Review: Renal Transplants - The Current Scenario

Dr. S. M. Ambike
Consultant Nephrologist
Head of Nephrology Dept.,
Jehangir Hospital, Pune, Maharashtra

Secretary - Pune Nephrology Group
## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>History of Renal Transplants</td>
<td>2</td>
</tr>
<tr>
<td>Factors Affecting Recipient</td>
<td>4</td>
</tr>
<tr>
<td>Eligibility for Renal Transplant</td>
<td></td>
</tr>
<tr>
<td>Donor Selection for Renal Transplants</td>
<td>8</td>
</tr>
<tr>
<td>Transplant Compatibility</td>
<td>11</td>
</tr>
<tr>
<td>Transplant Procedure</td>
<td>13</td>
</tr>
<tr>
<td>Transplant Rejection</td>
<td>16</td>
</tr>
<tr>
<td>Immunosuppressive Therapy in Renal Transplants</td>
<td>19</td>
</tr>
<tr>
<td>Long Term Complications Following Renal Transplant and their Management</td>
<td>24</td>
</tr>
<tr>
<td>Down the Memory Lane</td>
<td>30</td>
</tr>
<tr>
<td>References</td>
<td>31</td>
</tr>
</tbody>
</table>
Introduction

Since the first successful renal transplant between living patients undertaken in Boston in 1954 where a kidney from one twin was transplanted into another, renal transplantation has moved a long way from being at the cutting edge to being a well-established mature technology. Advances in immunosuppression, organ preservation, surgical techniques and perioperative management have resulted in greatly improved survival rates for renal transplants. Rejection rates have fallen over the years, and rejection is now an uncommon cause of early loss of a graft. Currently, live-donor grafts have a survival rate of 95% at 1 year while deceased-donor grafts have a survival rate of 89% at 1 year. The average life expectancy of a living donor graft is 20 years & that of a deceased donor graft is close to 14 years.

Renal transplantation usually results in an improved life-style and improved life expectancy as compared to patients on dialysis. On the long run, the overall cost too is lower as compared to the alternative of remaining on dialysis. Hence, renal transplantation is now considered the treatment of choice for patients with end stage renal disease (ESRD). The success of renal transplantation has led to an increased demand of the procedure as well as increased acceptance of patients considered as “high risk” candidates for transplantation.

The main problem encountered today is the shortage of donor organs. Moreover, the incidence of ESRD continues to increase every year and is likely to worsen further with the increasing incidence of obesity & diabetes. As the incidence of ESRD increases, the demand for kidney transplants too would continue to increase. Unfortunately, the number of available donors always far lags behind the demand.

Better graft survival, especially those received from live donors, has resulted in an improved patient survival. The 1 year survival rate in patients who have received a live donor transplant has been reported to be 98%, the 5 year survival rate as 90% and the 10 year survival rate as 76%. The improved patient survival has also brought to the forefront, the long term complications associated with renal transplants.
like increased propensity to various infections as well as malignancy due to the continued life-long use of immunosuppressant drugs, an "epidemic" of cardiovascular disorders and problems like diabetes or worsening of diabetes control, anemia, osteoporosis, gout etc. It is important that the primary care physician be aware of these complications and its effective management as many kidney transplant recipients are likely to follow-up with them for routine medical care.

History of Renal Transplants

Human kidney transplantations were initially performed in the 1930s. However, as there was no knowledge of transplantation immunology or organ preservation techniques at that time, all the transplants were unsuccessful, mostly because of graft rejection.

The first cadaveric kidney transplantation was performed on June 17, 1950, on Ruth Tucker, a 41-year-old woman with polycystic kidney disease. Although the donated kidney was rejected ten months later because no immunosuppressive therapy was available at the time, the intervening time gave Tucker’s remaining kidney time to recover and she lived another five years.

The first successful kidney transplant between living patients was undertaken in 1954 in Boston in the US on December 23, 1954, at Brigham Hospital. The surgery was performed by Joseph Murray, J. Heartwell Harrison, John P. Merrill and others. The transplant was done between identical twins, Ronald and Richard Herrick, to eliminate any problems of an immune reaction. Ronald was the donor. Richard survived for 8 years after the transplantation. For this and later work, Dr. Joseph Murray received the Nobel Prize for Medicine 1990.

The major barrier to organ transplantation between genetically non-identical patients lay in the recipient’s immune system, which would treat a transplanted kidney as a "non-self" and reject it. Thus, having medications to suppress the immune system was essential.

With a better understanding of transplant immunology, investigators began to focus on ways to depress the recipient’s immune system. The earliest successful immunosuppression combination of azathioprine and prednisone resulted in
The initial successful immunosuppression with azathioprine and steroids improved the survival in the 1960s between non-identical donors. Prolonged survival of human renal transplants, and by the mid-1960s this regimen emerged as the standard for post-transplantation immunosuppression. It was not until cyclosporine was introduced into immunosuppressive regimens in the late 1970s and early 1980s that the modern era of transplantation began.

The mainstay of immunosuppression therapy today remains directed at the inhibition of the molecular pathways of T-cell activation and function. The drugs used include calcineurin inhibitors (tacrolimus and cyclosporine) that interfere with the interleukin-2 gene activation protein NF-AT (nuclear factor of activated T cells), corticosteroids (prednisone) that interfere with T-cell growth factors and antigen presentation, and agents that interfere with T-cell proliferation (azathioprine and mycophenolate mofetil, which are antimetabolites, and sirolimus, which inhibits targets of rapamycin).

Many transplant recipients also receive antilymphocyte induction therapy to immobilize their existing T cells. These agents include polyclonal antibody preparations such as antilymphocyte globulin and antithymocyte globulin, or monoclonal antibody preparations such as OKT3. Recently, more specific biological inhibitors of T-cell function have been introduced. They include the anti-interleukin-2 receptor antibodies, basiliximab and daclizumab. Immunosuppressive regimens that eliminate steroid use and reduce calcineurin inhibitors are being developed by combining existing medications with newer agents. The aim of these new regimens is to optimize recipient immunosuppression while minimizing the deleterious side effects of the drugs.

Introduction of Cyclosporine in the late 1970s and early 1980s dramatically reduced the rates of acute rejection episodes and improved survival.
Factors Affecting Recipient Eligibility for Renal Transplant

The patient receiving the kidney usually has end-stage renal disease (ESRD). ESRD is defined as a glomerular filtration rate < 15 ml/min. Conditions which can lead to ESRD include diabetes mellitus, malignant hypertension, infections and focal segmental glomerulosclerosis; genetic causes include polycystic kidney disease, a number of inborn errors of metabolism and autoimmune conditions such as lupus. Of these, diabetes is the most common cause of ESRD.

Cause of ESRD:

The cause of ESRD is by and large never a contraindication to renal transplant. However, some conditions are recurrent and can affect the transplanted kidney.

Certain diseases like primary glomerulonephritis, diabetic nephrosclerosis tend to recur in the transplanted kidney

Like if a patient has glomerulonephritis which was responsible for causing ESRD, there is a 5% to 20% chance of recurrence of glomerulonephritis following transplantation. However, it is difficult to predict either the risk of recurrence or the aggressiveness with which recurrent disease may progress in an individual transplant recipient.

Thus despite the risk of recurrent glomerulonephritis, there is no contraindication to a first kidney transplant in patients with ESRD due to primary glomerulonephritis and an otherwise eligible patients with ESRD due to primary glomerulonephritis should be offered transplantation. However, patients should be made aware of the risk of recurrent disease during their pretransplant evaluation.

