

Prince of Wales Hospital renal and transplant unit

Renal transplant handbook

1 Scope

To be used by members of the East Coast Renal Services transplant service.

2 Purpose

To maintain consistent and high standard care for patients receiving renal transplants.

3 Abbreviations

Abbreviation	Explanation	Abbreviation	Explanation
AMR	Antibody-mediated rejection	HSV	Herpes simplex virus
APTT	Activated partial thromboplastin time	KCC	Kidney Care Centre (Prince of Wales)
ATN	Acute tubular necrosis	IA	Immunoabsorption
BKV	BK virus	IV	Intravenous
BP	Blood pressure	INR	International normalised ratio
CMV	Cytomegalovirus	LFT	Liver function test
CXR	Chest x-ray	MDT	Multi-disciplinary team
CVC	Central venous catheter	MRSA	Methicillin resistant staphylococcus aureus
CVP	Central venous pressure	NAT	Nucleic acid testing
DBD	Donation after brain death	NODAT	New Onset Diabetes After Transplant
<u>DCD</u>	Donation after cardiac death	NOAC	New/Novel oral anticoagulant
DGF	delayed graft function	NOMS	National organ matching system
DSA	Donor specific antibody	PCA	Patient controlled analgesia
DVT	Deep vein thrombosis	PE	Pulmonary embolus
ECRS	East Coast Renal Services	PO	By mouth
EMR	Electronic medical records system	PTASR	Post-transplant antibody screen routine
FBC	Full blood count	TB	Tuberculosis
HepB	Hepatitis B	UEC	Urea, Electrolytes and Creatinine
HepC	Hepatitis C	UO	Urine output
HIV	Human immunodeficiency virus	USS	Ultra sound scan
HLA	Human leucocyte antigen	VZV	Varicella zoster virus

4 Monitoring compliance with and the effectiveness of the guideline

The care of patients with renal transplants, and whether or not this is following the agreed guidelines, is routinely reviewed at the East Coast Renal Services (ECRS) meeting.

Equality and diversity statement

This document complies with the Prince of Wales service equality and diversity statement.

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1 General information

1.1 Day-to-day procedures and policies

1.1.1 Problems

Problems arising in renal transplant patients should be directed to the renal registrar or transplant surgical fellow as appropriate. If you can't get hold of a registrar, contact the nephrologist or transplant surgeon on call.

1.1.2 Transplant patients on Parkes 9W

The following patients are eligible for admission in order of priority:

1. Patients immediately post-transplant
2. Other transplant patients who do not need specialised care such as CCU, ICU etc.

The day-to-day management of renal transplant patients on 9W is the responsibility of the advanced nephrology trainee and nephrology resident.

1.1.3 MRSA

Patients who are known to be MRSA positive should be admitted to a single room on ward P9W. If no single room is available, then the situation should be discussed with the infection control team (contact via switchboard), but - unless the patient is deemed to be at very high risk - admission to an 'open' bed on P9W will usually be allowed.

Staff handling (touching) patients with MRSA or at risk of MRSA (screen not yet known to be negative) should wear gloves and plastic aprons, wash their hands, and use alcoholic Chlorhexidine for hand hygiene according to LHD guidelines.

1.1.4 Phone calls

Patients may phone P9W or the transplant junior doctors via the switchboard at any time. Please **discuss all such calls** with senior staff (medical or surgical, registrar or consultant, as appropriate). In those recently transplanted (within the first three months) there should be a very low threshold for getting patients to come to the clinic. **Patients should not be asked to come directly to the ward – if it seems likely that an urgent admission will be required the patient should be directed to the emergency department.**

GPs/ doctors in other hospitals may phone P9W or the nephrology registrar about a renal transplant patient at any time. **If you are unsure, take details and contact senior staff (medical or surgical registrar or consultant, as appropriate).**

Any advice given to patients or to other doctors by telephone should be logged as a telephone summary on the patient's medical record or electronic medical records system (EMR).

1.1.5 Research protocols

These are an important part of the transplant unit's work. All staff are expected to help and assist with these when required to do so.

2 Pre-operative admission and assessment for JMO

2.1 Fitness for transplantation

Inform consultant on-call as soon as you have clerked in and taken the necessary bloods from any patient admitted with the intention of transplantation. This is particularly important if you have any doubts about their fitness to undergo the procedure, or should the patient require dialysis

2.2 Routine clerking

Complete the renal transplant admission **but before** taking a history and examining the patient, ensure all bloods have been taken (as detailed below) and have arrived in the lab.

Give particular attention to:

- Potassium (see 2.4), and baseline creatinine if pre-dialysis
- Native urine output
- Human leucocyte antigen (HLA) match and cytomegalovirus (CMV) status of recipient and donor – this information will be communicated by the transplant co-ordinator to the on-call nephrologist
- Any symptoms indicating new or worsening cardiovascular disease or of infection.

2.3 Routine tests

- **Urgent pre-operative blood tests: biochemical profile including electrolytes + bicarbonate (UEC), liver function test (LFT), full blood count (FBC), CRP and glucose** (marked as urgent)
- **Cross-match 2 units** (more if Hb<80 g/L, bleeding tendency or on warfarin)
- **Virology – Routine 'Transplant Assessment' virology:** select human immunodeficiency virus (HIV), HepB, HepC, HSV, CMV and varicella zoster virus (VZV).
- **ECG**
- **Chest x-ray (CXR)** (only if clinically indicated)
 - **Note:** CXR will be done in recovery to assess CVC line position
- Research samples if required – see separate protocols.

2.4 Is dialysis required?

- All patients should have a potassium of <5.5mmol/L at the time of transplantation
- If there is a high probability of delayed graft function (DCD kidney), patients should have a potassium of <5.0mmol/L at the time of transplantation.
- There is often considerable delay between admission and transplantation, allowing potassium to rise above the admission value! **Haemodialysis patients with Potassium >5.0mmol/L should receive dialysis.**

2.5 Consent

For transplantation, and for involvement in any research protocols (latter will be obtained by senior member of staff). The consent form for transplantation is normally completed in advance and filed in the patient's notes. This needs to be countersigned by the admitting doctor to confirm validity.

2.6 Antibiotic prophylaxis

Prescribe: Cephazolin 2g IV at induction¹.

Note: For penicillin allergic patients prescribe Vancomycin 1g IV + Ciprofloxacin 400mg IV to be given at induction only.

2.7 Antithrombotic medication

Prescribe VTE prophylaxis: Heparin 5000units subcut BD, starting post-op.

Note: For patients at high risk of thromboembolism, e.g. previous history of recurrent deep vein thrombosis (DVT) or pulmonary embolus (PE), prescribe heparin infusion to start post-op at **12units/kg/hr IV**, without bolus, using the standard preparation of 25,000 units per 250mL (100units/mL).

Note: Monitoring of activated partial thromboplastin time (aPTT) should initially be 6 hourly until two successive aPTTs in the range of 40-70sec for the first 48 hours. If no bleeding and after consultation with surgeon continue heparin as per hospital heparin infusion policy ([SESLHDPR/402](#)).

Note: Stop aspirin while patients are on intravenous heparin.

Note: Current Clopidogrel treatment is a contraindication to proceeding with surgery, patients on Clopidogrel should be made "interim".

Note: Newer oral anticoagulants ("NOACs") should not be used in patients with end-stage kidney disease.

2.8 Patients on warfarin

Patients who are therapeutically anticoagulated with warfarin should, in general, have this reversed before transplantation:

- **On admission check international normalised ratio (INR) urgently**
- Before doing anything else speak to a senior surgeon – if there is a very high risk of graft thrombosis some may wish **not** to reverse warfarin.
- However, in most patients:
- **If INR >1.5 administer vitamin K 2mg intravenously (IV)**. In the majority, anticoagulation will be effectively reversed within six hours, and further blood products will not be required.
- Repeat INR around one hour prior to surgery.
- If the INR remains >1.5 then organise prothrombin complex (Prothrombinex) to be administered following the induction of anaesthesia as follows:
 - INR 1.5-2.9 give 15 units/kg Prothrombinex
 - INR >2.9 give 30units/kg Prothrombinex

- **Following surgery repeat INR.** The half-life of vitamin K-dependent clotting factors is less than that of warfarin, and some 'rebound' of INR may occur
 - If INR post-surgery is <2 then begin heparin infusion at 12units/kg/hr IV, without bolus, monitor aPTT 6 hourly aiming at aPTTs in the range of 40-60sec for the first 48 hours. If no bleeding and after consultation with surgeon continue heparin as per hospital heparin infusion policy (SESLHDPR/402).
- Warfarin may be restarted once the patient has stable graft function and it is clear that there is no immediate need to perform a biopsy. Remember to continue heparin until INR is therapeutic.

2.9 Initial Immunosuppression (see section 3)

Depending upon immunosuppressive regimen **prescribe:**

- Mycophenolate Mofetil 1000 mg PO
- Tacrolimus 0.075mg/kg PO
- Basiliximab **OR** Thymoglobuline® IV
- Methylprednisolone 500 mg IV to be given in operating theatre at graft reperfusion

***Note all medications for pre and post transplant care should be prescribed on admission. See Section 3 for standard immunosuppression protocols and supportive medications.**

2.10 Vascular access

Patients receiving a renal transplant may be on haemodialysis, peritoneal dialysis or pre-dialysis (sufficient native renal function not to require regular dialysis). Following transplantation (especially deceased donor transplantation) many patients require acute dialysis (for example to correct dangerous hyperkalaemia).

- For **haemodialysis patients** with a functioning **fistula or graft** then the anaesthetist will insert a standard triple-lumen central line.
- For **haemodialysis patients** using a **tunnelled dialysis catheter** an additional triple lumen central line should be inserted - the dialysis catheter will likely be required for dialysis. An exception could be uncomplicated live donor transplantation, where there is a reasonable expectation of primary graft function, and the dialysis catheter used temporarily for central venous pressure (CVP) measurements.

2.11 If the transplant doesn't happen

If a patient is admitted to the ward for renal transplantation, and this does not go ahead (for instance because it is found that there are problems with the cross-match, or there are other difficulties) please inform senior medical cover without undue delay. Referring nephrologists and other hospitals are placed in a difficult and embarrassing position if their patients are sent home and they don't know why. The patients or their relatives are almost invariably on their doorstep the next morning!

Appendix 1 is a simple form to be filled in and faxed immediately to the referring unit, explaining why transplantation was not performed. A copy should be given to the patient.

3 Immunosuppression

The majority of patients receive the same initial immunosuppressive regimen. Subsequent modification may be appropriate depending on the post-transplant course, and it is important to document the following markers of immunologic risk:

- HLA match at HLA-A, B and DR (as per NOMS form)
- Is the patient non-sensitized, sensitized or highly-sensitized (determined by screening for HLA antibodies)?
- Is this a first transplant, or has the patient received previous transplants?
- Was a previous transplant lost to acute rejection?

3.1 Immunosuppressive protocols (see appendix 2):

The determination and definition of individual immunological risk will generally depend on a combination of recipient-specific and donor-specific factors (prior transplant, degree of sensitisation, presence of DSA to matched donor, HLA mismatch, eplet mismatch, etc.)

The origin (cold ischaemia time) and type of donor (DBD/DCD) are strong predictors of DGF. DGF remains an important risk factor for biopsy-proven rejection even in a contemporary cohort of kidney transplant recipients and thus immunologic risk.

Very high immunologic risk patients are those who have been identified as being at especially high immunologic risk because of their immunological profile, something that will have been discussed at the time of assessment and at the transplant MDT.

There are 3 baseline immunosuppressive protocols, which differ in the target blood Tacrolimus level and Prednisolone dose as well as the agent used for induction therapy:

1. Protocol for low immunologic risk (3.1.1)
2. Protocol for intermediate immunologic risk (3.1.2)
3. Protocol for very high immunologic risk (3.1.3)
4. Protocol for steroid-free immunosuppression (3.1.4)

All of the immunosuppression protocols currently used are Tacrolimus-based.

There may be occasions where Cyclosporin is used in place of Tacrolimus, usually in patients previously intolerant of Tacrolimus or who develop intolerable Tacrolimus-related side-effects, or patients at high-risk of post-transplant diabetes (impaired OGTT pre-transplant).

Cyclosporin is prescribed as **Neoral**[®] at 7mg/kg/day⁷, divided into two doses. See **appendix 6** for target levels of Cyclosporin (cyclosporin levels are measured 2 hours (+/- 15 minutes) post morning dose – "C2").

Protocols for the use of other agents e.g. Cyclosporin/Sirolimus/Everolimus are not part of the standard immunosuppressive regimen, but may be part of a trial protocol. In those instances, the eligibility of the patient and the target blood drug levels will be determined by the study protocol.

3.1.1 Low immunologic risk patients

Initial immunosuppression for low immunologic risk patients¹³

Day 0 (day of transplant)

- Basiliximab 20mg IV ^{2,4} prior to transplant (or within 12 hours of return to ward).
- Tacrolimus 0.075mg/kg PO ^{2,4}
- Mycophenolate mofetil 1000mg PO^{2,4}
- Methylprednisolone 500 mg IV in theatre at graft reperfusion⁴

From Day 1

- Tacrolimus 0.075mg/kg PO BD ^{2,4} (08:00 and 20:00).
- Target level 6-10 microg/L^{6,7,8}
- Mycophenolate Mofetil 1000mg PO BD ^{2,4,5} (08:00 and 20:00).
- Prednisolone 30mg PO mane (08:00)⁴

*Alternative to Mycophenolate: Azathioprine 2mg/kg⁴ PO daily (08:00).
Maximum dose 200mg.*

Day 4

- Basiliximab 20mg (second dose) IV ^{2,4}

3.1.2 Intermediate immunologic risk patients

These patients should be prescribed a more intensive protocol than the standard protocol (ask the consultant in charge):

- The patient is highly-sensitised **and/or**
- The kidney is a poor HLA match (2DR mismatches, or 2B and 1DR mismatch) **and/or**
- There is a low level DSA (<2000MFI) with negative crossmatch (including flow in live donors)

Under these circumstances modify the protocol as follows, or consider thymoglobulin induction (see 3.1.3).

Initial immunosuppression for intermediate immunologic risk patients¹³

Day 0 (day of transplant)

- Basiliximab 20mg IV prior to transplant (or within 12 hours of return to ward) ^{2,4}.
- Mycophenolate mofetil 1000mg PO^{2,4}
- Tacrolimus 0.075mg/kg PO PO^{2,4}
- Methylprednisolone 500 mg IV⁴ in theatre at graft reperfusion

From Day 1

- Tacrolimus (Prograf) 0.075mg/kg PO BD (08:00 and 20:00) ^{2,4,7}.
- Target level 8-14 microg/L. ^{6,7,8}
- Mycophenolate mofetil 1000mg PO BD (08:00 and 20:00).^{2,4,5}
- Prednisolone 30mg PO mane (08:00) ⁴

Day 4

- Basiliximab 20mg (second dose) IV^{2,4}

3.1.3 Very high immunologic risk patients

Some patients will be identified as being at **especially high immunologic risk**, something that will have been discussed at the time of assessment and at the transplant MDT.

