ikawalit Transplant Protocol
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Dedication

I dedicate this book to my inspirational wife Lara who have always been there for me, and have never doubted my dreams, no matter how crazy they might be. Also to my wonderful Kids Afif , Noor and Jana, they are the reason I get up every day and push myself to do more and be better than the day before.

To my mother Tamara and my father Afif they are my inspiration in everything I do and every choice I make.

iKawalit
Transplant Protocol

Joseph Murray and Hartwell Harrison performed the first transplantation of a kidney graft between identical twins on December 23, 1954. This success was followed by 7 successful transplantations between identical twins. However, the attempts at cadaveric renal transplantation universally resulted in graft failure due to rejection. Early attempts to control the immune system used total body irradiation. In 1959, Hamburger and Merrill irradiated 2 transplant recipients, the donors were nonidentical twins. Both of these recipients had successful outcomes. In June 1960, Kuss and colleagues were faced with rejection in a kidney transplant recipient who received the graft from an unselected donor. They used 6-mercaptopurine in this patient, an immunosuppressive agent, and reversed the rejection process.

In the 1960s and 1970s, utilization of corticosteroids, azathioprine, and the early polyclonal antilymphocytic agents was based largely on individual center experience without rigorous multicenter trials or predetermined end-points[1]. In the last two decades, all the new immunosuppressive agents have been introduced after clinical trials. The first clinical trials for cyclosporine were designed in the late 1970s and early 1980s, the primary end-point used was "improvement of patient and graft survival," which cyclosporine indeed achieved[2] . Although the benefits of cyclosporine were clear cut, its capacity to produce both acute and chronic nephrotoxicity was soon recognized to be a major side effect [3]. In 1985, OKT3, the first monoclonal antibody used in clinical medicine, was introduced into routine clinical care based on its capacity to successfully treat first acute rejection episodes[4]. But the toxicity of the drug tended to restrict its use to acute rejection that was resistant to high-dose steroids. With these medications—cyclosporine, azathioprine, corticosteroids, and the antibody preparations—the transplant community entered the 1990s achieving a success rates of up to 90% and minimal mortality in many centers.

In the 1990s tacrolimus (FK506) was introduced into liver transplantation and eventually into renal transplantation as an alternative to cyclosporine because of its ability, proven in randomized clinical trials, to produce equivalent patient and graft survival[5]. Mycophenolate mofetil (MMF) was found to be a more effective adjunctive agent than azathioprine by virtue of its fewer side effects and its capacity to reduce the incidence of acute rejection episodes when used with cyclosporine[6], and later with tacrolimus[7], and corticosteroids. Two new humanized monoclonal antibodies, basiliximab and daclizumab, both targeted against the interleukin-2 (CD25) receptor, were approved for use in renal transplantation in 1998, again because of their ability to reduce the incidence of acute rejection episodes[8,9]. Thymoglobulin, a polyclonal antibody available in Europe for several years, was approved for use in the US for the treatment of acute rejection[10]. In late 1999, sirolimus (rapamicin) was added to the immunosuppressive menu, again because when combined with cyclosporine and corticosteroids, it reduced the incidence of acute rejection episodes[11, 12]. Several new agents are currently being evaluated to be used as part of the transplant.

The different approach for kidney transplantation and its complications reported in several medical journals confirm the dilemma that we face as transplant nephrologists, It is similar to a "multiple choice questions" faced by transplant nephrologists as we attempt to take advantage of our experience and our limited long term studies. This book will attempt to provide guidelines that can clear the way for young nephrologists on how to approach kidney transplantation based on evidence based medicine and our own experiences. I will try to review the recent recommendations and guidelines that involve Kidney transplants and I will include my personal standing orders and follow up sheets.

Part I. **Guidelines for Evaluation, Selection and Preparation Of the potential transplant recipient** [13-17]

General Evaluation Guidelines:

- All patients with end stage renal disease should be considered for renal transplantation unless they have absolute contra-indications, because renal transplantation offers a better life expectancy and quality of life than dialysis.
- Long duration of dialysis, previous incidence of recurrent infections, cancer, cardiovascular disease or gastrointestinal complications should not be considered as absolute contra-indications to renal transplantation, despite these conditions increasing the risk of post-transplant morbidity and mortality.
- Psychological evaluation of transplant candidates may be useful in assessing compliance with future immunosuppressive treatment. Poor compliance significantly worsens the outcome of renal allografts.
- Comprehensive information on renal transplantation should be given to all potential candidates with ESRD, including mortality, morbidity, results compared with dialysis, and also data concerning the different sources of kidneys, including marginal organs.
- Specific transplant evaluation should only be performed after clear acceptance is given by the patient. Inclusion on the waiting list is the final step of the procedure and requires formal informed consent.

Contraindications for transplantation:

A. There are few absolute contra-indications to renal transplantation. These include uncontrolled cancer, HIV positive status, active systemic infections and/or any condition with life expectancy < 2 years.

B. Candidates for renal transplantation, particularly those older than 50 years of age, should be screened for the presence of pre-existing cancer.

C. In patients with previous cancer, renal transplantation should only be considered if there is no evidence of persistent cancer. It is recommended that the waiting time between tumor treatment and transplantation be based on the type of cancer.

D. After renal transplant, general preventive measures of surveillance for occurrence of de novo cancer are recommended.

Risk of recurrence after transplantation of pre-existing malignancies:

Low recurrence rate (0-10%)

Incidentally discovered renal tumors, Lymphomas
Testicular, uterine cervical, thyroid carcinoma

Intermediate recurrence rate (11-25%)

Carcinoma of the uterine body
Wilm's tumours
Carcinomas of colon, prostate, breast

High recurrence rate (>26%)

Carcinoma of bladder
Sarcomas
Skin Cancers (melanomas and non-melanomas)
Symptomatic renal carcinomas, Myelomas

Waiting period between treatment of cancer and transplantation:

Less than 2 years

Incidentally discovered renal carcinomas
In situ carcinomas
Small single focal neoplasms
Low-grade bladder cancer
Basal cell skin cancers

2 years

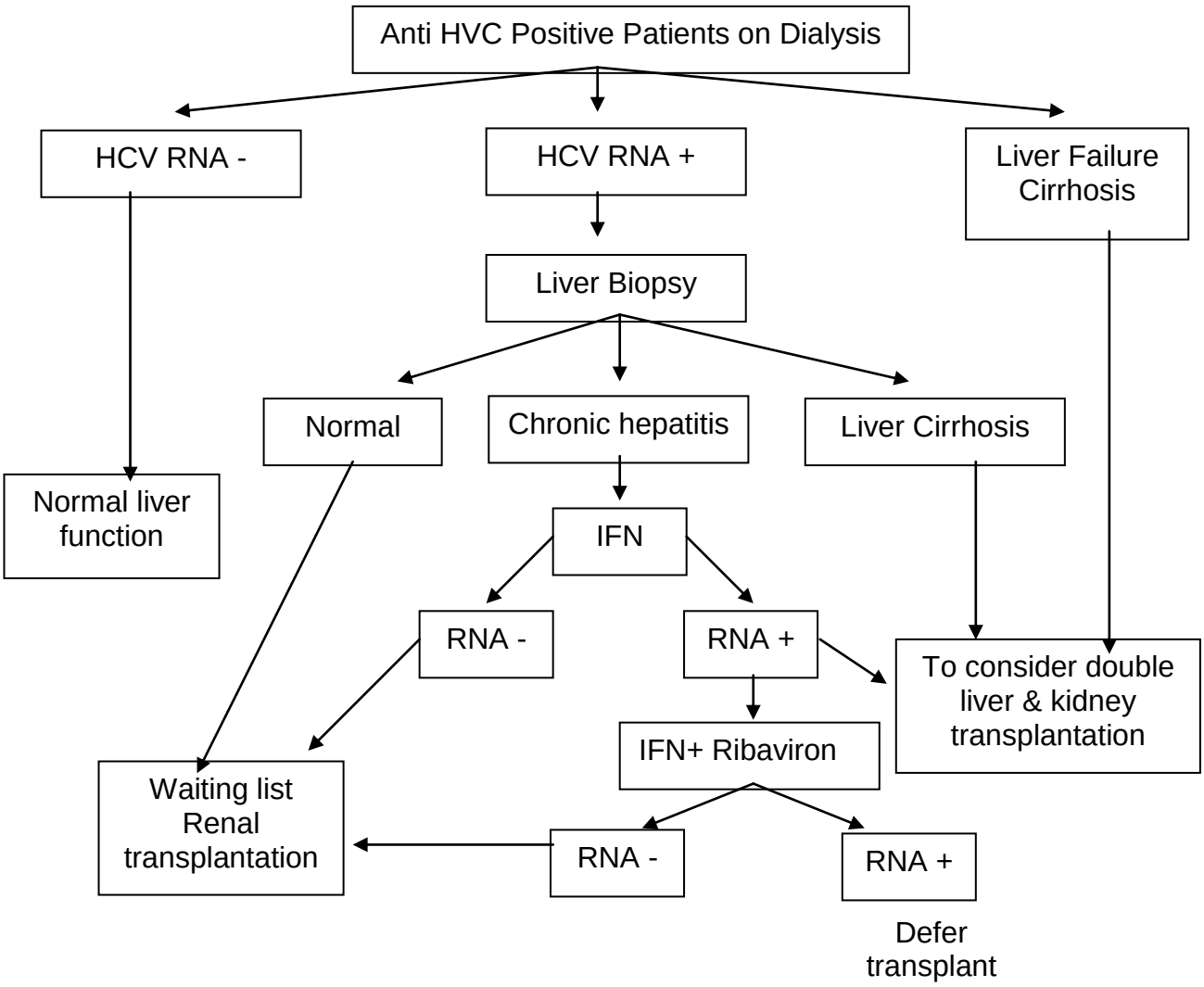
Most cancers except A and C

More than 2 years

Malignant melanomas
Breast carcinomas
Colorectal carcinomas
Non in situ carcinoma of the uterus

Hepatitis C virus (HCV) infection in kidney transplant recipients and kidney donors:

- All transplant candidates should be tested for anti-HCV antibodies. Anti-HCV positive patients with negative HCV viraemia are at very low risk of livr disease after renal transplantation. The presence of HCV-RNA in serum may be searched for in all prospective recipients with liver disease, even in cases where anti-HCV antibodies are not detectable.
- All HCV positive patients should be considered for renal transplantation, as this procedure is not associated with increased mortality compared with dialysis, at least not during the first post-transplant decade.
- HCV infected transplant candidates with elevated transaminase levels (alanine aminotransferase, ALT) should undergo a liver biopsy. In HCV-infected patients who display consistently normal liver enzymes, it is desirable, but not essential, to perform a liver biopsy, because HCV liver disease is often undetected.
- Transplant candidates with existing cirrhosis should not be considered for isolated renal transplantation, but should be considered for combined kidney and liver graft.
- Patients with chronic active hepatitis (CAH) might be offered a treatment with interferon (IFN~) prior to transplantation. They may be maintained on the active transplant waiting list during the period of IFN-~ administration, the drug being stopped if transplantation occurs before the end of planned therapy. Patients without improvement after IFN~ therapy may still be put on the waiting list for transplantation, but only after careful consideration and information. These decisions will be taken on an individual basis.
- Kidneys from HCV-infected living or cadaveric donors may be offered to HCV RNA-positive recipients with their consent and when permitted by the national law. Obtaining the donor and recipient HCV genotypes is desirable for further careful evaluation of the results.



Hepatitis B virus (HBV) infection in kidney transplant recipients and kidney donors:

- All transplant candidates should be tested for HBV infection. Hepatitis B surface antigen (HBsAg)-positive patients are at increased risk of death over the long term after renal transplantation compared with HBs Ag-negative patients, and should therefore be informed.
- Renal transplant candidates infected with HBV and who present with markers of viral replication, such as Hepatitis B envelope antigen (HBeAg) positive and/or HBV-DNA positivity, should undergo a complete evaluation for liver disease, including a liver biopsy (when ALT is elevated), because they are at increased risk of progressive liver disease after renal transplantation.
- Transplant candidates with existing cirrhosis should not be considered for isolated renal transplantation, but might be considered for a combined kidney/liver graft whenever possible.
- Transplant candidates with active liver disease (including chronic active hepatitis) should be offered treatment with interferon (IFN-~) and/or lamividine prior to renal transplantation. Patients without improvement after treatment may be registered for transplantation, but after very careful consideration and information.
- Kidneys from HBV infected living or cadaveic donors may be offered to already HBsAg positive recipients or HBV well protected recipients (active & passive immunization) with their consent and when permitted by the national law.

Recurrence of original renal disease:

- Focal and segmental glomerulosclerosis (FSGS) is not a contra-indication to renal transplantation despite the high risk for recurrence. Patients with recurrence have reduced graft survival. In case of living donation, the possibility of early recurrence leading to graft loss should be clearly explained to the potential donor. Approximately 15-50% of patients develop early recurrence of FSGS in the first allograft. It is almost impossible to predict which patient will have the recurrence after transplantation. Plasmapheresis and increased dosage of cyclosporine may be of value in severe cases.
- Membranous glomerulonephrilis (MN) is not a contra-indication to renal transplantation despite the fact that there is no effective treatment for recurrent MN and ~20-30% of adult patients may develop recurrence after transplantation.
- Membranoproliferative glomerulonephritis (MPGN) is not a contra-indication to renal transplantation. Type I MPGN may recur in children where it accounts for ~6% of graft failures, and in adults where the recurrence rate is ~50% and graft survival is poorer at 4 years. Most patients with type II MPGN show histological recurrence. Clinical recurrence is less common, ~10% in adults and 28% in children.
- IgA glomerulonephritis (IgAGN) is not a contra-indication to transplantation. The risk of recurrence is related to the length of post-transplant follow up, being almost 100% by 10-20 years. Patients with histological signs of recurrence have a lower probability of long term graft survival than patients without recurrence.
- In antiglomerular basement membrane glomerulonephritis (anti GBM GN), it is recommended to wait until the circulating anti-GBM antibodies measured by specific techniques (RIA or ELISA) have disappeared before transplantation. Anti-GBM GN tends to recur only in patients with circulating ant-GBM antibodies. Recurrence doesn't usually lead to graft loss.

Recurrence of systemic disease:

- Lupus nephritis is not a contra-indication to transplantation because the risk of recurrence after transplantation is low and does not affect prognosis.
- Henoch-Schonleen purpura (HSP) is not a contra-indication to renal transplantation despite the risk of recurrence. Histological recurrence may occur in about half of the cases and is more frequent in children than in adults. Graft survival rates are lower in patients with recurrence.
- At the moment, no recommendation can be proposed for fibrillay / immunotactoid glomerulopathy (FG) because little information is available of the subject: however recurrence seems to be frequent, although some cases showed good function in spite of recurrence.
- Renal amyloidosis associated with familial Mediterranean fever (FMF) is not a contra-indication to renal transplantation despite the fact that amyloidosis may recur after kidney allograft, because it can be prevented by early administration of colchicine. No recommendation can be proposed for the other causes of amyloidosis which overall, causes a 10-40% recurrence rate after renal transplantation.
- Light-chain deposition disease (LCDD) should be considered a contra-indication to renal transplantation because recurrence is frequent and associated with poor prognosis.

- Hemolytic-uraemic syndrome (HUS) is not a contra-indication to renal transplantation despite the well-established risk of recurrence although this risk is poorly defined. The effect of cylosporine and tacrolimus on recurrence is still unclear.
- Anti—neutrophilic cytoplasmic antibody-associated (ANCA) vasculitis is not a contra-indication to transplantation: there is low but substantial risk of recurrence, which is independent of the presence of circulating ANCA or type of vasculitis. Graft survival is similar in patients with ANCA-associated vasculitis and those with other causes of renal failure.
- Idiopathic mixed cryoglobulinemic nephritis (MCN) is not an absolute contra-indication to renal transplantation when there is no severe liver involvement. However, the risk of recurrence after transplantation is high, but it remains unclear whether recurrence is detrimental to graft survival, as very few cases have been described.

Recurrence of metabolic disease:

- Diabetic nephropathy
  Renal transplantation should be considered as the treatment of choice for many patients with diabetes mellitus despite almost inevitable histological recurrence a few years after renal transplantations. However, overt clinical nephropathy leading to late graft loss occurs in only a minority of patients.
- Type I primary hyperoxaluria
  Patients with this condition should generally be considered for combined kidney and liver transplantation because renal transplantation alone is associated with rapid recurrent deposition of oxalate and graft loss, and liver grafting corrects the enzyme deficiency. Few patients with pyridoxine-sensitive hyperoxaluria may receive preemptive kidney transplantation alone but in association with forced diuresis and early / prolonged pyridoxine administration.
- Cystinosis
  Renal transplantation should be recommended because the disease does not recur.
- Fabry's disease (alpha galactosidase defect)
  Fabry's disease is not a contra-indication to renal transplantation; limited information is available regarding recurrence.

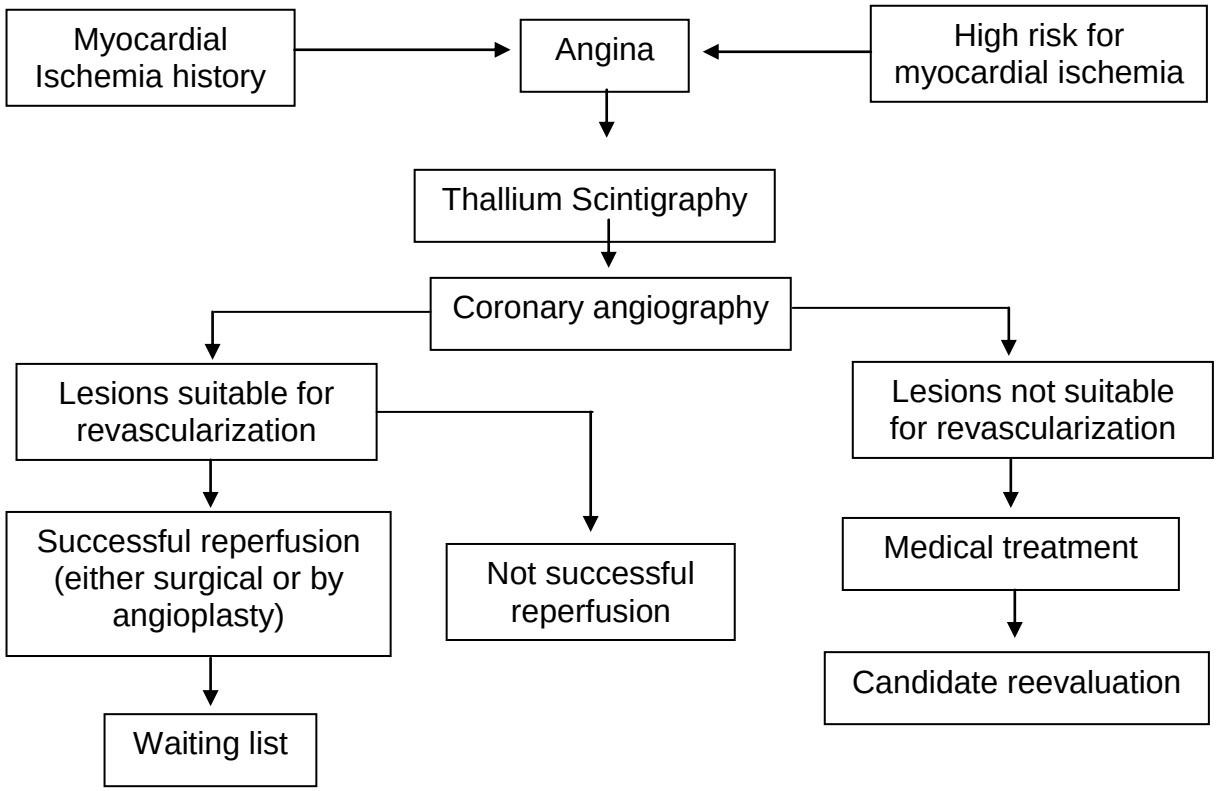
Specific medical concerns :

Diabetes Mellitus

- Kidney transplantation should be considered as the first therapeutic choice for all suitable patients with end stage renal disease. (ESRD) due to diabetes mellitus, because kidney transplantation is able to significantly extend survival as compared with dialysis.
- Diabetes ESD patients should be considered for an early and pre-emptive transplantation of either a simultaneous pancreas – kidney transplantation (SPK), a living related donor graft, or an early cadaver graft when residual glomerular filtration rate (GFR) decreases to <20ml/min.
- Diabetes mellitus should be considered as a serious co-morbid condition affecting transplant success and patient morbidity / mortality, mainly because of increased cardiovascular & infectious risk.
- Therefore, a thorough evaluation of diabetic transplant candidates is recommended with particular attention to the cardiovascular risk.

