

RENAL TRANSPLANT PROTOCOLS

Royal Infirmary of Edinburgh

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RENAL TRANSPLANT PATIENT ASSESSMENT

Work-up for renal transplantation carried out at local centre.

Lothian, Borders and Fife patients are seen at the transplant assessment clinic in Edinburgh run on a Thursday afternoon by Mr John Forsythe; Mr Murat Akyol; Mr John Casey.

A referral letter with a transplant recipient check-list and summary (appendix I-II) should be sent to the Transplant Unit (addressed to Mr J Forsythe; Mr M Akyol; or Mr J Casey, Consultant Transplant Surgeons). All the referred patients will be sent an appointment for an outpatient visit.

At time of initial assessment some or all of the following personnel will provide clinical input:

- Transplant surgeon
- Renal physician
- Anaesthetist

Transplant Co-ordinator

If indicated further assessment by social work department chiropody, dentistry, dietetics, dermatology, liaison psychiatry, (see Appendix II), and other related specialities may be sought.

Patients will have the opportunity for detailed discussion regarding kidney transplantation and will be counselled with respect to relative risks and benefits of cadaveric and living donor kidney transplantation.

An information booklet is also given to the patient to support the verbal information given at the assessment clinic.

Before Listing

Following initial outpatient assessment, those patients who are considered potentially suitable candidates and who remain willing to be considered for a transplant will undergo further investigation as required.

The transplant coordinator will arrange for copies of all the required investigations prior to listing.

When investigations are complete, the transplant team will review the results. Further investigations and/or treatments may be required at this time.

The decision about listing the candidate for kidney transplantation will be made by the transplant surgeons after discussion with the multi-disciplinary team and the patient.

A detailed letter regarding the patient assessment will be sent to the referring centre with a copy to the general practitioner.

If the patient is to be listed, the patient will be directly informed, verbally and in writing, by the transplant co-ordinator.

Transport requirements in the event of being called in for transplantation will be determined and arranged by the transplant co-ordinator.

UKT will be informed by the transplant co-ordinator as per unit procedure.

LOCAL RETRIEVAL

1. Tissue type to be established as soon as possible, usually from peripheral blood lymphocytes (see appendix IV).
2. Tissue type will phone the results of donor tissue-type and results of highly sensitised patients to donor transplant co-ordinator. Tissue typist will also fax tissue type results to UK Transplant (UKT).
3. UKT will inform the donor transplant co-ordinator of the allocation of the kidneys as per National and Scotland & Northern Ireland allocation schemes so that the kidneys can be packed and addressed to the appropriate centre.

UKT OFFER OF A KIDNEY

The on-call donor/renal recipient transplant co-ordinator will receive the offer of a kidney from UKT.

Transplant co-ordinator contacts transplant surgeon and asks for a decision as to whether the kidney should be accepted.

If the decision has been made to go ahead, then the transplant co-ordinator contacts the patients own local Consultant Nephrologist and the RIE on call Consultant nephrologist, to ensure that the patient is fit and should be called.

Transplant co-ordinator performs the following tasks:

- Contact of the patient.
- Arrangement of transport for the patient and his/her notes to the renal transplant unit.
NB: APD patients to bring own machine.
- Alert renal transplant unit and give details of patient and dialysis needs.
- Alert the renal registrar with the patient details.
- Alert the tissue typist with the patient details.

It is the responsibility of the surgeon and the transplant co-ordinator to arrange theatre and inform the anaesthetist to book the first available operating space.

It is the responsibility of the renal registrar to ensure the chosen patient is adequately dialysed and medically fit prior to operation.

The on-call renal / transplant SHO also liaises with BTS regarding grouping and saving.

Fife, Dundee, Aberdeen and Inverness patient arrangements

Transplant co-ordinator will discuss the patient with the surgeon and patient's local nephrologist. If the kidney is to be accepted, the transplant co-ordinator will also inform the RIE consultant nephrologist on-call.

The nephrologist or the transplant co-ordinator to contact the patient and arrange transport of the patient to the RIE.

The nephrologist arranges the patients notes and x-rays to be sent to the transplant unit ASAP.

If the patient requires dialysis this to be organised in Edinburgh. The MRSA and virology status of the patient must be known.

Remaining points as above.

WHEN THE KIDNEY ARRIVES AT THE UNIT

The kidney will arrive at the Transplant Unit HDU Ward 117.

Check that the kidney is surrounded by sufficient ice, if not, top up. (This is the responsibility of Ward 117 Nursing staff).

Send spleen and lymph nodes to BTS for lymphocytotoxic crossmatch. Please ensure that a SNBTS histocompatibility platelet immuno-haematology form is completed and sent with the lymph node and spleen to tissue-typing.

Note:

Two kidneys may arrive in Unit if the kidneys are from a local donor. These kidneys will be allocated according to UKT and may need to be sent to another centre. For kidney allocation rules please see UK Transplant web site at www.uktransplant.org

In this case the box containing the kidney to be sent should not be disturbed, it will be picked up by the courier service as arranged by UKT. UKT will inform the transplant unit where the kidney is going to. Transplant unit to clearly write name and address of where the kidney is going. Check with UKT whether it is right or left kidney if in any doubt contact donor transplant co-ordinator.

PRE-OP RECIPIENT MANAGEMENT

This is the responsibility of the Transplant FY/CMT

Full History and Examination

Particular points of note:

History

- cause of renal failure
- dialysis - type, when commenced
- time of last dialysis –normal target or dry weight
- access and any related problems
- Volume of urine output + history of past/present urinary tract problems
- infections - any recent
- CAPD peritonitis/exit site/access related
- other operations
- ischaemic heart disease
- peripheral vascular disease

Recipient blood group, tissue typing and virology (CMV, EBV,HIV, Hep B & C) must be recorded in the notes.

Donor details should also be included in recipient clerking - age, cause of death, blood group, tissue typing, virology and ischaemic time. The transplant co-ordinator will provide this information. *Avoid noting any further details that could compromise donor confidentiality if read by the patient.*

Examination

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

- fluid status
- peripheral pulses
- abdominal scars/hernias

Investigations

Blood Tests (phone laboratory to alert staff that sample is arriving) 60-70 mls blood required and should be taken as soon as patient is admitted.