These patients are also given induction therapy with Thymoglobulin, but in addition receive maintenance immunosuppression.

This same protocol may be used for patients with

- **weak donor-reactive HLA antibodies** (peak > current) not requiring antibody-removal, or for those with
- an **unexpected positive B-cell cross-match in whom it is considered reasonable to proceed with transplantation** (usually not available however till following day)

Initial immunosuppression for high immunologic risk patients¹³

Day 0 (day of transplant)

- Mycophenolate mofetil 1000mg PO^{2,4}
- Tacrolimus 0.075mg/kg PO^{2,4}
- Methylprednisolone 500mg IV at graft reperfusion⁴

On return to the ward

- Thymoglobuline® 1-1.5mg/kg IV^{4,8}
*ensure pre-medications per appendix 5

From Day 1

- Thymoglobuline® 1-1.5mg/kg IV for (3- 5 days)^{4,8}
*ensure pre-medications per appendix 5
- Tacrolimus (Prograf) 0.075mg/kg PO BD (08:00 and 20:00)^{2,4}
- Target level 8-14 microg/L^{6,7,8}.
- Mycophenolate 500-1000mg BD^{2,4} - *Discuss dose with consultant*
- Prednisolone 30mg PO mane (08:00)⁴

3.1.4 Special circumstances: steroid-free immunosuppression

Steroid-free immunosuppression may be used for some patients, including those with:

- a **6/6 antigen match**,
- **history of substantial steroid exposure** who are now off steroids,
- high risk of developing severe steroid-related side-effects (**e.g. history of considerable weight gain or psychosis**).

The decision to use steroid-free immunosuppression will have been discussed with the patient at the time of assessment, and at the transplant MDT, and will be recorded in the patient's notes, on the transplant database, and in the information provided by the transplant co-ordinator.

Steroid-free immunosuppression is associated with an excess risk of early acute rejection, and for this reason patients may receive **induction with a lymphocyte-depleting antibody (Thymoglobuline®)** followed by Tacrolimus and Mycophenolate maintenance therapy.

Thymoglobulin administration often leads to significant leucopenia⁴, so the maintenance Mycophenolate dose is lower (500 mg BD) than for Basiliximab-treated patients.

Steroid-free Immunosuppression¹³

Day 0 (day of transplant)

- Mycophenolate mofetil 1000mg PO^{2,4} pre-op
- Methylprednisolone 500mg IV at graft reperfusion²

On return to the ward:

- Promethazine 25mg PO 30 minutes prior to thymoglobulin^{4,9}
- Paracetamol 1g PO 30 minutes prior to thymoglobulin^{4,9}
- Thymoglobuline[®] 1.-1.5mg/kg IV^{4,8}
* ensure pre-medications per appendix 5

From Day 1

- Tacrolimus (Prograf) 0.075mg/kg PO BD (08:00 and 20:00)^{2,4}.
- Target level 8-12microg/L^{6,7,8}
- Mycophenolate mofetil 500mg PO BD^{2,4} (increase to 1000mg BD after completion of Thymoglobuline[®] cycle)
- Thymoglobuline[®] 1-1.5mg/kg IV continued for 3-5 days^{4,8}.
* ensure pre-medications per appendix 5

4 Immediate post-operative management

Following the completion of surgery and anaesthesia patients are transferred to the recovery area, where they may remain for several hours. They are then transferred to a bed on the transplant ward (P9W). It is important that the patient is **assessed in recovery**, especially with regard to the need for dialysis.

POTASSIUM

Undetected hyperkalaemia is the greatest danger in all post-operative renal patients. Potassium should be checked in recovery, immediately on arrival to ward, and again six hours later (or at least every 2 hours if Potassium >6.0 mmol/L) (see section 4.2).

A high serum potassium (>6.0 mmol/L) should always be discussed without delay with the renal registrar and may require urgent haemodialysis unless the patient has primary graft function, in which case it may be reasonable to observe and repeat the measurement in two hours (see below).

4.1 Management in recovery

The patient should be **reviewed in recovery** by the nephrology registrar, with particular reference to the following:

- **The purpose of this assessment is to determine if the patient is likely to need urgent dialysis, and that they are well enough to return to P9W to receive treatment.**
 - Is the patient **hyperkalaemic** (see also 4.2 below)?
 - Check potassium performed on venous blood sample. Check that UEC and FBC have been sent to laboratory
 - Has the patient received medical management for hyperkalaemia whilst in the operating department (insulin + glucose or salbutamol)? This information is recorded on the anaesthetic chart, and should also be communicated by the anaesthetist
- **Arrange chest X-ray and assess that tip of CVC line is correctly positioned**
- Is there evidence of primary graft function (urine output >100ml/hour unless high native UO)?
 - Check that blood pressure (BP), CVP and fluid replacement are adequate
- If the patient does not have primary graft function and
 - Potassium >6.0 mmol/L *or*
 - has already received medical management for ↑ potassium then plan dialysis.
- If you are concerned that the patient is too unstable to receive dialysis contact ICU (invasive monitoring and hemofiltration may be required) **and** the surgeon responsible for the patient.
- Check that the surgical drains are not filling quickly
 - The transplant fellow will contact the nephrology transplant registrar to agree a plan for further management.

4.2 Hyperkalaemia

4.2.1 Management of hyperkalaemia (Potassium >6mmol/L)

- Obtain a 12-lead ECG to identify signs of cardiac instability (peaked T waves and broad QRS complexes).
- If there is evidence of cardiac instability give 10mL calcium gluconate 10% IV over 5 minutes. Repeated after 5 minutes if needed.
- **Contact the renal registrar to discuss urgent dialysis**
- In most patients the ECG will be unremarkable. Management then depends on the presence of graft function:
- If the patient has primary graft function as indicated by urine output >100 ml/hour (unless high native urine output) then repeat potassium one and two hours later. If persistently >6.0 mmol/L consider dialysis.
- If there is no or little primary function then it is unlikely that there will be a sustained fall in potassium, and the patient should be dialysed without delay.
- Insulin and dextrose (10 units Actrapid insulin in 50 mL glucose 50% given IV over 15 minutes into a large vein) will reduce serum K⁺ by about 1 mmol/L for four hours if urgent treatment is required whilst waiting for dialysis.
- If a patient does receive insulin and dextrose, **blood glucose should be checked** hourly for four hours following the infusion.
- **Do not give Resonium A** – the efficacy when given orally in acute hyperkalaemia is negligible. Resonium A could be considered in patients with > 100mL/hour urinary output.

4.2.2 Monitoring of potassium

- During surgery potassium should be measured frequently by the anaesthetist using 'venous blood gas' samples. Note these results.
- Potassium should be measured following completion of surgery, once the patient arrives in recovery.
- If the patient has received '**medical management**' for ↑ potassium⁺, then there is likely to be a **rapid rebound** of serum potassium⁺ and measurements repeated every 1-2 hours. If there is no primary graft function then the patient will require dialysis unless all potassium measurements are <5.5mmol/L and not rising (see above).
- For other patients measure potassium again on transfer to the ward, and if <5.5mmol/L repeat six hours later.

4.3 Organising dialysis

- discuss with nephrology consultant on call first
- If dialysis is required on P9W then the nurse in charge is responsible for coordinating such requests (applies 0700 – 1900 Monday to Saturday).
- Outside of these hours contact the on-call haemodialysis nurse through switchboard

4.4 Analgesia

All transplant patients will be offered Patient Controlled Analgesia (PCA), provided there is no contraindication and a pump is available. Fentanyl is prescribed by the anaesthetist, with follow-up post op by the acute pain

service. **Fentanyl** is the preferred analgesic in renal transplant patients. Refer to the POWH Clinical Business Rule: [Patient Controlled Analgesia](#).

Use PCA prescription to chart:

Fentanyl 500microg in 50 mL sodium chloride 0.9%

Concentration: 10microg/mL *PCA Bolus:* 20microg/2mL.

Lock out period: Min 5 minutes (altered if necessary). *Background infusion:* nil.

In addition all patients should receive regular paracetamol 1g PO QID (may be given IV if required).

Note: Laxatives should be charted along with opioids to prevent constipation (e.g. Coloxyl and Senna BD).

4.5 Fluids

Immediately after transplantation the kidney is vulnerable to hypoperfusion injury. In the early post-operative period it is important to make vigorous efforts to 'optimise renal perfusion'.

In practice this means:

- **Maintaining UO:** Replacing fluid losses with IV crystalloid.
- **Maintaining BP:** usually achieved with adequate filling (CVP).
Note: In the acute setting a mildly elevated blood pressure (SBP <180mmHg) is acceptable because blood flow through the transplanted kidney is dependent on mean systemic BP.
- **Maintaining CVP:** as above (occasionally IV colloid or blood)

4.5.1 Crystalloid

The rate of urine output after transplantation is very variable.

- Patients may be oliguric if they produce little urine from their native kidneys and the graft suffers from acute tubular necrosis (ATN).
- By contrast, they may be polyuric, passing >10 litres per day.

The standard regime for crystalloid infusion should be:

Prescribe:

Sodium Chloride 0.9% (available in 1L bags) at a rate equal to the previous hours fluid output + 20 mL

If UO is >200mL/hr.: give sodium chloride 0.9% 100mL + 0.5 mL per each mL >200mL/hr. (i.e. UO = 300mL/hr., infusion rate = 150mL/hr.).

If UO is <50mL/hr.:

- BP low, CVP low: increase fluids /fluid boluses of sodium chloride 0.9% 200 – 500mL
- BP low, CVP high: consider catecholamines (dopamine)

4.5.2 Colloid

The CVP is measured from the midaxillary line, with the patient supine. It should **not** be pushed above 12 cm in an attempt to 'make the kidney work better' - pulmonary oedema is a more likely eventuality!

Prescribe:

500mL Sodium Chloride 0.9% and 100mL albumin 20%, to keep CVP 8-10 cm
Use blood sparingly if anaemia (Hb <70g/L or symptomatic), operative blood loss, or blood loss from drains is excessive.

Most patients return from theatre with a temporary 3-lumen central venous catheter, used for measuring CVP, performing initial blood tests and administration of fluids. Some patients with **tunnelled 2-lumen dialysis catheters** do not have an additional central line placed, with one lumen used intra-operatively for CVP measurement and blood tests. It is reasonable to continue CVP monitoring in this way for up to 24 hours post-transplant, but great care should be taken to 'lock' the line correctly.

4.6 Urine output

4.6.1 High urine output (polyuria)

Following transplantation some patients are polyuric (arbitrarily >200 mL/hr.). In these cases prolonged administration of the standard fluid regime is inappropriate: (a) it will be difficult (and not desirable) to get the CVP up to 8-10 cm, and (b) it will encourage massive urine output, leading to potentially dangerous electrolyte disorder, especially hypokalaemia.

If urine output is >200 mL/hr.:

- (a) Use the standard fluid regime (4.5.1) for the first 24 hours post-transplant then**
- (b) Reduce crystalloid input to equal total fluid output, thus ensuring gentle negative balance through insensible losses and avoiding 'tail chasing', whereby the patient passes a very large volume of urine and is rewarded by having even more fluid infused!
- (c) Some patients may require potassium with replacement crystalloid (40mmol/L). Check serum potassium at least twice daily [more frequently if urine output is massive] and add potassium if patient's potassium <4.0mmol/L.
- (d) If patient is receiving colloid infusion, stop and allow CVP to 'settle' <8cm.

4.6.2 Sudden decline in urine output

If urine output stops check that the catheter is not blocked by:

- Performing a bladder scan
- If necessary **gently** flushing the catheter with 50 ml of sodium chloride 0.9% to dislodge any blockage

Usually the catheter is **not** blocked, and **if a patient becomes abruptly anuric contact surgical Registrar (or consultant) immediately** (acute vascular occlusion may sometimes be recoverable if dealt with rapidly). An urgent ultra sound scan (USS) or Doppler is likely to be required. Continue to prescribe fluids as per protocol.

4.6.3 Delayed graft function (DGF)

This is defined as **either** the requirement for dialysis after the transplant (unless solely to manage hyperkalaemia in a patient with a falling creatinine), **or** oliguria (urine output <50 ml/hour) with failure of the serum creatinine to fall spontaneously.

DGF does not usually require any alteration to immunosuppression unless the patient is at high immunologic risk (see 3.1).

If DGF is prolonged, or there is evidence of Tacrolimus nephrotoxicity on a transplant biopsy, or there are markers of increased immunologic risk then immunosuppression **may be** modified as below (although there is little evidence to support this approach):

Modify maintenance oral immunosuppression as follows:

Reduce Tacrolimus to 0.05mg/kg PO BD (08:00 and 20:00).

Target trough level 5-8microg/L.

Continue Mycophenolate mofetil 1000mg PO BD (08:00 and 18:00)

Continue Prednisolone 30mg PO mane (08:00)

The evidence for a short-course of low-dose Thymoglobulin (1mg/kg IV for 2-3 days) practice is questionable, especially considering the increased risk of bacterial and non-CMV infections in thymoglobulin and risk of subsequent BKV infection in thymoglobulin treated patients with DGF. Most centres across the world do not use Thymoglobuline® for this purpose unless there is a specific immunologic reason.

4.6.4 Resolution of DGF

Once the transplant begins to function and the serum creatinine is falling spontaneously, then the Tacrolimus dose should be increased to achieve a target trough level of 6-10microg/L.

4.6.5 Patients unable to take oral medications

Following renal transplantation it is **very** unusual for patients to be intolerant of PO medications. If parenteral administration is required then the following is a guide. **For details consult the pharmacist.**

- **Tacrolimus.** Starting dose is 0.05mg/kg/24 hours as continuous IV infusion over 24 hours. ^{4,10}
- **Prednisolone.** Substitute with IV hydrocortisone, usually 50mg IV BD - TDS (1 mg prednisolone is roughly equivalent to 4mg hydrocortisone)².
- **Mycophenolate Mofetil.** IV dose is the same as PO dose, infused over 2 hours ^{4,10}.

4.7 Prophylaxis/ prevention of complications

4.7.1 Transplant renal vein thrombosis and DVT prophylaxis

Prescribe (for all patients, unless on therapeutic heparin infusion):

Heparin 5000units subcut BD⁴.

No subsequent aPTT monitoring is required

4.7.2 Gastric mucosal protection

Prescribe (for all patients):

Ranitidine 150 mg PO BD⁴

If ranitidine is contraindicated or patient already taking a proton pump inhibitor preadmission:

- use Omeprazole 20 mg PO mane⁴

4.7.3 Pneumocystis and fungal infection prophylaxis

Prescribe (for all patients):

Sulphamethoxazole/Trimethoprim 800/160mg HALF a tablet daily

indefinitely^{3,8}

(Alternatively: 800/160mg three times a week³)

If a patient is **allergic to** Sulphamethoxazole/Trimethoprim then it is still important that they receive prophylaxis against pneumocystis for the first twelve months.

