East Coast Renal Services incorporates the Renal Treatment Programmes of South East Sydney Illawarra Area Health Service (the Prince of Wales Hospital, Sydney Children’s Hospital and the St George Hospital in Sydney and Illawarra Regional Hospital, Wollongong).
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Introduction

This 3rd edition comes soon after the second with updates and additional sections on sensitised recipients.

Inevitably, in a five year period, changes in practice have been driven by publication of further trials and other research that make it necessary to update this transplant manual. Again it is the immunobiology that has advanced significantly making available a number of new immunosuppressive agents and protocols for the management of our transplant patients. New approaches to standard immunosuppressive regimes, management of potential viral infectious agents, advances in tissue typing and transplantation across previous barriers such as ABO and positive Xmatches are being developed to combat the increasing waiting times and continued shortage of donors. An increasing reliance on living donors has been observed across Australia with 40 –50% of renal transplants now coming from these generous individuals. The Banff classification of renal allograft biopsies has also been updated with more detail on antibody mediated rejection.

New technologies have been applied to X match with the development of bead flow techniques (Luminex). Application of desensitisation to enable transplant against ABO and T & B-cell Xmatches are described.

The changes in the allocation protocols of deceased donors increases the likelihood that patients who have been waiting a long time will be transplanted and it is essential that continual reassessment of these individuals occurs to ensure their fitness for transplantation.

There is an increasing emphasis on long-term graft survival and how to achieve it especially in recipients of deceased donors that are often marginal. Avoidance of nephrotoxicity in association with low rejection rates can now be achieved by judicious choice of immunosuppressive agents that may change during the first transplant year according to the individual recipient’s needs. Attention to the major risk factors that lead to death with a functioning graft will also enhance the overall benefit to our patients. This latter problem has been addressed by the development of a recipient Transplant Passport that engages the recipient in these preventative measures and I hope it will be a useful addition (I would like to acknowledge the contribution made by Pauline Paul to the development of the Passport). This is available as a separate document.

This revised edition of ECRS Transplant Manual attempts to address these advances and changes by providing published evidence to guide decisions about the management of our patients on the transplant waiting list and following successful transplantation.

I would like to thank many of my colleagues for suggestions, criticisms and editing of the manual. Again Liz Henness has provided assistance with the revision and I gratefully acknowledge her contribution.

Bruce Pussell,
Director of Renal Services, SESIAHS
March 2008

Advances in the immunobiology of transplantation have occurred at a rapid rate and contributed to enhanced graft and patient survival and improved quality of life for recipients. The increase in the number of therapeutic agents over recent years provides us with many combinations of immunosuppressive drugs that now enable them to be appropriately matched to individual patients and to be varied over time according to patient’s needs.

Dialysis and transplantation are effective therapies for end stage renal disease and are complementary. However successful renal transplantation improves survival, quality of life and is less costly than dialysis (1). Effective management of the patient with renal failure is best achieved when the patient is assessed at an early stage. A key aspect of this assessment is the role of the referring renal physician and the interaction between them and the physicians at the transplant centre.

The protocols and guides contained in this manual aim to focus attention on issues important in renal transplantation. These relate especially to pre-existing medical conditions in the potential recipient that may influence a successful outcome, and to continuing care for the recipient to ensure optimum long-term benefits.

Pre-emptive kidney transplantation in young patients confers considerable survival advantage when compared to similarly aged patients having dialysis prior to transplantation (2). There is therefore an emphasis on living kidney donation and assessment of the potential live donor.

Creating this document was no small task and many people have contributed with suggestions, criticisms, editing and writing. However, its existence is largely due to the efforts on one person, Liz Henness, and I wish to record our appreciation for her work.

Bruce Pussell
Chair, South East Health Renal Services
March 2003
SECTION 1: Pretransplant Patient Assessment
Contraindications for Kidney Transplantation

Indications for transplantation are based on the concept that the patient will derive benefit from the procedure and decisions are to be taken in consultation with the patient and their relatives. Input from transplant physician and surgeon, transplant nurse and assessment by clinical psychologist and social worker are all desirable.

In general the patient should have at least a 5 year life expectancy before being considered a candidate for transplantation. The ability to tolerate a particular immunosuppression regime, given the increasing variety of regimes and agents should be made on an individual basis.

The manual now includes a form for patients on the waiting list that acknowledges their intent to accept a transplant having had the procedure and potential complications explained usually during an education session.

Absolute contraindications for kidney transplant include, but are not limited to the following:

a. **Metastatic cancer.**

b. **Malignant tumour** with less than 2 years disease free since diagnosis and treatment.

c. **Ongoing or recurrent infections** that are not effectively treated.

d. **Cardiac disease** that is severe enough that the patient cannot tolerate surgery or is likely to reduce life expectancy to less than 5 years.

e. **Serious conditions** that limit life expectancy to less than 5 years.

f. **Noncompliance** with therapy in the past that would jeopardise future transplant function.

g. **Unacceptable (to the patient) side effects** of immunosuppressive drugs that mean that the benefits of remaining on dialysis outweigh transplantation.

h. **AIDS**, defined according to CDC definition of a CD4 count <200 cells/mm$^3$ for > 6 months. Patients with HIV infection (but not AIDS), stable CD4 counts >200 and receiving HAART can be considered for transplantation following specific education about risks and adjustment to IS drug therapy necessary because of effects of HAART on CyP450 enzymes.

All patients should be reviewed by the transplant surgeon to assess their suitability for transplantation.
Pre Transplant Screening and Evaluation

Malignancy

The course of malignant disease may be adversely affected by immunosuppressive drugs and it is unreasonable to subject a person to transplant surgery when their life expectancy may be very short. Community expectations demand that appropriate best use of available organs occurs and this may not be served by transplantation of the kidney into a person with malignant disease.

The recurrence-free waiting period between tumour therapy and transplantation varies according to the type of tumour. The following table is a guide and has been adapted from reference 3.

Table 1. Waiting period between cancer treatment and transplant.

<table>
<thead>
<tr>
<th>Waiting Period</th>
<th>Type of Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Basal Cell skin; Incidental, asymptomatic Renal Carcinoma; In situ Bladder or Cervical</td>
</tr>
<tr>
<td>At least 2 years</td>
<td>Large Renal; Wilm's; Invasive Bladder; Uterus; Testis, Thyroid; Prostate; Lymphoma; Squamous skin.</td>
</tr>
<tr>
<td>5 years</td>
<td>Melanoma; Breast; Invasive Cervical; Colorectal.</td>
</tr>
</tbody>
</table>

Cancer Screening in the Recipient

In addition to the history and physical examination it is recommended that the following tests be done annually in adults:

* Chest X-ray
* Mammogram in women over 40 years or with family history of breast cancer;
* Pap test in all women;
* PSA in men over 50 years;
* Renal ultrasound;
* Urine cytology in patients with analgesic nephropathy (in addition to U/S);
* Faecal occult blood and colonoscopy if positive.

A record of these tests and the date they were completed will be kept in the Pre-Transplantation Recipient Checklist (Appendix A).

General advice about preventive measures for cancer including stopping smoking, avoidance of sun exposure, self-examination of breast or testes can be given during education sessions.
Infections

Bacterial Infections

Clearly, bacterial infection such as osteomyelitis and tuberculosis precludes the use of immunosuppressive therapy. Diabetic ulcers should be healed before transplant. Active infection at the time of transplant needs to be assessed on an individual basis. For example, urinary tract infection, not associated with systemic features, may be treated with antibiotics prior to the transplant procedure.

HIV Infection

The improvement in survival of patients with HIV infection has caused some centers to reassess the previous absolute contraindication to transplantation. Patients being considered in these centers include those with a low or absent viral load and with a CD4 count of >200 and compliance with continuing antiviral therapy. AIDS remains an absolute contraindication.

Hepatitis C Infection

Renal transplant patients positive for HCV have an increased mortality over negative controls but the risks appear usually after the first decade\(^{(55)}\). The increased mortality rate progressively increases: <5% at 5 years, 10% at 10 years, and 20% at 20 years. Recent studies\(^{(54)}\) suggest that transplantation is still the best option for HCV +ve patients as the increased mortality is less than that of continuing on dialysis.

Patients with HCV infection and abnormal liver function tests should be referred to a hepatologist as they may need to undergo liver biopsy and be offered antiviral therapy prior to transplantation. The presence of cirrhosis may be an indication for combined liver and kidney transplantation or for pre transplant antiviral therapy. The later has had variable success and is best instituted prior to transplantation.

Some Australian transplant centres accept HepC positive donors for HepC positive recipients if the recipient is PCR positive. The national Renal Transplant Advisory Committee (RTAC) is undertaking a review to produce guidelines for such allocations.

Hepatitis B Infection

Vaccination should be undertaken as early as possible in patients with renal failure as response is better when done earlier. All patients on the transplant list should be vaccinated with a double dose of one of the following each time:

1. Energix - B, 20mcg/ml at 0, 1 and 6 months
2. HB Vax-, 40mcg/ml single dose at 0, 1 and 6 months

Three months after the completion of the vaccination course all patients will have the following serology completed, HepBsAg, HepBsAb and HepBcAb. All patients showing a HepBsAb level of <30IU/L will need to receive a second course. All previously vaccinated patients will be monitored every 6 months (March and August) for their Hepatitis B status and booster shots given as indicated.

HBV infection, especially if there is active viral replication, is a relative contraindication to renal transplantation. There are many reports of a significantly higher mortality in transplant patients who are HBV +ve, than those who are HBV –ve. In addition, HBV positivity is an independent poor prognostic indicator for survival following renal transplantation\(^{(55)}\) and mortality from liver disease following transplantation is more
There are some patients at low risk of cirrhosis (and therefore death) who are HBV positive. Such patients who are HepBeAg negative and HBV-DNA negative, and who do not have signs of active liver disease are at low risk. These patients may be considered for transplantation after weighing the risks and benefits on an individual basis.

Transplantation of kidneys from HBV positive donors is absolutely contraindicated for HBV negative recipients. Although such transplants into HBV positive recipients has shown similar survival to such recipients receiving HBV negative organs.

Hep B core antibody positive but surface antigen negative donors may be considered for transplantation to an immunized recipient with specific consent. Risk of transmission appears to be very low.\(^{(57)}\)

**Tuberculosis (TB)**

Past history of tuberculosis is not a contraindication for renal transplantation. All patients will be screened via a chest X-ray and mantoux test prior to transplant. Prophylaxis therapy consisting of isoniazid over 6 months should be considered for patients who have a positive mantoux test and have not previously been treated for TB, as well as patients from high-risk populations, after consultation with the respiratory and or infectious disease physicians.\(^{(8)}\).

**Screening for Infections** (See Appendix A)

- CXR
- Urine culture as indicated

Serology for:

- HIV antibody
- HBs antigen, HBcore antibody (if +ve then also do HBeAg & HBV DNA)
- HCV antibody
- CMV antibody
- EBV antibody
- HSV antibody
- HTLV 1 & 2 antibody
- Other cultures as indicated e.g., TB etc.
- Mantoux – PPD skin test.
- Dental Consultation and treatment for caries if necessary

**Cardiovascular Disease**

Cardiovascular disease (CVD) is defined as ischaemic heart disease, cerebrovascular disease or peripheral vascular disease. Cardiovascular risk factors have a major impact on survival following renal transplantation and hence all Renal Physicians endeavor to reduce this risk by careful pre-transplant assessment and interventions to correct risk factors such as smoking, lipids, obesity etc. Cardiac and peripheral vascular disease are contraindications when they impact on the life expectancy of the potential recipient. This is judged on an individual patient
basis. Pre-transplant coronary artery surgery improves outcomes post transplant
and prior angioplasty, bypass grafting or endarterectomy are not contraindications to
transplantation if current cardiac stress testing is normal.\(^{(10)}\)

Patients with any history of myocardial ischaemia, with risk factors or who are over
50 years should be fully investigated prior to the patient being placed on the waiting
list.\(^{(23)}\)

**Screening for Cardiovascular Disease** (See Appendix A)

Asymptomatic patients with cardiovascular risk factors such as age >50 years,
smoking (past or present), diabetes, strong family history, etc should be evaluated prior
to transplantation. This evaluation may include coronary angiography. Patients with
angina, a history of myocardial infarction or congestive cardiac failure and Diabetes
should be also considered for coronary angiography before any consideration is given
to renal transplantation.\(^{(9)}\) Of course, clinical indications will dictate the appropriate
investigations, the following guidelines are suggested as a minimal requirement:

* ECG
* Echocardiography
* Stress testing, either by exercise echocardiography or sestamibi scan
* Coronary angiography if there is any suspicious result.
* Carotid Doppler sonography
* Doppler sonography of Ilio-femoral vessels.
* Plasma lipids

Any abnormality will be investigated further to aid decisions on pretransplant
interventions. Some of these assessments will have to be repeated periodically as
the waiting time for transplantation lengthens, suggested time frames are included in
the table on the following page.

**Suggested Time Frames for Cardiovascular Screening**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Frequency of Investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG – low risk patients</td>
<td>Screening</td>
</tr>
<tr>
<td>ECG – patients &gt; 50</td>
<td>Screening then annually (Oct-Dec) unless clinically indicated</td>
</tr>
<tr>
<td>ECG – high risk patient</td>
<td>Screening then every 6 months (to be performed May-July and Oct-Dec) until transplant.</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Screening then yearly (Oct – Dec)</td>
</tr>
<tr>
<td>Stress Test &lt; 50y + low risk</td>
<td>Screening then every 2 years for low risk patients.</td>
</tr>
<tr>
<td>&gt;50y high risk</td>
<td>Screening then yearly unless clinically indicated.</td>
</tr>
<tr>
<td>Coronary Angiography</td>
<td>Screening, for all patients with existing cardiac disease and as indicated.</td>
</tr>
<tr>
<td>Carotid Doppler sonography</td>
<td>Screening and yearly (Oct-Dec) for high risk vascular patients.</td>
</tr>
<tr>
<td>Doppler of Ilio-femoral vessels</td>
<td>Screening and yearly (Oct-Dec) for high risk patients</td>
</tr>
<tr>
<td>Plasma Lipids</td>
<td>Screening and yearly (Oct-Dec) or as indicated</td>
</tr>
</tbody>
</table>

Patients who require revascularization surgery should be re-evaluated after a period
of 3 months with regards to their suitability for renal transplantation. Cardiology
consultation should occur as indicated.
Diabetes Mellitus

ESRD due to diabetes mellitus carries the highest risk for early death due to cardiovascular complications. The diagnosis of Type I or Type II diabetes mellitus should not by itself be considered a contra-indication for placement on the renal transplant waiting list.

The suitability of patients with type I or II diabetes mellitus for renal transplantation should be made on the presence of known risk factors such as cardiovascular disease, peripheral vascular disease and obesity which are detailed separately in this manual.\(^{11,12}\)

All diabetic patients will be screened at regular intervals for cardiac disease (See cardiovascular disease section for screening schedule).

Type 1 diabetic patients younger than 50 years of age and who have been screened for significant cardiac disease should be considered for either simultaneous kidney and pancreas transplantation or pancreas transplantation after successful living or cadaver donor kidney alone transplantation.\(^{11}\)

All patients with diabetic retinopathy should be seen in the eye clinic every 6 months. Retinopathy should be stable at the time of transplant as transplant patients have an increased risk of retinal bleeding if their retinopathy is unstable.\(^{13}\)

A HbA1c level should be measured at regular intervals, every 3-6 months for insulin treated patients and every 6-12 months for non insulin patients.\(^{14}\) If the HbA1c level is ≥ 8% the patient should be referred to an endocrinologist for review.

Obesity

Obesity is a well-established independent risk factor, irrespective of renal transplantation, for hypertension, maturity onset diabetes, ischaemic heart disease, intra-operative complications and wound related problems.\(^{15}\) Obesity defined by body mass index (BMI) of >30 is not an absolute contra-indication for placement on the waiting list for renal transplantation.\(^{16}\)

Being overweight (defined as BMI > 25) and obesity (BMI > 30) are independent risk factors for both decreased graft survival and patient survival.\(^{16}\) Patients who have the potential to receive a cadaver donor transplant should be advised of the significantly increased risk of delayed graft function\(^{13}\). Patients should also be warned of the increased risk of surgical, diabetic, infective and cardiovascular complications.\(^{15}\)

All obese patients should be continually monitored for maturity onset diabetes. (see monitoring guidelines below).

Advice and assistance in regards to weight loss should be given to the patient prior to transplantation; this may include referral to the dietician. Patients should also be warned of the significant risk of further weight gain post transplant.

Monitoring Guidelines for Diabetes in Obese Patients:

Fasting glucose levels should be measured at each clinic visit.
If the fasting glucose level is > 7.0mmol/L then the patient should be investigated further for diabetes mellitus.\(^{17}\)
HbA1c to be monitored if blood sugar levels are elevated.

Key Points:

The suitability of obese patients for renal transplantation should be made on the presence of additional known risk factors such as diabetes, cardiac
disease and peripheral vascular disease. Surgical complications may be significant and a surgical opinion is essential prior to the patient being placed on the transplant list.

Glucose levels to be monitored at regular intervals.

Patients to be referred to Dietician for management of weight gain.

**Note**

Body Mass Index (BMI) is calculated by dividing the patient’s weight (kg) by height (m)^2.

**Age**

Advanced age is not necessarily a contra-indication to renal transplantation. Patients who are 60 years of age and above may be considered for transplantation. These patients will be examined for other risk factors such as diabetes, cardiac disease, smoking and peripheral vascular disease in order to assess their suitability.\(^{16,19,20}\)

Improved patient selection, changes in immunosuppression regimens and living-related transplantation have increased the success rate of transplantation in the elderly (>60 years of age) patient.\(^{16}\) Graft and patient survival were found to be significantly better in patients aged 60 or greater without one of the major risk factors.\(^{19}\) Survival rates for patients transplanted are also better than for patients who remain on dialysis.\(^{19,20}\)

**Smoking**

Active smoking is not an absolute contra-indication for placement on the waiting list for a cadaveric renal transplant, nor is it for patients being assessed for a living related transplant.

Patients should be made aware that a history of smoking correlates with a decreased patient survival rate post transplant and contributes significantly to allograft loss.\(^{21,22}\)

Smoking cessation prior to renal transplantation has beneficial effects on graft survival and has a positive impact on known risk factors for cardiovascular disease.\(^{22}\)

Efforts should be made to encourage patients to cease smoking prior to transplantation to reduce morbidity and mortality. All patients should be referred to the QUIT program for advice on how to stop smoking.

**Genitourinary Abnormalities**

Generally, urological assessment should be undertaken in patients who have a urological cause of chronic renal failure or have had genito-urinary tract abnormalities. Consideration should be given to pre op CE and Cystogram in selected patients. Patients with a history of obstructive voiding or evidence of significant prostatic enlargement on ultrasound should be referred for a urology assessment / cystoscopy. Similarly those on the waiting list for many years and who are anuric may also need urological assessment.

**Recurrent Disease**

Renal transplantation is a treatment which may return renal function to the kidney but it does not necessarily remove the cause of the recipient’s original renal disease.\(^{23}\)

A patient’s primary renal condition should not preclude him/her from receiving a first renal transplant.

Careful consideration should be given to the primary disease in the native kidney.
when considering transplant options. Most diseases that affect the native kidney with
the major exceptions of Adult Polycystic Kidney Disease and Alport’s Syndrome, can
recur in the transplanted kidney but recurrence does not lead to graft loss in the
majority of cases.\textsuperscript{(24)}

\textbf{Polycystic Kidney Disease}

For patients undergoing a living related transplant the donor must be 30 years or older
and have an ultrasound showing no polycystic kidney disease in order to be eligible
as a donor.\textsuperscript{(10)}

\textbf{Alport’s Syndrome}

Patients with Alport’s syndrome have a hereditary abnormality of the glomerular
basement membrane (GBM) that lacks the Goodpasture antigen so anti-GBM disease
may occur in up to 2\% post transplant.\textsuperscript{(25)} Intensive family screening is recommended
for the presence of inherited kidney disease before consideration can be given for a
living-related transplant.

\textbf{Glomerulonephritis}

\textbf{Anti GBM Diseases}

Patients with antibody mediated glomerulonephritis (GN) due to anti-GBM antibodies,
should have inactive disease, as evidenced by negative anti-GBM antibody test prior
to being placed on the transplant waiting list.\textsuperscript{(25)}

\textbf{Focal Segmental Glomerulosclerosis (FSGS)}

FSGS is more likely to recur in patients who developed renal failure within 3 years of
presentation, have demonstrated mesangial proliferation, are younger than 15 years
of age or who had recurrence in a prior transplant.\textsuperscript{(25, 26)}

The risk of FSGS recurring for patients who have lost a previous graft to FSGS is as
high as 80\% and graft loss is as high as 50\%.\textsuperscript{(24)} Careful consideration should be
given to patients wishing to undergo a living-related transplant when a previous one
has failed due to FSGS recurrence.

\textbf{Immunoglobulin A Nephropathy}

Most patients experience recurrence, at least on biopsy, but loss of graft due to
recurrent disease in the early years post transplant is unusual.

\textbf{Haemolytic Uraemic Syndrome}

Some cases of sporadic HUS have recurred following transplantation. Predisposing
factors are complement factor H deficiency and presence of ADAMTZ. Factor H
levels can be measured by the Renal Laboratory (contact the lab directly) but as
yet we have not been able to have ADAMTZ 13 measured although some labs do
it as a research protocol. There have been reports of successful use in preventing
recurrence of HUS in those with predisposition to recurrent disease. Avoidance of
CNIs, use of MMF & steroids and rituximab have all been reported in successful
transplantation in patients predisposed to recurrence.

\textbf{Other GN}

May recur but again it is unusual as a cause of early graft loss. For other types
of GN, primary and secondary see the comprehensive discussion in the CARI
Guidelines\textsuperscript{(25)}, which can be found at http://www.kidney.org.au
Psychosocial Assessment

A complete psychosocial assessment is recommended for patients being assessed as either a transplant recipient or live donor. The social worker or clinical psychologist usually conducts this assessment.

The recommended areas for discussion are listed below.

**Illness Assessment:**
1. Illness history and the effect on patients functioning, understanding, reaction and adjustment.
2. Patient’s knowledge of transplantation

**Patient Assessment:**
1. Personal – Age, physical functioning, emotional functioning, major life stresses, ability to comply with medical regimen, history of substance abuse and religious beliefs.
2. Educational – level of education attained
3. Vocational – Type of occupation, length of employment, stability of present job.
4. Financial – Sources of income and adequacy for future medical needs

**Support System Assessment**
1. Family – members, roles, interactions, functioning and problem solving skills
2. Social – extended family, friends, social support network
3. Environmental – housing, transportation, need for travel alternatives

**Blood Transfusions**

Blood transfusions pre transplant are generally avoided due to the risk of presensitization. Indications for transfusions are entirely clinical and a white cell filter should be used. The Tissue Typing Laboratory of ARCBS (NSW TT) should be notified and a blood sample sent two weeks after the transfusion for testing for sensitisation and for the XMatch trays.

**Tissue Typing**

Tissue typing detects HLA class I and II molecules on the surface of recipient peripheral blood cells that will be used to determine matching with any future potential donor. This is done with the very sensitive DNA technology and if necessary can be used to differentiate subclasses at some sites. Crossmatching detects reactions between recipient antibodies and donor cellular antigens of both HLA class I and II and also non-HLA antigens. A number of techniques are available that have varying degrees of sensitivity.
For deceased donors the crossmatch is done by CDC (complement-dependent cytotoxicity) because of time constraints necessary to limit total ischaemic time for the kidney and the additional time that is required to perform the more sensitive assays. More sensitive technology may be available in the future.

In order for a patient to be tissue typed for the kidney recipient (KR) transplant waiting list the following procedure must be followed:

1) Email the tissue typing laboratory on ttcbo@arcbs.redcross.org.au and book a date for the Initial and Confirmatory tests to be performed.

2) The second is usually done at least one week later and can be collected either in the clinic, pathology collection centre or at the dialysis centre.

3) Fax the Activation Request Form (Appendix J) to the TT Lab on 9229 4534

4) Inform the patient of the date and time that the blood is to be collected. It is imperative that the blood reaches the blood bank by 0930 hours on the day that the blood test is scheduled for. Blood is usually collected on the day before the booking and sent to the Red Cross that afternoon to ensure it is there on time.

5) Fill in the details on the designated Tissue Typing Request Form, ensuring that you have indicated on the form the tests that are required.

6) Blood can be sent either by SEALS or in a taxi. If sent in a taxi it should be delivered to Specimen Reception at the Tissue Typing Laboratory, Red Cross Blood Bank, 294 Kent Street, Sydney.

7) Taxi vouchers are available from the Haemodialysis units.

**BLOODS REQUIRED FOR Initial and Confirmatory tissue typing**

- 60mls ACD (canary yellow top tube)
- 7mls EDTA (purple top tube)
- 0mls clotted blood (mustard tube)

**Maintaining Patients On The Transplant List**

Due to the accreditation requirements of the Tissue Typing Laboratory 10mls of blood in a clotted tube must be collected each month for all active patients on the Kidney Recipient (KR) list. If the Red Cross do not receive the monthly specimen the patient will not appear on the crossmatch trays and therefore will not be eligible to receive a kidney transplant for that month.

The “dry tube “ must be taken prior to the 18th of each month. The blood is taken to determine the current antibody status of the potential recipient. A Tissue Typing Test request form (Appendix J) must accompany each monthly sample - tick the box indicating that it is the monthly sample and enter the date of collection of the sample.
All tissue typing bloods should be sent to the Red Cross Blood Bank at the following address:

Tissue Typing Laboratory
Red Cross Blood Bank
294 Clarence Street,
Sydney, 2000

All tubes must be clearly labeled with the patient name, date of birth, date of collection and time of collection. Hospital labels may be used. Samples will not be accepted by the red cross if a date and time of collection are not recorded.

**Re-entry Transplant Bloods**

If a patient has been temporarily removed from the list and is to re-enter the following blood is to be collected:

Time off list < 6 months – 10mls clotted tube to TT Lab plus fax the Activation form to 9229 4534 notifying them of reactivation.

Time off list > 6 months - Book the test by email on ttcbo@redcross.org.au and fax the Activation Request form to 9229 4534.

Collect
* 60mls ACD (canary yellow top tube)
* 7mls EDTA (purple top tube)
* 10mls clotted blood (mustard tube)

If a patient is to re-enter the list after having a transplant – the following bloods should be taken:
* 60mls ACD (canary yellow top tube)
* 7mls EDTA (purple top tube)
* 10mls clotted blood (mustard tube)

**Bloods Required For Live Donor**

**STAGE 1:**
This is usually performed only on ABO compatible (for transplantation) recipients and donors although see Highly Sensitised recipients Section for alternative protocol. The following table illustrates ABO compatibility of recipients and donors.