- *FBC
- *U&E's + creatinine
- Baseline calcium/LFT's (results available post-op)
- *Clotting screen/INR (if on Warfarin) -
- *Tissue Typing (white clotted bottle for lymphocytotoxic Antibody, plus 5 ml EDTA sample.) see appendix IV
- Virology - CMV, HIV, Hep B + C (only if >1/12 since last test)
- *Glucose
- BM test on ward

*Results must be requested as Urgent. Patient may require dialysis pre-op, and if so, repeat biochem 30 mins after dialysis

Chest X-ray

ECG

MSSU - for gram stain and subsequent culture.

PD fluid for WCC and gram stain / culture if appropriate

Communication

Patient (see also consent section below)

Ensure potential recipients are aware that they will not definitely be getting the kidney until the result of the cross-match is known.

Inform patient re: ureteric stent insertion with cystoscopic removal required at 3 months, (usually as a day case). CAPD catheter also removed at the same time as ureteric stent. Do not give donor info to the recipient beyond what is necessary to explain any particular risks/techniques of the transplant.

Patients who are not suitable for transplant need discharge sheet with appropriate reasons.

Staff

Inform theatre and anaesthetist of any special problems.

Consent

Consent for HIV test - verbal consent should be obtained by the physician who clerks in the recipient.

Consent for the transplant operation should be obtained by the transplant surgeon. (mention central line, surgical drain, urinary catheter and ureteric stent).

Diabetes

Subcutaneous insulin should be omitted.

Insulin / Dextrose infusion must be established pre-operatively: standard sliding scale –

- BM < 6 mmol/l add 6 units Actrapid in 500mls Glucose 10%
- BM 6 – 9 mmol/l add 10 units Actrapid in 500mls Glucose 10%
- BM >9 mmol/l add 14 units Actrapid in 500mls Glucose 10%

Run Infusion @ 100 ml/hr and check glucose (BM stick) hourly

Other Considerations

Anti-viral and CMV prophylaxis (see below)

Rhesus sensitisation

Rh -ve young female recipients with a Rh +ve donor require anti D immunoglobulin at induction (can be given up to 72 hours later if overlooked initially).

PREOPERATIVE MANAGEMENT

Fasting – All patients should be fasted from four hours prior to the anticipated theatre time unless otherwise stated by surgeons or anaesthetists.

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

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

Haemodialysis – patient may require haemodialysis because:

- dialysis is due irrespective of transplant
- based on the results of admission U's & E's.

In practice, unscheduled haemodialysis is unlikely to be required except for hyperkalaemia.

Pre-operative Management of serum potassium

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

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

Notes

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

MEDICATION

(See sample drug Kardex – Appendices)

Patients "routine" medication

Anti-hypertensives are taken as usual pre-operatively except *ACE inhibitors and angiotensin II antagonists are omitted*. Other anti-hypertensives may also be selectively omitted post-operatively and re-introduced if required

NSAIDS – OMIT

Diuretics – OMIT

Warfarin – OMIT and reverse if necessary (a pre-transplant plan should have been made; discuss)

Aspirin – REVIEW

Antibiotic prophylaxis

Given at induction of anaesthesia:

Tazocin 4.5g IV, unless patient is allergic to penicillin, when give Vancomycin 1 Gram IV in Normal Saline over 2 hours and Ciprofloxacin 400 mgs infused over 60 mins.

Immunosuppression

ALL patients receive two doses of methylprednisolone:

- 500 mg IV Methylprednisolone at clamps off
- 500 mg IV Methylprednisolone 24 hrs later

Subsequent immunosuppression regimens are described below under Immunosuppression. Standard immunosuppression will be Tacrolimus (FK506) led triple therapy.

Plasma Exchange may also be considered in patients transplanted with known pre-formed antibody. A pre-transplant plan should have been made for these and for other patients with unusual circumstances. Discuss with Consultant Nephrologist, Consultant Transplant surgeon and BTS consultant.

DVT prophylaxis

Heparin 5000U/SC at anaesthetic induction and 5000U/SC/bd thereafter until mobile post operation (adhering to hospital protocol)

Antibiotics, methylprednisolone + heparin should all be prescribed in the drug kardex pre-operatively.

Anaesthetic Protocol

See Appendix VIII

LIVE DONOR MANAGEMENT

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

Blood samples will be taken at this visit for:

- repeat virology
- lymphocytotoxic crossmatch
- advance group and save

Admission is arranged 24 hours pre-op to the Transplant Unit. In exceptional circumstances if there are no beds available on Ward 206 then a bed will be found for the donor according to the nurse-charge of ward 206 in liaison with the hospital bed-manager.

On admission the donor should have received a full physical examination; blood pressure; temperature; urinalysis and urine specimen sent to bacteriology.

No pre-op X-Ray/ECG/ blood tests are necessary unless requested by Consultant.

Written consent for a nephrectomy should be obtained by the Consultant Transplant surgeon.

All donors should receive DVT prophylaxis with TED stockings, intra-operative pneumatic compression and heparin. Post-operative: heparin sub-cut 5000u BD.

Pre-op heparin should not be administered unless the Consultant Anaesthetist specifically requests.

Post-op fluid management: 4 - 6 hourly dextrose/saline

Any problems should be reported directly to the Consultant Surgeon.

POST-OP MANAGEMENT

Check FBC and Us & Es immediately post-op. Serum K⁺ must be known and result discussed with Registrar, if possible hyperkalaemia should be managed with Insulin/dextrose and nebulised Salbutamol rather than haemodialysis. Subsequent repeat Us & Es 12 hourly (more frequently if indicated or as decided by Registrar).

Arrange chest X-ray for position of central line.

Initial IV fluid replacement is Normal Saline at 40 mls/hr + last hour's urine output. This should be adjusted according to clinical assessment and CVP. Usual target CVP is 5-10 cm water. Boluses of Normal Saline (or colloid) may be needed to raise a low CVP. Failure of the patient to respond to IV Fluid with a rise in CVP or BP should raise possibility of bleeding. These measures should always be instigated by a senior member of staff. If there is a possibility of bleeding a transplant surgeon must be contacted.

Continuing IV fluid replacement should be maintained with alternating 5% Dextrose and Normal Saline initially – more dextrose if high volumes of urine.

Analgesia is by PCA morphine/Fentanyl. Inadequate pain relief may herald serious pathology and should be discussed with a senior surgical colleague/Anaesthetist. NSAIDs are absolutely avoided. Live donors will receive an epidural infusion (see appendix VI).