The alternatives are:

1. Dapsone 100mg daily PO³
2. Pentamidine isethionate 300 mg should be administered by inhalation once every four weeks³, (requires premedication with nebulised salbutamol to prevent bronchospasm) See POWH Clinical Business Rule: Pentamidine
3. Consider desensitisation to cotrimoxazole

*Note all alternatives require consultation with ID.

4.7.4 Candidiasis prophylaxis

Prescribe (for all patients):

Nystatin oral liquid 100 000 units (1mL) QID for one month post-transplant
Sodium Bicarbonate mouthwash 10mL QID for one month post-transplant

Candidiasis of the oropharynx (and urinary tract) is very common shortly after transplant.

If a patient has received induction immunosuppression with a T-cell depleting antibody (thymoglobulin) the increased risk of bacterial and fungal infections is managed best by careful observation, minimisation of environmental exposures, and early evaluation and treatment if symptoms occur.

4.7.5 CMV prophylaxis

All patients at risk of CMV infection should receive prophylaxis with oral Valganciclovir. Accordingly, prophylaxis should be given if **either** the donor (D) **or** the recipient (R) is CMV IgG seropositive (D+ or R+) irrespective of the immunosuppression used. The dose of Valganciclovir depends on the calculated creatinine clearance (using the Cockcroft-Gault formula).

Prescribe (for any D+ or R+ transplant):

Valganciclovir PO in dose appropriate to renal function

Cockcroft Gault creatinine clearance (ml/min)	Valganciclovir prophylactic dose (all PO)
≥ 60	900 mg daily ^{3,4}
40 – 59	450 mg daily ^{3,4}
25 – 39	450 mg every 2 days ^{3,4}
<25	450 mg twice weekly ¹⁰

All high-risk patients (D+, R-) receive Valganciclovir for six months, at risk patients (R+) receive Valganciclovir for three months^{3,8}

Donor / recipient serology	Duration of Valganciclovir prophylaxis
D+ R-	6 months ³
D+ R+	3 months* ³
D- R+	3 months* ³
D- R-	none

* 6 months in any recipient D+ **or** R+ treated with Thymoglobuline^{®3}

4.7.6 Tuberculosis (TB)

All patients being assessed for transplant will have a QunatiFERON Gold-in-Tube (QTF-GIT) test with referral to the tuberculosis clinic for those who are positive. Usual prophylaxis is isoniazid for nine months in total.

4.8 The 'standard prescription'

Most 'dialysis/ renal medications' including erythropoietin, phosphate binders (e.g. Calci-Tab[®], Alu-tab[®], Sevelamer or Lanthanum) and ferrous sulphate, should routinely be stopped. Aspirin should be stopped whilst patients are on intravenous heparin. However, **calcitriol** should be continued.

Anti-hypertensive medications should not be prescribed immediately post-operatively until it is clear that they are required, aside from **beta-blockers, which must not be withdrawn acutely.**

Avoid ACE inhibitors and angiotensin receptor blockers early post-transplant where calcium channel blockers are preferred.

Other medications should usually be continued: but examine **appendix 3**, which lists important drug interactions with Tacrolimus (or Cyclosporine).

Prescribed on the electronic medication record, regular immunosuppression should be clearly recorded to allow for daily alteration of dosing. This specifies a minimum of:

- Immunosuppression as described in **section 3.1.**
Ensure both doses of Basiliximab are prescribed.
- Sulphamethoxazole/Trimethoprim 800/160mg PO HALF a tablet mane
- Nystatin oral liquid 100 000 units (1mL) QID
- Sodium Bicarbonate 1% Mouth Wash 10mL QID
- Ranitidine 150mg PO BD (or omeprazole 20mg daily if already taking a proton pump inhibitor preadmission)
- Heparin 5000units Subcut BD
- Valganciclovir – if appropriate
- Antiemetics (e.g ondansetron and/or metoclopramide)
- Analgesia, (Paracetamol 1g PO QID plus PCA see section 4.4)
- Aperients (e.g Coloxyl and Senna 2 BD, Lactulose 20mL BD PRN)

5 Routine post-operative ward management

5.1 Blood tests

- A typical schedule for recently transplanted patients is shown below. Some additional tests are inevitable (for example, clotting studies before a planned biopsy).
- In the first 24 hours bloods are to be collected at least 12 hourly, or more often if clinically indicated.
- **Trough Tacrolimus levels** - taken **before** morning dose, available Mon to Fri (patients must be educated **not** to take their Tacrolimus before these blood tests). The sample must arrive in the lab before 10am in order to have a result the same day.
- **Serum** - 10 ml to virology and 10 ml to tissue typing (*DSA - post-transplant antibody screen routine) if clinically indicated.

	Mon	Tues	Wed	Thurs	Fri	Sat	Sun
FBC	✓	✓	✓	✓	✓	✓	✓
UEC	✓	✓	✓	✓	✓	✓	✓
Ca, Ph, Mg	✓		✓		✓		
Glucose*	✓		✓		✓		
LFT	✓		✓		✓		
Tacrolimus level	✓	✓	✓	✓	✓	✓	✓
DSA	HLA antibody screen only if clinically indicated						
Virology	CMV PCR only if clinically indicated						

* Screening for NODAT: see Appendix 10

5.2 Imaging - ultrasound

In the immediate post-operative period imaging is required to assess graft perfusion, identify ureteric obstruction (unusual if ureteric stent **in situ**), and identify fluid collections adjacent to the transplanted kidney. The preferred imaging modality is **ultrasound scanning and Doppler studies** (to assess the transplant artery and vein, and graft perfusion).

All patients require a baseline imaging study performed after the transplant. If there is good primary graft function and no concern over the state of the vascular anastomoses then an ultrasound scan should be performed the morning after the transplant operation.

An urgent ultrasound is required to confirm graft perfusion if there is unexpectedly poor initial graft function, if there is doubt concerning the vascular anastomoses or if there is an abrupt deterioration in graft function.

Scan request should say:
 Renal transplant *R or LIF* on *date*. *Baseline scan or clinical indication*.
 Remember to provide **all** relevant information, for example number of transplant arteries, whether or not there is graft function and your page number.

For **urgent scans** contact vascular lab (for Doppler studies) or out-of-hours radiology Registrar on-call via switchboard.

Note – if you think there may be a **transplant artery or vein thrombosis** then there is only a short time in within which the graft may be salvaged. An 'urgent' ultrasound in this setting should be immediate, and the consultant surgeon on-call contacted to arrange surgical exploration and revision.

5.3 Imaging – nuclear medicine studies

Routine DTPA or MAG3 scans are not performed. These scans provide information on graft perfusion and radio-isotope excretion (which is a marker of graft function), and may be useful under some circumstances:

- To assess regional perfusion of a transplant supplied by multiple renal arteries
- To identify a urine leak or (later after transplantation, once the ureteric stent has been removed) ureteric obstruction

Scan request should say:

Renal transplant *R or LIF on date. Indication for scan* – you must give all details, particularly arterial anatomy, whether or not there is graft function and the clinical question you wish answered (e.g. 'is lower pole perfused?' or 'is there evidence of urine leak?')

To discuss nuclear medicine imaging contact the department on ext. 22204.

5.4 Ureteric stents

Routine policy is for the ureteric anastomosis to be stented with an internal (double J) stent. This is normally removed at about 4-6 weeks by flexible cystoscopy, the procedure being covered with Ciprofloxacin 500 mg PO 1hr beforehand. Contact the transplant surgery registrar if:

- There is an indication to remove the stent early (recurrent UTI or troublesome haematuria)
- A patient has not received an appointment for stent removal by six weeks post-transplant.

5.5 Drains, lines, catheters

5.5.1 Surgical drain

- Usually removed at 48 hr. if drainage <100 mL/day.
- Not to be taken out without consent of surgical fellow.
- If there is a large amount of fluid in the drains then send a sample for biochemistry (sodium, potassium and creatinine) to make sure it is not urine

5.5.2 CVP line

- Usually removed four days post-transplant (after second dose of Basiliximab or on completion of Thymoglobuline® course).
- **Not** to be taken out without consent of renal registrar.

5.5.3 Permacath

- If the transplant is working well a Permacath can be removed 24 hours before discharge **if agreed by consultant nephrologist on transplant duty.**
- This procedure is performed under local anaesthetic by the renal registrar.
- If transplant function is uncertain, then do not remove the Permacath before discharge: Arrangements should be made for weekly flushing and locking to keep patent (there is no point in leaving a blocked Permacath **in situ!**). This can be done by nurses on P3W or dialysis as appropriate when the patient attends the transplant clinic.

5.5.4 Urinary catheter

- Usually removed on day five, but can be removed as early as day 3 in uncomplicated cases if agreed by the surgeons.
- Not to be taken out without consent of surgical fellow.

5.6 Adjustment of immunosuppression dose

The dose of immunosuppression that each patient receives is considered and adjusted, if necessary. It should not be altered without discussion with the registrar / consultant. The paragraphs below describe the principles and practice employed.

Note that there are important drug interactions with Tacrolimus, Cyclosporin and Azathioprine to consider - see appendix 3

5.6.1 Tacrolimus

Tacrolimus levels are measured on all ward patients on Mondays to Sundays however samples on Saturdays are not analysed until the next day. SEALS measures Tacrolimus levels by LC-MS/MS, which does not measure inactive metabolites and the levels are 20-50% lower than immunoassays. Immediately after transplantation we aim to maintain a trough level of 8microg/L (target range 6 -10microg/L^{4,6,7,8}) in those receiving the drug orally. In those receiving Tacrolimus as a continuous IV infusion (very rarely required) a 'steady state' level of 10-15microg/L is appropriate.

The dose is adjusted if the measured value falls outside the target range, **but:**

- If the reported trough level is very high ensure that the patient did not take their Tacrolimus dose before blood was drawn
- Remember that a 'stable' trough level is not usually achieved until the patient has been on the same dose for five 'half-lives' of the drug (which will be 3 days for tacrolimus², half life (T_{1/2}) 16 hours¹⁰). Accordingly, there is little point in changing the tacrolimus dose on consecutive days unless the trough levels are extreme.
- There are many factors that influence Tacrolimus levels, including:
 - Use of other drugs that affect Tacrolimus metabolism
 - Diet (Tacrolimus absorption is higher in starved patients)
 - Diarrhoea (also leads to increased Tacrolimus absorption)
 - A low serum albumin increases the proportion of free (active) drug

In stable patients in whom other medications are not being altered there is, **in general**, a linear relationship between Tacrolimus dose and measured trough level. Thus, if you double the dose you will double the trough level, but it will take two to four days.

Worked example: 80kg patient started off on tacrolimus 0.15mg/kg/d = 6mg BD. Trough level on post-transplant day five high at 17.5microg/L (target 6-10). Halving the dose to 3mg BD should lead to trough level 8-9microg/L within four days. Consider withholding the evening dose if >15microg/L.

5.6.2 Cyclosporin

The principles used for Tacrolimus dosing and dose adjustment apply equally to Cyclosporin. At present Neoral[®] is the only Cyclosporin brand used in the hospital, and is prescribed twice daily at 08:00 and 20:00. The usual starting dose is 7 mg/kg in total – thus for a 70kg patient = 490mg = 250mg PO BD.

Target Cyclosporin levels are measured two hours after the morning dose (“C2”).

5.6.3 mTOR inhibitors (Sirolimus and Everolimus)

Sirolimus and Everolimus are currently not used as part of the standard immunosuppression in patients in the immediate post-transplant period (because of a marked inhibition of wound healing). Clinical trial protocols will generally guide dosage of the mTOR and CNI. Much lower targets for CNI levels (10-20% of the usual target) are required when used with Everolimus or Sirolimus.

Sirolimus is best used **without** Cyclosporin, as there is a significant interaction, which results in elevated Sirolimus levels particularly when the drugs are co-administered.

Target trough mTOR levels, if used early following transplantation in combination with a CNI are:

- Sirolimus levels are 4-8ng/L ^{4,10}
- Everolimus levels are 3-8ng/L ^{4,10}

Sirolimus is administered once daily and Everolimus is used twice daily, Sirolimus has a longer half-life (60 hours ¹⁰) than Everolimus (30 hours ¹⁰). This means that the response to any dose adjustment will take several days (Everolimus) and up to a week (Sirolimus) to reach a new steady state.

5.6.4 Mycophenolate mofetil

Use of mycophenolate is most commonly limited by gastrointestinal side-effects (especially diarrhoea), which usually respond to dose reduction. In addition mycophenolate is also myelosuppressive, and in general causes more profound **lymphopaenia** than azathioprine.

For this reason mycophenolate dose adjustments should be based on absolute neutrophil count ², not total WBC:

Absolute neutrophil count (x10 ⁹ /mm ³)	Induction therapy	
	Basiliximab	Thymoglobulin
> 2.0	750-1000mg BD	500mg BD
1.0 – 2.0	250mg BD	250mg BD
< 1.0	STOP	STOP

5.6.5 Azathioprine

The starting dose of azathioprine is 2 mg/kg, approximated to the nearest 25mg. Do not exceed 200mg. The factor most commonly limiting the dose of azathioprine is dose-related marrow suppression ^{2,4}. Note that leucopenia does not correlate with therapeutic efficacy. If the total WBC is < 4.0, then the dose of azathioprine should be halved ² (rounded to the nearest 25 mg), and omitted completely if total WBC < 3.0.

Azathioprine must not be used in combination with allopurinol due to the risk of fatal toxicity ^{2,4}.

6 Investigation of graft dysfunction

This is the most common cause for concern in immediate post-transplant management. By far the most frequent cause of a graft failing to work initially (urine output from graft < 50 mL/hr. at 6 hr., or a rising creatinine) is acute tubular necrosis or ATN, for which there is no specific treatment.

If a graft functions initially, but then deteriorates (manifest by creatinine plateauing or rising), the differential is usually between urinary obstruction, rejection (rare nowadays before day five or six, except in sensitized patients with preformed donor-reactive HLA antibodies), Tacrolimus nephrotoxicity and ATN (if there has been an intercurrent haemodynamic stress).

Diagnosis therefore requires:

6.1 Urgent Doppler Ultrasound examination

In case of graft dysfunction an urgent Doppler Ultrasound examination will be required to exclude obstruction and confirm blood supply.

Contact vascular laboratory (or on-call radiology Registrar if out-of-hours)

Scan request should say:
Renal transplant on 'date' Rising creatinine. 'For biopsy if obstruction excluded – is the graft well perfused?' Make sure you include your contact details.

In theory any request for an urgent transplant USS received from P9W before 10.30 will be done that morning and certainly that afternoon. In practice **all** cases should be discussed with ultrasound. If there is difficulty in obtaining a USS contact senior medical (registrar / consultant) staff immediately.

6.2 Transplant biopsy

Performed as bedside procedure on P9W by senior registrar or medical staff.

6.2.1 Before procedure

Ensure platelet count, Hb and clotting have been checked in the preceding 24 hours.

- If platelet count < 80 x 10⁹/L, seek haematology advice – the procedure may need to be done under platelet cover.
- Send a G+H sample if Hb 80-90g/L and consider transfusion if <70g/L.
- Clotting should be normal.
- Check BP (should be < 160/90). Anxious, hypertensive patients may respond to a small dose of benzodiazepine (for example Diazepam 5mg PO) 60 minutes pre-biopsy

Ensure heparin has been withheld for the day prior to and the day of the biopsy and written consent has been obtained (usually by the performing clinician).