**Proteins and Antibodies Expressed by ABO Blood Groups**

<table>
<thead>
<tr>
<th>Patient Blood Type</th>
<th>Proteins Expressed</th>
<th>Antibodies Produced</th>
<th>Compatible to Receive Organs From:</th>
<th>Compatible to Give Organs to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB</td>
<td>A and B</td>
<td>None</td>
<td>A, B and O donors</td>
<td>only AB recipients</td>
</tr>
<tr>
<td>A</td>
<td>A only</td>
<td>B only</td>
<td>A and O donors</td>
<td>A and AB recipients</td>
</tr>
<tr>
<td>B</td>
<td>B only</td>
<td>A only</td>
<td>B and O donors</td>
<td>B and AB recipients</td>
</tr>
<tr>
<td>O</td>
<td>Neither A nor B</td>
<td>A and B</td>
<td>only O donors</td>
<td>A, B and O recipients</td>
</tr>
</tbody>
</table>
Recipient and Donor ABO typings must be faxed to the Central Booking Office, Tissue Typing Laboratory at the time of booking on 9229 4534. Stage one testing is as follows:

**Recipient:** HLA Typing - A, B, DR by SSP  
Auto T and B cell CDC crossmatches on both current and peak serum ABO

**Donor:** HLA typing - A, B, DR by SSP  
Allo T and B cell CDC crossmatches on both current and peak recipient serum ABO

**Luminex:**  
This test is based on bead technology using flow cytometry and is available from TT lab free of charge for the detection of class I and class II antibodies in a multiple screening test for live donor/recipient pairs. It is more sensitive than Flow Cytometry with isolated T & B cells. If positive then single antigen testing will be performed by the TT Lab to define the individual reactivity to antigens. It will eventually replace the PRA with a virtual estimation of reactivity.

**STAGE 2:**  
Stage 2 will involve flow cytometric crossmatches for both recipient and donor (current and peak serum) and a confirmatory HLA, A, B, DR typing by PCR-SSO. This testing is to be performed as a confirmatory crossmatch. In addition, for live donors/recipient crossmatching, the TT lab is now reporting results based on Luminex technology that is potentially more sensitive than ‘flow’. These results should be discussed with the TT lab if there is any inconsistency between the different types of crossmatch.

**STAGE 3:**  
CDC crossmatches, using current serum will be performed in Stage 3. This testing is performed as a final crossmatch 7-14 days prior to transplantation. It is recommended by Tissue Typing Services that this testing be done no earlier than 1 week post transfusion. The booking should be made as soon as the transplant date has been set.

**Bookings:**  
All bookings for the above tests are to be made by email. An email should be sent to tt cbo@redcross.org.au. An electronic template for these forms is available in the clinic or from the transplant coordinator.

The paper request form which must accompany all blood samples sent to the Tissue Typing Laboratory can be found in appendix J.
Assessment of a Person for Living Kidney Donation

The Renal Transplant Service will consider live kidney donation from people who are related or, if non-related are a spouse or close friend. For unrelated, altruistic donors please discuss this with one of the physicians for further advice. The state law in New South Wales requires us to be sure that the donor has not received any inducement to donate their organ.

People considered eligible as potential donors for a renal transplant should have normal renal function, be in good health with no major co-morbid conditions and be 65 years old or less. The Transplant Service has a policy that the potential donor is assessed and advised by their own renal physician and surgeon who are distinct from the recipient's team. This helps to ensure that there is no conflict of interest among the caring teams.

See Flow Chart in Appendix B

Initial assessment should be done in consultation with the person’s family doctor and should include:

- Full history, physical examination and urinalysis
- A blood group determination, obtained early in the assessment, to screen out those patients who are clearly ineligible donors based on ABO blood group incompatibility.

After the above assessment, the following investigations should be performed:

- Urine microscopy and MSU
- Spot urine for Protein/Creatinine ratio or 24 hour urine collection for protein and creatinine clearance or other test of GFR
- Biochemistry: urea, electrolytes, creatinine, calcium, magnesium and phosphate, liver function tests, fasting plasma glucose, Lipids in > 50 years.
- Full blood count and coagulation profile.
- Assessment of blood pressure by cuff blood pressure. If abnormal further assessment is indicated with either 24-hour monitoring or self-measurement by the patient at home.
- Chest X-ray and ECG
- Cardiac Echo and stress test if indicated i.e. donor >50 years or family history of heart disease
- Virology: Hepatitis B surface antigen, surface antibody and core antibody, and Hepatitis C, HIV, CMV, HSV, EBV and HTLV 1 & 2 antibodies
- Mantoux test.
- Renal imaging: Renal ultrasound is sufficient initially, as a renal angiography will be done closer to the operation time.
- Full Tissue Typing: blood from potential donor and recipient needs to be sent to the Red Cross by prior arrangement. (see Tissue Typing Procedure section)

At this stage a consultation with a renal physician should occur to review the results and determine suitability for kidney donation. If deemed appropriate consultation with a Liaison Psychiatrist should also be arranged.

Renal angiography by CT, MRA or conventional methods will need to be obtained
to define renal artery anatomy. If these investigations and consultations confirm the patient’s suitability, then they should undergo a formal pre-operative surgical consultation with the surgeon who will do the nephrectomy.

In some cases a formal family conference may be arranged with the donor and recipient and other significant family members, to ensure that both parties have received consistent information about the donor and transplant procedures.

Finally, repeat cross match between donor and recipient needs to be booked with the Tissue Typing Lab at NSW Red Cross Blood Transfusion Service 10 - 14 days prior to the operation.

A checklist for live donors can be found in Appendix B, recipients of live transplants will use the same Pretransplant checklist as the cadaveric recipients (Appendix A).

At the time of the final cross match, the recipient will be asked to sign the “Acknowledgement of Intent To Accept Renal Transplantation” form, which will be filed in the recipients notes. This form can be found in Appendix C.

The HighlySensitised Recipient

Sensitisation occurs when the patient is exposed to non-self HLA antigens from a previous transplant, blood transfusion, pregnancy or occasionally a precipitating cause is not found. Patel & Terasaki first demonstrated that this is a barrier to successful transplantation in 1969 (NEJM). Potential recipients who have a high level of antibodies have very long waiting times for deceased donor kidneys. Panel reactive antibodies (PRA) of >30% doubles the waiting time (UNOS data see www.unos.org). The potential of a successful transplant across these barriers results in advantages to the recipient in terms of survival, morbidity and quality of life and to the community in terms of considerable cost savings (Jordan S et al AJT 2003).

Stratifying the risk of rejection and immunosuppression:

The risks for transplantation can be assessed by currently available assays including Complement-dependent Cytotoxicity (CDC) assay, Flow cytometry and ELIZA/Microbead (Luminex) assays. These assays now define both the level of antibody and donor specificity and are useful in assessing risk.

The presence and strength of Anti-HLA specific antibodies have been shown to be important in determining graft outcomes in renal transplants (Mizutani, K et al AJT 2007) when using the sensitive Luminex technology. Even when CDC and Flow X-matches are negative there is an increased risk of antibody-mediated rejection (20% in donor specific antibody (DSA) positive and 2.5% in DSA negative recipients) although 12 month patient and graft survivals were not different (Patel AM et al AJT 2007).

Of course positive CDC is usually an unequivocal contraindication to successful
transplantation. To overcome these barriers a number of successful protocols have been applied: the John Hopkins protocol, in 2000, based on plasma exchange and CMV immunoglobulin (Montgomery et al Tx 2000); the Cedars-Sinai protocol using high dose IVIg (Jordan SC et al JASN 2004); and the Mayo Clinic protocol using a combination of agents (Dean PG et al Surgery 2005). Although the results of these protocol driven trials are widely published there are only a few randomised prospective studies available. The use of IVIg has been shown to be effective in a randomised, prospective trial for rescue in renal transplant steroid resistant rejection (Casadei DH et al Tx 2001). The NIH IGO2 study was a randomised, double blind, placebo controlled trial of IVIg vs placebo and showed decreased levels of antibodies in patients on the waiting list and improved transplantation rates with equivalent 2-year graft survival rates (Jordan SC, et al JASN 2004).

Stratifying the risk and therefore the pre-emptive therapy can reduce over-immunosuppression in the recipient yet provide acceptable success rates in terms of patient & graft survival. Monitoring, post transplant, with DSA testing and protocol biopsies can provide timely intervention to detect early Antibody Mediated Rejection (AMR). All the published protocols have applied some stratification to account for risk. The table below gives a consensus view of the risks.

<table>
<thead>
<tr>
<th>Risk</th>
<th>ABO Incompat</th>
<th>CDC T-cell</th>
<th>CDC B-cell</th>
<th>Flow T-cell</th>
<th>Flow B-cell</th>
<th>Luminex Class 1</th>
<th>Luminex Class 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>High</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
<td>+ DSA</td>
<td>+/- DSA</td>
</tr>
<tr>
<td>Medium</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+ DSA</td>
<td>+/- DSA</td>
</tr>
<tr>
<td>Low</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+ DSA</td>
</tr>
<tr>
<td>Very Low</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Unknown</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+ &amp; or +</td>
<td></td>
</tr>
</tbody>
</table>

DSA: donor specific antibody.

**Desensitisation Protocol based on Risk Stratification**

**Very Low Risk & Unknown**
- No induction therapy.
- IS with Tacrolimus, Mycophenolate, Steroid and Basiliximab
- Monitor post transplant for DSA by Luminex assay
- Protocol biopsy at day 5 – 7

**Low Risk**
- Induction with IVIg 1.5g/kg divided into three doses starting 7 days before transplant.
- Rituximab 375mg/m2, 10 days prior to transplant and check CD19 cells after 5 days
- IS with Tacrolimus, Mycophenolate, Steroids and Basiliximab
- Post transplant monitoring of DSA by Luminex (note for class 2 rituximab may interfere with the assay as B cells eliminated by rituximab, unless rituximab is eliminated by pronase treatment prior to testing (consult the TT lab).
- Protocol biopsy day 5 - 7
Medium Risk
- Induction with IVlg 1.5g/kg divided into three doses starting 7 days before transplant.
- Rituximab 375mg/m2, 10 days prior to transplant and check CD19 cells after 5 days
- Mycophenolate 1500mg/day divided dose starting 10 days prior to transplant
- Atgam induction starting day of transplant and continuing for 5 – 10 days
- IS with Tacrolimus, continuing Mycophenolate, Steroids
- Note DSA monitoring for Class 1 HLA antigens may not be possible in the presence of Atgam (TT lab is checking with the techs). So defer until Atgam has been completed. Also Rituximab as above.
- Protocol biopsy day 3 and 7

High Risk
- Plasma Exchange of 1.0 to 1.5 plasma volumes starting 10 days prior to transplant, every second day with replacement of 5% albumin and then IVlg 100mg/kg at the end of each exchange.
- Tacrolimus 0.2mg/kg/day and Mycophenolate 1500mg/day divided doses starting 10 days prior to transplant.
- Rituximab 375mg/m2, 10 days prior to transplant and check CD19 cells after 5 days
- Arrange repeat ABO and/or CDC Xmatch the day prior to transplant and proceed if negative or very low titre (< 1 in 16 dilution if ABO incompatible). If titre still high continue above for another 7 days and repeat ABO/CDC Xmatch.
- Atgam induction starting day of transplant and continuing for 5 – 10 days
- IS continuing with Tacrolimus, Mycophenolate plus Steroids
- Repeat Plasma Exchange and IVlg on days 3 and 5 post transplant. Note Atgam to be given post Plasma Exchange.
- Note DSA monitoring for Class 1 HLA antigens is not possible in the presence of Atgam. See above. Also Rituximab see above
- Protocol biopsy day 3, 7, 10 & 30 and at other times as indicated by graft function.

Treatment of Antibody Mediated Rejection
Biopsy confirmation that shows peritubular capillary vasculitis and/or glomerulitis with C4d staining. (The presence of tubulitis only, indicating T cell mediated rejection should be treated with conventional rejection therapy with Methylprednisolone and OKT3).
- Methylprednisolone 500mg IVI daily for 3 days
- Daily Plasma Exchange 1-1.5 volumes with 5% albumin replacement and 100mg/kg IVlg at the end of the exchange.
- Continue for 3 days and then re-biopsy on 4th day of therapy.
- If controlled, taper steroid back to 60mg/day and continue other IS.
- If uncontrolled continue Plasma Exchange daily for another 3 days and rebiopsy
- If still uncontrolled consider therapy with Rituximab if not given previously
Recommended Vaccinations

Generally vaccination should be undertaken prior to transplantation. Even then there is uncertainty in the immune response of patients with Kidney Failure and it may be useful to measure antibody titres post vaccination. Some live vaccines (BCG, Vaccinia, oral live cholera, live attenuated typhoid, Oral Polio Vaccine – OPV, MMR and varicella-zoster vaccines) should not be given to immunosuppressed individuals. In addition OPV should not be given to household contacts of such individuals – use IPV (inactivated poliovaccine) instead. Vi polysaccharide typhoid can be used in place of live attenuated typhoid.

Influenza A and B

Morbidity and mortality from influenza are increased in immunosuppressed patients. Therefore it is recommended that all patients who are on the transplant list or being assessed for a live transplant be vaccinated against influenza A and B annually.

Pneumococcus

Again increased morbidity and mortality are seen in immunosuppressed patients. Therefore, all patients should be vaccinated prior to transplantation. Revaccination is recommended every 5 years. Patients should receive either the 7-valent pneumococcal conjugate vaccine(7vPCV) if aged 9 years or less, or 23-valent pneumococcal polysaccharide vaccine (23VPPV) for older children and adults.

Hepatitis

All patients will be vaccinated for Hepatitis B prior to transplant. If vaccinated by their GP, correspondence will be required confirming this or recent HepBs Antibody test showing good response.

Tetanus

All patients should be vaccinated against Tetanus; booster shots should be given as required.

Varicella

All children and all adults without past evidence of infection will be vaccinated prior to transplantation.

Immunosuppressed travellers

General advice about consumption of potentially contaminated food and water and protection from mosquito bites should be given.

Avoid live vaccines of all types as detailed above.

Japanese encephalitis and rabies vaccines can be used when indicated.

Yellow fever vaccine should only be given to a person who must travel to a known infected area. If it is only a vaccination requirement from a health authority then a potential traveller should obtain a waiver from the health
authority or immigration.

References
Current information for travellers can be obtained from CDC at - http://www.cdc.gov/travel/index.htm or from WHO at http://www.who.int/ith
Pre-operative Renal Transplant Checklist

Prior to surgery the renal transplant recipient requires an extensive medical and nursing work up. In order to aid the nursing and medical staff in this process a Preoperative Renal Transplant Checklist has been developed as well as separate guidelines for the nursing and medical staff to follow. The checklist and guidelines can be found in Appendix D.

The registrar coordinating the transplant should give high priority to the following:

• Arrange for the kidney and papers to be delivered to the hospital - usually the blood bank
• Arrange a bed in the renal unit
• Notify the following people:
  • Vascular surgical registrar on call
  • Anaesthetist
  • Nursing Supervisor
  • Operating Theatres

• When organising theatre time remember that it takes a minimum of 2 hours to prepare a transplant patient for theatre, longer if they are to be dialysed prior to theatre. The theatre time should be coordinated with the vascular registrar, the theatre nurse and the renal unit.

• As soon as the patient arrives on the ward the pre-operative workup should begin with the staff aware of the total ischaemic time of the kidney.
SECTION 2: Transplant Therapy
Immunosuppressive Therapy

The primary goals of immunosuppression in transplantation include:

• decreasing the risk of acute rejection

• increasing short-term patient and graft survival

• increasing long-term graft survival

• meeting these goals safely whilst minimizing the toxic effects of the immunosuppressive agents used.

Currently 5 classes of drugs are used to suppress the immune response in organ transplant patients. These are calcineurin inhibitors (cyclosporin and tacrolimus), antimetabolites (azathioprine, mycophenolate mofetil and mycophenolic acid), the rapamycins (sirolimus and everolimus), corticosteroids and biologic therapies (polyclonal and monoclonal antibodies). Due to the different mechanisms of action of the drugs in each class, several agents may be prescribed concomitantly in order to achieve the best immunosuppressive coverage.

Standard Immunosuppressive Practice:

Currently the standard immunosuppressive practice for low risk living / cadaveric recipients is the use of a quadruple therapy regime. At present the most commonly used standard therapy consists of the following:

Recommended Standard Therapy

* Prednisolone
* Mycophenolate Mofetil or Mycophenolic Acid
* Calcineurin Inhibitor (Cyclosporine OR Tacrolimus)
* Basiliximab IV on days 0 (pre op) and 4 or Dacluzimab IV on Days 0 and 14.

High Risk Recipients

A patient is considered to be a high risk recipient if:

* 2\textsuperscript{nd} or subsequent graft, especially if first graft was lost due to early acute rejection
* High PRA\% (>50\%) - peak and/or current
* High risk recipient – one chance only
* +ve B cell X Match (Live donors only)

Antibody therapy should be considered as part of the induction regime for all high...
risk recipients. The choice of agent should be discussed with the renal physician prior to transplantation. Available antibody therapies are detailed further in the manual.

The variety of transplant drugs available allows numerous possibilities when considering combinations of immunosuppressive therapies to be used. Some other suggested alternative therapy combinations are listed below:

### Alternative Therapy Combinations

1. Prednisolone, Azathioprine and Cyclosporin
2. Prednisolone, Azathioprine and Tacrolimus
3. Prednisolone, Sirolimus and Cyclosporin
4. Prednisolone, Sirolimus and Tacrolimus
5. Prednisolone, Sirolimus and Mycophenolate Mofetil
6. Prednisolone, Sirolimus and Mycophenolic Acid
7. Prednisolone, Sirolimus and Azathioprine
8. Prednisolone, Everolimus and Mycophenolate Mofetil
9. Prednisolone, Everolimus and Azathioprine
10. Prednisolone, Everolimus and Cyclosporine
11. Prednisolone, Everolimus and Tacrolimus
12. Prednisolone, Everolimus and Mycophenolic Acid
13. Prednisolone, Mycophenolic Acid and Tacrolimus
14. Prednisolone, Mycophenolic Acid and Cyclosporin

When considering the immunosuppressive regime for the patient, please consult with the nephrologist in regard to current clinical trials available and the need for enrolment.

The mechanisms of action, common side effects, known drug interactions and recommended dosing for these drugs are detailed below.

### Calcineurin Inhibitors (CI)

Cyclosporin and Tacrolimus are both calcineurin inhibitors (CI). Their immunosuppressive effect depends on the formation of a complex with their cytoplasmic receptor proteins, cyclophilin for cyclosporine and tacrolimus-binding protein (FKBP) for tacrolimus. This complex binds with calcineurin. Inhibition of calcineurin impairs the expression of several critical cytokine genes that promote T-cell activation. These include those for interleukin-2 (IL-2), IL-4, interferon-gamma (IFN-gamma), and tumour necrosis factor-alpha (TNF-α). As a result of the calcineurin inhibition, cytokine production and lymphocyte proliferation are able to be limited.

Cyclosporin and Tacrolimus differ from their predecessor immunosuppressive
drugs by virtue of their selective inhibition of the immune response. They do not inhibit neutrophilic phagocytic activity as do corticosteroids (prednisone), nor do they suppress the bone marrow, as does azathioprine. When changing transplant recipients from one CI to another, no loading dose is required, Tacrolimus should be commenced at 0.15-0.2mg/kg/day (split dose to bd) and CyA commenced at 9-11mg/kg/day (split dose to bd).

Cyclosporin A (Neoral or Cicloral)

Cyclosporin A (CyA) is a fungal metabolite. The original formulation of cyclosporin, Sandimmun has largely been replaced by the micromulsion formulation Neoral. As Neoral is standard prescription, all comments below refer to this formulation and not the liquid Sandimmun.

Neoral is available as either capsule (0, 25, 50 and 100mg) or liquid (50ml bottles at 100mg/ml).

The bioavailability of CyA is quite variable. As a result it is generally not possible to determine the correct dose of CyA for individual patients without measuring blood levels. Since the conversion of patients from Sandimmun to Neoral, the CyA trough level has become less predictive of problems such as cyclosporine nephrotoxicity, or as an indicator of adequate immunosuppression. The two hour cyclosporine level (C2) is a useful supplement to the trough level.

Dosing and Monitoring:

Dosing of CyA in the immediate post operative period is determined by the measurement of daily (commencing day 2 post transplant) C0 and C2 levels. To ensure accurate, consistent CyA C2 monitoring, blood samples should be taken 2 hours post CyA dose, with a window of 15 minutes either side of the two hour post-dose time point. During the immediate post transplant period the dose of CyA will be witnessed by a staff member, the time it was taken will be documented and a level will be taken 2 hours later. Between day 7 and 10 an area under the curve (AUC) should be done using levels taken at C0, C2, C4 and C12.

C2 monitoring post discharge from hospital should be continued according to local protocols. It is recommended that C2 levels are taken for episodes of acute renal dysfunction, where the creatinine is suddenly elevated to 20-25% over baseline.

The aim is to achieve target blood levels of C2 by Day 5. Suggested C2 target blood levels are as follows:

<table>
<thead>
<tr>
<th>Time post–transplant (months)</th>
<th>C2 target blood concentrations (μg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1500 – 1700</td>
</tr>
<tr>
<td>2</td>
<td>1400 – 1500</td>
</tr>
<tr>
<td>3</td>
<td>1200 – 1400</td>
</tr>
<tr>
<td>4 – 6</td>
<td>1100 – 1200</td>
</tr>
<tr>
<td>7 – 12</td>
<td>850 – 1000</td>
</tr>
<tr>
<td>12 +</td>
<td>650 – 850</td>
</tr>
</tbody>
</table>
The formula to be used when adjusting the dose of Cylosporin A (provided the dose is not 50% above or below the old dose) is as follows:

**New Dose = Current Dose X \{\text{Desired C2 Target} / \text{Current C2 Level}\}**

**Side Effects:**
*CyA has numerous well documented side effects. Frequently seen side effects that should be taken into consideration when selecting the immunosuppressive regimen for the patient and that the patient should be regularly assessed post transplant for:*
- Nephrotoxicity
- Hypertension
- Neurotoxicity (tremors, paraesthesia, isolated seizures)
- Electrolyte and mineral imbalances (hyperkalaemia, hypomagnesaemia)
- Hyperlipidaemia
- Hepatotoxicity (increases in serum bilirubin and liver enzymes)
- Hirsuitism
- Gum hypertrophy
- Hyperuricaemia (gout)
- Neoplasia

CyA is metabolised by the cytochrome system (CYP3A) in the liver and gut and a large number of medications affect CyA blood levels. It is extremely important to measure CyA blood levels when medications that interact with CyA are being administered. A list of drugs known to interact with CyA are listed below:

**Drug Interactions:**
*Increase levels and increase toxicity: diltiazem, verapamil, allopurinol, steroids, oral contraceptive, macrolide antibiotics (e.g. erythromycin, clarithromycin), danazol, doxycycline, ketoconazole, fluconazole and itraconazole, metaclopramide and grapefruit juice.*
*Decrease levels and decrease effectiveness: carbamazepine, phenytoin, barbituates (e.g. phenobarbitone), ciprofloxacin, isoniazid, octreotide, rifampicin and St John’s Wort.*
*Increase Nephrotoxicity: Aminoglycosides (e.g. gentamicin, tobramycin), amphotericin, ciprofloxacin, colchicine and possibly NSAIDs (e.g. indomethacin, naproxen), angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists.*

**Tacrolimus (Prograf)**

Tacrolimus, like Sirolimus, is a macrolide antibiotic and like CyA is a calcineurin inhibitor. At the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP), which also binds Sirolimus and is responsible for the intracellular accumulation of the compound. A complex of tacrolimus-FKBP-12, calcium, calmodulin and calcineurin is formed and the phosphatase activity of calcineurin inhibited.
Absorption of Tacrolimus following oral administration can be rapid (within 0.5 hours) or can occur continually over a prolonged period of time, resulting in a relatively flat absorption profile. The half-life of tacrolimus varies between 3.5 and 40.5 hours. Trough levels therefore correlate well with the AUC.

**Contraindications:**
Tacrolimus is contra-indicated in patients hypersensitive to tacrolimus or other macrolides.

**Dosing and Monitoring:**
Tacrolimus is available in 0.5, 1 and 5mg capsules. The recommended starting dose for adults is 0.2mg/kg/day given in 2 divided doses and for children 0.3mg/kg/day given in 2 divided doses.

Monitoring of tacrolimus levels is recommended due to the toxicity and narrow therapeutic range of the drug. Recommended trough levels after transplantation are:

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Trough Level</th>
<th>μg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 – Week 4</td>
<td>10 – 15</td>
<td></td>
</tr>
<tr>
<td>Week 4 – Week 26</td>
<td>8 – 12</td>
<td></td>
</tr>
<tr>
<td>6 - 12 months</td>
<td>5-10</td>
<td></td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td>3 - 7</td>
<td></td>
</tr>
</tbody>
</table>

Note: If Tacrolimus is used in conjunction with Sirolimus the target levels for Tacrolimus are lower than the above by one step.

**Side Effects:**
- Nephrotoxicity
- Neurotoxicity (tremor, headache, insomnia, isolated seizures)
- Electrolyte and mineral imbalances (hyperkalaemia, hypomagnasaemia)
- Glucose intolerance (Diabetes)
- Gastrointestinal toxicity
- Cardiotoxicity

**Drug Interactions:**
**Agents that increase tacrolimus concentrations:** Erythromycin, Clotrimazole, Fluconazole, Itraconazole, Chloramphenicol, Ketoconazole, Diltiazem, Nifedipine, Cyclosporin, Verapamil, Cimetidine, Amphotericin B, Nefazodone, Sequinavir, Ritonavir, Nelfinavir, Clarithromycin and Omeprazole and Grapefruit juice.

**Agents that decrease tacrolimus concentration:** Drugs that are metabolized through the CYP3A enzyme system, Aluminum Hydroxide, Magnesium oxide, Sodium bicarbonate, Rifampicin and Dexamethasone.
Antimetabolites

Mycophenolate Mofetil (Cellcept)

Mycophenolate Mofetil (MMF) helps to prevent and treat graft rejection by inhibiting lymphocyte proliferation (both B cells and T cells). It is commonly used as a replacement for Azathioprine in a triple therapy regime.

Mycophenolate is converted to the active compound mycophenolic acid (MPA), which inhibits inosine monophosphate dehydrogenase (IMPDH), a key enzyme in purine synthesis. Without sufficient purine production, DNA and RNA synthesis (and related cell reproduction activities) are inhibited. Although all of the body's cells require purines to reproduce, non-lymphocyte cells are capable of reproducing in the absence of IMPDH via a rescue pathway (adenosine monophosphate DH). This allows mycophenolate to specifically inhibit T and B cell proliferation, without affecting the activity of other cells.

Mycophenolate differs radically in its mode of action from the calcineurin inhibitors and sirolimus in that it does not affect signaling pathways or the more proximal events following antigen recognition. Mycophenolate differs from azathioprine because of its selective effects on lymphocytes.

The half-life of mycophenolate is 12 hours. Following oral and intravenous administration, mycophenolate undergoes rapid and extensive absorption and complete presystemic metabolism by cleavage of the side ester to the active metabolite mycophenolic acid (MPA). There is no accumulation of MPA in hepatic or renal impairment and neither mycophenolate nor MPA is dialyzed.

