Advances in Transplantation

Pediatric Renal Transplantation

Dr. Kanav Anand*, Dr. PK Pruthi**

*MBBS, MD Pediatrics, Fellowship in Pediatric Nephrology, Pediatric Nephrologist
**MBBS, MD Pediatrics, MNAMS, Senior Pediatric Nephrologist, Division of Pediatric Nephrology, Institute of Child Health, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi

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Introduction:

Although there have been many advances in conservative renal replacement therapy, renal transplantation is still the best treatment that can be offered to children with end-stage renal disease (ESRD) in order to improve their quality of life. The mortality with dialysis is much higher compared to renal transplantation. In the current scenario, with advancement in immunosuppressive therapy and the quality of care available for young children, renal allograft and patient survival have improved tremendously. Young prepubertal children are more likely to have improved growth post transplantation compared to those undergoing chronic dialysis. As a result, renal transplantation is the preferred renal replacement therapy for children with ESRD. Nowadays children are even going in for primary or preemptive transplantation, so as to avoid dialysis when a living donor is available.

The most common cause of ESRD in children who undergo transplantation is congenital malformations of the kidney and urinary tract (40 percent), followed by glomerular disorders (25 percent) and hereditary/genetic renal diseases (15 percent), particularly focal glomerulosclerosis.

Renal transplantation is usually an elective surgical procedure as most of donors are live donors rather than cadaveric donors. Inputs from the pediatric nephrologist, transplant surgeon and pediatric intensivist are imperative in providing optimum perioperative care to the transplant recipient.

Units involved in renal transplantation usually have detailed protocols on pre and postoperative care of donors and recipients. These protocols are updated regularly depending on the prevailing standards of therapy.

Immediate Preoperative Period

Most patients of ESRD are on maintenance dialysis prior to transplantation. The need to dialyze the patient immediately before transplantation is guided by the presence of fluid overload, hyperkalemia and day of last dialysis. Most centers prefer to dialyze patients on the evening prior to transplantation, mainly to prevent hyperkalemia. It is essential to maintain serum potassium levels below 5.5mEq/L to prevent arrhythmia during anesthesia and surgery. The incidence of preoperative hyperkalemia is as high as 20-38 per cent in various studies. Potassium binding resins can be administered orally or rectally to prevent this complication.

Significant volume reduction should be avoided during dialysis to prevent intraoperative hypovolemia. Long standing uremia can cause platelet dysfunction resulting in excessive bleeding during surgery. Regular dialysis preoperatively can ameliorate this abnormality. While anemia can lead to complications during surgery, blood transfusions should be limited in the preoperative period to prevent alloimmunization and the risk of graft rejection. Transfusions can be given if necessary during surgery. A hematocrit level above 35 percent is acceptable. Most patients undergoing transplantation are on treatment with iron, folic acid and erythropoietin, which maintains hematocrit in this range.
A detailed clinical examination should be done to ensure fitness for surgery. Fresh crossmatch of patient sera for anti HLA antibodies, against donor mononuclear cells, is done by flowcytometry or ELISA 1-2 days prior to the surgery. Two units of blood are arranged from the blood bank. A chest X-ray is done to rule out any infection or fluid overload and electrocardiogram for arrhythmia. Urinalysis and culture are obtained 2-3 days before transplantation.

Blood samples are taken for complete blood counts, electrolytes and blood gases prior to surgery. Estimation of bleeding time, clotting time and prothrombin time is also necessary. Consent from the prospective donor and recipient is taken on appropriate forms.

**Surgery**

In infants and young children the allograft is placed intra-abdominally. The renal artery is connected to the aorta and renal vein to the inferior vena cava. In older children the graft is placed in the iliac fossa and the renal artery and vein are connected to common or external iliac artery and vein respectively. Advancements in the vascular techniques have decreased the incidence of allograft loss due to vascular thrombosis. The ureter is anastomosed to the bladder using uretero-neocystostomy. The arterial supply of lower ureteric segment should be preserved as ischemia here can cause ureteral obstruction or urinary leaks. With stringent aseptic practices and use of perioperative antibiotics, wound infections have become uncommon.

Pre-transplant native kidney nephrectomy/ nephroureterectomy are no longer a routine procedure. The native kidneys are left in place because they still may produce significant volumes of urine, secrete erythropoietin and convert vitamin D to its active metabolites. Unilateral or bilateral nephrectomy/nephroureterectomy is done in specific instances, such as large polycystic kidneys, significant proteinuria, poorly controlled hypertension and chronically infected kidneys.