If a biopsy is considered "urgent" or performed out-of-hours, take the sample to the histopathology lab. Ensure the consultant histopathologist on-call is aware of the biopsy so that an urgent preliminary report can be issued.

6.2.2 After procedure

- Bed-rest for six hours
- Routine post-biopsy nursing observations:
- Every 15 minutes HR & BP for two hours then
- Every 30 minutes HR & BP for two hours
- Macroscopically examine the urine for haematuria
- An increasing pulse rate, falling BP, macroscopic haematuria or pain over the transplanted kidney post-biopsy should prompt an immediate assessment including blood tests (esp. FBC), volume assessment and consideration of USS to check for developing haematoma.
- **If there are any concerns re the clinical status of a patient post-biopsy, immediately inform the renal Registrar (ideally the one who performed the procedure)**

7 Treatment of graft rejection

7.1 Methylprednisolone

The standard first-line treatment for rejection is high-dose IV steroids:

Prescribe:

Methylprednisolone 500 mg IV daily for three days^{2,4,10}.

This can be given through either a peripheral or a central line. Oral steroids should be discontinued for the duration of IV treatment.

Maintenance immunosuppression should be modified (see immunosuppression flowchart). All patients diagnosed with acute rejection should have a 10mL serum sample sent to tissue typing for **HLA antibody screen** (ARCBS). If antibody-mediated rejection (AMR) is suspected then contact tissue typing directly to arrange for the test to be performed urgently (ARCBS – call Narelle Watson (02) 9234-2356).

7.2 Thymoglobuline® (antithymocyte globulin - Rabbit)

The standard treatment for rejection refractory to methylprednisolone, or for an initial episode of **severe acute rejection**, is to administer a polyclonal T-cell depleting antibody. The preparation routinely used is rabbit anti-human thymocyte globulin (Thymoglobuline®).

- Administration of Thymoglobuline® needs to be supervised closely. In patients with fluid overload the first dose may rarely precipitate fatal pulmonary oedema (due to cytokine release making lung capillaries leaky).
- The patient must be reviewed by a senior member of staff (registrar / consultant) before Thymoglobuline® is given. If pulmonary oedema is present (obtain CXR), it requires treatment, almost certainly by dialysis, **before** treatment with Thymoglobuline® commences.
- The first dose of Thymoglobuline® should be administered under close supervision.
- For treatment of **acute rejection** thymoglobuline® should be given for a total of **7-14 days**, based on graft function, and severity of rejection as well as WBC, platelet and lymphocyte counts
- The treatment dose of Thymoglobuline® is **1.5mg/kg daily^{2,4} rounded to nearest 25mg**
- **See Appendix 5 for further information**

7.2.1 Oral immunosuppression in addition to Thymoglobuline®

- **Tacrolimus:** withhold during course of treatment then recommence on morning of final day of treatment
- **Mycophenolate mofetil:** reduce dose to 500mg bd during course of treatment (increase after course complete).
- **Steroids** should be continued, usually 30 mg Prednisolone mane.

7.2.2 Prophylaxis against infection in addition to Thymoglobuline®

- **Trimethoprim/ Sulphamethoxazole 160mg/800mg HALF a tablet PO** daily (if not already prescribed) ³
- **CMV prophylaxis with Valganciclovir** ³ if either donor *or* recipient is CMV IgG seropositive (D+ or R+), for at least three and possibly six months (see **section 4.7.5** for dosing).
- **Consider Aciclovir prophylaxis** for CMV D-/R- patients (to protect against other herpes virus infections, particularly herpes simplex virus (HSV) and VZV) ³.
- Nystatin oral liquid 100 000 units (1mL) QID for 30 days to protect against oral and oesophageal candidiasis.

8 Lymphocoele

Lymphocoeles are common and if both asymptomatic and not compromising vital structures (e.g. compressing the transplant ureter leading to obstruction) are best left alone. Such lymphocoeles often disappear.

The initial treatment for a **symptomatic** lymphocoele is drainage to dryness with a pig-tail catheter inserted under ultrasound guidance. If (when) it recurs, then repeat drainage alone is unlikely to be successful. Recurrent lymphocoeles require surgical fenestration.

9 Investigation / treatment of suspected CMV infection

9.1 Prevention

CMV **prophylaxis** with Valganciclovir is routinely prescribed to all patients at risk of CMV disease; that is those who are CMV IgG seropositive (R+) indicating past infection with CMV, or who receive an organ from a CMV seropositive donor (D+) (see **section 3.7.5**). Prophylaxis is given for either three or six months, and again to any patient who receives a lymphocyte-depleting antibody at any time following transplantation.

9.2 Investigation

Renal transplant recipients are susceptible to primary (CMV transmitted with the transplant) or secondary (re-activation) CMV infection. Without the use of prophylaxis, CMV is most commonly diagnosed between four and eight weeks post-transplant. In patients receiving prophylaxis it is most commonly diagnosed 2-10 weeks after Valganciclovir is discontinued, and can take a wide variety of forms:

- Asymptomatic CMV viraemia (identified by screening for CMV)
- CMV syndrome (viraemia with fever, flu-like symptoms, arthralgia and often abnormal LFTs and leucopenia)
- Tissue-invasive CMV disease (pneumonitis, colitis and CMV infection of the transplanted kidney).

The clinical expression of CMV ranges from a trivial febrile illness to a devastating condition with high fever and widespread organ involvement/

failure (gut, lung and liver particularly). Most typical is the patient with a fever of 40°C who looks and feels reasonably well.

Testing of patient suspected of having symptomatic CMV infection

- (1) PCR from blood (specimen in EDTA, order CMV PCR, for quantitative result).
- (2) Tissue to virology for PCR (when affected organ biopsied)
- (3) BAL for suspected CMV chest infection

Note - enterovirus, HSV and VZV PCR testing is available for patients with CNS symptoms

9.3 Treatment

In many cases CMV infection is a relatively mild, self-limiting illness, and the patient who feels well, with no evidence of organ involvement (e.g. normal liver function tests), and a low CMV titre (< 3,000 copies DNA/ml) may simply be observed with weekly CMV monitoring unless they meet criteria for treatment (see below) or counts fall below 300 copies/ml. Consider reduction in the mycophenolate dose, if possible

Treatment should be started if:

Asymptomatic

- PCR >3,000 copies/mL and primary infection (R-), or
- PCR >3,000 copies/mL and a threefold increase on repeat test, or
- PCR >10,000 copies/mL on two consecutive occasions

Symptomatic

- PCR >300 copies/mL

Asymptomatic patients should be treated with treatment-dose oral Valganciclovir (see table below) until the CMV PCR < 300 copies/mL for two consecutive weeks, followed by 11 weeks of prophylactic-dose Valganciclovir (assuming screening PCRs remain negative).

9.3.1 Valganciclovir

Creatinine clearance	Valganciclovir treatment dose ^{3,4,10}
>60	900 mg BD
40-59	450 mg BD
25-39	450 mg daily
10-24	450 mg every two days
<10	No suitable valganciclovir dose Use IV Ganciclovir

9.3.2 Ganciclovir

Symptomatic patients (or those with tissue-invasive disease) should receive IV Ganciclovir, dosed according to CrCl as follows:

Creatinine clearance	Ganciclovir treatment dose (Intravenous) ^{3,4,10}
>70	5 mg/kg BD
50-69	2.5 mg/kg BD
25-49	2.5 mg/kg daily
10-24	1.25 mg/kg daily
<10/dialysis	1.25 mg/kg 3x / week (after HD on HD days)
CRRT	2.5mg/kg daily
Cytotoxic antiviral – dose needs to be prepared in sterile pharmacy. IV Administration: give over 1 hour ¹⁰	

Monitor CMV PCR once per week whilst on treatment and switch from IV Ganciclovir to oral Valganciclovir (prophylactic-dose) when CMV < 300 copies/mL on 2 consecutive occasions. Oral Valganciclovir should be continued for a further 11 weeks assuming PCR remains negative.

FBC should also be closely monitored whilst on IV Ganciclovir as it can cause a profound pancytopenia. Stop Ganciclovir if²:

- a) Neutrophil count < $0.5 \times 10^9/L$, or
- b) Platelet count < $25 \times 10^9/L$

Following successful treatment, screen for reactivation by CMV PCR once a month until six months post-infection.

9.3.3 Immunosuppression

CMV viraemia is a consequence of immunosuppression. In addition to antiviral therapy, most patients should have immunosuppression reduced:

- **Reduce or stop mycophenolate** – (Val)ganciclovir increases bioavailability of mycophenolate
- However, remember that CMV infection actually **increases** the probability of acute rejection, so it is important to:
- Maintain therapeutic Tacrolimus levels
- Maintain steroid dose. In severely symptomatic patients on maintenance prednisolone (5mg mane) consider doubling to 10mg mane

9.3.4 Ganciclovir resistance

Clinical resistance to Ganciclovir should be suspected if the CMV count has not fallen by at least one log difference (i.e. 10-fold) after two weeks of therapy and/ or the patient has not improved clinically. In this circumstance:

- Consider (further) reduction in immunosuppression
- Discuss with consultant virologist
- Discuss alternative antiviral agents with ID (Foscarnet or Cidofovir)
- Consider CMV hyperimmune globulin

- Request test for genotypic resistance (results available in around 10 days)

9.3.5 Concurrent antimicrobial prophylaxis

Patients with CMV viraemia are at **increased risk** of opportunistic infection. If Trimethoprim/Sulphamethoxazole prophylaxis has been discontinued then **restart** Trimethoprim/Sulphamethoxazole 160mg/800mg HALF a tablet daily.

Antifungal prophylaxis with fluconazole is usually unnecessary.

10 Record and note keeping

This is vitally important: without records and notes we won't know what has happened. In addition to regular entries in the hospital notes, the renal transplant junior doctors are responsible for:

- Entering data into the events screen of the renal transplant database
- Updating the summary screen for the weekly audit meeting

Data to be captured includes diagnoses, current drugs, investigations, complications of transplantation and renal transplant biopsy results. Wherever possible the data should be entered using the drop down lists provided and the use of free text should be minimised.

11 Patient discharge

If a renal transplant works well, patients will be discharged on the 7th or 8th post-operative day. The **renal transplant registrar** should ensure that when patients are discharged from the ward:

- A completed discharge summary and medication prescription is generated. This is a **vital document** generated through the EMR system. It is essential that the information entered is both **accurate** and **comprehensive**.
- A **copy** of the discharge summary and medication prescription must be sent to the **referring hospital and/or nephrologist**, when the patient is not a regular POW client.
- A supply of correct medication is prescribed, with clear instructions as to how it should be taken (liaise with pharmacist and transplant recipient co-ordinator).
- An appointment is made for the patient to come to the next transplant clinic. They should be told that they can expect to come to clinics daily for the first 2 weeks and then three times a week for the first two months or so after discharge. Those patients with a double-J stent should be informed of this, and told that they can expect for it to be removed (day case cystoscopy) in 6-8 weeks.
- General advice: patients should be told to contact the ward directly if they develop **any** problems within the first month after discharge. The chance of rejection or other transplant complication is high during this period, and there should be a very low threshold for seeing the patient and checking the creatinine during this period. There is very little point telling a recently discharged patient to 'see their GP'!

12 Death of a patient

The transplant surgical and renal medical consultant on-call should be informed at the earliest opportunity if a patient on the ward dies, as should the surgeon who performed any recent operation (relatives often come round to our offices, and it's embarrassing if we don't know what has happened).

A clinical summary **must** be sent to the patient's GP and to the referring physician, by the transplant surgical fellow, and may require a brief dictated letter in addition to the mandatory EMR summary.

13 Living donors

13.1 Before surgery

When a living donor transplant is planned, the donor and recipient usually attend the clinic on a week-day during the preceding month for final cross-match and within 10 days prior to surgery for NAT of blood borne viruses (HIV, HBV, HCV). Female donors will also have β HCG testing done at the time to exclude pregnancy.

On admission the day before surgery donor and recipient attend the ward for bloods and clerking. You will need to check all results prior to the weekend to ensure donor and recipient are still fit for surgery and consents have been signed.

The recipient will attend P9W to be clerked by the renal transplant junior doctor. The recipient should already have a signed consent form in the notes. Any recipient allergies should be noted on the donor admission.

Donors are usually admitted to D2N (alternatively D2S or POW Private). Bloods (including crossmatch of two units of blood), ECG will normally be arranged by the living donor co-ordinators in the morning. The donor will have completed a consent to surgery at the time of the surgical review and the consent will be in the current medical record.

All donors should have below knee TED stockings on from admission.

Prescribe:

- 5000units of Heparin subcut **no later than 20:00 hours on the evening before surgery and again in the morning prior to surgery**
- 2L Glycoprep starting at 16.00 the day before surgery (Except for patients under Dr Ehsman and Dr Richards)
- Start Hartmann solution at 125mL/h at 18:00
- Administer Temazepam 10mg the night of surgery PRN
- Nil by mouth from midnight
- Cephazolin 2g IV at induction of anaesthesia (Vancomycin 1 g IV if penicillin cannot be given or MRSA considered a possibility)

13.2 After surgery

If an NG tube had been placed for technical reasons, this should come out in recovery when the patient returns to the ward.

Patients will be on patient-controlled analgesia on day 0, but this is to be taken down on day one.

Hb to be checked at 7 pm on Day 0 and the on-call Surgical Registrar informed of the result.

Prescribe:

- Heparin 5000units subcut BD at 18:00 until discharge.
- Regular paracetamol 1g PO QID from day 0.
- If pain is not controlled by paracetamol, Oxycodone PO will be charted.
- Tramadol 50-100mg QID PO PRN.
- Anti-emetic Ondansetron 8mg IV/PO 6 hourly PRN.

- Glycerin suppositories PRN: patients with previous history of constipation should have laxatives from day 1 post-operatively.

General management:

- Continue Hartmann solution at 125mL/hr, discontinue on day 2 post-op if tolerating free fluids
- Allow free fluids from Day 0 and breakfast and food from Day 1.
- IV fluids should come down on Day 1 unless the patient is unable to take PO fluids
- Urinary catheter should be removed on the morning after surgery, following surgeon's approval, unless there is concern about haemodynamic status or urinary output.
- Most patients will have a surgical drain, if one is present record drain volume daily and measure fluid amylase on Day 1 if left nephrectomy.
- Do not remove drain without discussion with surgeon.
- Aim to fully mobilize from Day 1. The physiotherapist will see donors daily for deep breathing/coughing exercises and mobilising.
- Aim for discharge 2 - 3 days post-op.
- The donors are seen in the surgeons rooms post discharge and in the transplant clinic at 1, 6 and 12 months and then on an annual basis by the living donor co-ordinators.

