**Kidney Transplant Guidelines**

<table>
<thead>
<tr>
<th>Full Title of Guideline:</th>
<th>Kidney Transplant Guidelines</th>
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<tbody>
<tr>
<td><strong>Author (include email and role):</strong></td>
<td>Keith Rigg, Consultant Transplant Surgeon, <a href="mailto:keith.rigg@nuh.nhs.uk">keith.rigg@nuh.nhs.uk</a></td>
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<tr>
<td>Division &amp; Speciality:</td>
<td>CAS/Renal and Transplant</td>
</tr>
<tr>
<td>Version:</td>
<td>8.4</td>
</tr>
<tr>
<td>Ratified by:</td>
<td>Renal and Transplant Senior Staff Meeting</td>
</tr>
<tr>
<td><strong>Scope (Target audience, state if Trust wide):</strong></td>
<td>Multidisciplinary kidney transplant team</td>
</tr>
<tr>
<td>Review date (when this version goes out of date):</td>
<td>31 January 2021</td>
</tr>
<tr>
<td>Explicit definition of patient group to which it applies (e.g. inclusion and exclusion criteria, diagnosis):</td>
<td>Kidney Transplant Recipients</td>
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<tr>
<td>Changes from previous version (not applicable if this is a new guideline, enter below if extensive):</td>
<td>Updated immunosuppression guidelines, new BK guidelines and minor wording changes</td>
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<tr>
<td>Summary of evidence base this guideline has been created from:</td>
<td>Literature review and expert opinion</td>
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*This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date or outside of the Trust.*
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This guideline has been registered with the Trust. However, clinical guidelines are ‘guidelines’ only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague. Caution is advised when using guidelines after the review date. This guideline should be used in conjunction with the relevant national guidelines and service specification listed below:

- UK Guidelines for Living Donor Kidney Transplantation (2011) and Addendum (2014)

Author: Mr KM Rigg, January 2018, Future Review January 2021 by Miss AJ Knight
1. Checklist for the unit nursing staff

i) Ensure all relevant sections of transplant care pathway are completed
   - If virtual cross-match patient will need to be prepared for theatre ASAP

ii) Give ‘Milestones’ document to patient

iii) Take blood samples for:
   - Full blood count and clotting (P1)
   - Electrolytes, urea and creatinine (P1)
   - Venous gas for K+ if HD patient - if K+ >5.5 plan for immediate dialysis
   - Blood glucose [HbA1c if patient is diabetic]
   - Calcium, phosphate, LFTs, lipids, serum PTH, ferritin and TSATs (routine)
   - Cross match 2 units of HEV negative blood (P1)
   - CMV IgG & IgM if CMV-ve, EBV and VZ immune status if negative or unknown (routine)
   - Flow cross match (samples send to Sheffield immediately)
     - 1 clotted and 4 EDTA.
     - Check with transplant coordinator as to whether to wait for lymph node and spleen before sending to Sheffield.
   - Pregnancy test - serum β-HCG in women of child-bearing age, or urine β-HCG if passes urine (P1). **Result must be known prior to theatre.**
   - Check if blood required for research purposes

iv) Other action on admission
   - When patient arrives inform medical F2/CMT and SpR
   - If virtual crossmatch keep patient nil by mouth. Otherwise allow patient to drink clear fluids and check with surgeon if patient can eat (>6 hours pre-op)
   - Measure height and weight
   - Swab exit site of CAPD catheter and neck lines
   - MRSA screen – two swabs from nose and perineum
   - Check HBV, HCV and HIV status from eMED virology screen
   - Urine sample for MSU (if passes urine)
   - Patient to have shower and put on gown

v) Two hours after blood samples have gone to Sheffield (or on admission if virtual crossmatch)
   - Keep nil by mouth
   - Drain PD fluid (patient on PD) and send fluid for culture
   - Check what drugs need to be given
   - Wrap fistula arm in gamgee. If no fistula, still protect non-dominant arm by fixing micropore along the forearm saying, "not to be used for vascular access".
   - Put on TED stockings
   - Prepare red box for theatre: required drugs (antibiotics, methylprednisolone, Basiliximab and 10% mannitol), notes with ECG and CXR with latest results (U&Es and FBC) documented.

*The flow cross-match needs to be negative to proceed with transplantation. The result is usually phoned to the transplant coordinator or Carrel ward from Sheffield, a confirmatory fax sent to the secretaries’ office and the surgeon should then be informed. Let transplant coordinator know immediately if cross match is positive so that further recipient can be called or kidney sent elsewhere. File confirmatory fax of cross match in notes.*
2. Checklist for Medical F2/CMT or Renal Team

It is important that a history and examination, blood tests, CXR and ECG are done as soon as the patient is admitted. That will allow for the kidney to be used elsewhere, if our patient is not fit for transplant.

i) History and examination with appropriate documentation in Care Pathway documentation

History (to include the following)
- Primary renal disease and dialysis history
- Previous transplants, admissions for transplantation
- Current health, recent hospital admission, recent infection
- Usual daily urine output and any urinary symptoms
- Drug history, in particular antihypertensive and lipid lowering medications
- Drug allergies if so check recorded on the notes and the current drug card – if no also record on drug card

Examination (to include the following)
- Blood pressure, chest, heart
- Signs of infections including exit site of PD catheter or dialysis catheter
- Fluid status
- Peripheral pulses, abdominal and femoral bruits
- Weight

ii) Arrange chest x-ray (if clinically indicated) and ECG

iii) Check for recent results
- HBV, HCV, HIV and CMV (computer and notes)

- All patients must be seen soon after admission by medical SpR to assess fitness for surgery, need for dialysis and review current medication
- Check immunosuppressive protocol with surgeon and prescribe accordingly.

v) Intravenous fluids
- Remember, patient can drink clear fluids up to 2 hours before surgery
- Administer iv fluid, if theatre time is changing (possible delay) and if patient is dry.
  - Diabetic patients will require glucose and insulin via peripheral line

vi) Assess the need for haemodialysis
- If required aim for 1kg above dry weight
- Use minimal heparin
- Check U&Es 60 minutes after dialysis
vii) Prescribe the following:

- Complete eVTE risk assessment and prescribe Enoxaparin 20mg at 1800 and daily until patient fully mobile and TED stockings unless peripheral vascular disease
- Methylprednisolone 500mg iv at induction
- Immunosuppression according to guidelines, but discuss with surgeon
- Co-amoxiclav 1.2g iv at induction (then 600mg at 8 and 16 hours post operatively). If penicillin sensitive prescribe cefuroxime 750mg iv, unless previous anaphylactic reaction when further advice should be sought from senior team members
- Aspirin 75mg oral daily at 12 midday
- Ranitidine 300mg oral nocte (omeprazole 20mg in patients with dyspepsia)
- Co-trimoxazole 480mg daily for 6 months.
- Sodium docusate 200mg nocte
- Isoniazid 300mg daily with pyridoxine 20mg daily for patients with a history or evidence of previous TB, previous exposure or who have previously lived in a country with a high incidence of tuberculosis infection. This would normally be given for six months.
- Valganciclovir tablets 450mg oral if CMV-ve recipient receiving CMV+ve kidney, but only give once CrCl >10. If the patient has prolonged DGF consider giving liquid at dose tabled below. [See separate CMV protocol for further details]

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended dosage (if using tablets)</th>
<th>Recommended dosage (if using liquid)</th>
</tr>
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<tbody>
<tr>
<td>&gt;60</td>
<td>900mg od</td>
<td>900mg od</td>
</tr>
<tr>
<td>40-59</td>
<td>450mg od</td>
<td>450mg od</td>
</tr>
<tr>
<td>25-39</td>
<td>450mg every 2 days</td>
<td>225mg od</td>
</tr>
<tr>
<td>10-24</td>
<td>450mg twice weekly</td>
<td>125mg od</td>
</tr>
<tr>
<td>&lt;10</td>
<td>Not recommended</td>
<td>100mg 3xwk (post HD where appropriate)</td>
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</tbody>
</table>

- 2% Bactroban nasal ointment; apply using a swab to the inner surface of each nostril tds for 5 days and Octenisan wash; apply once a day for 5 days; the patient’s hair should be washed with Octenisan on days 2 and 5.
- Do not prescribe dialysis medication (antihypertensive drugs, phosphate binders etc). Do continue alfacalcidol or calcium supplements if patient had had previous parathyroidectomy; and continue β-blockers if history of ischaemic heart disease. If live donor recipient discuss with anaesthetist
- Adult patients with aHUS may require treatment with eculizumab before they go to theatre/and following transplantation; an individual plan for each patient is documented on eMED in the ‘transplant notes’ section of eMED

3. Checklist for the surgeon

- Assess patient, assess suitability for appropriate clinical trial and obtain consent
- Inform anaesthetist; book theatre and let ward nursing staff know likely time for theatre – unless this has already been done by recipient coordinator.
- Check immunosuppression has been prescribed
- Check donor and organ characterisation details according to EUODD requirements (see NOP 001 & 002) and check faxed report of crossmatch
- Benchwork on kidney before recipient anaesthetized and send perfusion fluid for M,C & S
Checklist for anaesthetic staff

- Insertion of internal jugular line (preferred even if Permcat in situ). If Permcat has to be used, treat as sterile and ensure Citralock is aspirated (3ml). Ensure have large bore peripheral IV access.
- Give 500mg Methylprednisolone iv, 20mg Basiliximab and antibiotics at induction.
- Blood volume maintained using Geloplasma and crystalloids as appropriate to maintain a CVP of 7-11 mmHg and a mean arterial pressure of at least 80-90mmHg. Please discuss use of inotropes with surgeon before giving.
- During arterial anastomosis surgeon will ask for mannitol (250 ml of 10% or 0.25-0.5g/kg) and may ask for furosemide (40-80mg iv).
- Surgeon will insert Ropivacaine Accufuser as a TAP catheter at end of operation.
- Anaesthetist will set up Fentanyl PCA and prescribe oral Paracetomol.

Post-operative care

1. Recover patient as per Recovery Room protocol, observing and maintaining airway until patient is fully conscious. Monitor BP, CVP, pulse rate and oxygen saturation levels.

2. Replacement fluid. Give IV normal saline at 40ml + previous hours urine and drain output; but when patient arrives in recovery will need to base this on urine output in first 15-30 minutes and then multiply accordingly.