Cardiovascular Disease:

- As cardiovascular disease is the main cause of mortality after transplantation, careful evaluation is mandatory to detect and treat symptomatic coronary artery disease, congestive heart failure due to valvular failure or cardiomyopathy and pericardial constriction.
- As technical graft failure and impaired patient survival is often due to symptomatic peripheral artery disease, extensive pelvic vessel calcification, aortic and pelvic vessel dissection & symptomatic cerebral vessel disease should be excluded or treated in advance.
- As venous vessel disease such as post-thrombotic occlusion of the pelvic veins, radiation injury and retroperitoneal fibrosis of the pelvic and lower abdominal region carry a high risk of technical graft failure, these conditions should be excluded or treated in advance.



Older recipients:

- Advanced age per se in not a contra-indication to renal transplantation.
- In elderly (older) patients, renal transplantation should be offered because it increases the chance of survival compared with dialysis.
- In older recipients, careful assessment of their cardiovascular status and tailored immunosuppression are both recommended after renal transplantation because cardiovascular disease and infections are frequent causes of death and older recipients usually have less rejection.

Immunologic work-up of the recipient (and donor):

- ABO blood group should be ascertained for all candidates awaiting transplantation. (Look Part 2 page 1).
- The HLA-A, - B, and –DR phenotypes should be ascertained for all candidates awaiting transplantation. (Look part 2 pages 1&2).
- Cells for HLA typing should be obtained from ~20ml of recipient's peripheral blood using an appropriate anticoagulant.
- Comprehensive sets of reagents capable of detecting all commonly occurring HLA antigens within the relevant ethnic groups should be used and results should be accepted only if HLA antigens are unequivocally defined. If only one allele is identified at an HLA-locus, additional techniques should be employed to confirm true homo-or heterozygosity due to hitherto undetected allele.
- If the patient has been heavily transfused especially with non-leukodepleted blood within the previous 7 days, care should be taken in interpreting the level of mismatch since there is a risk of a "mixed field" result giving more than two alleles per HLA locus.
- When a relative is being evaluated for live donation and there is ambiguity with regard to the level of HLA matching, the immediate family members may be typed to obtain accurate HLA haplotype assignments and to identify any recombination between HLA genes.

Antibody screening to evaluate sensitization status:

- From time to time anti-HLA antibodies appear in a patient's blood that react against a potential donor. If unrecognized, these antibodies may cause hyperacute rejection of the transplant. Hence sequential serum samples should be routinely collected from the transplant candidate immediately before dialysis and at intervals no greater than 3 months.
- Sequential serum samples should be analyzed for antibody and freeze-stored ready for cross matching against a potential donor. Samples should be screened against a reference panel of cells selected to cover the majority of the HLA alleles in the donor population. The results should be expressed both as percentage panel reactive antibody (% PRA) and as the HLA specificity (s) that they react against.
- In serum samples with a high % PRA, careful analysis of the reaction patterns against the panel can often reveal allelic products against which the patient failed to make antibody. These windows of "non reactivity" may be used to predict and select cross-match negative donors.
- The most reactive sera available (highest % PRA) either after rejection and/or nephrectomy of a previously rejected graft, or after blood transfusion, should be identified by testing sera at frequent intervals in the 4 subsequent weeks after the event. The highest % PRA sera should be used in any subsequent cross-match test with a potential donor.

- A system should exist whereby the laboratory is notified every time a patient receives either a transfusion or treatment with anti-thymocyte; or –lymphocyte globulin or monoclonal antibodies such as OKT_3. Antibodies may linger in the serum and interfere with the antibody screening and cross-match tests.

Pre-emptive transplantation:

- Pre-emptive transplantation from either live or cadaveric donor results in equivalent or even better patient and graft survivals than transplantation performed after the start of dialysis. Pre-emptive renal transplantation should be encouraged for all patients whenever a living donor is available. Pre-emptive cadaveric transplantation may ideally be offered to all transplant candidates but is of particular importance for children and patients with diabetes mellitus; however cadaveric organ shortage makes this unlikely.
- Patients should have progressive deterioration in renal function and a creatinine clearance (15 mL/min/1.73m^2) to be eligible for pre-emptive transplantation.

Waiting List:

- Assignment to the transplant waiting list is the first crucial step for the patient, and this process should be seen to be transparent and to follow objective scientific principles after careful evaluation of the patient's medical history.
- The process of assignment should balance the possible success of a graft with the personal needs of the patient. Discrimination by age, gender, social & ethnic background is not acceptable.
- Due to the possible rapid change in the waiting recipient's medical condition, an update at regular intervals is recommended to avoid unexpected risks at the time of an offer of transplantation.
- The updated record available to the transplant center should contain information on the cardiovascular, on new infectious and viral diseases and on the lower urinary tract.
- Assessment may be performed every 6-12 months depending on the age and condition of the recipient.

Pre-operative transfusion

- Administration of random blood transfusions to first cadaveic kidney transplant candidates improved graft survival in patient's immunosuppressed with azatheoprine and steroids, and an effect, although reduced, was still observed in the early cyclosporine A (CyA) era. However, graft survival and rejection rates in non-transfused recipients are better today with the new immunosuppressive drugs that in previously transfused patients. As transfusion still carries a small risk of allo-immunization and transmission of infectious diseases, there are no robust indications at present to systematically give pretransplant blood transfusion to all transplant candidates. If contemplated, administration of pre-transplant transfusion should preferable be performed in the context of clinical study.
- Administration of donor-specific transfusion (DST) from living donor to non HLA-identical recipient improved graft survival in the azathioprine era. This beneficial effect appears still to prevail in the early Cyclosporine A era, but there are no data about the possible impact of DST with the present immunosuppressive regimens. Even with azathiopine or Cyclosporine A pre treatment, DST carries a risk of anti-donor sensitization precluding transplantation in up to 10% of patients. The decision to perform a DST should be made on a case-per-case basis.

- In patient with previous exposure to alloantigens, such as multiparous women, previously transplanted patients and those already HLA-sensitized, both random and donor specific transfusions carry an increased risk of anti-HLA sensitization. The risks and benefits of transfusing these patients should be carefully evaluated.
- The blood transfusions, whether random or HLA semi-identical or donor-specific, should meet the following requirements: (1) they should not be leukocyte free; (2) the number of units administered should be ≤ 3; (3) fresh rather than frozen blood should be given; and (4) the blood should be transfused at least several weeks before transplantation, as perioperative blood transfusions have no consistent effects.

Simultaneous transplantation of kidney and pancreas:

- Simultaneous kidney and pancreas transplantation should be offered to young recipients with juvenile onset diabetes mellitus as a first therapeutic option to prolong their survival.
- It may be carried out preemptively on early after the start of renal replacement therapy to avoid or retard diabetic complications.

Combined transplants with liver, heart & lung:

- Combined kidney and liver transplants should be offered to carefully selected recipients suffering from simultaneous renal and hepatic polycystic liver disease and primary hyperoxaluria.
- Combined kidney and heart (lung) transplants should be offered to carefully selected groups of recipients suffering from both chronic renal failure and severe heart failure irrespective of the cause (valvular, myocardial, coronary artery disease.)

Retransplants:

- Retransplants after early loss of a previous graft from rejection should be considered to be at increased risk of graft failure. Preventive measures such as improved HLA compatibility and adequate immunosuppression should be undertaken.
- Retransplants after early loss of a previous graft for technical reasons or late graft loss for any reason give similar results to first grafts and do not require special precautions. For retransplantation, nephrectomy of asymptomatic grafts is not necessary.

Indications for pretransplantation native nephrectomy:

- Chronic Renal Parenchymal infection
- Infected stone
- Heavy proteinuria
- Intractable hypertension
- Polycystic kidney disease: only in cases where kidneys are massive, recurrently infected, or recurrently bleeding.
- Acquired renal cystic disease: when there is a suspicion of adenocarcinoma
- Infected reflux Nephropathy : in cases of uninfected reflux nephropathy nephrectomy is not required, although most nephrologists recommend nephrectomy in sever form of uninfected reflux nephropathy because of the increase risk of recurrent urinary tract infection .

Pre-Transplant VACCINATIONS:

If previously unimmunized, adults should receive Polio, Tetanus and Diphtheria vaccines.
Administration of Pneumococcal, Meningococcal and Haemophilus Influenza type B Vaccinations are desirable. Live Varicella vaccine may also be considered .
Vaccinations should be documented in admission clerk in.

Evaluation and Selection of Donors[13-17]

Cadaveic Donors

Selection of donors:

- Any comatose patient with irreversible cerebral damage who appears likely to progress to brain death prior to terminal circulatory failure must be considered as a potential donor.
- Physicians caring for the potential donors should be encouraged to make early contact with the organ procurement team for assistance in the further management of the donor and the donor's family.
- Absolute contraindications against organ donation:

a) Previous or current history of cancer except for
   Non invasive brain tumors
   Non melanotic, non metastasizing skin tumor
   In situ cervical cancer
b) HIV positive serology, or a history of activities with high risk for HIV infection.
c) Uncontrolled or untreated septicemia and viral infections.
d) Hepatitis B+ve antigenemia is a contraindication for hepatitis B negative recipients where 'negative' is defined as HbsAg negative or hepatitis B antibody negative.
e) However, hepatitis B-positive antigenemia is not a contraindication for HbsAg+ve recipients.
f) Tuberculosis
g) Current Intravenous drug use
h) Severe hypertension
i) Oliguric acute renal failure

- Relative contraindications

a) Age greater than 60
b) Mild hypertension
c) Long term insulin dependent diabetes mellitus
d) Severe vascular disease
e) Suboptimal renal function

- At this time and in the absence of a 'gold standard', it is recommended that donors be evaluated on the basis of renal functions (calculated creatinine clearance, Cr Cl), age and vascular disease. Limits may be set as (1) CrCl . 60 ml/min as acceptable, (2) 50-60 ml/min as marginal and, (3) <50 ml/min as non acceptable for single kidney transplantation.

Determination of brain death:

A. It is determined that the procurement centers encourage standardization of the management of the brain-dead donor including easy to use forms to assist the responsible physician in the emergency situation, and in line with national laws and regulations.
B. Criteria of brain death.

Basic criteria for clinical neurological examination to be used:

- Known cerebral disease that can cause total cerebral infarction
- Normal body temperature (33ºC)
- Poisoning, sedation, and metabolic, electrolyte or acid base disturbances are ruled out.

Clinical Criteria:

- Unconscious. No reaction to speech, touch or pain
- Absence of spontaneous breathing
- Spontaneous muscular movements in area innervated by cranial nerves absent. Spinal reflexes in trunk or extremities may be seen.
- Defensive movements of head, extremities and trunk on painful stimuli absent. Spinal reflexes may be present.
- Reactions of pupils to light absent.
- Corneal reflexes absent bilaterally.
- Doll's eye movement absent
- Cardiocerebral reflexes absent (eye bulb pressure)
- Blinking reflexes absent
- Laryngeal reflexes absent
- Apnea test shows absence of spontaneous breathing.

C. Apnea Test:

- Calibrate the ventilator minute volume to reach normocapnia (arterial carbon dioxide pressure [aB-CO_2] at 5K Pa).
- aB-CO_2 before test is registered
- Ventilate with the above minute volume and 100% oxygen for 5 mins.
- Turn off the ventilator but let the oxygen flow down the endotracheal tube or tracheal cannula.
- Continue 5-10 mins monitor blood pressure and pulse frequency. Stop if signs of hypoxia are seen (e.g. arrhythmia).
  In cases of serious pulmonary damage, $Pa0_2$ can not be elevated above 10-12 K Pa, and the apnea test can only be performed for ~ 1 min. If the apnea test cannot be performed for >5 min, cerebral angiography should be carried out.
  Apnea test is read as positive when there is no spontaneous breathing during the test, in addition to a rise of at least 3K Pa in B-$pC0_2$ level after the test.

CLINICAL DETERMINATION OF BRAIN DEATH

Two examinations should be performed at least 2 hours apart	Exam 1	Exam 2
Date		
Time		
- Body temperature ≥ 33ºC	☐	☐
- No poison or sedation	☐	☐
- No serious metabolic, electrolyte or acid base disturbance	☐	☐
- No reaction to pain within trigeminal innervated area	☐	☐
- No spontaneous movement of eye, jaws, face, tongue or larynx	☐	☐
- No papillary reaction to light	☐	☐
- No corneal reflex	☐	☐
- No laryngeal or cough reflex	☐	☐
- No reflexive eye movement on turning the head	☐	☐
- No heart rate changes associated with pressure on eyes or carotid sinus	☐	☐
- No spontaneous breathing	☐	☐
- Apnea test	☐	☐

Exam No. 1 performed by Dr. _____

Exam No. 2 performed by Dr. _____

NB: If uncertain, cerebral angiography should be performed when all parts above have been checked, the patient may be declared deceased.

Support of the potential donor and optimizing organ function:

- Any comatose patient with irreversible cerebral disease should be identified as a potential donor and monitored carefully awaiting determination of brain death, evaluation and consent of organ donation and the final event of retrieval.
- The management of a potential donor should be basically similar to normal intensive care with the main objective is to support future function of renal, cardiac and /or pulmonary & liver grafts.
- A simplified goal for management is to maintain smear arterial pressure above 80, and maintain urine output between 75-125 ml/hr.
  A Swan Ganz catheter is inserted to gauge the different pressures.

Living Kidney Donors

- Use of kidneys from 'living donors' is recommended for renal transplantation whenever possible and is supported by the especially favorable results obtained after transplantation.
- Before being selected as a 'living donor', careful information should be provided to the potential donor and he or she should undergo a careful medical and physical evaluation, as listed in the donor evaluation form.
- After complete evaluation of the donor, formal written consent must be obtained from the donor
- Special care must be taken to ensure that a potential 'living related donor' does not fulfill any of the exclusion criteria listed below.

Exclusion criteria for a potential living kidney donor Kidney Disease

- Reduced glomerular filtration rate for his age & height
- Proteinuria >300 mg/day
- Microhematuria, except when a urologic evaluation and a possible kidney biopsy are normal
- Multiple kidney stones
- Multiple cysts
- Family history of autosomal dominant polycystic kidney disease (ADKD), unless ultrasound or CT scan is normal and donor age is >30 years
- Bilateral fibromuscular arterial dysplasia
- Three or more renal arteries.

Other Exclusion criteria

- ABO incompatible
- Cross-match positive
- Hypertension poorly controlled
- Diabetes Mellitus
- Cardiovascular Disease
- Pulmonary insufficiency
- Abuse of morphine, heroin or cocaine
- HIV positive
- Hepatitis B antigen-positive to a negative recipient
- Hepatitis C positive to a negative recipient
- Other severe infections
- Malignancy
- Long term use of nephritic drugs
- Age <18 years
- Previous major abdominal surgery

The 'living donor' should always be left with the best kidney. This will be decided after performing radio-nucleotide scan, using iothalamate or other radio- nucleotides to assess 'split kidney function'. In view of that and the nature of each kidney's anatomic blood supply, a decision will be made as to which kidney should be harvested.

Risks of kidney donation include:

- Short term surgical risks
- Theoretical and unlikely long-term risks of impaired kidney function and hypertension
- Psychological risks

It should be stressed however, that the long-term risk of kidney donation is very low and that the 'living donor' has a longer life survival than the general population, possible due to the positive selection.

Part II. The Transplant recipient from initial transplant hospitalization to 1 year post transplant [13-17]

ABO blood group matching guidelines:

- The first priority is to avoid mismatch for the ABO blood group antigens between donor and recipient.
- In cadaveric kidney transplantation, the donor should be ABO identical to the recipient and ABO blood group compatibility should be discouraged. This preserves the balance between demand and supply for different ABO phenotypes and counteracts the tendency for 0 patients to accumulate on waiting lists. It also reduces the risk of hemolytic disease.
- In live donor kidney transplantation, ABO identity or compatibility are equally acceptable.
- In highly selected minority of patients where the most suitable kidney is ABO mismatched and incompatible, transplantation is justified, provided special protocols, designed to minimize the risk of hipper acute rejection are followed.

Donor	**Recipient**			
	A	**B**	**AB**	**O**
A	Identical	Mismatched	Compatible	Mismatched
B	Mismatched	Identical	Compatible	Mismatched
AB	Mismatched	Mismatched	Identical	Mismatched
O	Compatible	Compatible	Compatible	Identical

HLA matching and mismatching guidelines:

- Top priority should be given to allocating donor organs to patients with no HLA-H, -B and DR mismatches. Kidneys from cadaveric donors should be allocated to recipients with least number of mismatches at HLA-A, -B and –DR loci, and thereafter according to major risk factors, including age and waiting time.
- When a living donor transplant is being considered, HLA matching is important, but of lower priority than with cadaveric donor transplants. Theoretically, if a choice exists between several live donors considered to be equally eligible by all other clinical criteria, priority should be given to the donor with the least number of HLA mismatches.
- Due to extensive polymorphism of HLA, only partial matching is achievable when allocating cadaveric organs to most patients. Hence consideration should be given to the relative “importance” of mismatches at the different HLA loci. Priority should be given to minimizing mismatches for HLA – DR. Once the level of DR mismatch has been agreed,the next priority is to minimize mismatches for HLA– B and finally HLA – A.
- In repeat transplants especially where the previous graft was lost rapidly within the first year, there is an increased risk of graft lost. Great care should be taken to establish the HLA specificities to which the recipient has developed antibodies. Repeat HLA – DR mismatches in retransplants should be avoided in all cases. However HLA – A and B mismatches may be repeated, provided the recipient failed to develop an antibody response to them and the cross-match test is negative with all available sera.

Pre-transplant antibody cross-matching guidelines:

- A cross-match test must be repeated in all cases immediately prior to transplantation using at least one technique that detects complement-dependent lymphocytotoxic antibodies. Selected stored sera from the patient should be tested against donor's mononuclear cells prepared from blood, spleen or lymph node. Sera selected for testing should include all samples from the transplant candidate that have been shown to contain antibodies to mononuclear cells.
- Other techniques such as flow cytometry cross-match may be used to confirm the complement dependent lymphocytotoxicity cross-match result, but the clinical relevance of a positive flow cytometry cross-match result in the absence of a positive lymphocytotoxicity cross match result is still under evaluation.
- A positive lymphocytotoxicity cross-match test with the current serum taken from the prospective recipient is a contra-indication to transplantation. But if a positive cross-match is attributable solely to IgM antibody directed to non-HLA antigens or to auto-antigens, the result may be ignored and the transplant performed.
- A complement dependent lymphocytotoxicity cross match test result that reacts positively with the transplant candidate's non-current or historical sera, but negatively with current sera should be considered as a contra-indication to transplantation in patients receiving retransplants and in all those with high panel reactive antibody (>40% PRA) unless it is attributable solely to IgM antibody to non HLA antigens or to auto-antigens.

(Once the patient is admitted, the transplant team will meet to review and confirm the above recommendations)

Should Dialysis be done routinely before transplant?

- Pre operative dialysis will not be performed routinely, except for patients with heart failure and /or hyperkalemia, otherwise the need to dialyze will be decided after clinical evaluation by the nephrologist.
- Pre operative hypovolemia should be avoided to prevent delayed graft function. Hypervolemia, should also be avoided to give room for intravenous infusion of fluids and medications intra-operatively.