13.3 The recipient

At the same time as pre-clerking the donor, you will also see the **recipient**. Routine assessment and investigation are as for all other recipients (see section 2.2). However make sure that you:

- Note if the recipient is **pre-dialysis**
- If so, is the potassium safe?
- If potassium is >5mmol/L are there any medicines (ACE inhibitors etc.) that should be stopped?
- Is pre-operative dialysis likely to be required – discuss blood results with transplant nephrology registrar.

For patients on regular haemodialysis, an appropriate pre-operative dialysis slot will have been organized by the live donor co-ordinators.

Is the recipient either warfarinized, or taking Clopidogrel? Seek advice.

13.4 Living donor coordinators

- Michelle Glasel 24437 (donors)
- Pauline Paul 24443 (recipients)

14 Haemodialysis

14.1 Routine haemodialysis

In-patient dialysis is coordinated by the nurse in charge on Kidney Care Centre (KCC) dialysis unit, ext. 24438 Monday to Saturday (07:00 – 19:00).

Many patients admitted to Ward P9W require regular haemodialysis e.g. regular haemodialysis patients admitted for access or other surgery. The dialysis unit should be informed as soon as such patients are admitted.

Whenever possible they should be dialysed in their regular dialysis slots. If this is not possible (e.g. because this clashes with the time of their operation), then the maximum possible notice must be given.

14.2 'Emergency' haemodialysis

Contact:

For **urgent dialysis on P9W** (07:00 – 19:00 [approx.], Monday – Saturday call **KCC haemodialysis** (ext. 24438) and speak to the nurse in charge (who coordinates in-patient dialysis)

Outside of these hours (and if no reply from unit): Emergency haemodialysis nurse on-call via switchboard.

The most common scenario arises after transplantation. The transplanted kidney is not working well, although there may be some function, and the question arises: "is dialysis needed?"

Indications for genuine emergency dialysis (as for any other patient with renal failure) are rare:

1. Dangerous hyperkalaemia [significant ECG changes]
2. Severe pulmonary oedema
3. Profound acidosis causing circulatory compromise
4. A gross 'uraemic' complication e.g. bleeding.

These situations should not be allowed to arise in a patient under supervision in hospital!

A decision should be made (usually by the renal registrar) on the 08:30 ward round each morning as to whether or not dialysis is required that day for any patient whose transplant function is poor. If it is, then **the haemodialysis unit should be informed as soon as possible, and certainly before 09:30.** The dialysis prescription should be completed and sent down with the patient – the nursing staff on the dialysis unit are unable to commence haemodialysis without this. If temporary access is required, this should be inserted immediately after the ward round so that the patient is ready to receive treatment.

Appendix 1: Patient not transplanted

Renal Transplant Ward (P9W)
Prince of Wales Hospital
Tel 02-9382 4473

Dear Dr

Re: (Patient label)

This patient came to Prince of Wales Hospital in anticipation of a renal transplant. This was not performed for the following reason(s):

The patient has been told the following:

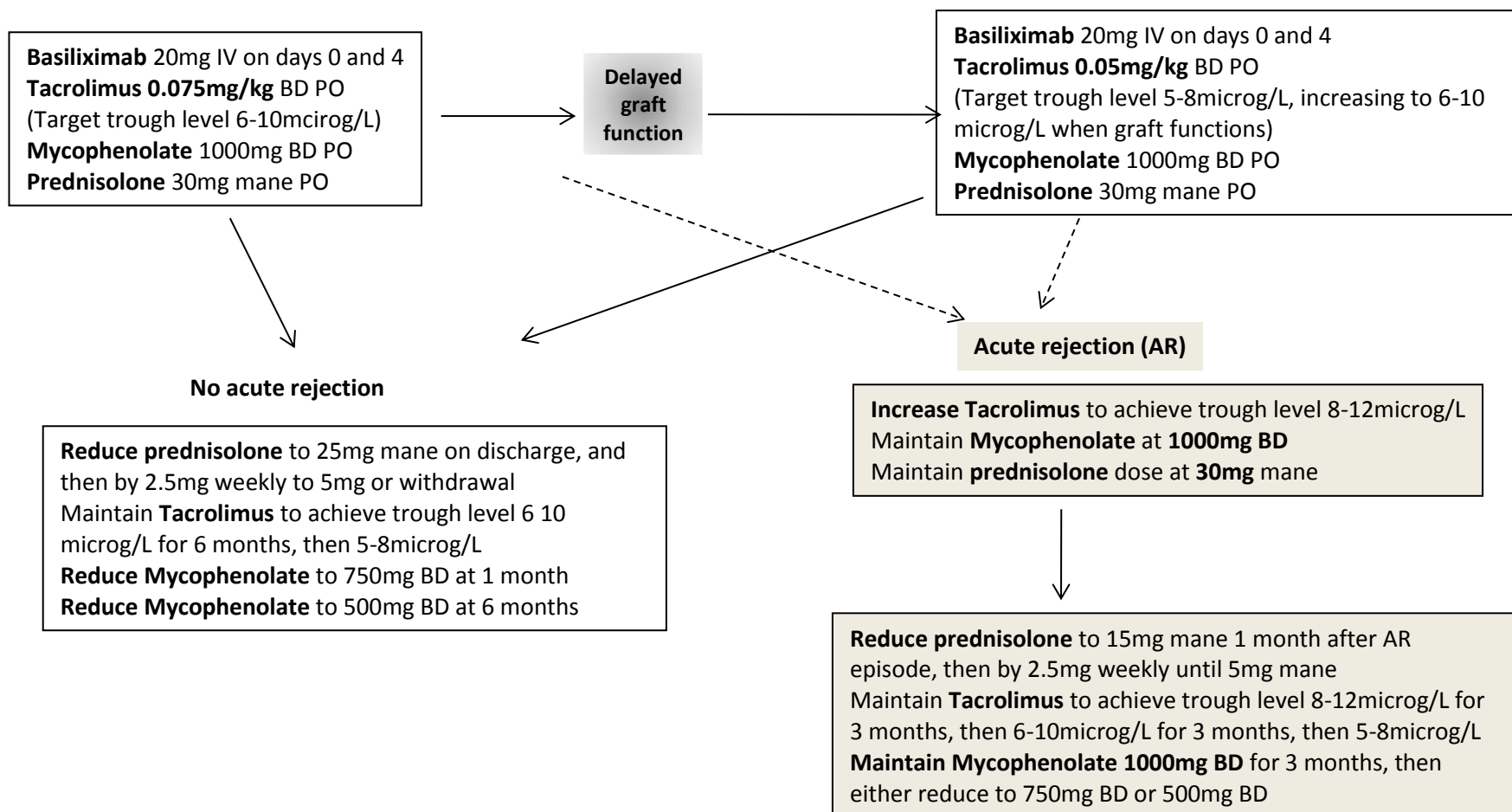
Signed

Fax/email copy of this form to the referring consultant:
St George Hospital - Fax: 02-9553 8192
St Vincent's Hospital - Fax: 02-8382 2032
Wollongong Hospital - Fax: 02-4227 6284

Appendix 2: Standard immunosuppression protocol flowchart

All live and deceased donor transplants

Delayed graft function (optional)



Appendix 3: Drug interactions^{2,4}

This list is not exhaustive and is intended as a guide only. Check ALL new medications for potential drug interactions with immunosuppressant regimen.

Tacrolimus (also Cyclosporin and Sirolimus)

Interaction effect	Drug class	Examples
Increase CNI and mTOR levels	Calcium channel blocker	Verapamil, Diltiazem, Lercanidipine, Nifedipine
	Antifungal agents	Ketoconazole, Fluconazole, Posaconazole, Itraconazole, Miconazole, Voriconazole
	Anti-retroviral agent	Indinavir, Saquinavir, Fosamprenavir, HIV-protease inhibitors
	Antibiotic	Erythromycin, Clarithromycin, Chloramphenicol, Chloroquine, Hydroxychloroquine, Doxycycline, Boceprevir,
	Other	Amiodarone
Decrease CNI and mTOR level	Anticonvulsant	Phenytoin, Carbamazepine, Barbiturates
	Anti-tuberculosis agent	Isoniazid, Rifampicin

Drugs which may potentiate Tacrolimus and Cyclosporin nephrotoxicity

- Amphotericin B
- Aminoglycosides (e.g. Gentamicin)
- NSAIDs (all of them)
- Sirolimus
- Colchicine

Drugs whose metabolism is altered by Cyclosporin or Tacrolimus

Cyclosporin potently inhibits metabolism of Simvastatin, Atorvastatin and Rosuvastatin, increasing the risk of myopathy and occasionally rhabdomyolysis. Cyclosporin-treated patients should only receive Pravastatin or Fluvastatin (where metabolism is independent of the CYP3A4 enzyme).

Tacrolimus has much less effect on simvastatin and atorvastatin metabolism, both of which may be prescribed in Tacrolimus-treated patients.

Calcineurin inhibitors may increase **colchicine** concentration and may cause myopathy, GI disturbances, renal and hepatic toxicity which may be fatal; avoid combination if possible, otherwise monitor carefully.

Cyclosporin inhibits biliary excretion of mycophenolate, leading to reduced enterohepatic recirculation and consequently **reduced** Mycophenolate exposure. Neither Tacrolimus nor Sirolimus share this effect. Accordingly a Mycophenolate dose of 500 - 750 mg BD in Tacrolimus-treated patients is equivalent to 1000 - 1500 mg BD in Cyclosporin-treated patients.⁵

Azathioprine

Allopurinol and Febuxostat increase the effect of azathioprine very significantly, with a high risk of profound (sometimes fatal) myelosuppression. If the patient is taking allopurinol do the following:

- Is allopurinol necessary? Following successful transplantation hyperuricaemia usually resolves. If the patient has not experienced troublesome gout then discontinue allopurinol and prescribe azathioprine.
- However, if the patient has recurrent acute gout, tophaceous gout, a history of uric acid kidney stones or urate-related nephropathy, then continue allopurinol. In these circumstances replace azathioprine with Mycophenolate mofetil 750mg BD.
- **Do not prescribe azathioprine and allopurinol/febuxostat together as there is a risk of fatal toxicity.**^{2,4}
- Consider testing for Thiopurine methyltransferase (TPMT) mutation²

Appendix 4: ABO blood group incompatible transplants

Background

In principle, solid organ transplants must be performed from a donor of an ABO blood group compatible with the intended recipient. The donor and recipient are **incompatible** if the recipient has pre-formed antibodies to donor ABO antigen(s) - A, B or both.

Donor Recipient	A	B	AB	O
A	Identical	Incompatible	Incompatible	Compatible
B	Incompatible	Identical	Incompatible	Compatible
AB	Compatible	Compatible	Identical	Compatible
O	Incompatible	Incompatible	Incompatible	Identical

Antibodies specific for blood group A or B carbohydrate antigens develop naturally during the first few years of life (likely in response to similar carbohydrate antigens on commensal gastrointestinal bacteria). Thus an individual without either A or B antigens (that is, ABO blood group O) develops antibodies to both A and B, and so on.

Antibodies to ABO antigens are important in transplantation because ABO antigens are expressed on endothelial cells. Thus, if a blood group A kidney is transplanted into a blood group B individual, pre-formed anti-A antibodies will bind to A antigen on the graft endothelial cells, activate complement and coagulation, and potentially destroy the graft. However, over the last 30 years it has become clear that:

- The quantity of natural antibody to non-self ABO antigens varies enormously between individuals
- Low levels of antibody appear **not** to be harmful to transplanted organs
- Transplantation is safe if anti-donor A or B antibody can be reduced to low levels at the time of transplantation.

In practice

ABO blood group **incompatible** live donors are now routinely considered. The most important issue is to determine the quantity of anti-donor A or B antibody in the recipient circulation. This is determined by the blood transfusion laboratory, and the result expressed as a **titre**.

The titre is the highest dilution of serum at which the antibody is able to agglutinate red blood cells.

Thus an anti-A titre of 1:8 means that a 1:16 dilution of serum (the next titre) is sufficient to render the antibody ineffective. A titre of 1:256 implies a much higher quantity of antibody. The laboratory reports the titre of both IgG and IgM antibodies.

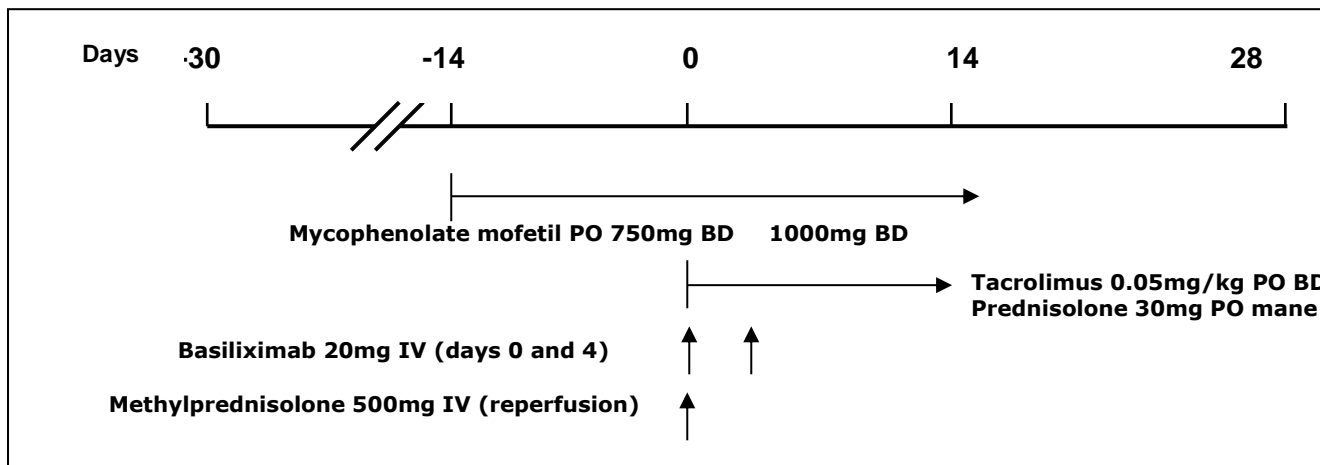
An ABO incompatible transplant can be performed if the titre of anti-donor A or B antibody is $<1:8$, or can be reduced to $<1:8$ by antibody removal (plasma exchange or immunoabsorption). The following protocols apply, depending on the recipient's starting titre of anti-donor antibody.

If you are looking after the recipient of an ABO blood group incompatible transplant you must read the section on administration of blood products.

Antibody removal not required

Use this protocol for any patient receiving an ABO incompatible transplant **not requiring antibody removal**:

- ABO incompatible pairs in which the recipient has no detectable IgG or IgM antibodies against the donor ABO blood group or
- ABO incompatible pairs in which the recipient ABO IgG or IgM titre (anti-A or anti-B) is **1:4 or less**



30 days (approx.) before the transplant – confirm anti-A or anti-B titre is 1:4 or less

14 days before the transplant – begin immunosuppressive treatment with mycophenolate mofetil 750mg BD. **Repeat ABO titre.**

One day before the transplant Repeat ABO titre.