3. Check fluid balance with STRICT observations of urine output. Inform surgeon of drop in urine output.

4. Organize a chest X-ray to check position of central line.

5. If CVP < 8 mmHg give 250ml Geloplasma in addition to replacement fluid (NB Ensure reliable CVP trace and it is important to interpret CVP in context of overall fluid assessment as readings may not be accurate)

6. If any problems or doubts, or if CVP remains below 8mmHg despite two boluses of colloid, speak to the consultant surgeon.

Points to note

- Check to see if patient has an AV fistula, and if so, do not monitor BP or take blood from fistula arm.
- If patient was previously on peritoneal dialysis, check PD catheter is capped off and secured to patient’s abdomen.
- Ensure contact number noted for surgeon and anaesthetist.
1. Nurse in cubicle with 1 to 1 transplant trained nurse where possible.

2. Check FBC and potassium as P1. If serum K⁺ rises it is preferable to avoid haemodialysis for 24 hours. If serum K⁺ > 6.0 perform 12 lead ECG. If changes and a delay in dialysis, give 10ml 10% calcium gluconate iv. Consider use of 1.4% NaHCO₃ instead of 0.9% saline or 50ml 50% glucose and 10 units Actrapid insulin iv or 5mg Salbutamol nebuliser. Discuss K⁺ problems with senior colleagues. Check urea, creatinine and electrolytes 4 hours later.


4. CXR to check position of central line, if not already done in recovery

5. **Replacement fluid.** Give IV normal saline at 40ml + previous hours urine and drain output.

6. If CVP < 8 mmHg give 250ml Geloplasma in addition to replacement fluid (NB Ensure reliable CVP trace and it is important to interpret CVP in context of overall fluid assessment as readings may not be accurate)

7. If any problems or doubts, or if CVP remains below 8mmHg despite two boluses of colloid, speak to the senior surgical/medical staff.

8. If Hb < 7.0g/dl or symptomatic contact senior medical/surgical staff before transfusing

Daily

Check
- Complete Care Grid and ensure relevant actions completed and signed off
- Fluid balance and weight
- Nutrition (patient may eat and drink when desires)
- Wound, chest etc
- Ensure hand washing guidelines adhered to
- Ensure immunosuppression screen kept up to date

Blood
- FBC, Electrolytes, urea and creatinine
- Glucose if patient diabetic or on large doses of steroids
- Check if extra blood required for research studies
- On Mondays & Thursdays only - LFTs, calcium & phosphate
- Tacrolimus and ciclosporin levels can be measured routinely on all weekdays and Saturday by arrangement. (The laboratory should be informed about patients requiring Saturday levels [ext 55087] and the sample must reach the lab by 0930).
  - Adoport or Prograf trough levels should be taken 12 hours after last dose with the first level on day 3; C2 ciclosporin levels should be taken 2 hours after the morning dose with the first level on day 3;
  - Advagraf trough levels should be taken 24 hours after last dose with the first level on day 3

Urine
- Urinalysis only if patient has history of FSGS (if +ve for protein send for PCR)
- MSU on day of catheter removal and/or if symptomatic

Removal of catheters and drains at discretion of surgeon, but in general:
- Drain at 1-2 days
- Accufuser and PCA at day 2; then continue paracetamol and add Tramadol or Oxycontin if extra analgesia required
- Urinary catheter at day 4

If patient has a fever, the following are required
- Clinical history and examination (chest, wound, exit sites, urine)
- Blood cultures immediately
- Urine for bacteriology (inc fungi) and swabs - throat, wound, exit sites
- PD fluid if PD catheter in situ.
- Consider CXR
- If CMV infection suspected send blood for PCR (5ml EDTA) to Microbiology at QMC (ext 64950)

Aim for discharge on day 5 for un-complicated patients
- Transplant nurse specialist review from day 3
- eTTOs day 4
- If DGF, plan for regular dialysis and biopsy
**Baseline immunosuppression**

Patients should be prescribed the appropriate immunosuppressive regimen depending on their immunological risk:

**Standard immunological risk:**
- Basiliximab, Adoport, azathioprine & prednisolone
- All transplants unless high immunological risk

**High immunological risk:**
- Basiliximab, Adoport, Mycophenolate mofetil and prednisolone
- Repeat transplant
- PRA >80%
- 2 DR mismatch
- ABOi/HLAi transplants
- Afro-Caribbean recipients

**Basiliximab**

Induction therapy with IL-2 receptor antagonist is routinely prescribed in patients:
- Basiliximab 20mg iv, two hours pre-operatively
- Basiliximab 20mg iv, on day four

**Rabbit-ATG (Thymoglobuline)**

Induction therapy with rabbit-ATG will be considered after discussion with the consultant surgeon and nephrologist for patients who:
- Are highly sensitised (%cRF >85%)
- Have a BMI>38 where a steroid free regimen planned (unless high immunological risk)

See Rabbit-ATG protocol on page 17

**Adoport**

- For deceased donor transplants give a loading dose of 0.15mg/kg two hours pre-operatively and then 0.15 mg/kg/day in two divided doses at 1000 and 2200 (best taken on an empty stomach, 1 hour before or two hours after food). If it is not possible to start the patients on oral Adoport immediately, give IV tacrolimus (0.05mg/kg as a 24 hour infusion) until the patient can take the drug orally.
- For living donor transplants give a loading dose of 0.15mg/kg for three days pre-operatively and on day of transplant. Be prepared to adjust on day 0 of transplant dependant on level. [Note: Also start azathioprine or MMF at the same time]
- Measure trough levels (12 hours post-dose) twice a week for the first three weeks and aim for target levels of 5-8ng/ml
- There should be no more than 2 changes per week.
Azathioprine

- Aim for 1.5mg/kg initially (round **down** to nearest 25mg increment) as single dose at 0800. Reduce dose if WCC <5.0 x10^9/l or falling. Stop if WCC below 4.0 x10^9/l. Beware lack of rise in WCC on high dose steroids - it may be followed by a dangerous fall in the white cell count. Reduce to 1mg/kg at one year.

Steroids

- Methylprednisolone
  - 500mg iv given at induction
- Prednisolone
  - 20mg from day 1
- At end of week 2, reduce prednisolone to 15mg/day
- At end of week 4, reduce prednisolone to 12.5mg/day
- At end of week 6, reduce prednisolone to 10mg/day
- From week 8 to week 12, reduce prednisolone down to a maintenance dose of a minimum of 5-7.5 mg/day, unless reason not to.

Mycophenolate mofetil (MMF)

- Start at 1g oral bd, but consider lower dose if weight <50kg. If it is not possible to start the patients on oral MMF immediately, give IV MMF at an equivalent dose until the patient can take the drug orally.

Alternative immunosuppression

There will be some patients who do not tolerate the above standard immunosuppression and will require alternative immunosuppression therapy and these are included here for completeness.

Mycophenolate sodium (MPS)

- Start at 720mg oral bd. If it is not possible to start the patients on oral mycophenolate sodium immediately, give IV MMF at an equivalent dose until the patient can take the drug orally.
- Reduce to 320mg oral bd after 14 days when given with Advagraf.

Note: Mycophenolate sodium 720mg po = MMF 1g po = MMF 1g iv

Advagraf®

- When switching from an immediate release tacrolimus e.g. Adoport, prescribe total daily dose of IR tacrolimus, as one daily Advagraf at 10am. For example, if on 2mg bd of Adoport give 4mg of Advagraf once daily
- Measure trough levels (24 hours post-dose) and aim for target levels of 5-8ng/ml
- There should be no more than 2 changes per week.
Ciclosporin

- Start oral ciclosporin at 6.5mg/kg every 12 hours as soon as tolerated (usually at the first or second dosing period after the transplant). If it is not possible to start the patients on oral ciclosporin immediately, give IV ciclosporin (2.33mg/kg/12h as a 2h infusion) until the patient can take the drug orally.
- Monitor the C\textsubscript{2} blood ciclosporin concentrations on Days 3, 5 and 7 after transplant (Day 0). Aim for a target blood ciclosporin of 1500ng/L. After Day 7 measure the C\textsubscript{2} blood ciclosporin concentrations on Days 10 and 14, and then weekly up to three months post-transplant. C\textsubscript{2} levels should be taken 2 hours ± 15 minutes after morning dose (avoid early sampling).
- Suggested C\textsubscript{2} targets are:

<table>
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<tr>
<th>Months following transplant</th>
<th>C\textsubscript{2} target (ng/ml)</th>
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<tbody>
<tr>
<td>0-1 months</td>
<td>1500 [but 500-700 if DGF]</td>
</tr>
<tr>
<td>1-2 months</td>
<td>1300</td>
</tr>
<tr>
<td>2-3 months</td>
<td>1100</td>
</tr>
<tr>
<td>3-6 months</td>
<td>900</td>
</tr>
<tr>
<td>&gt;6 months</td>
<td>700</td>
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These are target values not ranges. In the first month post-transplant be prepared to alter the ciclosporin dose by as little as 25mg to keep on target.

Envarsus\textsuperscript{®}

Envarsus\textsuperscript{®} is a once daily prolonged-release formulation of oral tacrolimus that has been approved for use in adult kidney transplant patients who are unable to use Adoport\textsuperscript{®}, Advagraf\textsuperscript{®}, Prograf\textsuperscript{®} or Modigraf\textsuperscript{®}, due to persistent tremor or other neurological disturbances.

Envarsus\textsuperscript{®} is available in 0.75mg, 1mg and 4mg prolonged-release tablets. A dose reduction is required when switching patients from Adoport\textsuperscript{®}, Advagraf\textsuperscript{®}, Prograf\textsuperscript{®} or Modigraf\textsuperscript{®} to Envarsus\textsuperscript{®} and the dose of Envarsus\textsuperscript{®} should be reduced as follows:

- **Non-black patients:**
  The total daily dose of Envarsus\textsuperscript{®} should be 30% less than the total daily dose of Adoport\textsuperscript{®}, Advagraf\textsuperscript{®}, Prograf\textsuperscript{®} or Modigraf\textsuperscript{®}, and given as a single dose, ONCE a day at 1000.

- **Black patients:**
  The total daily dose of Envarsus\textsuperscript{®} should be 15% less than the total daily dose of Adoport\textsuperscript{®}, Advagraf\textsuperscript{®}, Prograf\textsuperscript{®} or Modigraf\textsuperscript{®}, and given as a single dose, ONCE a day at 1000.