Intraoperative management includes appropriate fluid therapy and administration of immunosuppressive drugs, diuretics and antibiotics. Good hydration is important to ensure adequate blood flow to the allograft. A sluggish flow can promote its thrombosis and acute tubular necrosis. The central venous pressure (CVP) should be monitored and maintained between 10-12 cms of water during and after surgery. A good peripheral venous access should be established to deal with copious fluid replacement. Mannitol (0.5 g/kg) is given intravenously in the theatre before the arterial clamp to donor kidney is released followed by intravenous frusemide at a dose of 1-2 mg/kg. This causes brisk diuresis and prevents graft ischemia. The appearance of the renal allograft after completion of the anastomosis, and release of vascular clamps should be recorded in the notes. Intraoperative perfusion characteristics of the graft and intraoperative urine volume are good predictors of graft function.

**Postoperative Period**

The transplant team should evaluate the patient on arrival from the operating room. The initial assessment should include hemodynamic and respiratory stability. Most patients are awake and extubated.

The primary goal during immediate postoperative period is to promote and maintain renal perfusion and diuresis. This is achieved by administration of a combination of crystalloid and colloid solutions to replace urine output, insensible losses, gastrointestinal and third space losses. The patient requires close hemodynamic monitoring and meticulous fluid management in an intensive care unit. Details of routine monitoring and evaluation during the first 48 hours is mentioned in Table 1.
Table 1
Monitoring of transplant recipients during first 48-72 hours

<table>
<thead>
<tr>
<th>Monitoring Parameters</th>
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<tbody>
<tr>
<td>Urine output every 30 minutes for 6-8 hours and then every hourly</td>
</tr>
<tr>
<td>Blood pressure every 30 minutes for first 6 hours, every hourly for 24 hours and then 6 hourly</td>
</tr>
<tr>
<td>CVP* every hourly for initial 12 hours and then 4-6 hourly</td>
</tr>
<tr>
<td>Temperature hourly for initial 4 hours and then every 6 hourly</td>
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<tr>
<td>Weight once a day</td>
</tr>
<tr>
<td>Hemoglobin and complete counts daily</td>
</tr>
<tr>
<td>Blood sugar, urea, creatinine, electrolytes, calcium, phosphate, bicarbonate every 12 hourly</td>
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</table>

* CVP - Central venous pressure

Fluid Management

It is desirable to maintain adequate hydration to prevent hypovolemia and graft dysfunction. The CVP should be maintained at 10-12 cms of water. Careful monitoring of heart rate and blood pressure also detects any hypovolemic episodes. A detailed record of urinary output and drain volumes is maintained. Pediatric recipients of adult kidney frequently produce large volumes of urine during immediate post-operative period. Urine output is replaced with 5 per cent dextrose in 0.45 per cent saline and 10 ml sodium bicarbonate per liter, on a volume for volume, hourly basis. Insensible water losses are electrolyte free, and are replaced with 5 per cent dextrose solution. Blood loss incurred during and after surgery is also replaced. Maintenance potassium is added when serum potassium falls below 3.5mEq/L.

Maintaining adequate systemic pressure is imperative, since, the allograft is very sensitive to even brief episodes of hypoperfusion. Dopamine may be infused at a rate of 5-8 µg/kg/min to maintain a mean arterial pressure above 80 mmHg. The rates of infusion can be increased to 10µg/kg/min. While low dose dopamine is frequently used in a number of transplant units, for the first 48 hours, the benefits of this practice are controversial.

In patients having oliguria after the surgery, if the urine volume is below 2 ml/kg/hour and CVP measures above 12 cms then a single dose of furosemide (1 mg/kg) is given. If the CVP measures below 10 cms, a bolus of 10 ml/kg normal saline or 5-10 ml/kg 5 percent albumin is administered. Besides the CVP, clinical status and chest X-ray are also good measure of volume overload. If the renal functions are deranged and urine output is decreased, then the fluid is administered as insensible water losses (400 ml/m²) plus the urine output.

Polyuria (urine volumes of > 4 ml/kg/hr) can result in dyselectrolytemia. For these patients only 50-75 per cent of the output is replaced every hour. If urine flow rates are more than 8 ml/kg/hr, then the dextrose content of replacement fluid should be reduced to 2.5 percent. This replacement is continued for first 48 hours. If hyperglycemia or glucosuria occurs, plain insulin can be used as an intravenous drip or intermittent subcutaneous boluses (one unit of plain insulin neutralizes about 3-4g of dextrose). Hypocalcemia may also occur and should be monitored closely. Urinary phosphate wasting often results in hypophosphatemia. Phosphate supplements should be given if serum phosphate levels are below 3.5 mg/dL. After 48 hours if the kidney function tests are normal, the fluids are reduced to half of the urine output. By day 3 to 5 most children with satisfactory graft function do not require intravenous replacement of urinary fluid losses.
Fluid requirements are met with ad-lib administration of oral fluids.