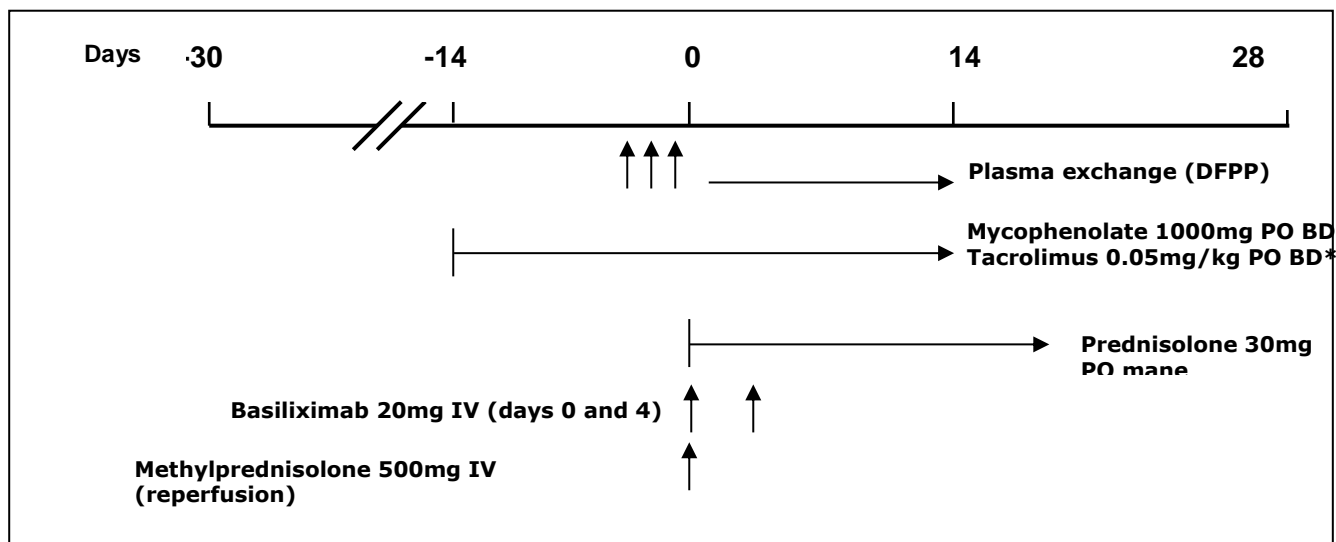
At the time of transplantation – methylprednisolone 500mg IV at the time of graft reperfusion.

Following transplantation:

- Start Prednisolone 30mg mane
- Start Tacrolimus 0.1mg/kg BD to achieve trough level 8-12µg/L
- Increase mycophenolate to 1000mg BD
- Give Basiliximab 20mg IV on days 0 and 4 (this must be **after** and not before a plasma exchange)
- Start prophylactic Valganciclovir, Nystatin oral liquid and ranitidine (see section 3.8)
- **Check ABO titre on post-transplant day seven.**

Antibody removal required – LOW TITRE

Use this protocol if the recipient anti-ABO IgG or IgM titre is >1:4 but no higher than 1:32



*Check Tacrolimus level on pre-operative day -10 and -7, and adjust dose to achieve trough level 4-8microg/L. Following transplantation increase the dose further aiming for a trough level of 8-12microg/L.

30 days (approx.) before the transplant – confirm anti-A or anti-B IgG and IgM titre

14 days before the transplant – begin immunosuppressive treatment with mycophenolate + tacrolimus – see above. Start prophylactic Trimethoprim/Sulphamethoxazole.

7 days before the transplant – check Tacrolimus level and adjust dose to achieve trough level 4-8microg/L. If tolerating mycophenolate 750mg BD then increase the dose to 1000mg BD. **Repeat ABO titre.**

3-5 days before the transplant – antibody removal with double filtration plasmapheresis (DFPP)

- For IgG or IgM titres 1:8 or 1:16 schedule 3 DFPP treatments on days -3, -2 and -1
- For IgG or IgM titres 1:32 schedule 4 DFPP treatments on days -4, -3, -2 and -1.
- Check anti-A or B titres at the beginning and end of the final treatment. The aim is for both IgG and IgM titres to be 1:4 or less on the morning of transplantation.
- **FFP from the same blood group of the kidney donor** must be used for the final exchange prior to transplant and the first exchange post-transplant.

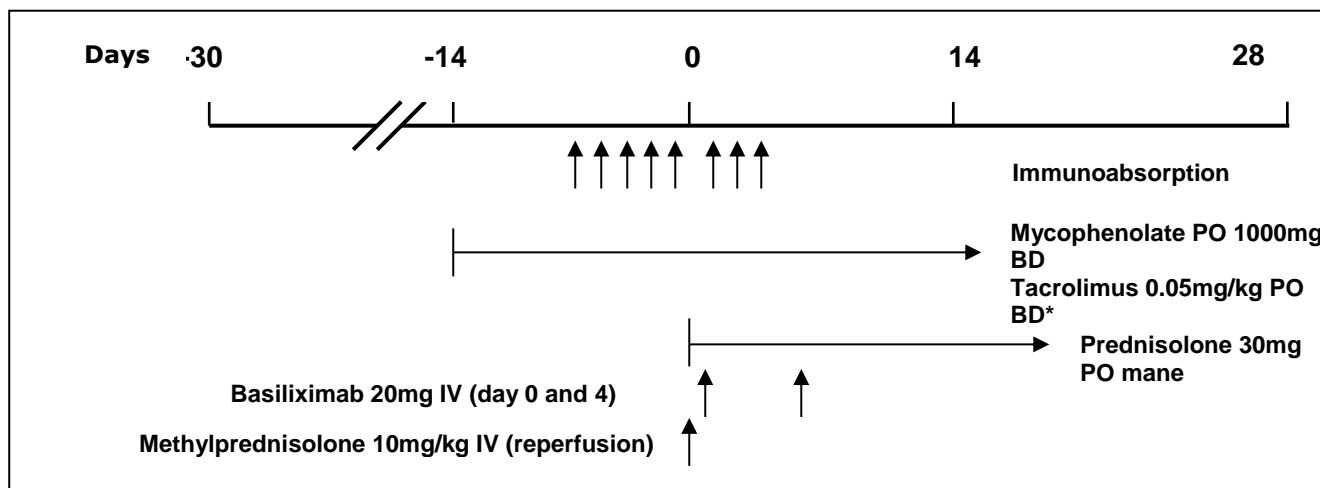
At the time of transplantation – methylprednisolone 500mg IV at the time of graft reperfusion.

Following transplantation:

- Start prednisolone 30mg mane
- Increase Tacrolimus to achieve trough level 8-12microg/L
- Continue mycophenolate at 1000mg BD
- Give Basiliximab 20mg IV on days 0 and 4
- Start prophylactic Valganciclovir, Nystatin oral liquid and ranitidine
- Post-transplant antibody removal **is not required** unless there is a rapid rise in anti-A or B titre. **Check ABO titre on post-transplant days one and seven**, or if there is graft dysfunction.

Antibody removal required – HIGH TITRE

Use this protocol if the recipient anti-ABO IgG or IgM titre is 1:64 or greater



*Check Tacrolimus level on pre-operative day -10 and -7, and adjust dose to achieve trough level 4-8microg/L. Once the patient begins immunoabsorption check Tacrolimus levels on Mon, Wed and Fri. Following transplantation increase the dose further aiming for a trough level of 8-12microg/L.

30 days (approx.) before the transplant – confirm anti-A or anti-B IgG and IgM titres.

14 days before the transplant – begin immunosuppressive treatment with Mycophenolate + tacrolimus. Start prophylactic Trimethoprim/Sulphamethoxazole

7 days before the transplant – check Tacrolimus level and adjust dose to achieve trough level 4-8microg/L. If tolerating mycophenolate mofetil 750mg BD then increase the dose to 1000mg BD. **Repeat ABO titre.**

7-10 days before the transplant – begin antibody removal using plasmapheresis (PP). The exact schedule for each patient will vary, but will typically comprise 5-7 treatments over 7-10 days depending on ABO antibody titre.

IVIg (0.5g/kg) will be administered after the last pre-operative PP

Ideally anti-A or B IgG and IgM titres are measured before and after each IA treatment, **but in practice a more limited regime is reasonable** (see below). The titre on the morning of transplantation should be 1:8 or less.

FFP from the same blood group of the kidney donor must be used for the final exchange prior to transplant and the first exchange post-transplant.

At the time of transplantation – methylprednisolone 10mg/kg IV at the time of graft reperfusion.

Following transplantation:

- Start prednisolone 30mg mane
- Increase Tacrolimus to achieve trough level 8-12microg/L
- Continue mycophenolate mofetil at 1000mg BD
 - Give Basiliximab 20mg IV day 0 and day 4 (this must be after and not before a plasma exchange)
- Start prophylactic Valganciclovir, Nystatin oral liquid and ranitidine
- Elective post-transplant antibody removal **is required** usually on post-transplant days 1, 3 and 6. **Check ABO titre on post-transplant day 7** or at any time if there is graft dysfunction.

Blood products in ABO incompatible transplants

All serum-based blood products (principally FFP but also platelets and cryoprecipitate) will contain natural anti-A or B antibodies derived from the blood donor. Accordingly great care is needed when administering such products to patients in whom anti-A or anti-B antibodies have been eliminated to facilitate an ABO incompatible transplant.

If the recipient is ABO group O, then use **donor ABO group FFP, platelets or cryoprecipitate** in the perioperative period, and if required in the first three months post-transplant (group AB products are also suitable, although AB cryoprecipitate does not exist).

If the recipient is not group O then use:

- Group AB FFP – which has neither anti-A or B antibodies and thus will not react with **either** the donor organ **or** the recipient
- Donor group platelets and cryoprecipitate. Although these products do contain small amounts of anti-A or anti-B and potentially react with the **recipient**, clinical consequences (haemolysis) are extremely unlikely. In these circumstances the transfusion laboratory provides 'high titre negative (HTN)' cryoprecipitate, meaning that blood donors with high titre anti-A or anti-B antibodies are not used.

Measuring ABO antibody titres during antibody removal

The anti-A or B IgG and IgM titres on the morning of transplantation should be **less than** 1:8, although in patients with a high starting titre 1:8 is acceptable.

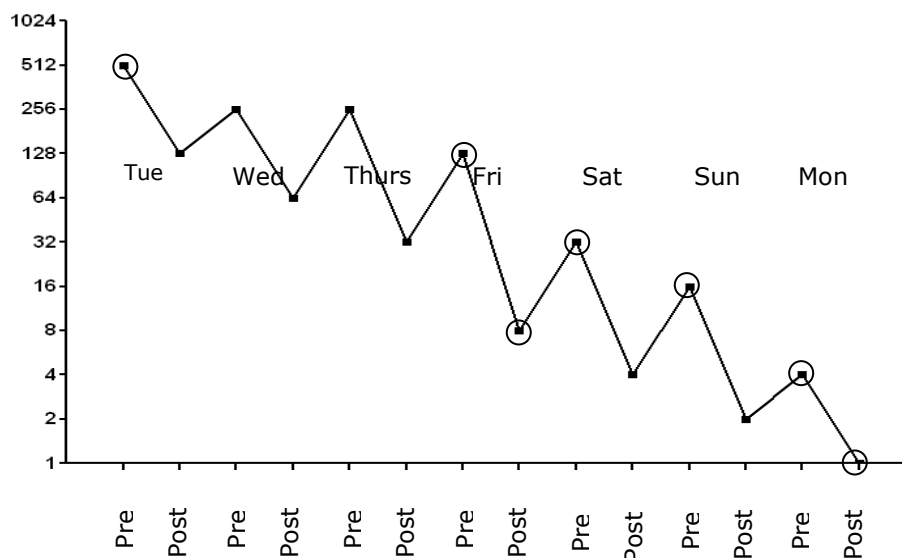
Samples for ABO titre go in a **4.5ml EDTA** container and must be labelled clearly indicating either pre- or post- antibody removal.

For low titre patients:

- Send a sample at the beginning of the first DFPP treatment
- Send samples pre- and post-DFPP on the day before transplantation (usually a Monday)
- The **pre**-treatment sample is a good estimate of the expected titre on the following morning

For high titre patients:

- Send a sample at the beginning of the first immunoabsorption (IA) treatment
- Send samples pre- and post-IA on the Friday before transplantation (see graph below – open circles represent samples analysed for ABO titre)
- Send **pre**-treatment samples on Saturday and Sunday (for analysis on Monday)
- Send samples pre- and post-IA on the day before transplantation (usually Monday). The pre-treatment sample should be 1:8 or less.



Appendix 5: Administration of ANTI-THYMOCYTE GLOBULIN (RABBIT) “Thymoglobuline®”

Administration of Thymoglobuline® needs to be supervised closely. In patients with fluid overload the first dose may rarely precipitate fatal pulmonary oedema (due to cytokine release making lung capillaries leaky). Hence:

The patient **must** be reviewed by a senior member of staff (registrar / consultant) before Thymoglobuline® is given. If pulmonary oedema is present (obtain CXR), it requires treatment, almost certainly by dialysis, **before** treatment with Thymoglobuline® commences.

The first dose of Thymoglobuline® should be administered under close supervision.

Protocol for the administration of Thymoglobulin®

- Before** treatment ensure that you have done all of the following:
 - Send blood for FBC, and 10 mL clotted sample to tissue typing
 - Document the donor and recipient CMV IgG status
 - Assess volume status, and if necessary obtain a CXR to exclude pulmonary oedema (conveniently done after insertion of a central line). Oliguric patients may require dialysis and ultrafiltration.
 - Midstream urine MC&S, and blood cultures if febrile.
 - Check patient has no known allergy to rabbit proteins or to any of the excipients of Thymoglobuline®: Glycine, mannitol
- Thymoglobuline® must be infused into a ‘high-flow’ vein. In practice this means a **central line or a PICC**, although in exceptional circumstances it is also possible to infuse into an AV fistula.
- The dose of Thymoglobuline® is **1-1.5mg/kg^{2,4,10}**. A single dose should not exceed 150mg. Round dose to nearest 25mg.
- Pre-medication 30 – 60 minutes prior to dose:**
 - Paracetamol 1g PO^{4,9}
 - promethazine 25mg PO ^{4,9}
 - Methylprednisolone 125mg IV ^{4,9}
- Reconstitution and Preparation for administration⁹
 - Allow 30 minutes for the vial to reach room temperature. Inject 5 mL of water for injections slowly down the side of each vial and not directly onto the powder to avoid foaming. Gently tilt and roll the vial. **Do not invert, swirl or shake.** This makes a concentration of 5 mg/mL)
 - The required dose should be diluted in 100-500 mL sodium chloride 0.9%. **The final concentration should be <0.5mg/mL.**
 - Thymoglobuline® must be infused via a 0.22 micron in line filter

5. Rapid infusion rates have been associated with case reports consistent with cytokine release syndrome. In rare instances, severe cytokine release syndrome can be fatal.⁹
6. **The first treatment dose should be infused over a minimum of 6 hours and subsequent doses over 4 hours.** If the patient develops an infusion reaction (see below) stop the infusion, wait for the symptoms to subside, and then restart at 50% the initial infusion rate. Infusion reactions are uncommon after the first dose.⁹
7. Most patients develop some of: fever, chills, rigors, myalgia, headache, tachycardia and either ↑ or ↓ BP. This is a **normal response** to the initial dose of thymoglobulin (cytokine release) and does not preclude subsequent treatment.^{4,9}
8. **First treatment:** set the flow rate to deliver the dose over a minimum of 6 hours for the first dose.
Watch for **anaphylaxis** (swelling of lips, tongue and pharynx, bronchospasm, hypotension). If these occur:
 - **Stop** the infusion at once
 - Activate a CODE BLUE
 - Lie patient flat, titrate oxygen to maintain saturation >90% and ensure venous access
 - Give adrenaline 0.5-1mg IM (= 0.5 mL 1:1000 adrenaline), repeated after 10 minutes if necessary
 - Given Promethazine 25mg (PO or IM) and hydrocortisone 200mg IV to prevent recurrence
9. **Subsequent treatments:** Set the flow rate to deliver the dose over 4 hours for subsequent doses. If the patient tolerated the first infusion well, review the need for pre-medication.
10. **Nursing Observations**
 - During the infusion the patient's vital signs (temperature, pulse, BP, respiratory rate and SpO₂) should be monitored every 30 minutes.
 - Frequency of vital signs following the completion of the infusion is dependant on the patient's clinical condition.
11. For treatment of **acute rejection** Thymoglobulin® should be given for a total of **7-14 days**, based on graft function, and severity of rejection as well as WBC, platelet and lymphocyte counts (lymphocytes subsets recommended at day 7 if used for >7 days), which should be **reviewed each day before prescribing Thymoglobuline®**:
12. WCC monitoring/Dose adjustment
 - If the **total lymphocyte** count is < 0.05 x 10⁹/L then **no** Thymoglobulin® should be given that day.
 - In addition, the dose of Thymoglobulin® is influenced by both total WCC and platelet count.