Renal Function:

The majority of renal transplant recipients are on dialysis at the time of transplantation. Although it has been argued that patients should not receive a transplant until dialysis has been established, evidence shows that preemptive transplantation, before dialysis is needed, is associated with lower morbidity and improved long-term outcome. Rather the Canadian Society on Transplantation consensus guidelines mentions that preemptive kidney transplantation is the preferred form of renal replacement therapy and should be encouraged where feasible. However, preemptive kidney transplantation should not proceed unless the measured or calculated glomerular filtration rate is < 20 mL/minute and there is evidence of progressive and irreversible deterioration in renal function over the previous 6–12 months.
Due to low availability of donors as compared to the patients requiring transplants, on ethical grounds it is ensured that the patient has a life expectancy of greater than 5 years to be eligible for a transplant. Candidates hence undergo a thorough screening to evaluate the risk-versus-benefit evaluation before being approved for transplantation. Significant, incurable terminal infectious diseases and cancer are often considered transplant exclusion criteria.

**Pre-transplant evaluation**

<table>
<thead>
<tr>
<th>Cardiac evaluation and fitness for major surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic functions</td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Malignancy</td>
</tr>
<tr>
<td>Major organ dysfunction</td>
</tr>
</tbody>
</table>

**Cardiovascular Status:**

All transplant recipients should be assessed for the presence of ischemic heart disease (IHD) before kidney transplantation. Transplantation is contraindicated in patients with IHD in the following situations:

- Patients with progressive symptoms of angina
- Patients with a myocardial infarction within 6 months
- Patients with severe diffuse disease, especially with positive non-invasive tests in whom intervention is not possible and in whom, expected survival is sufficiently compromised so that transplantation is not reasonable

Kidney transplantation should be deferred in patients with a history of stroke or transient ischemic attack for at least 6 months following the event. The patient should be stable, fully evaluated and treated with risk-reduction strategies before kidney transplantation.
Infections:

HIV was at one point considered to be a complete contraindication to transplantation. However, at many centres infected patients with end-stage kidney failure are considered for kidney transplantation if they meet the following criteria:

- Demonstrated adherence to a highly active anti-retroviral therapy (HAART) regimen
- Undetectable (< 50 copies/mL) HIV viral load for > 3 months
- CD4 lymphocyte count > 200/mL for > 6 months
- No opportunistic infections
- Willingness to use prophylaxis against congenital CMV, Herpes simplex virus, Pneumocystis carinii pneumonia and fungal infection
- Freedom from neoplasia

All transplant candidates should be screened for evidence of liver disease. Patients with liver disease should be followed by a gastroenterologist, who should re-evaluate their condition (with laboratory testing and diagnostic imaging) as clinically indicated for evidence of progression to cirrhosis and development of hepatocellular carcinoma. Transplant candidates with cirrhosis should not be considered for kidney transplantation alone, but may be considered for combined liver–kidney transplantation.

Patients who are HBsAg negative should be vaccinated against hepatitis B virus (HBV) if they are not already immunized. At least 1 dose of vaccine should be given before transplantation. HBV antibody status should be monitored and booster doses given when antibody concentrations fall below protective levels.

Long-term mortality after renal transplantation is higher in HBV-infected patients (i.e., HBsAg+) and they should, therefore, be fully informed. All transplant candidates infected with HBV should be assessed for evidence of viral replication by testing for serum transaminases, hepatitis B e-antigen (HBeAg) and HBV deoxyribonucleic acid (DNA). They should also undergo liver biopsy. Patients with active liver disease (including chronic active hepatitis) should be treated with lamivudine or interferon alpha in the pre- and post-transplant period. Patients treated in the pretransplant period who do not respond to therapy are at high risk for progressive liver disease after transplantation; such patients may hence be excluded from renal transplants.

Hepatitis B patients with active liver disease who do not respond to antiviral drugs are excluded from renal transplant.
Patients with hepatitis C virus (HCV) should be considered for kidney transplantation as the procedure is not associated with increased short-term mortality compared with dialysis.

Transplant candidates should be screened for tuberculosis with a careful clinical history, chest radiography, and purified protein derivative (PPD) skin testing. Patients with active tuberculosis (positive cultures, clinical signs and symptoms, or positive imaging studies) should receive adequate therapy with documented microbiologic and radiologic resolution before transplantation. Patients with latent tuberculosis (positive skin test or chest radiograph suggesting quiescent tuberculosis) without a history of adequate treatment or prophylaxis should be considered for prophylaxis pre- or post-transplant, provided no contraindications exist.

**Malignancy:**

Patients being evaluated for kidney transplantation, particularly those over 50 years of age, should be screened for pretransplant malignancy. Renal transplant candidates with a previous history of malignancy should be tumor free before proceeding with transplantation. Most renal transplant candidates with a history of malignancy should wait a period of time between successful treatment and transplantation. The length of time will depend on the type of malignancy.

**Age:**

Advanced age per se is not a contraindication to kidney transplantation. Improved patient and graft survival with current immunosuppressive protocols has broadened the application of kidney transplantation to selected elderly patients, and increasing numbers of patients over the age of 65 are receiving transplants. Although life expectancy is less, such recipients experience graft survival rates that are at least as good as those of younger patients. However, it is also important to realize that older recipients are at greater risk of perioperative complications, including death, largely due to infection and cardiovascular disease.

**Obesity:**

Obesity is not a contraindication for renal transplant. Obesity has been associated with hypertension, the development of type 2 diabetes mellitus, and increased risk of death in the general population. Obese patients undergoing kidney transplantation are similarly at risk of adverse outcomes. Moreover, they are at higher risk of delayed graft function and suffer from more wound complications, resulting in increased length of hospital stay. Obesity has been associated with a higher risk of graft loss and patient survival is also adversely affected. In patients with a BMI above 33 kg/m², the risks of transplantation are high. The increased risk
of death first becomes significant when BMI is 34–36 kg/m². The relative risk of death is even greater when BMI at transplant is above 36 kg/m². Thus transplantation at this level of BMI may be associated with unacceptably higher risk, needing careful consideration. It is prudent to strongly recommend weight reduction to a BMI < 30 kg/m² before kidney transplantation.

**Treatment Compliance:**

Candidates are typically screened to determine if they will be compliant with their medications, which is essential for survival of the transplant. History of psychiatric illness is not an absolute contraindication to kidney transplantation. However, such patients should be assessed to ensure that they are capable of giving informed consent and adhering to therapy.

**Donor Selection for Renal Transplants**

Kidney transplantation is typically classified as living-donor or deceased-donor (formerly known as cadaveric) transplantation depending on the source of the donor organ. Living-donor renal transplants are further characterized as genetically related (living-related) or non-related (living-unrelated) transplants, depending on whether a biological relationship exists between the donor and recipient. Deceased donor transplants are further characterized as Brain-dead (BD) or “beating heart” donors and Donation after Cardiac Death (DCD) or “non-beating heart” donors.

---

**Fig. 1. Types of Kidney Transplant**
Live Donor Transplants:

The live donors are usually family members and hence have at least partial compatibility for HLA antigens. In case of non-related donors, one aims for as close matching of the HLA antigens as possible. The donor should preferably have the same ABO blood group as the recipient. Being a universal donor, it is possible for a person with type O blood group to donate a kidney to an A, B or AB recipient. These days with highly potent immunosuppressive therapy being available, a kidney can be transplanted from the donor to the recipient even if there is no HLA or blood group matching. However, it is important to remember that a high degree of immunosuppression is associated with its own drawbacks. Hence, wherever possible, a close match of blood group and HLA antigens is sought for. As the Rh antigen is not expressed on the graft tissue, matching of the Rh blood group is not required.

All potential live donors are carefully evaluated on medical and psychological grounds. This is done to ensure that the donor is fit for surgery and has no disease which could bring undue risk or likelihood of a poor outcome for either the donor or recipient. The psychological assessment ensures that the donor has given an informed consent and has not been coerced.