A dose calculator is available for converting patients to Envarsus\textsuperscript{®} from Adoport\textsuperscript{®}, Advagraf\textsuperscript{®}, Prograf\textsuperscript{®} or Modigraf\textsuperscript{®}; this can be obtained from the renal pharmacist or any of the specialist transplant nurses.

A trough tacrolimus level must always be checked 5 to 7 days after switching any patient from Adoport\textsuperscript{®}, Advagraf\textsuperscript{®}, Prograf\textsuperscript{®} or Modigraf\textsuperscript{®} to Envarsus\textsuperscript{®}.

Tablets should be swallowed whole with fluid (preferably water), and should generally be taken on an empty stomach to maximise absorption. Specialist advice should always be sought from a renal pharmacist or pharmacy when converting patients from Envarsus\textsuperscript{®} to IV tacrolimus.
Delayed graft function

- Defined as the need for dialysis in the first 7 days post-transplant, excluding dialysis for hyperkalaemia alone.
- Request Doppler ultrasound scan for same or following day.
- Maintain fluid balance and assess need for dialysis on a daily basis.
- If no function by day 3-5 requires ultrasound and transplant biopsy. Depending on the result of this the dose Adoport may be further reduced.
- Transplant biopsy should be repeated at weekly intervals (or before if clinically indicated) for the first month and then fortnightly until the graft is functioning or deemed that it will never work.

Treatment of rejection

Treatment should be based on the result of a biopsy where practically and clinically possible. Bloods for DSAs and BK PCR should be taken before biopsy when clinically indicated.

First episode in standard risk patients
- 500mg methylprednisolone iv daily for three days.
  - Consider increasing dose of tacrolimus
  - Stop azathioprine and convert to Myfenax 1 g twice daily

Second episode in low risk patients (ensure 1st episode if recent was adequately treated)
- 500mg methylprednisolone iv daily for three days.

First episode in high risk patients
- Cellular rejection
  - 500mg methylprednisolone iv daily for three days.
- Vascular or antibody mediated rejection (see below for more details)
  - Convert to Myfenax if not already on it
  - Donor specific antibodies (DSA) for deceased donors and repeat cross-match and DSA for live-donor transplants
  - Consider plasmapheresis and ivIG if C4d and/or DSA positive (Discuss with consultant surgeon/physician)
  - Re-biopsy 2 days post-methylprednisolone.
Steroid resistant rejection
- Rabbit-ATG (see section 11)
- Re-biopsy at end of course and consider sirolimus/prednisolone therapy if still biopsy proven rejection

Acute Antibody Mediated Rejection (aAMR)
- Continue tacrolimus and Myfenax
- Steroids
  - Methylprednisolone 500mg IV given every day for 3 days
- Plasma Exchange
  - This should be started no sooner than 24 hours after a renal biopsy
  - 5 alternate day exchanges
  - Discuss with BTS regarding replacement fluid (albumin vs. FFP)
  - Monitor for hypocalcaemia, bleeding and infection
- Immunoglobulin (iv Ig)
  - Complete request/registration form on intranet available at [http://qpharmsql1/ivig/](http://qpharmsql1/ivig/)
  - 5 doses of **100mg/kg** given at the end of each plasma exchange
  - Prescribe as Octagam, start the infusion at 0.6ml/kg/h for first 30mins.
  - Then increase rate to 1.2ml/kg/hr for the remainder of the infusion.
- Repeat biopsy and DSA at end of 10 day treatment, or at discretion of consultant surgeon/nephrologist depending on response to treatment
- Consider Rabbit-ATG on an individual basis if biopsy findings suggest or if no response to above. The Rabbit-ATG can be given on non plasma exchange days or after the course of plasma exchange has finished

Late rejection
Defined as first acute rejection occurring after 6 months.
- Treat as above
- Check CNI level and consider increasing dose
- Consider non-adherence
- Consider other drugs, which may lower CNI level
- Repeat cross match and HLA antibody screening

Steroid tail
In some patients with acute rejection not amenable/responsive to other treatments a decision will be made to give a steroid tail. This starts at prednisolone 100mg po od and then reduced by 10mg per week until reach 20mg po od at which point a repeat biopsy will usually be performed. Further steroid reduction tail as per protocol above.
There are clinical situations where patients require conversion from Neoral to a tacrolimus preparation (Adoport, Advagraf, Prograf or Envarsus), or more uncommonly a tacrolimus preparation (Adoport, Advagraf, Prograf or Envarsus) to Neoral.

When patients require conversion from Neoral to tacrolimus then the last dose of Neoral should be given in the evening and tacrolimus started the following morning at 0800.

When patients require conversion from Advagraf or Envarsus to Neoral then the last dose of Advagraf should be given in the morning and Neoral started from the following morning.

When patients require conversion from Adoport or Prograf to Neoral (or vice versa), a dose of the initial CNI needs to be omitted before the new CNI is commenced i.e. there will be a 24 hour window between the last dose of the old CNI and the first dose of the new CNI.

In acute rejection the conversion should be covered with 500mg iv methylprednisolone (see section 7)

Indications
- Intolerance to MMF/MPS (including low WCC)
- Vascular rejection in patients on Adoport/Prograf/Advagraf/Envarsus and MMF/MPS preparations or not responding to conversion from Neoral to a tacrolimus preparation.
- Patients on MMF/MPS who had vascular rejection and required Rabbit-ATG
- Consider in newly diagnosed cancer

Conversion protocols

If patient on MMF/MPS and prednisolone ($\geq 0.1mg/kg/day$) switching to sirolimus and prednisolone

- Stop MMF/MPS and start daily dose of sirolimus 4mg daily.
- Blood test
  - U&Es, Hb, platelets, WCC, serum cholesterol, prior to conversion
  - U&Es every 2 days for 2 weeks
  - Sirolimus blood levels at day 5, 7, week 2 and 7 days after changing doses.
  - Check cholesterol at month 1, 3 and 6
Sirolimus levels

1. Maintain levels of 8-10 for the first 3 months and 5-8 for months 3-6
2. Maintain levels at lower end of 5-8 thereafter
3. Adjust sirolimus dose with abnormal serum cholesterol, transaminases, triglycerides and platelet and white cell counts

If patient on MMF/MPS and prednisolone (≥0.1mg/kg), with low WCC

- Use the same protocol as above using but under cover of 3 days of methylprednisolone i.v. (500mg/day)

If patient with acute rejection and not responding to ATG or a tacrolimus preparation (Adoport, Advagraf, Prograf or Envarsus)/MMF or MPS/prednisolone

- Use the same protocol as above for discontinuation of MMF/MPS or protocol below for discontinuation of tacrolimus as appropriate.

If patient on Adoport/Advagraf/Prograf/Envarsus, azathioprine and prednisolone (≥0.1mg/kg/day) converting to sirolimus and prednisolone

- Stop azathioprine and start sirolimus at 4mg/day.
- Check levels until levels of 8-10 reached (usually within 2 weeks).
- Reduce tacrolimus by 1/3, for two weeks
- Reduce tacrolimus by another 1/3, for two weeks and then stop

Sirolimus levels As above.

Kidney Transplant Guidelines
Transplant Unit, Nottingham University Hospitals NHS Trust

Immunosuppression
6. Withdrawal of immunosuppression in the failed transplant

Patients on triple therapy
- Stop azathioprine/MMF/MPS
- Reduce CNI by ½ for one month, then reduce by another ½ for one month, then stop.
- Then reduce prednisolone by 1mg/month

Patients on azathioprine/MMF/MPS/sirolimus and prednisolone
- Reduce azathioprine/MMF preparation/sirolimus by ½ for one month, then reduce by another ½ for one month, then stop.
- Then reduce prednisolone by 1mg/month

Patients on CNI and prednisolone
- As per triple therapy
The following step wise approach is recommended:

1. Confirm that new onset diarrhoea

2. Send stool for culture and Clostridium Difficile testing, and blood for CMV PCR

3. Reduce dose of the MMF, but this needs to be considered in context of overall immunosuppression

4. If patient on MMF, switch to corresponding dose of Mycophenolate sodium

5. If diarrhoea resolved aim to increase MPS dose if appropriate in context of overall immunosuppression

6. If diarrhoea not resolved aim to switch to Azathioprine after checking Thiopurine methyltransferase (TPMT) level if not already done.

7. Consider colonoscopy and/or referral to gastroenterology if no improvement or at any stage if symptoms and signs dictate
Introduction
Rabbit-ATG is a rabbit polyclonal antibody used for the prophylaxis of rejection as induction therapy and for the treatment of post-transplant steroid resistant rejection. It is irritant to peripheral veins and must be given via a central line (or occasionally through a fistula) as it causes thrombophlebitis. Irradiated blood products should be given if required during, or at any time after, Rabbit-ATG treatment because of the risk of transfusion associated GVHD – see trust guidelines Provision of Irradiated and Cytomegalovirus Negative Blood Components Procedure. Patients should be given a card and the NHSBT information leaflet explaining this – see http://hospital.blood.co.uk/media/3067/22595c0e-a77a-412e-b65d-be787a3ac939.pdf

Contra-indications
Use of Rabbit-ATG is contraindicated in patients with a history of allergy or anaphylaxis to rabbit proteins, or those who have acute infective (bacterial, viral or fungal) illness.

Preparation
- Obtain central venous access (ideally via internal jugular route). Rabbit-ATG can occasionally be given via a fistula, however subsequent thrombophlebitis may compromise the fistula and this route should only be used after discussion at Consultant level.
- If being given as induction therapy at the time of transplant, the test dose is given by a peripheral cannula after a negative crossmatch has been obtained. The full dose will be given through the central venous access gained in theatre.

Administer Test Dose
1. Prior to giving the test dose a baseline EDTA sample should be taken and sent to Immunology with the first post full dose sample (see monitoring below).
2. One ml of Rabbit-ATG (5mg) is mixed with 100ml 0.9% normal saline and given over 60 minutes via the peripheral or central line.
   - The purpose of the test dose is to see if the patient develops anaphylaxis. The signs of anaphylaxis are tingling in the extremities and around the mouth, swelling of the lips and larynx, bronchospasm, urgency of defaecation and hypotension.
   - Vital signs (TPR and BP) should be monitored every 15 minutes during the test dose infusion.
   - A doctor should be present throughout the administration of the test dose and any reaction should be treated with oxygen, 100mg hydrocortisone IV, 10mg chlorpheniramine IV and adrenaline given intramuscularly in a dose of 0.5-1mg (0.5-1ml adrenaline injection 1:1000). A severe reaction or anaphylaxis to the test dose is a contraindication to the therapeutic course.