**Dosing and Monitoring:**
Mycophenolate Mofetil is available in 250mg capsules and tablets, 500 mg tablets and 500mg intravenous infusion. The recommended dose for adults for all of these formulations is 1gm twice daily. The recommended dose for children of 2-18 years of either formulation is 500-700mg/m² twice daily with a maximum of 2g per day. Intravenous mycophenolate is rarely used. Guidelines for administration can be found in Appendix E.

Currently, concentrations of MPA are not routinely monitored in patients receiving mycophenolate. Further investigations are needed in regards to therapeutic drug monitoring of MPA before definitive recommendations can be made.

Haematology blood cell counts should be performed regularly. If significant neutropaenia develops then the dose should be interrupted or reduced. Mycophenolate doses can be safely reduced or held for short periods in the event of side effects as long as calcineurin inhibitors and prednisolone doses are maintained. Patients with active CMV disease may need their mycophenolate dose reviewed.

**Side Effects:**
Diarrhea, pancytopaenia, nausea, vomiting, bloating dyspepsia.

**Drug Interactions:**
- Tacrolimus – dose reduction of mycophenolate may be required with concomitant Tacrolimus treatment. (In adults reduce to 1.5g / day.)
• Azathioprine – concomitant administration may cause bone marrow suppression
• Acyclovir – may increase level
• Antacids with magnesium and aluminium hydroxide – may decrease level
• Cholestyramine – may decrease the level

Use in Pregnancy: - Category D
Adverse effects on foetal growth and development in experimental animals.

Use in lactation: It is not known if it is excreted in human breast milk but studies in experimental animals have shown excretion.

Mycophenolic Acid (Myfortic)

Mycophenolic Acid (MPA) helps to prevent and treat graft rejection by inhibiting lymphocyte proliferation (both B and T cells). It’s mechanism of action is similar to that of MMF (see above), however it is thought to reduce the incidence of gastrointestinal (GI) adverse events. This has not been supported by the literature, which has found MPA to be therapeutically equivalent to MMF (Salvadori et al) but no statistical significant differences in GI complications between MMF and MPA (Budde et al). It can be used as an alternative for Mycophenolate Mofetil in the triple immunosuppressive regime which is commonly used post transplant.

Dosing and monitoring
Mycophenolic acid is available in 360mg and 180mg tablets. The recommended dose for adults is 720mg twice daily. As with MMF, concentrations of MPA are not routinely monitored in patients receiving mycophenolate. Further investigations are needed in regards to therapeutic drug monitoring of MPA before definitive recommendations can be made.

Side Effects:
Leucopaenia, anaemia, thrombocytopaenia, diarrhoea, abnormal liver function tests and bloating.

Drug interactions:
• Tacrolimus – dose reduction of mycophenolic acid is usually required when switching from Cyclosporin to Tacrolimus treatment.
• Azathioprine - It is recommended that Myfortic not be administered concomitantly with azathioprine because such concomitant administration has not been studied.
• Acyclovir – may increase levels
• Antacids with magnesium and aluminium hydroxide – may decrease level
• Cholestyramine – may decrease the level

Use in Pregnancy: - Category D
Adverse effects on foetal growth and development in experimental animals.

Use in lactation: It is not known if it is excreted in human breast milk but studies in experimental animals have shown excretion.

Azathioprine (Aza)
AZA is a broad myelocyte suppressant. It inhibits the proliferation of promyelocytes in the bone marrow, and as a result decreases the number of circulatory monocytes
capable of differentiating into macrophages. Thus, it is a powerful inhibitor of the primary immune response and is valuable in preventing the onset of acute rejection. It is not effective in the treatment of rejection episodes themselves.

**Dosing and Monitoring:**
- AZA is available as a tablet (25mg and 50mg) or intravenous infusion. The recommended loading dose for adults is up to 3 mg/kg/day and 2 mg/kg/day for children. The maintenance dose for adults and children is 1 – 4 mg/kg/day orally when used as the primary immunosuppressant or 1- 2 mg/kg if used as an adjunctive therapy with a calcineurin inhibitor.
- Due to the similar activity profiles and potential for increased toxicity, combined use of AZA and mycophenolate is not recommended.
- Azathioprine does not require the monitoring of blood concentrations during therapy. However, patients must be monitored for evidence of potential bone marrow suppression. Full blood counts should be done each visit according to the follow up protocol.

Because AZA has been associated with hepatitis, monitoring of liver enzymes and bilirubin levels should also be performed.

**Side Effects**
Neutropaenia, leucopaenia and thrombocytopenia, neoplasia, alopecia, anaemia, nausea and vomiting, hypersensitivity reactions, hepatotoxicity, cholestasis and pancreatitis (rarely seen).

**Drug Interactions:**
- Allopurinol – interferes with the metabolism of AZA and can lead to AZA accumulation (increased levels). If Allopurinol and AZA are to be used together, the dose of AZA should be reduced by one-third to one-quarter of the usual dose.
- Products that affect leukocyte production e.g. co-trimoxazole and ACE inhibitors.
- Warfarin

**Rapamycins**

**Sirolimus (Rapamune®)**
Sirolimus (SRL) was registered for use as an anti-rejection therapy in Australia in 2002. Its immunosuppressive mechanism resides in its ability to block cytokine-simulated proliferation of T lymphocytes by interfering with their progression through the cell cycle. Sirolimus also has antiproliferative effects on a variety of other tissues and may affect wound healing and recovery from ATN.

Sirolimus may be used in the management of acute and chronic graft rejection, reducing the need for corticosteroids and cyclosporine. Due to its mode of action it can be complementary to both CI’s and mycophenolate. The terminal half-life in stable renal transplant patients after multiple oral doses is 62 +/- 16 hours. The effective half-life, however is shorter and mean steady-state concentrations are achieved after 5 to 7 days.

**Dosing Monitoring:**
Sirolimus is available in 1 and 2mg tablets (these should not be crushed) and 1mg/ml liquid solution. If being used in combination therapy with a calcineurin, a 6 mg loading dose (for patients greater than 40kg) is administered on the first day of treatment, and a maintenance dose of 2mg/day thereafter.
The appropriate loading dose for younger children is unknown. The recommended maintenance dose for those less than 40kg is 1mg/m\(^2\)/day, with adjustments made according to levels.

**Note:** If Sirolimus is used in conjunction with CyA the dose should be given 4 hours after the last dose of CyA.

Due to the long half-life of Sirolimus, trough levels accurately reflect exposure to the drug. A therapeutic trough level of 4-12ng/mL is recommended for patients receiving a calcineurin in combination therapy. For patients in whom a CI is not used, an initial trough level of 12 to 20 ng/mL is recommended. Trough level testing for Sirolimus is now done by SEALS based on an Immunoassay, which gives slightly higher levels than the previous HPLC method. The table below gives target levels by immunoassay.

Renal function should be monitored closely during concomitant administration of Sirolimus and calcineurin inhibitors (particularly CyA) because of potentiation of nephrotoxicity. Appropriate adjustment to the immunosuppressive regimen should be considered in patients with elevated serum creatinine levels.

For patients who are switched to Sirolimus due to intolerance of CI’s, a loading dose (depending on body size and time post-transplant) should be given on the morning after the last dose of the CI, which should then be discontinued. A maintenance dose should be commenced with a trough level to be taken on day 5-7 and as required until the desired trough level of has been reached. This abrupt switch avoids nephrotoxicity when used in combination with CNI and is associated with very low acute rejection rates following switch.

Target trough levels may be higher in individuals deemed to be at high risk e.g. rejection episode in last 3 months.

A table of recommended trough levels for patients on Sirolimus follows. Note that Immunoassay Tests have mostly replaced HPLC for sirolimus levels. The Immunoassy method is referred to below and reads about 20% higher than HPLC method.

### Sirolimus loading doses, maintenance doses and trough levels by patient type

<table>
<thead>
<tr>
<th>Time Post Transplant (months)</th>
<th>Loading Dose# Day 1</th>
<th>Initial Maintenance Dose Day 2 - 7</th>
<th>Target trough level (first measure day 5 - 7, then weekly till steady state)</th>
<th>Maintenance trough level over time</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3</td>
<td>8 – 10 mg</td>
<td>5 – 8 mg</td>
<td>12 – 18 ng/ml</td>
<td></td>
</tr>
<tr>
<td>3 - 12</td>
<td>8 – 10 mg</td>
<td>4 – 6 mg</td>
<td>10 – 15 ng/ml</td>
<td></td>
</tr>
<tr>
<td>&gt; 12</td>
<td>8 – 10 mg\‡</td>
<td>2 – 5 mg</td>
<td>5 – 10 ng/ml</td>
<td></td>
</tr>
<tr>
<td>&gt; 12 and high immunological risk</td>
<td>8 – 10 mg</td>
<td>5 – 8 mg</td>
<td>10 – 18 ng/ml</td>
<td>NA</td>
</tr>
</tbody>
</table>

\# The last dose of the CNI to be taken on Day 0. The CNI dose is not taken on Day 1.
\‡For very long stable patients the Loading Dose may be omitted.
Immunoassay method ~ 20% lower with HPLC. Levels should be measured weekly until stable, then every 1 to 3 months thereafter. Since sirolimus has a long half-life (about 5 days) more frequent measurements of trough levels are unnecessary.

When adjusting the maintenance dose of SRL the following formula is used:

New Maintenance Dose = Current maintenance dose X (desired target level divided by current trough)

**Side Effects:**
Hyperlipidaemia, lymphocele, peripheral oedema, anaemia, thrombocytopaenia, acne, arthralgia, hypokalaemia, increased lactate dehydrogenase (LDH) and rarely aseptic pneumonitis.

**Drug Interactions:**
**Agents that increase Sirolimus levels:** CYP3A4 inhibitors, cyclosporine, tacrolimus, diltiazem, nicardipine, verapamil, macrolide antibiotics, cisapride, metaclopramide, cimetidine, protease inhibitors, ketoconazole, danazol, erythromycin, bromocriptine and grapefruit juice.

**Acceptable calcium channel blockers are nifedipine and amlodipine.**

**Agents that decrease Sirolimus levels:** Rifampicin (CYP3A4 inducer), rifabutin, carbamazepine, phenobarbitone, phenytoin, octreotide (oral formulation only) and St John’s Wort.

**Mycophenolate/Azathioprine:** The use of sirolimus in combination with antiproliferative agents may cause myelosuppression and dose adjustment of both may be needed

**Everolimus (Certican®)**

Everolimus was registered for use as an anti-rejection therapy in Australia in 2005. Everolimus is derived from sirolimus and therefore its immunosuppressive mechanism is identical to that of sirolimus (see above Sirolimus section for mechanism of action).

Everolimus may be used in the management of acute and chronic graft rejection.

Everolimus is metabolized by the cytochrome P450 isoenzyme CYP3A4 and the P-glycoprotein countertransporter. The terminal half-life in stable renal transplant patients after multiple oral doses is 28 +/- 7 hours. Mean steady-state concentrations were reached by 4 to 6 days.

Like sirolimus, everolimus may potentiate cyclosporine renal toxicity through pharmacokinetic mechanisms. However, because of the synergistic potential between everolimus and cyclosporine, lower doses of cyclosporine may be used without loss of efficacy.

**Dosing Monitoring:**
Everolimus is available in 0.25mg, 0.5mg and 0.75mg tablets, which are not to be crushed.

The recommended daily dose of is 1.5mg/day, which is divided into two separate
doses. Everolimus may be administered in conjunction with the twice daily cyclosporine dose.

A loading dose of 0.75mg should be administered pre operatively.

Due to the relatively long half-life of everolimus, trough blood levels are used to monitor exposure to the drug. A therapeutic trough level of 3 – 8 ng/ml is recommended for patients receiving triple therapy. In clinical trials, levels below 3ng/mL have been associated with increased acute rejection rates and graft loss. Trough level testing for everolimus is available at SEALS.

Note: Everolimus may potentiate the renal toxicity of cyclosporine. Dose reduction of cyclosporine should be considered in patients with an elevated serum creatinine. Cyclosporine doses should not be reduced until an everolimus trough level of >3ng/ml has been reached.

Side Effects:
- Hyperlipidaemia
- Lymphocele
- Arthralgia
- Thrombocytopenia
- Anaemia
- Oedema
- Acne
- Hepatotoxicity
- Nephrotoxicity when used in conjunction with full strength Cyclosporine

Drug Interactions:

Agents that increase Certican levels: CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, erythromycin and ritonavir), cisapride astemizole, terfenadine.

Agents that decrease Certican levels: Rifampicin (CYP3A4 inducer), rifabutin, carbamazepine, phenobarbitone, phenytoin, octreotide (oral formulation only) and St John’s Wort.

Mycophenolate/Azathioprine: The use of everolimus in combination with antiproliferative agents may cause myelosuppression and dose adjustment of both may be needed.

References: 62

Corticosteroids

Corticosteroids achieve their effects by binding to steroid receptors on immune cells to block certain functions, such as the production of cytokines and gene expression. Corticosteroids exert their most critical immunosuppressive effect by blocking T-cell-derived and antigen-presenting cell-derived cytokine and cytokine-receptor expression. They inhibit the function of dendritic cells, which are the most important of the antigen-presenting cells.

The use of corticosteroids significantly reduces the number of circulating lymphocytes. Consequently, immunocompetent lymphocytes are not available in the general circulation to recognize and respond to foreign antigens from grafts. Any lymphocytes present at the graft site are inhibited from adhering to the graft tissues by the effects
of corticosteroids.

Corticosteroids also prevent macrophages from responding to interleukin-8, the lymphokine that normally causes macrophages to congregate in an inflamed region.

**Dosing and Monitoring:**
Corticosteroid therapy does not require monitoring of blood levels. Recommended steroid therapy for adults and children is as follows:

**Adults**
**Starting dose is 0.5mg/Kg/Day then reduced to:**
- **Week 1**  30mg/day
- **Week 2**  25 mg/day
- **Week 3**  20mg/day

Then reduce by 2.5mg/week until 10mg/day is reached. It is the aim that steroids be reduced to 10mg/day by 3 months.

**Children**
2mg/kg IV methylprednisolone daily for the first 2 days, changing to oral prednisone when tolerating oral medications. Then to be tapered as per the following schedule:

<table>
<thead>
<tr>
<th>Prednisone taper schedule for children:</th>
<th>Weight &lt; 20 kg</th>
<th>Weight &gt; 20 kg</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 3- 7</td>
<td>2 mg/kg</td>
<td>1.5 mg/kg</td>
<td>80mg</td>
</tr>
<tr>
<td>Days 7-14</td>
<td>1.5 mg/kg</td>
<td>1 mg/kg</td>
<td>60mg</td>
</tr>
<tr>
<td>Days 15-21</td>
<td>1 mg/kg</td>
<td>0.75 mg/kg</td>
<td>45mg</td>
</tr>
<tr>
<td>Days 22-28</td>
<td>0.7 mg/kg</td>
<td>0.5 mg/kg</td>
<td>40mg</td>
</tr>
<tr>
<td>Week 5</td>
<td>0.6 mg/kg</td>
<td>0.4 mg/kg</td>
<td>35mg</td>
</tr>
<tr>
<td>Week 6</td>
<td>0.5 mg/kg</td>
<td>0.3 mg/kg</td>
<td>25mg</td>
</tr>
<tr>
<td>Week 7 – 8</td>
<td>0.4 mg/kg</td>
<td>0.25 mg/kg</td>
<td>20mg</td>
</tr>
<tr>
<td>Month 3</td>
<td>0.3 mg/kg</td>
<td>0.2 mg/kg</td>
<td>15mg</td>
</tr>
<tr>
<td>Month 4</td>
<td>0.2 mg/kg</td>
<td>0.15-0.2 mg/kg</td>
<td>10mg</td>
</tr>
</tbody>
</table>

The taper may be modified for high risk transplant patients. If graft function is stable and there is still growth potential (and no previous rejection episodes) then alternate day dosing should be considered after 5 months.

Excessive corticosteroid doses and long term use are associated with a range of effects, some of which are listed below.

**Side Effects:**
* Endocrine effects: hypertension, adrenal suppression, effects on menstruation, weight gain, symptoms of Cushing’s syndrome, hyperglycaemia, impaired glucose intolerance and increased appetite.
* Electrolyte and metabolic disturbances, including hypokalaemia, fluid retention, and hypercholesterolaemia.
Neuropsychiatric effects, including aggravation of pre-existing conditions (e.g. schizophrenia, epilepsy) or abnormal elevation or depression of mood.

* Increased susceptibility to infection.

* Effects on musculoskeletal system, including osteoporosis, avascular necrosis and proximal myopathy.

* Cataracts / Glaucoma

* Effects on the skin, including acne, impaired wound healing, thinning of the skin, easy bruising and hirsutism.

* Effects on the gastrointestinal system, including indigestion, nausea, vomiting, gastritis and ulcer development.

## Biologic Therapies

### Monoclonal Antibodies

Monoclonal antibodies (Mabs) are preparations that contain antibodies produced from the clones of a single cell. Some monoclonal antibodies are chimeric which means that human and mouse elements have been used in their production. Currently three monoclonal antibody products are widely available for use in organ transplantation:

* OKT3 (Orthoclone T3®)
* Basiliximab (Simulect®)
* Daclizumab (Zenepax®)

**OKT3 (Orthoclone T3®)**

OKT3 is xenogeneic because the whole antibody is of murine origin. OKT3 is able to bind to T cells, resulting in a rapid and profound reduction in the number of T cells circulating in the blood, which is caused by complement-mediated lysis and trapping of the cells.

OKT3 is indicated for the treatment of acute allograft vascular rejection in renal transplant patients. It may also be used in the treatment of steroid-resistant acute rejection episodes.

**Contraindications:**

OKT3 should not be used in patients who:

* Have a previously demonstrated hypersensitivity such as anaphylaxis, serum sickness, or skin rash following OKT3 or other murine products.

* Are in fluid overload, as evidenced by chest x-ray or a greater than 3% weight gain within the week prior to planned OKT3

* Have uncontrolled hypertension

* Have a history of seizures or are predisposed to seizures

**Dosing and Monitoring:**

Because of its cytokine release action patients are prone to acute pulmonary oedema during first use. It is important therefore to ensure that the patient is not fluid
overloaded. If necessary administer IV diuretics or haemofiltration prior to use in patients with overt fluid overload.

**Adult:**
**Dose:** 5 mg IV daily for 7 - 14 days. Detailed administration instructions can be found in section 3 of the manual under the heading of REJECTION, subheading of Treatment.

**Paediatric:**
* If > 30kg the first dose will be 2.5mg and subsequent doses are 5mg daily.
* If < 30kg the first dose will be 1.5mg and subsequent doses are 2.5mg/day.
* Cyclosporin, mycophenolate and Imuran doses are to be reduced by 50% or stopped during the course of OKT3.

**Drug Interactions:**
Usage of concomitant medications (azathioprine, corticosteroids and cyclosporin) may increase the incidence and severity of neuropsychiatric, infectious, nephrotoxic, thrombotic and neoplastic events reported in patients treated with OKT3. Simultaneous use of indomethacin and OKT3 may increase the severity of encephalopathic and other CNS adverse events.

**Side Effects:**
Fever, chills, pulmonary oedema, dyspnoea, wheezing, chest pain, nausea, vomiting, diarrhoea, anaphylaxis, hypotension, tachycardia, tremor, headache and weakness.

**BASILIXIMAB (Simulect®)**
Basiliximab is a murine/human chimeric anti-Interleukin 2 monoclonal antibody. Basiliximab achieves its effects by binding to the surface of the activated T lymphocytes via the IL-2 receptor and inhibiting IL-2 mediated activation of lymphocytes. Basiliximab is indicated for the prophylaxis of acute organ rejection in renal transplantation and is now used routinely with a standard immunosuppressive regime. The terminal half-life is 7.2 +/- 3.2 days.

**Dosing and Monitoring:**
Adult:- 20mg IV, prior to or within 2 hours of implantation and on day 4 following surgery.
Paediatric:-
* < 35kg: 12mg/m² IV within 2 hours of implantation and on day 4 following surgery.
* > 35kg: same as adult dosing.
For children, IV promethazine (0.2-0.5mg/kg/dose – maximum dose 12.5mg) is given prior to second dose. For the second dose, IV methylprednisolone, 2 mg/kg should be given and the daily oral dose of steroids should be withheld. If a hypersensitivity reaction occurs then the second dose of Basiliximab should be withheld.

Basiliximab is administered as either an IV infusion (in 50 mls 5% Dextrose or 0.9% Saline) over 20-30 minutes or as a bolus push. It may be given via a peripheral or central line.
Side Effects:
Human anti-mouse antibody (HAMA) response, infections and anaphylactic reactions (rare). Due to the risk of anaphylaxis a resuscitation trolley should always be available at the place of administration.

Drug Interactions:
Because basiliximab is an immunoglobulin, no metabolic interactions are to be expected with basiliximab.

**RITUXIMAB (Mabthera®)**

Rituximab is a high-affinity, chimeric murine/human monoclonal antibody to CD20, a B cell surface antigen. It is a depleting antibody with a prolonged action - many months to years following a single course of therapy. In depleting B cells it directly inhibits B cell proliferation by antibody-mediated, cell-mediated and complement-mediated cytotoxicity. See Pescovic M 2004 for review. Although there are no controlled trials, as yet, of its use in transplantation, there are many case series of success in both pre-emptive use in patients with high PRA and in therapy of resistant antibody-mediated rejection (Becker YT et al 2004).

**Dosing and Monitoring:**
*Adult:* 375mg/m$^2$ as a single IV infusion  
*Paediatric:* 375 mg/m$^2$ - same as adult

**Side Effects:**
Fever is the most common (43%) followed by bronchospasm and hypotension (<10%) (Maloney DG, 1994). Symptoms are usually mild and respond to temporary cessation of infusion and recommencement at a slower rate. As yet no long term toxicity has been reported

**Polyclonal Antibodies**

Polyclonal antibodies bind to lymphocytes and usually result in rapid and profound lymphopenia. The number of T cells gradually increases following discontinuation of treatment, but the proliferative response of T cells continues to be impaired.

**Anti-Thymocyte Globulin (ATGAM®)**

Anti-lymphocyte antibodies are obtained from the injection of human thymocytes into horses. ATG can be used as an induction agent or for treatment of acute rejection episodes. It is contraindicated in patients who have experienced a previous reaction to ATG or any other equine gamma globulin, active infections, thrombocytopenia and pregnancy. In a small clinical study, ATGAM administered with other immunosuppressive therapy and measured as horse IgG had a serum half-life of 5.7 +/- 3 days.

**Dose and Monitoring:**
See also ‘Medication Administration’ in Nursing Section  
*Adults:*

**Induction Therapy:**
Recommended dose is 15mg/kg daily for 14 days, then on alternate days for a further
14 days. The first dose of Atgam should be administered within 24 hours before or after transplant.

Acute Rejection Therapy:
Recommended dose is 10 – 15mg/kg daily for 14 days. Additional alternate day therapy as above may be given.

Paediatrics
Acute Rejection Therapy:
5mg/kg to be given daily for 14 days. Check hospital policy for pre med to be given prior to administration and observations required.
The total daily dose of ATGAM is added to 0.9% saline and infused over at least four hours via a peripheral cannula, or dedicated line.

Side Effects:
Fever, rigor, leucopaenia, thrombocytopaenia, dermatologic reactions and anaphylaxis (rare).

Drug Interactions:
Atgam is not recommended for use in glucose or highly acidic solutions.

**Intravenous Immunoglobulin**

From POW Clinical Procedures Manual – see website for full details
Revised here to update criteria for Use published by NBA March 2008.

5.10 Intravenous Immunoglobulins (IVIG’s)
Intravenous Immunoglobulin is produced by the fractionation of pooled plasma to produce IgG concentrates. See Criteria for Use of IVIg at www.nba.gov.au/ivig/index.html revised March 2008

Kidney Transplant
• Pre-transplant when an antibody or antibodies prevent transplantation (donor specific anti-HLA or anti-blood group)
• Post-transplantation
• To treat steroid-resistant acute rejection which may be cellular or antibody mediated
• For prevention and/or treatment of rejection where other therapies are contraindicated or pose a threat to the patient or graft

The IVIG supplied will depend on the indication for use, and availability of products from Australian Red Cross Blood Service. Indications and category availability can be viewed on www.nba.gov.au/ivig/index.html. The products currently available are Intragam P®, Octagam® or Sandoglobulin®. If a product is declined by ARCBS for a specific patient, application for Individual Patient Use (IPU) can be made through POWH Drug and Therapeutics Committee. The administration of each product varies slightly and is outlined in Table 7 and Table 8 below.
### TABLE 7: Description of available IVIGs

<table>
<thead>
<tr>
<th>Description</th>
<th>Intragam P</th>
<th>Sandoglobulin</th>
<th>Octagam</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presentation</strong></td>
<td>3g (50mL) or 12g (200mL)</td>
<td>6g (50mL) or 12g (100mL)</td>
<td>2.5g (50mL) 5g (100mL) 10g (200mL)</td>
</tr>
<tr>
<td><strong>Additives</strong></td>
<td>Maltose</td>
<td>Sucrose</td>
<td>Maltose</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td>2-8o for up to 2 years &lt;25o and used within 3 months</td>
<td>2-8o (protect from light)</td>
<td>&lt;25o for up to 2 years</td>
</tr>
<tr>
<td><strong>Available from</strong></td>
<td>Blood Bank</td>
<td>Pharmacy</td>
<td>Pharmacy</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>0.4 - 0.6g/kg every 4 weeks 2g/kg total over 2-5 days</td>
<td>0.1-0.3g/kg every 3 - 4 weeks 0.4g/kg daily for 5 days</td>
<td>0.4-0.8g/kg starting dose then, 0.2 – 0.8g/kg every 3 - 4 weeks 0.8 to 1g/kg, day 1 repeated day 3 if needed or 0.4 g/kg daily 2-5 days</td>
</tr>
<tr>
<td>Autoimmune ITP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cautions / Contraindications</strong></td>
<td>Do not shake</td>
<td>Avoid Sandoglobulin in patients with renal impairment. Use Intragam P in patients with selective IgA deficiency and anti-IgA antibodies. Maltose will cause falsely elevated glucose reading on blood and urine test strips. Check product information for the test strips in use to ensure they are appropriate for use with maltose containing parenteral products.</td>
<td></td>
</tr>
</tbody>
</table>

5.10.1 Guidelines for administration
- IVIGs must be ordered by a MO.
- Patient must have a signed written consent for blood product administration.
- Oxygen and suction and emergency equipment must be readily available for use during the infusion.
- IVIGs must be checked as per Clinical Procedure Manual: Medication administration procedures and the batch number recorded in the patients medical records.
- Do not shake. This can destroy IgG molecules in the protein rich formula.
- Prime giving set with normal saline or 5% Glucose and administer via an infusion pump. Doses are usually rounded off to the nearest bottle size; however any unused portion should be discarded.
- A new giving set must be used for the infusion and discarded once the infusion is complete as per Administration sets and filters.
- Complete the blood product usage slip. Place the yellow copy in the medical records and return the white copy to blood bank.
<table>
<thead>
<tr>
<th>Infusion Type</th>
<th>Infusion Rate</th>
<th>Observations</th>
</tr>
</thead>
</table>
| **Initial Infusion**<br>Intragam P<br>Octagam<br>Sandoglobulin | Commence at 60mL/hr for 15 minutes,<br>*Increase rate by 60mL/hr every 15 minutes*<br>Maximum rate 240mL/hr<br>Commence at 60mL/hr for 30 minutes<br>*Increase rate by 60mL/hr every 30 minutes*<br>Maximum rate 300mL/hr<br>Commence at 15mL/hr for 60 minutes<br>*Increase rate by 15mL/hr every 30 minutes*<br>Maximum rate 60mL/hr | Rate increases should only occur if tolerated well. (Observations must be performed prior to each rate increase).<br>*Do not* increase rate if patient displays any adverse symptoms. (Including alteration in observations). See Table 9 for actions.<br>BP, Temp, Pulse and Resps<br>**Baseline**<br>*Then,*
Every 15 minutes until maximum rate reached
*Then,*
hourly until complete<br>Acutely ill or febrile patients will frequently not reach the maximum rate. Infusion rates for these patients should be raised cautiously. |
| **Subsequent Infusion** (within 8 weeks)<br>Intragam P<br>Octagam<br>Sandoglobulin | Commence at 60mL/hr for 15 minutes<br>*Increase to previously tolerated rate*<br>Maximum rate 240mL/hr<br>Commence at 60mL/hr for 30 minutes<br>*Increase to previously tolerated rate*<br>Maximum rate 300mL/hr<br>Commence at 30mL/hr for 30 minutes<br>*Increase by previously tolerated rate*<br>Maximum rate 60mL/hr |
5.10.2 Side Effects of Intravenous Immunoglobulins

Reactions and adverse events to IVIGs will more likely occur on first infusions, or infusions after a long break, than on repeat infusions. Symptoms are diverse and will range from mild to severe. Table 9 indicates symptoms, potential causes and management strategies.