When first degree relatives are donors, the graft survival rates at 1 year are 5-7% greater than those for deceased-donor grafts. The 5-year survival rates still favor a partially matched (3/6 HLA mismatched) family donor over a randomly selected deceased donor. In addition, the live donors provide the advantage of immediate availability. For both live as well as deceased donors, the 5-year outcomes are poor if there is a complete (6/6) HLA mismatch.

The survival rate of living unrelated kidney transplants is as high as that of a perfectly HLA matched (6/6) deceased kidney graft and comparable to that of kidneys from live related donors. This outcome is probably due to both a short cold ischemia time and extra care taken to document that the condition and the renal function of the donor are optimal before proceeding with a live unrelated donation.

Although it is well documented that the live donor can survive well on only a single kidney, there are concerns expressed about the potential risks to which the volunteer kidney donor is exposed. This includes potential risk of premature renal failure due to several years of increased blood flow and hyperfiltration in the remaining kidney. There are reports of the development of hypertension.
proteinsuria, and even lesions of focal segmental sclerosis in donors over long-term follow-up. Moreover, the problems associated with having a single kidney in the donor can become significant when other conditions like hypertension or diabetes develop. There are also occasional reports of hydrocele developing on the side of nephrectomy.

**Deceased Donor Transplants:**

Deceased donors can be divided into two groups:

**Brain Dead (BD) or Beating Heart Donors**

**Donation after Cardiac Death (DCD) or Non-beating heart donors**

Although "brain-dead" or "beating heart" donors are considered dead, the donor's heart continues to pump and maintain the circulation. This makes it possible for surgeons to start operation while the organs are still being perfused. During surgery, the aorta is cannulated, after which the donor's blood is replaced by an ice-cold storage solution. Due to the temperature of the solution, and since large amounts of cold NaCl solution are poured over the organs for a rapid cooling, the heart stops pumping.

"Donation after Cardiac Death" or "Non-beating heart" donors are undertaken from patients who do not meet the brain-dead criteria but, due to the unlikely chance of recovery, have elected via a living will or through family to have support withdrawn. In this procedure, treatment is discontinued (mechanical ventilation is shut off). After a time of death has been pronounced, the patient is rushed to the operating room where the organs are recovered. Storage solution is flushed through the organs. Since the blood is no longer being circulated, coagulation must be prevented with large amounts of anti-coagulation agents such as heparin. It is also possible to remove deceased-donor kidneys and maintain them for up to 48 hours on cold pulsatile perfusion or simple flushing and cooling. This approach permits sufficient time to undertake typing, cross-matching, transportation and selection of recipient to take place.

As with live donors, the deceased donors should be free of malignant neoplastic disease, hepatitis and HIV because of possible transmission to the recipient. Increased risk of graft failure exists when the donor is elderly or has renal failure and when the kidney has a prolonged period of ischemia and storage.

In India, till the passage of the Transplantation of Human Organs Act there was no comprehensive legislation regulating the removal of human organs. The Human Organs Transplantation Act (HDTA) which was passed in 1994 legalised 'brain death' and made removal of organs permissible after proper consent.
death and made removal of organs permissible after proper consent.

Transplant Compatibility

The ultimate goal of matching a donor kidney with the person seeking transplantation is identification of an organ that will be tolerated indefinitely by the body of the recipient who takes medications to prevent rejection. It is helpful to divide donor and recipient matching into three distinct areas: blood type matching, tissue type matching and crossmatching. Each is a distinct and important aspect of donor and recipient matching for which specific, complex laboratory tests have evolved. Each applies to kidneys from both live donors and deceased donors.

Blood Type Matching

The importance of blood group matching in transfusion has been known for many years, and it is equally important in kidney transplantation. The four major blood types in humans correspond to the type of glycoproteins on the surface of the blood cells. Type A cells carry type A glycoproteins and type B cells carry type B glycoproteins. Type AB cells have a mixture of both A and B glycoproteins. Type O cells have neither.

Humans also naturally have antibodies to the glycoproteins their own cells lack. These antibodies are responsible for causing serious (and sometimes fatal) reactions when they attack their targets. Since people with type A cells have antibodies to type B glycoproteins, a donor with type B blood is not compatible with a type A recipient. Similarly, those with type B cells have antibodies to type A glycoproteins, indicating a type A donor is not compatible with a type B recipient. Individuals with type AB cells lack antibodies to these glycoproteins and are therefore compatible with any potential donors (with regard to blood type matching). Those with type O have antibodies against both type A and type B cells and therefore require type O kidney donors. Thus, the person with blood type AB is the universal kidney recipient and the person with blood type O is the universal kidney donor.

The Rh factor relates only to a particular cell type in the blood, is not part of the kidney and hence is not important in kidney matching.

Tissue Matching:

Tissue matching is a very complex area involving testing the similarity of certain proteins, called antigens, between the donor and recipient. We all have many genes, some of which determine the expression of these antigens. For kidney transplantation, we currently look at six of these, called major histo-compatibility complex or HLA (human leukocyte antigens). By analyzing which six of these
Long-term outcomes in kidney transplantation do relate to matching, which is the reason for seeking the best possible match. Specifically, antigens both individuals have, we are able to determine the closeness of tissue matching. It is well accepted that the best possible organ for an end-stage renal disease patient is a fully HLA compatible kidney. A six-antigen match (both people have the same set of six antigens) is hence the best compatibility between a donor recipient pair who is not identical twins. This match occurs 25 percent of the time between siblings having the same mother and father and also occurs from time-to-time in the general population.

Long-term outcomes in kidney transplantation do relate to matching (as well as other factors), which is the reason for seeking the best possible match. Analysis of thousands of transplants consistently shows that six-antigen matched kidneys have the best statistical results, followed progressively by five antigens, and then four antigens, etc. For this reason, when a close match is available, it is preferred. Yet, today, the immunosuppressive medications used to prevent rejection have improved to the extent that even transplants with no tissue match (a zero match) may still provide good outcomes. For this reason, good tissue matching is considered a benefit, but not a requirement for a good outcome.

Along with the six major HLA antigens mentioned above, other Non-HLA “minor” antigens can also play a crucial role in transplant rejection. 5% of HLA-identical renal allografts are rejected, often within the first weeks after transplantation. These failures represent prior sensitization to Non-HLA antigens. Non-HLA antigens are relatively weak when initially encountered and are therefore suppressible by conventional immunosuppressive therapy. Once priming has occurred, however, secondary responses are much more refractory to therapy.

Cross Matching:

The final test of compatibility between a kidney donor and recipient is the cross-match used to identify the presence of preformed antibodies that would cause rejection from that specific donor. The basic test involves mixing the serum of the recipient’s blood containing antibodies with lymphocytes from the donor. Killing of the lymphocytes indicates the presence of antibodies.

The three past medical events that may cause a recipient to have antibodies are pregnancy, blood transfusion or prior transplantation. Hence, patients awaiting renal transplants are not transfused. Refinements in laboratory techniques for cross-matching have led to very sensitive and accurate testing that is probably responsible for some of the improved outcomes.

The final test of compatibility between a kidney donor and recipient is the cross-match used to identify the presence of preformed antibodies that would cause rejection from that specific donor.
The three past medical events that may cause a recipient to have antibodies are pregnancy, blood transfusion or prior transplantation of kidney transplantation. Although this testing is now highly complex and may involve as many as ten to fifteen different/separate tests, the final result is fairly simple. If the cross-match is positive, the recipient has responded to the donor (antibodies were present and killed the cells) and transplantation should not be carried out. A negative cross-match means the recipient has not responded and transplantation may proceed.