Administering Full Dose Rabbit-ATG
1. Prescribe
   - 100mg IV hydrocortisone, 10mg IV chlorpheniramine and 1g oral paracetamol to be given 60 minutes prior to each dose, but not before the test dose as it may mask any anaphylactic reaction.
   - Cotrimoxazole 480mg bd for the duration of the course and three months after.
   - Nystatin suspension (1ml qds) for duration of the course.
   - Oral valganciclovir for 3 months (unless both recipient and donor CMV negative D-/R-).
Adjust dose of valganciclovir depending on renal function (see CMV protocol) and FBC (see below).

2. The initial main infusion should be 2mg/kg dissolved in 250-500ml of 0.9% normal saline (maximum concentration 1mg/2mls) infused via a central line over 8-12 hours (minimum 6 hours) and should be administered using an infusion pump with a 0.22 micron in-line filter.

3. Measure and record vital signs (TPR and BP) immediately prior to initiating infusion, every 15 minutes for the first hour, every 30 minutes for next hour and then hourly until the infusion is complete.

4. A course usually lasts 10-14 days. It is usually advisable to give the first few doses over 12 hours; subsequent doses can be given over 8 hours.

**Monitoring Rabbit-ATG Therapy**

1. Absolute CD3 counts are used to monitor Rabbit-ATG therapy.

2. The Immunology laboratory at QMC provides the monitoring service. They need to be informed as soon as a patient is started on Rabbit-ATG. Please telephone the immunology laboratory (during normal working hours) on 64957.

3. **During the course an EDTA sample should be taken between 8-9am, everyday Monday-Friday and dispatched immediately via a taxi to the Immunology Laboratory at QMC for measurement of the absolute CD3 count.**

4. **Pharmacy also needs to be informed as early as possible if Rabbit-ATG will be required for that day, but that will depend on when the CD3 count is available.**

**Modification of Immunosuppression**

- Continue 20mg prednisolone daily
- Stop azathioprine, mycophenolate mofetil and sirolimus for the duration of the Rabbit-ATG course. Restart only when total WCC > 4.0 x10⁹/l.
- Discuss reduction of ciclosporin or tacrolimus dose with transplant surgeon.

**Modification of Rabbit-ATG dose**

The best indicator of optimal immunosuppression is the maintenance of the absolute CD3 count below 0.05 x10⁹/l. Subsequent dose of Rabbit-ATG should be modified according to the following criteria:

**Omit Rabbit-ATG if any one of the following criteria is met:**

- Absolute number of CD3 positive cells is < 0.050 x 10⁹/L
- **OR** Platelet count ≤ 50 x10⁹/L
- **OR** Total WBC ≤ 4.0 x10⁹/L

**Give half dose Rabbit-ATG (1mg/kg) if any one of the following criteria is met:**

- Absolute number of CD3 positive cells is between 0.051-0.079 x10⁹/L
- **OR** Platelet count between 51-75 x10⁹/L
- **OR** Total WBC is between 4.1-5.0 x10⁹/L

**Otherwise give full dose.**

If CD3 monitoring is not available e.g. at the weekend, then the aim is to maintain the total lymphocyte count below 3% of the total white blood cell count.

**NB** Rabbit-ATG (Thymoglobuline) can be given as a repeated course.
Causes of early graft dysfunction

**Arterial thrombosis**
Usually occurs within 48 hours of transplantation and manifested as primary non function or sudden cessation of urine output with rapid rise in creatinine. Diagnosed by isotope scan or Doppler ultrasound. Treatment - transplant nephrectomy (requires 2 units of blood crossmatched). Rarely may be secondary to severe acute rejection.

**Venous thrombosis**
Usually occurs in the first 7 days post transplant. Diagnosis and treatment as above.

**Acute rejection**
Patient may be asymptomatic, have flu-like symptoms or be very unwell. Clinical signs include fever, graft tenderness and swelling, weight gain and oedema, hypertension and fall in urine output. Creatinine will be elevated or "off the line". Gold standard for diagnosis is biopsy. Treatment - outlined below.

**Ciclosporin / Tacrolimus nephrotoxicity**
Manifested by raised levels of ciclosporin / Tacrolimus and may be accompanied by other physical signs such as tremor. Extra trough/C\textsubscript{2} levels should be considered and dose reduced accordingly. If levels rise/fall suddenly check any new drugs prescribed.

**Ureteric obstruction**
Patient is usually asymptomatic, but urine output may fall and creatinine rises. Should be regularly looked for in patients with DGF. Ultrasound is the first line investigation although some pelvicalyceal dilatation is normal in transplanted kidneys. If U/S is positive antegrade pyelography should be arranged followed by percutaneous nephrostomy (PCN). Clotting should be checked for this and prophylactic antibiotics given. Insertion of an indwelling double J stent or less often surgical reconstruction are the treatments. May also be caused by BK virus.

**Urinary leak**
Consider when patient complains of severe peri-graft/lower abdominal pain. There may be associated swelling in the lower abdomen, flank, upper leg and genital regions. Urine output may fall and creatinine may rise. If drain still *in situ* send fluid and urine for comparative U&E's. Ultrasound often not helpful, although usual first line investigation. Diagnosis usually confirmed by antegrade pyelography or by reexploration of graft. Other imaging may be helpful. Small leaks can be managed by PCN, but larger leaks usually require surgical revision. Antibiotic cover is usually required for urinary leaks.
Lymphocele
May be a cause of ureteric obstruction, a swollen leg or localised swelling. Diagnosis made by ultrasound; asymptomatic lymphoceles usually require no treatment. If symptomatic or diagnosis uncertain then arrange for U/S guided percutaneous drain and send fluid for U&Es (to exclude urinoma) and culture. Remove drain when stopped draining. First recurrence should ideally be treated by laparoscopic fenestration.

UTI
Treatment of Symptomatic Infection
- For uncomplicated UTI treat with Coamoxiclav 625mg tds po for 3 days, unless sensitivities suggest otherwise
- If complicated UTI or transplant pyelonephritis (patient requires admission, septicaemia, marked deterioration in renal function) or transplant pyelonephritis treat with oral ciprofloxacin or intravenous cefuroxime.

Prophylaxis of Recurrent Urinary Tract Infection
- Consider prophylaxis after three symptomatic infections depending on time interval.
- Treat third infection as above, and then commence Trimethoprim 100mg nocte for six months depending on recent sensitivities.
- If breakthrough infection occurs patient requires an ultrasound scan of transplant and native kidneys and reconsider type of prophylaxis e.g. cefalexin 250mg at night in the light of urine culture.
- If infection recurs after six months prophylaxis treat with appropriate antibiotic, then long term prophylaxis with Trimethoprim.
- In all cases it is important to remember the possibility of an underlying cause such as a bladder problem or infection in the native kidneys. General advice such as a high fluid intake and regular emptying of the bladder is also important.
- If recurrent infections persist consider referral to urologist.

Transplant pyelonephritis
CSU/MSU may be positive or negative, suspect if urine cloudy. If acute pyelonephritis is suspected use oral ciprofloxacin or intravenous cefuroxime. There may be few symptoms or signs; often it is only recognised on biopsy.

Graft transmitted disease e.g. CMV
Rare.

Recurrent disease
Diagnosed by biopsy. Treatment may be possible.

Progress/fate of kidney pair may be informative
The following recommendations are taken from the BTS/BSHI *Guidelines for the detection and characterisation of clinically relevant antibodies in solid organ transplantation*, which are available at [www.bts.org.uk](http://www.bts.org.uk)

For HLA antibody screening, 7-10ml of blood in a clotted tube is required and this should be sent fresh to the H&I laboratory at NBS, Longley Lane, Sheffield.

**Pre-transplant**

Patient serum samples must be taken at 14 days and 28 days following transfusion of any blood products and no less than three monthly for routine antibody monitoring.

**Post- transplant**

Serum samples should be taken at the following times post-transplant:
- 14 days
- 1 month
- 12 months
- and annually thereafter.

Additional samples should be obtained at times of graft dysfunction due to rejection; significant unexplained increase in proteinuria; and at 14 days and 28 days following transfusion of any blood products.

In patients being treated for acute antibody mediated rejection measure DSA on a weekly basis until treatment completed; and at 14 days and 28 days. No further DSA measurements required unless change in clinical picture.

In patients where DSA identified out with the context of rejection then repeat in one month; and if no change in clinical situation or in treatment (e.g. change in immunosuppression or biopsy findings) then no further testing required.
These guidelines are subdivided into six parts

**Part 1 – Introduction**
Definitions used
Serological tests required pre- and post-transplantation.

**Part 2 – CMV Protocol A**
Covers patients whose:
- CMV serostatus at the time of transplantation is D+/R-.
- CMV serostatus at the time of transplantation is D+/R+ or D-/R+ AND the patient receives antilymphocyte preparations.

**Part 3 – CMV Protocol B**
Covers patients whose:
- CMV serostatus at the time of transplantation is D-/R+.
- CMV serostatus at the time of transplantation is D+/R+
NB if a D+/R+ or D-/R+ patient receives antilymphocyte preparations they should transfer to protocol A.

**Part 4 – CMV Protocol C**
Covers patients whose:
- CMV serostatus at the time of transplantation is D-/R-.

**Part 5 – Antiviral drugs used for CMV**
- Valganciclovir
- Ganciclovir
- Foscarnet

**Part 6 – Evidence base**
**Part 1 – Introduction**

**Definitions**
- **CMV infection** is defined as the detection of CMV. This will usually be by PCR of an EDTA blood sample.
- **CMV disease** is defined as infection plus CMV syndrome and/or CMV tissue invasive disease manifest by clinical signs and symptoms as given below.
- **CMV syndrome** comprises fever, leucopenia, thrombocytopenia and malaise.
- **CMV tissue invasive disease** is defined by the presence of organ-specific symptoms or signs, plus (ideally) the detection of CMV in biopsies and bronchoalveolar lavage fluid, or the fundoscopic changes of chorioretinitis.
- **Clinical Failure:** failure to improve clinically after 14 days treatment with antiviral drugs.
- **Drug failure:** no reduction in viral load after 14 days treatment with antiviral drugs.

