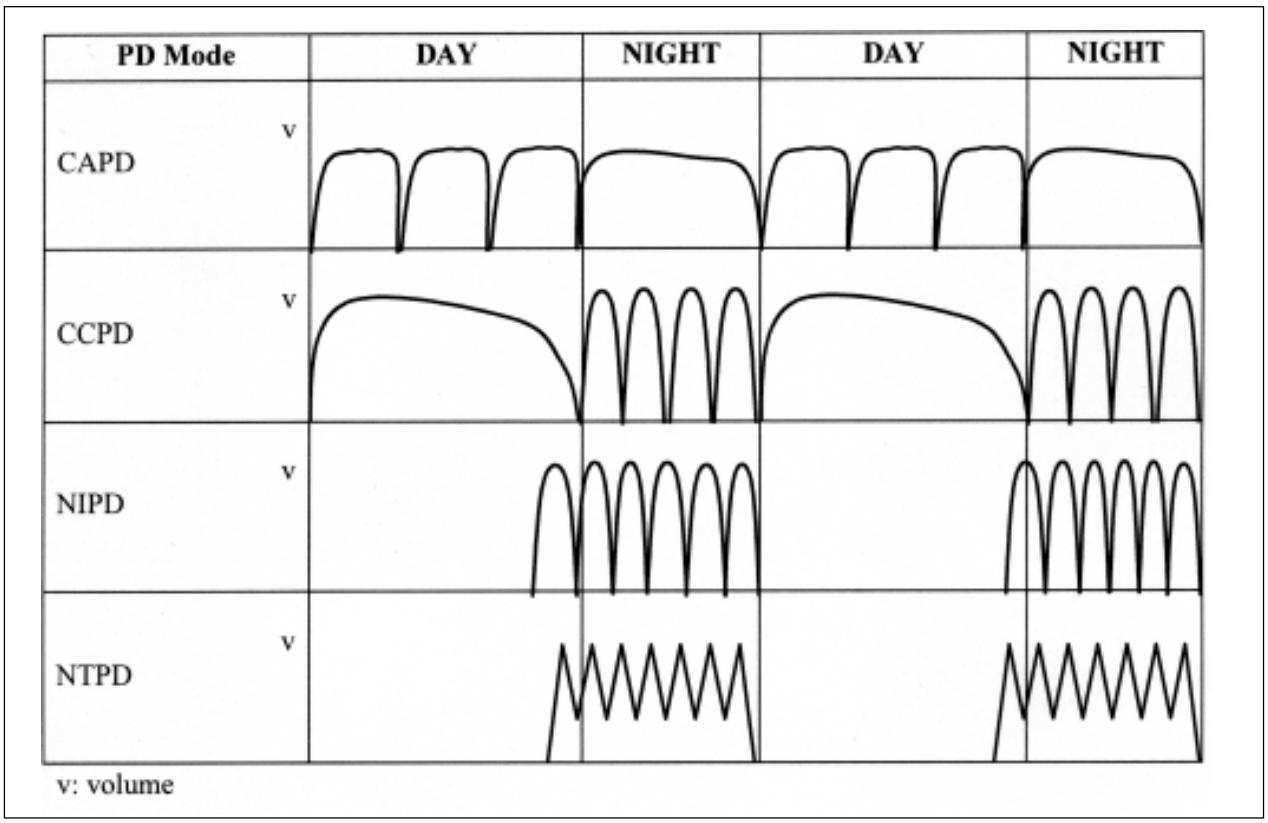

Figure 1 Different modes of peritoneal dialysis.

Table 1 Peritoneal dialysis adequacy targets recommended by K/DOQI 2000

	CAPD	CCPD	NIPD
Weekly Cr Clearnace (L/1.73 m^2)	60	63	66
Kt/V	2.2	2.1	2.0

adequate dialysis. If they are suboptimal, dialytic dose and/or duration of dialysis may need to be increased. However, their application in children need further evaluation and it may be difficult for anephric children to meet such targets.[9]

Peritoneal Dialysis in Infants

There has been increasing success with chronic PD in infants in recent years.[10,11] Survival rate of infants put on PD reached 80% for those who didn't have significant non-renal co-morbidities.[12] It is a demanding treatment requiring much back-up support, but the outcome of growth and development seems to justify this intensive approach. It has been suggested that RRT in infants should no longer be considered experimental, but rather the standard of care.[13] However, in counseling parents, the importance of co-morbidities need to be addressed. Their understanding and involvement need to be gained, as it is going to be a long term care that they have to participate in. In fact, consensus have not been reached amongst paediatric nephrologists, and there are legal, economic, social and ethical issues for considerations.[14]