These days however, it is possible to do a kidney transplant even in the event of a positive cross match. This is done by carrying out desensitization prior to transplant whereby the levels of preformed anti-donor antibodies are reduced.

Transplant Procedure

Donor Kidney Retrieval:

Conventionally, the donor procedure had been an open laparotomy through a single incision of 4–7 inches (10–15 cm). However, live donation is now being increasingly performed by laparoscopic surgery. First performed in 1995, the laparoscopic donor nephrectomy has evolved from an experimental procedure to being the standard of care for kidney procurement at many major centres for living-donor renal transplantation. When compared with open donor nephrectomy and "mini-incision" donor nephrectomy, the laparoscopic approach is associated with a shorter hospital stay and time to return to preoperative activity, less patient discomfort and lower overall costs. As a consequence, the procedure has increased the overall donor pool by making kidney donation more appealing to the general population. Improved surgical techniques and instrumentation as well as increased experience with the procedure have addressed initial difficulties of ureteral cision and preservation of adequate vascular length. Concerns over donor safety have also been addressed. Laparoscopic nephrectomy is associated with less blood loss and fewer complications than open procedures. Selective renal arteriography should be performed on donors to rule out the presence of multiple or abnormal renal arteries because surgical procedure is difficult and the ischemic time of the transplanted kidney is long when there are vascular abnormalities.
The laproscopic procedure has also undergone many advances recently. In January 2009, the first kidney transplant was performed at Saint Barnabas Medical Centre through a two-inch insertion. In the same year, at the John Hopkins Medical Centre, a healthy kidney was removed through the donor’s vagina. This procedure was chosen as the patient previously had a hysterectomy. Vaginal donation promises to speed recovery and reduce scarring. The recent advance of single port laproscopy requiring only one entry point at the naval is another advance with potential for more frequent use.

Clinicians have always been aware of the prolonged warm ischemia time for laparoscopic nephrectomy. However, the effect of this on graft function was largely unknown. In an analysis of the United Network for Organ Sharing (UNOS) database, recipient and graft outcomes from 2743 laparoscopically procured grafts and 2576 grafts procured through an open approach were compared. It was noticed that laparoscopic nephrectomy may be associated with delayed graft function. However, the 1-year acute rejection rates and graft survival rates were similar for both groups. Although delayed early graft function has been associated with poorer long-term outcomes, no study has yet compared long-term graft outcome of laparoscopic versus open donor nephrectomy.

**Recipient Procedure:**

Adequate haemodialysis should be performed within 48 hours of the surgery, and care should be taken to see that the serum potassium levels are not elevated. This helps in preventing intraoperative cardiac arrhythmias.

The transplant surgery takes about three hours. In most cases the barely functioning existing kidneys are not removed, as this has been shown to increase the rates of surgical morbidities. Therefore, the kidney is usually placed in a location different from the original kidney, often in the right iliac fossa. The right iliac fossa is usually preferred as the right vessels are “more horizontal” with respect to each other and therefore, easier to use in the anastomoses.
The blood vessels of the donor kidney are connected to the arteries and veins in the recipient's body. The renal artery of the donor kidney is often connected to the external iliac artery and the renal vein to the external iliac vein in the recipient. When this is complete, blood will be allowed to flow through the kidney again. The final step is connecting the ureter from the donor kidney to the bladder. In most cases, the kidney will soon start producing urine.

**Intra-operative Fluid Management:**

Blood loss is usually minimal and does not pose a problem even in patients who are anaemic secondary to their end stage renal disease. Hence, transfusion of blood products is an exceedingly rare event during kidney transplantation.

One of the important goals in kidney transplant patients is to maintain adequate intravascular perfusion pressure and to correct existing or pre-existing (e.g. dialysis) hypovolemia to facilitate immediate graft function. Immediate urine production is seen in over 90% of living donor kidney transplants and between 40% and 70% of cadaveric transplants. Mannitol, loop diuretics and dopamine have been used to increase urine output and improve graft function. Fluid status can be modified by infusion of either crystalloid or colloid. Kidney transplantation can mostly be performed without colloid infusion because of the short duration of surgery, minimal blood loss, and preserved capillary permeability.

There has been some discussion of whether any particular crystalloid is better than the others in terms of postoperative graft function. More than 90% of patients receive normal saline (NS) or NS-based solutions during their transplant. In one study NS was compared to Ringer's lactate for intraoperative intravenous fluid therapy during kidney transplantation. Contrary to the common perception, significantly higher rates of hyperkalemia and metabolic acidosis were noted in the NS group when compared to Ringer's lactate. Ringer's lactate was considered a safe choice for fluid management during kidney transplantation. 1

In the past, aggressive fluid loading has been considered essential during kidney transplantation. However, this has been questioned and it is now believed that overly aggressive fluid administration is not required, and euvolemia during kidney transplantation is sufficient. 9

**Post-operative Care:**

Depending on its quality, the new kidney usually begins functioning immediately. Living donor kidneys normally require 3-5 days to reach normal functioning levels, while deceased kidney donations stretch that interval to 7-15 days.
Post operative diuresis should be closely monitored. In some instances, it may be massive, reflecting the inability of ischemic tubules to regulate sodium and water excretion; with large diureses, massive potassium losses may occur. Most chronically uremic patients have some excess of extracellular fluid, and it is useful to maintain an expanded fluid volume in the immediate postoperative period.

Acute tubular necrosis (ATN) if occurs may cause immediate oliguria or may follow an initial short period of graft function. ATN is most likely when cadaveric donors have been under-perfused or if the interval between cessation of blood flow and organ harvest (warm ischemic time) is more than a few minutes. Recovery usually occurs within 3 weeks, although periods as long as 6 weeks have been reported. Cyclosporine therapy prolongs ATN, and some patients do not diurese until the dose is reduced drastically. Many centres avoid starting cyclosporine for the first several days, using Anti-Lymphocytic Globulin (ALG) or a monoclonal antibody along with mycophenolic acid and prednisone until renal function is established. Details of immunosuppressive therapy are discussed later.

**Transplant Rejection**

Allograft rejection is caused by several elements of the immune system, including antibody, complement, T cells and other cell types. Acute rejection can occur in 10-25% of people after transplant during the first 60 days. Rejection does not necessarily mean loss of the organ, but it may necessitate additional treatment and medication adjustments.

Acute rejection can occur in 10-25% of people after transplant during the first 60 days. Rejection does not necessarily mean loss of the organ, but it may necessitate additional treatment and medication adjustments.

Early diagnosis of rejection allows prompt institution of therapy to preserve renal function and prevent irreversible damage. Clinical evidence of rejection is rarely characterized by fever, swelling and tenderness over the allograft. Rejection may only present with rise in serum creatinine with or without a reduction in urine volume. When the renal function is good initially, the rise in serum creatinine level is the most sensitive and reliable indicator of possible rejection and may be the only sign.

**Mechanism of Rejection and its Management:**

Rejection of the renal allograft can be hyper-acute, acute or chronic.
Hyper-acute Rejection:

A hyper-acute graft rejection also called as an acute antibody-mediated rejection (AMR) occurs when antibodies to the renal allograft HLA antigens are already present in the recipient's body. Features include accumulation of neutrophils and monocytes in peritubular and glomerular capillaries and deposition of C4d. C4d is a degradation product of the Complement protein C4. Detection of AMR is substantially easier since the introduction of C4d staining. Antibodies to donor HLA class I or II antigens are present in roughly 90% of patients who have C4d deposition.

Cross-matching the donor's lymphocytes with the recipient's serum can help to determine the risk of acute AMR. If the cross-match is positive, the transplant procedure is usually abandoned. However, if one wishes to go ahead with the transplant despite the presence of a mismatch, then the preformed antibodies in the recipient's body need to be reduced. The antibodies can be reduced by plasmapheresis of blood or by administration of pooled immunoglobulin or both.