**Serological tests pre-transplantation**
- CMV IgG and IgM should be repeated immediately prior to transplantation in patients who were IgG negative when last tested.

**Serological tests post-transplantation**
- Serological testing for CMV should not be used for the assessment of CMV infection and disease post-transplantation.
- It may be useful to test patients who were CMV negative at the time of transplantation at 6 and 12 months post-transplantation, to determine if there has been asymptomatic seroconversion.
Part 2 - CMV Protocol A

These guidelines apply to the following patients:
- CMV serostatus at the time of transplantation is D+/R-.
- CMV serostatus at the time of transplantation is D+/R+ or D-/R+ AND the patient receives antilymphocyte preparations.

Valganciclovir prophylaxis

- These groups of patients should receive anti-CMV prophylaxis with valganciclovir.
- The dose is based on renal function and this is detailed in part 5.
- At each clinic attendance the valganciclovir dosage should be reviewed in light of the current renal function.

NB If the transplanted kidney is functioning poorly and the patient is on dialysis valganciclovir should not be used. Either use iv ganciclovir (see Part 5) or follow Part 3 – CMV protocol B.

Screening for CMV after prophylaxis

- Following their 3 month course of valganciclovir these patients will be monitored for CMV infection.
- An EDTA blood requesting CMV viral load should be sent every 2 weeks.

Screening for CMV in symptomatic patients

- CMV can occur at any time post transplantation so an EDTA blood sample requesting CMV viral load should be sent if a patient has symptoms that could be attributable to CMV, (even if the patient is on valganciclovir prophylaxis). This includes patients with unexplained fever, neutropaenia, thrombocytopenia, elevated liver enzymes, GI symptoms including oesophagitis or colitis and respiratory symptoms, particularly if there is pneumonitis.
- Consider testing in patients with acute rejection or with bacterial and other opportunistic infections as these could be due to the indirect effects of CMV.
- Other samples such as BAL and tissue biopsies can also be sent for CMV PCR in addition to the EDTA blood sample.
- Other tests: also consider sending nose and throat swabs in viral transport media for diagnosis of viral respiratory infections infections by immunofluoresence and culture and, particularly if weight loss has occurred, consider sending an EDTA blood for EBV PCR.

When to treat CMV

- Treatment should be instituted in any patient with a CMV viral load $\geq 3 \times 10^3$ copies/ml.
- If a patient has a detectable CMV viral load but $< 3 \times 10^3$ copies/ml then the test should be repeated to determine what the viral load is doing. Depending on the result of the 2nd test and the clinical condition of the patient the consultant may decide to treat or to continue to monitor the patient.
Treating CMV

- See Part 5 for full details of antiviral drugs and dosages.
- Valganciclovir given orally is suitable for most patients but dosage should be modified if there is renal impairment.
- Ganciclovir given intravenously should be used in patients on renal dialysis and in patients who are unable to take oral drugs or in whom absorption from the GIT may be impaired. The dosage should be modified if there is renal impairment.
- Foscarnet given intravenously is an alternative in patients where there is evidence of drug failure or where valganciclovir or ganciclovir cannot be tolerated. Dosage should be modified if there is renal impairment and it is significantly nephrotoxic.
- FBC and U&Es should be closely monitored in all patients on these antiviral drugs, and dose adjustment or interruption may be required.
- If there is evidence of drug failure (defined as no reduction in viral load after 14 days treatment) with both oral valganciclovir and iv ganciclovir, consider changing to iv foscarnet.
- If there is clinical failure (defined as failure to improve clinically after 14 days treatment) but no evidence of drug failure then other causes for the patient’s signs and symptoms should be sought.

Treatment duration and monitoring

- Pre-emptive therapy in asymptomatic individuals:
  - Take a repeat EDTA blood sample for CMV viral load and then commence treatment. If CMV is not detected in this repeat sample then treatment can be stopped immediately.
  - If the repeat sample is also positive for CMV then the patient should be treated until CMV is undetectable by Q-PCR in two consecutive samples.
  - To minimise treatment duration in this group, EDTA blood samples for Q-PCR can be sent twice a week.
  - After treatment for CMV patients should be monitored every 2 weeks for 3 months.

- Treatment of CMV syndrome and CMV tissue invasive disease:
  - Patients with CMV syndrome or patients who have progressed to CMV end organ disease should be treated until CMV is negative by Q-PCR in two consecutive samples. In addition, the minimum duration of therapy should be 3 weeks.
  - EDTA blood samples for Q-PCR should be sent at least weekly during antiviral therapy.
  - After treatment for CMV patients with CMV syndrome should be monitored twice weekly for the first month then weekly for a further 2 months, by sending an EDTA blood sample for CMV viral load.
  - After treatment for CMV patients who have had tissue invasive disease are at increased risk of relapse. In these patients the options are:
    - Monitoring strategy - CMV viral load measurements twice weekly for the first month then weekly for a further 2 months (as for CMV syndrome), or Consolidation strategy - Give valganciclovir at prophylactic dosage for 3 months.
  - The decision as to which strategy to adopt will be made on an individual patient basis at the weekly transplant meeting.

Review of immunosuppression

- Following a diagnosis of CMV disease the patient’s immunosuppressive regimen should be reviewed.
- Reduction in immunosuppression may be appropriate but this must only be undertaken after consultation with the appropriate consultant.
Part 3 - CMV Protocol B

These guidelines apply to the following patients:

- CMV serostatus at the time of transplantation is D-/R+.
- CMV serostatus at the time of transplantation is D+/R+.

NB if a D+/R+ or D-/R+ patient receives antilymphocyte preparations they should transfer to Part 2 – CMV protocol A.

Screening for CMV in symptomatic patients

- CMV can occur at any time post transplantation so an EDTA blood sample requesting CMV viral load should be sent if a patient has symptoms that could be attributable to CMV. This includes patients with unexplained fever, neutropaenia, thrombocytopenia, elevated liver enzymes, GI symptoms including oesophagitis or colitis and respiratory symptoms, particularly if there is pneumonitis.
- Consider testing in patients with acute rejection or with bacterial and other opportunistic infections as these could be due to the indirect effects of CMV.
- Other samples such as BAL and tissue biopsies can also be sent for CMV PCR in addition to the EDTA blood sample.
- Other tests: also consider sending nose and throat swabs in viral transport media for diagnosis of viral respiratory infections by immunofluorescence and culture and, particularly if weight loss has occurred, consider sending an EDTA blood for EBV PCR.

When to treat CMV

- Treatment should be instituted in any patient with a CMV viral load \( \geq 3 \times 10^3 \) copies/ml.
- If a patient has a detectable CMV viral load but \(< 3 \times 10^3 \) copies/ml then the test should be repeated to determine what the viral load is doing. Depending on the result of the 2nd test and the clinical condition of the patient the consultant may decide to treat or to continue to monitor the patient.

Treating CMV

- See Part 5 for full details of antiviral drugs and dosages.
- Valganciclovir given orally is suitable for most patients but dosage should be modified if there is renal impairment.
- Ganciclovir given intravenously should be used in patients on renal dialysis and in patients who are unable to take oral drugs or in whom absorption from the GIT may be impaired. The dosage should be modified if there is renal impairment.
- Foscarnet given intravenously is an alternative in patients where there is evidence of drug failure or where valganciclovir or ganciclovir cannot be tolerated. Dosage should be modified if there is renal impairment and it is significantly nephrotoxic.
- FBC and U&Es should be closely monitored in all patients on these antiviral drugs, and dose adjustment or interruption may be required.
- If there is evidence of drug failure (defined as no reduction in viral load after 14 days treatment) consider changing to iv foscarnet.
- If there is clinical failure (defined as failure to improve clinically after 14 days treatment) but no evidence of drug failure then other causes for the patient’s signs and symptoms should be sought.
Treatment duration and monitoring

- **Pre-emptive therapy in asymptomatic individuals:**
  - Take a repeat EDTA blood sample for CMV viral load and then commence treatment. If CMV is not detected in this repeat sample then treatment can be stopped immediately.
  - If the repeat sample is also positive for CMV then the patient should be treated until CMV is undetectable by Q-PCR in two consecutive samples.
  - To minimise treatment duration in this group, EDTA blood samples for Q-PCR can be sent twice a week.
  - If CMV was detected during the first 3 months after transplantation then the patient should return to twice weekly monitoring after completion of treatment.
  - If CMV was detected after the early post transplant period then the patient should be monitored every 2 weeks for 3 months, after completion of treatment.

- **Treatment of CMV syndrome and CMV tissue invasive disease:**
  - Patients with CMV syndrome or patients who have progressed to CMV end organ disease should be treated until CMV is negative by Q-PCR in two consecutive samples. In addition, the minimum duration of therapy should be 3 weeks.
  - EDTA blood samples for Q-PCR should be sent at least weekly during antiviral therapy.
  - **After treatment** for CMV patients with **CMV syndrome** should be monitored for recurrence of CMV. If CMV was detected during the **first 3 months after transplantation** then the patient should return to twice weekly monitoring after completion of treatment. If CMV was detected **after the early post transplant period** then the patient should be monitored twice weekly for the first month then weekly for a further 2 months.
  - **After treatment** for CMV patients who have had **tissue invasive disease** are at increased risk of relapse. In these patients the options are:
    - **Monitoring strategy** – monitor as for CMV syndrome (above), or **Consolidation strategy** - Give valganciclovir at prophylactic dosage for 3 months.
  - The decision as to which strategy to adopt will be made on an individual patient basis at the weekly transplant meeting.

Review of immunosuppression

- Following a diagnosis of CMV disease the patient’s immunosuppressive regimen should be reviewed.
- Reduction in immunosuppression may be appropriate but this must only be undertaken after consultation with the appropriate consultant.
Part 4 - CMV Protocol C

These guidelines apply to patients whose CMV serostatus at the time of transplantation is D-/R-.

The risk of CMV in this patient group is very low and for this reason neither prophylaxis nor monitoring and pre-emptive therapy are warranted.

Screening for CMV in symptomatic patients.