Immunosuppression

See Immunosuppression section

Infection prophylaxis

All patients on triple therapy receive COTRIMOXAZOLE 480 mg daily for the first three months to prevent *Pneumocystis carinii* pneumonia.

If the patient is sensitive to Septrin then the Sulphonamide de-sensitisation protocol should be instigated (see specific section).

For the management of CMV negative recipients who receive a kidney from a CMV positive donor refer to the CMV protocol.

Blood Tests

U's & E's daily marked "PRIORITY"; result returned by fax

FBC daily

LFTs, glucose, urate, Ca and PO₄ – daily

Tacrolimus or Ciclosporin level - M/W/F

MSU each Monday and at other times if clinically indicated.

Chart all results on flow sheets and plot creatinine on log graph daily.

Tubes and drains

Redivac drain removed at 24 - 48 hours at surgeon's discretion.

Urinary catheter removed at day 5 unless the patient is anuric (may be removed earlier) or the patient is polyuric (may be removed later)

Post-op anuria

Check catheter function. Gentle catheter irrigation should only be performed after surgical consultation and preferably by the surgeon. Seek advice urgently if urine output has started but subsequently ceased.

Graft dysfunction

Any drop in urine output, rise in creatinine or change in log creatinine slope should be discussed immediately with a senior colleague. Management will depend on the clinical situation but acute rejection must always be suspected. The physical signs are often absent and urgent investigation is required.

- Review fluid tolerance and clinical signs (fluid balances, graft tenderness, wound)
- Check Tacrolimus / Ciclosporin result, and also show lymphocyte count etc.
- Graft ultrasound scan - will exclude obstruction.
- Graft Doppler - assesses flow in renal artery and vein (may also comment on intra-renal vascular resistance).
- Graft biopsy - for definite diagnosis of rejection.

Renal Biopsy (See Page 36)

A routine graft biopsy is performed around day 5 if there is delayed graft function and subsequently at weekly intervals until function is established. This is to diagnose acute rejection co-existing with ATN.

Any deterioration in graft function may require a graft biopsy which will be requested by a senior member of staff. Refer to biopsy protocol (See page 36).

Heparin should be stopped the evening prior to the planned biopsy.

Treatment of Rejection

See Diagram on page 35

Delayed Graft Function

Due to prolonged ischaemic times/ATN etc., not all kidneys function immediately and some take a few days or even weeks before functioning. During this time the aim is to ensure that we are not missing concomitant rejection or other catastrophe.

- **Day 1** – Duplex scan/Routine immunosuppression. Alternatively Basiliximab may be given Day 0 and Tacrolimus dosage halted.
- **Day 5** – If no evidence of improvement then biopsy to exclude rejection.
- **Around day 12** – Repeat Duplex/biopsy.

Discharge and follow-up

Uncomplicated patients usually discharged day 10-14.

See below for patients from other hospitals. Patients are usually seen three times monthly at first, in the OPD 1 Transplant Clinic on Monday, Wednesday and Friday mornings. An appointment and transport if required must be arranged prior to discharge. If there is no clinic or if patient needs to be seen more frequently then they will be seen in ward 206 following discussion with the nurse in-charge.

Appointments in ward 206 - If patient needs to attend for bloods on day when there is no transplant clinic in OPD1 the patient will attend ward 206. Appointments should be recorded in the Diary including what tests are required, any special arrangements and the date of the next appointment. Patients should always attend before 9.15 am so that their drug assays may be run the same day. Blood forms should be completed in advance so that the phlebotomist can take their blood during the ward round.

Tacrolimus / Ciclosporin / MMF shared care protocol must be included with the immediate discharge letter. Formal discharge summary is dictated as soon as possible.

At each out-patient review the following are checked:

- Blood pressure, (pulse, temperature; if necessary)
- Weight
- Blood taken for U & Es, LFT, CAP, FBC and Tacrolimus/Ciclosporin
- MSU
- Urine dipstick
- Medication - any alteration to immunosuppression required should be documented on the patients medication sheet which was issued to the patient on discharge, and up-dated on the patient's computerised record by the clinician making the alteration.
- PTH checked 1 month, 3 months and 6 months

Results of out-patient bloods must be checked as soon as possible and patients may be recalled for repeat checks or 'phoned' to alter their dose of Tacrolimus/Ciclosporin. Any alteration to dose should be documented in the patients case notes and on the drug screen of Proton.

Aberdeen, Dundee and Inverness patients

Transferred when stable as an in-patient to the Renal Unit at the referring Hospital (as out patients only if recovery quick or transfer delayed).

Prior to discharge the centre must be contacted before and on day of discharge. A copy of the patient transfer details sheet (medical and nursing) (Appendix V) with a computer printout of the biochemistry, haematology, Tacrolimus results and discharge letter should accompany patient on transfer and/or faxed to receiving unit.

Fife patients

Transferred from Out-patient department when stable. A letter must be sent to the patient's local consultant prior to transfer.

Three months

- Ureteral Stent and CAPD catheter should be removed at this time unless specific reasons for leaving or removing earlier.
- Check PTH, Lipids.
- Prednisolone dosage should be 10mg in patients not treated for rejection (see steroid reduction)

Six months

- Check PTH, Lipids.
- Prednisolone dosage should be 5-7.5mg in patients not treated for rejection - consider withdrawal at 12 months (see steroid reduction and withdrawal)

Long-term follow-up

There are many factors to be considered. More detailed guidance is available in the outpatient protocols booklet, available separately. Major considerations besides graft function include:

- Immunosuppression: consider long-term level
- Urine infections
- Hypertension
- Hyperlipidaemia
- Glucose intolerance
- Arterial disease risk profile - weight, smoking, diet (lipids, hypertension)
- Gout and uric acid (note dangerous interaction between allopurinol and azathioprine)
- Bones - osteoporosis, renal osteodystrophy, hyperparathyroidism
- SKIN - sun avoidance, surveillance
- Contraception
- Pregnancy advice
- Cervical smears - annually

Late (>3 months) presentation with altered function

Acute rejection and drug toxicity remain important causes at all stages of a transplant. Review all the features mentioned above under post-op management – graft dysfunction. Consider too:

- Recurrent primary disease
- Infection – polyoma virus, CMV or other
- Graft artery stenosis

Biopsies should be examined with all these possibilities in mind – so include samples for electron microscopy and immunofluorescence.

IMMUNOSUPPRESSION

Methyl Prednisolone 500 mg IV just prior to releasing clamps and again at 24 hours.