Hypertension is common in the immediate post-transplant period. During the first month following transplantation, it occurs in 80 and 60 percent of recipients of allografts from deceased and living related donors, respectively. But the incidence decreases with time. The etiology is multifactorial and includes pre-existing hypertension, volume overload and medications like steroids and cyclosporine. Hypertension can be managed with the use of calcium channel blockers like sustained release preparation of nifedipine (0.5-2 mg/kg daily) or amlodipine (0.1-0.5 mg/kg/day). Other medications that can be used are beta-adrenergic antagonists like atenolol (1-2 mg/kg/d), alpha-receptor blocker prazosin (0.1-0.4 mg/kg/d) or a central adrenergic agonist clonidine (10-40 µg/kg/d). ACE inhibitors should be avoided in the immediate post-transplant period as they may decrease the perfusion of the allograft.

Complications

Impaired graft function frequently complicates the initial post-transplant period. Early non-function with oligoanuria chiefly reflects pre-transplant events that have compromised graft function. These include hypovolemia in the donor or recipient, unrecognized recipient immunity against donor tissue or complications of the surgical procedure.

Oligoanuria in the immediate post-transplant period should be thoroughly evaluated. All pre and post-renal causes should be excluded. Decreased intravascular volume is the chief pre-renal cause of graft dysfunction. Common causes of early graft dysfunction are mentioned in Table 2. Pre-renal dysfunction is managed with administration of intravenous fluid boluses and is usually reversible.

Table 2

Causes of early allograft rejection

<table>
<thead>
<tr>
<th>Cause</th>
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<tr>
<td>Hypovolemia</td>
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<tr>
<td>Acute tubular necrosis</td>
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<tr>
<td>Hyperacute, acute rejection</td>
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<tr>
<td>Catheter obstruction</td>
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<tr>
<td>Arterial or venous thrombosis</td>
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<tr>
<td>Urine leak</td>
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Hematuria is an expected consequence of ureteral transplantation and if associated with poor urinary flow can result in clot formation and obstruction of urinary catheter. Catheter obstruction also increases intraluminal pressure in the bladder, thereby threatening the ureteral anastomosis. Bladder catheter should be irrigated, flushed and if necessary, changed. If this does not alleviate the oliguria or gross hematuria, a renal ultrasound should be done to rule out ureteral obstruction and/or dilatation of the renal graft pelvis. Presence of ureteral obstruction may require surgical intervention. If oligoanuria persists despite these measures acute tubular necrosis (ATN) or vascular thrombosis (arterial or venous) should be suspected.

ATN commonly occurs due to persistent hypovolemia or prolonged cold ischemia time. This is usually reversible.
Vascular thrombosis is usually a result of unsatisfactory surgical technique. Clinically such a patient will present with graft tenderness, pain and decreased urine output. Vascular thrombosis of the renal artery or vein is the third most common cause of graft failure in children receiving renal transplants. High risk patients for thrombosis are extremely young donors or recipients. Other risk factors include hypercoaguable state like nephrotic syndrome, venous malformation in the recipient, pretransplant peritoneal dialysis, hypotensive episode during or after surgery and the presence of multiple arteries. Prophylactic therapy with heparin, low-molecular-weight heparin, and/or aspirin to prevent thrombosis for those with an increased risk of thrombophilia has been successful in preventing graft loss. In some centers, low-molecular-weight heparin is used prophylactically in all pediatric renal transplant recipients. Although vascular thrombosis is usually observed within the first few days following transplantation, it can be seen as late as three weeks post-transplant.

It is essential to evaluate all patients of oligoanuria with an ultrasound doppler and a radionuclide renal scan. Doppler helps in differentiating a vascular obstruction from an episode of rejection or urinary leak. If the flow study reveals no demonstrable blood flow to the graft, a prompt surgical reexploration is necessary. A majority of these grafts would finally be lost and patients rever back to hemodialysis.

Hematomas and lymphoceles may develop after the surgery and impinge on the allograft vessels or the ureters causing impaired function. Post-surgical bleeding is usually managed conservatively, with blood and blood products, and does not require re-exploration on most occasions.

**Hyperacute Rejection**

Hyperacute rejection occurring within the first minutes following transplantation results from preformed cytotoxic antibodies in recipient against donor class I or II HLA antigens. These antibodies bind to the endothelial surfaces of the arterioles on the graft, activate complement, and lead to severe vascular injury, including graft thrombosis and obliteration of graft. It manifests with fever, rapid development of dysuria, graft tenderness and swelling within first week of transplant. Apart from radiological investigations, a renal biopsy is of significant help in diagnosing hyperacute rejection. Blood levels of panel reactive antibodies (PRA) level are high in such patients. The availability of modern crossmatching techniques has greatly reduced the incidence of hyperacute rejection. In case of a rare occurrence, the patient may be treated with pulse methyl-prednisolone (30-40 mg/kg/day) for 3 days. Besides steroids, other immunosuppressive agents like monoclonal (OKT3) and polyclonal antibodies (anti-thymocyte and antilymphoblast globulins) have been used for treatment of rejection. These antibodies bind to various T cell receptors, leading to their inactivation. Administration of monoclonal antibodies against interleukin-2 receptors (basiliximab, daclizumab) may be useful in some cases. Intravenous immunoglobulins and plasmapheresis have also been recommended for the treatment of episodes of rejection, which are resistant to the above therapies.

**Acute Rejection**

Acute rejection is the main cause of allograft dysfunction in the first post-transplant year. It may be seen at anytime post-surgery but most commonly in the first six months. It is defined as an acute deterioration in allograft function, generally detected by an elevation in the serum creatinine level, which is associated with specific pathologic changes in the graft obtained via an allograft biopsy. The two principal histologic forms of rejection are acute cellular rejection and acute antibody-mediated rejection. Most episodes of acute rejection are predominantly cellular and are reversible with appropriate treatment. Patients often present with fever, deranged renal functions, graft tenderness and oliguria. The differential diagnosis includes urinary tract infections,
cytomegalovirus infection and cyclosporin toxicity. Besides infection screen and cyclosporin blood levels, an ultra-sound doppler and a nuclear scan often help in distinguishing between these conditions. Graft biopsy is however essential to establish the diagnosis of rejection. About 75 per cent of these rejection episodes reverse on treatment with methyl-prednisolone. Treatment with monoclonal antibodies (OKT3) is recommended for treatment of patients who do not respond to treatment with steroids.

Other Complications
Patients should be ambulated by 24-48 hours and should start on a liquid diet by the third day. Mild to moderate pain may occur at the incision site in the first week. Severe pain or absence of bowel sounds by 48-72 hours should be investigated to exclude rejection, perinephric hematoma and urinary leak. Fever in the first week could be due to postoperative complications like atelectasis, wound, urinary tract or central line infections. More than 90 percent infections in the first post-transplant month are due to problems related to surgery, drains and catheter.

Most opportunistic infections are uncommon during this period and usually occur beyond the first 2 months of surgery. These include infections due to cytomegalovirus, Ebstein-Barr virus, BK (polyomavirus) virus, mycobacteria and pathogenic protozoa like toxoplasma and pneumocystis. These patients are also more predisposed to fungal infections including cryptococcosis and aspergillosis.

Diagnosing these infections is often difficult due to concomitant immunosuppression. A high index of suspicion is thus necessary.

Immunosuppression
The goal of immunosuppression is to prevent acute rejection while minimizing the drug side effects. In children who undergo renal transplantation, immunosuppression is divided into the three following categories:

- Induction therapy – Intensive immunosuppression administered during the perioperative period to prevent acute rejection
- Maintenance therapy – Immunosuppressive therapy to prevent acute rejection after the perioperative period
- Treatment of acute rejection – Immunosuppressive therapy to treat acute rejection

In general, immunosuppression should be highest during the first three months after transplantation when the risk of acute rejection and allograft loss is greatest. Immunosuppression is tapered slowly to a maintenance level by 6 to 12 months post-transplantation.