Rituximab, an anti-CD20 monoclonal antibody that targets B lymphocytes (which produce antibodies) is also used to reduce these antibodies.

In a recent study, a combination of rituximab and high-dose intravenous immune globulin (IVIG) was used to desensitize 16 of 20 highly sensitized patients, allowing transplantation by either living or deceased donor kidneys. Graft and patient survival at 1 year were 94% and 100% respectively, although the incidence of AR, including AMR, was high (60%). AMR was treated by giving high pulse dose of steroids (methylprednisolone IV), rituximab and intravenous immune globulin. Patients with a very severe reaction were also subjected to plasmapheresis. The results of this study are encouraging, larger trials are needed to evaluate the efficacy and safety of this approach.

Acute Rejection:

An acute rejection is usually a T cell mediated rejection. Pathologically, acute T cell mediated rejection (TCMR) is manifested by the accumulation of mononuclear cells (mostly T cells and macrophages) in the interstitium, accompanied by inflammation of tubules and sometimes of arterioles. Cellular rejection is mediated by lymphocytes that respond to HLA antigens expressed within the organ. The CD4+ lymphocyte responds to class II (HLA-DR) incompatibility by proliferating and releasing proinflammatory cytokines that augment the proliferative response of both CD4+ and CD8+ cells. CD8+ cytotoxic lymphocyte precursors respond primarily to class I (HLA-A, B) antigens and mature into cytotoxic effector cells. The cytotoxic effector ("killer") T cells cause organ damage through direct contact and lysis of donor target cells.

Acute rejection is usually managed with a pulse of methylprednisolone, 0.5 − 1 g IV,
administered immediately upon diagnosis and continued once daily for 3 days. When the drug is effective, the results are usually apparent within 96 hrs. Failure to respond is an indication to use antibody therapy, either in the form of murcmonab-CD3 (OKT-3) or antithymocyte globulin.

**Chronic Rejection:**

Chronic renal allograft rejection also called chronic allograft nephropathy (CAN) is defined as a clinical entity characterized by a progressive deterioration of kidney transplant function. It is the most common cause of graft loss in surviving patients. Despite more than a decade of intense effort, there is no single mechanistic explanation for the clinical entity of CAN; rather, it seems to represent a spectrum of interrelated processes between the host and the allograft, resulting in progressive kidney tissue injury including immune- and non-immune-mediated injury mechanisms. Possible mechanisms include chronic immune rejection, inflammation, drug toxicity, and chronic kidney injury from secondary factors.\(^2\)

Characteristics of biopsy include transplant glomerulopathy, peritubular capillaropathy, transplant arteriopathy, and loss specifically, interstitial fibrosis and tubular atrophy (IF/TA).\(^4\) Chronic vascular changes with intraluminal proliferation and medial hyper trophy are commonly found.\(^7\) Any one of the above findings, when accompanied by C1d deposition in peritubular capillaries and by circulating donor-specific antibody, is diagnostic of chronic AMR and portends a poor prognosis.

To prevent chronic rejection transplant recipients, by and large, require judicious use of immunosuppressants indefinitely for the lifespan of the graft. Control of systemic and intrarenal hypertension with ACE inhibitors is thought to have a beneficial effect on the rate of progression of chronic allograft rejection.
Immunosuppressive Therapy in Renal Transplants

Transplant recipients, by and large, require immunosuppression indefinitely for the lifespan of their graft to prevent rejection. Long-term maintenance of immunosuppression requires ensuring a balance between suppressing rejection against the allograft and the toxicities associated with therapy, such as infections and malignancy.

Long-term maintenance of immunosuppression requires ensuring a balance between suppressing rejection against the allograft and the toxicities associated with therapy, such as infections and malignancy.

**Commonly employed Immunosuppressants**

<table>
<thead>
<tr>
<th>Calcineurin Inhibitors (CNI): Cyclosporine A, Tacrolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimetabolites: Azathioprine, Mycophenolate mofetil</td>
</tr>
<tr>
<td>Corticosteroids</td>
</tr>
<tr>
<td>mTOR Inhibitors: Sirolimus, Everolimus</td>
</tr>
</tbody>
</table>

Table 2. Immunosuppressants used to prevent transplant rejection.

Immunosuppressive drugs commonly employed include:

**Calcineurin Inhibitors:**

Cyclosporine:

Cyclosporine is a fungal peptide with potent immunosuppressive activity. It acts on the calcineurin pathway to block transcription of mRNA for IL-2 and other proinflammatory cytokines, thereby inhibiting T cell proliferation. Although it works alone, cyclosporine is more effective in conjunction with corticosteroids and antimetabolites and clinical results have been highly impressive. Among its toxic effects (nephrotoxicity, hepatotoxicity, hirsutism, tremor, gingival hyperplasia, diabetes), only nephrotoxicity presents a serious management problem.

Tacrolimus:

Tacrolimus (previously called FK506) is a fungal macrolide that has the same mode of action as cyclosporine as well as a similar side-effect profile; it does not, however, produce hirsutism or gingival hyperplasia. De novo diabetes mellitus is more common with tacrolimus. The drug was first used in liver transplantation and now many substitute it for cyclosporine during renal transplants.

**Antimetabolites:**

Azathioprine:

Azathioprine, an analogue of mercaptopurine, was the keystone to
immunosuppressive therapy in humans but with the availability of more effective agents, its use has reduced. Azathioprine inhibits the synthesis of DNA, RNA, or both. Therapy with azathioprine was generally added to cyclosporine as a means of decreasing the requirements for the latter. Side effects of Azathioprine include leukopenia and occasionally thrombocytopenia, which responds to dose reduction. Excessive amounts of azathioprine may also cause jaundice, anaemia, and alopecia. If it is essential to administer allopurinol to tackle hyperuricaemia, then the dose of azathioprine must be reduced as inhibition of xanthine oxidase by allopurinol delays the metabolism of azathioprine. Where possible, this combination is best avoided.

Mycophenolic acid:

Mycophenolate mofetil or mycophenolate sodium, both of which are metabolized to mycophenolic acid, is now used in place of azathioprine in most centres. It has a similar mode of action and a mild degree of gastrointestinal toxicity but produces minimal bone marrow suppression. Its advantage is its increased potency in preventing or reversing rejection. Moreover, patients with hyperuricemia can be given allopurinol without adjustment of the mycophenolic acid dose.

Corticosteroids:

Corticosteroids are important adjuncts to immunosuppressive therapy. Among all the agents employed, prednisone has effects that are easiest to assess, and in large doses it is usually effective for the reversal of rejection. In general, 200 – 300 mg prednisone is given immediately before or at the time of transplantation and the dose is reduced to 30 mg within a week. The side effects of the corticosteroids, particularly impairment of wound healing and predisposition to infection, make it desirable to taper the dose as rapidly as possible in the immediate postoperative period. Many patients tolerate an alternative-day course of steroids without an increased risk of rejection. A major effect of corticosteroids is on the monocyte-macrophage system, preventing the release of interleukin (IL) 6 and IL-1. Many centres now have protocols for early discontinuance or avoidance of steroids because of long term adverse effects on bone, skin, and glucose metabolism.

mTOR inhibitors:

Sirolimus:

Sirolimus (previously called rapamycin) is another fungal macrolide but has a different mode of action; i.e. it inhibits T lymphocyte activation and proliferation downstream of the IL-2 and other T-cell growth factor receptors thus preventing the response to IL-2 and other cytokines. It binds to and inhibits a protein kinase designated mTOR, which is a key enzyme in cell cycle progression. Inhibition of mTOR blocks cell-cycle progression at the G1 to S phase transition. Sirolimus can be used in conjunction with cyclosporine or tacrolimus, or with mycophenolic acid,
to avoid calcineurin inhibitors. Its use with tacrolimus alone shows promise as a steroid-sparing regimen.