- If the **total WCC** is $< 2.5 \times 10^9/L$ then reduce the Thymoglobulin[®] dose by 50%, and if $< 2.0 \times 10^9/L$ *do not* give any Thymoglobulin[®], whatever the lymphocyte count⁴.
- If the **total platelet** count is $< 80 \times 10^9/L$ then reduce the Thymoglobulin[®] dose by 50%, and if $< 50 \times 10^9/L$ *do not* give any Thymoglobulin[®], whatever the lymphocyte count.

13. Oral immunosuppression in addition to Thymoglobuline[®]

- **Steroids** should be continued, usually 20 mg Prednisolone mane (withhold if IV methylprednisolone given as pre-medication).

- **Tacrolimus.**

For induction (3-5 days of Thymoglobuline[®]): It is important that Tacrolimus levels are therapeutic before the end of the Thymoglobuline[®] course. The best approach is to maintain Tacrolimus treatment with a target trough level of 6-10 microg/L. This allows easy upward-titration of Tacrolimus dose to achieve higher therapeutic levels (8-12 microg/L) if required, usually on the day following the last Thymoglobuline[®] dose.

For treatment of severe rejection (up to 14 days of Thymoglobuline[®]): consider withholding during course of treatment then recommence on the day prior to final dose.

- **Anti-proliferative drugs** (Mycophenolate, Azathioprine and Sirolimus)

For induction (3-5 days of Thymoglobuline[®]): Use standard dose of anti-proliferative drugs.

For treatment of severe rejection (up to 14 days of Thymoglobuline[®]): Reduce the dose of Mycophenolate to 500mg BD during course of treatment.

- *If baseline WBC count is $< 4.0 \times 10^9/L$ all of these should be **omitted** once Thymoglobuline[®] treatment is started.*
- *Anti-proliferative drugs should be reintroduced based on platelet and WBC count, usually mycophenolate mofetil 500 mg BD once it is clear that platelets are maintained at $> 100 \times 10^9/L$ and WBC count $> 3.0 \times 10^9/L$.*
- *Aim to reintroduce anti-proliferatives **before** the final dose of Thymoglobuline[®].*

14. Prophylaxis against infection should include:

- **Trimethoprim/Sulphamethoxazole 160/800mg PO half a tablet** daily (if not already prescribed) continued indefinitely.^{3,4}
- **CMV prophylaxis with Valganciclovir** if either donor *or* recipient is CMV IgG seropositive (D+ or R+), for at least three and possibly six months (see **section 4.7.5** for dosing).^{3,4}
- **Consider aciclovir prophylaxis** for CMV D-/R- patients (to protect against other herpes virus infections, particularly herpes simplex virus (HSV) and VZV).^{3,4}
- Nystatin oral liquid 100 000 units (1mL) QID for 30 days to protect against oral and oesophageal candidiasis.

Appendix 6: Acute antibody-mediated rejection (AMR)

Background:

1. AMR occurs early following transplantation, incidence reported from 0-8%
2. Most frequently occurs in sensitised patients (blood transfusion, pregnancies) and those with previous failed allografts (i.e. exposure to foreign HLA)
3. Characterised by endothelial cell injury lining blood vessels, inflammatory infiltrates and intravascular coagulation. Capillary endothelium can express both class I and II antigens
4. Anti-donor specific antibodies (**DSA**) are involved by binding to vascular endothelial cells resulting in activation of complement ('endothelium activation'), increased permeability of endothelium and resultant inflammation, thrombosis and ischaemia. Most DSA are typically directed against donor HLA antigens and circulating de novo DSA can precede renal allograft loss by 6 months to 8 years
5. Studies have indicated that DSA to class I and class II detected by sensitive methods pre-transplant, even at low levels, can be associated with severe AMR post-transplant
6. C4d (split product generated during complement activation of classical pathway triggered by anti-DSA) deposition in peritubular capillaries (PTC; could be widespread involving >50% sampled capillaries or focal) correlated with the detection of de novo DSA in recipient's serum; i.e. capillary C4d staining is a specific marker of anti-HLA alloantibody-dependent allograft injury. Significance of focal C4d staining uncertain
7. Acute tubular necrosis/delayed graft function (i.e. ischaemic injury) does not lead to C4d deposition in PTC
8. Cardinal features of AMR include:
 - Morphologic evidence of tissue injury
 - Immunopathologic evidence for antibody-mediated action (i.e. C4d deposition)
 - Serologic evidence of circulating antibodies to donor HLA or to other donor endothelial antigens
9. Characteristic morphological features alone or in combination include:
 - Accumulation of polymorphonuclear neutrophils and monocytes/macrophages in cortical PTCs
 - PTCs are dilated
 - Presence of glomerulitis with neutrophils and/or monocyte infiltration
 - Arteriolar and glomerular fibrin microthrombi
 - Severe vasculitis with fibrinoid necrosis
10. Only the presence of C4d staining is sensitive (95%) and specific (96%) for circulating anti-donor antibodies in patients with AMR occurring in the first 3 months post-transplant (n=67, Mauiyyedi S et al, JASN 2002)
11. AMR often coexists with cellular (T cell mediated) rejection which may reflect early and specific T and B cell co-operation. Detection of class-switched allo-antibody is invariably associated with the clinical expansion of T cells with indirect allo-specificity; i.e. indirect pathway T cells can provide 'help' to allo-

specific B cells leading to the eventual development of a pool of memory B cells. These observations do indicate that treatment targeting T and B cells in AMR may be appropriate

12. AMR is relatively unresponsive to high-dose steroids and T cell-targeted therapies
13. Conventional therapies achieve a 1-year allograft survival of only 15-50%. Positive C4d staining is an independent poor prognostic indicator for immediate graft survival and increased risk of long-term graft dysfunction with early allograft loss
14. Transplant glomerulopathy was found to be associated with C4d glomerular deposits and with peritubular capillary basement membrane multilayering (features indicating chronic allograft nephropathy, CAN). It has been shown between 17-61% of typical 'chronic rejection' cases with arterial and/or glomerular pathological changes had capillary C4d deposition
15. 'Accommodation' may occur in certain transplant recipients whereby circulating anti-HLA allo-antibodies and C4d on biopsies may be present without apparent deleterious consequences suggesting that the relationship between allo-antibodies and allograft function is not clear cut

Banff criteria for antibody-mediated rejection:

Table 1. Revised classification of antibody-mediated rejection¹

Acute/active ABMR; all three features must be present for diagnosis

1. Histologic evidence of acute tissue injury, including one or more of the following:
 - Microvascular inflammation ($g > 0$ and/or $ptc > 0$)
 - Intimal or transmural arteritis ($v > 0$)
 - Acute thrombotic microangiopathy, in the absence of any other cause
 - Acute tubular injury, in the absence of any other apparent cause
2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:
 - Linear C4d staining in ptc (C4d2 or C4d3 by IF, or C4d > 0 by IHC)
 - At least moderate microvascular inflammation ($[g + ptc] \geq 2$)
 - Increased expression of gene transcripts indicative of endothelial injury
3. Serologic evidence of DSAs (HLA or other antigens)

Chronic, active ABMR; all three features must be present for diagnosis

1. Morphologic evidence of chronic tissue injury, including one or more of the following:
 - Transplant glomerulopathy ($cg > 0$), if no evidence of chronic TMA
 - Severe ptc basement membrane multilayering (requires EM)
 - Arterial intimal fibrosis of new onset, excluding other causes
2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:
 - Linear C4d staining in ptc (C4d2 or C4d3 by IF, or C4d > 0 by IHC)
 - At least moderate microvascular inflammation ($[g + ptc] \geq 2$)
 - Increased expression of gene transcripts indicative of endothelial injury
3. Serologic evidence of DSAs (HLA or other antigens)

C4d staining without evidence of rejection; all three features must be present for diagnosis

1. Linear C4d staining in ptc (C4d2 or C4d3 by IF, or C4d > 0 by IHC)
2. $g = 0$, $ptc = 0$, $cg = 0$ (by light microscopy and by EM if available), $v = 0$; no TMA, no ptc basement membrane multilayering, no acute tubular injury
3. No acute cell-mediated rejection (Banff 97 type 1A or greater) or borderline changes

Abbreviations:

ABMR, antibody-mediated rejection; DSAs, donor specific antibodies; EM, electron microscopy; HLA, human leukocyte antigen; IF, immunofluorescence; IHC, immunohistochemistry; ptc, peritubular capillaries; TMA, thrombotic microangiopathy.

Available treatment options:

1. **Plasmapheresis (PP)** –
 - remove preformed allo-antibodies
2. **Intravenous immunoglobulin (IVIg)**
 - Passively binds DSA and IgG, which actively inhibits IgM formation and further propagation of humoral cascade
 - Inhibits complement-mediated endothelial cell injury
 - Neutralisation of auto-antibodies
 - Down-regulate antibody synthesis by inhibiting B- and T cell proliferation
 - Increase B cell apoptosis
3. **Combination of PP/IVIg**
 - reverses 90-95% AHR
4. **Rituximab** (anti-CD20-depleting agent)
 - A human/mouse chimeric anti-CD20 monoclonal antibody
 - The potency of rituximab to deplete B cells has been well documented with an absence of circulating CD20+ B cells for up to 12 months by inducing cell lysis via complement and antibody-dependent cytotoxicity
 - Binds to CD20, a transmembrane molecule located on pre-B and mature B lymphocytes (CD20 involved in the activation of cell cycle initiation)
 - This approach needs to be investigated before it can be recommended as standard therapy for AMR, but has been used in refractory cases as rescue therapy[#]

[#]Results from a phase III, multicentre, randomized, placebo-controlled trial (RITUX ERAH) that examined the effect of rituximab (+plasmapheresis, IVIG) on a composite measure of graft loss or absence of improvement of renal function, in patients with AMR showed no advantage of rituximab over control for the graft loss or renal function outcome.

(Sautenet B et al. *Transplantation* 2015; Epub).

5. **Eculizumab** (complement inhibitor)
 - Preliminary clinical trials
 - Blocks the deleterious pro-inflammatory consequences of in-situ complement activation triggered by anti-donor allo-antibodies
 - High cost medication requires Individual Patient Use (IPU) approval prior to use.

Treatment Protocol

Once AMR is established which should include morphologic evidence of tissue injury, immunopathologic evidence for antibody-mediated action (i.e. C4d deposition) ± serologic evidence of circulating antibodies to donor HLA or to other donor endothelial antigens, treatment should consist of:

- PP alternate daily for at least 4 sessions followed by IVIg 0.5g/kg post-PP (total of 2g/kg). Further PP depending on clinical and biochemical response⁸
- IV Methylprednisolone ± thymoglobulin if T cell mediated rejection present (tubulitis/lymphocytic tubulo-interstitial infiltrate)⁸

-
- If on Cyclosporin, change from Cyclosporine to Tacrolimus (aim level 7-12microg/l)/mycophenolate combination for maintenance immunosuppression⁸
 - Monitor DSA titres pre-treatment and following treatment (not a guide to treatment) and then 6-monthly
 - Use Valganciclovir for CMV prophylaxis during treatment even in low-risk patients (i.e. CMV positive to positive transplants)
 - In refractory cases: Rituximab 375mg/m² (single dose) to be considered – check circulating CD19+ B cells 3-7 days post-dose
 - Protocol biopsies/DSA monitoring in all patients

Appendix 7: Management of BK virus infection

Summary

BK virus causes tubulointerstitial nephritis and ureteral stenosis in up to 10% of kidney allograft recipients and causes allograft failure in 15-50% of affected individuals. About 85% of patients who develop BK viraemia do so within the first 3-4 months after transplantation.

The two principal approaches to the management of BK virus-associated nephropathy (BKVAN) in kidney allograft recipients are:

- A screening strategy for detection of infection prior to the development of clinically significant nephropathy. This involves periodic monitoring for BK virus activation in urine or blood to start early intervention.
- A treatment strategy to allow for expanding BKV-specific cellular immune responses, curtailing of BKV replication in the graft and clearance of BKV viraemia. This involves:
 - decreasing immunosuppressive medications to patients with a presumptive or biopsy-proven diagnosis of BKVAN, *and*
 - considering to administer antiviral agents to patients with only biopsy-verified BKVAN, progressive allograft dysfunction and/or sustained high-level plasma BKV load.

Because effective and safe antiviral therapies are lacking, among all renal allograft recipients, a screening for BKV replication has become the key recommendation to initiate and guide a stepwise reduction of immunosuppression, rather than a treatment strategy for BK-induced nephropathy.

Screening of BK virus-associated nephropathy (see flow diagram)

Screening methods include urine cytology (decoy cells) and PCR-based detection of urine or plasma BK virus DNA. Positive tests for decoy cells or urinary viral load should be confirmed within 4 weeks and/or followed by quantitative (real-time) PCR detection of plasma BK virus DNA with threshold levels for presumptive disease (plasma DNA load $>10^4$ copies/ml*).

** Cut-off levels for viral detection should be based on PCR assays used at individual institutions.*

In low-incidence diseases with a serious adverse outcome, such as BK infection, the test's PPV and sensitivity critically determine its practical utility for screening, rather than specificity - which can be deceptively high. The PPV for urinary decoy cells is 5-15% and thus excessively low. The PPV for DNA load $>10^4$ copies/ml is 45%.