Standard immunosuppression will be Tacrolimus (FK506) led triple therapy.

- Tacrolimus 0.1 mg/kg/day given as two doses at 1000 and 2200
- Prednisolone 20 mg once daily at 0800
- Azathioprine 1-2 mg/kg (usually 75-100 mg) once daily at 0800

Patients who have an increased risk of rejection will receive Tacrolimus led triple therapy, but with MMF substituted for Azathioprine.

- Tacrolimus as per standard regime
- Prednisolone as per standard regime
- Mycophenolate Mofetil 2 grams/day given as two doses at 0800 and 2000 (note: not at the same time as Tacrolimus)

High risk patients may include:

- Previously sensitised patients - those with panel reactive antibody titres of > 50%.
- FACS +ve crossmatch
- B cell +ve crossmatch
- More than one transplant in the past
- Past episodes of graft loss due to acute rejection
- HLA mismatch - non favourable

Basiliximab may also be given to patients with expected delayed graft function (see page 11) to allow reduced Tacrolimus dose (0.05mg/kg/day given as two doses), and sometimes to patients believed to be at increased risk of rejection. Regimen shown below.

BASILIXIMAB

(SIMULECT)

Indication

- High risk patients receiving kidney transplants (as above)
- All patients receiving pancreas or kidney/pancreas transplants
- Patients expected to have delayed graft function e.g. NHBD grafts.

Dose

- 20mg given 2 hours prior to transplantation
- 20mg given on day 4 post transplant

The first dose must not be administered until it is absolutely certain that the patient will receive the graft.

Reconstitution

5ml water for injection (provided) should be added to the vial containing the Basiliximab powder. Shake the vial gently to dissolve the powder.

The solution should be used immediately. (It can be stored for 24hours in the fridge or 4 hours at room temperature.)

Administration

There are two possible routes of administration

Intravenous bolus injection, or Intravenous infusion over 20-30 minutes. (Final volume of at least 50ml using sodium chloride 0.9% or dextrose 5%.)

Compatibility

Basiliximab should not be mixed with other medicines/substances and should always be given through a separate infusion line.

Adverse Effects

Severe acute hypersensitivity reactions have been observed both on initial exposure and re-exposure to basiliximab. These include anaphylactoid-type reactions. If severe hypersensitivity reaction occurs, therapy with basiliximab must be permanently discontinued and no further dose administered.

Side Effects

Basiliximab does not appear to add to the background of side effects seen in organ transplantation patients as a consequence of their underlying disease and concurrent administration of immunosuppressants.

PREDNISOLONE

Prednisolone is normally reduced according to the following schedule:

20 mg daily	1 month	started on day 2
15 mg daily	1 month	
10 mg daily	1 month	
5 mg daily	thereafter	

This schedule may be altered if rejection occurs.

All patients to receive Ranitidine (150 mgs od) along with Prednisolone.

After 3 months continue minimum of 5 mg or 7.5 mg if >75 kg in weight.

Keep on maintenance dose until the end of the first year and then review.

At one year, cessation of prednisolone should be considered – see steroid withdrawal protocol. Caution should be exercised in patients with an “increased risk” of rejection. Cautions relating to Steroid withdrawal include: -

- FACs +ve
- >2 transplants
- Panel reactive antibodies > 50% / highly sensitised patients
- Rejection episodes > 1 or more acute rejection episodes Banff grade > II
- Late acute rejection i.e., occurring after 6 months.

Steroid withdrawal

Steroid withdrawal should be discussed with the patient and they should be informed of the risk of rejection. The steroids should be withdrawn according to the following schedule:

- Decrease by 1 mg per month till 0mg
- Monthly measurements till at least 3 months after cessation.

Steroid-induced osteoporosis

All patients should receive additional elemental calcium, this may be as one or two tablets per day depending on dietary intake.

- If GFR > 50 mls/min AdCalD3 (or similar) should be used.
- If GFR < 50 mls/min Alfacalcidol and Calcichew should be used.

Bisphosphonates

IV Pamidronate may be used in the initial post transplant period in patients with - known osteopenia or osteoporosis, a history of one or more previous transplants, 2 or more episodes of rejection (treated with high dose steroid therapy) or a history of previous disease management with steroids.

All patients should be given advice on:

- Diet
- Weight
- Exercise
- Smoking cessation

See also the Renal Unit Handbook on this topic.

TACROLIMUS

(FK506/PROGRAF)

Current indication

As the lead agent in standard triple therapy for all patients.

Dosage

0.1 mg/kg/day in 2 divided doses (normally between 2 mg and 5 mg bd).

Preparation

Tacrolimus is available as 0.5 mg (cream), 1 mg (white) and 5 mg (greyish red) capsules. The brand is Prograf.

Administration

Oral route in most instances (well absorbed even in those with NG tubes). It is administered usually at 10 am and 10 pm. The capsules are taken on an empty stomach either 1 hour before or 2 - 3 hours after meals.

Contents of the capsule can be suspended in water for NG administration.

One fifth of the oral dose can be given as a continuous IV infusion in saline via non PVC bags/tubing if absolutely necessary.

Levels

Whole blood trough levels to be checked on Mondays, Wednesdays and Fridays. The target level for the first six months is 10 ng/ml (range 8-12 ng/ml) and 5-10 ng/ml after six months. In adult kidney transplant patients steady state may be reached 2-3 days after starting therapy or changing dose.

Contra-indications

Live vaccines are not to be given to immunosuppressed patients. (See pages 43+44).

Tacrolimus is contra-indicated in pregnancy. As it is not known to what extent Tacrolimus may influence the efficacy of oral contraceptives it is generally recommended that other forms of contraception be used.

Side Effects

The most frequent side effects seen with Tacrolimus include:

- abnormal kidney function (similar to Ciclosporin)
- tremor
- headache
- parasthesia

Less common side effects are:

- diarrhoea
- hypertension

- hyperglycaemia
- hyperkalemia
- hypomagnesaemia
- visual and neurological disturbances (affected patients should not drive or operate machinery)
- hypertrophic cardiomyopathy (in paediatric patients with trough levels >25 mg/ml).

Interactions

Potential interactions due to effects on hepatic microsomal enzymes.