**TABLE 9: Side Effects**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Symptoms</th>
<th>Causes</th>
<th>Action/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-Moderate</td>
<td>• Headache</td>
<td>Usually infusion rate too high</td>
<td>• Stop the infusion</td>
</tr>
<tr>
<td></td>
<td>• Facial flushing / pallor</td>
<td>(symptoms resolve within 5–10 mins</td>
<td>• Notify a MO to review patient</td>
</tr>
<tr>
<td></td>
<td>• Non-urticarial skin rash</td>
<td>of stopping infusion)</td>
<td>• Antihistamine may be required</td>
</tr>
<tr>
<td></td>
<td>• Itching</td>
<td></td>
<td>• If symptoms resolve, recommence and continue the infusion at a lower rate for</td>
</tr>
<tr>
<td></td>
<td>• Nausea and vomiting</td>
<td></td>
<td>the remainder of the infusion.</td>
</tr>
<tr>
<td></td>
<td>• Slight fall in BP (&lt; 10-15mmHg, no SOB)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Abdominal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pain at injection site</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Chills</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Usually infusion rate too high (symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Stop infusion and call 777</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Treat with oxygen and drugs (adrenaline,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• NOTE: If anaphylactic reaction occurs do not</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Stop infusion and call 777</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Treat with oxygen and drugs (adrenaline,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Complement release by macrophages as part</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Caution should be used in patients with a</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Caution should be used in patients with a</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Management of symptoms as ordered following</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Usually transient</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>• Precipitous fall in BP (&gt; 10-15mm/Hg with</td>
<td>Immune response</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dyspnoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Chest tightness</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Anaphylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed Onset</td>
<td>• Nausea</td>
<td>Complement release by macrophages</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Vomiting</td>
<td>as part of inflammatory response,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Chest pain</td>
<td>in the presence of infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Rigors</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Aching legs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Flu like symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Usually transient</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Can cause red cell sensitisation and difficulty in cross matching.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cytomegalovirus: Prophylaxis and Therapy

Introduction

Cytomegalovirus (CMV) is a common Herpes Virus infecting 30 – 100% of the adult population depending on the country of residence. Without prophylaxis, symptomatic infection will develop post transplantation in 60 – 90% of patients who have a negative titre (Recipient negative - R –ve) and who receive an organ from a donor with a positive IgG titre for CMV (Donor positive - D +ve). If the recipient has been exposed to the virus previously (R +ve), reactivation of the virus is likely but usually results in less severe clinical disease. Immunosuppression increases the risk of reactivation and the additional use of antibody therapy for induction or rejection further increases the risk 5 fold.

Infection may be asymptomatic. Signs and symptoms of infection vary but include:
- Mononucleosis syndrome – severe ‘flu-like symptoms
- Decreased white cell count
- Hepatitis
- Gastrointestinal tract ulceration – especially oesophagitis
- Retinitis
- Meningoencephalitis
- Pneumonitis
- Myocarditis
- An increased risk of acute rejection

It is important to make a distinction between prophylaxis and therapy in CMV infection. CMV prophylaxis is usually used when there is an increased risk of infection and CMV therapy is used when there is evidence or suspicion of active disease. Both are discussed below.

Diagnosis

A high degree of suspicion should be maintained. Periodic surveillance, with measurement of IgM and IgG antibody titres, if previously negative, should be performed weekly for the first 3 months, monthly until 6 months and thereafter as indicated clinically in a patient who is antibody negative. Known antibody positive patients should have blood PCR at these times.

CMV culture of blood (buffy coat) and urine require prolonged incubation times. Early antigen and viral PCR tests for viral particles are also of use in the diagnosis of infection and results are usually available within 24 – 48 hours. The virology laboratory will give advice in an individual patient with suspected disease and should be consulted prior to despatching specimens from the patient.

CMV Prophylaxis

Prophylaxis is used in patients who have a high risk of developing CMV disease. Indications for prophylaxis are:
Donor +ve, Recipient –ve (see * below and CMV Therapy as well)
Donor +ve, Recipient +ve.
Donor +ve, Recipient unknown until status determined by lab, then according to indications above.
Donor –ve, Recipient +ve and use of antibody therapy for induction or rejection - use Valganciclovir

When both donor and recipient have a negative titre for IgG antibody, prophylaxis is not usually required.


*In Donor +ve, Recipient –ve receiving antibody therapy, consider pre-emptive therapy with Valganciclovir – see CMV therapy for details regarding dosing.
The following agents have been shown to provide prophylaxis against CMV disease: Valacyclovir; Valganciclovir, Ganciclovir; and CMV Hyperimmune Globulin. (59)

Valacyclovir (Valtrex)
Valacyclovir is a pro-drug of acyclovir with increased oral bioavailability – 54% compared with 10 – 20% with acyclovir. It inhibits DNA polymerase and is effective against Herpes simplex, Varicella zoster, CMV and possibly EBV. The plasma half-life (T1/2) is 2-3 hours and the intracellular T1/2 is -2 hours.

Lowance et al (999) (28) reported a multi-centre placebo-controlled trial involving 616 patients treated for 90 days post transplant. Although the trial had some deficiencies – only 30% received triple immunosuppressive therapy, 10% were non-compliant and 20% had incomplete follow-up – valacyclovir was effective prophylaxis compared to placebo. In the D +ve, R -ve, disease was reduced from 25% to 4% at 6 months and in all R +ve patients, disease was reduced from 6% to 1%. Viraemia, viruria, graft rejection, other herpes infections and other non-herpes viral infections were also significantly reduced. There was however no patient or graft survival advantage. This trial used a high dose regime and therefore had a significant side effect incidence.

Side effects
Include reversible neuropathy, gastrointestinal disturbance, headache, rash, encephalopathy and TTP.

Dosing for Prophylaxis
Dosing needs to be adjusted for renal function and in children < 50kg a paediatric nephrologist should be consulted. Guidelines are as follows:
Immediately post-transplant – 500mg orally twice daily and then according to the following regime:

<table>
<thead>
<tr>
<th>Cr Cl (mls/min)</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25</td>
<td>Valacyclovir 500mg bd, po</td>
</tr>
<tr>
<td>25 &lt; 50</td>
<td>Valacyclovir 1g bd, po</td>
</tr>
<tr>
<td>50 &lt; 75</td>
<td>Valacyclovir 1g tds, po</td>
</tr>
<tr>
<td>&gt; 75</td>
<td>Valacyclovir 1g qid, po</td>
</tr>
</tbody>
</table>
Duration of therapy
It is recommended that prophylactic therapy be continued for 12 weeks.\textsuperscript{(28)}

Valganciclovir (Valcyte)

Valganciclovir (VG), a designer drug, is a valine ester pro-drug of ganciclovir (Gan), developed to overcome the low bioavailability of the parent drug. VG has approximately 60% bioavailability compared to Gan of around 6-10%. VG action is the same as the parent drug.

After extensive use in CMV retinitis in AIDS patients it has been the subject of a randomized, controlled trial against oral Gan in solid organ transplant patients (Paya C et al, AJT, 2004)\textsuperscript{(58)}. This study randomized 372 patients in a ratio of 2:1 of VG: Gan. The endpoint of CMV disease was similar and CMV viraemia at 6 months was significantly lower with VG.

VG CMV drug resistance was absent in one large prospective study of 301 transplant recipients (Boivin G et al, JID, 2004)\textsuperscript{(29)}.

In Donor +/Recipient - use valganciclovir instead of valacyclovir because of greater risk of infection and disease.

Side Effects.
The safety profile was similar with one exception – more neutropaenia with VG. Others were similar to Gan and included diarrhoea, tremor, headache, nausea, insomnia, oedema and back pain. There was no difference in acute rejection episodes.

Dosing for Prophylaxis.
Dosing needs to be adjusted for renal function based on Cockcroft – Gault eGFR:

<table>
<thead>
<tr>
<th>eGFR</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60 mL/min</td>
<td>450mg twice daily</td>
</tr>
<tr>
<td>40 – 60</td>
<td>450mg once daily</td>
</tr>
<tr>
<td>25 – 40</td>
<td>450mg every second day</td>
</tr>
<tr>
<td>10 – 25</td>
<td>450mg twice a week</td>
</tr>
<tr>
<td>&lt;10</td>
<td>450mg once weekly post dialysis.</td>
</tr>
</tbody>
</table>

Duration of therapy
It is recommended that prophylactic therapy be continued for 12 weeks.
Note VG must be handled as a cytotoxic agent.

Ganciclovir
Oral ganciclovir is no longer available in Australia and so is not used in prophylaxis.
For IV Ganciclovir see therapy in next section.

CMV Hyperimmune Globulin
CMV IgG provides passive immunisation. There is no good data to show that CMV IgG provides effective prophylaxis. Snydman et al \textsuperscript{(30)} reported a meta-analysis of open-label and randomised trials of CMV immune globulin, that revealed as many as 30% of patients still developed a CMV clinical syndrome following CMV immune globulin treatment. However, compared to placebo there was an overall reduction in disease of about 50% with therapy.
Contraindications
• Individuals who have had a true anaphylactic reaction to a human immunoglobulin preparation.
• Individuals with selective IgA deficiency who have antibodies against IgA should not receive the preparation since these patients may experience severe reactions to the IgA which is present in trace amounts.

Precautions
• CMV immunoglobulin contains no antiseptic. It must, therefore be used immediately after opening the ampoule or bottle; any unused portion should be discarded.
• Do not use if the solution has been frozen.
• CMV immunoglobulin may be diluted up to four times its volume in either 0.9% Saline or 5% Dextrose.
• CMV immunoglobulin should be administered separately from other intravenous fluids or medications.
• The preparation should be allowed to reach room temperature prior to administration.

Side effects:
Reactions tend to be related to the rate of infusion and are most likely to occur within the first hour. Reactions include abdominal pain, headache, chest tightness, facial flushing or pallor, feeling hot, dyspnoea, non-urticarial rash, itching, hypotension, nausea and vomiting.

Should a reaction occur the infusion should be stopped. If the patient’s condition improves the infusion is usually recommenced at a slower rate.

Some patients may develop delayed adverse reactions to CMV immunoglobulin. These include nausea and vomiting, chest pain, rigors and aching legs. Such reactions occur following completion of the infusion, usually within 24 hours.

Duration of therapy
CMV immunoglobulin is administered intermittently for 16 weeks at the following times: -
Pre-operatively or day one or two post transplantation at a dosage of 150mg/kg
At two and four weeks post transplant at a dosage of 100mg/kg
At weeks six, eight, twelve and sixteen weeks post transplant at a dosage of 50mg/kg.

CMV antibody titres should be measured on each occasion, just prior to the commencement of the infusion.
The following information should be recorded in the CMV register: -
• Patient’s name
  • Date of transplant
  • Medical record number
  • Drugs used for immunosuppression and rejection episodes
• CMV antibody titres
• Possible adverse reactions to globulin
• Any clinical suspicion to CMV related disease.

CMV Therapy

Therapy is usually reserved for active clinical disease. However those recipients deemed to be at very high risk of disease, such as D +ve, R –ve, receiving antibody (anti-lymphocyte globulin or OKT3), may also require active treatment.

Ganciclovir

The preferred treatment of CMV disease is with Ganciclovir administered intravenously, initially, and then switching to oral Valganciclovir. **Ganciclovir is metabolised to ganciclovir triphosphate where it acts as an inhibitor of viral DNA polymerase. It has excellent in vitro activity against all Herpes viruses. Again numerous trials using different regimes and duration’s of therapy make interpretation difficult.**

Side effects

Include bone marrow suppression (common), nephrotoxicity (renal tubular crystallisation), fever, headache, phlebitis (when given IV), rash and encephalopathy.

Dosing for therapy

The dose should be adjusted for renal function according to the following regime:

<table>
<thead>
<tr>
<th>CrCl</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10mls/min or Dialysis</td>
<td>Ganciclovir 1.25mg/Kg IV post dialysis</td>
</tr>
<tr>
<td>≥ 10 &lt;25mls/min:</td>
<td>Ganciclovir 1.25mg/Kg IV once daily</td>
</tr>
<tr>
<td>≥ 25 &lt;50mls/min:</td>
<td>Ganciclovir 2.5mg/Kg IV once daily</td>
</tr>
<tr>
<td>≥ 50 &lt;75mls/min:</td>
<td>Ganciclovir 2.5mg/Kg IV 12 hourly</td>
</tr>
<tr>
<td>≥ 75mls/min:</td>
<td>Ganciclovir 5mg/Kg IV 12 hourly</td>
</tr>
</tbody>
</table>

Administration of IV Ganciclovir

Ganciclovir for IV administration must be handled as a cytotoxic agent.

Duration of Therapy

Intravenous therapy is usually given for at least 2 weeks according to clinical response. The patient may then be transferred to oral therapy with dosing similar to prophylactic regime and continued for a minimum of 3 months.

Consideration can be given to long term oral treatment for severe infection involving vital organs such as retinitis, myocarditis etc.

Consideration should be given to reducing the dose of Mycophenolate in patients receiving Tacrolimus and Prednisolone.
BK Virus Nephropathy or Polyomavirus Nephropathy

Virology of Polyomavirus

Polyomavirus hominis types 1 & 2 (or BK & JC named from the initials of the first 2 cases described (Gardiner SD, Lancet, 1971)) is an unenveloped DNA virus with capsids of 45 uM diameter that contain double stranded DNA of 5300 bp. A third virus - simian SV40 is rare in humans but there is 70-75% homology between BK, JC & SV40. The virus is taken up by the cell by endocytosis and transferred to the nucleus, where replication and assembly occurs and seen as nuclear-inclusion structures.

Incidence

90% of the population is seropositive for polyomavirus, but disease is rare. Humans are the natural host for BK & JC and simians for SV40. For BK virus, latency is in the urogenital tract and require specific events for reactivation and disease. BK is detected in 10 - 45% of renal transplant recipients and 6% develop nephropathy (Hirsch HH, NEJM, 2002; Bressollette-Bodin C, AJT, 2005). Infection occurs in non-renal transplants but disease is rare.

Nephropathy

Infection is common as indicated by serological or virological evidence of exposure but replication and disease leading to nephropathy and graft loss is unusual accounting for about 6 - 10% of graft failures.

Repllication requires evidence of multiplication of viral particles eg. in cell culture, electronmicroscopic evidence of virions or detection of viral DNA in non-latency sites such as plasma. Replication can be found in 10 - 45 % of renal transplant recipients as the presence of ‘decoy’ cell on urine cytology. These are renal epithelial cells containing viral particles but are not diagnostic of disease.

Disease occurs when viral replication causes organ dysfunction demonstrated on tissue biopsy. Pathology usually shows the affected tubular cells. Clinical manifestations include:
* Ureteric stenosis
* Transient transplant dysfunction; and
* Progressive graft failure

Onset of disease ranges from 6 weeks to many years post-transplant and appears to need the combination of renal damage, immunosuppression and a susceptible host to induce disease (Tong CYW, NDT, 2004).

Predisposing Factors for Disease:

- Transplanted since 1994
- Tacrolimus and Mycophenolate combination
- Acute rejection in first month post-transplant
- Total number of rejection episodes
- Intensity of immunosuppression
Factors not associated with risk:
- CMV co-infection
- Use of Anti-lymphocyte preparations
- HLA Mismatches

Diagnosis
Screening by Urine Cytology. Detection of Decoy Cells in urine by phase contrast or Pap stain, is a simple test with a high negative predictive value.
DNA techniques. Plasma PCR has 100% sensitivity and 88% specificity. Note that urine PCR has very poor specificity and sensitivity because of the ubiquitous nature of the virus and does not represent replication. Viral load estimates of > 10,000 copies has 95% positive predictive value.

Renal Allograft Biopsy. A diagnosis of BK Nephropathy can only be made by graft biopsy and is characterised by acute tubular epithelial cell necrosis (Nickeleit V, Current Opinion in Neph & HT, 2003). In addition a biopsy may be used:
- for exclusion of rejection and other causes of dysfunction;
- to gauge severity or staging
- to enable detection of in situ mRNA (Randhawa PS, Transplantation, 2002)

Prognosis
Graft loss in 50% at 6 months following histological confirmation of BK Nephropathy.

Therapeutic Interventions.
The following options for intervention have been reported but there is no level 1 or 2 evidence to support these.

Reduction or change of immunosuppression. Although there are no studies, a reduction or change of IS therapy may be appropriate in the absence of rejection on biopsy. Change from Tacrolimus to Cyclosporin and from Mycophenolate to Azathioprine has been advocated along with reduced doses. Use of Lefluonamide (in place of mycophenolate and azathioprine) has been shown to eradicate viraemia and stabilise renal function in case reports.

Treatment of Rejection. If present on biopsy it has been suggested that rejection may be treated with anti-lymphocyte agents as these agents are not risk factors for BK nephropathy.

Antiviral Therapy. Reduced doses (10 - 15% of the usual dose) of Cidofovir has been reported by some to show improvement or stabilisation (Tong CYW, NDT, 2004; Kuypers DRJ, AJT, 2005). Viraemia was eliminated or reduced and long term graft survival reported.

Outcome.
Untreated 50% loss of graft in 6 months and better with reduced IS and antiviral therapy.
No increased incidence in subsequent grafts following suitable interval to allow immunity to clear the virus - suggested 3 - 6 months. Removal of non-functioning graft has been advocated to eliminate residual viral source (Hirsch HH, AJT, 2006).
**Pneumocystis carinii Pneumonia (PCP)**

PCP can cause substantial morbidity and mortality after transplantation. Prophylaxis with trimethoprim/sulfamethoxazole (TMP/SMX) is strongly recommended for the first 3 months. Patients receiving TMP/SMX for prophylaxis will commence therapy within the first 48 hours post transplant. The mean serum half-life of trimethoprim is 10 hours and sulfamethoxazole 8 to 10 hours.

**Dosing for prophylaxis**

Low dose TMP/SMX is administered to all transplant patients. Recommended dose is single strength one tablet per day or double strength one tablet alternate days for patients > 50kg and 3mg/kg (of the trimethoprim component) Monday/Wednesday/Friday if <50kg.

If the patient is unable to take TMP/SMX because of an allergy or G6pD deficiency, then nebulised pentamidine should be used monthly for 3 months.

**Duration of therapy**

It is recommended that patient's receive prophylactic therapy for a minimum of 3 months and maximum of 12 months post transplant.
SECTION 3: Post-Transplant Management
Preliminary Comments

The goals of transplantation are:
(i) patient safety and
(ii) satisfactory transplant function.

In the vast majority of cases, both of these aims can be achieved successfully. However, it is important that they be kept in correct order as a wide range of hazards may be encountered during the post-transplant period. The following are guidelines for safe transplantation. They do not take into account the many variations in clinical management that may be required for the individual patient. There is no substitute for regular clinical surveillance (in some cases, several times each day) and extreme awareness of potential complications.

Medications Post Transplant

* Immunosuppressants as per designated protocol
* Nilstat drops QID
* Sodium Bicarbonate mouth washes QID
* Ranitidine Hydrochloride 50 mg IV, BD, converting to 150mg BD orally for 3 months, or long term if previous history of peptic ulcer disease, or a proton pump inhibitor.
* Sulfamethoxazole/Trimethoprim for prophylaxis of pneumocystis pneumonia either single strength 1 tablet per day or double strength 1 tablet every second day for a minimum of 3 months.
* CMV prophylaxis as per protocol
* Consider temporarily stopping Statins immediately post transplant.

Post Transplant Investigations: > 24 hours Post Transplant

* Daily UEC, Ca, Phosphate, Magnesium, Uric acid, LFT’s, Glucose and FBC
* Daily C2 CyA levels commencing from Day 2 post transplant. Evening and morning CyA doses will be charted according to these levels.
* Daily Tacrolimus trough levels from day 2 post transplant.
* Sirolimus/Everolimus level day 5 – 7 post transplant then weekly thereafter.
* MSU when macroscopic haematuria has cleared and catheter removed.
* Blood transfusion should be avoided post transplant because of the risk of exposing the patient to new HLA antigens. However it should be considered if the Hb < 80 g/L. The decision to transfuse will depend on the rate of change of the haemoglobin,
the cause(s) of low haemoglobin and presence of comorbidities.

* Blood should be administered to transplant patients through a white cell filter.

* Patients on EPO prior to transplantation should continue until they have demonstrated the ability to maintain their own haemoglobin.

* An MSU or CSU should be collected if the patient is febrile (> 37.2), the urine looks turbid or if they are complaining of burning, stinging or dysuria.

* A swab should be collected if the suture line, drain site or TLC exit site is red and inflamed, has exudate present or if the patient is febrile (> 37.2).

* Blood culture should be collected if the patient’s temperature is ≥ 37.5

**Chest X-ray**

Postoperatively a chest X-ray will be performed if the patient develops respiratory symptoms such as cough, wheeze and dyspnoea to rule out infection and / or fluid overload.

A chest X-ray will also be performed prior to the commencement of OKT3 therapy.

**Renal Imaging**

Clearly, the urgency to image the transplant urinary tract will be influenced by transplant function. In the presence of satisfactory urine output, falling serum creatinine and stable clinical features, such investigations may be delayed until they are more convenient for both the patient and staff. Greater urgency exists when there is delayed graft function. Again, clinical assessment will help to determine whether arterial doppler or transplant ultrasound has a high priority.

**Renal Doppler Studies**

Done on Day 1 post transplant. If Day 1 occurs on the weekend a scan will be performed on the first working day post transplant, unless urgently required.

**Renal Ultrasound**

Performed on day 1 post transplant. May be done on a weekly basis if indicated while the patient is in hospital.

It will provide information concerning the size of the kidney, whether there is ureteric obstruction or a perinephric collection (e.g.: urinary leak).
Normally kidney allografts may enlarge by 20% over a 2 to 3 week period following transplantation. However, an increase in renal volume of more than 30% over baseline value is significant. The enlargement may be due to acute rejection or ureteric obstruction, resulting in hydronephrosis and dilatation of the pelvicalyceal system.

**Renal Perfusion Scan**
Performed as indicated to assess perfusion of the kidney, doppler studies day 1 post transplant are the preferred option.

**Renal Angiography**
Renal angiography is performed as indicated in the post transplant period. It is usually performed in-patients with unexplained deterioration in blood pressure control, which is typically resistant to antihypertensives, or in patients with an abnormality on doppler.

Angiography is used to diagnose renal artery stenosis. For a renal artery stenosis to be significant the degree of narrowing needs to be > 70%.

**Possible Investigations**

**Renal Biopsy**
Protocol renal biopsies are not performed unless they are required as part of a clinical trial. Indications for a renal biopsy are as follows:-
* to determine if Acute Tubular Necrosis is a cause of primary non-function day 5 - 7 post operation
* diagnosis of acute rejection in a patient who is anuric or oliguric during the postoperative period.
* to distinguish cyclosporin toxicity from acute rejection, as the symptoms are similar.

**Surgery Post Transplant**
All patients with a functioning graft must have an IV cannula inserted and be prehydrated if they need to fast. These patients must not be allowed to become dehydrated.

In patients with a non-functioning graft, fluid administration must be planned very carefully.

The patient may take their antihypertensives and immunosuppressive agents with a sip of water on the morning of the operation or procedure.

All patients, regardless of age, must have an ECG prior to surgery.

**Rejection**
Rejection is one of the commonest causes of renal dysfunction in the post transplantation
period. It is a process, which can be classified as either hyperacute, acute or chronic on the basis of clinical, aetiological and pathological parameters.

The clinical manifestations of rejection may include: -
* Rising serum creatinine
* Painful/tender graft
* Sudden weight gain
* Fever
* Fall in urine output
* Hypertension
* Coagulation abnormalities including thrombocytopenia
* Malaise

Clinical suspicion of rejection is best confirmed by a renal biopsy done in conjunction with an ultrasound. The BANFF Criteria for Renal Allograft Rejection[^31] can be found in appendix F.

**Hyperacute Rejection**

Hyperacute rejection occurs within the first 24 hours of transplantation. Hyperacute rejection is a rapid form of rejection caused by the presence of preformed cytotoxic antibodies in the transplant recipient. There are 3 ways the patient may develop these antibodies: after a previous failed transplant, as a result of a blood transfusion and following pregnancy.

This entire process can occur very rapidly once the arterial and venous clamps are removed and the kidney revascularized. In severe cases the kidney never distends properly with blood and rapidly becomes blue. The graft becomes haemorrhagic and oedematous and if not removed may rupture. Patients are invariably anuric or oliguric and often have a fever and graft tenderness. The renal scan shows little or no uptake of dye, and there may be evidence of intravascular coagulation.

Hyperacute rejection once established is irreversible. Fortunately with current tissue typing and X-matching protocols this is a rare occurrence.

**Acute Rejection**

The incidence of acute rejection is greatest in the first 3 months, less in the next 6 months and relatively uncommon one year following transplant.

There are 2 basic types of acute rejection:-

**Humoral Rejection or Acute Vascular Rejection**

Humoral rejection is caused by the patient producing the antibodies that are responsible for acute humoral rejection. This form of rejection is rare and usually responds well to treatment. Treatment is usually with plasma exchange and IV immunoglobulin to deplete specific antibody, however, the new monoclonal antibody to B cells, Rituximab, has been successful in case reports (Becker YT et al, 2004) - see also
Immunosuppression section. However when response to treatment is inadequate, nephrectomy must be considered because of the severe systemic reaction that may occur.