PRE-Operative recipient management:

A) Full History and Examination (*the patient is usually evaluated and prepared prior to admission***)**

History

- *cause of renal failure*
- *dialysis - type, when commenced*
- *time of last dialysis –normal target or dry weight*
- *access and any related problems*
- *Volume of urine output + history of past/present urinary tract problems*
- *infections - any recent*
- *CAPD peritonitis/exit site/access related*
- *other operations*
- *ischaemic heart disease*
- *peripheral vascular disease*
- *Recipient blood group,tissue typing and virology (CMV,EBV,HIV,Hep B & C) must be recorded in the notes.*

Examination

- *A full physical examination of the patient should be performed and should include observation of:*

fluid status
peripheral pulses
abdominal scars/hernias

Investigations

Blood Tests should be taken as soon as patient is admitted.

- Complete Blood Count(CBC) + platelet count
- Fasting and random blood sugar
- Electrolytes
- Blood Urea Nitrogen (BUN) & creatinine
- Hepatic profile
- Prothrombin Time (PT) & Partial Prothrombin Time (PTT)
- Blood group & cross match for 2 units of whole blood or packed RBCs.
- Electrocardiogram
- Chest-XR
- Urine analysis + culture & sensitivity if the patient is passing urine.
- PD fluid for WBC and gram stain / culture if appropriate
- Tissue Typing (white clotted bottle for lymphocytotoxic Antibody,
- Virology - CMV, HIV, Hep B + C (only if >1/12 since last test)

Results must be requested as Urgent. Patient may require dialysis pre-op,

B) PRE-operative medical orders considerations:

- **Fasting –** All patients should be fasted from four hours prior to the anticipated theatre time unless otherwise stated by surgeons or anaesthetists.
- **Fluid balance** – A critical appraisal of the patient's fluid status must be performed, and

should include - supine and erect blood pressure recordings, detailed assessment of JVP and peripheries. Patients may well be relatively fluid deplete, especially those undergoing haemodialysis. Once the final results are known and it is accepted that the patient is going ahead to transplant, then any obvious fluid depletion should be corrected, by intravenous therapy. The insertion of a central line in the pre-operative phase is not indicated, except in unusual circumstances. (A central venous line is inserted immediately after induction of anaesthesia to allow central venous pressure monitoring and guide fluid replacement, both pre-operatively and post-operatively)

- **Peritoneal dialysis** – continue CAPD until immediately pre-op (abdomen should be emptied 30 - 45 minutes pre-operatively). APD as usual if transplant delayed till morning. Otherwise, only if indicated by biochemistry.
- **Haemodialysis** – patient may require haemodialysis

B) Pre-operative Management of serum potassium

The objective is to ensure that the serum [K+] is ≤ 5 mmol/l when the patient goes to theatre. It is the responsibility of the renal doctor to obtain the potassium result and act upon it.

• *If serum [K+] >6.5, the patient will usually require haemodialysis. Inform registrar/consultant and follow immediate measures for hyperkalaemia*
• *If admission serum K+ >5.5 , plan will depend on circumstances.*
• *If serum [K+] 5 - 5.5:*
maintenance regime plus insulin/dextrose given as 5 units actrapid and 50 ml 50% dextrose over 15 minutes.
Nebulised salbutamol 5 mg six hourly
Potassium should be checked after 60 minutes.
• *Patients who fail to respond may require dialysis.*
• *If serum [K+] ≥ 4 and surgery is likely to be more than six hours later:*
500ml of 10% dextrose at 40 ml/hr (non-diabetic patients)
500ml of 10% dextrose with 16 units Actrapid at 40 ml/hr (for diabetic patients)

Notes

1. Post-dialysis potassium must be checked from a venous sample taken at least 5 minutes after the end of dialysis.
2. The maintenance regime is only designed to prevent a rise in serum [K+] and is not appropriate when the serum [K+] requires reduction.
3. There is no place for calcium resonium or sodium bicarbonate in the control of pretransplant potassium.

C) Post-operative Management points to remember :

- **Anti-hypertensives** are taken as usual pre-operatively except *ACE inhibitors and angiotensin II antagonists are omitted***.** Other anti-hypertensives may also be selectively omitted post-operatively and re-introduced if required
- **NSAIDS** – OMIT
- **Diuretics** – OMIT
- **Warfarin** – OMIT and reverse if necessary (a pre-transplant plan should have been discussed)
- **Aspirin** – REVIEW
- **Antibiotic prophylaxis**(our recommendations)

Given at induction of anaesthesia:

Tazocin 4.5g IV, unless patient is allergic to penicillin, then you can give Vancomycin 1gram Intravenously in Normal Saline over 2 hours and Ciprofloxacin 400 mgs infused over 60 minutes.

- **Immunosuppression**(our recommendations)

ALL patients receive induction therapy

methylprednisolone:

500 -1000 mg IV Methylprednisolone given over one hour , two hours before the transplant

*Basiliximab **(if indicated)***

The first dose will be given 20 mg IV one hour before transplant

- **DVT prophylaxis**(our recommendations)

Heparin 5000U/Subcutaneously (SC) at anaesthetic induction and 5000U/SC/ once to twice daily thereafter until mobile post operation.

Pneumatic Pump plus Elastic stocking .

Live donor management-points to remember:

Live kidney donors will be seen at the Transplant Assessment Clinic two weeks prior to the scheduled transplant date.

- Blood samples will be taken at this visit for:

✓ repeat virology

✓ lymphocytotoxic cross match

- Admission is arranged 24 hours pre-op to the Transplant Unit.
- On admission the donor should have received a full physical examination; blood pressure, temperature; urinalysis and urine specimen sent to bacteriology.
- Pre-op X-Ray/ECG/ blood tests are requested.
- Written consent for a nephrectomy should be obtained by the Consultant Transplant surgeon.
- All donors should receive DVT prophylaxis with TED stockings, intra-operative pneumatic compression and heparin. Post-operative: heparin sub-cut 5000u twice daily.
- Pre-op heparin should not be administered unless the Consultant Anaesthetist specifically requests.
- Post-op fluid management
- **Any problems should be reported directly to the Consultant.**

Initiation and Maintenance Therapy

Standard regimen

The triple regimen of
1. Calcineurin inhibitors either cyclosporine or tacrolimus
2. Methyl Prednisolone
3. Mycophenolate Mofetil
4. The addition of Interlukin 2 receptor blockers Basiliximab for induction is recommended in our protocol especially when corticosteroids are to be decreased rapidly following transplantation or when the calcineurin inhibitor is to be administered at reduced doses as followed in our guidelines

Dosage & mode of administration

Cyclosporine

- An intravenous dose of 5-6mg/kg given as a single dose over 4- 12 hours prior to surgery. Thereafter, a microemulsion form of cyclosporine is given at a dose of 5-10mg/kg/day orally or through a feeding tube. This dose will be split to be given every 12 hours starting from day 1, to maintain drug level specified in the table (150-350, measured by HPLC or RIA method)
- The starting dose of 5-10mg/kg/day will be adjusted and tapered gradually (~5% per week) to reach a dose of 3-5mg/kg/day orally at the end of 3 months.Since there is a variation from person to person regarding the required dose, trough levels will be checked regularly to guide the necessary dose for each patient.

Approximate therapeutic ranges for cyclosporine (mg/ml) as oral form

Months After Transplantation	HPLC and MonocLonal RIA
0 - 2	150 – 200
2 - 6	100 – 150
> 6	- 100

- The above trough levels are only general guidelines to monitor therapy. Exceptions to these general guidelines may apply, in highly sensitive patients.These circumstances will be specified and addressed by the Physician.

Tacrolimus (FK 506)

- It can be used as an alternative to Cyclosprine for induction.
- The recommended starting dose is: 0.15 – 0.30mg/kg/day administered in a split dose orally every 12 hours. The first dose is to b given preoperatively by mouth.
- The dosage will be adjusted to achieve trough levels between: (10-12 ng/dl) during the first 3-6 months. Thereafter dosage will be adjusted to achieve lower trough levels between 5-8 ng/dl.

NB: There is marked variation in dose between individuals (ie: some require only 2mg/day, and others require ten times that dose to achieve the same drug levels).

Methylprednisolone

Day 0 : Given intra-operatively in a dose of 1gm IV over 60 minutes.
Day 1-3 : Give 500 - 150mg IV over 30-60 minutes
Day 4-7 : Give 100mg of prednisone PO
Day 8-10 : Give 60mg PO daily
Day 10-14 : Give 40mg PO daily

Prednisone

- Day 15-3 months: Give 20-30mg PO daily
- At 4 months will aim at a dose equivalent to or less than 15mg PO daily.
- Dose will be tapered gradually to long term maintenance dose of 7.5-5mg.

MMF (Mycophenolate Mofetil)

- It will be given in the standard dose of 1000mg orally twice daily on an empty stomach.
- Doses can safety be reduced or held for short periods in cases of intolerable side effects.
- In the rare circumstances in which the patient can't tolerate it at all, shifting to Azathioprine is considered in an oral dose of 1-3 mg/kg/daily.

Basiliximab

- It will be given in 2 doses of 20mg IV each, first dose given within 2 hrs before surgery, and the 2nd dose is given on postoperative day 4.

Daclizumab

- It will be given in a dose of 1mg/kg IV, first dose prior to transplant, and once every other week for a total of 5 doses.

Antihypertensives:

- Preference will be given to Calcium channel blockers (Diltiazem and amlodipine) as some studies suggest that they improve 1 year graft survival by 5-10%.
- Calcium channel blockers are known to elevate the levels of calcineurin inhibitors, which might help reduce the doses of these medications.
- All classes of antihypertensives can be used in transplant patients, and different combinations can be used to control the blood pressure.

CMV Prophylaxis:

Who must receive prophylaxis?

- All CMV sero-negative recipients receiving a kidney from a CMV sero-positive donor (D+/R-) or CMV non-typed donors.
- All CMV sero-positive recipients treated with polyclonal or monoclonal antibodies for steroid resistant acute rejection or those who received the antibodies as part of induction therapy.

Prophylaxis Regimen:

There are 5 different modalities of preventive treatment. Any of them can be used according to availability of medications & physician's preference. All regimen are to be started on the day of surgery (day 0).

1. Ganciclovir orally: given for 12 weeks at a daily dose of 3000mg (1000mgx3) adjusted to GFR.
2. Granciclovir administered intravenously for 14 days at a daily dose of 10mg/kg adjusted to GFR, given in split dose of 5mg/kg Q12hrs. Then 5mg/kg once daily thereafter.
3. Weekly Intravenous infusion of hyperimmunoglobulin for 6 weeks with high dose of 400mg/kg once/wk or a low dose of 150mg/kg at surgery, 10mg/kg at 2&4 weeks, 50mg/kg at weeks 6,8,12&16.
4. Oral Valacyclovir given for 90 days at daily dose of 8000mg (2000mgx4) adjusted to GFR.
5. Oral Valgancyclovir given for 100 days at daily dose of 900mg, adjusted to GFR.

"Ganciclovir and Valganciclovir yielded the best results, followed by Valacyclovir. One of these should be used preferentially".

EB virus prophylaxis:

- The indications and guidelines are similar to that of CMV. Acyclovir in a dose of (800mg –3200mg) is given for at least 3 months. Ganciclovir and Valacyclovir can also be used as recommended above for CMV.

Bacterial Prophylaxis

Approximately 5% of patients develop pneumocystis carinii pneumonia (PCP) after renal transplantation if they do not receive prophylaxis. Therefore, all renal transplant recipients should receive PCP prophylaxis.

- **First line**

Timethoprim/ Sulfamethoxzole (TMP/SMX) given orally at a dose of 80/400mg daily,or (TMP/SMX) orally at a dose of 160/800 given 3 times/week for at least 4months.Patients who are treated for rejection should receive TMP/SMX prophylaxis for 3-4 months.

- **Second Line**

Dapsone 100mg once daily .

Consider dose reduction to 50mg daily in severe renal dysfunction (creatinine clearance<10ml/min).

- **Third Line**

Nebulised pentamidine 300mg every 4 weeks – details from www.ircg.us.com .

VACCINATIONS:

Pre-Transplant

If previously unimmunised, adults should receive Polio, Tetanus and Diphtheria vaccines.Administration of Pneumococcal, Menningococcal and Haemophilus Influenza type B vaccinations are desirable. Live Varicella vaccine may also be considered - it is available on a named patient basis from pharmacy. Vaccinations should be documented in admission clerk in.

Post-transplant

Live vaccines should not be given to immunosuppressed patients. Influenza vaccine is inactivated and therefore safe.

The following are live vaccines:

- Oral Polio vaccine (OPV, Sabin).
- Oral Typhoid vaccine (Vivotif).
- Measles
- Mumps
- Rubella
- Rubella vaccine (Erverax)
- BCG vaccine.
- Varicella vaccine - not in UK.
- Yellow fever (Arilvax).

- **Polio/Typhoid**

There are inactive alternatives for the oral polio and typhoid vaccines. Household contacts of immunosuppressed patients should also receive inactive polio vaccine as they will excrete live polio for up to 6 weeks post vaccination if they receive live polio vaccine.

- **MMR**

There is no risk of infection from vaccinees. Immunosuppressed patients who have come into contact with measles should receive HNIG (Human Normal Immunoglobulin) as soon as possible after exposure. HNIG may be given to pregnant women with proven Rubella infection where termination is unacceptable.

- **Varicella**

Varicella Zoster Immunoglobulin (VZIG) is indicated in patients who have had significant exposure to Chickenpox or Herpes Zoster and who have no antibodies to the VZ Virus. If required VZIG should be administered within 7 days of the initial contact.

- **Yellow Fever**

For patients intending to travel to countries where a Yellow Fever certificate is required they should obtain a letter of exemption from a medical practitioner. Yellow Fever occurs in tropical Africa and South America.

Surgical and Medical Complications of Renal Transplantation and Diagnostic Methods [18-25]

Normal Transplanted Kidney

Surgical Technique

The transplanted kidney is usually placed extraperitoneally in the patient's right iliac fossa,with end-to-side anastomosis to the external iliac vasculature. Cadaveric kidneys are typically harvested with an intact main renal artery and an attached portion of the aorta. The piece of the aorta is trimmed to an oval configuration and then anastomosed in an end-to-side fashion to the recipient external iliac artery. With kidneys from living donors, a portion of the aorta cannot be harvested; in these cases, either an end-to side anastomosis of the donor renal artery to the recipient external iliac artery or an end-to-end anastomosis to the recipient internal iliac artery is performed. The donor renal vein is always sutured in an end-to-side fashion to the recipient external iliac vein. The currently preferred method for restoring urinary drainage is ureteroneocystostomy a procedure by which the ureter is implanted directly into the dome of the bladder. However, ureteroureterostomy or pyeloureterostomy may also be performed.

Ultrasonographic Findings

Morphologically, the transplanted kidney is very similar to the native kidney, and many of the subtle differences are attributed to the improved resolutionof the former. There is well-defined renal parenchyma peripherally, with a highly reflective echogenic sinus centrally. In distinction from the native kidney, the renal pyramids are more commonly visualized within the transplant, being hypoechoic relative to the parenchyma itself. The iliac and transplant vessels can be identified with color Doppler ultrasonography. Many different indices have been assessed in an attempt to quantify "flow," and these include the pulsatility index (PI), resistive index (RI), systolic-diastolic ratios, and diastolic-systolic ratios. The 2 most commonly used ratios are the PI and RI.

Urologic Complications

Urologic and vascular complications do occur and have a substantial impact on morbidity and mortality. Approximately two thirds of early urologic complications are apparent in the first month after transplantation. The prevalence of urologic complications varied from 10% to 25%, with a mortality rate ranging from 20% to 30%. In these patients, ureteroureterostomy or pyeloureterostomy was performed to restore urinary tract continuity. Currently,
patients who undergo ureteroneocystostomy have a lower incidence of urologic complications (1%–8%) with very low patient mortality.

Urine Leaks and Urinomas

Urine leaks manifest in the early postoperative period with pain, swelling, and discharge from the wound. Extravasation of urine may occur from the renal pelvis, ureter, or ureteroneocystostomysite. Leaks at the ureterovesical anastomosis are related to the surgical technique or distal ureteral necrosis. Urinomas vary in size and are usually found in the first 2 postoperative weeks between the transplanted kidney and the bladder. On ultrasonography, a urine leak or urinoma appears as a well-defined anechoic fluid collection with no septations that increases in size rapidly. Drainage may be performed with ultrasonographic guidance, and the higher creatinine level of the fluid

compared with its serum concentration differentiates a urine leak from a seroma or lymphocele (Figure 1).,

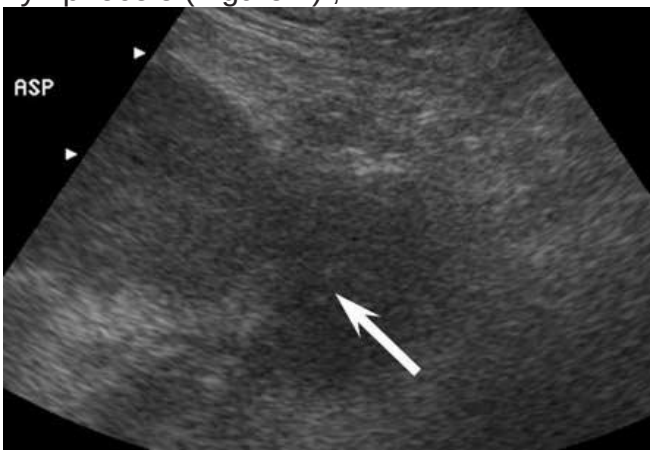


Figure1

A cystogram may show leakage from the bladder and an isotope scan is often helpful. Radionuclide studies show extravasation of radiotracer into an area that was initially "cold." Delayed scintigrams should be obtained because accumulation of the radiotracer may be slow. Small urine leaks may be treated with percutaneous nephrostomy and stent placement.

Calculous Disease

Renal transplantation recipients, compared with the general population, are at increased risk for development of urinary calculi, and approximately 1% to 2% have clinically relevant stones. In the first year after transplantation, 15% of patients may be hypercalcemic, which increases the risk of renal stones. The diagnosis of urinary calculi is suspected when renal function suddenly deteriorates. The patient does not have typical renal colic because the transplanted kidney is denervated. Percutaneous nephrostomy tube placement is valuable because it provides low-pressure drainage and allows renal function to stabilize. Antegrade pyelography can then be used to give exact definition of the collecting system and position of the stone .

Urinary Obstruction

Urinary obstruction occurs in approximately 2% of transplantations and almost always within the first 6 months after the procedure. Obstruction of the transplanted kidney may occur at any location but is most frequent at the site of implantation of the ureter into the bladder. More than 90% of ureteral stenoses occur within the distal third of the ureter . Narrowing at the ureterovesical junction may be caused by scarring secondary to ischemia or rejection, by technical error during the ureteroneocystostomy, or by kinking. These events account for more than 50% of obstructions that cause a ureteral stricture. Less common causes include pelvic fibrosis, calculi, papillary necrosis, fungus balls, clots, and compression from an extrinsic mass such as an adjacent peritransplant fluid collection. Urinary obstruction manifests by a rising level
of serum creatinine. Obstruction may be difficult to differentiate from chronic rejection because both cause rising creatinine levels. In addition, mild dilatation of the collecting system may occasionally be seen in cases of chronic rejection. Ultrasonography can be used to confirm the diagnosis of hydronephrosis ; however, intrarenal edema and fibrosis associated with rejection may prevent the normal hydronephrotic response. Some transplant recipients may have substantial obstruction but little or no renal dilatation. Mild to moderate dilatation of the transplanted pyelocaliceal system and ureter may occur secondary to a full bladder.

