



Overview of a paediatric renal transplant programme

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Introduction. Renal transplantation is the therapy of choice for children with end-stage renal failure. There are many challenges associated with a paediatric programme in a developing country where organs are limited.

Methods. A retrospective review was undertaken of 149 paediatric renal transplants performed between 1968 and 2006 with specific emphasis on transplants performed in the last 10 years. Survival of patients and grafts was analysed and specific problems related to drugs and infections were reviewed.

Results. On review of the total programme, 60% of the transplants have been performed in the last 10 years, with satisfactory overall patient and graft survival for the first 8 years post transplant. At this point, transfer to adult units with non-compliance becomes a significant problem.

Rejection is less of a problem than previously but infection is now a bigger issue – specifically tuberculosis (TB), cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infections with related complications. A wide variety of drugs are available for tailoring immunosuppression to minimise side-effects.

Conclusion. It is possible to have a successful paediatric transplant programme in a developing country. However, to improve long-term outcomes certain issues need to be addressed, including reduction of nephrotoxic drugs and cardiovascular risk factors and providing successful adolescent to adult unit transition.

S Afr Med J 2006; **96**: 955-959.

Renal transplantation has undoubtedly become the therapy of choice for children with end-stage renal failure,¹ allowing them to return to a fairly normal way of life at home and to return to school. However paediatric renal transplant programmes have many challenges especially in a developing country. Optimising renal allograft survival is important because of limited resources to treat irreversible renal failure.^{2,3} Paediatric numbers remain low compared with adult programmes

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and contribute approximately 2% of any national dialysis programme.⁴

Patients and methods

A retrospective folder review was done of all patients < 16 years old who received renal transplants at Red Cross War Memorial Children's and Groote Schuur Hospitals' combined Transplant Unit from August 1968 to April 2006. The first paediatric transplant was performed in August 1968 and to date 149 renal transplants have been performed in 132 patients. Eighty-nine (60%) transplants have been performed in the last 10 years (1995 - 2005). The number of paediatric renal transplants per year is shown in Fig. 1.

Fourteen children received 2 grafts, 2 children 3 grafts and 1 child 4 grafts (2 at another centre). Gender distribution was 67 males and 65 females, who ranged in weight from 8 kg to 63 kg. Thirty-five (24%) received grafts from living related donors

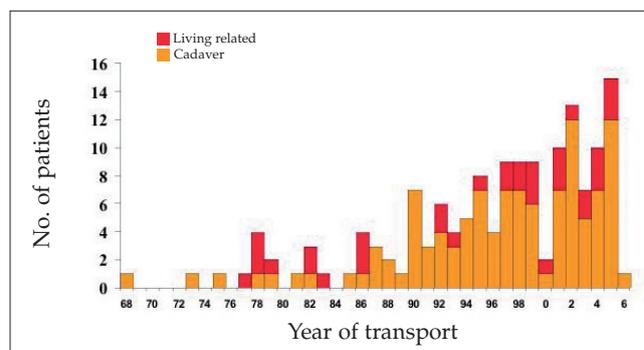


Fig. 1. Number of paediatric renal transplants by year.



and 114 (76%) were cadaveric transplants. Age at the time of transplant is shown in Fig. 2.

Four combined liver-kidney transplants were performed, 3 for primary hyperoxaluria and 1 for polycystic kidney disease with hepatic fibrosis. These patients have currently survived between 2 and 6 years post transplant and all have adequate graft function. Causes of renal failure are shown in Table I. HLA matching is not ideal and often 5 or more mismatches are present.

Our first-line immunosuppression remains cyclosporin, azathioprine and prednisone, but we do have the ability to tailor immunosuppression to suit individual patients. Other drugs used include tacrolimus (Prograf/FK), mycophenolate mofetil (MMF) and sirolimus (Rapamycin). We use steroids and wean to 2.5 mg on alternate days (or 0.05 mg/kg/day) as the lowest dose – no complete steroid withdrawal or steroid avoidance is practised.

Induction agents (basiliximab, daclizumab) in the form of interleukin (IL) 2 receptor blockers have been used and, for cost containment, we have used daclizumab for smaller children (9 cases) and basiliximab for bigger children (7 cases).

Acute rejection has been biopsy proven and then treated

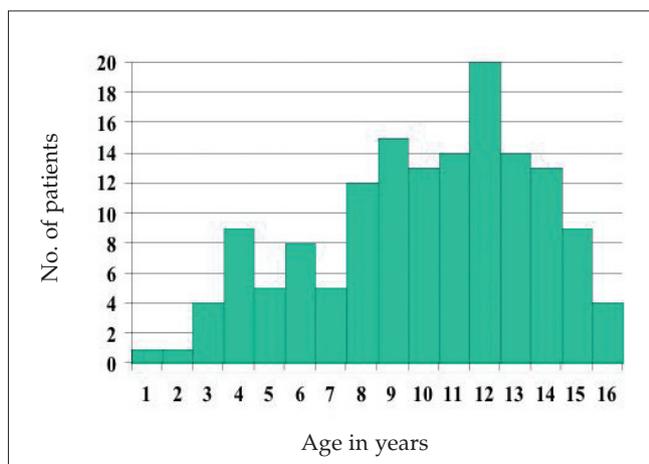


Fig. 2. Age at time of transplant.

Table I. Causes of renal failure in 149 transplanted children

Primary disease	Frequency (%)
Glomerulonephritis	19
Renal dysplasia	18
Posterior urethral valves	16
Reflux nephropathy	12
Systemic lupus erythematosus	9
Polycystic kidney disease	7
Glomerulosclerosis	7
Other	12

with 'pulsed' intravenous methylprednisolone in dosing of 10 mg/kg/dose for 3 - 4 doses followed by increased oral steroids.

Complications resulting in graft loss have included rejection (1 graft lost due to hyperacute rejection) and surgical problems (2 cases of vascular thrombosis), with infections remaining the biggest problem.

Tuberculosis (TB) is endemic in our region (638 cases/100 000 population) and often presents late. During transplant workup, every patient is screened for TB (history of contact or previous TB, skin testing, gastric washings for bacilli and chest X-ray) and prophylaxis is not routinely used. Epstein-Barr virus (EBV) and cytomegalovirus (CMV) infections also remain a major issue. Identification of CMV and EBV status of both donor and recipient is performed and where necessary 2 weeks of intravenous ganciclovir prophylaxis is administered.

Vaccinations that have been added to our routine immunisations schedule (polio, haemophilus b, diphtheria, pertussis, tetanus, hepatitis B) include hepatitis A and varicella zoster. Adequate immunisation prior to transplant is important with continued surveillance of non-live vaccines on a regular basis post transplantation.

Adolescent issues include our current adolescent cut-off age of 13 years after which the patients are transferred to an adult renal service in large referral hospital. This part of the programme produces most of the compliance issues with recent action implemented including preceding psychosocial input and transition at older age (Fig. 3).

Statistics. Kaplan Meier plots were used for calculating patient and graft survival.

Results

Survival figures

In the last 10 years we have performed 89 paediatric renal transplants; 68 patients are being followed up locally. Notably we are following up 38 patients who are 'over age' according to our cut-off of 13 years (see Fig. 3).

Graft survival for the overall programme is 72% at 1 year and 55% at 5 years. For the period 1995 - 2005 graft survival is

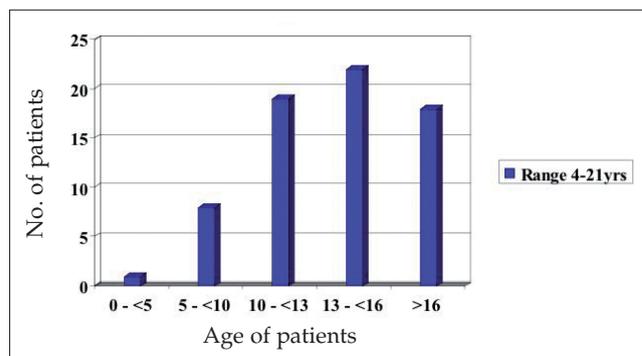


Fig. 3. Age of renal transplant patients followed up at RHX.



91% at 1 year and 80% at 5 years, but then starts dropping off at 7 years to 72% (Figs 4 and 5). Patient survival during this period is 96% at 1 year and 88% at 5 years.

This compares favourably with paediatric figures elsewhere; patients transplanted from 1993 to 1995 in the UK⁵ have a 1-year graft survival of 79% and a 5-year survival of 68%, and North American⁶ 5-year graft survival was 73% for cadaveric and 81% for living-donor recipients over the same time period.

Mortality in the group transplanted in the last 10 years (1995 - 2005) was 8/89 (9%). Causes of death include sepsis in 3 cases (2 of CMV and 1 of Gram-negative sepsis), recurrence of primary disease in 2 (focal segmental glomerulosclerosis), non-compliance with chronic rejection in 3 and hepatitis B infection in 1.

Surgical complications were few and included vascular thrombosis leading to graft loss in 2/89 cases (2.3%), ureteric leak in 1 case (successfully repaired), and 3 cases

of vesicoureteric reflux (VUR) with recurrent urinary tract infections (requiring re-implantation of ureter).

In the light of our small donor pool³ the HLA matching of our cadaver transplants in our paediatric patients was poor, with 60/89 (68%) of our patients having 5 or more mismatches out of 6.

Immunosuppression

Drugs used by our patients include azathioprine (40%), tacrolimus (25%), cyclosporin (24%), MMF (6%) and Rapamycin (5%). We have used similar proportions of both cyclosporin (49%) and tacrolimus (51%). Cyclosporin is significantly cheaper than tacrolimus and for cost-effectiveness this has been our first-line agent. In our paediatric patients on cyclosporin, cosmetic side-effects including hirsutism and gum hypertrophy have been significant problems. This together with rejection episodes has resulted in conversion to tacrolimus in individual cases.

Tacrolimus was implicated in diabetes mellitus in 8/131(6%) paediatric transplants (5 renal and 3 liver) currently being followed-up by our unit. Mean age at transplant was 10 years 4 months and mean age at diagnosis 11 years. Patients who developed diabetes had common risk factors: high body mass index, previously high dosage of steroids and high mean trough tacrolimus level of 10.4 ng/ml. There was also an increased incidence in our black patients – 4/8 (50%) patients who developed diabetes were black despite this group being only 28/89 (31%) of our total programme.

MMF is increasingly being used as a calcineurin-sparing agent but diarrhoea has been a significant problem especially in adolescent patients. If tolerated, we have reduced our cyclosporin to achieve trough levels less than 50 ng/ml and tacrolimus to less than 5 ng/ml. In 3 cases we have successfully stopped calcineurin drugs and have maintained their grafts on MMF and low-dose alternate-day steroids only.

Rapamycin has also been used as a calcineurin-sparing agent but we have seen many of the side-effects described including high cholesterol (50%), interstitial pneumonitis (2 cases), severe bone-marrow suppression with thrombocytopenia and bleeding tendency (1 case) and proteinuria (2 cases). We have not had problems of delayed wound healing, as we have not used this agent in the early post-transplant period.

IL2 receptor blockers have been increasingly used as induction agents, especially in view of our poor HLA matching. This resulted in an acute rejection rate of only 3/16 (18.8%) compared with historic controls of 16/23 (70%). There has therefore been a significantly overall shorter stay in hospital with the potential to use lower doses of steroids. Long-term graft survival still remains to be seen. When comparing the drugs used, no rejection was noted in 4/7 cases on basiliximab and 9/9 cases on daclizumab, suggesting that daclizumab in our setting appears to have a better outcome, but this needs larger studies.

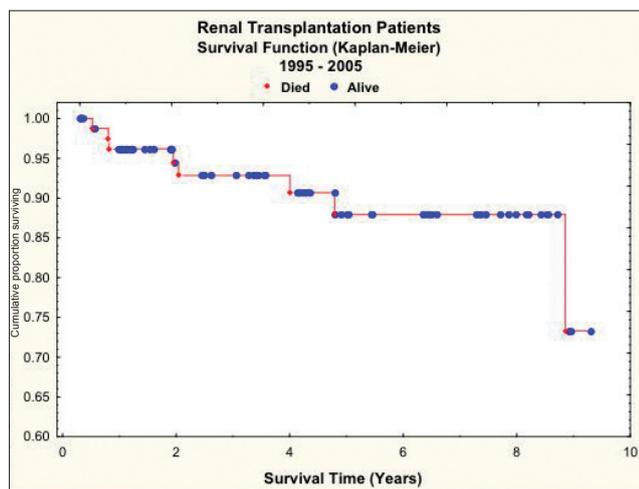


Fig. 4. Patient survival, 1995 - 2005.

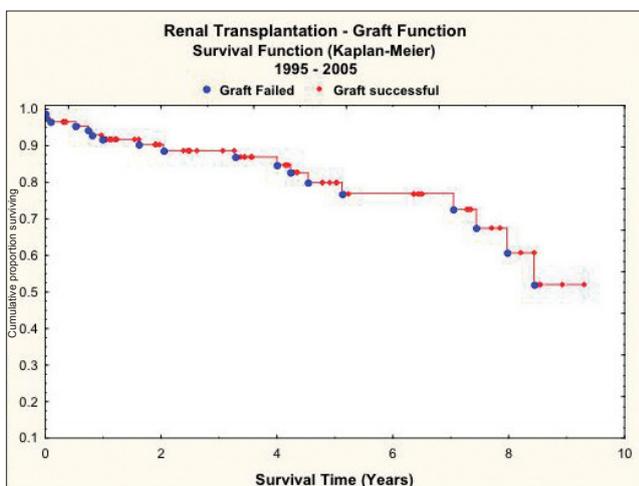


Fig. 5. Graft survival, 1995 - 2005.



Infectious complications

TB represents a significant problem. During the period 1996 - 2004, the incidence of TB was 7/72 (9.7%) in our transplant patients. Presentation was 10 months to 8 years post transplant with symptoms of fever and cough in all and weight loss in most. No patients were on prophylaxis. With the exception of one renal case, the rest all had pulmonary TB with pericardial involvement in 2 cases. Immunosuppression at the time of diagnosis consisted of cyclosporin, azathioprine and prednisone. Diagnosis was made on finding acid-fast bacilli using a combination of sputum, nasogastric aspirate and bronchial lavage. In one case, a fine-needle aspirate of the lung produced the acid-fast bacilli. All the cases were typically mycobacterium TB and fully sensitive to rifampicin and INH. Three cases had had an increased dose of steroids in the preceding 3 months. An increased cyclosporin dose (up to 5 times) was required once starting the rifampicin. All cases were successfully treated with no loss of patient or graft.

Fatal CMV infection was seen in a 13-year-old girl with renal dysplasia and Fanconi's anaemia who received a CMV-mismatched organ (donor CMV positive: recipient CMV negative) in February 2001. Prophylactic intravenous ganciclovir was given for 2 weeks, but unfortunately she developed a pneumonia requiring ventilation 11 months later and died of CMV pneumonia.

EBV-driven post-transplant lymphoproliferative disorder (PTLD) was seen in 1 renal transplant who presented with a nodal mass in his inguinal region. Immunosuppression was reduced and ganciclovir and rituximab (anti-CD 20 agent) were given together with chemotherapy. Therapy remains successful together with preserved renal function.

Other serious infections in this group of patients have included disseminated varicella with transverse myelitis, *Pneumocystis jiroveci* pneumonia and cat scratch disease (*Bartonella henselae*). All were treated successfully and retained their grafts.

Vaccinations

Audit of vaccination status in a group of 32 cases with age range 93 - 225 months (mean 148 months) reviewed post transplant found protective immunity to hepatitis A (53% patients), hepatitis B (19% patients) and varicella (72% patients).

Adolescent transplant transition

We have had difficulty with transition of adolescents to adult units in the last 10 years with 5 adolescents having lost their grafts and 2 dying within 1 year of transfer despite adequate renal function at time of transfer. We have good 1- and 5-year graft and patient survival but our long-term outcome in the adolescent age group is significantly worse than in younger transplant recipients, as is reported universally.

Discussion

Paediatric transplantation poses numerous challenges, not only the conventional problems of acute rejection and infection, but also technically creative surgery to accommodate the significant size range (our group ranged from 8 kg to 63 kg) of paediatric patients. There may be further challenges in a developing country including difficult social circumstances, poor HLA matching (68% of our patients had 5 or more mismatches) as well as a limited number of donors exacerbated by the high incidence of HIV infection. In order to try and increase our donor pool, we may need to expand the current pool of living related donors (24%) beyond just the parents and potentially also consider non-heart-beating donors.

Whereas previously acute rejection was our biggest concern, this has now become easier to manage, by using the newer immunosuppressant agents including induction with IL2 receptor blockers. Our acute rejection rate has reduced to 18.8% using 2 initial doses of IL2 receptor blockers (both basiliximab and daclizumab used in 2-dosing regimen). Despite the initial cost of this form of therapy, these agents have allowed us to use an overall cheaper immunosuppressive protocol (such as cyclosporin and azathioprine) in our setting where cost containment is important.

However, the consequences of increased immunosuppression and reduced rejection are increased infection; this is highlighted by problems such as CMV infection or EBV-driven PTLD. This is particularly a problem in the young patient with no previous CMV or EBV exposure who receives a donor organ-recipient mismatch. The advent of qualitative and, more recently, quantitative polymerase chain reaction (PCR) testing will have a significant impact on both monitoring and management of these viruses. Intravenous ganciclovir is costly and inconvenient and hopefully prophylaxis will be made easier with the introduction of the oral valganciclovir form. As yet no vaccines are available for these two viruses.

TB is endemic in our region – our rate of TB in paediatric transplant patients was 9.7% – and together with HIV infection, raises issues of drug resistance, choice and duration of prophylactic agents.⁶ Our patients developed TB 10 months to 8 years post transplant and it would thus be futile using prophylaxis for TB in the first 6 months only. Drug interactions between anti-TB drugs and immunosuppressants are also a concern.

On review of the vaccination status in a small group of our patients, hepatitis B levels were low post transplant with *Varicella* rates best overall. Paediatric studies have shown loss of antibodies to vaccinations within 6 months post-transplant.⁷ Awareness of adequate vaccination pre-transplant, specifically live-attenuated vaccines, with regular post-transplant monitoring, is important in reducing complications from these infections.



In an established paediatric programme, with 1- and 5-year results which are satisfactory by international paediatric standards, despite all the problems of a developing country, emphasis on long-term graft and patient survival becomes an important focus. In view of this, we have tried to limit nephrotoxicity often caused by calcineurin inhibitors by using renal-sparing immunosuppressants. MMF has been useful in reducing dosing or even ceasing calcineurin inhibitors completely in those with chronic allograft nephropathy⁸ and we have managed to use MMF and steroids as dual therapy only, with stable renal function so far in 3 of our patients.

Sirolimus has also been well described as a renal-sparing agent,⁹ but we have seen a significant number of drug-related side-effects including interstitial pneumonitis and thrombocytopenia with purpura. In 2 cases we have noticed unexplained new-onset proteinuria, which has been described by a few centres as a concern.

In those patients on calcineurin inhibitors, cyclosporin has been responsible for significant cosmetic effects (hirsutism and gum hypertrophy). These patients have usually been changed to tacrolimus therapy but this has also had problems of diabetes in 6% of our renal transplant in which 50% were black paediatric patients (relatively higher incidence than that of the total programme which consists of 31% black patients).

Children's growth in paediatric transplantation has received much attention recently and this is particularly important at a centre where growth hormone is not easily available. Steroids as immunosuppression have attracted negative press recently. In response to this, there have been three main approaches: (i) steroid elimination or avoidance in the first place¹² with use of heavier immunosuppression such as a prolonged course of daclizumab; (ii) steroid withdrawal in those who had steroids at time of transplant;¹³ or (iii) steroid preservation at low dosing. We use the last approach using low-dose (0.05 mg/kg/day) alternate-day steroids. A recent review by Marks and Trompeter¹⁴ also encouraged steroid preservation to prevent exchanging acute rejection for infection including EBV/PTLD. They suggest that steroids remain superior to many other immunosuppressive drugs in terms of cost and past experience, suggesting that it may be more sensible to remove calcineurin inhibition.

Long-term outcomes are greatly affected by adolescent issues and this is clearly seen by our results at 1 and 5 years compared with the group more than 7 years post transplant (Figs 4 and 5). This is notoriously the most difficult group of patients to follow up, a problem for colleagues in both paediatric and adult units alike, and we have this in common with the rest of the world.¹⁵ This is particularly problematic where resources are limited, with adolescent issues similar to those in developed countries, but different economic constraints resulting in patients not being offered repeat dialysis or transplant.

In response to our poor long-term graft survival in adolescence, we have set up a combined transplant clinic with our adult and paediatric team based at the adult unit. This includes social support in the form of psychiatrists, nurses and social workers.

Challenges in the transition period include overcoming the fear of an unknown hospital, adjusting to a different patient/doctor ratio and increased independence in terms of their own health care. The move is preceded by psychological input in the form of workshops and one-to-one interviews prior to transfer to the adult unit.

We also delay the transfer to at least 16 years of age and often even older until patients are mature enough to do the transition with their independence established. Preparation of our younger adolescents, involving them in their own renal function results and medication adjustments, is also important with a positive goal of seeing transition to an adult unit as a successful 'graduation' process. A 'champion' on the adult service is required – be that a nurse or a doctor – so that the patients feel comfortable at the time of transfer by identifying a familiar face involved with them throughout the transition period.

Other factors affecting long-term outcome also depend on decreasing cardiovascular risk factors by reduction of steroid dosing, careful attention to body mass index to prevent obesity and inclusion of statins where necessary.

Despite all the challenges of a developing country, a successful paediatric transplant programme is possible, provided one is aware of all the pitfalls including infection, nephrotoxic drugs and adolescent transition.

Thanks to Jeanette Raad for statistical assistance.

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Accepted 29 June 2006.