Tacrolimus is extensively metabolised via the hepatic microsomal cytochrome P450 3A4 isoenzyme. Concomitant use of substances known to inhibit or induce cytochrome P450 3A4 (CYP3A4) may affect the metabolism of tacrolimus. Therefore:

Inhibitors of CYP3A4 may decrease metabolism of tacrolimus and thus increase tacrolimus blood levels, e.g.

clotrimazole	diltiazem
fluconazole*	nicardipine
ketoconazole*	danazol
itraconazole*	grapefruit juice (naringenin)
erthromycin*	ethinyl oestradiol
clarithromycin*	omeprazole
nifedipine	

Inducers of CYP3A4 may increase metabolism of tacrolimus and thus decrease blood levels, e.g.

rifampicin*
phenobarbitol
phenytoin*

*Drugs marked with an asterisk will require a dose adjustment of Tacrolimus in nearly all patients. Other listed drugs may require dose adjustment only in individual cases.

Tacrolimus itself has a powerful inhibitory effect on CYP3A4. Thus concomitant use of tacrolimus with drugs metabolised by CYP3A4 dependant pathways may affect the metabolism of such drugs. For this reason Ciclosporin A should not be co-prescribed with tacrolimus. Patients switched from Ciclosporin to Tacrolimus should receive the first tacrolimus dose at least 24 hours after the last Ciclosporin dose.

Interactions due to cumulative toxicity/synergistic effects

Concurrent use of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects may increase the degree of toxicity. Enhanced nephrotoxicity has been observed with co-administration of:

Ciclosporin A
Amphotericin B
Ibuprofen
Sirolimus (Rapamune)

Hyperkalaemia

As tacrolimus may cause hyperkalemia, high potassium intake or potassium sparing diuretics should be avoided.

Interactions due to plasma protein binding of Tacrolimus

Tacrolimus is extensively bound (>98%) to plasma proteins so competition with other highly protein bound drugs may result in displacement of either drug. This displacement may not be reflected in the blood levels of Tacrolimus or other drugs. Therefore, dosage adjustment may not be needed unless clinical signs and symptoms suggest otherwise.

Other interactions

- Vaccinations may be less effective and the use of live attenuated vaccines should be avoided.
- Administration of Tacrolimus with a meal of moderate fat content reduces the oral bioavailability of the drug.
- Complementary medicines may cause a variety of interactions (See page 40).

This is not a comprehensive list of potential interactions with Tacrolimus. For further information please ask a member of staff or consult the transplant unit pharmacist.

CICLOSPORIN

Current Indication

No longer a first line agent but some transplant patients will still have Neoral (previous formulation Sandimmun but nearly all patients are on Neoral) as the lead agent in their immunosuppression regime.

Dose

Starting dose is 8 mg/kg/day in 2 divided doses.

Preparation

Ciclosporin is available 10 mg (yellow / white), 25 mg (blue / grey), 50 mg (yellow / white) and 100 mg (blue / grey) capsules and as a 100 mg/ml oral solution. The brand name is Neoral.

Administration

Oral route in most instances. It is administered usually at 10 am and 10 pm. Oral solution should be diluted immediately before taking. May be diluted in orange juice or squash, apple juice or water (not grapefruit juice - see interactions). Needs to be stirred well. Measuring device should not come into contact within the diluent.

One third of the oral dose can be given as a slow intravenous infusion in normal saline or dextrose 5% over 2-6 hours if absolutely necessary.

Contra-indications/Cautions

Live vaccines are not to be given to immunocompromised patients.

Neoral should be used with caution during pregnancy.

Ciclosporin passes into breast milk so mothers should not breast feed their infants.

Side effects

The most frequent side effects seen with Ciclosporin include:

abnormal kidney function	hepatic dysfunction
hypertrichosis	gingival hypertrophy
tremor	gastrointestinal disturbances
hypertension	burning sensations of hands and feet

Less common side effects are:

headaches	rashes (possible allergic origin)
weight increase	oedema
mild anaemia	pancreatitis
hyperkalaemia	neuropathy
hyperuricaemia	reversible dysmenorrhoea
hypomagnesaemia	muscle weakness, cramps or myopathy
hypercholesterolaemia	

Interactions

Potential interactions due to effects on hepatic microsomal enzymes

Inhibitors of cytochrome P450 which may **decrease** metabolism of Ciclosporin and thus **increase** Ciclosporin blood levels include:

clarithromycin	erythromycin	nicardipine
danazol	fluconazole	oral contraception
diltiazem	ketoconazole	verapamil

Inducers of cytochrome P450 which may **increase** metabolism of Ciclosporin and thus **decrease** blood levels include:

Barbiturates	phenytoin
carbamazepine	rifampicin

Interactions due to cumulative toxicity / synergistic effects

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

Other interactions

- Vaccines may be less effective and the use of live attenuated vaccines should be avoided.
- Owing to its possible interference with the gastrointestinal cytochrome P450 enzyme system, grapefruit or grapefruit juice should not be taken 1 hour prior to Ciclosporin dosing and grapefruit juice should not be used as a diluent for the oral solution.
- This is not a comprehensive list of all potential interactions with Ciclosporin. For further information please ask senior members of staff or consult the transplant unit pharmacist.

Levels

Whole blood trough levels are measured by the laboratory on Mondays, Wednesdays and Fridays. The assay changed on Jan 10th 2005 as shown.

The table shows results pre and post 10th Jan 2005

Ciclosporin Assay (nmol/L)

OLD	NEW
50	32
100	69
150	107
200	144
250	182
300	219
350	257
400	294
450	332
500	369
550	407
600	444
650	482
700	519
750	557
800	594

Target range

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

After 6 months 50 – 100mmol/L

AZATHIOPRINE

Current indication

Third agent in standard triple therapy.

Dose

Initially 1-2 mg/kg once daily.

Maintenance 1 mg/kg once daily.

Monitoring

No monitoring of drug levels is required.

Preparation

Azathioprine is available as 25 mg and 50 mg tablets. There are both generic and brand (Imuran) forms on the market.

Administration

Virtually exclusively oral although an IV preparation is available.

Contra-indications

Pregnancy

Bone marrow dysfunction, i.e. Patients who are known to be leucopaenic or thrombocytopaenic.

Reduce dose if hepatic dysfunction is present.

Drug interactions

Allopurinol must not be co-prescribed as an inhibition of xanthine oxidase results in potentially fatal accumulation of azathioprine and its metabolites. An alternative uricosuric-benzbromarone is available on a named patient basis. Contact transplant unit pharmacist for further details.