In all cases, when the patient's bladder is full, the bladder should be emptied, and the transplant should be imaged again. Ultrasonography also shows lymphoceles, hematomas, abscesses, and urinomas that may cause ureteral obstruction. Scintigraphy may show urinary obstruction. In a patient with early partial obstruction, good perfusion and prompt uptake of the radiotracer may be seen; however, in a patient with functionally relevant hydronephrosis, radioactivity is retained in the collecting system. Delayed images (obtained 2–4 hours after injection) are useful for differentiating an obstructed ureter from a dilated but unobstructed ureter because an unobstructed system shows clearance into the bladder.
Treatment of urinary tract obstruction consists of stent placement, balloon dilation, or correction of the source of extrinsic compression of the collecting system, such as a lymphocele. Balloon dilation of posttransplantation ureteral stricture procedures has an overall success rate of ureteral dilatation in 90% of cases. However, surgical reconstruction may be required for long or recurrent strictures.

Peritransplant Fluid Collections:
Peritransplant fluid collections have been reported in up to 50% of renal transplantations and include urinomas, hematomas, lymphoceles, and abscesses.
The clinical relevance of these collections is largely determined by their size, location, and possible growth. In the immediate postoperative period, small hematomas or seromas manifesting as crescentic peritransplant fluid collections are almost expected. Their size should be documented at baseline examination because any increase in size may warrant intervention. Growing collections may be indicative of urine leaks, abscesses, or vascular injury. Different types of peritransplant fluid collections can be partially differentiated on the basis of the time interval after transplantation. Urinomas and hematomas are most likely to develop immediately after transplantation, whereas lymphoceles generally occur 4 to 8 weeks after the surgical procedure.
The ultrasonographic characteristics of peritransplant fluid collections, however, are entirely nonspecific, and ultimately, diagnosis may be made only with percutaneous aspiration.

Hematomas:
Hematomas are common in the immediate postoperative period, but they may also develop spontaneously or as a consequence of trauma or biopsy. They are usually small and resolve spontaneously. Large hematomas can displace the transplanted kidney and produce hydronephrosis. On ultrasonography, hematomas have a complex appearance. Acute hematomas are echogenic and become less echogenic with time. Chronic hematomas even appear anechoic, more closely resembling fluid, and septations may develop. Similarly, on computed tomography (CT), the appearance of hematomas also is time dependent. Acute hematomas have high attenuation components , and chronic\ hematomas contain liquefied and serous portions of intermediate attenuation. On scintigraphy, hematomas show a "cold defect." Size, location, and growth determine the relevance of these collections. Because an increase in size may indicate the need for surgical intervention, the size of any such collection should be documented on the baseline ultrasonographic scan. More complex collections identified later in the postoperative period with clinical evidence of infection may represent abscesses.

Lymphoceles:
Lymphoceles are the most common peritransplant fluid collections. They usually occur 4 to 8 weeks after surgery and affect up to 20% of patients. The cause of these collections is likely the disruption of the normal lymphatic channels during perivascular dissection or disruption of hilar lymphatic vessels. Most lymphoceles are discovered incidentally and do not require therapy. However, because of their potential to exert a mass effect, lymphoceles can impair renal function by producing hydronephrosis or can cause conditions such as edema of the leg, abdominal wall, scrotum, or labia. On ultrasonography, lymphoceles are anechoic and may have septations (Figure 2). Similar to other peritransplant fluid collections, they can
become infected, with development of a more complex appearance. On CT, lymphoceles have variable characteristics and are usually sharply circumscribed . Their CT attenuation values are typical of those of water and usually lower than those of recent hematomas and abscesses. On scintigraphy, a large photopenic region can be seen to exert a mass effect in the transplant. Small lymphoceles are monitored ultrasonographically, and large ones, if they grow or causehydronephrosis, should be drained. Lymphoceles can be treated with either percutaneous or surgicaltechniques. Percutaneous therapy varies from simple aspiration to placement of a drain, with or without sclerotherapy.

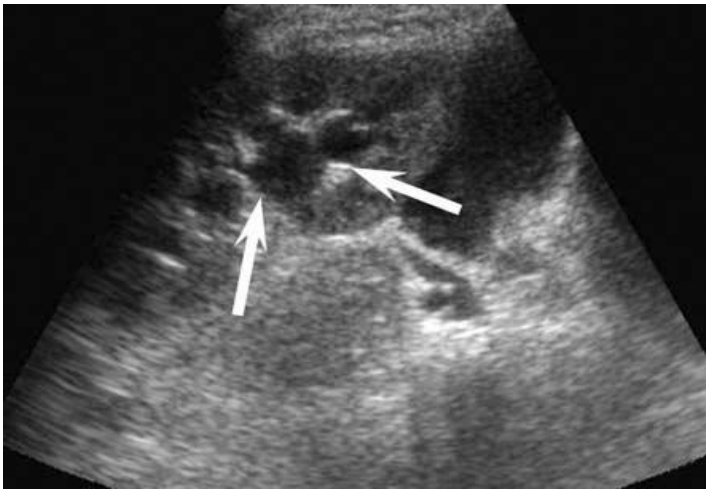


Figure 2

Infections and Abscesses:
More than 80% of renal transplant recipients have at least one case of infection during the first year after transplantation. Early diagnosis of and intervention for infectious diseases can help prevent loss of graft function and improve patient outcome. Patients frequently have multiple infections, and immunosuppressive medications, indwelling catheters, and frequent glycosuria are all risk factors. Peritransplant abscesses are uncommon complications and usually develop within the first few weeks after transplantation. These abscesses may be caused by pyelonephritis or bacterial seeding of a lymphocele, hematoma, or urinoma. Acute bacterial nephritis, renal abscesses, or perinephric abscesses may occur. The ultrasonographic appearances of infections and abscesses are quite variable. Abscesses have a complex, cystic, nonspecific appearance on ultrasonography ; however, on CT, they manifest with gas, which serves to differentiate them from other collections. The presence of low-level echoes in a dilated pyelocaliceal system in a febrile patient suggests pyonephrosis.Abscesses may be treated with either ultrasonographically guided or CT-guided percutaneous drainage.

Vascular Complications:

Vascular complications are seen in less than 10% of renal transplant recipients, but those are important causes of graft dysfunction. In contrast to other causes of transplant dysfunction, vascular complications have high associated morbidity and mortality. Once identified, vascular lesions are usually easily repaired. Although angiography remains the standard for diagnosis of vascular complications, ultrasonography performed with duplex and color Doppler modes is an excellent noninvasive modality for evaluating the affected vessels.

Transplanted Artery Stenosis:

Transplanted artery stenosis is usually a late complication and the most common vascular complication of transplantation, reported in up to 10% of patients. Evaluation for renal artery patency should be performed in patients with severe hypertension refractory to medical therapy or with hypertension combined with either an audible bruit or unexplained graft dysfunction. Moderate hypertension alone is not a reliable marker for renal artery stenosis because up to 65% of transplant recipients have nonrenovascular hypertension. Stenoses usually occur at the anastomosis or at the proximal donor artery and are directly related to surgical technique. Approximately half of renal artery stenoses occur at the anastomosis, and end-to-end anastomoses have a 3-fold greater risk of stenosis than end-to-side anastomoses. Doppler ultrasonography has proved to be an excellent noninvasive modality for evaluating the renal artery. Initially, the course of the artery is mapped by using color Doppler techniques. With proper adjustment of the controls, the stenotic segments will appear as regions of focal color aliasing, which can then be evaluated with duplex Doppler techniques to characterize and grade the abnormality.

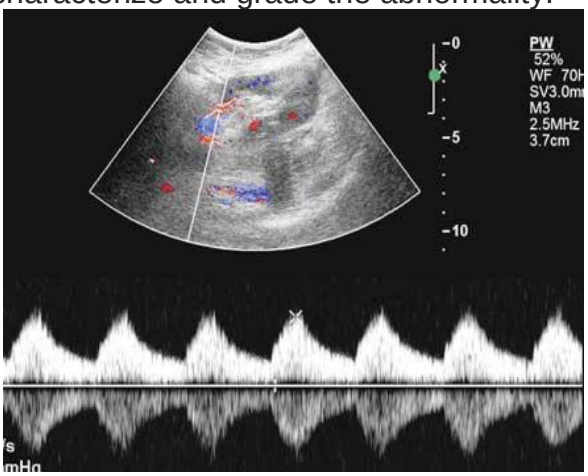


Figure 3

Doppler criteria for major stenosis include the following: (1) velocities of greater than 2 m/s or a focal frequency shift of greater than 7.5 KHz (when a 3-MHz transducer is used), (2) a velocity gradient between stenotic and prestenotic segments of more than 2:1, and (3) marked distal turbulence (spectral broadening). With this intrarenal approach (Figure 3), an observation of tardus parvus waveforms may be helpful, but they are variably present. The proposed criteria for detecting proximal renal artery stenosis are a prolonged acceleration time (>0.07 seconds),which is the time from the start of systole to the systolic peak; a diminished acceleration index (<3.0 m/s2), which is the slope of the systolic uptake; a decreased RI (<0.56); and loss of a normal early systolic compliance peak. Patients with abnormal Doppler ultrasonographic findings but with no clinical abnormalities should be followed clinically.

Surgical correction of graft renal artery stenosis is usually successful, but it is associated with substantial morbidity. Primary treatment of graft renal artery stenosis by means of percutaneous transluminal angioplasty with or without stent placement results in good patency and is associated with substantial early improvement in blood pressure and creatinine levels.

Kidney Infarction:

Renal artery thrombosis is a rare complication of transplantation that occurs soon in the early postoperative period and almost invariably leads to graft loss. Associated findings include severe rejection, severe tubular necrosis, and faulty surgical anastomosis. Patients with renal transplant infarction have an absence of urinary output, often with swelling and tenderness over the graft and anuria. Although the graft itself is denervated, the inflammation within the transplanted kidney may incite an inflammatory response in the adjacent visceral peritoneum, with local pain in this location. On ultrasonography, a segmental infarct appears as a poorly marginated hypoechoic mass or a hypoechoic mass with a well-defined echogenic wall. If the infarction is global, the kidney will appear hypoechoic and be diffusely enlarged. On color or power Doppler ultrasonography, segmental infarcts appear as wedgeshaped areas without color flow, although these findings may also be seen in severe pyelonephritis or transplant rupture. Renal artery thrombosis is diagnosed on ultrasonography when duplex and color Doppler techniques fail to show intrarenal venous and arterial flow. However, because these findings may mimic those of severe rejection (Figure4), if any doubt exists as to the nature of the ultrasonographic findings, angiography or MR angiography may be performed. Dynamic enhanced MR imaging can be useful for diagnosing both segmental and global infarctions as well as renal artery thrombosis. A percutaneous angiographic thrombolytic technique may be valuable in treating infarctions and renal artery thrombosis. Early diagnosis and treatment are vital for allograft salvage.

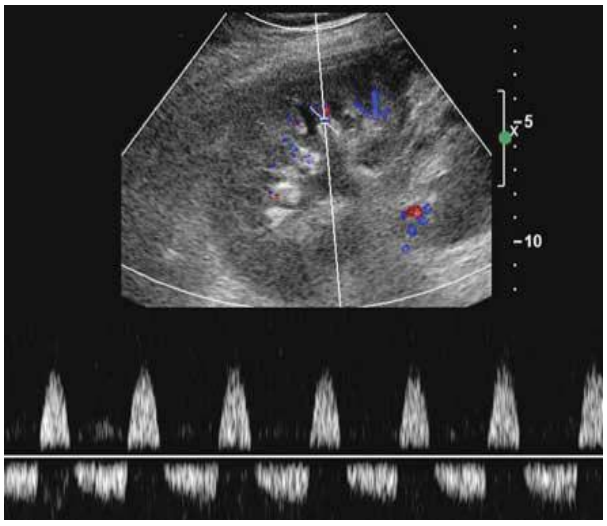


Figure 4

Arteriovenous Fistulas and Pseudoaneurysms:
Percutaneous biopsy is commonly performed in transplant recipients when rejection is suspected. Arteriovenous fistulas and pseudoaneurysms are occasionally seen after graft biopsy. Gross hematuria is seen after 5% to 7% of biopsy and is usually self-limiting; however, massive or persistent hematuria may occur.6Color and duplex Doppler ultrasonography easily shows AVFs. Arteriovenous fistulas also appear as abnormal high-velocity turbulent flow isolated to a single segmental or interlobar artery and paired vein that produces aliasing on color Doppler images. Most complications after biopsy are treated conservatively, and most pseudoaneurysms resolve spontaneously. If, however, a pseudoaneurysm shows progressive enlargement or an unusual size (>2 cm in diameter), intervention is warranted. Selective transvascular catheterization may be used.

Renal Vein Thrombosis:
Renal vein thrombosis is rarely a cause of transplant dysfunction, with an occurrence rate of less than 5%. It occurs within the first week after transplantation and is manifested clinically by sudden oliguria, graft tenderness, and swelling. An increased prevalence of renal vein thrombosis in left lower quadrant allografts has also been attributed to compression of the left common iliac vein between the sacrum and the left common iliac artery (silent iliac artery compression syndrome). On gray scale ultrasonography, renal vein thrombosis may manifest with an enlarged kidney. On Doppler ultrasonography, venous flow is reduced or absent, and there is increased resistance on the arterial side, often resulting in reversed diastolic flow.

Doppler Ultrasonography and RI
The Doppler RI ([peak systolic velocity – end diastolic velocity]/peak systolic velocity) was advanced as a useful parameter for quantifying the alterations in renal blood flow that may occur with renal disease. An elevated RI was initially considered a finding specific for rejection. Multiple researchers have since documented the lack of specificity of an elevated RI., the sensitivity and specificity of Doppler ultrasonography for the diagnosis of rejection were 43% and 67%, respectively, when a threshold RI of 0.90 was applied. Because of these discouraging results, most physicians consider an elevated RI to be a nonspecific marker of transplant dysfunction. A PI of less than 1.5 or an RI of less than 0.7 can be regarded as normal, whereas a PI of greater than 1.8 or an RI of 0.9 should be regarded as abnormal.

Acute Tubular Necrosis:
This is common in the early transplant period, with 10% to 30% of patients requiring dialysis in the early stages. Delayed graft function is principally related to the donor and the donor kidney, especially the warm ischemic time. Acute tubular necrosis is initially present in most cadaveric grafts and resolves spontaneously over the first 2 weeks, depending on the degree of ischemic insult. It is infrequently seen in patients whose transplants are from living related donors
In those patients with ATN requiring dialysis, recovery usually occurs within 1 to 2 weeks after transplantation but can be delayed for up to 3months.

Drug Toxicity
Drug nephrotoxicity is another cause of diminished renal function. Cyclosporine has the greatest nephrotoxic potential, with its vasoconstrictive effect on the afferent glomerular arterioles. Management of drug levels and renal biopsy are traditional but imperfect in diagnosis.

Rejection [26-33]

Immunobiology of rejection

The antigens responsible for rejection of genetically disparate tissues are called histocompatibility antigens; they are products of histocompatibility genes. Histocompatibility antigens are encoded on more than 40 loci, but the loci responsible for the most vigorous allograft rejection reactions are located on the major histocompatibility complex (MHC).

In humans, the MHC is called the human leukocyte antigen (HLA) system and is located on the short arm of chromosome 6, near the complement genes. Other antigens cause only weaker reactions, but combinations of several minor antigens can elicit strong rejection responses. The MHC genes are codominantly expressed, which means that each individual expresses these genes from both the alleles on the cell surface. Furthermore, they are inherited as haplotypes or 2 half sets (one from each parent). This makes a person half identical to each of his or her parents with respect to the MHC complex. This also leads to a 25% chance that an individual might have a sibling who is HLA identical.

The MHC molecules are divided into 2 classes. The class I molecules are normally expressed on all nucleated cells, whereas the class II molecules are expressed only on the professional antigen-presenting cells (APCs), such as dendritic cells, activated macrophages, and B cells. The physiological function of the MHC molecules is to present antigenic peptides to T cells, since the T lymphocytes only recognize antigen when presented in a complex with an MHC molecule. The class I molecules are responsible for presenting antigenic peptides from within the cell (eg, antigens from the intracellular viruses, tumor antigens, self-antigens) to CD8 T cells. The class II molecules present extracellular antigens such as extracellular bacteria to CD4 T cells.

Mechanisms of rejection:

The immune response to a transplanted organ consists of both cellular (lymphocyte mediated) and humoral (antibody mediated) mechanisms. Although other cell types are also involved, the T cells are central in the rejection of grafts. The rejection reaction consists of the sensitization stage and the effector stage.

- *Sensitization stage*

  In this stage, the CD4 and CD8 T cells, via their T-cell receptors, recognize the alloantigens expressed on the cells of the foreign graft. Two signals are needed for recognition of an antigen; the first is provided by the interaction of the T cell receptor with the antigen presented by MHC molecules, the second by a costimulatory receptor/ligand interaction on the T cell/APC surface. Of the numerous costimulatory pathways, the interaction of CD28 on the T cell surface with its APC surface ligands, B7-1 or B7-2 (commonly known as CD80 or CD86, respectively), has been studied the most. In addition, cytotoxic T lymphocyte–associated antigen-4 (CTLA4) also binds to these ligands and provides an inhibitory signal.

Typically, helices of the MHC molecules form the peptide-binding groove and are occupied by peptides derived from normal cellular proteins. Thymic or central tolerance mechanisms (clonal deletion) and peripheral tolerance mechanisms (eg, anergy) ensure that these self-peptide MHC complexes are not recognized by the T cells, thereby preventing autoimmune responses.

At least 2 distinct, but not necessarily mutually exclusive, pathways of allorecognition exist, the direct and indirect pathways. Each leads to the generation of different sets of allospecific T cell clones.

- *Direct pathway*

  In the direct pathway, host T cells recognize intact allo-MHC molecules on the surface of the donor or stimulator cell. Mechanistically, host T cells see allo-MHC molecule + allo-peptide as being equivalent in shape to self-MHC + foreign peptide and, hence, recognize the donor tissue as foreign. This pathway is presumably the dominant pathway involved in the early alloimmune response.

- *Indirect pathway*

  In the indirect pathway, T cells recognize processed alloantigen presented as peptides by self-APCs. Secondary responses such as those that occur in chronic or late acute rejection are associated with T cell proliferative responses to a more variable repertoire, including peptides that were previously immunologically silent. Such a change in the pattern of T cell responses has been termed epitope switching or spreading.

  A link between self-MHC + allopeptide-primed T cells and the development of acute vascular type rejection has been demonstrated to be mediated in part by accelerated alloantibody production.

- *Molecular mechanisms of T cell activation*

  During T cell activation, membrane-bound inositol phospholipid is hydrolyzed into diacylglycerol (DAG) and IP3. This increases the cytoplasmic calcium. The elevation in calcium promotes the formation of calcium-calmodulin complexes that activate a number of kinases as well as protein phosphatase IIB or calcineurin. Calcineurin dephosphorylates cytoplasmic nuclear factor of activated T cells (NFAT), permitting its translocation to the nucleus, where it binds to the IL-2 promoter sequence and then stimulates transcription of IL-2 mRNA.

- *Effector stage*

  Alloantigen-dependent and independent factors contribute to the effector mechanisms. Initially, nonimmunologic "injury responses" (ischemia) induce a nonspecific inflammatory response. Because of this, antigen presentation to T cells is increased as the expression of adhesion molecules, class II MHC, chemokines, and cytokines is upregulated. It also promotes the shedding of intact, soluble MHC molecules that may activate the indirect allorecognition pathway. After activation, CD4-positive T cells initiate macrophage-mediated delayed type hypersensitivity (DTH) responses and provide help to B cells for antibody production.

  Various T cells and T cell-derived cytokines such as IL-2 and IFN-γ are upregulated early after transplantation. Later, ß-chemokines like RANTES (regulated upon activation, normal T cell expressed and secreted), IP-10, and MCP-1 are expressed, and this promotes intense macrophage infiltration of the allograft. IL-6, TNF-α, inducible nitric oxide synthase (iNOS) and growth factors, also play a role in this process. The

growth factors, including TGF-ß and endothelin, cause smooth muscle proliferation, intimal thickening, interstitial fibrosis, and, in the case of the kidney, glomerulosclerosis.