Most centers follow an immunosuppression protocol comprising an induction with Anti-thymocyte globulin/OKT3/Alemtuzumab/basiliximab followed by maintenance with combination of corticosteroids, antimetabolites (azathioprine / MMF) and calcineurin inhibitor (cyclosporine / tacrolimus); however, immunosuppression may require modifications as per patient's characteristics. Immunosuppression is begun 12 hours prior to the transplant with oral cyclosporine and azathioprine at doses of 7.5mg/kg and 5mg/kg respectively. Intravenous methylprednisolone is infused at doses of 10 mg/kg (diluted in normal saline and given over 20-30 minutes), two hours prior to the surgery. The next dose of cyclosporine and azathioprine is administered 6-8 hours following surgery. Therapy with oral prednisolone is started from the next day at doses of 2 mg/kg/day, with a gradual reduction to approximately 0.12 to 0.16 mg/kg per day within a 6 to 12 month
period. Alternate-day dosing is often administered 6 to 12 months post-transplant to minimize the effect of corticosteroids on growth. Cyclosporine is administered at the dose of 10-12 mg/kg/day for the first fortnight and then tapered to 8-10 mg/kg/day over the next two weeks. Azathioprine is continued at doses of 1-2 mg/kg/day. Some centers prefer to use tacrolimus, another calcineurin inhibitor instead of cyclosporine. Mycophenolate mofetil (MMF) has replaced azathioprine in most transplant centers in the developed countries. This drug is a more specific inhibitor of lymphocyte proliferation and has less bone marrow toxicity. Randomized trials have shown that the use of tacrolimus and MMF is superior to cyclosporine and azathioprine respectively in the prevention of acute rejection episodes and chronic allograft nephropathy.

Monitoring

Urine output is carefully monitored during the first 3-4 days of surgery. The bladder catheter is usually removed after 48 hours. Vitals are initially monitored every 30-60 minutes and then 2 hourly. The central venous pressure is initially measured hourly and then 6 hourly. If blood pressure and urine output is normal, the CVP catheter is removed after 48-72 hours. A rise of body temperature may occur because of infection or rejection. Blood levels of urea, creatinine, sodium, potassium, calcium, phosphate, hemoglobin and counts are measured every 12 hours initially and then once daily. A blood cyclosporine level (C2 level or trough) is done at the end of first week. The accepted 12-hour trough levels of cyclosporine are between 250-300 ng/ml in the first two transplant months. Recently peak drug levels (C2), 2 hours after oral dosing are measured at many centers. These levels correlate better with drug exposure as compared to trough levels and the accepted target levels in the first two months of transplant vary between 1500-2000 ng/ml. The trough levels vary with the methodology of testing. High performance liquid chromatography (HPLC) is the most specific method to measure the unmetabolized drug. Other methods like radioimmunoassay and enzyme linked immunoabsorbent assay are cheaper and easier to perform though they overestimate the drug levels by almost 20-30 percent. A DTPA scan is done to assess graft function after 72 hours. If there are no complications in the post-operative period, most patients are ready for the discharge by the second week of surgery.

After discharge, graft function should be assessed at least thrice weekly for 2 weeks, twice weekly and weekly for a month each, and then at monthly intervals.

Other Medications

Antibiotic prophylaxis with cephalosporins is given for the initial 3-5 days. Urinary prophylaxis with cotrimoxazole (2mg/kg trimethoprim) is begun when the serum creatinine falls below 1.5 mg/dL and is continued for three to six months; this also prevents opportunistic infections with pneumocystis and toxoplasma. Oral antifungal prophylaxis with nystatin/fluconazole is also given during this period. Pain is relieved using paracetamol. Prophylaxis against acid peptic disease is provided with histamine-2 receptor blockers or proton pump inhibitors for 1-2 months. Ganciclovir prophylaxis for cytomegalovirus disease is usually reserved for high-risk patients (donor positive; recipient negative serology). The prophylaxis for such patients is given intravenously with ganciclovir for the first 2 weeks and then orally with either ganciclovir or valganciclovir for 3 months.

Survival

Over few decades, there has been gradual but steady improvement in graft survival as a result of introduction and widespread use of calcineurin inhibitors and other immunosuppressive agents. As per the 2010 NAPRTCS
(North American Pediatric Renal Trials and Collaborative Studies) annual transplant report, the one, three and five year allograft survival rates are 96.5, 91.5 and 84.3 percent for living donor recipients, and 95.1, 84.1 and 78 percent for deceased donor recipients.

Factors that affect renal allograft survival include:

- **Donor source** – Allograft survival is better with kidneys from living versus deceased donors.
- **Donor age** – Poorer allograft survival is associated with renal allografts from deceased donors younger than 2 years of age or older than 50 years of age. In the former, poorer allograft survival may be due to a higher incidence of primary nonfunction and allograft thrombosis.
- **Histocompatibility matching** – Better the match between donor and recipient, higher are the chances of an improved allograft survival.
- **Recipient** – Infants and adolescent recipients have a lower allograft survival rate.
- **Acute rejection episodes and subsequent infection with either cytomegalovirus or BK virus are associated with decreased allograft survival time.**

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**Further reading**