Cell Mediated
Acute cellular rejection is the commonest type of rejection in the first year post transplant. Cellular rejection is usually graded as severe, moderate or mild using pathological criteria based on the extent of cytodestructive criteria. (See Appendix F)

Treatment
First acute rejection episodes are treated with intravenous methylprednisolone at 250 - 500mg, daily for 3 days. Oral prednisolone will be ceased for the 3 day period and recommenced at 40mg per day with subsequent reductions as indicated. All other medications unless specified by a renal physician will continue unchanged.

Steroid unresponsive rejection will be treated with OKT3 for 7 - 14 days (depending on response), according to the protocol on the following page:

OKT3 Administration
Due to the major side effect of pulmonary oedema associated with OKT3 administration the following must be done prior to the first dose:
* Ensure that the patient is not fluid overloaded (weight should be <3% above ideal)
* Chest X-ray is clear
* Temperature <38°C
* White cell count > 3.0 X 10^9/L.
* Ensure that an artificial airway, adrenaline, oxygen and additional hydrocortisone are at hand.

Severe reactions usually only occur with the first 1 - 2 doses of OKT3, because of this the following prophylaxis will be given 30 – 60 minutes prior to the first 2 doses:

Adults: Day 1 and 2
* Methylprednisolone 250mg IV (Day 1) and 125mg IV (Day 2)
* Paracetamol 1gm oral
* Promethazine 25mg oral
Paediatrics:
Day 1
* IV Methylprednisolone 2mg/kg 60 mins prior to OKT3 (withhold oral daily dose)
* IV Promethazine (phenergan 0.2-0.5 mg/kg – maximum dose 12.5mg)
* Panadol 15mg/kg orally
* 30 minutes after OKT3 has finished give hydrocortisone 100mg IV.
Day 2
* IV promethazine (phenergan) 0.2-0.5 mg/kg – maximum dose of 12.5mg)
* Panadol 20mg/kg
* 30 minutes after OKT3 has finished – hydrocortisone 100mg IV.
* give OKT3 5mg IV daily for 7 -14 days – drawn up through a 0.22 micron filter, and injected through a fresh needle over < 1 minute
* continue oral prednisolone at same dose
* stop other adjunctive immunosuppressive therapy for first 7 days of 14 day treatment then recommence on day 8
* commence oral valacyclovir prophylaxis according to protocol (see page 38-40)
* continue patient on sulfamethoxazole/trimethoprim as per prophylaxis guidelines. If the patient is no longer taking prophylaxis for PCP, initiate according to guidelines on page 44.

Observations:
* First and second doses – BP, temperature and pulse rate prior to administration, then every 15 minutes for first 2 hours and then half hourly for 2 hours until stable
* Subsequent doses – BP, temperature and pulse rate prior to dose and then 4th hourly unless exaggerated response occurred with previous doses

Adverse Reactions:
See earlier monoclonal antibody section. Do not administer with any other drug solutions.

**Chronic Rejection**

Late graft losses are usually characterized by an insidious deterioration of graft function, accompanied by any of the features of acute rejection. The patient usually remains well and it is only the slow rise in the serum creatinine and blood urea, often with the development of proteinuria, which betray the development of chronic rejection.

Chronic rejection causes a gradual strangling of the blood supply to the kidney. The lumen of the arteries become progressively smaller due to intimal proliferation and the tubules and glomeruli are overtaken by fibrosis. Often the interstitial fibrosis has a striped pattern.

Once established chronic rejection is intractable leading to a gradual and complete loss of graft function necessitating the reintroduction of some form of renal replacement therapy.
Post-Transplant Frequency and Timing of Outpatient Visits

While in hospital, patients are monitored on a daily basis, since any adverse changes may be the first signs of graft rejection, toxicity from drug therapy, or graft failure. After leaving the hospital, patients continue to be monitored in the transplant clinic. A suggested schedule for follow up visits post transplant is as follows:

<table>
<thead>
<tr>
<th>Time after Transplant</th>
<th>Visit Interval</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge –30 days</td>
<td>Daily</td>
<td>Screen for acute rejection (high risk), postoperative complications, and adverse effects of immunosuppressive medications. CMV- IgG, IgM Antibody Titre (if previously negative) and DNA PCR weekly</td>
</tr>
<tr>
<td>1 – 3 months</td>
<td>2 x week</td>
<td>Screen for acute rejection (high risk), opportunistic infections, adverse effects of immunosuppressive medications, and compliance (especially children and adolescents). CMV – IgG, IgM Antibody Titre (if previously negative) and DNA PCR weekly</td>
</tr>
<tr>
<td>3 – 6 months</td>
<td>1 x week</td>
<td>Screen for acute rejection (moderate risk), opportunistic infections, adverse effects of immunosuppressive medications, compliance (especially children and adolescents). CMV – IgG, IgM Antibody Titre (if previously negative) and DNA PCR monthly</td>
</tr>
<tr>
<td>6 – 12 months</td>
<td>2nd weekly</td>
<td>Screen for acute rejection (moderate risk), opportunistic infections, adverse effects of immunosuppressive medications, compliance (especially children and adolescents). CMV – IgG, IgM Antibody Titre (if previously negative) and DNA PCR at month 12 if previously –ve</td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td>Monthly</td>
<td>Screen for graft dysfunction, cardiovascular disease risk, cancer, adverse effects of immunosuppressive medications, general health maintenance and compliance.</td>
</tr>
<tr>
<td>&gt; 2 years</td>
<td>2 – 4 monthly</td>
<td>Screen for graft dysfunction, cardiovascular disease risk, cancer, adverse effects of immunosuppressive medications, general health maintenance and compliance.</td>
</tr>
</tbody>
</table>
Recommended Investigations Post Transplant

In addition to monitoring the patient's general health the health of the transplant organ is also monitored very carefully. Patients who receive renal transplants are at a greater risk for a variety of illnesses than the general population. While some of these conditions may be associated with preexisting patient conditions others may be associated with the use of immunosuppressive therapies. Conditions commonly associated with morbidity in renal transplant patients are outlined in the table below.

### Conditions Commonly Associated with Morbidity in Renal Transplant Patients

<table>
<thead>
<tr>
<th>Depression / anxiety</th>
<th>Hypertension</th>
<th>Skin problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diverticulitis</td>
<td>Metabolic disorders</td>
<td>Steroid-associated diabetes</td>
</tr>
<tr>
<td>Gastrointestinal effects</td>
<td>Musculoskeletal problems</td>
<td>Stroke</td>
</tr>
<tr>
<td>Haematologic effects</td>
<td>Osteoporosis</td>
<td>Urinary tract infections</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Pneumonia</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Avascular Necrosis of long bones especially the femoral head</td>
<td>Cataracts and other ocular diseases</td>
<td></td>
</tr>
</tbody>
</table>

The morbidity and mortality rates associated with renal transplantation and the use of immunosuppressive therapy are high. However, many post transplant complications can be prevented, or at least more effectively treated, if they are detected earlier, rather than later. The Westmead group noted that by 10 years 100% of their combined Kidney-Pancreas transplants had evidence of nephrotoxicity. Of the potential health threats faced by renal transplant patients, the conditions associated with the highest rates of mortality are coronary artery disease, infections, malignancy and liver failure.

Guidelines for monitoring the patients post transplant are detailed below, these guidelines are applicable to both adult and paediatric renal transplant recipients. They cover outpatient screening for and prevention of diseases and complications that commonly occur post transplant.

### Graft Function

A large proportion of patients eventually develop acute/chronic graft dysfunction. Early detection of acute rejection, nephrotoxicity resulting from CNI use, chronic allograft nephropathy and renal dysfunction may enable therapy to be commenced that may prolong graft survival. Measuring function can also help predict patient compliance with therapies.
Function and stability should not be taken for granted at any time after transplantation. Clinical signs of rejection and dysfunction are notoriously unreliable, repeated laboratory testing is therefore recommended. Some centres perform routine or protocol biopsies at 3, 6 and 12 months post-transplant to detect subclinical rejection and evidence of CNI toxicity.

**Cardiovascular Disease**

Cardiovascular disease (CVD) is defined as ischaemic heart disease, cerebral vascular disease or peripheral vascular disease. Cardiac diseases are the most common cause of death, in 2001 29% of deaths post transplant were due to cardiac disease. Patients with histories of pre transplant CVD, diabetes (including post transplant diabetes), smoking, hyperlipidaemia, hypertension, hypoalbuminaemia and allograft dysfunction and rejection are at increased risk for post transplant CVD complications. Pre-existing CVD should not be seen as a reason to avoid risk factor management post transplant. All patients should be actively screened for CVD and the appropriate intervention undertaken, especially high risk patients. Both type 1 and type 2 diabetes greatly increases the risk of CVD.

Elevations in low-density lipoprotein cholesterol (LDL) contribute to the pathogenesis of atherosclerosis, it is also known that low levels of high-density lipoprotein cholesterol (HDL) contribute to CVD as well.

The most important cause of hyperlipidaemia post transplant is immunosuppressive therapy. Corticosteroids, cyclosporin, tacrolimus, sirolimus and everolimus all cause elevations in lipids to varying degrees. Other causes include diet, weight gain, genetic predisposition, proteinuria, and possibly decreased renal function.

Corticosteroids, cyclosporine and tacrolimus can all elevate blood pressure after renal transplantation. Observational studies have found that allograft dysfunction is also associated with subsequent CVD complications. Decreased renal function and proteinuria can contribute to other risk factors such as, hyperlipidaemia and hypertension.

**Diabetes**

Diabetes mellitus is associated with cardiovascular disease, infections, retinopathy, nephropathy and neuropathy. The early detection, prevention and treatment of diabetes may reduce the frequency of these complications in renal transplant patients. Diabetic control post transplant may become more difficult and patients should be monitored closely. About 20% of non diabetic patients develop hyperglycaemia after transplantation. Older patients, obese patients and patients with a strong family history of diabetes are at higher risk.

Corticosteroids, cyclosporine and especially tacrolimus all contribute to glucose intolerance.
It is recommended that fasting or postprandial blood glucose levels in adults be measured according to the following schedule:

* Months 1 to 3 - at least weekly
* Months 4 to 6 at least every 2 weeks
* Months 6 to 12 at least monthly
* After the first post transplant year, fasting glucose and / or glycosylated haemoglobin levels should be measured at least yearly or as indicated.

**Lipids**

* All patients should be screened for fasting cholesterol, LDL, HDL and triglycerides at 3, 6 and 12 months post transplant.
* Low risk patients should then be screened annually or as indicated.
* High risk patients or those with borderline or previously high lipid levels should have a complete fasting lipid profile every 3 months or as indicated from month 12 onwards.
* High levels should be treated in consultation with the renal physician.
* Changes in the immunosuppressive regime, graft function or cardiovascular disease may warrant additional screening.
* The incidence of Rhabdomyolosis may be increased with the combined use of statins and high doses of CNIs. It is recommended that routine check of CK level.

**Infection**

All patients receiving immunosuppressive therapy are at risk of developing infection. Infections are often opportunistic and may be caused by organisms that normally inhabit the patient or hospital environment. Commonly seen infections are:

**CMV**

Acute CMV infection usually manifests itself as fever, leukopaenia, thrombocytopenia, myalgias, and flu like symptoms. End organ involvement may cause nephritis, retinitis, hepatitis, gastrointestinal bleeding and /or pneumonia. Prophylaxis and treatment recommendations have been outlined earlier in the manual.

**Influenza A and B**

Influenza is a potentially fatal infection in immunocompromised patients. It is also associated with significant morbidity and cost. It is recommended that transplant recipients receive an annual influenza vaccination between March and May each year.

**Pneumocystis carinii Pneumonia (PCP)**

Pneumocystis carinii pneumonia usually occurs 1 to 6 months after transplantation.
It typically presents with fever, nonproductive cough, arterial-alveolar mismatching, and diffuse interstitial infiltration or focal air-space consolidation. Diagnosis is made by bronchoalveolar lavage.

Therapy should be initiated after consultation with infectious disease physician. Prophylactic therapy has been outlined earlier in the manual.

Screening for Hep B, Hep C and HIV
Adults will be screened every 3 months for the first year then annually. Children will be screened annually.

Tuberculosis (TB)
Patients with a past history of TB or previous positive X-ray or Mantoux require prophylaxis. The appropriate therapy should be decided after consultation with the respiratory and infectious disease teams.

Malignancy

Skin Cancer
Skin cancers are more aggressive in transplant recipients than in the general population. The incidence of multiple cancers is high, and many patients have several different types of skin malignancies that are prone to recurrence and metastasis. The onset of squamos cell and basal cell carcinomas occurs at a younger age among transplant recipients, compared with the general population. Skin cancers can be detected clinically and can often be cured by excision.\(^{32}\)

All patients should be made aware of the risks of sun exposure. Avoiding sun exposure, use of sunblock and wearing protective clothing should all be recommended to the patient.

It is recommended that each patient has a skin assessment either in the dermatology clinic or by their nominated physician on a yearly basis, or as indicated after transplant. Patients with a history of SCC or BCC prior to transplant will have more frequent checks as required.

Post-Transplant Lymphoproliferative Disease (PTLD)
Post transplant lymphoproliferative disorders (PTLD) are abnormal proliferations of lymphoid cells that result from immunosuppression.\(^{35}\) Renal transplant recipients are at the greatest risk of developing lymphoproliferative diseases in the first year after transplant. The reported incidence of PTLDs in Australia and New Zealand is 1-2% \(^{33}\)

Epstein-Barr virus (EBV) is a human DNA-transforming herpesvirus that primarily targets B lymphocytes.\(^{10}\) Transmission of EBV in transplant recipients is most commonly through the transplanted organ. As there is a high rate of association between EBV and PTLD, patients should be screened for EBV prior to or at the time of transplant. Sero-negative recipients of an organ from a seropositive donor are at the highest risk of developing PTLD, particularly if they receive prolonged or repeated courses of antilymphocytic therapy.\(^{10}\) Treatment needs to be planned in consultation
with an oncologist.

Pap smears, mammograms, faeces occult blood and prostate checks will also be performed on a yearly basis in cooperation with the family doctor. If faeces is positive for blood, a colonoscopy should be performed.

**Bone and Bone Marrow**

**Osteoporosis**

IS drugs are toxic to bones and transplant recipients may experience loss of bone associated with high rates of fracture. Steroids, cyclosporin and tacrolimus have osteopenic effects whilst mycophenolate and rapamycins are not toxic to the skeleton (Cunningham J, Transplantation 2007 79:62-67)

Osteoporosis is defined as bone mineral density > 2.5 SD below the adult mean value (t-score).\(^{(35)}\) It may lead to bone pain and fractures. Following are recommended guidelines as to the frequency of screening:-

- Previous fractures and X-rays of the affected regions are important as documentation of existing skeletal disorders.
- All potential adult transplant recipients should have a lumbar spine and hip, bone mineral density (BMD) scan at the time of placement on the transplant waiting list. This test should be repeated every 2 years until transplantation.
- All patients should undergo a lumbar spine and hip BMD scan at 6 - 12 months post transplant. All paediatric patients should have an annual bone age left wrist and left knee X-ray.
- Patients with an abnormal scan at 12 months post transplant should have a repeat scan on a yearly basis as this is allowed with Medicare provided the patient remains on steroids.
- Patients with a normal scan at 12 months post transplant should undergo lumbar spine and hip bone mineral density studies at 36 months then as indicated.
- Patients should be assessed for adequate Calcium dietary intake.
- Parathyroid Hormone (PTH), Calcium, Phosphate and Magnesium levels should be reviewed every 3 months.

**Treatment.**

Until recently there has been no good quality evidence for the use of osteoporosis therapies to improve BMD in renal transplant recipients or in CKD. A recent study stratifying Cr Cl with therapy in CKD has shown benefit in terms of BMD improvement and fracture. Whether this can be used following renal transplant recipients has not been studied. See Ishani A et al JASN 2008 (reference 66)

**Nutrition**

**Hypophosphataemia**

Hypophosphataemia is defined by serum phosphate levels of < 0.7 mmol/L. Hypophosphataemia may cause muscle weakness and possible osteomalacia, most recipients are asymptomatic.

Serum phosphate levels should be measured every visits during the first 6 months, every 2 months until the end of the first year, and then annually. Replacement therapy is indicated for persistently low levels.
**Hypomagnesaemia**

Hypomagnesaemia is defined as serum total magnesium levels < 0.7 mmol/L. Consequences of hypomagnesaemia may include muscle weakness, hypokalaemia, hypocalcaemia, cardiac arrhythmias and possibly hypertension and neurotoxicity. Patients should be screened monthly for the first 6 months, and then every 6 to 12 months. Patients receiving large doses of diuretics should be screened more frequently. Replacement therapy is indicated for patients with persistently low levels.

**Hyperuricaemia**

Hyperuricaemia is especially common among patients who receive CyA, diuretics and patients with reduced renal function. Hyperuricaemia may cause gout, nephrolithiasis and renal failure. Serum uric acid should be measured at least once during the first 2 to 3 months post transplant. Additional screening may be warranted in patients with reduced renal function and patients treated with diuretics.

**Hyperparathyroidism**

Resistant hyperalbunaemia due to hyperparathyroid may require surgical intervention if not resolved with alternative therapy in the first 12 months post transplant.

**Growth and Development of Children**

Children of different ages grow at different rates. The fastest growth occurs in the first 2 years of life and during puberty. Most children experience continued reduction in growth after renal transplantation. Although the incidence of growth failure and delayed development is high, there are several steps that can be taken to improve growth. Therefore, close monitoring of growth and intervention as warranted is recommended.

It is recommended that children have their height and weight recorded at each visit. For all children < 3 years of age, height and weight should be recorded monthly. Referral for consideration of growth hormone therapy should be made if height or growth velocity is ≤ 25 percentile for bone age and GFR <30ml/min/1.73m².

**Pregnancy**

When pregnancy is contemplated after renal transplant it is recommended that women should defer this until at least 1 – 2 years post transplant, with the following criteria being met:

- serum creatinine value less than 200μmol/L
- minimal or no proteinuria
- normal, or well controlled blood pressure
- no evidence of acute rejection in previous 12 months
- normal allograft ultrasound
- pregnancy safe drug regimen. (see table below)
Reports in the literature show that approximately 30% of pregnancies do not progress beyond the first trimester due to spontaneous or therapeutic abortion. Over 90% of pregnancies that progress beyond the first trimester end successfully.\(^{(34)}\)

Hypertension is the most common complication experienced by pregnant women with a transplant. Careful consideration should be given to the anti hypertensive drug regimen. ACE inhibitors should be ceased as they may be associated with serious adverse fetal effects.\(^{(35)}\)

Urinary tract infections, including potentially serious pyelonephritis, occur in up to 40% of pregnant transplant recipients. They are particularly common in patients who developed end – stage renal disease due to reflux nephropathy.\(^{(36)}\)

CMV disease remains the most frequent cause of viral infection post transplantation, however if the patient waits 1-2 years post transplant, she will have passed the peak time for CMV infection.\(^{(31)}\) Congenitally acquired CMV infections are devastating to the foetus.

In human studies low birth weights, prematurity, neonatal jaundice and respiratory distress syndrome have been reported in kidney transplant recipients.\(^{(36)}\)

The true impact of pregnancy on long term renal allograft function is not yet fully understood. Sturgiss et al \(^{(37,38)}\) found that pregnancy might have a minor effect on long-term graft function and/or survival. Kok et al \(^{(39)}\) found that pregnancy occurring at least 2 years after transplantation has no significant adverse effect on the outcome of allograft function and maternal survival.

**Immunosuppressive Drugs in Pregnancy**

Medications used in pregnancy can be associated with adverse outcomes due to teratogenicity or to physiological effects throughout pregnancy. A very limited number of drugs are known to be teratogens and the potential for teratogenicity is limited to the period of organogenesis.

**Glucocorticoids**

The most commonly used glucocorticoids are the short-acting agents; prednisone, prednisolone and methyl prednisolone.\(^{(35)}\) It is known that prednisone can cross the placenta, yet it is considered relatively safe in pregnancy. Adrenal insufficiency and thymic hypoplasia have occasionally been described in infants of transplant recipients, but these problems are unlikely if the dose of prednisone has been decreased to 5-10mg/day.\(^{(35)}\)

Doses of prednisone greater than 20mg /day have been associated with serious maternal infections and possibly cleft palate.\(^{(40)}\) In spite of this, patients with rejection should be treated with high dose steroids.\(^{(10)}\)
Azathioprine

Azathioprine crosses the placenta but is not converted in the immature foetal liver to 6-mercaptopurine. The immature foetal liver lacks the enzyme inosinate pyrophosphorylase needed for conversion, and the foetus is relatively protected from the effects of the drug.\(^{(35)}\).

In high doses (6mg/kg), azathioprine is teratogenic in animals but, at doses of ≤ 2mg/kg/day, no anomalies have been described in offspring.\(^{(41)}\)

Azathioprine can cause transient gaps or breaks in human lymphocyte chromosomes, but it is not known whether it is associated with the development of malignancies in offspring or other abnormalities in the next generation.

Azathioprine has been associated with dose-related myelosuppression in the foetus, but without clinical implications if the mother’s blood leukocyte count is > 7500/μl.

The Calcineurin Inhibitors

Cyclosporin

Cyclosporine or cyclosporine microemulsion have not been associated with teratogenicity or mutagenicity.\(^{(35)}\) Cyclosporin is present in the foetal circulation at the same concentration as in the mother.

Human data has shown that administration of cyclosporin was associated with low birth weights, a higher incidence of maternal diabetes, hypertension and renal allograft dysfunction. Although breast fed infants have no detectable levels, use of cyclosporin during lactation is not recommended.

Cyclosporin metabolism appears to be increased during pregnancy and higher doses may be required to maintain plasma levels in the therapeutic range. Close monitoring of cyclosporin blood levels is recommended.\(^{(42)}\) Some of the pregnancies in cyclosporin treated women were complicated by pre-eclampsia. Cyclosporine increases production of thromboxane and endothelin, which have both been implicated in the pathogenesis of pre-eclampsia. Because of this, some physicians have suggested that the dose be limited to 2-4mg/kg/day.\(^{(43)}\)

Tacrolimus

Tacrolimus has been used in pregnancy but the total reported literature is too small at this time to be conclusive. The use of tacrolimus during pregnancy has been associated with neonatal hyperkalaemia and renal dysfunction. Patients treated with tacrolimus should be expected to be at increased risk for gestational diabetes.\(^{(44)}\)

Tacrolimus is excreted in breast milk. It is therefore recommended that mothers should not breast-feed while receiving tacrolimus.

As with cyclosporin, patients taking tacrolimus require frequent monitoring of renal function and drug levels.

Mycophenolate

For both mycophenolate mofetil and mycophenolic acid, there are no adequate and
well controlled studies in pregnant women. There is concern based on animal studies that the risk of birth defect or abortion may be increased. Adverse effects on foetal development (including malformations) occurred when pregnant rats and rabbits were dosed with mycophenolate sodium and or mycophenolate mofetil.

Due to the limited date available, mycophenolate is not recommended for use in pregnant women.

The Rapamycins

Sirolimus

Sirolimus may cause immunosuppression in the infant. It was embryo/foetal toxic in rats at dosages of 0.1mg/kg/day and above. Embryo/foetal toxicity was manifested as mortality and reduced foetal weights (with associated delays in skeletal ossification). However no teratogenesis was evident. Women of child bearing age who are receiving sirolimus should be advised to use effective contraception whilst they continue on the drug and for up to 12 weeks after cessation.

Everolimus

There is no adequate data from the use of everolimus in pregnant women and the potential risk to the foetus is unknown. Everolimus is not recommended for use in pregnancy. Women of child bearing age who are receiving everolimus should be advised to use effective contraception while they are receiving the drug and for up to 8 weeks after treatment has been stopped.

The rapamycins are not recommended for use in pregnancy

Rituximab

Animal reproduction studies have not been conducted with Rituximab. It is not known whether Rituximab can cause foetal harm. Since Immunoglobulin G (IgG) is known to cross the placental barrier, rituximab may cause B cell depletion in the foetus.

Individuals of childbearing potential should use effective contraceptive methods during treatment and for up to 12 months following treatment.
## Transplant Medications in Pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Experience in Pregnancy</th>
<th>Teratogenicity</th>
<th>Placental Transfer</th>
<th>Physiological Impact</th>
<th>Breast Feeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pred</td>
<td>Extensive</td>
<td>Unlikely</td>
<td>Limited</td>
<td>Glucose intolerance, Hypertension</td>
<td>No restriction</td>
</tr>
<tr>
<td>Aza</td>
<td>Extensive</td>
<td>Minimal</td>
<td>Yes</td>
<td>Anaemia, Leukopaenia, Thrombocytopenia Maternal and foetal</td>
<td>Limited secretion</td>
</tr>
<tr>
<td>CyA</td>
<td>Large</td>
<td>Minimal</td>
<td>Yes</td>
<td>Hypertension Fetal growth restriction</td>
<td>Not</td>
</tr>
<tr>
<td>Tac</td>
<td>Limited</td>
<td>Limited</td>
<td>Yes</td>
<td>Hypertension Hyperglycaemia</td>
<td>Not</td>
</tr>
<tr>
<td>MMF</td>
<td>Very limited</td>
<td>Very limited</td>
<td>-</td>
<td>-</td>
<td>Secreted in milk of rats</td>
</tr>
<tr>
<td>MPA</td>
<td>Very limited</td>
<td>Very limited</td>
<td>-</td>
<td>-</td>
<td>Secreted in milk of rats</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Very limited</td>
<td>Very limited</td>
<td>-</td>
<td>-</td>
<td>Secreted in milk of rats</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Very limited</td>
<td>Very limited</td>
<td>-</td>
<td>-</td>
<td>Secreted in milk of rats</td>
</tr>
<tr>
<td>OKT3</td>
<td>Very limited (+)Animal data resorption and malformation</td>
<td>Yes</td>
<td>Cytokine</td>
<td>Unlikely secretion</td>
<td></td>
</tr>
<tr>
<td>Rituximab (Mabthera)</td>
<td>Very limited</td>
<td>Very limited</td>
<td>Yes</td>
<td>Possible B cell depletion in foetus</td>
<td>Not known if excreted in breast milk</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>Extensive</td>
<td>None</td>
<td>Yes</td>
<td>None</td>
<td>No restriction</td>
</tr>
</tbody>
</table>

(Adapted from: Reference 44)
Kidney Transplant Follow up Schedule

A guideline to the frequency of testing for renal transplant recipients for the first 12 months can be found in attachment G. It is recommended that this guideline be followed and individual patient records be kept of the dates that the procedures have been performed. A tracking sheet for patient follow up can be found in appendix H.

A detailed review of the long term management of the renal transplant recipient can be found in the European Best Practice Guidelines For Renal Transplantation (Part 2).\(^{47}\)

Long Term Follow Up

The factors that affect long term renal graft survival are:

* death of the patient with a functioning graft, usually due to cardiovascular disease or malignancy
* chronic allograft nephropathy, where drug toxicity may play a significant role,
* poor compliance with intermittent rejection and nephron loss and
* recurrent disease in the graft.