Endothelial cells activated by T cell–derived cytokines and macrophages express class II MHC, adhesion molecules, and costimulatory molecules. These can present antigen and thereby recruit more T cells, amplifying the rejection process. CD8-positive T cells mediate cell-mediated cytotoxicity reactions either by delivering a "lethal hit" or, alternatively, by inducing apoptosis.

- *Apoptosis*

  The final common pathway for the cytolytic processes is triggering of apoptosis in the target cell. After activation of the CTLs, they form cytotoxic granules that contain perforin and granzymes. The granzymes are inserted into the target cell cytoplasm where granzyme B can trigger apoptosis through several different mechanisms, including direct cleavage of procaspase-3 and indirect activation of procaspase-9. This has been shown to play the dominant role in apoptosis induction in allograft rejection.

- *Role of natural killer cells*

  The natural killer (NK) cells are important in transplantation because of their ability to distinguish allogenic cells from self and their potent cytolytic effector mechanisms. These cells can mount a maximal effector response without any prior immune sensitization. Unlike T and B cells, NK cells are activated by the absence of MHC molecules on the surface of target cells (“missing self” hypothesis).

- *Role of innate immunity*

  Although T cells have a critical role in acute rejection, the up-regulation of proinflammatory mediators in the allograft is now recognized to occur before the T cell response; this early inflammation following engraftment is due to the innate response to tissue injury independent of the adaptive immune system. Several recent studies have examined the role of Toll-like receptor (TLR) agonists and TLR signals in allorecognition and rejection.

  These innate mechanisms alone do not appear sufficient to lead to graft rejection itself. However, they are important for optimal adaptive immune responses to the graft and may play a major role in resistance to tolerance induction. The development of methods to blunt innate immune responses, which has potential implications for a wide variety of diseases, is likely to have a significant impact on transplantation, as well.

Clinical Stages of Rejection

ANTIBODY-MEDIATED REJECTION:

Antibodies that can mediate rejection include those against HLA molecules, endothelial-cell antigens, and ABO blood-group antigens on endothelial cells and red cells. Most recipients do not have antibodies against HLA molecules before transplantation unless they were sensitized by exposure to alloantigens through pregnancy, blood transfusion, or previous transplantation.

- *Antibodies against Blood-Group Antigens*

  Kidneys selected for transplantation are routinely assigned to recipients with a compatible blood group; however, ABO-incompatible kidneys have been successfully transplanted with the use of an experimental protocol that entails perioperative removal

of antibodies from the recipient by means of plasmapheresis or immunoadsorption. After they have been removed, anti–blood-group antibodies can rise to pretreatment levels after transplantation, adhere to the microvasculature, and activate complement, yet they generally do not injure the endothelium. This anomaly has been attributed to "accommodation" within the kidney, but the mechanism responsible for this benign response is unknown. In contrast, injury to the graft by anti-HLA antibodies is frequently insidious, and accommodation is uncommon.

- *Hyperacute Rejection*

  Rejection of the renal graft that occurs almost immediately after release of the vascular cross-clamps is classified as hyperacute. Instead of "pinking up" as a result of normal reperfusion, the kidney appears flaccid and mottled, reflecting the deposition of antibodies against HLA antigens expressed on the endothelium of the glomeruli and microvasculature. Activation of the classic complement cascade within the graft is followed by endothelial necrosis, platelet deposition, and local coagulation. In these cases, the initial organ transplantation procedure usually ends with removal of the graft. Improvements in cross-matching techniques that can better detect donor-specific antibodies before surgery have largely eliminated this problem.

- *Acute Antibody-Mediated Rejection*

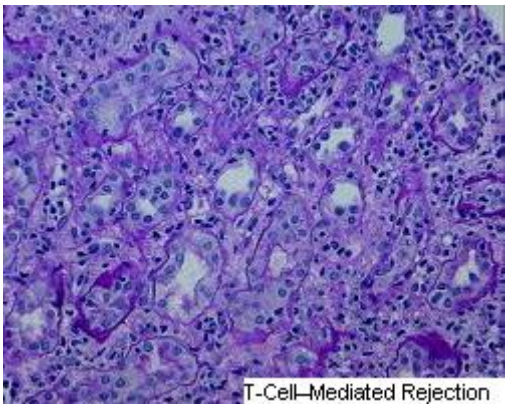
  Antibody-mediated rejection often begins within days after transplantation (or within weeks, if antilymphocyte antibody therapy was given). The main feature is rapid graft dysfunction due to inflammation. An anamnestic response engendered by previous exposure to the relevant antigen rapidly generates high titers of complement-fixing antibodies. The main targets of these "recall" antibodies are MHC antigens displayed by the endothelium of the donor peritubular and glomerular capillaries. Agonistic angiotensin II type 1 (AT1)–receptor antibodies have also been associated with corticosteroid-resistant vascular rejection accompanied by malignant hypertension, but their pathogenic role remains unclear. The damaged endothelial cells release various injurious molecules: von Willebrand factor and P-selectin, which promote platelet aggregation; cytokines and chemokines, such as interleukin-1α, interleukin-8, and chemokine (C-C motif) ligand 2 (CCL2), which cause leukocytes to adhere to glomeruli (glomerulitis) or to dilated peritubular capillaries (margination); and the chemoattractants C3a and C5a. C4d, a marker of classic complement activation, is frequently found in peritubular capillaries C5b triggers the assembly of the membrane-attack complex (C5b–C9), which causes localized endothelial necrosis and apoptosis, as well as detachment of endothelial cells from the basement membrane. Microthrombi, with hemorrhage and arterial-wall necrosis and infarction, occur in severe cases.

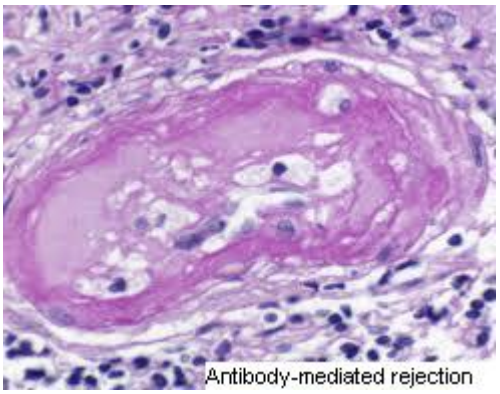
  Early diagnosis and treatment are essential for salvaging grafts undergoing acute antibody-mediated rejection. Treatments include removal of antibodies by plasmapheresis or immunoadsorption, high-dose pulses of glucocorticoids, intravenous

immune globulin, and antiproliferative agents. Supplementary therapies include rituximabor antilymphocyte antibody, if there is concurrent T-cell–mediated rejection. These treatments can be useful when given as prophylaxis to highly sensitized or ABO-mismatched recipients. Eculizumab (a monoclonal antibody that inhibits the cleavage of C5) and bortezomib (a proteasome inhibitor that can inhibit plasma cells) are new, investigational agents that have shown promise in preliminary studies of antibody-mediated acute rejection, but the results require confirmation. Detection of potentially harmful antibodies before transplantation should prompt a search for an alternative donor or an aggressive approach to post-transplantation management.

T-CELL–MEDIATED REJECTION:

- *Antigen Presentation*
  The most common form of acute allograft rejection is initiated when donor alloantigens are presented to the T lymphocytes of the recipient by antigen-presenting cells (APCs). Immature dendritic cells within the graft carry donor antigens from the transplanted organ to the recipient's draining lymph nodes and spleen; during their journey, these antigens mature into APCs. The recipient's antigen-presenting dendritic cells also participate and circulate through the graft. The APCs then home to lymphoid organs, where they activate the recipient's T cells. These T cells differentiate into various subgroups and return to the graft, where they take part in destroying the transplanted organ.
- *Dendritic cells*
  Dendritic cells and macrophages present antigen to T cells efficiently, but B cells can also function in this way by capturing and presenting antigens with the use of their surface immunoglobulins and MHC class II molecules. Even tubular epithelial and endothelial cells can present antigen to activated T cells. Sensitization can occur in the periphery or in tertiary lymphoid organs that develop within the transplanted kidney.


T-Cell–Mediated Rejection


Antibody-mediated rejection

The 2007 Updates on the Banff Classification

Scoring of ptc

Biopsies with inflammatory cells in <10% of cortical peritubular capillaritis (PTC) are scored as ptc0, regardless of the number of cells in the most severely involved PTC. If ≥10% of PTCs are inflamed, the ptc score is based upon the highest number of all types of luminal inflammatory cells in the most inflamed cross-sectioned PTCs in the cortex. The types of cells should be noted: only mononuclear cells, a minority (≤50%) of neutrophils or a majority (>50%) of neutrophils. The extent of capillaritis should also be noted: focal ≤50% versus diffuse >50% of PTCs involved. PTCs that are cut in a longitudinal plane of section should not be scored.

Ptc should not be scored in medulla, due to the association of vasa recta infiltrates with acute tubular necrosis (ATN), and in vessels surrounding nodular lymphoid aggregates (due to confusion with lymphatics). Areas of pyelonephritis, and adjacent to infarcts, should also be avoided for ptc scoring.

C4d scoring

Scoring of C4d staining is based on the percentage of stained tissue on IF/IHC that has a linear, circumferential staining pattern in PTC . The minimal sample for evaluation is 5 HPF of cortex and/or medulla without scarring or infarction. Biopsies with IF/TA may have reduced PTC density that could affect the extent of staining . On IF, staining should be >1+ in intensity. The report should indicate the actual percentage of tissue involved and the potential significance .

C4d deposition without morphological evidence of active rejection

By consensus the term ‘C4d deposition without morphologic evidence of active rejection’ is added to the Banff diagnoses under the antibody-mediated category .

The criteria for this diagnosis will be (i) presence of complement fixation (e.g. C4d) in PTC, (ii) lack of histologic evidence of acute or chronic rejection (cellular or humoral) with lack of glomerulitis (g = 0), TG (cg = 0), ptc (ptc = 0) and PTC basement membrane lamination (assessed by electron microscopy <5 layers), (iii) presence of DSA. If borderline inflammation (i1) or ATN is present, the diagnosis is indeterminate, since this lesion might be related to antibody. Other potential causes of the ATN (e.g. ischemic injury, calcineurin inhibitor toxicity, etc) should be ruled out.

Acute Rejection [25-32]

When to suspect rejection?

- Rapid increase within 1-2 days in their plasma creatinine concentration greater than 10-25% over baseline with or without decrease in urine output.
- Graft tenderness or fever.
- Consider Surveillance biopsies in prolonged delayed graft function.

NB: Baseline creatinine is the most recent creatinine concentration prior to the diagnosis of rejection.
Once rejection is suspected, a kidney biopsy is recommended.

Treatment Acute Cellular rejection:

- **Methylprednisolone**

1. Pulse dose of Methylprednisolone is given as follows:
2. For 3-5 days give Methylprednisolone 500mg intravenously over 30-60 minute
3. Once pulse dose is given, we put the patient back on the same dose of prednisone he was on without tapering.

If pulse steroid course fails we can use :

- **Antithymocyte globulin(ATG)**
  The recommended dose is 1.5mg/kg/day intravenously for 7-14 days.
  The ATG is mixed in saline and infused over 4-8 hours in central vein. The concentration should not exceed 4mg/ml.
  To avoid allergic reactions, the patient should receive intravenous pre-medication consisting of:

1. Hydrocortisone 50mg IV
2. Diphenhydramine 50mg
3. Acetaminophen 650mg orally
4. All given 30 minutes before injection.
5. Acetaminophen should be given before and 4 hours after commencement of the infusion for fever control.
6. Vital signs are monitored every 15 minutes during the first hour of infusion and then ½ hourly until the infusion is complete.
7. MNF, cyclosporine & tacrolimus can be stopped during the course, or given in lower doses.
8. If Antithymocyte globulin treatment fails, a review of the biopsy results is done, and OKT_3 therapy is considered.

- **OKT_3**

  Standard dose: 5mg given as intravenous bolus through a Millipore filter for 7-14 days.

  Protocal Recommendation for OKT_3 use

1. Before administration of first dose, patient should be edema free, within 3% of dry weight, temprature should be reduced to below 37.8, and have a negative chest radiograph
2. Use high-dose diuretics, dialysis, or ultra filtration alone to achieve euvolemia.
3. Administer pre-medication 15-60 minutes before first and second dose consisting of methylprednisolone IV 5-8mg/kg; Diphenhydramine hydrochloride, 50mg IV, and acetaminophen, 500mg PO.
4. Before first and second dose, monitor vital signs every 15 minutes for 2 hours, then every 30 minutes for 2 hours.
5. Pre-medication is not required for remainder of the course; use acetaminophen p.r.n. for fever.
6. If OKT_3 is stopped for more than one dose, repeat first dose precautions.
7. Continue low dose of calcineurin-inhibitor, or MMF during the course.
8. If calcineurin-inhibitor is continued, use half dose; return to full dose 2 days before completion of the course and ensure therapeutic levels.
9. After first 2 doses, continue prednisolone according to the protocol schedule.
10. Use antiviral and antibacterial prophylaxis.
11. During second course of OKT_3, monitor CD_3 levels at least twice weekly.
12. After the first 2 doses, encourage hydration for patient dieresis.
13. Consider outpatient administration after 3rd dose in stable patients.
14. If there is no response to OKT_3, a switch in baseline immunosuppression from cyclosporine to Tacrolimus is considered.
15. Once ATG or OKT3 is contemplated, the patient should be put in isolation, preferably a positive pressure room.

Treatment Antibody Mediated or Humoral Acute Rejection:

Unfortunately, the outcome of treatment is uniformly worse than that in acute cellular rejection. So, although the current diagnosis of Antibody Mediated rejection (AMR) requires the concomitant presence of Donor Specific Antibodies (DSA), C4d, and histopathological evidence of AMR, treatment may be initiated in circumstances where the above criteria may not be fulfilled in entirety. This depends on the risk factor profile of the patient (sensitized patient, history of pregnancies, and blood transfusions) and presence or absence of organ dysfunction. Treatment is often initiated in situations of diffuse C4d positivity with allograft dysfunction even in the absence of DSA or histological evidence of AMR. The inability to measure DSAs in these cases may be related to the presence of non anti-HLA antibodies, to antigen not present on the single-bead assays, or to the possibility that the DSAs may be completely adsorbed onto the allograft. Similarly, patients with positive DSA and histological evidence of AMR may not demonstrate any C4d activity, and treatment is often initiated in these patients as well, especially in the presence of allograft dysfunction. C4d in such cases of acute AMR may be negative for a number of reasons. Immunohistochemistry (IHC) is known to be

less sensitive compared to immunofluorescence (IF) staining. Also, areas with necrosis may stain falsely negative for C4d and hence, care must be taken to ensure that viable areas of the biopsy specimen are stained for C4d . Even with these inadequacies, there has been good progress made in developing treatments for AMR. The primary goal in AMR treatment involves targeting the reduction/removal of DSAs and elimination of the B-cell/plasma cell population responsible for the production of these antibodies.

The presence of a vast array of therapeutic modalities signifies the ineffectiveness of one drug or one particular combination therapy to reverse or treat AMR successfully in all scenarios. All of these treatments have been used in different combinations by different groups without a good control arm, resulting in poor evidence to argue for the superiority of one treatment regimen. These treatment modalities are also used for pretransplantation desensitization protocols to abrogate positive crossmatch in highly sensitized patients.

Intravenous Immunoglobulin (IVIG)

This is the most commonly used agent either alone or often, in combination with plasmapheresis. Although the exact mechanisms involved are not clear, they appear to involve multiple processes such as neutralization of complement fixing antibodies, alteration in the activity of complement, modulation of Fc receptor activation and function, and regulation of T and B lymphocytes . Recent research has elucidated the possible role in this immunomodulation, for a specific subtype of IgG which possesses sialylated glycan residues near the Fc receptor. These sialylated IgGs were shown to bind to lectin receptor SIGN-R1 or DC-SIGN leading to increased expression of inhibitory Fc receptor (FcR), FcgammaRIIb on inflammatory cells, thereby attenuating inflammation . IVIG is routinely used in one of two doses: high (2 gm/kg) or low (100 mg/kg per session). Low-dose IVIG is mostly used in combination with plasmapheresis where it may help replenish depleted IGs. Initial studies used IVIG at high-doses without plasmapheresis and described a fair degree of success in desensitization prior to transplant and also for treating antibody-mediated rejection . IVIG is generally safe and well tolerated in most patients with occasional side effects such as aseptic meningitis, volume overload, and rarely acute kidney injury possibly related to high osmotic load. Sucrose-based IVIG preparation is to be avoided, while glycine-based preparations are relatively safe.

Plasmapheresis (PP)

Plasmapheresis is very effective in reducing the antibody load but needs to be used in conjunction with other therapies that target the antibody producing mechanisms. The most common type of Plasmapheresis performed is plasma exchange, with albumin being the most common replacement fluid used. It is usually performed on alternate days with a 1–1.5 volume exchange with albumin (commonly) or fresh frozen plasma. Most institutions also follow each PP session with low-dose IVIG (100 mg/kg) . DSAs are monitored along with renal function to document the effectiveness of the therapy. Treatment, if successful, is continued until the level of antibodies has dropped to safe levels along with improvement in renal function. Plasmapheresis is generally well tolerated. Side effects are relatively uncommon and are related to the use of vascular access (infections, bleeding), volume removal, type of replacement fluid used (coagulopathy, hypovolemia, allergic reactions and a small risk of blood borne infection transmission), hypocalcemia, and side effects related to use of anticoagulants.

Immunoadsorption with Protein A (IA)

IA was studied in a randomized controlled trial in Europe where it proved very successful in reversing severe AMR. Both arms underwent a switch to tacrolimus from cyclosporine, along with treatment for ACR (steroids/ATG) as needed. The study was initiated at a time when PP and IVIG were still not universally used for AMR treatment.

The study was stopped early because of significant success rate in the IA group (80% versus 20%). It was, however, a small study (5 patients in each group), with a higher prevalence of diffuse C4d in the control group. Considering the widespread acceptance of IVIG and PP for treatment of AMR and unavailability of IA in the USA, a head-to-head study of IA with PP and IVIG will be necessary to prove its superiority, prior to its acceptance as an alternative to IVIG and PP.

Rituximab

Rituximab is an anti-CD20 monoclonal antibody that induces profound depletion of B-cells and was initially approved for the treatment of B-cell lymphoma. It has since been tested in multiple immune-mediated disorders with varying degrees of success. Rituximab has been used to treat AMR in a number of uncontrolled studies.

Most of the studies reported so far with the use of Rituximab have reported favorable outcomes. Becker et al. treated 27 patients with AMR with a single dose of rituximab. Twenty-two of these patients also received ATG and plasmapheresis . At a mean of 605 days of followup, only 3 grafts were lost to rejection. Faguer et al. also reported 81% graft survival at 20 months in 8 patients with the use of 4 doses of Rituximab along with PP, mycophenolate, tacrolimus and steroids . Kaposztas et al. reported their experience with use of Rituximab in combination with PP. Twenty-six patients were treated with Rituximab along with PP and IVIG. The graft outcomes were compared to historical controls who had been treated with PP ± IVIG alone. The two-year graft survival for patients treated with rituximab plus PP was significantly better at 90% when compared to the 60% survival in the PP cohort. However, the doses of IVIG were higher in the Rituximab group, and the use of IVIG was also statistically associated with a better graft outcome on Kaplan-Meier analysis, raising concerns for a confounding effect. Lefaucheur et al. also compared the use of 2-week doses of Rituximab along with high-dose IVIG and PP with historical controls who had received high-dose IVIG alone and reported a 91.7% graft survival, compared to 50% with high-dose IVIG alone [53]. The mechanism of action of Rituximab in AMR is not clear, given that the plasma cells do not express CD20 on their surface. However, the depletion of CD20-positive subset of B-cells may attenuate the antibody generation process. The standard dosing of Rituximab is 375 mg/m^2/wk for 2–4 weeks. Rituximab results in prolonged and profound B-cell depletion which may cause reactivation of latent viruses such as hepatitis B, C, cytomegalovirus (CMV), and also mycobacterium tuberculosis. It also carries a boxed warning for progressive multifocal leukoencephalopathy (PML) caused by JC virus.