**Everolimus:**

Everolimus is a derivative of sirolimus used for preventing graft rejection, along with cyclosporine and corticosteroids.

**Biologicals (Antibodies to Lymphocytes):**

When serum from animals made immune to host lymphocytes is injected into the recipient, a marked suppression of cellular immunity to the tissue graft results. The action on cell-mediated immunity is greater than the action on humoral immunity. A globulin fraction of serum, antilymphocyte globulin (ALG), is the agent generally employed. For use in humans, peripheral human lymphocytes, thymocytes, or lymphocytes from spleens or thoracic ducts of rabbits, or goats to produce antilymphocyte serum, from which the globulin fraction is then separated. A rabbit antithymocyte globulin (thymoglobin) is the agent most commonly in use currently.

Monoclonal antibodies against defined lymphocyte subsets offer a more precise and standardized form of therapy. OKT3 is directed to the CD3 molecules that form a portion of the T-cell antigen-receptor complex and is thus expressed on all mature T cells.²

---

### Biological Agents Commonly Used

<table>
<thead>
<tr>
<th>Biological Agents Commonly Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Thymocyte Globulin (ATG)</td>
</tr>
<tr>
<td>Anti-Lymphocyte Globulin (ALG)</td>
</tr>
<tr>
<td>Monoclonal Antibodies: OKT-3</td>
</tr>
<tr>
<td>IL-2 Receptor blockers: Basiliximab, Daclizumab</td>
</tr>
</tbody>
</table>

Table 3. Biologicals used for induction therapy & to treat acute rejection

Another approach to more selective therapy is to target the 55-kDa alpha chain of the IL-2 receptor, which is expressed only on T cells that have been recently activated. Two such antibodies to the IL-2 receptors are basiliximab and daclizumab, which are in use for prophylaxis of acute rejection in the immediate post transplant period. They are effective in decreasing the acute rejection rate and have few adverse side effects.

**Optimising Immunosuppression:**

There is no single generally accepted immunosuppressant regimen, and different centres have achieved good results with a variety of strategies. Therapy should be tailored to the individual patient. Several factors affect the intensity of immunotherapy required, including the source (living or cadaveric) and degree of HLA histocompatibility, and the age, race and panel reactive antibody titre of the recipient.
donor source (living or cadaveric) and degree of HLA histocompatibility, and the age, race and panel reactive antibody titre of the recipient.\textsuperscript{23}

\textbf{Triple Therapy:}

A widely used approach consists of triple therapy with a calcineurin inhibitor (cyclosporine or tacrolimus), an anti-proliferative (azathioprine or mycophenolate mofetil), and a corticosteroid (prednisolone). Triple therapy is popular because it allows the use of lower doses of nephrotoxic calcineurin inhibitors and the eventual tapering or even elimination of corticosteroids in some patients. Many variations of triple therapy regimens have been used.

Azathioprine has largely been replaced by mycophenolate mofetil, which lowers the incidence of acute rejection and reduces the risk of chronic allograft failure.

Tacrolimus has been substituted for cyclosporine because it appeared to be more effective in preventing acute rejection. Although it has been suggested that this does not lead to improved survival of either patients or grafts, a systematic review concluded that use of tacrolimus did improve graft survival, with a 44\% reduction in graft loss within the first 6 months of transplantation; acute rejection was reduced by almost a third and severe rejection by half. In 1990's more than 3/4\% of the patients were discharged on cyclosporine while in the last decade the trend has changed with more than 3/4\% of the patients now being discharged on tacrolimus. Although tacrolimus may have a better blood pressure control than cyclosporine, patients are two to three times more likely to develop diabetes and to have neurological adverse effects. The choice of calcineurin inhibitor is therefore strongly influenced by adverse effect profiles.

There is some evidence of synergism between sirolimus and cyclosporine and addition of sirolimus to cyclosporine-based regimens may reduce the incidence of acute rejection. Combining sirolimus with tacrolimus instead of cyclosporine may be even more effective. However, sirolimus may augment the nephrotoxicity of both cyclosporine and tacrolimus, and its use with full-dose calcineurin inhibitors has been associated with significantly reduced rates of allograft survival. In an attempt to reduce the chronic allograft nephropathy associated particularly with calcineurin inhibitors, sirolimus has been given with azathioprine or mycophenolate mofetil, as an alternative to cyclosporine-based protocols. Comparable rejection rates and better renal function have been reported.
Quadruple Therapy:

Sequential quadruple therapy is where antibody-based induction therapy is given postoperatively, in addition to triple therapy. Induction therapy in renal transplantation provides improved short- and long-term graft outcomes compared with placebo. The antibodies are usually stopped once good graft function is achieved. The regimen may improve long-term graft survival in patients with delayed graft function.

Polyclonal lymphocyte-depleting antibodies are associated with a low incidence of rejection but evidence of their benefit in terms of graft survival is lacking; rabbit antithymocyte immunoglobulin (thymoglobulin) appears to be better than that of equine origin. Use of muromonab-CD3 (OKT-3) has declined because of poor tolerability and an increased risk of lymphoproliferative disease. The more specific interleukin-2 receptor monoclonal antibodies basiliximab and daclizumab are widely used and appear to reduce the incidence of rejection episodes without increased toxicity. Alemtuzumab has also been used, but data for this drug are comparatively limited.

Some consider the interleukin-2 receptor antibodies (IR-2RA) to be the first-line choice for induction therapy because of their superior safety profile. While there appears to be no difference between thymoglobulins and IR-2RA in terms of efficacy, acute rejection in high-risk patients appears to occur less often with thymoglobulins, which may be the preferred choice in patients who are highly sensitised or receiving a second transplant. Basiliximab or daclizumab, used as part of a cyclosporine-based regimen, are recommended as options for induction therapy in children and adolescents undergoing renal transplantation, irrespective of immunological risk.

Corticosteroid-Free Immunosuppression:

As immunosuppressant regimens have developed, the role of corticosteroids has come to be questioned, mainly because of the adverse effects associated with their prolonged use. Studies indicate that corticosteroids withdrawal is feasible in many patients initially given triple therapy and complete avoidance of corticosteroids may be possible with induction therapy using interleukin-2 receptor antibodies. There has been debate about the long-term consequences of this for graft survival, with a possible increased risk of acute or chronic rejection, and a high proportion of patients who need to resume corticosteroid therapy. In a systematic review and a meta-analysis of the randomized controlled studies about steroid avoidance or early withdrawal after a few days in patients receiving a kidney transplant, it was concluded that steroid avoidance or early withdrawal within the first 2 weeks is safe in kidney transplant recipients receiving induction with anti-interleukin-2 receptor
antibodies or thymoglobulin and a drug regimen based on calcineurin inhibitor and mycophenolate mofetil. However, it is crucial to individualize therapy, and caution is advised for high-risk patients, such as sensitised, previously transplanted patients, or those with previous acute rejection episodes.

**Long Term Complications Following Renal Transplant and their Management**

There has been a remarkable rise in the number of kidney transplant recipients (KTR) over the last decade. Increasing use of potent immunosuppressants, which are also potentially diabetogenic and atherogenic, can result in worsening of pre-existing medical conditions as well as development of posttransplant disease. An increasing numbers of KTR present to their primary care physicians posttransplant for routine medical care. Similar to native chronic kidney disease patients, KTRs are vulnerable to cardiovascular disease as well as a host of other problems including bone disease, infection and malignancies. Deaths related to complications of cardiovascular disease and malignancies account for 60–65% of long-term mortality among KTRs. Management of hypertension, dyslipidemia, smoking, diabetes and bone disease should be incorporated into the long-term care plan of the KTR to improve outcomes.