The aims of long term follow-up therefore are to detect, prevent and treat those factors.

Long term graft survival is usually measured by the graft half-life i.e. the time in years taken for 50% of grafts to be lost, or in reverse, that still survive excluding the first 6 months. The half-life from ANZDATA is approximately 10 years for cadaver grafts and 20 years for living related grafts.\(^{33}\)

Death with a functioning Graft

The three most common causes of death in the late post transplant period are cardiovascular disease (CVD), infection and cancer. Unfortunately, a large percentage of deaths that do occur in the late post transplantation period are premature and therefore continued observation of the following risk factors is recommended.

CVD

* Hypertension
* Lipids
* Smoking
* Diabetes
* Obesity

Infection

Infection is an inevitable risk of immunosuppression.\(^{10}\) Commonly seen infections in the post transplantation period are detailed in the following table.

Common Post-Transplant Infections
Viral
Chronic hepatitis (Hep B and C)
Influenza
Lymphoproliferative disorders (Epstein-Barr viruses)
Kaposi’s sarcoma (herpes virus 8)
Squamos cell carcinomas

Bacterial
Urinary tract infections
Intraabdominal sepsis
Cellulitis
Pneumonia
Tuberculosis

Opportunistic
Pneumocystis pneumonia
Toxoplasmosis
Nocardiosis
Aspergillosis
Listeriosis
Candidiasis

Cancer
Certain cancers are increased in patients receiving immunosuppressive therapy, the most common are:
* Post-transplant lymphoproliferative disease (PTLD): prevention and treatment
* Skin cancers, especially lip carcinomas, SCC, and Kaposi’s sarcoma
* Solid organ cancers, kidney and liver.
* Leukaemia
* Oesophageal, cervix insitu and invasive, rectal and anal.

Despite suggestions from Europe that both breast and rectal cancer might occur less frequently in transplant recipients, the rate of breast cancer in female Australian transplant recipients remains equal to that of the age matched general population.\(^{33}\)

The only two cancers that occur less frequently in the Australian / New Zealand population of transplant recipients are ovarian and prostate cancer. These cancers should still be screened for on a regular basis.

There is emerging evidence that non-melanoma skin cancer has a much lower incidence in patients receiving sirolimus therapy.\(^{52}\)

Chronic Allograft Nephropathy
Chronic allograft nephropathy is second only to ‘death with a functioning graft’ as the most common cause of late allograft failure. The signs of chronic allograft nephropathy
are as follows:
* Creatinine creep
* Proteinuria of > 0.5g / 24 hours
* Biopsy proven:
  * Calcineurin inhibitor toxicity
  * Recurrent Glomerulonephritis
  * Viral Infection

**Non Compliance**

Noncompliance with medication is a major cause of renal allograft failure among adult and adolescent transplant recipients. It is important to suspect and identify non-compliers in order to intervene. Research has shown the following to be indicators of potential non compliance:
* Patients with limited knowledge about their disease and the role of immunosuppression
* Forget the names of the drugs they are taking
* Young age

Patients with accidentally low trough levels of immunosuppressive drugs usually correlate with non-compliers. Recipients who do not attend outpatient clinic visits and recipients who do not comply with regular blood/urine analyses are usually non-compliers.(45,46)

**Recurrent disease in the graft**

Briganti et al (53) reported that their analysis of ANZDATA identified that allograft loss due to the recurrence of glomerulonephritis occurred with a 10-year incidence of 8.4 percent. The type of glomerulonephritis, the sex of the recipient, and the peak level of panel reactive antibodies were independent predictors of the risk of recurrence. Recurrence was the third most frequent cause of allograft loss at 10 years, after chronic allograft nephropathy and death with a functioning allograft.

However, the overall 10-year incidence of allograft loss was similar among transplant recipients with biopsy-proved glomerulonephritis and among those with other causes of renal failure

They concluded that recurrence is an important cause of allograft loss for those with renal failure due to glomerulonephritis. But they did not identify any risk factors that warranted altering the approach to transplantation.
SECTION 4: Hospital Specific Protocol for Prince of Wales Hospital
Pre-Transplant Immunosuppression Dosing

As detailed earlier in the manual, many combinations of immunosuppression can be used. It is common practice to give a pre-operative loading dose of most immunosuppressants to be used as maintenance therapy post transplant. The following is a suggested guide to the amount of immunosuppression to be used as loading doses for the different regimes:

Adults
* Cyclosporin: 9 mg/kg / day PO. Half of total dose to be given prior to theatre.
  OR
* Tacrolimus: 0.20mg/kg / day PO, Half of total dose to be given prior to theatre.
* Mycophenolate: 1 - 2gm/ day PO, Half of total dose to be given prior to theatre.
* Methyprednisolone: 500mg given intraoperatively IV (send to theatre with patient)

Children
* Prednisone - 2mg/kg, PO (maximum 120mg)
* Neoral (Cyclosporin) – 14mg/kg, PO
* Tacrolimus – 0.15mg/kg, PO
* Mycophenolate 500-700 mg/m² (maximum 1gm) or Azathioprine 2mg/kg
* Methylprednisolone 10mg/kg IV (given intraoperatively)

The above oral medications are to be given with a small sip of water prior to theatre.

Antibody Therapy
Recommended dosing levels for antibody therapy to be given as part of the induction regime are as follows:

Basiliximab (Simulect):-
Adult: 20mg IV, prior to or within 2 hours of surgery and on day 4 following surgery.
Paediatric: 12/mg/m² IV, given in theatre or within 2 hours of implantation and on day 4 following surgery.
Intraoperative Treatment

* Central line should be inserted

* Consideration should be given to antibiotic prophylaxis in patients who have had a recent infection e.g. peritonitis, UTI, or have vascular access. Ideally, prophylaxis will be based on the antibiotic sensitivity of the organism. However if sensitivities are not available prior to transplant, prophylaxis may include Vancomycin or the physicians choice of Cephalosporin.

* Fluids should be administered according to the guidelines, which can be found in the postoperative observation/procedure - medical section. Lasix may be administered if urine output is not established immediately.

Record the following times:
* time kidney taken out of ice
* time venous clamp removed
* time arterial clamp removed
* time urine output begins

Administer the following Methylprednisolone:
Adult: 500mg, IV methylprednisolone given at time clamps are released in theatre.
Paediatric: 10mg/kg IV methylprednisolone given at time clamps are released in theatre.

Preparation of the Room – Nursing

After the patient has been transferred to the operating theatre the bedside area and room should be prepared in the following way:
* Ensure that the bed, bedside table, locker, walls and floor are thoroughly cleaned. Assess for need to terminally clean the room
* Ensure that a minimum of the following equipment is in the room: oxygen tubing, hudson mask, guedel airway, Y-suction catheters FG 12 x2 in the emergency pack and ensure emergency equipment is functioning.
* Collect the following equipment which is to remain in the patients room for their entire stay in hospital,
  - Sphygmomanometer and stethoscope
  - Drip stands x 2
  - Spirit level
  - 3 Infusion pumps
* Ensure that all equipment is wiped down with methylated spirits prior to being brought into the room.
* Check that there are adequate quantities of 4% NSA and gelofusion available on the ward. There should be at least 4 bottles of each.
Preparation of the Trolley - Nursing

Use a large trolley with two drawers. Clean it thoroughly with methylated spirits and line the drawers with blue sheets. Place the following in the draws of the trolley:

- Alco wipes x 12
- Betadine wipes x 12
- Needles 18g, 21g, 23g and 25g x 10 of each
- Syringes, 2ml, 5ml, 10ml and 20ml x 6 of each
- Ampoules of water and saline for injection x 6 of each
- Intravenous bungs x 4
- Wound swab sticks x 4
- IV methylprednisolone: 500mg x 2 and 40mg x 4
- Dressing packs x 4
- Large combines x 3
- Drain dressings x 3
- Gauze squares x 5 packs
- Opsite small and large x 2 of each
- Sterile Saline 30ml sachets x 5
- Sterile gloves x 4 pairs
- Micropore and elastoplast x 1 roll or each
- Permanent marking pen
- Lanolin, mouthwash, sodium bicarbonate mouth wash and nilstat x 1 of each
- Blood tubes, red, purple and blue top x 4 of each
- Blood gas syringes x 2
- Venigard and venijet needles x 3 of each
- Tourniquet
- Peripheral cannulae, 18g and 20g x 2 of each
- Infusion set, burette and blood pump set x 1 of each
- Sterile specimen jars x 4 of each
- Blood Culture bottles x 1 set
- Drainage bags x 2 of each
- Alcohol 70% and Betadine x 1 of each
- Blue sheets x 6

Immediate Post Operative Care

Medical

The patient will be met in recovery by the renal registrar and time permitting, a senior member of the nursing staff.

The following will be monitored whilst the patient is in recovery:-
* UEC’s, and electrolytes (to be taken immediately)
* FBC (to be taken immediately), transfuse ONLY if Hb < 7.0g/L or <8.0g/L and active haemorrhage or impaired haemodynamics.
* Urine output – check IDC for patency. If necessary diuretics may be used to establish a urine output.
* Maintenance of patient haemodynamics including amount of fluid status.
* Intravenous fluids – match urine output plus 20% (initially)
* Check function of CVP line
* Oxygen therapy at 4 –6 L/min, monitor oxygen saturations
* Chest x-ray should be taken and reviewed to check the position of the central line either in recovery or upon return to the ward.
* Wound drains: check amount of drainage, colour of drainage etc.
* Check wound for signs of ooze and haematoma.
* Patient controlled analgesia (PCA) should be running through one of the lumens of the central line (not the brown).
* Confirm administration of methylprednisolone in operating theatre.
* Check vascular access for patency.

**Medical Contacts Post Transplant**

The first call should be made to the on call renal resident and if they are not available then the renal registrar. For paediatrics, the paediatric nephrologist will accept the first call.

If the renal registrar is uncontactable or if it is after hours and the situation is urgent the medical registrar should be called as well as the renal consultant responsible for the patient.

**Nursing**

1. Senior nurse from transplant team to attend recovery with the registrar whenever possible.

2. When the patient returns to the ward the following should be checked:-
   * Respiratory status and level of consciousness
   * Wound for signs of ooze and haematoma
   * Drains for signs of excessive drainage
   * IDC for the presence of clots and amount of drainage
   * Ensure IDC and drains are well secured to the patient to prevent traction form occurring.
   * The settings on the PCA machine are correct
   * Vascular access for patency

3. Record blood pressure, pulse, CVP and respiration as follows:-
   * Every 30 minutes for 2 hours then,
   * Every hour for 8 hours or until stable then,
   * 2nd hourly for 8 hours or until stable,
   * Then 4th hourly
4. The urine output should be measured and recorded hourly. If the patient has a urine output of zero mls this must be recorded on the fluid balance chart and a comment documented about the action taken.

5. Care of the Triple Lumen Central Line:-
   * Ensure CVP manometer is connected to the brown lumen
   * Administer fluid replacement as charted via intravenous pump

6. Check wound drains for excessive ooze and drainage every hour.

7. Check respiratory status and level of consciousness (the patient should be able to lift their head off the pillow).

8. Check oxygen saturation hourly for 8 hours or until stable. Administer Oxygen therapy.

9. Record Patient Controlled Analgesia observations as per protocol.

10. Blood sugar levels (BSL) should be checked QID while on high dose steroids for patients who did not suffer diabetes pre transplant, and action taken if BSL > 14mmol/L.

11. BSL’s should be checked hourly on patients on insulin infusions and 2nd hourly on patients with pre existing diabetes, not on insulin infusions. Notify RMO if BSL ≤4 mmol/L and ≥ 20 mmol/L.

12. Check vascular access for thrill and bruit hourly for 4 hours then 4th hourly for 24 hours, as it is in the immediate postoperative period that it may clot.

The RMO/Renal Registrar should be notified if:-

* There is a marked change in the patient’s vital signs.
* There is deterioration or marked increase in the patient’s urine output.
* If the urine becomes heavily blood stained.
* There is excessive drainage or ooze from the wound and/or drains.
* If the wound drainage increases and the urine output decreases, or the colour of the drainage fluid starts to resemble urine.
* If the patient starts to complain about excessive pain over the graft.
* If the patient’s fistula ceases to function.
* Systolic blood pressure is < 100mmHg – as this may result in poor graft perfusion and the patient’s vascular access may clot.
* Diastolic blood pressure is > 100mmHg as this may cause the rupture of the graft’s vascular anastamosis.
* A temperature may be due to hyperacute rejection, blood transfusion reaction or septicaemia. Blood cultures should be taken when temperature is > 37.5°C.
**Respiratory distress** as this may be due to the inadequate reversal of muscle relaxants.

* **CVP < 8** – as this may be due to hypovolaemia and result in inadequate perfusion of the graft.

* **CVP > 12** – as this may be due to fluid overload and result in pulmonary oedema, especially in patients who are oliguric or anuric in the immediate postoperative period.

## Multidisciplinary Pathway

A multidisciplinary pathway has been developed for post transplant care.

A copy of this can be found in Appendix I.
**Medical**

**General**

**Fluid Management**
Fluid is usually replaced at last hours urine output plus 20 – 50mls / hour. The goal is to have a urine output of 200-400 mls/hr.

**Decreased urine output**
If the post transplant urine output is low (<50 mls/hour) and if after clinical and haemodynamic evaluation, the patient is felt to be hypovolaemic normal saline boluses are given in 250-1000ml increments.

If the patient is found to have normal or increased intravascular volume, frusemide should be given. For recipients of a cadaveric organ transplant, 100-200 mg of IV lasix should be given, for living related recipients, start with 20-40mg of IV lasix.

If diuresis follows, the urine output should be replaced vol per vol with normal saline.

**Increased urine output**
If the urine output is excessive the next hours fluid replacement should be reduced. Therefore if the next hours urine output is > 1000mls/hr, the next hours rate of fluid replacement may be reduced by up to 300mls. If the urine output remains more than 700mls/hr than the fluid replacement rate should again be reduced by up to 300mls.

**Hypertension**
Control should be individualized depending on severity and other patient factors.

**Blood Tests**
As per clinical pathway.

**Anti-Lipid Therapy**
If medically feasible anti-lipid therapy will be ceased in the immediate post-operative period due to the potential for rhabdomyolysis in patients receiving calcineurin inhibitors and statins. The need for lipid therapy will be reevaluated at 3 months post transplant unless indicated earlier.

**Delayed Graft Function**
Delayed graft function (DGF) or renal dysfunction is commonly seen in the immediate post transplant period in cadaver renal transplants. The risk factors associated with an increased incidence of DGF are:

- **Donor factors:** brain injury, donor hypovolaemia and hypotension, prolonged cold or warm ischaemic times, older donors and donors with hypertension or vascular occlusive disease, oliguric donor, injury incurred during procurement.

- **Recipient factors:** high PRA% (>50%), mean arterial blood pressure of < 100 mm Hg and female donor to male recipient. \(^{(48)}\)

It was also shown that delayed graft function on the basis of acute tubular necrosis is an independent risk factor for acute rejection and suboptimal graft function at 1 year. \(^{(48)}\)
Rejection

Hyperacute Rejection
Is very rare today with current crossmatching and tissue typing technology. Always occurs within the first 24 hours of transplant. It is due to preformed antibodies to donor antigens present in the recipient’s serum at the time of transplantation. A kidney with hyperacute rejection will usually not respond to therapy and therefore will need to be removed.

Acute Rejection
This is the most common cause of graft dysfunction in the early and late period. It is seen most commonly in the first 90 days after transplant. The clinical signs of acute rejection are fever, weight gain, oliguria, oedema, hypertension and tenderness over the graft. An increase in serum creatinine of > 20% and a decrease in urine output are common signs of acute rejection. Treatment options are detailed later in this manual.

Nephrotoxicity
Nephrotoxicity due to calcineurin inhibitors is often difficult to distinguish from acute rejection early in the post transplant period and a biopsy is needed to differentiate.

Vascular
Vascular obstruction in either an artery or vein may occur in the first few days. Diagnosis is confirmed by doppler flow studies. The most common types of obstruction are listed below.

Renal Artery Thrombosis

Causes:
Thrombosis may occur due to a technical complication such as kinking of the renal artery, atherosclerotic disease in the donor or recipient, disparate donor/recipient arterial segments as in the transplantation of paediatric kidneys into adult recipients, or the presence of multiple renal arteries. Thrombosis may also occur due to hyperacute rejection, CyA related or tacrolimus related arteriopathy, or a hypocoagulable state such as the presence of antiphospholipid antibody in a patient with lupus nephritis.(49)

Signs:
It may present as a sudden cessation of urine output in a previously functioning graft.

Diagnosis:
Is suggested by Doppler flow study and may be confirmed by a renal angiogram.

Treatment:
Surgical exploration and thrombectomy.

Renal Vein Thrombosis

Causes:
Renal vein thrombosis is a relatively rare complication. The causes of renal vein thrombosis include: mechanical compression by haematoma or lymphocele, angulation or kinking of the renal vein, stenotic lesion at the anastomosis, or a
hypocoagulable state. (49)

**Signs and Symptoms:**
Pain and tenderness over the renal graft site with haematuria, proteinuria and oliguria. The graft is swollen with accompanying swelling of the ipsilateral lower extremity.

**Diagnosis:**
Doppler or angiogram.

**Treatment:**
Exploration and thrombectomy.

**Renal Artery Stenosis**
Renal artery stenosis can occur as an early or late complication of transplantation.

**Causes:**
Atheromatous occlusive vascular disease either in the donor or the recipient vessels, intimal hyperplasia in response to intraoperative trauma, or by immunologic factors.

**Signs and Symptoms:**
Severe hypertension with worsening renal function in the absence of acute rejection and C\(_\text{yA}\) or Tacrolimus nephrotoxicity. A bruit may be heard over the graft site. A sudden decline in renal function following treatment with an ACE inhibitor.

**Diagnosis:**
Doppler is used as a screening test with confirmation by renal angiography.

**Treatment:**
Percutaneous transluminal angioplasty conducted simultaneously with diagnosis +/- stent.

**Lymphocele**

**Cause:**
Lymphoceles are collections of lymph caused by leakage from severed lymphatics that overlay the iliac vessels.

**Signs and Symptoms:**
Lymphoceles may present by producing ureteral obstruction; by compressing the iliac vein, leading to leg swelling; or as an abdominal mass.

**Diagnosis:**
Ultrasound

**Treatment:**
Percutaneous aspiration should be performed if there is suspicion of a ureteral leak, obstruction or infection. Percutaneous aspiration is associated with a high recurrence rate with a potential for persistent lymph leak and risk of infection. Other options include surgical marsupialization or the creation of a peritoneal window.

**Surgical Drains**
If the colour of the drainage fluid appears yellow in colour, if the urine output suddenly
decreases and the output from the drains increases the patient may have a urine leak. The drainage fluid should be analysed for urea, creatinine and electrolytes, cell count and gram stain to differentiate a urine leak from a lymphocele, haematoma and to rule out infection.

A fluid collection with a creatinine greater than the serum creatinine suggests a urine leak, a cell count compromised predominantly of lymphocytes suggests a lymphocele, and a Gram stain primarily of neutrophils and bacteria suggests an infection.\textsuperscript{[59]}

**Stent Removal**

Stents are removed cystoscopically 4 – 6 weeks post transplant if not removed at the time the catheter is removed when the stent is tied to the catheter.

**Urological**

**Urine Leak**

*Cause:*
The uretero-vesicular junction is the most common site for leaks to occur, leaks may also occur in the upper urinary tract.

*Signs and Symptoms:*
Delayed graft function, rising serum creatinine, decreased urine output, pain (burning in character), swelling and discharge from wound or drain.

*Diagnosis:*
Ultrasound, showing a fluid collection, or renal scan.

*Treatment:*
Nephrostomy and ureteral stent placement or surgical intervention.

**Obstruction**

This is the most common urologic complication following transplantation and may occur as an early or late complication.

*Causes:*
Urethral stenosis (especially if prior history of transurethral resection of the prostate, or bladder neck obstruction secondary prostatism), ureteral strictures, ureteric ischaemia (due to poor blood supply) fluid collections (e.g. lymphocele, haematoma etc), and occasionally blood clots or stones. Diabetic patients may have a functional obstruction from a neurogenic bladder.

*Signs and Symptoms:*
Unexpected rise in serum creatinine, or failure to fall post transplant, hyperkalaemia (due to tubular back leak and reabsorption), a sudden increase of CsA levels on a stable dose (due to failure to excrete cyclosporine and its metabolites).

*Diagnosis:*
An ultrasound should show hydronephrosis or fluid collection. Percutaneous antegrade pyelogram should determine the site of the obstruction.

*Treatment:*
Ureteric obstruction is initially managed by placement of a percutaneous nephrostomy that relieve obstruction and allows the renal function to improve. Treatment options
include balloon dilatation or surgical reconstruction.

**Infection**
CMV disease is a CMV infection accompanied by sign(s) and/or symptoms of the disease. The most common sign of infection is a fever (>38°C), other signs of infection are; leucopaenia, thrombocytopaenia and elevated ALT. Blood products should be administered from CMV negative donors if possible. A leucocyte filter should be used when administering packed red blood cells, whole blood and platelets.
Nursing

Details of some of the following can be accessed in the ‘Clinical Standards and Procedures’ manual located on the ward

Vital Signs

- In the initial post-operative period the patient will have a PCA for pain control. Observations are according to the PCA protocol and the patient’s condition.
- Central venous pressure (CVP) monitoring should be conducted at the following intervals:
  - Hourly for the first 4 hours
  - 2nd hourly for next 4 hours
  - The once per shift for the duration of the line

Temperature

- Record 4th hourly
- Report any fever > 37.2
- Blood cultures should be collected if temperature ≥ 37.5
- If the temperature is >37.5 then the following cultures/swabs should be done:
  - Peripheral and central line blood cultures
  - MSU, wound and drain site swabs
  - Drain fluid specimen for M/C/S
- The suture line, drain sites and TLC should be inspected for signs of redness, exudate and inflammation

Pulse

- Record 4th hourly
- If the pulse is irregular or the patient is tachycardic (≥ 100 bpm) an ECG should be attended.

Blood Pressure

- Record 4th hourly (if stable)
- The patient should have lying and standing blood pressures

Respirations

- Record 4th hourly

Fistula Observations

- 4th hourly for the first 48 hours
- Then once per shift thereafter

The following abnormalities should be reported to the RMO:-

- Diastolic BP > 100 mmHg
- Systolic BP > 150 mmHg
- Systolic BP < 100 mmHg
- Postural drop > 20 mmHg
• Abnormal respiration rate of effort
• Tachycardia, irregular heart rate
• Temp > 37.2
• If fistula no longer patent

Central Venous Pressure
The central venous pressure (CVP) corresponds to the right atrial pressure and reflects the end diastolic pressure (preload) in the right ventricle when the tricuspid valve is opened.

The CVP measurement provides information about three parameters:-
• Central venous blood volume (blood returning to the heart)
• Vascular tone
• The effectiveness of the heart as a pump.

Medical staff should specify a postoperative target CVP range. If the CVP range falls significantly the medical officer should be notified and a fluid challenge is usually administered.

In order to obtain an accurate CVP the following procedures should be followed in accordance with the Clinical Standards and procedures manual section 5.C.7:
• The patient should be positioned either lying flat or with the head of the bed elevated at 20 degrees. It is preferable to perform the subsequent CVP measures with the patient in the same position in order to minimise variability in measurements.
• The 0 point of the manometer must be level with the fourth intercostal space. This position corresponds with the midaxillary line of the patient and can be determined by measuring approximately 5cm below the sternum. This point on the chest should be marked with a cross to ensure consistency with future readings.
• The manometer should be connected to the brown lumen of the central line, as this is the largest. All other infusions should be connected to the other lumens of the central line. 5% Dextrose should be administered through the brown lumen in order to ensure the lumen is kept patent.
• If the system is patent the fluid column falls freely and a slight fluctuation of the fluid column is apparent. This fluctuation follows the patient’s respiratory pattern and will fall on inspiration and rise on expiration due to changes in the interpulmonary pressure.

Triple Lumen Catheter (TLC)
• The TLC remains in for 4 – 5 days following transplant.
• Ensure that the TLC is secured well to the patient in order to prevent traction from occurring on the exit site. In accordance with Section 5.C2 of the Clinical Standards and Procedure Manual
• The dressing and lines should be changed on Monday, Wednesday and Friday. The change of lines and dressing should be documented both on the nursing care plan, CVC line change/dressing form and in the patient notes. Lines should be changed with each disconnect procedure in accordance with the clinical standards and Procedures Manual Section 5.C.3 and dressing in accordance

- Fluids are changed at the end of each 24 hour period. No flask or bag should remain hanging for longer than 24 hours.
- A daily inspection of the entry site should be made with any signs of redness and inflammation reported to the RMO and a swab taken. Results should be documented on the nursing care plan and in the patient notes.
- Upon removal of the TLC the tip should be sent for culture and sensitivity.

**Indwelling Catheter (IDC)**

- Continue to measure urine output hourly.
- Ensure that the catheter is tapped well to the patient’s thigh, in order to prevent traction on the catheter, which may result in the catheter becoming dislodged. Please ensure the tape is not constricting the catheter tubing.
- Observe IDC for patency, excessive clots or frank bleeding. If the urine is very blood stained the tubing should be milked frequently to prevent clots from forming in the tubing. If the urine output decreases the catheter should be checked for kinks or clots and the resident or senior nurse notified. A bladder scan should be considered in order to establish if the bladder is empty or full. If it is suspected that the catheter is blocked the a specialist practice nurse should assess the IDC and consider flushing it. The medical team should be notified about any changes to the IDC. The IDC should never be clamped (including for ultrasound) as this may lead to disruption of the vesicoureteric anastomosis.
- 4th hourly perineal and catheter care should be attended in accordance with Section 3.D of the Clinical Standards and Procedure Manual. The IDC will remain insitu for 7 -10 days to allow the vesicoureteric anastomosis to heal.

Note: Renal transplant patients will pass most of their urine from midday to 0500 hours, and there may be a reduction in the output from 055 hours to midday. This is thought to be due to a reversal in the diurnal pattern of the kidney.

Notify the medical staff if:-

- The patient suddenly becomes anuric
- The patient’s urine output increases or decreases significantly over a two-hour period and there is a large residual seen on bladder scan.
- The urine suddenly becomes heavily blood stained
- There is concern about patency of the IDC following flushing.

**Bladder Irrigation**

- Some patients may need to have their bladder irrigated in the immediate post operative period due to excessive clot formation. Refer to Section 13.C of the Clinical Standards and Procedure Manual for this procedure.
- When manually irrigating the catheter no more than 30 mls of normal saline should be instilled at a time. If you are unable to withdraw the fluid after gently
pulling back on the syringe then a further 30 mls should be instilled. If the catheter is still blocked, the catheter will need to be changed.