Chronic Haemodialysis

Chronic haemodialysis for children needs to be done in the hospital, three times a week. Each session lasts for about 4 hours. Vascular access for chronic HD in children is a surgical challenge. Shunts and grafts are usually not easy to be applied to children and they are prone to complications. Arteriovenous fistulas can be done with good results for those having body weight of ≥20 kg. Failures are commonly due to thrombosis and stenosis. Advances in microsurgery may help in producing better results.[15] For young children, a permanent central catheter can be placed subcutaneously either via the internal jugular or subclavian

vein, which may be able to last some months or years.[16] This type constituted 67% of the vascular access children had while on chronic HD as reported in the Annual Report of NAPRTCS.[5] In adolescents, vascular access is easier, and haemodialysis becomes a matter of choice for them amongst the different modes of RRT. In a paediatric dialysis programme in North America in the 90s, HD patients constituted about 40% of those put on dialysis.[17] Adequacy of dialysis is also considered to be important for haemodialysis, and Kt/V is recommended to be more than 1.2 per session and pre- and post-dialysis urea reduction of ≥65%.[18]

Renal Transplantation

Renal transplant is regarded as the preferred mode of RRT, as it saves patients long term inconvenient and routine procedures of dialysis and its complications. Either cadaveric or live kidneys can be used. Adult kidneys can be placed in small children. However, those transplants done in recipients or using donors less than 6 years old generally have less favourable results as reported in NAPRTCS,[19] though some specialized centers have reported results of transplants done in recipients under 5 years of age to be comparable with older children.[20,21] Thus, depending on experience and expertise, it is not unreasonable to keep infants on dialysis until they are 4-5 years old before performing transplantation. Living transplant gives better results than cadaveric; and pre-emptive transplantation (without going through dialysis) avoids the morbidities of dialysis. Since the use of cyclosporin as immunosuppressant in the 80s, graft rejections have been reduced; and with tacrolimus (FK506), Mycophenolate Mofetil (MMF), OKT3, antithymocyte globulin (ATG), and newer monoclonal antibodies as potent immunosuppressants in high risk situations, better results can be achieved.

RRT in Adolescence

Adolescence is a period which needs special attention. It can be a difficult time for those suffering from chronic illnesses to go through. Short stature, dark complexion and sexual underdevelopment in ESRD may affect self-image,[22] and dialytic procedures hindering peer group activities. Anxiety and depression may result and some of them may have psychological maladjustment and personality problems. If schooling is jeopardized because of frequent hospital admissions, education will be adversely affected which will have great impact on their future development and social achievements. For those transplanted, some may also have long term drug compliance problem which results in graft loss.[23,24] Thus, this group of patients need to be carefully managed and closely monitored, seeing to their drug compliance and psychological adjustment. Psychological counselling and support are needed.

ESRD Children in Hong Kong

In Hong Kong, the incidence of ESRD in children under 15 years old was estimated to be 4.1 per million children population in a survey reported in 1993.[25] In that report, the main causes include chronic glomerulonephritis (27.5%), dysplasia/hypoplasia (18.2%), heredofamilial diseases (13.6%), and pyelonephritis (9.1%). According to the Renal Registry of the Hospital Authority (HA), the average number of new cases aged under 18 per year put on RRT was 12 in the past three years (1999-2001); and the prevalence or average number of patients aged under 18 on RRT for those three years were 20 for PD, 8 for HD and 15 for TX (Table 2).[26] In view of the small number of ESRD in children, the Hospital Authority in 1999 decided to co-ordinate the services of dialysis and transplant to be delivered at the Paediatric Nephrology Centre at Princess Margaret Hospital (PMH), with the aim to build up the expertise required for better patient outcome and to improve cost-benefit effectiveness.

PMH Experience

Automated Peritoneal Dialysis (APD)

Before APD was introduced in 1996, CAPD was the main mode of PD. Thereafter, nearly all children requiring

Table 2 ESRD children aged ≤18 years on RRT in Hong Kong 1999-2001

	1999 (Dec)	2000 (Dec)	2001(Dec)
Peritoneal dialysis (PD)	20	19	22
Haemodialysis (HD)	8	9	6
Transplanted (TX)	12	14	18

Source: Cumulative Annual Report 2001, Renal Registry, Hospital Authority Hong Kong

dialysis were put on APD instead. In reviewing 24 children, 13 boys and 11 girls, who were put on APD, 17 were on CCPD, 2 on high dose CCPD, 2 on tidal PD and 3 on NIPD. The mean age was 11.2±5.4 years and mean duration of APD 25.5±17 months. As for dialysis adequacy, the mean Kt/V urea was 2.88±0.95 and combined weekly creatinine clearance was 65.9±35.1 litre/1.73m^2. These results met the K/DOQI recommendations of ≥2.1 and ≥63 litre/1.73 m^2 respectively.[8]

The incidence of peritonitis rate was very low with 1 infection every 87.5 patients months or annualized peritonitis rate of 0.138 (Table 3). NAPRTCS reported a peritonitis rate of 1 infection every 13.3 patient-month or annualized peritonitis rate of 0.90.[5] With meticulous training and supervision of parents and patients by dedicated staff, we have been able to reduce the peritonitis rate to a very low rate. Causative organisms included gram-positive organisms (42.8%), gram-negative organisms (28.5%), atypical mycobacterium (14.2%), and cultures were negative in 14.2%.