Side Effects

Bone marrow suppression - usually reversible following cessation.

Cholestatis and disturbed liver function - again usually reversible.

Pancreatitis

Dose may require to be altered depending on WCC, i.e., reduce if $WCC < 4.0$, stop if $WCC < 3.0$ and re-introduce at a lower doses when $WCC > 3.0$.

MYCOPHENOLATE MOFETIL (MMF)

Current indication

As a substitute for azathioprine in alternative triple therapy regimen for patients at high risk of rejection and following resistant rejection in patients treated with standard triple therapy.

Dose

(500 mg to) 1g twice daily, depending on concomitant immunosuppression and renal function.

MMF is best absorbed on an empty stomach, either one hour before or two hours after a meal, but gastrointestinal side-effects may be alleviated by taking MMF with food and further splitting the daily dose.

Monitoring of MMF blood levels is not needed.

Mode of action

MMF is rapidly hydrolysed following absorption to mycophenolic acid (MPA), the active metabolite. MPA is a potent inhibitor of inosine monophosphate dehydrogenase (IMPDH) and therefore inhibits the de novo pathway of guanosine nucleotide synthesis. B and T lymphocytes are critically dependent on the de novo pathway and so MPA inhibits B and T lymphocyte proliferation and also B-cell antibody formation.

Preparation

MMF is available as 250 mg capsules (blue-brown) and 500 mg tablets (lavender). The brand name is CELLCEPT.

Contra-indications

Pregnancy

Side-effects

Neutropenia. Gastro-intestinal bloating, cramps, diarrhoea, vomiting.

Drug interactions

Tacrolimus increases the AUC of MPA, the active metabolite of MMF. By 3 months post transplant the increase is such that the dose of MMF may need to be reduced with time post-transplant to maintain stable systemic exposure to MPA.

Cholestyramine and antacids - may bind MMF and significantly reduce absorption.

Drugs which undergo tubular secretion, e.g. Aciclovir, theoretically may impair secretion of MMF and have raised blood levels themselves during concurrent administration.

Drugs which interfere with enterohepatic recirculation potentially may reduce the efficacy of MMF.

SIROLIMUS

(Rapamune. Should not be prescribed as rapamycin.)

Indication

As an adjunct to or substitute to a calcineurin phosphatase inhibitor for immunosuppression in patients in whom ciclosporin/tacrolimus have been implicated in allograft pathology.

Contraindications

Hypersensitivity to Sirolimus and its derivatives.

Pregnancy and breast feeding

Presentation, dosage and administration

1mg and 2mg tablets. Doses should be given on an empty stomach

Day 1	8mg daily
Day 2	6mg daily
Day 3+	2mg daily adjusted according to levels

Monitoring

Target range 5-15ng/ml depending on whether it is an adjunct to or substitute for a CNI.

Side Effects

Raised triglycerides and cholesterol	Thrombocytopenia	Mouth Ulceration
Anaemia	Neutropenia	Proteinuria
Hypokalaemia	Arthralgia	Epistaxis
Delayed wound healing	Lymphocele	Rash
Oedema	Infections	
PTLD	Diarhoea	

Drug Interactions

Compounds which modulate CYP3A4 activity may effect Sirolimus levels. Drugs and substances which may increase sirolimus levels include:

Diltiazem	Bromocriptine
Azole antifungals	Cimetidine
Macrolide antibiotics	Danazol
Prokinetic agents	Protease inhibitors
Grapefruit	

Drugs which may decrease Sirolimus levels

Rifampicin	Anticonvulsants
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Caution should be exercised with concomitant administration of nephrotoxic drugs.

ANTI-THYMOCYTE GLOBULIN (ATG)

Indication

Rejection resistant to steroids is now uncommon but ATG may be used in some circumstances, e.g., persistent biopsy proven rejection despite two courses of methylprednisolone.

Contra-indications

- known allergy to rabbit proteins
- acute viral illness
- full anaphylactic response to the test dose

Dosage and administration

The aim of therapy is to suppress the absolute CD3 cell (T cell) count to below $0.05 \times 10^9/L$ ($<50/microlitre$) for 14 days. ATG is given daily until the CD3 cell count has reached this level, then repeated if it rises above this level. Response varies, but most patients need 2-3 full doses over the 14 day treatment period. A test dose is given and followed 24h later by the first full dose.

Test dose

Symptoms during or after an ATG infusion are common. This is due to a systemic inflammatory response which occurs when T cells are activated by binding ATG. Symptoms of this 'cytokine release syndrome' include headache, fever, arthralgia, rigors and hypotension. Pulmonary oedema may occur in severe cases. True anaphylaxis is rare but it may occur.

All patients should have a test dose first, to identify those who will develop severe reactions including anaphylaxis.

Signs of anaphylaxis are tingling in the extremities and around the mouth, swelling of the lips and larynx, bronchospasm, tenesmus, hypotension. It should be treated in the usual way with hydrocortisone 100mg IV, chlorpheniramine 10mg IV; 0.5ml adrenaline 1:1000 IM may be necessary.

- Give 5 mg ATG in 100 ml NaCl 0.9% infused through a peripheral vein over 1 hour. Have hydrocortisone, chlorpheniramine and adrenaline available close by.
- Premedicate with paracetamol 1g orally, chlorpheniramine 10mg IV.
- Reconstitute the contents of one vial (25mg) with accompanying diluent (5 ml water for injections), giving a solution of 5 mg ATG per ml.
- Take 1 ml of solution and add to 100 ml NaCl 0.9%.
- Observe patient closely, monitoring BP, pulse and temperature according to the following schedule:

Time after test dose	Frequency of observations
0 - 2 hrs	15 mins
2 - 4 hrs	30 mins
thereafter	hourly

Administering and monitoring Test Dose and Subsequent doses

See full protocol in the online version of this guide.

Monitoring

See also Test Dose section. Symptoms of some sort are common (approx 25%) during administration and may be unpleasant for the patient. They include rigors (4%), fever (15%), arthralgia (10%), erythema (10%) and pruritic skin eruptions (10%). Symptoms are most commonly seen after the first injection and decrease during the course of treatment.

Other side effects include thrombocytopenia (5%), neutropenia (5%) which may prevent continuation of the treatment course, and serum sickness. Severe cytokine release syndrome and true anaphylaxis are rare (<1%) but can be fatal.