- CMV infection and disease may occur in this patient group, either because serological tests on the donor and/or recipient were inaccurate or inaccurately reported (hopefully rare events) or because the patient has acquired CMV from social contacts in the 'normal' way.
- EDTA blood sample requesting CMV viral load should be sent if a patient has symptoms that could be attributable to CMV. This includes patients with unexplained fever, neutropaenia, thrombocytopaenia, elevated liver enzymes, GI symptoms including oesophagitis or colitis and respiratory symptoms, particularly if there is pneumonitis.
- Consider testing in patients with acute rejection or with bacterial and other opportunistic infections as these could be due to the indirect effects of CMV.
- Other samples such as BA and tissue biopsies can also be sent for CMV PCR in addition to the EDTA blood sample.
- Other tests: also consider sending nose and throat swabs in viral transport media for diagnosis of viral respiratory infections infections by immunofluorescence and culture and, particularly if weight loss has occurred, consider sending an EDTA blood for EBV PCR.

If CMV infection or disease is confirmed then treatment and further monitoring should be as per Part 2 - Protocol A.
Part 5 - Antiviral drugs used for CMV

Valganciclovir
This comes as 450 mg tablets. Dosage adjustment is required according to creatinine clearance. Serum creatinine or creatinine clearance levels and full blood count should be monitored carefully. Therapy should not be initiated if the absolute neutrophil count is < 500 cells/μl or the platelet count is < 25000/μl or the haemoglobin is < 8 g/Dl. Valganciclovir levels for resistance testing should be checked by sending blood immediately pre dose then 3hrs post dose in a yellow topped bottle.

<table>
<thead>
<tr>
<th>Cr Cl (mL/min)</th>
<th>Treatment dose</th>
<th>Prophylactic dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60</td>
<td>900 mg bid</td>
<td>900 mg od</td>
</tr>
<tr>
<td>40-59</td>
<td>450 mg bid</td>
<td>450 mg od</td>
</tr>
<tr>
<td>25-39</td>
<td>450 mg od</td>
<td>450 mg every 2 days</td>
</tr>
<tr>
<td>10-24</td>
<td>450 mg every 2 days</td>
<td>450 mg twice weekly</td>
</tr>
<tr>
<td>Patient on haemodialysis</td>
<td>Do not use</td>
<td>Do not use</td>
</tr>
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</table>

Ganciclovir
Ganciclovir should be treated as a cytotoxic and therefore will always be made up by pharmacy. It is given as an infusion over one hour. Dosage adjustment is required according to creatinine clearance. Serum creatinine or creatinine clearance levels and full blood count should be monitored carefully. Therapy should not be initiated if the absolute neutrophil count is < 500 cells/μl or the platelet count is < 25000/μl.

<table>
<thead>
<tr>
<th>Cr Cl (mL/min)</th>
<th>Treatment dose</th>
<th>Prophylactic dose</th>
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</thead>
<tbody>
<tr>
<td>≥ 70</td>
<td>5 mg/kg q 12h</td>
<td>5 mg/kg/day</td>
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<tr>
<td>50-69</td>
<td>2.5 mg/kg q 12h</td>
<td>2.5 mg/kg/day</td>
</tr>
<tr>
<td>25-49</td>
<td>2.5 mg/kg/day</td>
<td>1.25 mg/kg/day</td>
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<tr>
<td>10-24</td>
<td>1.25 mg/kg/day</td>
<td>0.625 mg/kg/day</td>
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<tr>
<td>&lt;10 (Patient on haemodialysis)</td>
<td>1.25 mg/kg 24 hourly, but given after dialysis on dialysis days</td>
<td>0.625 mg/kg 24 hourly, but given after dialysis on dialysis days</td>
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Foscarnet
This comes as a clear, colourless liquid containing 24 mg/mL foscarnet salt. It should be given as an infusion over one hour. If given by a peripheral vein it should be diluted in equal parts with either 5% dextrose or sodium chloride 0.9%. Ensure adequate hydration. Dosage adjustment is required according to creatinine clearance and changes may be required during the course of treatment. Serum creatinine, creatinine clearance levels, full blood count, calcium and magnesium should be monitored carefully. It is significantly nephrotoxic. Although it is licensed to be used 8 hourly, haematology gives it 12 hourly by splitting the total daily dose into 2 divided doses rather than 3. In addition there is an option to give an induction dose for the first week or so depending on response and then switch to a maintenance dose.

<table>
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<tr>
<th>Cr Cl (mL/min/kg)</th>
<th>Treatment dose</th>
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<td>&gt; 1.6</td>
<td>60 mg/kg every 8 hours</td>
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<tr>
<td>1.6-1.4</td>
<td>55 mg/kg every 8 hours</td>
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<tr>
<td>1.4-1.2</td>
<td>49 mg/kg every 8 hours</td>
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<tr>
<td>1.2-1.0</td>
<td>42 mg/kg every 8 hours</td>
</tr>
<tr>
<td>1.0-0.8</td>
<td>35 mg/kg every 8 hours</td>
</tr>
<tr>
<td>0.8-0.6</td>
<td>28 mg/kg every 8 hours</td>
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<tr>
<td>0.6-0.4</td>
<td>21 mg/kg every 8 hours</td>
</tr>
<tr>
<td>&lt; 0.4</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>
Part 6 – Evidence base


Razonable RR, Emery VC. Management of CMV infection and disease in transplant patients. Herpes. 200411:77-86.


European Best Practice Guidelines for Renal Transplantation. Section iii: the transplant recipient from initial transplant hospitalization to 1 year post-transpl. Nephrol Dial Transplant. 2000 15; S 7 52-85

Indications

- Delayed graft function
- Acute allograft dysfunction
- To monitor treatment of rejection (e.g. following ATG)
- Slow progressive deterioration in allograft function
- Worsening proteinuria
- Possible recurrence of primary renal disease
- Protocol biopsy

Contra-indications

- Uncontrolled hypertension (BP >160/90)
- Abnormal clotting – platelets <100,000, APTT ratio > 1.2, INR > 1.2
- Severe anaemia (Hb < 8 g/dl)
- Significant hydronephrosis (mild dilatation of the pelvicalyceal system is common in renal allografts)
- Active renal infection

Always bear in mind the clinical circumstances e.g. in a patient with slowly deteriorating graft function and a haemoglobin of 8.5g/dl the biopsy would probably be best delayed until the anaemia is corrected, in a patient with acutely deteriorating graft function it may well be appropriate to proceed with the biopsy.

Arrangements for biopsy

Patients will usually be admitted to Bramley or Carrel Ward. The indications for a biopsy must have been approved of by a Consultant prior to admission or during the admission. Transplant biopsies are carried out in the treatment room on Bramley Ward. Under certain circumstances (e.g. failure to obtain renal tissue, overweight patients, collections around the transplant) biopsies will be carried out by one of the interventional radiology Consultants under real-time ultrasound guidance in the X-ray department. Elective transplant biopsies are usually carried out as day cases.

Procedure prior to admission

1. Formal ultrasound should have been performed beforehand to detect perinephric fluid collections and to ensure that there is no significant hydronephrosis. In newly transplanted patients particularly those with delayed graft function, a Doppler study should also be requested to exclude renal vein thrombosis.
2. If the patient is seen in Outpatients the indication for a biopsy is noted, urinalysis (and urine protein:creatinine ratio if dipstick proteinuria) and renal function are requested in addition to any other tests relevant to the case.
3. Treat urinary tract infections adequately before biopsy.
4. The need for biopsy is explained to the patient and the benefits and risks of the procedure made clear. For elective biopsies patients should be provided with written information about the biopsy procedure (Patient information leaflets are available.)
5. For elective biopsies, anti-platelet agents (aspirin and clopidogrel) should be stopped 7 days before the biopsy. NSAIDs should be stopped 24 hours before procedure. Warfarin should ideally be stopped 7 days before the procedure and the patient converted to heparin if clinically indicated. Heparin (including prophylactic and LMW) should be stopped at least 24 hours pre-procedure. Anti-coagulation should ideally not be restarted until 24 hours post-biopsy.

On admission

1. Out-patients will be seen in transplant clinic on the day of the procedure by one of the transplant nurses.
2. Check FBC, INR, APTT and APTT ratio either the day before or on the morning of the biopsy. Ensure the patient is group and saved.
3. Ensure that BP is < 160/90. If above this discuss with medical staff.
4. Check patient has read the information leaflet and understands this.
5. Get the results of the FBC, Platelets and clotting. If results are abnormal discuss with one of the SpRs or Consultants.
6. If creatinine is >300 \( \mu \text{mol/l} \) consider use of desmopressin (20 micrograms in 50 mls 0.9% sodium chloride given over 30 minutes pre-procedure). This is contra-indicated in patients with known ischaemic heart disease.
7. Complete the biopsy proforma and signed off by the Renal doctor. Specifically ask about bleeding disorders, anti-platelet and anticoagulant therapy.
8. The Renal SpR should ensure that the histology technicians know there will be a biopsy (including biopsies carried out in radiology)
9. If an infection risk e.g. blood borne virus positive or possible renal tuberculosis, the renal SpR must inform histology so that the biopsy can be handled and processed correctly.
10. Urgent biopsies (where the result is needed the same day) some ideally be carried out before mid-day.

Consent

Written informed consent should be obtained for all renal transplant biopsies. The appropriate consent form should be used (usually Form 3, but Form 1 should be used if sedation is being considered). Consent should be obtained by the SpR / Consultant. The following information should be conveyed: -

- The transplant kidney is localised using ultrasound and the procedure is performed under local anaesthetic.
- If the biopsy causes a lot of bleeding from the kidney transplant, a blood transfusion may be necessary or very occasionally an operation to stop the bleeding which could involve having the kidney transplant removed.
- In less than 5 out of a hundred biopsies there is visible bleeding in the urine that stops by itself.
- In less than 3 out of a thousand biopsies there is more severe bleeding that requires a blood transfusion.
- In less than 1 in a thousand biopsies an operation is needed to stop the bleeding and this may mean removing the kidney.
- Although deaths have occurred following complications of biopsies this is extremely rare.

Reiterate the indications for the biopsy prior to obtaining consent.
Complications

1. Serious bleeding is usually apparent clinically within a few hours. Severe pain is often an early sign of serious bleeding.
2. A repeat ultrasound is usually able to distinguish a peri-renal haematoma from intra-renal or subcapsular bleed.
3. A dilated collecting system and/or echogenic material in the bladder indicates serious bleeding into the collecting system.
4. For continued bleeding inform the transplant surgeons at an early stage, exploration and transplant nephrectomy may be necessary.
5. Long-term complications include arterio-venous fistulae.