APD is the preferred mode of peritoneal dialysis, sparing patients having to do dialysis in the daytime; thus enabling the child normal schooling and allowing normal work for parents. And with such mode, we have been able to reduce peritonitis to a very low rate.

Chronic Haemodialaysis

Fifteen children who had more than 3 months of HD from Jan 90 to Feb 02 were reviewed. There were 11 boys and 4 girls, of a mean age at initiation of HD of 14.2±5.47 yr. Reasons of choosing HD were mainly abdomen unsuitable for PD in 10, inadequate dialysis by PD in 1, and patients' choice in 4. The mean duration of HD was 22.7±21.15 mons (3-68 mons) (Table 4). Vascular access used were permanent central catheter in 12 and AVF in 3. The average dialysis adequacy as measured by Kt/V was 1.45±0.26, which met the K/DOQI recommendation of ≥1.2 (Table 4).

There were no major complications and most problems were related to vascular access and catheters. A total of 38 permanent catheters were used and each lasted for a mean duration of 3.7 mons. (1-18 mons). Catheters related complications included: 24 blockage, 9 catheter related bacteraemia (CRB), 3 disolodgement, and 1 cracked catheter. Among those put on HD, 10 were full-time students and 1 was part-time studying; there were 1 doing part-time job and 3 being unemployed.

Chronic haemodialysis is a safe and effective dialysis modality in children without major complications in our hands, and some adolescents prefer it to PD. The main problem is vascular access in the small child. Most children are able to continue with full-time studying, which is important in reducing the impact of the disease (including treatment) on a long-term basis.

Renal Transplantation

From 4/92 to 2/02, there were 19 children (14 males, 5 females) transplanted with 20 kidneys with 1 child having a second transplant (Table 5). The mean age at transplantation was 15.3±4.5 years (6.7-22.0 yrs), and the mean duration of follow up was 2.4±2.4 yrs (0.3-9.8 yrs). 7 grafts were from living donors, and 13 from cadaveric donors of which 7 were from local donors. The overall mean

Table 3 Automated peritoneal fialysis program at PMH

No. of patients	24
Sex (M:F)	13:11
Mean age (yr)	11.2±5.4
Mean duration (mons)	25.5±17
Mean Kt/V	2.88±0.95
Weekly Cr Cl (L/1.7m^2)	65.9±35.1
Peritonitis rate	1 in 87.5 patient-mons

Table 4 Chronic haemodialysis program at PMH

No. of patients	15
Sex (M:F)	11:4
Mean age at start (yr)	14.2±5.47
Mean duration (mons)	22.7±21.15
Reasons for choosing HD:	
Abdomen unsuitable for PD	10
Indequate dialysis by PD	1
Patients' choice	4
Vascular access: perm cath (%)	80
A-V fistula (%)	20
Kt/V (mean)	1.45±0.26

Table 5 Renal transplantation at PMH

No. of patients	19
Sex (M:F)	14:5
Mean age at Tx (yr)	15.3±4.5 yr
No. of grafts	20
Cadaveric	13
Living	7
Duration of follow up (yr)	2.4 (0.3-9.8)

waiting time for those done locally was 4.4±2.3 years (range: 3.0-8.9 years). There were 3 pre-emptive transplantation. Triple therapy of prednisolone, cyclosporin and azathioprine was the basic immunoimpressive therapy used; and other immunosuppressants used were MMF (11), FK506 (3), ATG (3) and zenapax (2). There were 5 who had chronic hepatitis B infection and they were covered with lamivudine prophylaxis. None had liver dysfunction at the time of last follow up.

Of a mean duration of follow up of 2.4 yrs (range: 0.3-9.8 yrs), 15 children were free from any acute rejection (AR). Eight AR episodes occurred in 5 grafts in which 1 graft had 4 AR episodes and was suffering from chronic allograft nephropathy (CAN). A total of 3 grafts were lost: 1 due to resistant AR, 1 due to recurrence of FSGS, and 1 due to CAN. The longest surviving graft was done nearly 10 years ago; and the majority of grafts were done in the recent few years. For cadaveric transplant, graft survival rates were 92% & 81% at 1 yr & 3 yrs; and for living transplant, they were both 100% respectively. Patients' survival rate was also 100% with no mortality. For the North American paediatric transplants as reported in the NAPRTCS (Table 6), the cadaveric graft survival rates were 81% & 70% at 1 and 3 years , and living grafts were 91% & 85% at 1 yr and 3 yrs respectively[19] (Figure 2). It seems that we are having better results; and the likely reasons are that we had not been transplanting children under 5 years of age, and that the North American results had included transplants done in the 80s, when experiences and immunosuppresants might not be as good as now. For long-term outcome, we have to follow up our patients for more years for evaluation.