Interactions

There is a risk of over-immunosuppression, hence the following schedule should be followed:

DRUG	DAYS					
	0	1	2-7	8-14	15-30	31+
ATG	Test	Full	*	*		
Tacrolimus/Ciclosporin	Y	N	N	Half dose	Full dose	Full dose
Prednisolone	Y	Y	Y	Y	Y	Y
Azathioprine/ MMF	Y	N	N	Y	Y	Y

Tacrolimus reinstated after 1 week at dose of 0.05mg/kg divided into two doses [or half previous established dose]. Ciclosporin at dose 3mg/kg divided into two doses [or half previous doses].

Continue PCP and CMV/HSV prophylaxis for 3 months after treatment with ATG.

Ordering

Mon-Fri 8:30 – 17:00: Contact unit pharmacist.

Out of hours: contact resident pharmacist, bleep 2268. A small stock is held in pharmacy.

Storage

Both the dry powder and reconstituted solution to be stored in fridge (+4C), usually on ward 117; protect from light.

CMV INFECTION AND PROPHYLAXIS

Valganciclovir is prescribed for prevention of CMV disease in high risk transplant patients identified as follows:

- Renal transplant - CMV –ve recipient of CMV +ve donor
- Liver transplant - CMV –ve recipient of CMV +ve donor
- Simultaneous kidney-pancreas transplant (SKP) - All transplant recipients except CMV –ve recipients of CMV –ve donors

Prescription is initiated in hospital within 10 days of transplantation. Therapy will be continued in primary care for up to a total of 90 days treatment for which a shared-care protocol will be provided.

Valganciclovir is available as 450mg tablets (pink) and the brand name is Valcyte®. The tablets should be taken with food and not broken or crushed.

The initial valganciclovir dose is dependent on renal function as shown in the table below:

Creatinine clearance (ml/min)	Prophylactic dose
>60	900mg od
40 to 59	450mg od
25 to 39	450mg every 2 days
10 to 24	450mg twice weekly

FBC and LFTs must be monitored daily during therapy.

Testing for CMV infection

Surveillance is not routine since introduction of valganciclovir. Investigate any episode of illness which might be CMV related, at any stage following a transplant operation.

Check CMV serology together with samples of EDTA blood for buffy coat culture and serum sample for PCR. These should be requested following discussion with the Virologist.

An EDTA (9 ml or 3 x 2.5 mls sample for CMV should be sent to Virology whenever is clinically relevant. ON request form include details of illness (e.g. pyrexia or hepatitis etc.) Request CMV PCR and CMV culture. Please try to ensure samples reach Virus Lab by midday, and within 2h. The rapid culture may provide an answer sooner than PCR in some cases.

It will often be appropriate to send respiratory or other samples to virology - bronchoalveolar lavage or induced sputum for investigation as usual or colon biopsies.

ALTERED GRAFT FUNCTION

An increase in creatinine may be caused by a number of processes, but common causes are:

- Rejection
 - Infection, e.g. urine, CMV
 - Tacrolimus / Ciclosporin toxicity
 - Altered fluid balance
-
- Less common causes are:
 - Vascular catastrophe
 - Mechanical problem - urinary obstruction (less likely if ureteric stent present), lymphocele

A patient whose creatinine has increased requires careful assessment, as the classic signs of rejection (pyrexia, tender graft) are rarely present with current immunosuppressive agents.

- Review patient's fluid status and fluid balance charts;
- Check FBC
- Note particular decrease in urine volumes, tender graft;
- Check for pyrexia;
- Culture urine, PD fluid;
- Consider CMV PCR and rapid culture.
- Get Tacro / CyA level
- Consider USS to exclude mechanical/vascular problem, with Duplex to confirm patency of major vessels

RISK FACTORS ASSOCIATED WITH GRAFT FAILURE

Criteria for High Risk status

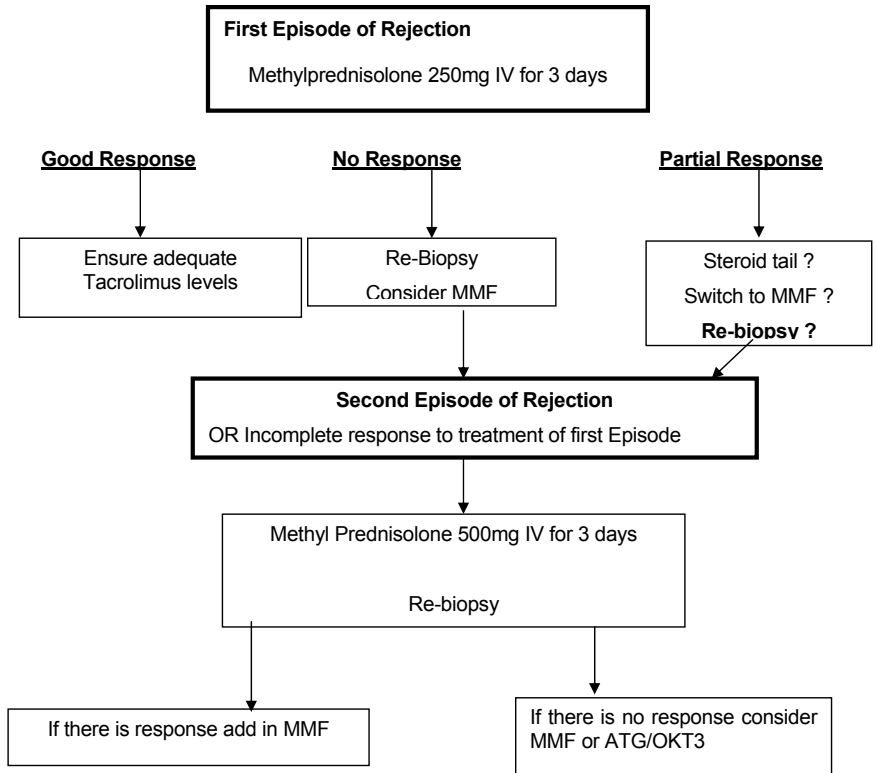
There are a number of risk factors that have been identified as probable causes for graft failure in kidney transplantation. Many of these can be identified prior to surgery. They include:

- HLA mismatch - non favourable
- Preformed antibodies to HLA (a panel reactivity of 50-100%)
- Number of previous transplants
- The presence of delayed graft function (the requirement for dialysis during the first week after transplant except for hyperkalaemia).
- The number of rejection episodes / severity of rejection episodes
- Donor age
- Ischaemic time

Management

Taking the above factors into account, patients who are at greater risk of graft failure may be identified. Where a patient has been identified as being at risk, MMF should be used in preference to azathioprine and / or Basiliximab added to the immunosuppressive regime. Plasma Exchange and other treatment options may also be considered in certain circumstances e.g. preformed HLA antibodies.