Patients can also manifest acute infusion reactions, which usually occur within 30–120 minutes and may be mild or severe, such as bronchospasm, angioedema, acute respiratory distress syndrome, cardiogenic shock, and anaphylaxis. These have often been reported in leukemic patients with high pretherapy leukocyte counts .

Change of Maintenance Immunosuppression (IS)

Initiation or augmentation of anti B-cell maintenance therapy is routinely done when AMR is identified. The most commonly used agent for this purpose is mycophenolate mofetil. It is also common practice to change to a calcineurin-based immunosuppression, specifically to tacrolimus, if patients are not on a calcineurin inhibitor (CNI).

Bortezomib

Bortezomib is a novel proteosome inhibitor that is approved for the treatment of multiple myeloma. Proteasomes are involved in breakdown of ubiquitinated proteins and are present both in the nucleus and cytoplasm. Inhibition of proteasomes can lead to decreased nuclear factor-Kappa B activation, cell cycle arrest, endoplasmic reticulum stress, and increased cell apoptosis . This action is pronounced in plasma cells likely because of the high antibody turnover and high endoplasmic reticulum activity. Dosing has been the standard myeloma dosing of 1.3 mg/m^2/week, with 4 doses given over 2 weeks.

Eculizumab

Eculizumab is a humanized monoclonal antibody directed against complement protein C5. It binds to the C5 protein with high affinity, thereby inhibiting conversion of C5 to C5b and preventing formation of the membrane attack complex (C5–9). Initially approved for use in paroxysmal nocturnal hemoglobinuria (PMH), it was also recently approved for use in atypical hemolytic-uremic syndrome. Prior vaccination against meningococcus and pneumococcus is necessary.

Splenectomy

It has also been used in resistant AMR patients with good success rate . However, because of the long term risk of infections in immunosuppressed individuals and the surgical risks involved, this is not a commonly used therapy for AMR.

Part III. Long term management of the Transplant Recipient [13-17]

All renal transplant recipients should undergo regular laboratory check-ups at least every 2-3 months and regular medical visits as out-patients every 3-4 months after the first year post-transplant.

Routine work up includes:

- Renal function (serum creatinine & urea)
- Urine analysis + urine culture
- CBC + platelet
- Liver functions
- Electrolytes & other chemistries (sodium, potassium, chloride, $HC0_3$, Calcium, Phosphorous and Uric Acid)
- Immunosuppressive drug concentration
- Cardiovascular risk factors (blood glucose, cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides)

Complete annual evaluation:

- Ultrasound examination of the graft and native kidneys
- Chest x-ray
- Monitoring of few blood tumor antigens, such prostate specific antigen (PSA)
- Complete examination of the skin
- Faecal occult-blood testing
- Regular mammography in women
- Cardiovascular evaluation
- Evaluation of risks of infection and cancer

Chronic Graft Dysfunction:

Any significant deterioration in graft function should be investigated using the appropriate diagnostic tools and, if possible, therapeutic interventions should be initiated. The usual causes of a decline in glomular filtration rate after the first year include transplant-specific causes such as:

- Chronic allograft nephropathy
- Acute rejection episodes
- Chronic calcinurin inhibitor nephrotoxicity
- Transplant renal artery-stenosis
- Ureteric Obstruction
- Immunodeficiency-related causes
- Non-transplant-related causes, such as recurrent or de novo renal diseases and bacterial infections.

Any new onset and persistent proteinuria of >0.5g/24 hr should be investigated and therapeutic interventions should be initiated. The usual causes include:

- Chronic allograft nephropathy
- Transplant glomerulopathy
- Recurrent or de novo glomerulonephritis

Work up include:

- Ruling out ureteric obstruction by ultrasound and/or helical CT
- Ruling out transplant renal artery stenosis by, doppler study, digital subtraction angiography, and/or magnetic resonance angiography
- Measuring calcineurin levels.
- Renal biopsy

Immunological Factors:

- All recipients of an allogeneic kidney graft should take life-long maintenance immunosuppressive medication. Whereas there is no immunological test to diagnose chronic allograft dysfunction, circumstantial evidence suggests that immunological factors play an important role in its pathogenesis. This evidence is based on experimental data, the beneficial effect of sharing HLA antigens between donor and recipient and post-transplantation immunological monitoring studies.

Non-alloimmune factors:

- Whereas immunological mechanisms dominate in the initiation and propagation of the injury that leads to chronic allograft dysfunction and nephropathy, there is circumstancial evidence that non-immunological factors, such as advanced donor age, hyperfiltration, overweight, delayed graft function, heavy proteinuria, smoking, arterial hypertension, hypercholesterolemia and hypertriglyceridemia, play a role as aggravating or progression factors. Intervention is recommended to prevent or, if possible, treat all these factors.
- As arterial hypertension is very frequent among renal transplant patients and associated with increased graft (and patient) loss, it is recommended to aim at a blood pressure less than 130/85 mmHg in renal transplant patients and <125/75 mmHg in recipients with proteinuria >1g/day.

De Novo Renal Disease after transplantation:

- Acute pyelonephritis is relatively frequent in the transplanted kidney and carries a risk of septicemia. The condition should be recognized and the patient should be treated promptly.
- After initiation of any drugs known to induce the development of interstitial nephritis in the transplant patient, it is recommended to monitor renal function and abnormalities in order to detect any side effects rapidly. If interstitial nephritis is observed, it is recommended to stop the offending drug, and to initiate appropriate treatment.
- De Novo membranous nephropathy should be considered in cases of proteinuria and nephritic syndrome after transplantation. Viral infection, such as HCV, should be excluded.
- In the case of development of graft dysfunction in a transplant patient with Alport's syndrome, one should consider additionally the possibility of de novo anti-glomerular basement membrane (Anti-GBM) glomerulonephritis.

Late recurrence of primary glomerulonephritidies:

- In the case of recurrent focal and segmental glomerulosclerosis (FSGS), aggressive treatment with high-dose cyclosporine in children, ACE inhibitors and/or Angiotensin II antagonists, plasma exchange or immunoadsorption may result in remission in some patients.
- In the case of recurrent membranous nephropathy (MN) and recurrent membranoproliferative glomerulonephritis (MPGN), there is no specific treatment. However, control of risk factors, such as hypertension, heavy proteinuria and hyperlipidemia, and prevention of thrombotic complications are recommended.
- In the case of recurrent IgA glomerulonephritis, use of additional steroids is not yet a validated treatment. The control of risk factors, such as hypertension, heavy proteinuria and hyperlipidemia, and prevention of the thrombotic complications are recommended.
- In the case of recurrent anti-glomerular basement membrane (anti-GBM) glomerulonephritis with reappearance of anti-GBM antibodies, it is recommended to initiate plasma exchange and to treat with appropriate immunosuppressive agents (e.g. cyclophosphamide).

Late recurrence of other diseases:

- In the rare case of recurrent lupus nephritis, no particular treatment is recommended. Only in the few patients with clinically evident flare up is a reinforcement of immunosuppression recommended.
- Recurrence of Henoch-Schönlein purpura may occur even in the absence of clinical signs and symptoms. The prognosis for the graft may be severe, particularly in adults.
- In the case of recurrent ANCA-associated renal of systemic vascutits, it is recommended to reinforce the immunosupression with appropriate agents.
- Since diabetic nephropathy recurs almost invariably after transplantation, strict control of diabetes and hypertension, and the use of ACE inhibitors and/or angiotension II receptor antagonists are recommended in order to prevent or slow the risk of recurrence.

Late Steroid or Cyclosporine Withdrawal:

- In order to reduce or avoid long-term serious adverse effects of corticosteroids, such as bone fractures, diabetes mellitus, arterial hypertension, osteoporosis and eye complications, steroid withdrawal should be considered.
- Steroid withdrawal is safe only in a proportion of graft recipients and is recommended only in low-risk patients. The efficacy of the remaining immunosuprression should be considered. Careful assessment of pros and cons of withdrawal has to be made.
- After steroid withdrawal, graft function has to be monitored very carefully because of the risk of a delayed but continuous loss of function due to chronic graft dysfunction. In the case of functional deterioration or dysfunction, steroids should be readministered.
- Cyclosporine withdrawal might be considered in order to ameliorate nephrotoxicity, arterial hypertension, lipid disorders and hypertrichosis. This can be carried out with no significant long-term risk of progressive graft losses. The efficacy of the remaining immunosuppression should be considered. After cyclosporine withdrawal, careful monitoring for acute rejection is recommended.
- Conversion of immunosuppressive drug therapy is recommended to avoid or reduce drug specific adverse effects, and is generally safe for long-term graft outcome.

Non-compliance:

- Detection of non-compliers should be a permanent concern, since it is associated with late graft dysfunction and graft loss.
- Non-compliance starts during the first year and may increase thereafter. Therefore specific educational programs should be repeated and adapted to the need of the transplant recipient, or the delivery of few but clear messages.

Cardiovascular disease postransplant:

It is very common post-transplant, and is an important cause of morbidity and the first cause of mortality in renal transplant recipients. Therefore detection and early treatment is mandatory.

Important risk factors include:

- Pre-transplant cardiovascular disease
- Arterial hypertension
- Uremia with graft dysfunction
- Hyperlipidemia
- D.M.
- Smoking
- Immunosuppressive treatment

All these factors should be the target of intervention.

Pre-transplant cardiovascular disease is a major risk factor for post-transplant cardiovascular disease. Therefore, prior to transplantation, it is mandatory to detect & treat symptomatic coronary artery disease, heart failure due to valvular failure, and pericardial constriction.

Arterial Hypertension:

- Pretransplant arterial hypertension, chronic allograft nephropathy and immunosuppressive therapy are the most frequent causes of post-transplant arterial hypertension.
- Blood pressure control should aim at (<130/85 mmHg for renal transplant recipients without proteinuria, and <125/75 mmHg for proteinuria patients).
- In patients with uncontrolled hypertension and/or renal function deterioration, underlying causes should be excluded, especially transplant renal artery stenosis.

Hyperlipidemia:

- Risk factors should be identified by regular screening (at least once a year) for cholesterol, HDL, LDL and triglyceride blood levels. Level should be kept as recommended in (page 8, Part 2)
- Management is the same as for dialysis population, with modification of immunosuppressive protocol when appropriate.
- Patients should be carefully monitored for adverse effects of lipid lowering agents or interactions with immunosuppressive drugs.

Post transplant diabetes mellitus:

- It should be identified by regular (every 3 months) fasting blood glucose and/or glycated hemoglobin (HbA1c) measurements. Treatment should achieve euglycemia.
- Immunosuppressive therapy should be adjusted to reverse or ameliorate post-transplant diabetes mellitus.

Smoking:

- Active measures against smoking is recommended since it is associated with high frequency of cardiovascular disease.

Obesity (BMI >30 kg/m^2):

- There is increased prevalence of cardiovascular disease in obese patients after transplantation. Appropriate dietary & lifestyle measures should be recommended.

Immunosuppressive Therapy:

- Calcineurin inhibitors and cortico-steroids contribute to the prevalence of cardiovascular risk factors, such as arterial hypertension, hyperlipidemia and hyperglycemia, and this effect is dose dependent. Reduction of the doses, withdrawal and/or switching to another drug could be useful.

Cancer Risk After Renal Transplantation:

Post Transplant lymphoproliferative disease:

- In the first transplant year, recipients are at their highest risk of developing lympho-proliferative diseases (PTLDs), which are induced most often by Epstein-Barr virus (EBV) infection. Patients should therefore be screened prior to or at the time of transplantation.
- In rare cases (<5%) where the recipient is EBV seronegative, he or she has a 95% likelihood of receiving an organ from an EBV-seropositive donor, which translates into a high risk of primary EBV infection with seroconversion soon after transplantation. In such cases, the recipient should receive a prophylactic antiviral treatment with acyclovis, valacyclovis or ganciclovir, starting at the time of transplant and lasting for at least 3 months. The specific recommendations given for CMV prophylaxis could be applicable in this situation.
- The treatment of PTLD should be based on accurate pathology with extensive cell markers and phenotyping. *The treatment modalities are as follows:*

I. Reduction of basal immunosuppression in all cases (either maintain only steroids, or decrease by at least 50% the calcineurin inhibitor drugs and stop other immunosuppressive drugs).
II. In the case of EBV-positive B cell lymphoma, antiviral treatment with acyclovir, valacyclovir ,ganciclovir or valganciclovir may be intiated for at least 1 month or according to the blood level of EBV replication when available.
III. In the case of rare lymphomas from the mucosal-associated lymphoid tissue (MALT) with positive Helicobacter Pylori, full eradication of H-pylori should be carried out with a validated protocol. Subsequent H. pylori prophylaxis should be implemented to avoid relapse.
IV. In the case of CD_{20}-positive lymphomas, treatment with rituximab, a chimeric monoclonal antibody directed against CD20, should be carried out with one I.V. injection per week for 4 weeks.
V. In the case of diffuse lymphomas or improper response to previous treatment, CHOP (cyclophosphamide, doxorubicine, vincristine and prednisone) chemotherapy should be used alone or in combination with rituximab.
VI. Complete cessation of immunosuppression with or without graft nephrectomy should be considered.

Skin Cancers:

- Due to the high prevalence, it is important to inform patients about self-awareness.
- The most frequent skin tumor in transplant recipients is squamous-cell carcinoma. Primary prevention should include avoidance of sun exposure and use of protective clothing.
- Recipients with pre-malignant skin lesions (warts, epidermodysplasia verruciformis or actinic keratoses) should be referred early to a dermatologist for active treatment and close follow-up.
- All skin cancers should be completely removed.
- Secondary prevention for recipients should include close follow-up by a dermatologist (at least every 6 months), the use of topical retinoids to control actinic keratoses and to diminish squamous-cell carcinoma recurrence, and reduction of immunosuppression whenever possible.
- In recipients with multiple and/or recurrent skin cancers, the use of systemic retinoids, could be recommended for months/years. If well tolerated, in addition to further reduction in immunosuppression whenever possible.

Solid Organ Cancers:

- All renal transplant recipients should have regular ultrasonography of their native kidney for screening of renal carcinoma, which is observed at much higher incidence in both, dialyzed and transplant patients.
- All male renal transplant recipients aged 50 and over should have a yearly prostate specific antigen (PSA) test prior to a regular digital rectal examination.
- All female renal transplant recipients should have a yearly cervical (PAP) smear together with regular pelvic examination and regular mammography, according to national recommendations where available.
- All recipients should undergo a fecal occult-blood testing as a screening for colorectal cancer & other (pre-malignant) lesions, according to national recommendations where available.
- In all these conditions, it is recommended to reduce immunosuppressive whenever possible.

Renal Cell Carcinomas

- Renal cell carcinomas in the allograft kidney can be inadvertently introduced by means of the transplanted organ or de novo tumor development enhanced by immunosuppression. Renal cell carcinomas are generally less aggressive in transplanted kidneys than in native kidneys. The prevalence of renal adenocarcinomas may be increased, with 90% of the tumors occurring in the native kidney and 10% occurring in the transplanted kidney.

Late infections post transplant

Documentated CMV disease:

Documentated CMV disease [symptomatic infection]-(*Testing for CMV infection Check CMV serology together with samples of EDTA bloodfor buffy coat culture and serum sample for PCR. The rapid culture may provide an answer sooner than PCR in some cases.It will often be appropriate to send respiratory or other samples to virology – bronchoalveolar lavage or induced sputum for investigation as usual or colon biopsies.)*

This group of patients must receive curative treatment in the form of:

- Intravenous ganciclovir at daily dose of 10mg/kg (5mg/kgx2) adjusted for GFR for at least 14 days, followed by oral ganciclovir at daily dose of 3000mg (1000mgx3) for 1-3 months.
- Alternatively:
  Intravenous ganciclovir for at least 5 days at 10mg/kg/day, followed by oral ganciclovir at a daily dose of 3000mg (1000mgx3) for a longer period (12 weeks).

Pneumocystis carinii pneumonia:

- Approximately 5% of patients develop Pneumocytosis carinii pneumonia (PCP) after renal transplantation if they do not receive prophylaxis. PCP is a severe disease, with high fatality rate. Therefore, all renal transplant recipients should receive PCP prophylaxis. The treatment of choice is trimethoprim-sulfamethoxazole (TMP-SMX), at a dose of 80/400 mg/day or 160/800 mg every other day, for at least 4 months. Patients who are treated for rejection should receive TMP/SMY prophylaxis for 3-4 months.
- In case of TMP-SMY intolerance, aerosolized pentamidine (300 mg once or twice per month) is an alternative.
- The first-line treatment of PCP is high-dose TMP-SMX. Patients with a $Pa0_2$ of <70 mmHg initially should be treated parenterally, and the administration of additional steroids should be considered.

Tuberculosis:

- Tuberculosis is not rare after renal transplantation, and can be life-threatening. Treatment of active TB in renal transplant recipients should be the same as in the general population. Quadruple therapy combining rifampin, isoniazid, ethambutol & pyrazinamide, followed by a 4 months double therapy with isoniazid and rifampin. The drug ethambutol should not be used initially if the rate of resistance to isoniazid is less than 4% in the community.
- As rifampin will reduce the plasma concentration of calcineurin inhibitors. The blood levels of these agents must be monitored closely. Rifabutin may be used as an alternative to rifampin, as this drug is a less potent inducer of the microsomal P450 enzymes.
- Renal transplant candidates and renal transplant recipients should be screened for latent TB infection. Patients considered to have latent TB infection are defined as: (i) those who display a 5 mm (renal transplant recipient) or a 10 mm (dialysis patients) induration, after tuberculin skin testing; (ii) those with chest x-ray images suggestive of TB infection; (iii) those with a history of past TB infection that was not treated adequately; and (iv) those who have been in close contact with infectious patients. The preferred treatment of latent TB infection is isoniazid 300 mg/day for 9 months.

Bone Disease

- All kidney-transplanted patients should undergo a systematic evaluation of their skeletal status, including pre-transplant history of renal osterdystrophy, history of fractures and plasma concentration of calcitropic hormones. Measurement of bone minimal density is optional but should be done if possible.
- Prednisone therapy should be given at the lowest possible dosage. Vitamin D treatment (ergocalciferol or 1,25-dihydroxyvitamin D) is highly recommended.
- Optimal prevention of bone disease by Vit D treatment, sufficient calcium intake, sex hormone substitution and appropriate use of thiazide diuretics should be considered.
- In established osteopenia, bisphosphonate treatment should be considered despite limited information in transplant recipients.
- In patients with Glomerular Filtration Rate, less than 50 ml/min after transplantation, uremic osteodystrophy should be prevented.
- **Possible work-up and evaluation of the kidney transplanted patient:**
  - ✓ Plasma PTH levels, calcium, phosphorus, magnesium, albumin, alkaline phophatases, osteocalcin, 25-hydroxyvitamin D, 1,25 dehydroxyvitamin D, testosterone (in men), oestrogen, FSH, LH (in women), thyroid function tests.
  - ✓ Urinary calcium and, if normal GFR, markers of bone resorption.
  - ✓ Bone densitometry at transplantation, after 6 months and then yearly.
  - ✓ X-ray of the affected region
- **Prophylaxis and/or treatment of post-transplant bone disease:**
  - ✓Vitamin D (Calcitriol 0.25-0.5 mg/day or 600 units of cholecalciferol/day)
  - ✓Calcium intake of 1000 mg/day; post-menopausal women 1500 mg/day.
  - ✓Avoid loop diuretics, if possible, and use thiazides
  - ✓Restore normal thyroid and/or gonadal functions
  - ✓Treat persistent hypophophatermia and hypomagnesemia
  - ✓Treat persistent hyperparathyroidism(*we recommend using A calcimimetic agent;cinacalcet)*
  - ✓Use the lowest possible dose of steroids
  - ✓Use of bisphophorates might be considered in some patients as treatment of severe osteopenia and fractures in patients with good and stable (GFR > 60 ml/min, or serum creatinine < 160 umol/L).or we have recently used the FDA Approved Denosumab for Treatment Osteoporosis at High Risk for Fracture with good results.
  - ✓Cessation of smoking
  - ✓Initiation of exercise

Anemia:

- It is relatively common after renal transplantation. Post transplant anemia may be caused by allograft dysfunction, or the use of purine synthesis inhibitors (azatheoprine and MMF). ACE inhibitors and angiotension II receptor antagonists may cause anemia. It is usually reversible after withdrawing the offending agent.
- Treatment should follow the same principles as in chronic renal failure.