**Cardiovascular Disease:**

The annual risk of death due to cardiovascular disease (CVD) in KTRs is 3.5–5%, as opposed to 9% in dialysis patients. CVD appears 20 years earlier in KTRs compared with the general population. Although the incidence of myocardial infarction decreases after the first three months post-transplantation, events related to congestive heart failure (CHF) are one of the most common causes of hospital admissions in KTRs. Thus, management of CVD should include modifying risk factors related to both CVD and CHF. The traditional risk factors do not fully predict the incidence of cardiovascular disease in KTR. The implicated non-traditional risk factors include proteinuria, C-reactive protein, homocysteinemia and various immunosuppressive regimens. Some major risk factors of CVD are:

**Management of hypertension, dyslipidemia, smoking, diabetes and bone disease should be incorporated into the long-term care plan of the KTR to improve outcomes.**
Obesity:

Obesity is not uncommon in KTRs. Moreover, patients can gain an additional 5–15 kg by 1 year post-transplant. Obesity has been associated with an increased risk for developing diabetes, CHF, atrial fibrillation and decreased graft survival. Weight gain post-transplant has been attributed to the use of corticosteroids as well as an increase in appetite secondary to cessation of dialysis. Lifestyle modification remains the mainstay of therapy. A significant weight loss and improvement in low-density lipoprotein (LDL) has been noticed with dietary intervention. Improvements in high-density lipoprotein (HDL) have been shown to occur with exercise training. Patients should be cautioned against usage of over-the-counter weight loss preparations. Orlistat, a pancreatic lipase inhibitor, has been reported to be associated with sub-therapeutic calcineurin inhibitor (CNI, e.g., cyclosporine, tacrolimus) levels. Gastric bypass surgery might be effective for achieving long-term weight loss in resistant cases, though immunosuppressant doses may have to be increased thereafter due to inadequate drug absorption. Moreover, recent data suggest that obesity surgery can be associated with hyperoxaluria and nephrolithiasis, which could potentially compromise the renal allograft.

Cigarette Smoking:

Smoking confers a 30% risk of death secondary to CVD-related complications. In contrast, smoking cessation is associated with a reduction in mortality. Successful kidney transplantation has been demonstrated to be a strong incentive for patients to quit smoking. Multifaceted programs incorporating both behavioral and pharmacologic therapy have been shown to be effective. Similar to the general population, nicotine replacement therapy can be used. Bupropion has been reported to result in a reduction in cyclosporin concentrations. Some centers report using varenicline without any significant drug-drug interactions.

Hypertension:

Similar to the general population, hypertension in KTR is defined as a systolic blood pressure > 140 mmHg and/or a diastolic blood pressure > 90 mmHg. KTRs are likely to have hypertension due to multiple factors including pre-transplant hypertension, allograft dysfunction leading to chronic kidney disease (CKD) and the use of corticosteroids and CNIs.

Retrospective analyses have demonstrated an incremental association between elevation of blood pressure (BP) and graft failure. Based on data from the general population, the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines have recommended BP goals of <130/80 mmHg for all KTRs. When possible, ambulatory BP monitoring is recommended because a circadian "non-dipping" pattern is often seen in KTRs. Such patients might require higher doses of anti-hypertensive medications in the evenings. The
management of hypertension should include simultaneous initiation of lifestyle modification and drug therapy. Similar to recommendations for the general population, weight loss (if BMI>25 kg/m²), regular moderate exercise, limited alcohol intake (<2 drinks/day in men and <1 drink/day in women) and dietary sodium restriction (<2.4 g/day) are recommended. Most patients would require combination therapy for optimal blood pressure control. Calcium channel blockers, especially dihydropyridine derivatives like nifedipine are often used initially. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) should be used as first-line therapy for patients with proteinuria > 1 g/day. Pharmacotherapy needs careful attention because of potential drug interactions. For example, the non-dihydropyridine calcium channel blockers like diltiazem result in an increase in CNI concentration. Close follow-up (weekly for 2 weeks, then monthly) of blood pressure, serum creatinine, electrolytes and haemoglobin levels (when ACEIs or ARBs are used) is recommended. If blood pressure is not controlled despite medical therapy, causes of secondary hypertension, e.g., graft renal artery or iliac artery stenosis, should be explored.

Dyslipidemia:

Hypercholesterolemia and hypertriglyceridemia are seen in 40–80% and 40–60% KTRs, respectively. Multiple factors including obesity, diabetes, hypothyroidism, proteinuria and diuretic use are implicated. Immunosuppressive agents including CNIs, sirolimus and corticosteroids can result in elevated total cholesterol, LDL, lipoprotein (a) and triglyceride concentrations. Serum total cholesterol concentration is an independent predictor of both cardiovascular and peripheral vascular disease in KTRs. Dyslipidemia needs to be treated aggressively as if for secondary prevention. The treatment of dyslipidemia is based on the recommendations of the National Cholesterol Education Program (NCEP) III. Recommended target goals are LDL < 100 mg/dl, non-HDL cholesterol (calculated as: total cholesterol – HDL cholesterol) < 130 mg/dl and a triglyceride concentration < 150 mg/dl. Patients should be counselled about diet, weight loss and moderate exercise. Diet composition should include < 200 mg/day cholesterol, < 7% saturated fat and increased fibre (10–25 mg/day). Statins are the mainstay of pharmacotherapy. Statins should be initiated in low doses of 5–20 mg. If maximal statin dosage is not effective, combination therapy with ezetimibe can be used. Hypertriglyceridemia (> 500 mg/dl) is usually treated with gemfibrozil, though some centers use niacin or omega-3 fish oils to avoid the additive risk of myopathy when using fibric acid derivatives with a statin. Bile acid sequestrants should be avoided as they interfere with the enteral absorption of CNIs.

Diabetes:

Approximately 20% of KTRs have pre-transplant diabetes. Another 12–25% develop post-transplant diabetes mellitus (PTDM), which is associated with various
### Goals of Treatment

<table>
<thead>
<tr>
<th>Blood Pressure:</th>
<th>BP &lt; 130'/80 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids:</td>
<td>( \text{LDLc} &lt; 100 \text{ mg/dL} )  &lt;br&gt; ( \text{Non-HDLc} &lt; 130 \text{ mg/dL} )  &lt;br&gt; ( \text{Triglycerides} &lt; 150 \text{ mg/dL} )</td>
</tr>
<tr>
<td>Blood Glucose:</td>
<td>( \text{FPG} &lt; 126 \text{ mg/dL} )  &lt;br&gt; ( \text{HbA1c} , 7% \text{ to } 7.5% )</td>
</tr>
</tbody>
</table>

Table 4. Treatment goals after renal transplant

Factors including metabolic syndrome, hepatitis C, and therapy with diuretics, CNIs, corticosteroids and sirolimus. PTDM is associated with significantly higher rates of graft loss, cardiovascular morbidity and mortality as well as overall mortality. Microvascular complications including neuropathy, nephropathy and retinopathy seem to be accelerated in PTDM. Diabetes is diagnosed by fasting plasma glucose (FPG) > 126 mg/dl or a 2-h plasma glucose > 200 mg/dl during an oral glucose tolerance test. Screening FPG measurements every 3 months for the first year and annually thereafter is recommended. Once diagnosed with diabetes, patients should undergo measurements of HbA1c every 3 months (starting at 3 months post-transplant) and annual spot urine protein: creatinine. Recommended goals of care include blood pressure < 130'/80, FPG < 126, HbA1c 7–7.5%, spot urine protein: creatinine ratio < 200 mg/g and LDL < 100 mg/dl. In the absence of significant co-morbidities, weight loss and moderate exercise (30min/day on most days of the week) is recommended for all diabetics. Almost all KTRs will require phamcotherapy with at least one agent. The choice of initial therapy might vary based on patient and physician preference. The use of aspirin for primary prevention is recommended in patients with co-existing diabetes and CKD.