Biopsy

After ultrasound localisation or under real-time ultrasound control the upper or lower pole of the transplant kidney is usually biopsied with a 16 gauge spring-loaded needle. The pathology technician is present to view the sample under a dissecting microscope to make sure that adequate numbers of glomeruli are obtained. Early transplant kidney (<3 months following transplant) biopsies are just sent for light microscopy only, unless recurrence of original disease is considered. Transplant biopsies older than 3 months are sent for light microscopy, immunofluorescence and electron microscopy.

Post biopsy

Patients who have had transplant biopsies should remain supine for 2 hours post biopsy and continue bed rest for the following 4 hours. The nursing staff check BP and pulse quarterly for 2 hours, then hourly for 2 hours and then hourly for 2 hours. Urine samples should be kept from each voiding and kept at the patient’s bedside to check for macroscopic haematuria and if present to assess if this is clearing.

Simple analgesics may be required. If the patient develops severe pain / macroscopic haematuria or falling BP/ rising pulse rate they should be seen urgently by senior member of the team (SpR or above). Nurse in charge should contact the SpR / Consultant directly if he/ she has any concerns.

Providing the observations are stable and no macroscopic haematuria patients are discharged home 6 hours after the biopsy. Ideally the person who has carried out the biopsy should review the patient at some stage prior to discharge.

Prior to discharge ensure that the patient has contact details for the ward and transplant clinic and is aware that they should contact clinic / the ward if they have any concerns. Ensure that appropriate follow-up in clinic has been arranged (the timing of this will depend on the circumstances).

Indications for admission overnight post-biopsy include:
- Macroscopic haematuria
- Severe pain
- Uncontrolled hypertension

If patients are admitted then the Renal SpR / Consultant should be informed.
1. **Introduction.** Kidney transplantation reduces cardiovascular risk by restoring renal function. However, new cardiovascular risk is introduced via hypertension, dyslipidaemia, impaired glucose tolerance and NODAT. This new risk is in part due to immunosuppressive medication such as calcineurin inhibitors [CNI], corticosteroids and mammalian target of rapamycin inhibitors1. Death with a functioning graft is a common outcome for kidney transplant recipients. Cardiovascular disease is a common cause of death in this group, exceeded only by death due to malignancy and infection.

2. **Hypertension** is a common problem in renal transplant recipients, affecting approximately 70% of patients. Both graft survival and patient survival are adversely influenced by poor blood pressure control.

**Recommendations:** [Appendix 1. Flow chart]

a] Blood pressure should be checked and recorded at each clinic visit

b] If clinic BP > 130/80 mmHg then confirm diagnosis with 24 hour BP monitor [ABPM] or home BP monitoring [HBPM].
Note that 24-hour ambulatory blood pressure recordings correlate with target organ damage, cardiovascular risk and treatment effect, better than clinic blood pressure readings.

c] If mean ABPM or HBPM > 125/75 mmHg then start anti-hypertensive therapy [including lifestyle modification].

d] Choice of anti-hypertensive agent should follow the BHS/NICE guidelines2 [http://guidance.nice.org.uk/CG127].

e] Inhibitors of the renin-angiotensin system maybe more effective at reducing proteinuria and should be considered first line therapy in this patient group. However, these agents should be used with caution in the first 3 months post transplant and in those patients with suspected transplant renal artery stenosis.

f] BP monitoring: Target clinic BP < 130/80. If ‘white coat’ effect has been established then ABPM or HBPM is recommended [target BP < 125/75].
A lower clinic BP target of 125/75 is recommended for patients with significant proteinuria [PCR> 50 mg/mmol or ACR> 35 mg/mmol]3

g] Resistant hypertension [particularly, in combination with graft dysfunction and oedema] may be due to transplant renal artery stenosis and should be investigated according to local practice.
3. **Dyslipidaemia** is common post kidney transplantation. Studies have not shown any added benefit of statin therapy in this patient group.

**Recommendations:**

a] Fasting lipids should be measured annually

b] Kidney transplant recipients with increased primary or secondary cardiovascular risk should receive statin therapy in accordance with NICE guidelines for the general population4. [www.nice.org.uk/nicemedia/pdf/CG67NICEguideline.pdf]

c] The choice of statin therapy and dose should take into account renal function and concurrent immunosuppressive therapy. In particular, simvastatin [Maximum dose 20 mg] should be used with caution in patients with eGFR< 30 ml/min and/or patients taking Tacrolimus or Calcium Channel Blockers. Simvastatin should be avoided in patients taking Cyclosporine.

4. **Anti-platelet therapy** is an important component of therapy for primary and secondary prevention of cardiovascular disease. There is no specific evidence relating to their use in this patient group.

**Recommendations:**

a] Kidney transplant recipients with increased primary or secondary cardiovascular risk should receive anti-platelet therapy in accordance with NICE guidelines for the general population.

5. **NODAT** is a serious and common post transplant complication. The incidence of NODAT in kidney transplant recipients has been reported to be 4% - 25%. NODAT increases the risk of fatal and non-fatal cardiovascular events and reduces both graft and patient survival. Risk factors for the development of NODAT include, age>40 years, Male, African American ethnicity, obesity, FH of DM, calcineurin inhibitors, mTOR inhibitors and corticosteroids5.

**Recommendations:** [Appendix 2. Flow chart]

a) Risk factors for NODAT should be documented and high-risk patients identified. Pre-transplant baseline evaluation should include a complete medical and family history, including documentation of glucose history. Fasting Plasma Glucose [FPG] or IFCC should be tested at regular intervals and a 2-hour oral glucose tolerance test (OGTT) be performed in those with normal FPG or IFCC6.

b) Post transplant screening for NODAT should include weekly FPG or IFCC for the first month, then at 3, 6 and 12 months, then annually. Consider OGTT when normal FPG in high-risk patients or IFG5.

c) Patients who develop NODAT should be managed according to NICE guidelines for diabetes mellitus [www.nice.org.uk/CG66]. Modification of immunosuppressive regime should be considered to improve glucose control. This may include:

- Steroid reduction or withdrawal
- Minimisation, withdrawal or substitution of CNI
- Switching from tacrolimus to cyclosporin
- Avoidance of tacrolimus/sirolimus combination.
6. **Lifestyle modification** is an essential component of reducing cardiovascular risk in this patient group. This should include, smoking cessation, balanced diet, exercise, weight reduction [if BMI>30] and moderation of alcohol consumption.

**Suggested audit measures [annual]**

1] % Kidney transplant patients with clinic BP < 130/80
   [< 125/75 if 24 hour BP or Home BP]
2] % Kidney transplant patients treated with statin therapy according to NICE guidelines
3] % Kidney transplant patients with NODAT
4] % Kidney transplant patients that smoke
5] % Kidney transplant patients with BMI > 30

**References:**

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3] Post-operative Care of the Kidney Transplant Recipient.
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   Renal Association Guidelines.
   February 2011

   Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease.
   March 2011

5] New onset diabetes after transplantation [NODAT]: an overview
   Phuong-Thu T Pham, Phuong-Mai T Pham, Son V Pham, Phuong-Anh T Pham and Phuong-Chi T Pham
   *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy* 2011:4 175-186

**POST KIDNEY TRANSPLANT HYPERTENSION GUIDELINES FLOWCHART [Appendix 1.]**

- **Clinic BP** <130/80
  - **YES**
    - No action
  - **NO**
    - ABPM or HBPM

- **Mean BP** < 125/75
  - **YES**
    - No action
  - **NO**
    - Start BP medication

- **PCR>50 or ACR >**
  - **YES**
    - **ACEI or ARB [A]**
      - Avoid first 3 months post transplant
      - Avoid if transplant renal artery stenosis suspected
  - **NO**
    - Patient black or > 55 years
      - **YES**
        - CCB [C]
      - **NO**
        - **ACEI or ARB [A]**

- **BP>130/80**
  - **A+C**
  - **A+C+D [Diuretic]**

---

**Transplant renal artery stenosis**

Consider if:
1. Resistant hypertension and/or
2. Transplant dysfunction and/or
3. Peripheral Oedema

---

**Resistant hypertension**

A + C + D + consider further diuretic or alpha blocker or beta blocker
NODAT FLOW CHART [Appendix 2]

Pre – transplant

Risk Stratification

Low Risk

High risk

Standard Immunosuppression Regime


Post - transplant

Further Risk factors

Obesity [post TX]

CNI

Steroids

Sirolimus

Post – Transplant Screening [FPG or IFCC]

Weekly for 1st month, 3, 6 and 12 months then annually

FPG normal [< 6 mmol/l]

IFCC [< 42 mmol/mol]

High risk

OGTT [2 hours]

< 7.8 = normal

7.9-11 = IFG

> 11 = Diabetes

Low risk

Continue screening

FPG = IFG [6-7 mmol/l]

IFCC [42-53 mmol/mol]

Lifestyle modification

Review medication

FPG = Diabetes [> 7 mmol/l]

IFCC [> 53 mmol/mol]

Lifestyle modification

Review medication

Refer to secondary care
Osteoporosis following renal transplantation

Introduction

Renal transplantation, in common with other organ transplants, can lead to osteoporosis. Patients receiving a renal transplant are unique in that the majority have pre-existing bone disease (renal osteodystrophy). Based on bone histomorphometry renal osteodystrophy can be separated into 2 forms: high turnover disease, caused by persistent hyperparathyroidism; or low bone turnover, as in adynamic bone disease or less often osteomalacia. Secondary hyperparathyroidism remains the most common bony abnormality in the pre-dialysis and dialysis population. However adynamic bone disease is an increasingly recognised abnormality, particularly in diabetics and may be associated with an increased risk of fracture.

A functioning renal transplant corrects many of the abnormalities of calcium and phosphate metabolism that lead to renal osteodystrophy. However significant skeletal complications can develop in patients with functioning grafts. The reasons for this are multifactorial. Corticosteroids play a major role and the degree of bone loss relates to cumulative steroid dose. Persistent hyperparathyroidism and renal dysfunction also predispose to bone loss. Additional factors include hypogonadism, poor nutrition, immunosuppressive medication such as ciclosporin and tacrolimus and the menopausal state.