Table 6 Comparing transplants with NAPRTCS*

	PMH	NAPRTCS
% Male	73.7	59.9
% Age (yr): <5	-	21.3
6-12	20.0	34.3
13-17	50.0	39.3
>18	30.0	5.1
% Living donors	35	48
Main waiting time (mons)	17	55
Graft survival at 1 yr (%)		
Cadaveric	92	81
Living	100	91
Graft survival at 3 yrs (%)		
Cadaveric	81	70
Living	100	81
Patient survival at 1 yr (%)		
Cadaveric	100	96
Living	100	97

*The 1997 Annual Renal Transplantation in Children Report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Pediatr Transplant 1999;3:152-67.

Looking into the Future

With the reorganization of dialysis and transplant services, we have been able to achieve results that we have not been able to do before. Automated PD has been more welcome by parents and children than CAPD, and we have been able to provide it to all of our PD children, and peritonitis had been reduced to a very low rate as recorded. We have also been successful in dialyzing neonates up to infancy with satisfactory growth and development. Haemodialysis is a safe procedure and what we need to overcome is the problem of vascular access in small children. Transplant is on the way and we have been successful in transplanting 5-6 years old children. We look forward to transplanting younger children when patient volume and experiences accumulate.

With dialysis and transplantation, ESRD children are able to be kept alive for many years, even for those born with the disease and requires RRT from birth. If they could be tied over the first few years by PD, success rate of transplant will be increased. For bigger children, there should not be much problem for PD to last some 7-8 years, and likewise for HD, and TX for another 10-15 years as an average. For those failing transplant, re-transplant is possible. Many on long term RRT have enjoyed a reasonable quality of life. The required complexity of care demands expertise from a multi-disciplinary team, which includes paediatric nephrologists, dialysis and transplant nurses, paediatric urologists, transplant surgeons, nutritionists/dietitians, social workers, and clinical psychologists. No matter by PD, HD or TX, meticulous and expert care are very important, as avoidance of complications will enable the procedures to last longer, enhancing the chance of survival of these unfortunate children. If they could be given some 20 to 30 years of life, we never know what new treatment modalities will be available by then to allow them another 20 or 30 years to live.

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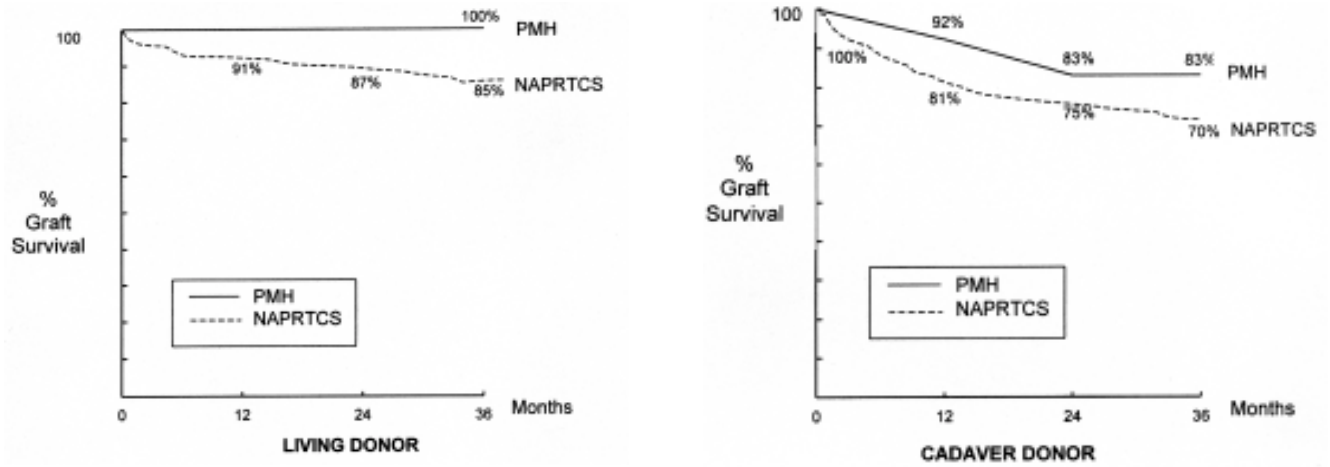

Figure 2 3 years actuarial graft survival in children from Living donor and Cadaveric donor renal transplantation. Results compared with the 1997 Annual Report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Pediatr Transplant 1999;3:152-67.

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