TREATMENT OF REJECTION



NB: Patients should receive PCP prophylaxis and CMV prophylaxis for 3 months from the time of the last dose of methyl prednisolone

Antibody mediated rejection; discuss

RENAL ALLOGRAFT BIOPSY

Renal allograft biopsies are usually performed under USS guidance in x-ray department by the radiologist. Urgent biopsy requests should be discussed with a Consultant Radiologist.

All patients must have:

Consent

- must be obtained by the doctor requesting the biopsy.
- patients informed of risks:
 - significant bleeding (requiring blood transfusion / further surgical intervention) is approximately 1-2%.
 - the risk of graft loss is <1 in 250 biopsies.

Clotting screen

- For biopsy to proceed results required:
 - Platelets > or = to 60 x 10⁹L
 - PT - prolongation of < 3 seconds.
 - if patient on Warfarin an INR of < or = 1.5. APTT normal.
 - Group and save.

Heparin discontinued

Aspirin / Warfarin discontinued.

Fluids only for a while before the procedure

Results, Consent Form and Pathology Form must be attached to front of case notes for the attention of radiologist. If samples are required for EM and immunofluorescence then this must be clearly indicated on the request card. These are required if de novo / recurrence of a primary glomerulonephritis is suspected – consider in any biopsy more than 3 months post-transplant.

Pathology Department contacted and told of the biopsy and arrangements made to collect the specimens. INCLUDE request for elective microscopy and immuno-fluorescence in all samples over 3 months post transplant.

Pathology request forms Must be filled in by the doctor requesting the biopsy. Unless otherwise stated it will be assumed that samples for light microscopy and frozen section are required. If sample for immunofluorescence or electron microscopy is required this must be stated on the form.

Out of hours, the on call Pathologist can be contacted via RIE switchboard

Post biopsy observations – every 15 mins for first 30 mins, every 30 mins for 2 hours, 4 hourly.

PNEUMOCYSTIS PROPHYLAXIS

Standard prophylaxis is cotrimoxazole 480mg once daily for the first three months. If extra treatment for acute rejection has been required, prophylaxis should extend to three months after that treatment.

Desensitisation should be considered if patients are unable to tolerate low dose Co-trimoxazole for PCP prophylaxis.

Desensitisation protocol for cotrimoxazole

First Line

Paediatric Co-trimoxazole suspension (240mg/5ml) diluted 1:20 (2.4mg/ml Co-trimoxazole).

Day	Volume	Dose of Sulphamethoxazole
1	1ml	2mg
2	2ml	4mg
3	4ml	8mg
4	8ml	16mg
5	12ml	24mg

Paediatric Co-trimoxazole suspension (240mg/5ml)

6	1.25ml	55mg
7	2.5ml	110mg
8	5ml	240mg
9	10ml	480mg
10	10ml/1 tablet	480mg

Second Line

Dapsone 100mg od

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

Third Line

Nebulised pentamidine 300mg every 4 weeks – details from pharmacy.

VACCINATIONS

Pre-Transplant

If previously unimmunised, adults should receive Polio, Tetanus and Diphtheria vaccines.

Administration of Pneumococcal, Meningococcal and Haemophilus Influenza type B vaccinations are desirable. Live Varicella vaccine may also be considered - it is available on a named patient basis from pharmacy. Vaccinations should be documented in admission clerk in.

Post-transplant

Live vaccines should not be given to immunosuppressed patients. Influenza vaccine is inactivated and therefore safe. The following are live vaccines:

- Oral Polio vaccine (OPV, Sabin).
 - Oral Typhoid vaccine (Vivotif).
 - Measles
 - Mumps
 - Rubella
 - Rubella vaccine (Erverax)
 - BCG vaccine.
 - Varicella vaccine - not in UK.
 - Yellow fever (Ariavax).
- } MMR vaccine (MMR II, Priorix)

Polio/Typhoid

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

Inactivated vaccine is available on a named patient basis via pharmacy.

MMR

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

Varicella

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

Yellow Fever

For patients intending to travel to countries where a Yellow Fever certificate is required they should obtain a letter of exemption from a medical practitioner. Yellow Fever occurs in tropical Africa and South America. Up to date information is available from pharmacy or WHO publications.

Malaria Prophylaxis

Up to date information on Malaria prophylaxis for a given destination is available from pharmacy.

The following table gives an indication of interactions:

	Tacrolimus	Ciclosporin
Choloroquine	? ↑ tacrolimus (cP450 3A4)	↑ CyA (CP450 3A4)
Proguanil	No interactions likely	No interaction likely
Mefloquine	? ↑ tacrolimus (displacement from plasma protein)	No interaction likely
Doxycycline	? ↑ tacrolimus (CP450 3A4)	↑ CyA (CP450 3A4)

COMPLEMENTARY MEDICINES

There is currently insufficient information on the pharmacokinetics of complementary medicines to enable a judgement on whether they are likely to interact with conventional medicines and whether dosage reduction is necessary in renal impairment. Due to a lack of regulation, adverse effects such as nephrotoxicity may be attributable to impurities rather than the active principle.

Below is an extremely limited list of information on complementary medicines -- for specific queries the Welsh Drug Information Centre specialist file and Micromedex may be consulted via pharmacy. There is also a very useful database at <http://www.nlm.nih.gov/medlineplus/druginformation.html>

Complementary Medicine	Issue
St John's Wort	↓ CyA levels reported due to CYP450 3A4 induction. May therefore ↓ tacrolimus levels
Garlic Papaya Danshen Dong quai Ginger	↑ INR therefore avoid peri-operatively
Xaiochai hutang	↑ Prednisolone levels
Chinese herb (Aristolochia) Juniper Pennyroyal	Renal damage
Ginko	Cyclo-oxygenase inhibitor and PAF antagonist
Echinaecea	'Immunostimulant' - stimulates TNF secretion in vitro

APPENDICES

All available from web version via www.edren.org

Or internally via <http://proton/EdREN> on the Intranet.

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Appendix II	Guidelines to be used with Renal Transplant Assessment Check-list
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