- Excessive force should not be used when trying to draw back on the syringe as this may lead to disruption of the vesicoureteric anastomosis.
- If clot retention is going to be a chronic problem in the postoperative period the patient may require intermittent closed circuit irrigation. When setting up the irrigation set a burette should be connected to the bag or irrigation fluid in order that the amount instilled each hour can be accurately recorded.
- 30mls should be instilled each hour and when the urine is measured the 30mls should be subtracted from the total volume to give the hours urine output.
- On the fluid balance chart the following should be recorded:-
  - Amount of irrigation fluid instilled each hour
  - Amount emptied each hour
  - Final urine output

**Post IDC Removal**

- Following removal of the catheter the patient should be encouraged to void every 2-3 hours. The bladder must not be allowed to become over distended. Post void residuals should be measured each time for the first 24 hrs.
- An MSU will be taken after catheter removal.
- Once the catheter is removed patients should be educated to measure and record their own urine output. It is the nurse’s responsibility to ensure that this is being done and report any changes.
- The patient may pass small volumes of urine very frequently due to a reduction in bladder capacity while they were anuric. It may take up to three months before the patient regains a normal bladder capacity.
- If the patient complains of burning or stinging when they pass urine or are febrile (>37.5) then an MSU should be collected.

**Fluid Balance / Fluid Replacement**

- Clearly label the each of the lumens on the central line as 1, 2 and 3
- Fluid replacement is dependent on the patient’s urine output and clinical status. Fluid is usually replaced at last hours urine output plus 20-50 mls/hour. The fluids should be infused via an infusion pump and each hour both the rate of the infusion and the volume to be infused will be dialed up on the pump. It is important to remember that:
  - A well-hydrated patient with a functioning graft will have their urine output replaced hourly
  - A well-hydrated patient with a nonfunctioning graft may only require 500mls in 24 hours.
- A strict fluid balance chart should be kept at all times during the patient’s entire admission. The fluid balance chart should be totaled at the end of the 24 hour period and recorded on the fluid summary chart. Drain output must be recorded at 2400 each shift.
- Patient’s with a non functioning graft or partially functioning graft usually remain on a fluid restriction of 500-1000mls/day – this includes both intravenous and oral fluids.
• Patient’s with a functioning graft are usually not restricted and in some cases may need to be encouraged. This depends on the patient’s clinical status. The following needs to be considered when assessing fluid status:
  - Weight in relation to previous days
  - Total daily urine output
  - Presence of oedema
  - Blood pressure – both lying and standing
  - Jugular venous pressure
  - Skin turgor
  - Moistness of mucous membranes
  - Whether the patient is thirsty

Patients who were on a stringent fluid restriction prior to transplantation (<800mls) may find it extremely difficult to keep up with their fluid intake in the postoperative period. These patients may require frequent reminders and encouragement to drink.

Notify the RMO/Renal Registrar if:
  - The patient suddenly becomes anuric
  - The patient’s urine output increases or decreases significantly over a two hour period.
  - The urine suddenly becomes heavily blood stained.
  - The IDC becomes blocked.

Weight
The patient should be weighed daily, preferably before breakfast.

An increase in weight may indicate:
  • Fluid overload
  • Rejection

A decrease in weight may indicate:
  • Loss of excess fluid volume
  • Dehydration

Wound Care
  • The dressing is left intact for 48 hours unless there is an indication to take it down earlier. (i.e. excessive ooze or if the patient is having a renal ultrasound)
  • Once the dressing has been taken down the wound should be washed daily with antiseptic soap and left open.
  • A daily inspection of the wound should be made and findings documented on the wound care chart and in the patient notes.
  • Any signs of redness and inflammation should be reported to the RMO and a swab taken. Remember that immunosuppressive therapy may mask the signs of infection.
  • The staples / sutures are usually left intact for 14 days.
  • Once the staples / sutures are removed the wound should be steristriped. The
steristrips should be left insitu until they fall off of their own accord.

**Drains**

- The patient will return to the ward with 1-3 drains insitu. The following should be checked:-
  - That the drains are well tapped to the patient to prevent traction on the exit site, remove the brown elastoplast and replace with white elastoplast if no contraindications.
  - Observe the wound and drainage for signs of haemorrhage, haematoma and excessive pain hourly. If the drainage is excessive both the renal and surgical registrar should be notified.
  - If the colour of the drainage is yellowish, or if the urine output suddenly decreases and the output from the drains increases the patient may have a urine leak. The renal registrar should be notified immediately and a specimen of drainage fluid sent for chemical analysis (urea, creatinine and electrolytes)
  - The output from the drains should be recorded on the fluid balance chart and fluid summary every day.
  - Drainage bags should be marked daily - this shows the amount of drainage for the previous 24 hour period. Drainage bags should be changed PRN.
- The dressings around the drains remain intact for 48 hours.
- Once the dressing has been taken down the wound should be washed daily with antiseptic soap and then redressed, cleaning the exit site with normal saline, then applying betadine and covering the drains with a dressing (NAD or drain dressing).
- If using haemovac drains, they will need to be revaced every couple of hours to prevent clots from forming in the tubing.
- For patients still requiring haemodialysis, the drains should be inspected frequently for signs of increasing ooze or drainage for the first four hours after dialysis.

**Blood Sugar Levels (BSL)**

- The patient without pre transplant diabetes should have their BSL checked QID for the first 48 hours and then BD providing that they are <10mmol/L.
- If the BSL is to be checked once daily then it should be checked in the evening as this is when the patient is most likely to experience hyperglycaemia secondary to steroids.

**Notify RMO/Renal Registrar if:**

**The patient has 2 readings > 14 mmol/L in a 24 hour period.**

**Diabetic Patients**

- Diabetic patients will require their BSL’s to be monitored 2nd hourly.
- If the patient with diabetes is on an insulin infusion, then the BSL’s should be monitored hourly and rate adjusted as per insulin infusion protocol.
• The insulin infusion will need to be changed every 24 hours.
• The RMO should be notified if a BSL is <4 mmol/L or >20 mmol/L.
• Patients on an insulin infusion will require close monitoring of their serum potassium.
• Daily urinalysis for glucose and ketones should be attended.
• Note: Patients with diabetes may have a tendency to become hyperglycaemic in the evenings as a result of taking prednisone.

**Analgesia**

• Encourage use of PCA. Excessive pain over the graft in the first 48 hours may be due to hyperacute rejection.
• The settings on the PCA machine should be checked and compared with the PCA order at the beginning of each shift to ensure they are correct.
• The PCA bag should be changed every 24 hours.
• Administer antispasmodics for bladder spasms as prescribed. Bladder spasms are very common and may be severe in the post-operative period. Some patients may experience bladder spasms until the catheter is removed.

**Notify the medical staff if:-**

• The patient complains of excessive pain over the graft.

**Physiotherapy**

• The patient should be seen as early as possible after surgery by the physiotherapist and then daily.
• Encourage deep breathing and coughing exercises every 2 hours in the initial post-operative phase (whilst awake) to prevent post-operative complications including chest infections and thromboembolic events.
• Encourage passive leg exercises
• Encourage early ambulation, the patient may get out of bed to be weighed on the first day post op.

**Mouth Care**

• Ensure that the patient is charted for nilstat drops and sodium bicarbonate mouth wash. Instruct patient on how and when to use these.
• The patient should be encouraged to brush their teeth with a soft bristled toothbrush after each meal.
• Inspect the mouth daily for signs of sores or ulcerations. Any lesions in the mouth or on the lips should be reported to the RMO immediately.

**Nutrition**

• The patient will remain nil by mouth until bowel sounds are present, then they will progress from sips of water, to clear fluids, free fluids, light diet and then a full diet.
  • If the patient is passing urine and their urea and creatinine levels are
approaching normal they may have a relatively free diet. However salt and potassium may still need to be restricted.

- Steroids may result in an increase in appetite and the patient may find that they are continually hungry.
- If the patient requires dialysis following transplantation then they will need to remain on the diet they were on prior to transplantation.
- Due to the patient’s immunocompromised state they will need to be on an immuno diet. This diet excludes the majority of foods which have a high probability of causing food poisoning or opportunistic infections (e.g. Listeria)
- The dietician should see the patient prior to discharge.

**Dialysis Post Transplant**

Primary non-function may occur in the immediate post transplant period. Indications for dialysis are generally no different from those that apply in other situations of acute renal failure and include:

**Indications**
- Oliguria (or no increase from pre transplant output) greater than 24 hours despite volume replacement and in the absence of obstruction and / or urine leak.
- Hyperkalaemia – if unable to treat medically
- Severe metabolic acidosis
- Volume overload (not responding to diuretic)
- Rising creatinine and urea levels.
- Prior to commencement of OKT3 in presence of volume overload.

**Peritoneal Dialysis (PD)**
- Is still possible after transplant unless the surgeon has entered the peritoneal cavity, or the PD catheter has been removed.
- If PD is required after the operation, smaller volumes may need to be used initially to prevent leaks from occurring. While the patient is on PD the drains should be checked frequently for excessive drainage which may indicate the leakage of dialysis fluid into the drains. If this occurs the patient should be capped off and the medical staff notified.

**Immunosuppressants and Dialysis**
- Cyclosporin, mycophenolate, tacrolimus, sirolimus and prednisolone are not removed during haemodialysis or peritoneal dialysis.
- Azathioprine is removed during haemodialysis but not during peritoneal dialysis.
Medication Administration - Nursing

Methylprednisolone

Compatibility
Methylprednisolone may be reconstituted and infused with Normal Saline, 4% Dextrose and 0.18% saline and 5% Dextrose.

Dilution
- Supplied with Fluid to reconstitute powder
- Doses of 1-60mg should be diluted in 30mls of compatible solution
- Doses of 61-125 mg should be diluted in 50 mls
- Doses of 125 – 500mg should be diluted in 100mls
- Doses over 500mg should be diluted in 200mls

Note: If the patient is on a fluid restriction doses up to 1gm may be diluted in 100mls.

Rate of Infusion
- 20 –125 mg infuse over 30 minutes
- 126-500mg infuse over 1 hour
- over 500mg infuse over 2 hours

Cyclosporin (Neoral or Sandimmun)

Cyclosporin can be administered either orally or intravenously. Oral administration of CyA has been detailed earlier in the manual. To administer intravenous CyA the following procedure should be followed:

Compatibility:
Normal Saline, 4% Dextrose and 0.18% Saline and 5% Dextrose

Dilution:
- Dilute in 100 mls of compatible fluid.
- As CyA is an oily liquid, when it is added to the burette containing the IV fluid it should be agitated to mix the solution.

Rate of Infusion:
Given over 2 hours

Precautions:
- Risk of anaphylaxis with IV administration
- May interact with PVC IV infusion tubing
- Do not give with Ketoconazole

Mycophenolate Mofetil (MMF)

The intravenous MMF administration guidelines can be found in Appendix D.
Rapamycin (Sirolimus) - Liquid preparation

Dilution:
- Sirolimus liquid is to be diluted in a minimum of 60mls of water or orange juice.
- Sirolimus should be mixed in a crockery cup (not plastic) and stirred vigorously for 1 minute, then taken immediately.
- Pour a further 120mls of water or orange juice into the cup and drink the solution.
- Grapefruit juice, apple juice or other liquids are not to be used to dilute the sirolimus solution.

How to administer Sirolimus:
- Remove the safety cap from the solution bottle and replace it with the blue adapta cap that has been provided.
- Insert the syringe that has been provided in the opening of the adapta cap and depress the plunger of the syringe completely before filling.
- Invert the bottle with the syringe attached.
- Withdraw the exact amount of solution as charted.
- Measure the solution so that the top of the black line plunger is even with the line corresponding to the exact amount, which is prescribed.
- Place the bottle down in the upright position and carefully remove the syringe.
- Add Sirolimus to the patient’s choice of liquid.

Precautions:
- Sirolimus liquid concentrate must be stored protected from light and kept refrigerated at 2 –8 °C.
- Do not mix sirolimus solution in a paper, plastic or polystyrene cup.
- Sirolimus must be administered at least 4 hours after the morning dose of cyclosporin.
- Once the oral solution has been opened, the contents should be refrigerated and used within 1 month.
- Sirolimus oral solution may develop a slight haze when refrigerated; this haze does not affect the quality of the product. If such a haze occurs, allow the product to stand at room temperature and shake gently until the haze disappears.

Azathioprine (AZA)

Compatibility
The intravenous formulation of Azathioprine is compatible with 0.9% Sodium Chloride, 4% Dextrose & 0.18% Saline and 5% Dextrose.

Dilution
- Added to a 100ml flask of Normal Saline in pharmacy or reconstituted by the registrar.
Rate of Infusion
• Administer over 30 minutes

Precautions
• This drug is a cytotoxic agent, cytotoxic precautions must be adhered to when administering AZA and when discarding the empty flask. The empty flask, gown and gloves worn must be discarded in the purple cytotoxic waste bins.
• White cell count must be > 4 X 10^9/L
• The dosage of (AZA) should be reduced if allopurinol is commenced.

OKT3 (Orthoclone T3)

OKT3 Administration
Due to the major side effect of pulmonary oedema associated with OKT3 administration the following must be ordered and reviewed by the medical team prior to the first dose:
• Ensure the patient is not fluid-overloaded (weight should be < 3% above ideal).
• Chest X-ray is clear.
• Temp < 38°C
• White cell count > 3.0 X 10^9/L.
Ensure that an artificial airway, adrenaline, oxygen and additional hydrocortisone are at hand.
Severe reactions usually occur only with the first 1 -2 doses, because of this the following prophylaxis will be given 30 -60 minutes prior to the first 2 doses:
Adults
• Methylprednisolone 250mg IV (Day 1) and 125mg IV (day2).
• Paracetamol 1 g oral
• Promethazine 25mg oral.
OKT3 is drawn up through a 0.22 micron filter and injected through a fresh needle over < 1 minute.
OKT3 should be administered by a medical officer.

Observations
For the first and second dose:
• BP, Temp and pulse prior to administration and then every 15 mins for 2 hoursthen half hourly for 2 hours
For the subsequent doses:
• Bp, Temp & pulse prior to administration and then 4th hourly

Side Effects: Anaphylaxis, fever, pulmonary oedema, dyspnoea, wheeze, nausea, vomiting, chest pain, tachycardia, hypotension, tremor, headache and weakness.

ATGAM (or ATG)

Compatibility
• 0.9% saline
• Do not run other IV medications or fluids into the same line as the ATG.
• ATG is incompatible with solutions containing dextrose.

Dilution

• ATG should be diluted in 250-500mls of 0.9% saline.

Rate of Infusion

• Infuse over at least 4 hours with an intravenous pump.

Points to remember when administering ATG:

1. Thirty minutes prior to the commencement of the infusion the following should be administered:
   - 25mg of phenergan IMI
   - 125mg of Methylpred AND/OR 100 mg of hydrocortisone
   - Panadol x 2
2. Panadol should be given every 4 hours for the duration of the infusion.
3. Five minutes prior to the commencement of the infusion a set of baseline observations should be done.
4. During the infusion observations should be done every 30 minutes.
   - If the temperature is > 37.5° C the rate of the infusion should be decreased, and attempts made to reduce the temperature.
   - If the temperature is > 38° C the infusion should be stopped and the RMO notified.
5. Observe the patient for signs of anaphylaxis, such as: wheezing, dyspnoea, chest tightness, hypotension and tachycardia.

Precautions

• Note the ATG batch number and date. Record any adverse reactions.
• Monitor the white cell count (WCC) and platelets daily.
• The WCC should be greater than 3.0 x 10^9/L. If less than 3.0 the dosage of ATG should be reduced or withheld
• The platelet count should be greater than 100 x 10^9/L. If less than 100 the dosage of ATG will need to be reduced.

CMV Hyperimmune Globulin

Method of Administration

Each 30ml ampoule of CMV hyperimmune globulin contains 1.8g of CMV IgG and needs to be further diluted in 60mls of Normal Saline. The infusion should be commenced at rate of 1ml/min.

If the patient experiences no adverse reactions the rate of infusion should be increased every 5 minutes by 1ml/min to a maximum rate of 4ml/min

Observations during infusion

Baseline observations should be recorded just prior to the commencement of the infusion. Following commencement of the infusion the following observations should be recorded:

• BP and Pulse every 5 minutes for the first 20 minutes
BP and Pulse every 15 minutes for 1 hour
• BP and Pulse every 30 minutes until the infusion is completed.

If the patient experiences any adverse reactions the infusion should be stopped, the RMO or registrar notified immediately. If the patient’s condition improves then the infusion should be recommenced at 1ml/minute. The patient’s vital signs should be recorded every 15 minutes for the remainder of the infusion.

How to order CMV Hyperimmune Globulin
The medical staff will need to ring the Red Cross Blood Transfusion Service (RCBTS) and order it.
The RCBTS will then send the immunoglobulin via courier to the blood bank at the hospital.

The phone number of RCBTS in the city: 9229-4444.

**Simulect (Basiliximab)**

**Dose:**
20mg should be given within 2 hours of theatre and again on day 4 post-transplant

**Compatibility:**
• 0.9% Normal Saline or 5% Dextrose
• Separate line, do not run with other IV medications.

**Dilution:**
Dilute in ≥ 50 mls of Normal Saline or 5% Dextrose

**Rate of Infusion:**
• Infuse over 20 -30 minutes.

**Mabthera (Rituximab)**

**Pre-medication:**
Administer as prescribed

**Rate of Infusion:**

<table>
<thead>
<tr>
<th>Time</th>
<th>Rate of Infusion</th>
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<tbody>
<tr>
<td>Initial Rate 0 - 60 minutes</td>
<td>50 mg/h</td>
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<tr>
<td>If no reaction after 60 mins</td>
<td>50 mg/h increments at 30 minute intervals</td>
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<tr>
<td>Maximum Rate</td>
<td>300 mg/h</td>
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</table>

**Observations:**
Baseline: Temp, Pulse, Blood Pressure and Respiratory Rate
Followed by: 15 minute T, P, BP, R for the entire infusion
**Expected side effects:**

**Fever Chills and Rigors:**
Are experienced by approx 50% of all patients. These generally occur within 30 minutes and up to 2 hours after commencing the infusion. If these occur, slow or cease the infusion until the patient’s symptoms have improved. Recomence the infusion at half the rate prior to the reaction and increase as tolerated.

**Transisent Hypotension:**
Slow or cease the infusion until the patient's symptoms have improved. Notify RMO. Recomence the infusion at half the rate prior to the reaction and increase as tolerated.

**Shortness of Breath, Dyspnoea or an Audiblel Wheeze (Rare)**
Ceased the infusion immediately. Notify RMO immediately. Administer appropriate treatment i.e. O2 therapy and observations.

**Hypersensitivity Reactions (Rare)**

Cease infusion immediately. Notify RMO immediately. Administer appropriate treatment i.e. O2 therapy, observations.
Transplant Waiting List – Recipient Summary

Contact Details
Name:     DOB:   Consultant: 
Address:  
Contact: (h)       (m)   (NOK)    (other) 
Name:       Name:  

Medical History (Diabetes, Cardiac, Cerebral, PVD, Chronic infections, chronic lung disease, malignancy, anticoagulants)

Allergies:  

Cause of Renal Failure: 

Dialysis
Start date:   Mode:    Access: 

Surgical History (CABG, Abdominal Surgery, Surgery for PVD etc)

Previous Transplant History
Date of Transplant:      Side of Transplant: 
Date and cause of Graft Failure:  

Transplant Waiting List:
Current PRA %   Peak PRA % 
Date of serum:   Date of Serum: 
Tissue Typing: HLA A:   B:   DR: 
Cross match history:  
Special requests: 

Other Issues
<table>
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<tr>
<th>INVESTIGATIONS</th>
<th>Date</th>
<th>N/A</th>
<th>Results/Action/Outcome</th>
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<tr>
<td>Date</td>
<td>N/A</td>
<td>Results/Action/Outcome</td>
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# Appendix B

## Live Donor Checklist

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Date</th>
<th>Result, action &amp; outcome</th>
<th>Date</th>
<th>Result, action &amp; outcome</th>
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<td>1) Blood Tests:</td>
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<td>a) ABO group</td>
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<td>b) FBC, PI &amp; APTT</td>
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<td>c) Biochemistry</td>
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<td>i) Creatinine</td>
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<td>ii) Elects</td>
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<td>iii) LFT’s</td>
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<td>iv) Glucose</td>
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<td>iv) CMV Ab</td>
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<td>vi) HSV Ab</td>
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<td>vii) HTLV 1&amp;2</td>
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<td>2) Microurine C &amp; S</td>
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<td>3) 24 hr Urine</td>
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<td>b) Protein</td>
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<td>4) Tissue Typing &amp; X-match</td>
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<td>5) Imaging –</td>
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<td>a) CXR</td>
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<td>c) ECG</td>
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<td>e) Cardiac Stress Test*(define)</td>
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<td>h) Ilio-femoral Doppler*</td>
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<td>6) For Women –</td>
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<td>a) Mammogram*</td>
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<td>b) Pap smear*</td>
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<td>7) For Men – PSA*</td>
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<td>8) Psychiatric consultation</td>
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<td>9) Renal angiogram</td>
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<td>10) Surgical Consult</td>
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<td>12) Repeat X-match</td>
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* As indicated
Appendix C: Consent Forms

Acknowledgement of Intent to Accept Renal Transplantation

(To be completed with the second set of tissue typing blood samples)

Health Care Interpreters are available for the signing of patient education documents in Public Hospitals. Please ring 9515-9500

Acknowledgement by Patient

I, __________________________________ of _________________________________

request that I join the Transplant Waiting List so that an operation of renal transplantation can be performed on me if a suitable kidney becomes available. I understand that an assurance has not been given that the operation will be performed by a particular surgeon.

The nature of the operation has been explained to me by ________________________

I understand that the risks from the operation are usually from one of three sources.

Firstly, the complications of the operation itself include infection, bleeding, clotting, blockage of urine flow, poor function, and rejection of the kidney.

Secondly, although every effort has been made to screen the donor for transmissible disorders, there can be no guarantee that the donor did not have such a disorder (e.g., Infection, cancer).

Thirdly, the drugs required to control rejection have side effects, specific for each drug and these have been explained to me.

I also understand that I will not be told any details of the donor which could reveal his or her identity.

Other forms of alternative treatment for kidney failure have been explained to me. I understand that kidney transplantation is a treatment for renal failure, not a cure and that I will need to take drugs to suppress rejection indefinitely. I understand that signing this form does not interfere with my legal rights in the event of negligence nor bind me to accept an offer of a particular kidney for transplantation.

I have had explained to me the need for collecting data on me for the ANZDATA national survey of people receiving a kidney transplant. The information collected will be protected from disclosure to other parties not involved with ANZDATA. Only data that does not identify me as an individual will be released publicly. I have no objection to this data being collected.

DATED this ______________ day of ______________ 200________

Signed __________________________________________

Interpreter (if applicable) _____________________________ Witness
Certification by a Person wishing to direct the donation of their Kidney for Transplantation to a Relative or Friend

Pursuant to the Human Tissue Act 1983, I, __________________________
Date of Birth: __________________________
of: __________________________
Date of Birth: __________________________
certify that:
I am willing to donate my kidney to:

Name of Recipient________________________Relationship: ____________

And that I have been given both written and verbal information about kidney transplantation, including living donor transplantation.

Such information has included:
• The reason for using a live donor as opposed to deceased donation;
• A full description of the procedure;
• Implications of the procedure, such as preparation for surgery by drugs or diet, hospital admission;
• Risks inherent in the procedure including:
  o Surgical risks;
  o Immediate complications as a result of the procedure including risk of kidney failure;
  o Risk of death;
  o Long term risks.
• The process of recovery for the donor, including:
  o Physical rehabilitation and length of expected recovery time;
  o Level of probable pain or discomfort after procedure;
  o Inhibition of normal activity;
• Time off work required (and related financial impact such as access to life insurance etc.)
• The likely outcomes for the recipient (including possibility of failure of the donation, possible complications, prospects of success);
• Possible changes to the donor/recipient relationship (including possible feelings of ‘ownership’ towards the recipient by the donor), the donor feeling the need or

East Coast Renal Services, includes the Hospital Renal Treatment Programmes of the Prince of Wales, Sydney Children’s and St George Hospitals in Sydney and the Illawarra Regional Hospital in Wollongong, NSW, Australia
• right to make demands upon the recipient, and that the donor may be the object of feelings of gratitude by the recipient;
• That I may choose not to proceed with donation at any time before surgery and that it is not a foregone conclusion that donation will occur once donor assessment has begun.

Name: ________________________________
Signed: ______________________________
Witness Name: _________________________
Signature ______________________________
Date: ________________________________
Certification by a Medical Practitioner of Intent of a Person to Donate a Kidney for Transplantation

Pursuant to the Human Tissue Act 1983, I, ___________________________ , a medical practitioner, other than the medical practitioner who will perform the surgery to remove the tissue, certify that:

- the donor's written consent was given in my presence;
- the donor had explained to him or her, before the consent was given, the nature and effect of the removal of the organ from the donor's body;
- at the time the consent was given, I am satisfied that:
  - the donor was not a child;
  - the donor was of competent mind; and
  - the consent was freely given.
- 24 hours, or more, will have passed from the time this consent was given till the time of the donation.

Medical Practitioner:
Name: ___________________________
Signature: _______________________

Witness:
Name: ___________________________
Signature: _______________________
Date: ___________________________
## Appendix D

### Pre-operative Renal Transplant Checklist for Recipients

<table>
<thead>
<tr>
<th>Patient arrival time to ward:</th>
<th>Scheduled time for theatre:</th>
<th>Time left ward for theatre:</th>
<th>Please initial boxes and comment where applicable.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes  No  N/A  Result/Action/Outcome</td>
</tr>
</tbody>
</table>

**CONTACT:**
- Vascular Surgeon
- Anaesthetist
- Nephrologist, discuss clinical trials and immunosuppressive regime
- Theatre staff
- Bed Manager (in hours)
- Nursing Supervisor (after hours)
- Ward Staff
- Haemodialysis (if required)

**GENERAL:**
- Fasting (time of last meal)
- Dialysis
  - Date and type of last dialysis
  - Required pre transplant?
- CAPD patients drained out and capped off
- Vascular access function assessed
- Weight and height
- Urinalysis (if possible)
- Clip (nipple to mid thigh)
- Shower (antibacterial soap)
- Theatre attire

**BLOODS:**
- UEC, FBC, LFT’s, CaMgP04, Albumin BSL, Chol, Trigs, Pregnancy Test, CMV titre, Hep B & C, HIV
- X match 4 units

**MICROBIOLOGY:**
- PD fluid (blood culture bottles and yellow top specimen jar)
- PD exit site swab
- MSU (if possible)
### MISCELLANEOUS:
- IV therapy commenced

**Anti IL 2 Antibody:**
- Name and dose:…………………………..

**Antilymphocyte Therapy:**
- Name and dose:………………………

### Medications:
- Cyclosporine A
- Methylprednisolone 500mg (to be supplied to theatre)
- Mycophenolate
- Tacrolimus
- Sirolimus
- Azathioprine
- Ranitidine
- Antibiotics

**Trial Drug:**
- Name:……………………

### Other tests:
- ECG
- Chest X-ray

### Hospital Consent:
- Should detail side of transplant, cadaver/living related and insertion of central line

**Transplant Specific consent**

**Medical admission complete**

**Nursing admission complete**

**Nursing report written**

**Anaesthetic consult**

**PCA education (time permitting)**

**Physiotherapy consult (if time)**

**Transport arranged to take research bloods to Blood Bank (for NSW donors only)**

---

**Final assessment of the checklist to be made by a registered nurse. Please print your name and the date below once this has been done.**

**Checked by:_________________________ Date Checked:_________________________**
Recipient Preoperative Workup – Medical

Notify Nephrologist and discuss whether to accept kidney on offer.
Notify LifeLink of acceptance of kidney and request that kidney be delivered to Blood Bank at POWH.
Arrange admission – contact bed manager and complete recommendation for admission form.
Notify vascular surgeon, anaesthetist and book theatre
Patient history and physical exam
Urgent bloods:-
FBC and UEC’s (including Ca, PO4 and potassium)
LFT’s, BSL, Lipids – Chol, Trigs, HDL and LDL
APTT, PT
G + H 4 units
Serology: Hep B and C, HIV and CMV and EBV status
PD specimens: gram stain, MC&S, WCC. Mark all forms URGENT and ask them to phone the results through to the ward.
ECG and Chest X-ray
Obtain an informed consent for cadaveric renal transplant and insertion of a Triple Lumen Catheter. Check that the “Intent to Accept Transplant” acknowledgement has been signed.
Ask Nephrologist about potential for participation in any clinical trials. If eligible, consent the patient for the trial(s) and follow the relevant protocol(s).
Consider the CMV status of the recipient and donor. A decision should be made in regards to whether prophylaxis for CMV is indicated.
Consider antibody therapy for high risk recipients (see page 21 of manual).
Prescribe immunosuppressive drugs as per protocol
Contact blood bank (ext 29145) to check if the kidney has arrived, if yes collect and place in fridge in theatre.
Recipient Preoperative Workup – Nursing

Contact nursing supervisor to notify them of transplant and ensure adequate staffing.

Nursing admission
Baseline observations: temperature, pulse, blood pressure, weight and height.
- BSL
- Urinalysis (if possible)
ECG
CXR

Check the patient has signed the consent and that the consent is legal. The consent should detail the side of transplant, whether the kidney is cadaveric or living related and insertion of a triple lumen central line. Also check patient has signed the “Acknowledgement of Intent to Accept Renal Transplant” consent.

Pre-op clip from nipple to mid thigh.
The patient should have a wash with antibacterial soap and dress in theatre attire.
Patients on peritoneal dialysis must be drained out and capped off prior to theatre.
Pre-op chest physiotherapy (time permitting)
Pre-op PCA education (time permitting and if PCA CNC on duty)

The following specimens need to be collected:
- Peritoneal dialysis fluid (in yellow top specimen jar and blood culture bottles)
- PD exit site swab
- Throat and nasal swabs for MRSA
- MSU and Urinalysis (if possible)
- Virology – urine and mouthwash

Administer immunosuppression as charted
Ensure IV Methylprednisolone is charted to be given intraoperatively when the clamps are released and goes to theatre with the patient.
- A nursing report needs to be written.
Appendix E

Intravenous Mycophenolate Administration Protocol

Mycophenolate is available for infusion as a sterile lyophilised white to off-white powder. It is reconstituted and diluted with 5% glucose. Intravenous administration is recommended for those patients who are unable to take oral medication.

Mycophenolate IV should be reconstituted to a concentration of 6mg/ml and must be administered by slow intravenous infusion over a period of 2 hours.

Caution 1:
Mycophenolate IV infusion should never be administered by rapid or bolus intravenous injection.

Caution 2:
Mycophenolate IV solution should not be mixed or administered concurrently via the same catheter with other intravenous drugs or infusion mixtures. Mycophenolate IV is incompatible with the following solutions: 0.9% Normal Saline, Ringers and lactated Ringer’s solution.

Dose for Renal Transplant:
The IV dose for renal transplantation is 1g twice daily.

Administration:
Mycophenolate may be administered as a peripheral intravenous infusion. The risk of phlebitis or thrombosis of the infused vein is 4%. Mycophenolate should be diluted and infused in 5% dextrose over at least a two hour period. The preparation for infusion instructions follow:

Preparation of infusion solution:

Step 1:
- a) Reconstitute the contents of each vial by injecting 14mls of 5% glucose IV solution.
- b) Gently shake the vials to dissolve the drug.
- c) Inspect the resulting solution for particulate matter and discoloration prior to further dilution. Discard any vial in which particulate matter or discoloration is observed.
- d) Two reconstituted vials should be added to 40mls of 5% glucose for infusion. If using a 250ml bag, withdraw 110ml of 5% glucose, 28mls of this solution can be used when reconstituting the 2 vials as described in step one above.

Step 2:
- a) Further dilute the contents of two reconstituted vials with 140mls of 5% glucose IV for a total volume of 168mls and a final concentration of 6mg/ml.
- b) Inspect the infusion for particulate matter and discoloration, discard the infusion solution if any is observed.
- c) Infuse at a rate of 60ml/hour through a peripheral vein. No other infusion solutions or medications should be administered through this vein during the infusion of mycophenolate.

Once reconstituted mycophenolate can be kept for up to 4 hours when stored at 15-30° C. Commencement of administration of the infusion should be within 4 hours of reconstitution.
Appendix F

BANFF Criteria Diagnostic Categories for Renal Allograft Biopsies


1. **Normal**

2. **Antibody-mediated changes** (may coincide with categories 3, 4 and 5 and 6)
   Due to documentation of circulating antidonor antibody, and C4d or allograft pathology
   *C4d deposition without morphologic evidence of active rejection*
   C4d+, presence of circulating antidonor antibodies, no signs of acute or chronic rejection TCMR or ABMR (ie. g0,cg0,ptco, no ptc lamination). Cases with simultaneous borderline changes or ATN are considered indeterminate
   **Acute antibody-mediated rejection**
   C4d+, presence of circulating antidonor antibodies, morphologic evidence of acute tissue injury, such as (Type/Grade):
   I. ATN-like minimal inflammation
   II. Capillary and/or glomerular inflammation (ptc/g >0) and/or thrombosis.
   III. Arterial - v3.
   **Chronic active antibody-mediated rejection**
   C4d+, presence of circulating antidonor antibodies, morphologic evidence of chronic tissue injury, such as glomerular double contours and/or peritubular capillary basement membrane multilayering and/or interstitial fibrosis/tubular atrophy and/or fibrous intimal thickening in arteries.
   C4d -ve . Suspicious for antibody mediated rejection in presence of morphologic evidence of tissue injury and alloantibody.

3. **Borderline changes:** ‘Suspicious’ for acute T-cell mediated rejection (may coincide with categories 2, 5 & 6). This category is used when no intimal arteritis is present, but there are foci of tubulitis (t1, t2 or t3) with minor interstitial infiltration (i0 or i1) or interstitial infiltration (i2 or i3) with mild (t) tubulitis.

4. **T-cell-mediated rejection** (TCMR, may coincide with categories 2, 5 & 6)
   **Acute T-cell-mediated rejection (Type /Grade):**
   IA. Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of moderate tubulitis (t2)
   IB. Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of severe tubulitis (t3)
   IIA. Cases with mild to moderate intimal arteritis (v1)
   IIB. Cases with severe intimal arteritis comprising >25% of the luminal area (v2)
   III. Cases with transmural arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocyte inflammation (v3).
   **Chronic active T-cell-mediated rejection.**
   ‘Chronic allograft arteriopathy’ (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neo-intima)

5. **Interstitial fibrosis and tubular atrophy**, no evidence of any specific aetiology
   Grade:
   I. Mild interstitial fibrosis and tubular atrophy (<25% of cortical area)
   II. Moderate interstitial fibrosis and tubular atrophy (26 - 50%)
   III. Severe interstitial fibrosis and tubular atrophy/loss (>50%)

6. **Other:** Changes not considered to be due to rejection - acute and/or chronic - (may include isolated g, cg or cv lesions and coincide with categories 2 - 5
# Appendix G

## 0 - 12 Month Follow up Schedule

<table>
<thead>
<tr>
<th>Test / Procedure Required</th>
<th>Time Frame for Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biochemistry</strong> UEC, LFT, Ca, PO4, Mg BSL, Albumin</td>
<td>Every visit</td>
</tr>
<tr>
<td><strong>Haematology</strong> FBC</td>
<td>Every visit</td>
</tr>
<tr>
<td><strong>Lipids</strong> Chol, Trigs, HDL, LDL</td>
<td>Month 3, 6 and 12</td>
</tr>
<tr>
<td><strong>PTH</strong></td>
<td>Month 3, 6 and 12</td>
</tr>
<tr>
<td><strong>Fasting Glucose</strong></td>
<td>Transplant to 3 Mths 4 – 6 months 6 – 12 months Weekly 2nd weekly Monthly</td>
</tr>
<tr>
<td><strong>CMV:</strong> IgG and IgM Antibody Titre</td>
<td>Transplant – 3 months – weekly 6 – 12 months and as indicated</td>
</tr>
<tr>
<td><strong>CMV:</strong> PCR as indicated</td>
<td></td>
</tr>
<tr>
<td><strong>Epstein-Barr virus</strong></td>
<td>Every 3 months if Neg</td>
</tr>
<tr>
<td><strong>Hepatitis B and C and HIV</strong></td>
<td>Every 3 months, then annually. Annually in children</td>
</tr>
<tr>
<td><strong>Drug Levels</strong> Tacrolimus, Sirolimus</td>
<td>Trough level every visit</td>
</tr>
<tr>
<td><strong>Drug Levels</strong> Cyclosporin</td>
<td>Trough level or C2 level as per local policy, every visit</td>
</tr>
<tr>
<td><strong>Urine</strong> Urinalysis / MSU urine for 24 hour protein OR P/C ratio</td>
<td>Every visit Monthly</td>
</tr>
<tr>
<td><strong>Doppler / U/S</strong></td>
<td>Day 1 – 2 and then as indicated</td>
</tr>
<tr>
<td><strong>Stent Removal</strong></td>
<td>4 - 6 weeks Antibiotics ordered</td>
</tr>
<tr>
<td><strong>DTPA scan and GFR</strong></td>
<td>Day 30, sooner if indicated</td>
</tr>
<tr>
<td><strong>Renal Biopsy</strong></td>
<td>When clinically indicated Consider 6 and 12 month protocol biopsy</td>
</tr>
<tr>
<td><strong>Chest Xray</strong></td>
<td>Yearly</td>
</tr>
<tr>
<td><strong>Bone Mineral Density / Dexa Scan</strong></td>
<td>12 months If abnormal at 12 months then every 12 months If normal at 12 months then at month 36</td>
</tr>
<tr>
<td><strong>X-rays</strong></td>
<td>As indicated of prior fractures for assessment</td>
</tr>
<tr>
<td><strong>Pap smear – all women</strong></td>
<td>Yearly</td>
</tr>
<tr>
<td><strong>Mammogram - &gt; 40 years of age</strong></td>
<td>Yearly</td>
</tr>
<tr>
<td><strong>PSA &gt; 50 years of age</strong></td>
<td>Yearly</td>
</tr>
<tr>
<td><strong>Faeces – occult blood</strong></td>
<td>Yearly or as indicated</td>
</tr>
<tr>
<td><strong>Dermatology Review</strong></td>
<td>Yearly or as indicated</td>
</tr>
<tr>
<td><strong>Influenza A and B Vaccination</strong></td>
<td>Yearly between March and May</td>
</tr>
</tbody>
</table>
# Appendix H

## Initial 12 Month Post Transplant Tracking Log

<table>
<thead>
<tr>
<th>TEST / PROCEDURE</th>
<th>Date Removed:</th>
<th>Date performed:</th>
<th>Month 3 Date Due:</th>
<th>Month 6 Date Due:</th>
<th>Month 12 Date Due:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent Removal (4 – 6 weeks)</td>
<td></td>
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<tr>
<td>DTPA Scan and GFR</td>
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</tbody>
</table>

**PLEASE RECORD DATE TEST PERFORMED IN THE COLUMNS BELOW**

- Lipids (Chol, Trig, HDL, LDL)
- PTH
- EBV
- Hep B (sAg and sAb)
- Hep C
- HIV
- Chest Xray
- Bone Mineral Density Scan
- Pap Smear (all women)
- Mammogram > 40 years
- PSA Males > 50 years
- Faeces – occult blood
- Dermatology Review
- Influenza A and B vaccination
Appendix I

Multidisciplinary Pathway

EAST COAST RENAL SERVICES

Multidisciplinary Pathway for Renal Transplant

PROCEDURE: Renal Transplant

Date of admission:

Date of transplant:

Anticipated date of discharge:

Actual date of discharge:

<table>
<thead>
<tr>
<th>Name</th>
<th>Contact Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician</td>
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</tr>
<tr>
<td>Surgeon</td>
<td></td>
</tr>
<tr>
<td>Registrar</td>
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<tr>
<td>Pharmacist</td>
<td></td>
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<tr>
<td>Social worker</td>
<td></td>
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<tr>
<td>Dietician</td>
<td></td>
</tr>
<tr>
<td>Clinical Psychologist</td>
<td></td>
</tr>
<tr>
<td>Transplant Coordinator</td>
<td></td>
</tr>
</tbody>
</table>

Information regarding documentation of clinical pathways.
The clinical pathway is to remain in the patient’s observation / medication chart. Always assess whether an intervention is appropriate for the individual patient. **The clinical pathway does not take the place of a physician order.**

PROCEDURE: Complete details as required – affix patient bradma, insert date etc. After an intervention has been completed please initial in the appropriate box. If the event is not applicable to the patient please write N/A in the box. Interventions that have not been initialed need to be reviewed or recorded as a variance.

VARIANCE: Any event noted on the clinical path not occurring within the 24 hours or an event that occurs and is not printed on the clinical pathway eg infected cannula. Record the variance code in the column titled “variance”. Document the variance on the variance sheet at the back of this document.

VARIANCE SHEET: Document date, day of stay and variance code. Briefly describe the variance and action taken. Sign each variance entry noted and document variance and evaluation of patient progress and care in the patient’s notes.
<table>
<thead>
<tr>
<th>Clinical Pathway</th>
<th>Day of Transplant</th>
<th>Initials</th>
<th>Var Code</th>
<th>Day 1</th>
<th>Initials</th>
<th>Variance Code</th>
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<td>q 2nd hourly whilst on PCA</td>
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<td>q CVC dressing intact</td>
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<td>q Dry dressing to wound</td>
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<td>q Mobilise with assistance as needed</td>
<td>q Self mobilisation</td>
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<td></td>
<td>q Sit out of bed</td>
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<td>q Daily physiotherapy</td>
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<td></td>
<td>q Change diet in CBORD</td>
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<td><strong>Hygiene</strong></td>
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<td>q Record 24 hr fluid balance</td>
<td>q Record 24 hr fluid balance</td>
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<td>q Aperient if bowel not opened</td>
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<td><strong>Discharge Planning</strong></td>
<td>q Social worker assessment of support post discharge</td>
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<td>q Social worker assessment of family needs post discharge</td>
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<td><strong>Day 5</strong></td>
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q Fistula observations daily  
q BSL’s as per protocol | q 4th hourly observations  
q Fistula observations daily  
q BSL’s as per protocol |
| **Fluid Management** | q Oral fluid replacement  
q Encourage oral fluids  
q Daily weight  
q Daily fluid assessment | q Oral fluid replacement  
q Daily weight  
q Daily fluid assessment |
| **Investigations / Laboratory tests and treatments** | q Daily bloods  
q Daily CyA level  
q Daily Tacrolimus level  
q Record results on flow chart  
q Other: | q Daily bloods  
q Daily CyA level  
q Daily Tacrolimus level  
q Sirolimus level  
q Record results on flow chart  
q Other: |
| **Medication**      | q IV antibiotics  
q Immunosuppression agents as per protocol  
q Record doses on flow chart  
q Oral medications  
q Supervised self medication | q IV antibiotics  
q Immunosuppression agents as per protocol  
q Record doses on flow chart  
q Oral medications  
q Supervised self medication |
| **Review by:**      | q Members of transplant team  
q Vascular surgery team  
q Other: | q Members of transplant team  
q Vascular surgery team  
q Other: |
| **Patient Education** | q Patient education attended  
q Medication education attended | q Patient education attended  
q Medication education attended |
| **Wound and drain dressings and observation** | q Wound exposed | q Wound exposed |
| **Mobility and physiotherapy** | q Self mobilisation  
q Anti-embolic stockings  
q Daily physiotherapy | q Self mobilisation  
q Anti-embolic stockings  
q Daily physiotherapy |
| **Nutrition**       | q Immuno diet  
q Change diet in CBORD  
q Dietician education / review | q Immuno diet |
| **Hygiene**         | q Self caring with assistance as required  
q Daily catheter care | q Self caring with minimal assistance  
q Daily catheter care |
| **Elimination**     | q Record 24 hr fluid balance  
q Record bowel function | q Record 24 hour fluid balance  
q Record bowel function |
<p>| <strong>Discharge Planning</strong> | q Other: | q Other: |</p>
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<td>q Oral fluid replacement q Daily weight q Daily fluid assessment</td>
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<td>q Daily bloods q Daily CyA level q Daily Tacrolimus level q Record results on flow chart q Other:</td>
<td>q Urinalysis q Daily bloods q Daily CyA level q Daily Tacrolimus level q Area Under Curve (day 7-9 ) q Record results on flow chart q Other:</td>
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<td>q Immunosuppression as per protocol q Supervised self medication</td>
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<td>Day 8</td>
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<td>q Daily weight</td>
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<td>q Daily fluid assessment</td>
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<td>q Daily Bloods</td>
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<td>q Daily physiotherapy</td>
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<td>q Daily physiotherapy</td>
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<td><strong>Nutrition</strong></td>
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<td>q Immuno diet</td>
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<td>q Dietician consult (d 9-11)</td>
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<td>q Dietician consult (d 9-11)</td>
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<td>q Self caring</td>
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<td><strong>Elimination</strong></td>
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<td>q Record 24 hr fluid balance</td>
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<td>q Record 24 hr fluid balance</td>
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<td>q Record bowel function</td>
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<td>q Record bowel function</td>
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<td><strong>Discharge Planning</strong></td>
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<td>q Social work consult prior to discharge (day 9-11)</td>
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                               | q Fistula observations daily  
                               | q BSL's as per protocol       | | q QID observations  
                               | q Fistula observations daily  
                               | q BSL's as per protocol       | | |
| Fluid Management                 | q Oral fluid replacement  
                               | q Daily weight  
                               | q Daily fluid assessment       | | q Oral fluid replacement  
                               | q Daily weight  
                               | q Daily fluid assessment       | | |
| Investigations / Laboratory tests and treatments | q Daily Urinalysis  
                               | q Daily Bloods  
                               | q Daily CyA level  
                               | q Daily Tacrolimus level  
                               | q Record results on flow chart | | q Daily Urinalysis  
                               | q Daily Bloods  
                               | q Daily CyA level  
                               | q Daily Tacrolimus levels  
                               | q Record results on flow chart | | |
| Medication                       | q Immunosuppression as per protocol  
                               | q Patient independent with medication administration  
                               | q Discharge script sent to pharmacy (by 2pm) | | q Immunosuppression as per protocol  
                               | q Patient independent with medication administration | | |
| Review by:                       | q Members of transplant team  
                               | q Vascular surgery team  
                               | q Other: | | q Members of transplant team  
                               | q Vascular surgery team  
                               | q Other: | | |
| Patient Education                | q Medication education attended  
                               | q Patient education attended  
                               | q Other: | | q Medication education attended  
                               | q Patient education attended  
                               | q Other: | | |
| Wound and drain dressings and observation | q Wound exposed | | | | q Wound exposed | | |
| Mobility and physiotherapy       | q Independent mobilisation  
                               | q Anti-embolic stockings  
                               | q Daily physiotherapy | | q Independent mobilisation  
                               | q Anti-embolic stockings  
                               | q Daily physiotherapy | | |
| Nutrition                        | q Immuno diet  
                               | q Dietician consult (day 9-11) | | | q Immuno diet  
                               | q Dietician consult (day 9-11) | | |
| Hygiene                          | q Self caring | | | | q Self caring | | |
| Elimination                      | q Record 24 hr fluid balance  
                               | q Record bowel function  
                               | q IDC removed  
                               | q MSU post IDC removal  
                               | q Patient to measure and record own urine output | | q Record 24 hr fluid balance  
                               | q Record bowel function  
                               | q IDC removed  
                               | q MSU post IDC removal  
<pre><code>                           | q Patient to measure and record own urine output | | |
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<p>| Discharge Planning               | q Social Work consult prior to discharge (day 9 - 11) | | | | q Social work consult prior to discharge (occurs day 9-11) | | |</p>
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<th>Initial (Please Print)</th>
<th>Action Taken</th>
<th>Explanation Of Variance</th>
<th>Variance Code</th>
<th>Day Of Stay</th>
<th>DATE</th>
</tr>
</thead>
</table>

Instructions: Enter the variance code from the attached table if there is a variance code noted on the day sheet.

Aim: To identify those factors which affect length of stay and outcome.

Variance Record For: Renal Transplant
Department of Nephrology
PRINCE OF WALES HOSPITAL
<table>
<thead>
<tr>
<th>HOSPITAL</th>
<th>CLINICAL</th>
<th>PATIENT</th>
<th>COMMUNITY / FAMILY</th>
</tr>
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<tbody>
<tr>
<td>111 Delay in dispensing of discharge medications</td>
<td>110 Delay in dispensing medications</td>
<td>112 Other</td>
<td>111 Other</td>
</tr>
<tr>
<td>109 Stock unavailable</td>
<td>108 Interpreter not available</td>
<td>107 Hospital wide ADO</td>
<td>106 Test / procedure not available on weekends</td>
</tr>
<tr>
<td>105 Delays in diagnostic testing</td>
<td>104 Delays in diagnostic testing</td>
<td>103 Equipment not available</td>
<td>101 Delays in services</td>
</tr>
<tr>
<td>102 Patient not fasting</td>
<td>102 Patient not fasting</td>
<td>103 Equipment not available</td>
<td>101 Delays in services</td>
</tr>
<tr>
<td>104 Delays in diagnostic testing</td>
<td>104 Delays in diagnostic testing</td>
<td>103 Equipment not available</td>
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<td>103 Equipment not available</td>
<td>101 Delays in services</td>
<td>101 Delays in services</td>
</tr>
<tr>
<td>215 Blood test not done</td>
<td>214 Medication prescribing error</td>
<td>210 Unexpected injury</td>
<td>209 Observations stable</td>
</tr>
<tr>
<td>213 IV fluids required error</td>
<td>213 Medication prescribing error</td>
<td>208 Hypertension</td>
<td>207 Patient requires further education</td>
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<tr>
<td>211 Delay in IVC removal</td>
<td>206 Skin breakdown</td>
<td>206 Late mobilization</td>
<td>205 Decubitis Ulcer</td>
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</tbody>
</table>
PRINCE OF WALES HOSPITAL

Department of Nephrology

Multidisciplinary Clinical Pathway for Renal Transplant

Day of Discharge

Date of discharge:

To be done prior to discharge:

1) Post IDC removal MSU taken and sent to pathology
2) Clinic appointments made for daily review by referring physician
3) Other follow up appointments made (e.g. Diabetes, Dermatology clinic)
   Clinic:  Date of appointment:
   Clinic:  Date of appointment:
4) Appointment made for stent removal  Yes  N/A  Date for removal:
5) Appointment for PD catheter removal Yes  N/A  Date for removal:

Items to be given to patient on day of discharge:

1) Discharge letter given to patient
2) Copy of Transplant flow chart (faxed)
3) Copy of clinical pathway (faxed)
4) Discharge Medications
5) Medication summary and dosette box from pharmacist

Discharge checklist completed by:

please print name  .......................................................

...
Appendix J

Red Cross Tissue Typing Form

<table>
<thead>
<tr>
<th>Request Form for Tissue Typing Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Recipient: __________________________</td>
</tr>
<tr>
<td>Address: _________________________ Phone: ___</td>
</tr>
<tr>
<td>Tissue Typing Service (NSW) ___________ Date: ___</td>
</tr>
</tbody>
</table>

**Specimen Requirements**

- **Bone Marrow:** Submit at least 2g of bone marrow or 10mL of bone marrow aspirate.
- **Blood:** Submit at least 10mL of whole blood or 3mL ofuffy coat.
- **Lymph nodes:** Submit at least 10mL of lymph node aspirate.
- **Tissue samples:** Submit at least 1g of tissue sample.

**Additional Information**

Please ensure all information is completed on the Request Form and submit with the specimens.
# Tissue Typing Activation Request Form

**Tissue Typing Services - NSW**
294 Kent St, Sydney, 2000.

**FAX TO:** 02 9229 4534

---

**ACTIVATION REQUEST**

**Organ(s) Required**

The patient needs to be activated onto the NSW ACT transplant waiting list for the following:

- [ ] Heart
- [ ] Kidney
- [ ] Liver
- [ ] Lung
- [ ] Pancreas
- [ ] Pancreas Islets
- [ ] Other: ___________________________

**Medicare Number:** ___________________________

**Name:** ___________________________

**Date of Birth:** __/__/______

**Gender:** M / F

**Ethnic Origin:** ___________________________

**Diagnosis:** ___________________________

**Anzdata Code:** ___________________________

**Patient's Doctor:** ___________________________

**Hospital:** ___________________________

---

**Patient Details**

**Medicare Number:** ___________________________

**Name:** ___________________________

**Gender:** M / F

**Ethnic Origin:** ___________________________

**Date of Birth:** __/__/______

**Diagnosis:** ___________________________

**Anzdata Code:** ___________________________

**Patient's Doctor:** ___________________________

**Hospital:** ___________________________

---

**Dialysis History:** **MUST BE COMPLETED**

**Dialysis Centre:** ___________________________

**Dialysis Type:** ___________________________

**Date of first dialys:** __/__/______

**Reason for dialysis:** ___________________________

**Transplant Details:** __________________________

---

**Transfusion History:**

**Number of Transfusions:** ___________________________

**Last transfusion date:** __/__/______

**Note:** Please notify laboratory of any transfusions. A serum sample is required 2 weeks post-transfusion from all patients.

---

**Pregnancy History:**

**Number:** ___________________________

**Date of last pregnancy:** __/__/______

---

**Transplant History:**

<table>
<thead>
<tr>
<th>Transplant No.</th>
<th>Transplant Date</th>
<th>Transplant Hospital</th>
<th>Graft Failure Date</th>
<th>Cause of Graft Failure</th>
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<tbody>
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<td>3</td>
<td><strong>/</strong>/______</td>
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</tr>
</tbody>
</table>

**Comments (any other relevant information):** __________________________

**Name:** __________________________

**Signature:** __________________________

**Date:** __/__/______

---

**Anzdata Code:** __________________________

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**East Coast Renal Services**
References:

17. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications.


33. Dialysis and Transplant Registry (ANZDATA).


Mizutani K, Terasaki P et al. The importance of Anti-HLA-specific antibody


70 Montgomery RA et al. Plasmapheresis and intravenous immunoglobulin provides effective rescue therapy for refractory humoral rejection and allows kidneys to be successfully transplanted into cross-match-positive recipients. Transplantation 2000; 6: 887-895