Leukopenia:

- Azathioprine and mycophenolate mofetil are common causes. The combination of allopurinol & azathioprine should be avoided. It is usually related to the dose, which might be reduced.
- Other drugs as ganciclovir & TMP-SMX can also cause leukopenia.
- Moreover, a number of infections, particularly viral infections (e.g. CMV) and overwhelming bacterial infections, may be associated with granulocytopenia.

Erythrocytosis:

The first-line treatment should be ACE inhibitors or angiotension II receptor antagonists.

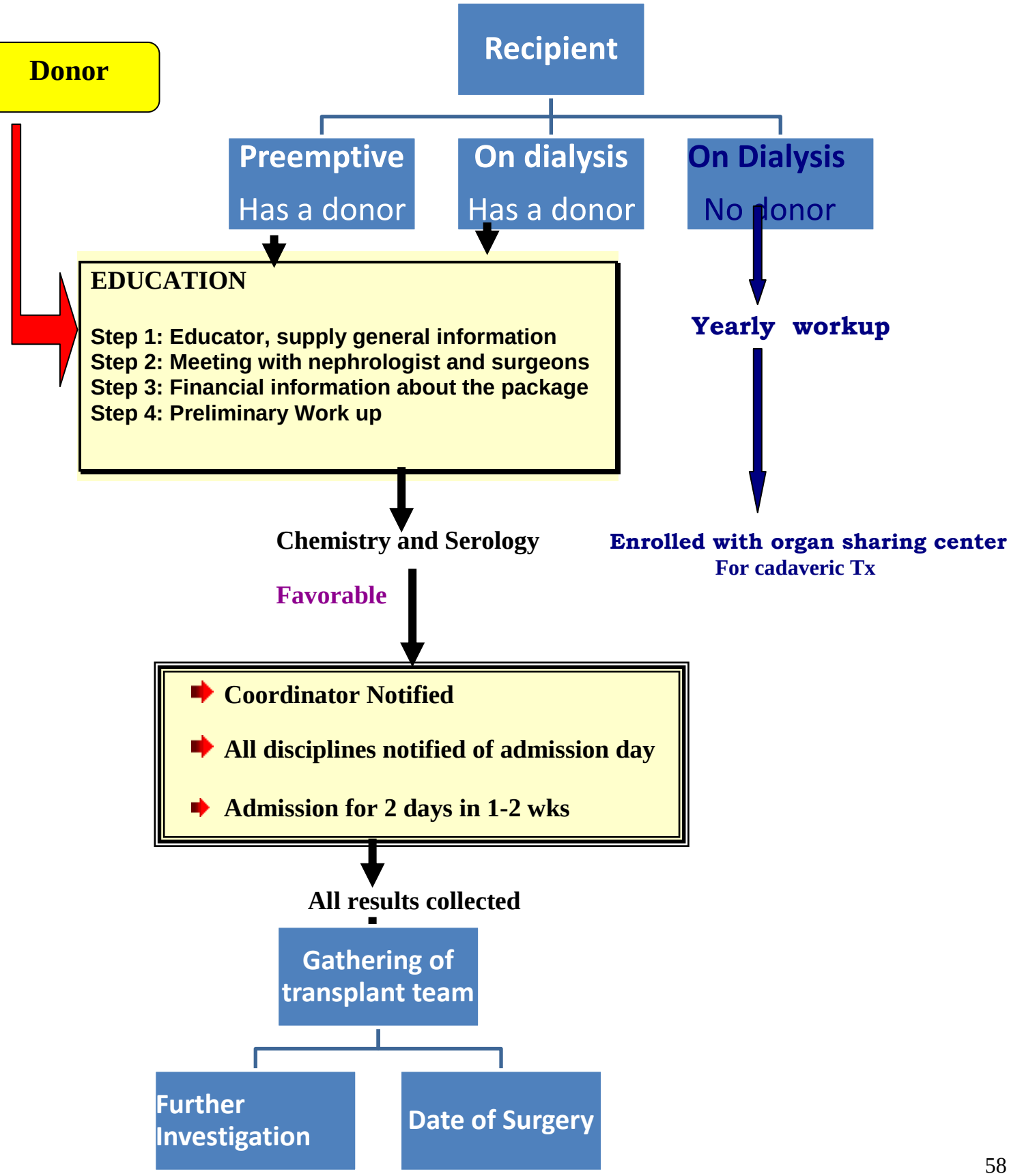
Pregnancy in renal transplant recipients:

- Renal transplantation restores fertility, and successful pregnancies have been reported. In women with normal graft function, pregnancy usually has no adverse effect on graft function and survival. Therefore, women of child bearing age who consider pregnancy should receive complete information and support from the transplant team.
- Pregnancy could be considered safe about 2 years after transplantation in women with good renal function, without proteinuria, without arterial hypertension, with no evidence of ongoing rejection and with normal allograft ultrasound.
- Pregnancy after transplantation should be considered a high-risk pregnancy and should be monitored by both an obstetrician and the transplant physician. Pregnancy should be diagnosed as early as possible. The principal risks are infection, proteinuria, anemia, arterial hypertension and acute rejection for the mother, and prematurity and low birth weight for the fetus.
- Pregnant women and transplanted patients are at increased risk of infections, especially bacterial urinary tract infections and acute pyelonephritis of the graft. Urine cultures should be performed monthly and all asymptomatic infections should be treated. Monitoring of viral infections is also recommended.
- Acute rejection episodes are uncommon but may occur after delivery. Therefore, immunosuppression should be re-adjusted immediately after delivery.
- Because pre-eclampsia develops in 30% of pregnant transplant patients, especially those with prior arterial hypertension, blood pressure, renal function, proteinuria and weight should be monitored every 2-4 weeks, with more attention during the third trimester. Anti-hypertensive agents should be changed to those tolerated during pregnancy. ACE inhibitors and angioternsion II receptor antagonists are absolutely contraindicated.
- Immunosuppressive therapy based on cyclosporine or taclorimus with or without steroids and azathioprine may be continued in renal transplant women during pregnancy. Other drugs, such as mycophenolate mofetil and sirolimus, are not recommended based on current information available. Because of drug transfer into maternal milk, breastfeeding is not recommended.
- Vaginal delivery is recommended, but caesarian section is required in at least 50% of cases. Delivery should occur in a specialized center. In the puerperium, renal function, proteinuria, blood pressure, cyclosporine/tacrolimus blood levels and fluid balance should be closely monitored.

The Elderly:

- In elderly kidney transplant recipients, immunosuppression has to be adapted to avoid both rejections and adverse effects.
- Renal transplantation can extend the duration and quality of life in elderly patients with end stage renal disease.
- Aggressive treatment of cardiovascular disease in elderly recipients is recommended because of the high number of deaths with functioning graft

Diagram showing the process for kidney transplant



KIDNEY TRANSPLANT

History &Physical

Age_____Wt_____
Sex_____
MR#_____
Duration of Dialysis_____Kidney Biopsy_____
Type of Dialysis_____
Type of access_____
Major cause of ESRD_____

	YES..	NO.		**PMHX**	YES..	NO .
DM				Previous Kidney Transplant		
Retinopathy				Cancer		
HTN				Hepatitis C		
IHD				Hepatitis B		
CHF				HIV		
UTI				Kidney stones		
Reflux-Neph				Smoking		
TB				IVDA		
Abd Surgery				Parathyroid Surgery		

	Yes	No
DM		
HTN		
Kidney Disease		

- Immunization_____
- Allergy _____

Physical	WNL	NOT		WNL	NOT
Vitals			Heart		
HEENT			Abd		
LN			GU		
SKIN			Ext		
LUNGS			CNS		
			Access		

Laboratory Work up Results for Donor

RECORD NO.	:	NATIONALITY:	
NAME	:	AGE/SEX :	
ADDRESS	:		
TEL. NO.	:		
DIAGNOSIS	:		

	ONS	***DATE***	***RESULTS***	***DATE***	***REMARKS***
PRIMARY	Blood Group				
	Soc. Work up Study Psychological Work up				
	Cross Matching				
	HLA – Typing				
EMATOLOGY	CBC				
	Different Count				
	Sickling				
	ESR				
	Platelet				
	PT				
	PTT				
	Malaria Film				
HEMIST	Renal Function Test				
	Electrolytes				
	LFTS(Liver function tests)				
	Alb./Glob.T.Protein				

RY	Serum Electrophoresis				
	Blood sugar X 3				
	Other biochemistry				
	24 hrs. urine for Pro. & Cr. clearance				
	ONS	***DATE***	***RESULTS***	***DATE***	***REMARKS***
	24 hrs. urine output				
	Urinalysis				
	S/A, O/B, OVA, PARA				
SEROLOGY	RPR & TPHA				
	HIV				
	HbsAg, HbcAb				
	HCV (PCR)				
	Brucella titer				
	Schistosoma titer				
	ANF				
	CMV Ab, Both IgM and IgG				
	EBV Ab, Both IgM& IgG				
	Varicella Zoster Ab				
	Immunology, C_3, C_4				
	IgG, IgM, IgA				
	PPD x2				
	Pregnancy test				
RADIOLOGY& E	Chest X-Ray, PA & lat				
	Renal angiogram,or CT angiogram, or MRA of renal vessels				
	IVP				
	U/S of Abdomen & Pelvis				
	Iothalamate or DTPA study				

KG **CONSULTATION**	EKG				
	UROLOGY				
	Opthalmology (Optional)				
	Gastroenterology(optional)				
	ENT(optional)				
	Cardiology(optional)				
	Pulmonary(optional)				
	Dental(optional)				
	Obs&Gynae, Pap smear				
SCREENING	Mammogram PSA Sigmoidoscopy				
OTHER					

Laboratory Work up Results for Recipient

RECORD NO.	:	NATIONALITY:	
NAME	:	AGE/SEX :	
ADDRESS	:		
TEL. NO.	:		
DIAGNOSIS	:		

	ONS	***DATE***	***RESULTS***	***DATE***	***REMARKS***
PRIMARY	Blood Group				
	Soc. Work up Study Psychological Work up				
	Cross Matching				
	HLA – Typing				
EMATOLOGY	CBC				
	Different Count				
	Sickling				
	ESR				
	Platelet				
	PT				
	PTT				
	Malaria Film				
HEMIST	Renal Function Test				
	Electrolytes				
	LFTS (liver function tests)				
	Alb./Glob.T.Protein				

RY	Serum Protein Electrophoresis				
	Blood sugar X 3/ HBa1c				
	Lipid Panel & Other biochemistry				
	24 hrs. urine for Pro. & Cr. clearance				
	ONS	***DATE***	***RESULTS***	***DATE***	***REMARKS***
	24 hrs. urine output				
	Urinalysis				
	S/A, O/B, OVA, PARA				
	Cytotoxic Antibody				
SEROLOGY	RPR & TPHA				
	HIV				
	HbsAg, HbcAb				
	HCV (PCR)				
	Brucella titer				
	Schistosoma titer				
	ANF				
	CMV Ab, both IgM& IgG				
	EBV Ab, both IgM & IgG				
	Varicella Zoster Ab				
	Immunology, C_3, C_4				
	IgG, IgM, IgA				
	PPD x2				
	Pregnancy test				
RADIO&CARD	Chest X-Ray, PA & lat				
	US of Abdomen and Pelvis				
	Voiding Cystourethrogram (optional)				
	EKG				
	Echocardiogram				

IO CONSULTATION	UROLOGY				
	Opthalmology				
	ENT				
	Cardiology				
	Pulmonary				
	Dental				
	Obs & Gynae, Pap smear				
SCREEN	Mammogram PSA Sigmoidoscopy				
OTHER	GG6PD 50 low ? hematology				
	DST				
	FINAL CROSSMATCH				

Standing Orders: Preoperative
Renal Transplant – Recipient

STANDING ORDERS	Yes	Individual Carrying Out Orders		
		Initials	Date	Time
1. Admission Orders: Admit to unit: _____				
2. Attending physician:_____				
3. Signed consent forms present in patient's health record: ☐ Form *MED-002 Authorization and Consent for Performance of Operation or Other Procedures* (stating whether for living related or cadaveric renal transplant). ☐ Form *MED-004 Authorization and Consent for Administration of Anesthesia*. ☐ Form *BLB-001 Authorization and Consent for Transfusion of Blood and Blood Products*.				
4. NOTIFY TRANSPLANT COORDINATOR AND NEPHROLOGIST ON CALL				
5. Outpatient health record to inpatient unit				
6. Vital signs Q_____H ☐ daily weight				
7. Blood Work Required:				
☐ CBC ☐ Electrolytes ☐ Hepatic profile				
☐ PT and PTT ☐ Blood group				
☐ Cross match for 2000 cc of whole blood or packed RBCs ☐ Panel Reactive Antibodies (PRA) ☐ Lymphocyte cross match with the donor				
8. ECG, chest x-ray				
9. Urinalysis, culture and sensitivity if patient is passing urine				
10. NPO after midnight				
Medications: 11.1 Cyclosporine _____ milligrams intravenous infusion over_____hours starting at _____ hours.				
11.2 Cyclosporine_____ milligrams orally every 12 hours at _hours and _____ hours and _____ hours				
11.3 Methylprednisolone _____ milligrams intravenous infusion over _____hours starting at _____ hours				
11.4 Basiliximab _____ milligrams intravenous over ____ hours starting at _____ hours				
11.5 Daclizumab _____ milligrams intravenous over _____ hours starting at _____ hours				
11.6 (tacrolimus) _____ milligrams orally every 12 hours at ___ hours and __ hours				
11.7 (MMF) _____ milligrams orally every 12 hours at ___ hours and ____ hours				
11.8 Azathioprine _____ milligrams orally every 12 hours at _____ hours and _____ hours				
12. Other medications:				
13. Antibiotics_____ on call to OR				
14. Diet:_____				
15. Hemodialysis as per physician's order				
16. **These orders are valid from _____ to _____**				

ADDITIONAL ORDERS				
Orders	**Yes**	**Individual Carrying Out Orders**		
		Initials	**Date**	**Time**

All blanks must be filled in.
If the order is to be carried out, initial or tick (√) in the "yes" column. If there is no initial or tick in the "yes" column, the order will NOT be carried out.
This form must be signed by the ordering physician before any orders can be carried out.

Signature of Ordering Physician:	**Ordering Physician's Stamp:**	**Date and Time Ordered:**

Nursing Staff			
Initials	**Name**	**ID Number**	**Signature**

Renal Transplant - Recipient

STANDING ORDERS				
	Yes	Individual Carrying Out Orders		
		Initials	Date	Time
1. Admit to Intensive Care				
2. Vital signs _____ minutes until stable, then Q _____				
3. Central venous pressure Q1H				
4. Assess temperature Q4H, notify the physician if 38°C				
5. Draw blood for culture and sensitivity: 5.1 Draw 2 sets of blood cultures and sensitivity tests if patient develops a fever equal to or greater than 38°C 5.2 Send blood for _____ levels at _____ hours				
Notify physician if systolic blood pressure is greater than 180 or is less than 110 mm Hg				
Notify physician if arrhythmias or hyperkalemia				
Hourly input-output chart				
Notify physician if urine output is greater than 600 mL/hour or is less than 80 mL/hour				
NPO, may rinse the mouth with mouthwash PRN(except medicine)				
Two way Foley catheter to urometer with closed drainage				
12. Check access sites for clotting Q4H				
half normal saline intravenously at __ milliliter/hour until first hour urine is measured then follow number 14 fluid guidelines				
14. Fluid guidelines:				
14.1 1/2 normal saline intravenously				
14.2 Add _____ to the above fluid				
14.3 Hourly urine output:				
0-200 milliliter/hour – give 30 milliliter plus previous hour's output				
200-400 milliliter – give fluids equal to previous hour's output				
400-600 milliliter – give 30 milliliter less than previous hour's output				
These amounts can be changed if central venous pressure is greater than 14 or is less than 8				
15. Activity:				
15.1 Bed rest, on back or on non-transplant side				
15.2 Mask isolation (all visitors must wear a mask)				
15.3 Start tri-flow, deep breathing, coughing, and leg exercises Q1H when fully awake				
15.4 Daily body weight				
16. **Do not draw blood from access site**				
Electrolytes, serum creatinine, CBC STAT, and 4 times daily in first 24 hours.				
Notify the physician of the results immediately				
18. Medication**:**				
18.1 Cyclosporine_____ milligram orally at _____				
18.2 **Tacrolimus**___ milligram orally at ___ hours and ____ hours				
18.3 Methylprednisolone _____ milligram intravenously over _____ hours starting at _____ hours				
18.4 Prednisolone _____ milligram orally at _____ hours				

STANDING ORDERS				
	Yes	Individual Carrying Out Orders		
		Initials	Date	Time
18.5 Mycophenolate Mofetil ___ milligram orally at ___ hours and _____ hours				
18.6 Azathioprine _____ milligram orally at ____ hours and _____ hours				
Other medication:				
19. Cyclosporine level to be sent daily at _____ hours Prograf level to be sent daily at _____ hours				
20. **These orders are valid from _____ to _____**				

ADDITIONAL ORDERS				
Orders	Yes	Individual Carrying Out Orders		
		Initials	Date	Time

All blanks must be filled in.
If the order IS to be carried out, initial or tick (√) in the "yes" column. If there is no initial or tick in the "yes" column, the order will NOT be carried out.
This form must be signed by the ordering physician before any orders can be carried out.

Signature of Ordering Physician:	Ordering Physician's Stamp:	Date and Time Ordered:

Nursing Staff			
Initials	Name	ID Number	Signature

STANDING ORDERS OF DR ISSA KAWALIT : INPATIENT POSTOPERATIVE RENAL TRANSPLANT - RECIPIENT

STANDING ORDERS				
	Yes	Individual Carrying Out Orders		
		Initials	Date	Time
1. Transfer to inpatient unit_____.				
2. Vial signs Q4H.				
3. Daily body weight.				
4. Patient to wear mask when with visitors, ambulating in the unit.				
Diet _____ fluid limit_____mL.				
6. Daily dressing with _____.				
Encourage patient to cough, deep breaths, triflow spirometer every 4 hours.				
8. Activity: _____.				
9. Check access site every 8 hours.				
10. Foley's catheter to gravity.				
11. Input and output chart.				
12. Daily complete blood count, electrolytes, glucose, serum creatinine.				
13. Medication:				
13.1 Cyclosporine_____ milligrams orally at ____				
13.2 Tacrolimus __ milligrams orally at ____ hours and ____ hours				
13.3 Methylprednisolone _____ milligram intravenously over _____ hours starting at _____ hours.				
13.4 Prednisolone _____ milligrams orally at ___ hours.				
13.5 MMF _____ milligrams orally at _____ hours and _____ hours.				
13.6 Azathioprine _____ milligrams orally at _____ hours and __ hours.				
Other medication:				
Antibiotics _____ _____ milligrams intravenously.				
15. Cyclosporine level sent daily at _____ hours. Tacrolimus level sent daily at _____ hours.				
16. **These orders are valid from _____ to _____.**				

ADDITIONAL ORDERS				
Orders	Yes	Individual Carrying Out Orders		
		Initials	Date	Time

Additional Orders				
Orders	Yes	Individual Carrying Out Orders		
		Initials	Date	Time

All blanks must be filled in.
If the order is to be carried out, initial or tick (√) in the "yes" column. If there is no initial or tick in the "yes" column, the order will NOT be carried out.
This form must be signed by the ordering physician before any orders can be carried out.