### Cerebrovascular Disease:

The pathogenesis and management of cerebrovascular disease is closely linked with that of CVD. Compared with the general population, the yearly incidence of cerebrovascular events is elevated in KTRs (0.8–1.34%) but lower than patients on dialysis (3.3%). Strokes have been reported to contribute to 17% of all-cause mortality. Prior history of polycystic kidney disease is associated with a higher incidence of hemorrhagic stroke. Unfortunately, lipid lowering therapy does not result in a reduced risk of stroke. Prevention of stroke requires aggressive management of traditional risk factors, especially hypertension.

### Anemia:

Anemia, reported in 40–46% of KTR, is an independent predictor for the development of CVD. Multiple factors including micronutrient deficiency (iron, folate and vitamin B₁₂), CKD, cytomegalovirus, parvovirus and drugs (e.g., immunosuppressants, valganciclovir, trimethoprim-sulfamethoxazole, ACEI, ARB) can contribute to post-transplant anemia. Anemia present postoperatively in KTRs tends to resolve over a period of 6 months. Hemoglobin levels should be followed at least once every 3–6 monthly late post-transplant. All patients with anemia should undergo a workup with red blood cell (RBC) indices, reticulocyte count, iron studies
and stool for occult blood. Transplant patients have creatinine clearances between 30 ml to 50 ml/min and can be considered like any other CRF patient for supplemental erythropoietin. For patients being treated with erythropoiesis-stimulating agents, the recommended therapeutic goal for hemoglobin level is between 11–12 g/dl.

**Gout:**

Decreased renal urate clearance can occur after KT leading to hyperuricemia (10–84%) and gouty arthritis (2–28%). Risk factors include CNI use (cyclosporin > tacrolimus), obesity and use of thiazides. In the absence of ESRD, low-dose colchicine (0.15–0.6 mg/d) can be used for therapy, though an abrupt or insidious myoneuropathy may develop as an adverse reaction. Owing to this concern, some centres avoid colchicine and prefer using low-dose corticosteroids instead (20–30 g/day for 3–5 days). Non-steroidal anti-inflammatory drugs (NSAID) should be used cautiously and only for a short duration (<5 days) in the absence of significant CKD. Gout involving a single, easily accessible joint is probably best treated with an intra-articular corticosteroid injection. Allopurinol should be dose-adjusted according to creatinine clearance when used for prophylaxis and, importantly, must not be used in patients prescribed azathioprine due to the risk of significant toxicity.

**Depression:**

Up to 22% of KTRs experience moderate to severe depressive symptoms. In a retrospective study (n=47,839) based on Medicare claims, it was noted that a diagnosis of depression was associated with a nearly two times higher risk of graft failure and death with a functioning graft. The authors surmised that the higher rates of graft loss could be related to non-adherence with treatment regimens among depressed patients. Therapeutic interventions may include individual and group psychotherapy as well as pharmacotherapy with selective serotonin reuptake inhibitors such as citalopram.

**Bone Disease:**

Bone disease in KTR differs from 'steroid-induced' osteoporosis seen after transplantation of non-renal solid organs. In KTR, bone disease is worsened by the frequent pre-existing bone damage accrued during dialysis and prior CKD. Osteoporosis is evident in 10–44% of KTRs by 3 years post-transplantation. The fracture risk for KTRs maintained on corticosteroids has been reported to be four times that of the general population. The use of bisphosphonate, vitamin D or calcitonin is associated with an improvement in BMD as well as a reduction in fracture risk.
Treatment recommendations for Bone Disease include:

- Minimizing steroid dose
- Encouraging weight-bearing exercise
- Ensuring daily intake of calcium (1,000 mg/day for men and 1,500 mg for postmenopausal women) and vitamin D (400–1,000 IU) and treating vitamin D deficiency (<30 ng/ml) when present
- Treating persistently low serum phosphate (<2.5 mg/dl) with oral supplementation
- Considering parenteral bisphosphonate therapy for BMD t-score < -2.

Malignancies:

An increased risk of multiple common and rare cancers have been reported among KTRs. It has been proposed that the increased risk of malignancy in this population is secondary to viral re-activation because of immune deficiency induced by use of immunosuppressive agents. Because of the higher risk of cancers in this population, various groups have recommended a more intensive screening strategy.

Infections:

Serious infections are responsible for 14–16% of all deaths among KTRs. Most opportunistic infections are seen between 2 and 6 months post-transplant. After 6 months post-transplant, the risk of infection diminishes. However, patients with more intense exposure to immunosuppressive agents continue to be vulnerable to opportunistic infections. CMV, EBV and invasive fungal infections are encountered because of chronic immunosuppression and are very often a cause of graft dysfunction. Bacterial urinary tract infections (UTI) are the most common infection during the late period and are responsible for significant morbidity and mortality. All patients with suspected UTIs should undergo urinalysis and a urine culture. UTIs with no systemic symptoms can be treated empirically with an oral fluoroquinolone or as guided by local sensitivity data. Patients with acute pyelonephritis need inpatient admission for parenteral antibiotic administration. Timely and appropriate vaccination can prevent substantial morbidity and mortality in KTRs. Immune response is lost when the vaccine is administered prior to the transplant as the efficacy of vaccination is frequently blunted post-transplant. All KTRs should receive common killed vaccines. Live attenuated vaccines (measles-mumps-rubella, nasal influenza, rotavirus, varicella-zoster) are usually contra-indicated.
Down the Memory Lane

My association with nephrology started from my second house post when I had the opportunity to work under Dr. V.V. Shanbhag, Professor & Head of the Dept. of Medicine & Nephrology at Nair Hospital in Mumbai. Dr. Shanbhag was one of the pioneers of Nephrology in India. Through his efforts he had set up the Hemodialysis unit at Nair hospital which was called AKD or Artificial Kidney Division. After post-graduation, I worked as a Lecturer in Nephrology at BJ Medical College & Sasson General Hospital in Pune, which exposed me to the fine intricacies of Nephrology.

I joined Jehangir hospital in Pune as a Consultant Nephrologist in 1992 and we initiated and set up the transplant program in 1998. Our first patient of renal transplant died one year later. The cause of death was however not graft failure but tuberculosis. Our second patient who had received transplant the same year is hale and hearty even after 14 years and follows up in our OPD regularly with normal kidney function.

Till date we have completed 229 transplants. We began with 8 to 12 renal transplants a year. However, today we perform anywhere between 45 to 50 transplants in a year. The survival rates at our institute are given in the table below:

<table>
<thead>
<tr>
<th>Survival Years</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>88%</td>
</tr>
<tr>
<td>3 years</td>
<td>72%</td>
</tr>
<tr>
<td>5 years</td>
<td>56%</td>
</tr>
</tbody>
</table>

Table 5. Transplant Survival Rates at a Tertiary Hospital in India

The survival rates in the initial years were low due to a number of factors. However, improvement in procedures as well as immunosuppressive therapy has improved our survival rates considerably. Our 1 year survival rate in 2010 was 92% and in 2011 was 95%. These rates are comparable to those reported from the West. Jehangir hospital was also the first institute in Pune to do a "swap transplant". Needless to say, there is still a lot more to be done. One now looks forward to renal transplants without the need to use lifelong immunosuppressive drugs. What is now experimental now, using simultaneous bone marrow transplants from the donor, is likely to be a reality in the days to come. Only time will tell.
References: