

## KIDNEY TRANSPLANTATION IN CHILDREN

Sanjeev Gulati, Vijay Kher

Fortis Institute of Renal Sciences & Transplantation, Sector B, Pocket 1, Aruna Asaf Ali Marg,  
New Delhi - 110070, India

**Abstract :** There are various modalities to treat children with ESRD i.e. hemodialysis, chronic ambulatory peritoneal dialysis and renal transplant. Satisfactory rehabilitation of uremic children can be achieved by renal transplantation, with dialysis only bridging the period of terminal insufficiency, until transplantation becomes possible. With recent advances in medical technology and availability of expertise, transplantation has become the gold standard for management of children with chronic kidney disease. Currently it is recommended that all children with chronic kidney disease should be worked up for a pre-emptive kidney transplant (transplant without prior dialysis). All potential pediatric recipients of transplants should receive standard immunizations at least 6 weeks prior to transplantation. The immunosuppressive protocol consists of induction antibody treatment (referred to as quadruple immunosuppression) followed by CNI, MMF/ azathioprine and prednisone. The major limiting factor for this protocol in our country is the affordability. The long term outcome is excellent. In the Swedish study of children, which evaluated long term outcomes in children who received cyclosporine, prednisolone, and azathioprine, 5 and 10 year allograft survival rates were 77 and 66 percent, respectively. Patient survival is better in pediatric renal transplant recipients than adults.

### INTRODUCTION

The point prevalence of end stage renal disease (ESRD) in the pediatric population is 55 per million-child population<sup>1</sup>. There are various modalities to treat children with ESRD i.e. hemodialysis, chronic ambulatory peritoneal dialysis and renal transplant. Satisfactory rehabilitation of uremic children can be achieved by renal transplantation, with dialysis only bridging the period of terminal insufficiency, until transplantation becomes possible<sup>2</sup>.

### INDICATIONS

With recent advances in medical technology and availability of expertise, transplantation has become the gold standard for management of children with chronic kidney disease. Currently it is recommended that all children with chronic kidney disease should be worked up for a pre-emptive kidney transplant (transplant without prior dialysis). In developing countries, considerations of cost remains a major impediment in its widespread use<sup>3</sup>.

### CONTRAINDICATIONS

Children with acute or chronic active infection and those with malignancy are not generally candidates for kidney transplantation. Most centers consider transplantation in a child who has been disease free for 2 years following treatment of cancer.

Transplantation is also contraindicated in any child or family with a history or high likelihood of noncompliance with a prescribed medication regimen. Active systemic lupus erythematosus and Goodpasture disease are also contraindications to transplantation because these processes can damage an allograft. The success rate of renal transplantation in very young children, especially those younger than 1 year, is significantly less than that in older children. Therefore, carefully evaluate all alternatives for treatment of ESRD. Generally, continuous ambulatory peritoneal dialysis (CAPD) is the preferred method of treatment of children younger than 1 year. However, CAPD may not be possible because of peritoneal scarring. Hemodialysis is difficult in very small children. In such persons, transplantation may be the best option.

### LABORATORY EVALUATION

- Twenty-four-hour urine collection for creatinine clearance
- Complete blood cell count
- Basic metabolic panel
- Coagulation evaluation
- Viral titers (HBV, HCV, HIV, EBV, HSV)
- Panel reactive antibody

### IMAGING EVALUATION

- Chest radiography
- Imaging of the kidneys and renal vessels
- In the past, this included intravenous pyelography and angiography.

However, current radiologic techniques provide suitable imaging of the entire urinary tract with 3-dimensional computed tomography (3D CT) scanning or magnetic resonance angiography (MRA) using gadolinium to demonstrate the vascular anatomy.

### IMMUNIZATIONS

All potential pediatric recipients of transplants should receive standard immunizations at least 6 weeks prior to transplantation .

Special attention needs to be given to the live-attenuated vaccines, including varicella and measles-mumps-rubella (MMR), because the risk of active disease following vaccination is increased in children who are immunocompromised. Similarly, inactivated polio vaccine (IPV) is indicated, rather than oral polio vaccine (OPV). Family and household contacts also should receive MMR and varicella vaccine as indicated.

Although the HBV vaccine is routinely administered to all children now, nonimmunized children still must be immunized with this vaccine. The recommended dose schedule is at 0, 1, 2, and 6 months. Periodically monitor the antibody level after transplantation and administer a booster to those with low titers (<10 mIU/mL) .

It is suggested that routinely an annual influenza vaccine should be given to children with transplants and their family and/or household contacts.

## OPERATIVE PROCEDURE

In larger children, as in adults, the renal allograft is placed in the iliac fossa outside the peritoneal cavity. A curved lower abdominal (Gibson) incision is made in either lower quadrant, and the iliac vessels are exposed. The renal artery is anastomosed either to the external iliac or the internal iliac artery.