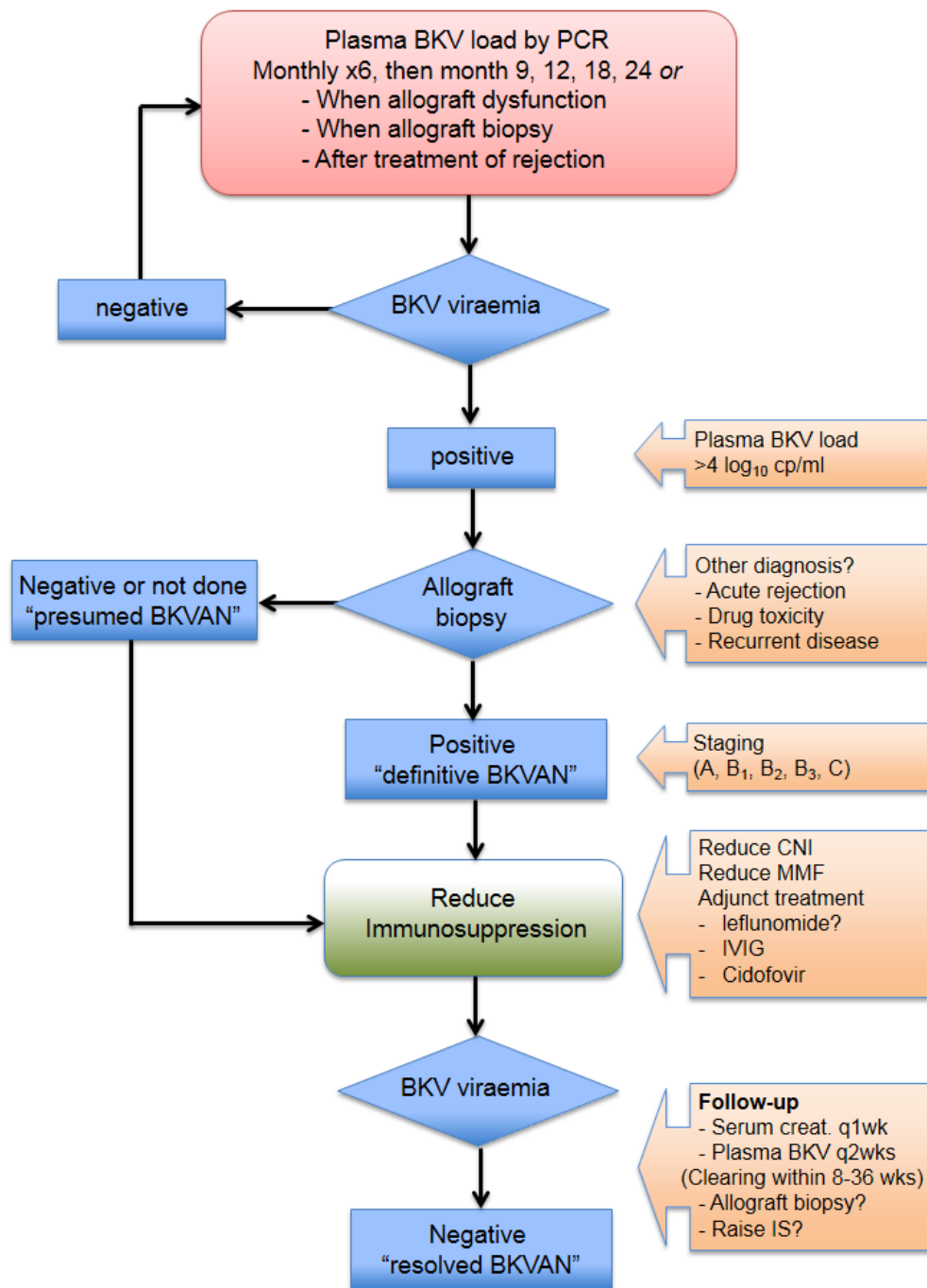
Quantitative viraemia is currently preferred by KDIGO for screening and offers superior predictive characteristics, and being a laboratory test, yields better reproducible intratest imprecision.

An approach is to screen all renal transplant patients with plasma DNA load by PCR as follows:

- monthly at months 1 to 6 and at months 9, 12, 18, and 24 post-transplant *or*
- when renal allograft dysfunction occurs *or*
- when an allograft biopsy is performed for allograft dysfunction *or*

- after treatment of rejection.

Suggested approach for screening and management of BKV-associated clinical syndromes



If plasma BK-PCR becomes positive, further evaluation and treatment is based upon the serum creatinine concentration.

- If the serum creatinine concentration is increased compared with baseline values, a kidney biopsy should be performed. If the kidney biopsy shows:
 - both BK nephropathy plus interstitial inflammation, options for treatment include administering intravenous immune globulin (IVIG), decreasing immunosuppression, and treating with antiviral therapy.

- BK nephropathy only, treat with decreased immunosuppression and antiviral therapy.
- no evidence of BK nephropathy, decrease immunosuppression and continue to monitor blood BK-PCR every two weeks until the assay becomes negative.
- If the serum creatinine concentration is not increased compared with baseline values, a diagnosis of "presumptive" BKVAN should be made in patients with sustained plasma BKV DNA >10⁴ copies/ml.

Treatment of BK virus-associated nephropathy (BKVAN)

The cornerstone of therapy is to decrease immunosuppressive medications.

For patients with "definitive" BKVAN only

- Strategy 1:
 - Step 1: reduce antiproliferative drug by 50%
 - Step 2: reduce CNI by 25-50% in one or two steps*
 - Strategy 2:
 - Step 1: reduce CNI by 25-50% in one or two steps*
 - Step 2: reduce antiproliferative drug by 50%
 - Monitor serum creatinine in 1-2 week intervals and BKV load in 2-4 week intervals
- (* Tacrolimus level <6microg/mL, Cyclosporin trough level <120microg/mL, Sirolimus level <6mirog/mL)

For patients with "presumptive" BKVAN with or without rise in serum creatinine concentration

- decrease immunosuppression and monitor blood BK-PCR every 2-4 weeks until the assay becomes negative.
- if the serum creatinine concentration increases during the monitoring period, a kidney biopsy should be performed.

For patients with "definitive" BKVAN and concomitant rejection* or in those with histopathologic changes that are indistinguishable from those of rejection

*** The diagnosis of acute rejection concurrent with BKVAN is only considered secure if one finds endarteritis, fibrinoid vascular necrosis, glomerulitis, or C4d deposits along peritubular capillaries**

- Treat acute rejection with IV methylprednisolone with subsequent reduction in maintenance immunosuppression, Step 1 / Strategy 1 or 2
- Consider administering IVIG 2g/kg on 4 divided doses over 5-7 days.

For patients with "definitive" BKVAN who have progressive allograft dysfunction or sustained high-level plasma BKV load despite a maximal decrease in immunosuppressive therapy for a period of several weeks' to months' duration, administration of antiviral therapy should be considered, although efficacy has not been proven.

Antiviral agents that have been associated with anecdotal success include, Leflunomide, IVIG and Cidofovir. None have been approved by the FDA for the treatment of BKVAN.

Leflunomide

Administered orally as a replacement for discontinued Mycophenolate mofetil

Dosage: loading dose of 100mg for 5 days, followed by an initial maintenance dose of 40mg daily¹¹. If available, blood levels should be measured and target levels of 50 to 100microg/mL should be aimed for.¹¹

Monitoring: Regular blood counts and liver function tests once a month, plasma BKV loads once every two weeks. Significant toxic effects have been described including hepatitis, haemolysis, thrombotic microangiopathy, bone marrow suppression and fungal pneumonia.

(This is on formulary at Prince of Wales Hospital for this indication.)

Cidofovir

Dosage: 0.25 to 0.5mg/kg IV, at 1–3 weekly intervals¹⁰.

Monitoring: The patients should be followed closely by serial measurements of serum creatinine concentration, leukocyte counts, eye symptoms and vision (uveitis up to 35%), as well as bi-weekly plasma BKV load.

Pre and post hydration with 1L sodium chloride 0.9% should be considered for each dose⁴.

Note: Requires prior approval with Infectious Diseases and an Individual Patient Approval

Note: Requires sterile reconstitution in pharmacy cytotoxic suite (cytotoxic antiviral).

Intravenous immunoglobulin (IVIG)

Dosage: from 0.2 to 2.0 g/kg in conjunction with reduced immunosuppression. Commercially available IVIG preparations contain high titres of potent BKV neutralizing antibodies.

Acute rejection after reduced immunosuppression for presumptive or definitive BKVAN should be treated according to standard protocols

If acute rejection is diagnosed in allograft biopsies, after clearance of plasma BKV DNA and BKVAN by histology, anti-rejection treatment is indicated and a judicious increase in maintenance immunosuppression be considered.

However, administration of lymphocyte depleting agents should be done after careful evaluation of the competing risks of failure to control rejection and recurrence of BKVAN.

Appendix 8: Outpatient management

Minimum attendances:

First 15 days:	daily except Sundays if well
2 – 6 weeks:	three times per week
7 – 12 weeks:	twice per week
3 – 6 months:	once per week
6 – 12 months:	once per fortnight
12 – 24 months:	once per month
>24 months:	once every 2 – 4 months.

Aim to return patient to referring hospital at 2 weeks, depending on clinical progress. Detailed letter required. Please discuss if in doubt.

Dose of prednisolone if uncomplicated and rejection-free

Prednisolone PO daily dose:

1 week	30mg
2 weeks	27.5mg
3 weeks	25mg
4 weeks	22.5mg
5 weeks	20mg
6 weeks	17.5mg
7 weeks	15mg
8 weeks	12.5mg
9 weeks	10mg
10 weeks	7.5mg
3 months on	5mg

But – ensure Tacrolimus levels are satisfactory before reducing dose. Some patients (prolonged DGF, those already on maintenance steroid, those who have had an acute rejection episode, antibody-incompatible transplants) may require more gradual steroid reduction –ask!

Mycophenolate dose if uncomplicated and rejection-free

Mycophenolate

At around 8-12 weeks reduce mycophenolate mofetil to 500mg bd

Tacrolimus target levels to adjust dose of Prograf if uncomplicated and rejection-free

Tacrolimus:

Target trough level	microg/L
0 - 2 wks.	6 - 10
2 - 4 wks.	6 - 9
4 - 24 wks.	5 - 8
6-12 mths.	3 - 7
Beyond 1 yr.	2 - 5

Cyclosporin target levels to adjust dose of Neoral if uncomplicated and rejection-free

Months post-transplant	C2 (microg/L)	C0 (microg/L)
< 1 month	1500 - 1800	200 - 350
months 2 & 3	1000 - 1500	150 - 250
months 4 - 6	700 - 1200	150 - 200
months 7-12	500 - 800	100 - 200
Long term	400 - 600	50 - 150
With Everolimus		40 - 80

Other medications:

Plan to stop

- | | |
|---------------------------------------|--------------|
| 1. Nystatin/Sodium Bicarbonate m/wash | 4 weeks |
| 2. Valganciclovir | 3 - 6 months |
| 3. Ranitidine | 6 months |
| 4. Cotrimoxazole | indefinitely |

Note:

These regimens may not be appropriate for all. Please discuss if in doubt

Appendix 9: Discharge letter template

PRINCE OF WALES HOSPITAL
DEPARTMENT OF NEPHROLOGY
LEVEL 3, HIGH STREET BUILDING
PHONE: 9382 4473 / 4447
FAX: 9382 4409

RENAL TRANSPLANT DISCHARGE LETTER



Department of Renal Medicine
St George Hospital
Gray Street,
Kogarah, NSW 2217

Dear XX,

Patient name: _____ **DOB:** _____ **MRN (POWH):** _____

Usual nephrologist/unit: _____

Admitted: _____ **Discharged:** _____

Renal physician at POWH: _____

Type of Transplant: DBD DCD SCD ECD LD

Date of transplant: _____

Recipient surgeon: _____ **Donor surgeon:** _____

Past medical history:

--

Serology:

	CMV IgG	EBV IgG	Hep B sAg	Hep B sAb	Hep B cAb	Hep C IgG	HIV IgG
Donor							
Recipient							

Immunological risk factors:

	Blood group	HLA Class I			HLA Class II								
		A	B	C	DRB1	DQB1	DQA1	DPB1	DRB3/4/5				
Recipient													
Donor													

Previous Donor																	
-----------------------	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

Current PRA (%):	Peak PRA (%):	Donor specific antibody?
DSA specificities and MFI:		

Transplant summary:

Operative Information:

Donor kidney:		Implanted:	
Number of arteries:		Warm ischaemic time:	
Number of veins:		Cold ischaemic time:	
Number of ureters:		Ureteric stent placed?	Yes <input type="checkbox"/> / No <input type="checkbox"/>
Intraoperative complications:			

Initial function:

1. SCr-fall >10% within 24hr
2. SCr-fall >10% within 25-72hr
3. No spontaneous fall in SCr within 72hr, no dialysis
4. Dialysis within 72hr

Induction Immunosuppression:

- Basiliximab induction / Thymoglobulin
- Prednisolone / Mycophenolate / Azathioprine / Initiated on Tacrolimus / Cyclosporine
- Plasma exchange / IV immunoglobulin

Current Medications:

Drug	Dose	Frequency	Drug	Dose	Frequency

Recent Tacrolimus/Cyclosporine doses and levels:

Date:							
Dosage:	Morning						
	Evening						
Creatinine:							
Level:							
Current target range:							

Ongoing issues:

Many thanks for your ongoing care of this patient.

Kind regards,

Appendix 10: Screening for New Onset Diabetes after Transplantation (NODAT)

A diagnosis of new-onset diabetes after transplantation (NODAT) carries with it a threat to the renal allograft, as well as the same short- and long-term implications of type 2 diabetes seen in the general population.

Definition of NODAT:

NODAT is present if the patient has:

- symptoms of DM,
- casual plasma glucose ≥ 11.1 mmol/L,
- abnormal OGTT, with a 2-h value of ≥ 11.1 mmol/L,
- 8hr fasting plasma glucose ≥ 7.0 mmol/L.

Screening for NODAT:

- All patients should have a fasting blood glucose measured weekly during the first 4 weeks post-transplant, then at 3 and 6 months post-transplant, and then yearly.
- A glycated haemoglobin (HbA1c) can be checked after three months post-transplant, particularly if it is difficult to obtain fasting plasma-glucose levels.
- An OGTT performed at 10 weeks post-transplant may help to predict longer-term hyperglycaemia.
- Self-testing of blood glucose in the afternoon during the early post-transplant phase has been associated with an increased rate of detection of NODAT
- Among patients who have HbA1c $>6\%$, we recommend home BSL monitoring and assessment of an HbA1c quarterly.

Management of NODAT:

- Additional therapy beyond diet and exercise is not recommended until the HbA1c is $>7\%$.
- Metformin improves insulin sensitivity, which is often affected in NODAT. The safety of metformin in kidney transplant recipients with sufficient renal function has been formally demonstrated.

Drug References:

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