Signature of Ordering Physician:	Ordering Physician's Stamp:	Date and Time Ordered:

Nursing Staff			
Initials	Name	ID Number	Signature

KIDNEY TRANSPLANT FOLLOW UP

Name
MR#

Date	. .	. .	. .	..	. .	. .	. .	..	..	..	. .	. .	. .	. .	…
Cr															
Cyclo															
Progr															
K															
Na															
Ca															
PO4															
BUN															
HGB															
WBC															
PLT															
Gluc															
Mg															
UA															
Chole															
HDL															
LDL															
Trig															
GOT															
GPT															
Bilr															
Albu															
Ferretin															
Fe															
TIBC															
Hga1C															

	Date	**Date**		**Date**	**Date**
ECHO			Opthalm		
Renal U/S			Dermatology		
EKG			Dental		
CXray					
Kidney Bx					
Colonoscopy					
PSA					

Discharge Follow-up Instructions

Clinic Visits Frequency :

1) Twice weekly x 1month
2) Once weekly x 1 month
3) Once every 2 weeks for 2 months
4) Once monthly for 8 months
5) Once every 2 months

Tests done on each visit:

1) KFT, LFT, BS, electrolytes
2) Calcineurin Inhibitor Levels
3) CBC
4) Urine Analysis

Tests done monthly for 6 months, then every 3 months thereafter are:

1) Liver Function Tests (LFT)
2) Lipid panel
3) PTH
4) In addition to above
5) Serology monitoring

Annual Evaluation requirement:

1) Ultrasound of graft and native kidney
2) Chest X-ray
3) Complete skin exam
4) Fecal occult blood testing
5) Cardiovascular evaluation
6) Dermatology evaluation
7) Monitor prostate specific antigen (As applicable)
8) Regular mammography/Pap smear(As applicable)

Threshold and Target LDL Cholesterol Levels

Risk Category	**Drug Treatment Threshold LDL**	**Drug treatment target LDL**
0-1 Risk Factor	190 mg/dl	<160mg/dl
2 Risk Factor	160mg/dl	<130mg/dl
Ischemic Heart Disease	130mg/dl	100mg/dl

Overview of the High PRA Rescue Protocol

1) Details of the first protocol [34]

Before transplant. The following timetable shows the details of the protocol before transplantation. It was designed to include oral immunosuppressants before the first plasmapheresis treatment, followed by a maximum of six plasmapheresis treatments on alternate days . The recipient also receives seven days of intravenous hyperimmune globulin (IVIG, total dose of 500 mg/kg, divided over 7 days), which is an intravenous protein solution that can reduce anti-human antibody levels, and prevent the antibody from coming back. The donor-recipient crossmatch is repeated on the morning following each plasmapheresis treatment .While the crossmatch is running in the lab, the patient receives dialysis. If the crossmatch is negative, then the transplant is performed in the early afternoon, and the protocol shifts over to the *after transplant* section. The donor and recipient remain out-patient until the day of the transplant.

Week 1

- *Friday - Sunday*

1. Recipient takes a standard dose of mycophenolate mofetil one gram by mouth twice daily.

Week 2

- Recipient takes standard doses of the following modern immunosuppressant medications:

1. Mycophenolate mofetil, as listed above.
2. Tacrolimus at a starting dose of 0.05 mg/kg by mouth twice daily. Dosage adjustment for a 12-hour trough blood level of 15 ng/ml.
3. Prednisone 0.25 mg/kg twice daily.
   In addition, the follow prophylactic medications are given concomitantly:
4. Omepazole 20mg by mouth once daily to prevent gastritis.
5. Myconazole oral gel by mouth four times daily to prevent infections of the mouth and esophagus.

- *Monday*
  Plasmapheresis
  IVIG infusion
- *Tuesday*
  Crossmatch
  IVIG infusion
  Possible transplant (if crossmatch is negative)
- *Wednesday*
  Plasmapheresis
  IVIG infusion
- *Thursday*
  Crossmatch
  IVIG infusion
  Possible transplant (if crossmatch is negative)
- *Friday*
  Plasmapheresis
  IVIG infusion

- *Saturday*
  Crossmatch
  IVIG infusion
  Possible transplant (if crossmatch is negative)
- *Sunday*
  IVIG infusion (last dose)

  Week 3
  Monday
  Plasmapheresis IVIG infusion

- *Tuesday*
  Crossmatch
  Possible transplant (if crossmatch is negative)
- *Wednesday*
  Plasmapheresis
- *Thursday*
  Crossmatch
  Possible transplant (if crossmatch is negative) <
- *Friday*
  Plasmapheresis
- *Saturday*
  Crossmatch
  Possible transplant (if crossmatch is negative)
-
  After transplant. After transplantation, patients receive 10 days of OKT3, which is a powerful intravenous antirejection drug. They keep taking the oral immunosuppressants that were started at the beginning of the protocol. The remainder of the postop management is the same as that of other kidney transplant recipients.

2) Details of the second protocol [34]

The recipients started taking mycophenolate mofetil (MMF, 750 mg twice daily, p.o.) and tacrolimus (0.05 mg/kg twice daily, p.o., target trough level 10-12 ng/mL) two days before the first plasmapheresis. Methylprednisolone 1,000 mg i.v. was started at the time of the surgery, and the steroid dose was tapered to an oral dose of prednisolone. The combined immunosuppression of the MMF, tacrolimus and prednisolone were continued through the post-transplantation period. In addition, basiliximab (4 mg i.v. on day 0 and day 4) used for induction therapy. The plasmapheresis (one plasma volume exchange with 4% albumin and/or fresh frozen plasma) performed three times a week preoperatively. Intravenous immunoglobulin (IVIG, 100 mg/kg) administered immediately after each plasmapheresis. After the second and fifth plasmapheresis, crossmatching and DSAs will be evaluated. Patients with a negative crossmatch and no donor specific reactivity proceeded to transplantation. The transplant patients received 10 days of OKT3 (muromonab-CD3) (5 mg daily, i.v.) after the transplantation. Or rituximab (instead of OKT3) (375 mg/m^2 of body surface area, i.v.) administered three days before the first plasmapheresis and one day before transplantation until the CD20 and CD19-positive lymphocytes level was undetectable.

3) Details of the third protocol [35]

human polyclonal intravenous immune globulin (10% formulation) given twice (2 g per kilogram of body weight on day 0 and day 30), plus rituximab given twice (1 g on day 7 and day 22), could reduce the rate of, or eliminate, a positive cross-match in highly HLA-sensitized patients awaiting transplantation at Cedars–Sinai Medical Center. The rituximab dose was based on data from published reports concerning rituximab use in patients with rheumatoid arthritis or autoimmune diseases

Protocol Biopsies in Kidney Transplantation [34-41]

Improvements in short-term endpoints such as acute rejection have been substantial compared with the degree of long-term survival benefits. This has prompted investigators to explore alternative short-term endpoints. Protocol biopsies early after transplantation have detected subclinical disease, which has excited clinical investigators and prompted them to consider this as a potential surrogate marker for evaluating transplantation outcome. The benefit of the protocol biopsy at 1, 6, and 12 posttransplantation has shifted from detection of acute rejection to early diagnosis of CAN and complications secondary to over-immunosuppression, such as BKV nephritis. The role of the protocol biopsy can be summarized as follows:

- High-risk recipients: The protocol biopsy in high-risk renal transplant recipients is of immense value. It has the potential to diagnose antibody-mediated acute rejection, possibly allowing for intervention. Thus, one has to consider using this tool when transplanting high-immunologic-risk recipients.
- Detection of BKV nephritis: BKV nephritis is an increasing problem, and the protocol biopsy can detect subclinical disease. This is of great importance at a time when complications of over-immunosuppression are occurring more than suboptimal immunosuppressive therapy.
- Detection of CAN: Early detection of CAN can potentially alter the course of renal disease by eliminating nephrotoxic immunosuppressants. Although such an approach could potentially lead to acute rejection, this approach could benefit selected low-risk recipients with appropriate clinical biopsy surveillance after conversion.

Drugs In formations

- ✓ **BASILIXIMAB**

Indication
• High risk patients receiving kidney transplants (as above)
• All patients receiving pancreas or kidney/pancreas transplants
• Patients expected to have delayed graft function e.g. NHBD grafts.
Dose
• 20mg given 2 hours prior to transplantation
• 20mg given on day 4 post transplant
The first dose must not be administered until it is absolutely certain that the patient will Receive the graft.
Reconstitution
5ml water for injection (provided) should be added to the vial containing the Basiliximab powder. Shake the vial gently to dissolve the powder.
The solution should be used immediately. (It can be stored for 24hours in the fridge or 4 hours at room temperature.)
Administration
There are two possible routes of administration
Intravenous bolus injection, or Intravenous infusion over 20-30 minutes. (Final volume of at
least 50ml using sodium chloride 0.9% or dextrose 5%.)
Compatibility
Basiliximab should not be mixed with other medicines/substances and should always be given through a separate infusion line.
Adverse Effects
Severe acute hypersensitivity reactions have been observed both on initial exposure and reexposure
to basiliximab. These include anaphylactoid-type reactions. If severe
hypersensitivity reaction occurs, therapy with basiliximab must be permanently discontinued
and no further dose administered.
Side Effects
Basiliximab does not appear to add to the background of side effects seen in organ transplantation patients as a consequence of their underlying disease and concurrent administration of immunosuppressants.

✓ TACROLIMUS

Current indication
As the lead agent in standard triple therapy for all patients.
Dosage
0.1 mg/kg/day in 2 divided doses (normally between 2 mg and 5 mg bd).
Preparation
Tacrolimus is available as 0.5 mg (cream), 1 mg (white) and 5 mg (greyish red) capsules.
Administration
Oral route in most instances (well absorbed even in those with NG tubes). It is administered
usually at 10 am and 10 pm. The capsules are taken on an empty stomach either 1 hour before or 2 - 3 hours after meals.
Contents of the capsule can be suspended in water for NG administration.
One fifth of the oral dose can be given as a continuous IV infusion in saline via non PVC bags/tubing if absolutely necessary.
Levels
Whole blood trough levels to be checked on Mondays, Wednesdays and Fridays. The target level for the first six months is 10 ng/ml (range 8-12 ng/ml) and 5-10 ng/ml after six months. In adult kidney transplant patients steady state may be reached 2-3 days after starting therapy or changing dose.
Contra-indications
Live vaccines are not to be given to immunosuppressed patients.
Tacrolimus is contra-indicated in pregnancy. As it is not known to what extent Tacrolimus may influence the efficacy of oral contraceptives it is generally recommended that other forms of contraception be used.
Side Effects
The most frequent side effects seen with Tacrolimus include:
• abnormal kidney function (similar to Ciclosporin)
• tremor
• headache
• parasthesia
Less common side effects are:
• diarrhoea
• hypertension
• hyperglycaemia
• hyperkalemia
• hypomagnesaemia
• visual and neurological disturbances (affected patients should not drive or operate machinery)
• hypertrophic cardiomyopathy (in paediatric patients with trough levels >25 mg/ml).
Interactions
Potential interactions due to effects on hepatic microsomal enzymes.
Tacrolimus is extensively metabolised via the hepatic microsomal cytochrome P450 3A4 isoenzyme. Concomitant use of substances known to inhibit or induce cytochrome P450 3A4 (CYP3A4) may affect the metabolism of tacrolimus. Therefore:
Inhibitors of CYP3A4 may decrease metabolism of tacrolimus and thus increase tacrolimus blood levels, e.g. clotrimazole diltiazem fluconazole nicardipine
Ketoconazole , danazol ,itraconazole, grapefruit juice (naringenin)
erythromycin ethinyl oestradiol ,clarithromycin, omeprazole ,nifedipine

Inducers of CYP3A4 may increase metabolism of tacrolimus and thus decrease blood levels, e.g. rifampicin*phenobarbitol phenytoin
.
Tacrolimus itself has a powerful inhibitory effect on CYP3A4. Thus concomitant use of tacrolimus with drugs metabolised by CYP3A4 dependant pathways may affect the metabolism of such drugs. For this reason Ciclosporin A should not be co-prescribed with tacrolimus. Patients switched from Ciclosporin to Tacrolimus should receive the first tacrolimus dose at least 24 hours after the last Ciclosporin dose.
Interactions due to cumulative toxicity/synergistic effects
Concurrent use of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects may increase the degree of toxicity. Enhanced nephrotoxicity has been observed with coadministration of:
Ciclosporin A
Amphotericin B
Ibuprofen
Sirolimus (Rapamune)

Hyperkalaemia
As tacrolimus may cause hyperkalemia, high potassium intake or potassium sparing diuretics should be avoided.
Interactions due to plasma protein binding of Tacrolimus
Tacrolimus is extensively bound (>98%) to plasma proteins so competition with other highly protein bound drugs may result in displacement of either drug. This displacement may not be reflected in the blood levels of Tacrolimus or other drugs. Therefore, dosage adjustment may not be needed unless clinical signs and symptoms suggest otherwise.

- ✓ **CICLOSPORIN**

Dose
Starting dose is 8 mg/kg/day in 2 divided doses.
Preparation
Ciclosporin is available 10 mg (yellow / white), 25 mg (blue / grey), 50 mg (yellow / white) and 100 mg (blue / grey) capsules and as a 100 mg/ml oral solution.
Administration
Oral route in most instances. It is administered usually at 10 am and 10 pm. Oral solution should be diluted immediately before taking. May be diluted in orange juice or squash, apple juice or water (not grapefruit juice - see interactions). Needs to be stirred well. Measuring device should not come into contact within the dilutent.
One third of the oral dose can be given as a slow intravenous infusion in normal saline or dextrose 5% over 2-6 hours if absolutely necessary.
Contra-indications/Cautions
Live vaccines are not to be given to immunocompromised patients.
Neoral should be used with caution during pregnancy.
Ciclosporin passes into breast milk so mothers should not breast feed their infants.
Side effects
The most frequent side effects seen with Ciclosporin include:
abnormal kidney function hepatic dysfunction
hypertrichosis gingival hypertrophy
tremor gastointestinal disturbances
hypertension burning sensations of hands and feet

Less common side effects are:
headaches rashes (possible allergic origin)
weight increase oedema
mild anaemia pancreatitis
hyperkalaemia neuropathy
hyperuricaemia reversible dysmenhorrhoea
hypomagnesaemia muscle weakness, cramps or myopathy
hypercholesterolaemia

Interactions

Potential interactions due to effects on hepatic microsomal enzymes

Inhibitors of cytochrome P450 which may **decrease** metabolism of Ciclosporin and thus **increase** Ciclosporin blood levels include:
clarithromycin erythromycin nicardipine
danazol fluconazole oral contraception
diltiazem ketoconazole verapamil

Inducers of cyctochrome P450 which may **increase** metabolism of Ciclosporin and thus **decrease** blood levels include:
Barbiturates phenytoin
carbamazaepine rifampicin

Interactions due to cumulative toxicity / synergistic effects

• Take care when using Ciclosporin in combination with compounds known to have nephrotoxic effects, e.g.: aminoglycosides, ciprofloxacin, trimethoprim, amphotericin B, melphalan and NSAIDs.
• Concurrent administration of Ciclosporin with HMG-CoA reductase inhibitors may enhance risk of rhabdomylosis.
• Concomitant administration of nifedipine and Ciclosporin increases the rate of gingival hyperplasia when compared to that for Ciclosporin alone, particularly in the presence of poor oral hygiene.
• Since Ciclosporin may cause hyperkalemia, potassium sparing diuretics, potassium supplements and high potassium intake should be avoided.

Other interactions

• Vaccines may be less effective and the use of live attenuated vaccines should be avoided.
• Owing to its possible interference with the gastrointestinal cytochrome P450 enzyme system, grapefruit or grapefruit juice should not be taken 1 hour prior to Ciclosporin dosing and grapefruit juice should not be used as a dilutent for the oral solution.

Target range

For first 6 months 100 – 125 mmol/L (new assay)
After 6 months 50 – 100mmol/L

- ✓ **AZATHIOPRINE**

Current indication
Third agent in standard triple therapy.
Dose
Initially 1-2 mg/kg once daily.
Maintenance 1 mg/kg once daily.
Monitoring
No monitoring of drug levels is required.
Preparation
Azathioprine is available as 25 mg and 50 mg tablets.
Administration
Virtually exclusively oral although an IV preparation is available.
Contra-indications
Pregnancy
Bone marrow dysfunction, i.e. Patients who are known to be leucopaenic or thrombocytopaenic.
Reduce dose if hepatic dysfunction is present.
Drug interactions
Allopurinol must not be co-prescribed as an inhibition of xanthine oxidase results in potentially fatal accumulation of azathioprine and its metabolites. An alternative uricosuricbenzbromarone is available on a named patient basis.
Side Effects
Bone marrow suppression - usually reversible following cessation.
Cholestatis and disturbed liver function - again usually reversible.
Pancreatitis
Dose may require to be altered depending on WBC, i.e., reduce if WCC<4.0, stop if WBC <3.0 and re-introduce at a lower doses when WBC>3.0.

- ✓ **MYCOPHENOLATE MOFETIL (MMF)**

Current indication
As a substitute for azathioprine in alternative triple therapy regimen for patients at high risk of rejection and following resistant rejection in patients treated with standard triple therapy.
Dose
(500 mg to) 1g twice daily, depending on concomitant immunosuppression and renal function.
MMF is best absorbed on an empty stomach, either one hour before or two hours after a meal, but gastrointestinal side-effects may be alleviated by taking MMF with food and further splitting the daily dose.
Monitoring of MMF blood levels is not needed.
Mode of action
MMF is rapidly hydrolysed following absorption to mycophenolic acid (MPA), the active metabolite. MPA is a potent inhibitor of inosine monophosphate dehydrogenase (IMPDH) and therefore inhibits the denovo pathway of guanosine nucleotide synthesis. B and T lymphocytes are critically dependent on the de novo pathway and so MPA inhibits B and T lymphocyte proliferation and also B-cell antibody formation.
Preparation
MMF is available as 250 mg capsules (blue-brown) and 500 mg tablets (lavender).

Contra-indications
Pregnancy
Side-effects
Neutropenia. Gastro-intestinal bloating, cramps, diarrhoea, vomiting.
Drug interactions
Tacrolimus increases the AUC of MPA, the active metabolite of MMF. By 3 months past transplant the increase is such that the dose of MMF may need to be reduced with time post-transplant to maintain stable systemic exposure to MPA.
Cholestyramine and antacids - may bind MMF and significantly reduce absorption.
Drugs which undergo tubular secretion, e.g. Aciclovir, theoretically may impair secretion of MMF and have raised blood levels themselves during concurrent administration.

- ✓ **SIROLIMUS**

Indication
As an adjunct to or substitute to a calcineurin phosphatase inhibitor for immunosuppression in patients in whom ciclosporin/tacrolimus have been implicated in allograft pathology.
Contraindications
Hypersensivity to Sirolimus and its derivatives.
Pregnancy and breast feeding
Presentation, dosage and administration
1mg and 2mg tablets. Doses should be given on an empty stomach
Day 1 8mg daily
Day 2 6mg daily
Day 3+ 2mg daily adjusted according to levels
Monitoring
Target range 5-15ng/ml depending on whether it is an adjunct to or substitute for a CNI.
Side Effects
Raised triglycerides and cholesterol , Thrombocytopeania , Mouth Ulceration
Anaemia ,Neutropenia ,**Proteinuria ,**Hypokalaemia, Arthralgia ,Epistaxis
Delayed wound healing ,Lymphocele ,Rash ,Oedema Infections
PTLD, Diarhoea
Drug Interactions
Compounds which modulate CYP3A4 activity may effect Sirolimus levels. Drugs and substances which may increase sirolimus levels include:
Diltiazem Bromocriptine
Azole antifungals Cimetidine
Macrolide antibiotics Danazol
Prokinetic agents Protease inhibitors
Grapefruit
Drugs which may decrease Sirolimus levels
Rifampicin Anticonvulsants

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