In past decades when allograft survival rates were significantly lower, use of the internal iliac artery for a first kidney transplant was more common because this left the external iliac artery available for subsequent grafting. Currently, most kidney transplants are performed using the external iliac artery for blood supply. The renal vein is anastomosed to the external iliac vein. With the kidney perfused, the ureter is anastomosed to the bladder, using an extravesical technique that avoids opening of the bladder.

Infants and small children require modification of the standard surgical approach because of their size. Although transplantation of a small kidney into a young child can be performed using the approach and technique described above, most children receive an adult-sized kidney transplant. Through a midline incision, the peritoneal cavity is entered and the great vessels are exposed. The renal vessels are then anastomosed to the abdominal aorta and inferior vena cava. The common iliac artery and vein can also be used, depending on the size of the kidney and the recipient. The ureter is anastomosed to the bladder as described above.

Approximately 1 in 4 children presenting for transplantation have ESRD from urologic abnormalities. A small but significant proportion of these children have abnormal urine storage function due to a neurogenic bladder, lower urinary tract obstruction, reflux, or a congenital anomaly of the bladder or urethra (eg, exstrophy, posterior urethral valves). In addition, some children may have lost their bladders as a consequence of malignancy, radiation, or scarring from chronic infection. Despite these challenges, kidney transplantation can be successful in these patients.

Several reports describe drainage of a kidney transplant ureter to an augmented bladder, an incontinent urinary conduit, or a continent urinary reservoir with allograft survival comparable to that in children with normal bladders (Hatch, 1993). Such recipients are at increased risk of urine infections; therefore, closely monitor them. When necessary, clean intermittent catheterization has been successfully used in these patients to drain the urine.

## MEDICAL THERAPY

Modulation of the normal immune response mechanisms is a vital prerequisite to successful organ transplantation. The cascade of immunologic events triggered by the presence of foreign antigens can be interrupted or diminished at several key points.

### Antibodies

Many antilymphocyte antibodies have been used in transplantation. Polyclonal antibodies provide a relatively less specific impairment of lymphocyte activity. Monoclonal antibodies (ie, muromonab-CD3, daclizumab, basiliximab) provide more specific inhibition of lymphocyte function. Antibodies are used for induction (temporary use immediately following transplantation, while other immunosuppressive agents are adjusted) and for treatment of acute rejection.

- *Names* - Antithymocyte globulin (eg, Thymoglobulin, Atgam), muromonab-CD3 (Orthoclone OKT3), daclizumab (Zenapax), basiliximab (Simulect)

- *Method of action* - In general, antibodies used in immunosuppression interfere with the function of T lymphocytes; lysis of lymphocytes with a resulting lymphopenia caused by some agents; some antibodies cover or impair function of cell surface markers necessary for recognition and processing of foreign antigens in the cascade of the immune response; others may result in an increase of suppressor T lymphocytes

- *Dose* - Varies according to center and use
- *Antithymocyte globulin (Atgam), dose* - 10-15 mg/kg/d IV administered once daily for 5-14 days; many centers vary the duration, discontinuing the antibody when cyclosporine or tacrolimus levels are consistently within therapeutic range
- *Daclizumab dose* - 1 mg/kg IV on the day of transplant and repeated at weeks 2, 4, 6, and 8 following transplantation; some centers use only 2 doses in adults and older pediatric recipients (teenagers)

- *Basiliximab dose:* Children aged 2-15 years - 12 mg/m<sup>2</sup> IV administered within 2 hours prior to transplantation and repeated 4 days following transplantation

Patients older than 15 years - 20 mg IV administered within 2 hours prior to transplantation and repeated 4 days following it.

### Corticosteroids

Methylprednisolone dose - 10 mg/kg IV immediately prior to transplant with relatively rapid conversion to prednisone and tapering of dose over 12 weeks to baseline dose of 0.3 mg/kg/d PO. *Adverse effects* are hirsutism, acne, hypercholesterolemia, hyperlipidemia, avascular necrosis of the hip, glucose intolerance, growth retardation, gastritis, gastric ulcer, obesity, cataracts, impaired wound healing and mood alteration. In an effort to increase growth of pediatric recipients of kidney transplants and to avoid adverse effects, some centers taper and ultimately discontinue corticosteroids within 1 year of transplantation. Others have used steroid free protocols along with aggressive induction and maintenance therapy.

### Antimetabolites

These are useful adjunctive agents in any immunosuppressive protocol.

#### Mycophenolate mofetil, Azathioprine

- *Method of action:* Inhibition of cell proliferation. Mycophenolate mofetil blocks inosine monophosphate dehydrogenase, an enzyme necessary for purine synthesis specifically in lymphocytes. This provides more specific immunosuppression for transplantation than azathioprine. Azathioprine impedes purine synthesis, thus impairing cell division and proliferation.
- *Dosage:* Mycophenolate mofetil, dose- 1200 mg/m<sup>2</sup>/d PO divided in 2 doses. Azathioprine, dose - 1-2 mg/kg PO once daily.

### Calcineurin inhibitors

These constitute the sheet anchor of most modern day immunosuppressive protocols.

- *Method of action* - They block production of or action of IL-2 or other cytokines
- *Dosage* - Cyclosporine, 8-10mg/kg/d PO divided twice daily; dose adjusted to maintain trough whole blood level of 325-

400 ng/mL or a 2-hour peak level of 1,000-1,200 ng/mL; absorption and metabolism vary considerably; therefore, adjust dose individually; very young children and those with rapid metabolism of the drug may require 3 doses per day to maintain adequate trough level

- **Tacrolimus:** 0.2-0.3 mg/kg/d PO divided twice daily; dose adjusted to maintain trough whole blood level of 9-12 ng/mL in first 3 months following transplantation
- **Sirolimus:** 2 mg/m<sup>2</sup> PO once daily, administered 4 hours following cyclosporine; dose adjusted to maintain trough whole blood level of 8-15 ng/mL; simultaneous ingestion of fat may decrease absorption; patients should take sirolimus consistently either with or without food; it should not be taken with grapefruit juice (impairs absorption).

#### **Adverse effects of immunosuppressants**

- **Cyclosporine** - Hypertension, nephrotoxicity, hirsutism, gingival hyperplasia, neuropathy, increased susceptibility to infections, increased risk of malignancy
- **Tacrolimus** - Nephrotoxicity, neurotoxicity, hyperglycemia, hyperkalemia, increased susceptibility to infections, increased risk of malignancy
- **Sirolimus** - Hypercholesterolemia, hyperlipemia, hypertension, rash, increased susceptibility to infections, increased risk of malignancy, interstitial pneumonitis

#### **Current Immunosuppressive Protocols**

Data in children from the NAPRTCS study suggests that antibody induction therapy gives better results in pediatric transplantation<sup>4</sup>. Most centres have started using induction antibody treatment (referred to as quadruple immunosuppression) the major limiting factor being the affordability. At SGPGIMS, which has emerged as one of the largest pediatric transplant centres in our country, so far performed more than 100 kidney transplants in children. In our initial experience with 39 kidney transplants, a triple drug regimen of Csa, Aza and Prednisone was the cornerstone of immunosuppression in this public sector hospital<sup>5</sup>. We also observed that discontinuation of Csa was a major reason for poorer long term graft survivals<sup>5</sup>. There has been a dramatic increase in the use of tacrolimus instead of cyclosporine in view of the cosmetic advantages and superior potency. It has been estimated that treating 100 recipients with tacrolimus instead of cyclosporine for the first year after transplantation avoid 12 patients having acute rejection and two losing their graft but causes an extra five patients to develop insulin dependent diabetes. In our country too, use of tacrolimus is gaining popularity in pediatric transplants. We were amongst the first to use tacrolimus based protocol in children in our country. In our series of the last 30 children at SGPGIMS, we changed over to Tacrolimus, MMF and Prednisone as the standard immunosuppressive protocol. The major limitation to its widespread use remain the easy availability of drug level estimation. In contrast quadruple immunosuppression using antibody induction with tacrolimus has been the norm at leading private sector hospitals (Kher et al. personal communication) Excellent rehabilitation was observed with most children with functioning grafts, attending their school or college normally, doing well in both curricular and extracurricular activities<sup>8</sup>.

## **FOLLOW-UP CARE**

### **Laboratory studies**

- Complete blood cell count: CBC is performed to detect leukopenia (potential adverse effect of some immunosuppressive agents), leukocytosis (evidence of infection), and anemia.
- Serum electrolytes and liver enzyme tests: These tests are performed to monitor K<sup>+</sup>, PO<sub>4</sub> (hypophosphatemia common following successful kidney transplantation), and liver enzymes (hepatotoxicity from immunosuppressive medications).
- **CNI trough levels:** Because absorption and metabolism of cyclosporine and, to a lesser degree, tacrolimus can vary considerably, periodically measuring trough drug levels is important.

### **Imaging studies**

- **Ultrasonography:** By far the most useful imaging technique following transplantation, ultrasonography allows rapid visualization of the kidney, the collecting system, and the vessels. Color Doppler ultrasonography detects abnormalities of blood flow, including kinking of the artery or vein and thrombosis. Ultrasonography also aids in the detection of obstruction (hydronephrosis), lymphocele, urine or blood leakage (perinephric fluid collection), and kidney stones (rare).

Over the last decade there has been tremendous improvement in patient and graft survival. However these children remain at risk of numerous complications. The important *long-term complications* are as follows: (A.) Infections; (B.) Acute rejection; (C.) Chronic rejection; (D.) Renal artery stenosis; (E.) Malignancy; (F.) Growth; (G.) Graft loss; (H.) Patient death.

## **RENAL ALLOGRAFT SURVIVAL**

The outcome of renal transplantation in children has improved over the last several decades, a period which coincides with the introduction and widespread use of cyclosporine and other immunosuppressive agents<sup>11</sup>. In addition to the efficacy of newer immunosuppressive regimens, other general factors implicated in the success or failure of a renal allograft in children include<sup>12</sup>:

- (1.) source of donor kidney living-related donors;
- (2.) HLA compatibility;
- (3.) age of the donor and recipient;
- (4.) presence of preformed anti-HLA antibodies (sensitization);
- (5.) prolonged cold ischemia time;
- (6.) ethnicity of the recipient;
- (7.) history of focal glomerulosclerosis;
- (8.) acute rejection episodes;

The most common etiology of allograft loss among children and adolescents is rejection. Acute and chronic rejection caused almost half of the kidney transplant losses reported by members of the NAPRTCS<sup>11</sup>. This was true for both initial and second kidney transplant failures. Other causes in order of decreasing frequency include technical complications including thrombosis, death with a functioning kidney, recurrent or de novo kidney diseases, primary nonfunction, noncompliance with immunosuppression, and others. In our series the 1-year patient and graft survival was 89%. Three year patient and graft survival was 70%. Kaplan Meier revealed actuarial graft survival at 5 years of 50%. Twelve children discontinued CsA after 1 year post transplant and 5 of these had a

graft loss. Graft losses were significantly greater in patients who discontinued CsA (5/12 vs 2/22) as compared to those who continued CsA<sup>3</sup>.

## PATIENT SURVIVAL

Patient survival is better in pediatric renal transplant recipients than adults. In most pediatric series, mortality rates have decreased in recent years<sup>13</sup>. In data from the North American Registry, seven-year patient survival exceeded 90 percent in all recipients of living related or cadaveric donors, other than 0- to 1-year-old recipients of cadaveric donor kidneys. Patient survival is higher for living related graft recipients than for cadaveric graft recipients. Patient survival is significantly lower for very young (<1y) recipients<sup>11</sup>. Infant recipients of cadaveric kidneys have the highest mortality rate. The mortality is higher for very young children, and may vary with the underlying renal disease. As an example, the outcome after renal transplantation may be worse in children with lupus nephritis.

## GROWTH

Most children have an improvement in statural growth after successful renal transplantation; however, complete catch-up growth is infrequent<sup>14</sup>. The most important factors limiting growth after renal transplantation are renal graft function and corticosteroid therapy: Catch-up growth is only observed with normal or nearly normal function of the allograft. Growth is impaired when the dose of corticosteroids is above 5 mg/m<sup>2</sup> per day. These agents interact with the growth hormone insulin-like growth hormone axis, and are therefore associated with decreased levels of growth hormone and insulin-like growth hormone activity. Children who receive living-related donor (LRD) grafts appear to have better growth compared to those who receive cadaveric (CAD) donor grafts<sup>15</sup>. Growth hormone can be used safely in children who are more than 1 year post transplant and have stable graft function. Recently there has been a tendency to use steroid free protocols/ steroid minimization. In our anecdotal experience they have resulted in significant gain in

height without any increased rejection rate.

Thus renal transplant has revolutionized the therapy of children with end stage kidney disease. From what once considered an experimental procedure, it has over the last 3 decades evolved as the gold standard for therapy of these children.

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## LITERATURE REVIEW

### *Recovery of renal function after 90 days on dialysis: implications for transplantation in patients with potentially reversible causes of renal failure*

*Siddiqui S et al Clin Transplant 2008; 22: 136-140. ýý 2008 Blackwell Munksgaard*

Late recovery of renal function in patients requiring dialysis is a well recognized but an uncommon phenomenon. Moves to increase the number of live donor transplants and the recognition that early transplantation is associated with better graft survival; it is possible that patients who are going to recover renal function may be transplanted unnecessarily. Prospective survey of patients receiving dialysis for more than 90 d in south west Scotland from 1 January 1994 to 31 December 2005. Routine measurement of residual renal function by combined urea and creatinine clearance allowed us to detect late recovery whenever this occurred. Eight of 202 (4%) patients recovered sufficient renal function to stop dialysing after 90-d treatment. The likely cause of the renal failure in five of these patients was atheroembolism. One with atherosclerotic renovascular disease had been stented and would have received a live related renal transplant had his sister not had second thoughts about the procedure. **Conclusion:** It may be sensible to postpone transplantation in patients with certain types of renal failure, perhaps particularly patients with renovascular disease who have recently undergone a failed revascularization procedure.