Around 3-7% of lumbar spine bone mass may be lost following renal transplantation. This is far greater than the bone loss seen in post-menopausal females (1-2%). Bone loss is rapid within the first year, following which rates of bone loss appear to slow or partially reverse. There is some variation in the reported rates of bone loss. This may reflect both differences in the type and severity of renal osteodystrophy present prior to transplantation, as well as differences in treatment following transplantation. Bone loss may predispose to fractures. Fracture prevalence rates of between 11-19% have been reported in non-diabetic renal transplant recipients, with rates of 45% in insulin dependent diabetics.

Guidelines now exist both at a local and national level regarding the prevention and management of corticosteroid induced osteoporosis. The complex nature of post renal transplant bone disease makes it difficult to apply these guidelines directly to renal patients. However it is clear that our patients are at risk of developing long-term skeletal complications following transplantation and we should have a policy for their management. We have attempted to define the current best clinical practice for these patients. This is based on the available evidence particularly from studies in corticosteroid-induced osteoporosis. The evidence base relating to renal patients is increasing but remains fairly weak.

Osteoporosis – Definition

Currently based on WHO bone mineral density criteria: -

<table>
<thead>
<tr>
<th>Bone Density</th>
<th>T Score Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal BMD</td>
<td>T score better than −1.0</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>T score between −1.0 and −2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>T score less than −2.5</td>
</tr>
</tbody>
</table>
Management of Newly Transplanted Patients

Rationale

- Assess bone mineral density in the immediate post-transplant period to identify high-risk patients and those with established osteoporosis.
- All patients to receive general lifestyle advice.
- At 3 months post-transplant, start treatment for patients who have evidence of hypogonadism, vitamin D deficiency or persistent hyperparathyroidism.
- Repeat BMD at 12 months. This will identify patients who have lost the most bone density, or who have failed to respond to therapy or both and may be helpful in determining whether a particular patient should be investigated in more detail with a view to additional therapy.
- If BMD t-score is equal to or less than -2 at the time of transplant or at subsequent evaluations, therapy with bisphosphonates should be commenced unless contra-indications are present.

Investigations

**a) Biochemistry**

<table>
<thead>
<tr>
<th>Timing</th>
<th>Routine</th>
<th>Bone specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>At transplantation</td>
<td>Ca, Phos, Alk phos</td>
<td>iPTH</td>
</tr>
<tr>
<td>3 months post-transplant</td>
<td>Ca, Phos, Alk phos</td>
<td>iPTH, 25 (OH) Vit D, Serum CTX&lt;sup&gt;1&lt;/sup&gt;, Male: Testosterone, LH, SHBG&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>6 months post-transplant</td>
<td>Ca, Phos, Alk phos</td>
<td>iPTH</td>
</tr>
<tr>
<td>12 months post-transplant</td>
<td>Ca, Phos, Alk phos</td>
<td>iPTH, Serum CTX&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup>Overnight fasting sample

**b) DXA Monitoring**

Bone mineral density at the lumbar spine, hip and whole body and lumbar spine morphometric x-ray absorptiometry (HISS request BD.AL, BD.FL, BD.WB, MXA) should be measured within the first week following transplantation and 1 year post-transplant. After the first year the requirement for & frequency of DXA monitoring will depend on the clinical picture.

**Patient Education, Life Style Advice and General Management**

Information about the risk of corticosteroid-induced osteoporosis should be given as part of the pre-transplant assessment process. It should be repeated in the information given predischarge following a successful transplant.

Life style factors known to adversely affect bone can be modified.

- Stop smoking.
- Avoid excessive alcohol intake.
- Encourage weight bearing physical activity (e.g. walking). Avoid immobility.
- Avoid falls (e.g. check home for loose carpets etc. - particularly relevant to elderly patients).
- Ensure adequate calcium and vitamin D intake.
- An elemental calcium intake of 1000-1500mg and vitamin D intake of 400 IU are recommended. This can be obtained with appropriate dietetic advice e.g. 1 pint per day of skimmed milk provides 700-800mg of calcium (¼ pint of milk can be exchanged for a low fat yoghurt). If intake is not sufficient despite dietary advice prescribe Calcichew D3 Forte 1 tablet daily (provides 1.2g calcium carbonate and 400IU vitamin D).
- Minimise Corticosteroid dose. Corticosteroid doses should be kept to the minimum dose possible that is compatible with adequate graft function.
Specific Treatment Options

a) Vitamin D insufficiency
Vitamin D deficiency is an easily correctable risk factor for bone loss. Patients with a 25 (OH) Vit D level <30nmol/l should receive treatment with Calcichew D3 forte 1 tablet bd provided serum calcium is <2.6 mmol/l. If calcium >2.6 mmol/l treat with ergocalciferol 50,000 International Units once a month for 6 months.

b) Hypophosphataemia
Kidney transplant patients who develop persistently low levels of serum phosphate (<0.8 mmol/L) should be treated with phosphate supplementation (prescribe Phosphate Sandoz 1 tablet bd).

c) Hyperparathyroidism
PTH levels decrease markedly soon after transplantation. However numerous studies have demonstrated a long-term persistence of secondary hyperparathyroidism in up to 50% of renal transplant recipients, even in those with normal renal function. Vitamin D insufficiency may contribute to secondary hyperparathyroidism.

- Correct vitamin D insufficiency with parent vitamin D. If PTH remains elevated despite restoration of normal vitamin D levels change Calcichew D3 forte to calcitriol 0.25mcg nocte.
- Normocalcaemic patients with secondary hyperparathyroidism should be treated with calcitriol 0.25 mcg nocte.
- Hypercalcaemic patients with significant secondary hyperparathyroidism should not receive calcitriol. At present the only treatment options are i) continued observation (involution of parathyroid gland hyperplasia takes a long time) or ii) surgical parathyroidectomy (consider if serum Ca persistently >2.8 mmol/l, osteoporosis, evidence of vascular calcification or if patient symptomatic of hypercalcaemia). In the future calcimimetics are likely to play a major role in the management of these patients.

d) Female Hypogonadism
A large proportion of pre-menopausal women on dialysis either have irregular or no menstrual periods. Diagnosis of the menopause in dialysis patients requires the measurement of FSH and oestrogen, because a simple history of cessation of menses is insufficient. Hormone replacement therapy (HRT) effectively prevents bone loss related to oestrogen deficiency. However data from the Womens Health Initiative (WHI) revealed that oestrogen-progesterone therapy did not reduce cardiovascular deaths, and increased the risk of stroke, breast cancer and venous thromboembolic events. This data has led to a change in our recommendations for the use of HRT for the prevention/ treatment of osteoporosis.

- Post Menopausal Females
  HRT is no longer recommended in this group for the prevention or treatment of osteoporosis. The selective oestrogen receptor modulator raloxifene, is licensed for the prevention and treatment of osteoporosis in the non-transplant setting. There is no data on its use in renal transplant recipients. Fracture data is also lacking at the hip.

- Pre Menopausal Females with amenorrhoea (>6 months)
  The above comments relating to the WHI are not applicable to the use of oestrogen in premenopausal hypoestrogenic women. Sex hormones are known to either stimulate or inhibit the cytochrome P450 pathway and may potentially alter ciclosporin or tacrolimus blood levels. Therefore, a continuous, rather than a cyclical HRT regimen is recommended in allograft recipients. Suitable preparations include Premique (625 μg oestrogen +
medroxyprogesterone acetate 5mg) and Kliofem (oestradiol 2mg + norethisterone acetate 1mg). It should be remembered that HRT does not provide contraception and non-hormonal contraception will be needed.

An alternative strategy is the use of a low strength combined oral contraceptive pill. Menstruation often begins within 3-6 months of successful transplantation and oestrogen therapy may often be stopped after 6 months.

- **Risk of venous thromboembolism**

Due to concerns about venous thromboembolism in the immediate post operative period HRT should be started in fully mobile patients 4 weeks following transplantation. The combined OCP should be avoided during the first 3 post-operative months.

d) **Male Hypogonadism**

Hypogonadism is also common in men with end stage renal failure, and is a recognised risk factor for osteoporosis. Following successful transplantation testosterone levels will often normalise after a period of months. Provided there are no contra-indications to testosterone therapy, hypogonadal men (defined as a serum testosterone of <8nmol/l) should be treated with IM sustanon 100mg initially, 200mg four weeks later and then 250mg every four weeks as a maintenance dose (transdermal testosterone preparations are an alternative, but are significantly more expensive). Testosterone treatment may cause prostatic enlargement. In older men this may cause symptoms and limit the use of testosterone. Prostatic specific antigen (PSA) and a lipid profile should be measured prior to therapy and at 6 monthly intervals thereafter. The presence of hypogonadism should be reassessed after 12 months of therapy.

e) **Bisphosphonates**

Bisphosphonates are potent antiresorbing agents that increase bone mineral density in post-menopausal osteoporosis and corticosteroid induced osteoporosis. There is also growing evidence of their efficacy in renal transplant patients, although one particular concern is that they may potentially be harmful in patients with low turnover adynamic bone disease. They should only be used after careful consideration of their potential risks and benefit and the relative paucity of data on their use long-term in transplant recipients. This assessment process may involve additional investigations such as a bone biopsy. Bisphosphonates should not be given to women who may become pregnant. Oral bisphosphonates are contraindicated in patients with a GFR <35mls/min or active upper gastrointestinal disorders.

Alendronate (70mg weekly) and pamidronate are the two most widely studied bisphosphonates in transplant patients. Risedronate (35mg/week) is an alternative oral bisphosphonate. Pamidronate is given as an IV infusion (1mg/kg – max 90mg every 3 months) – its use in post-transplant osteoporosis is unlicensed and should be restricted to those patients who are known to be intolerant of oral bisphosphonates.

Provided they are tolerated and renal function allows, bisphosphonates should be continued for 5 years in patients who remain on corticosteroids. Decisions about continuing treatment after 5 years need to be made individually taking into account the patient’s history, risk factors and the severity of bone loss. Patients should be referred back to the bone clinic where this assessment can take place.

**Management of Established Transplant Patients (>1 year post-transplant)**

A 3 site DXA scan (lumbar spine, hip and whole body) and spinal MXA scan should be carried out in all established transplant recipients who have not been scanned as part of their early post-transplant workup. Management should be based on BMD and is outlined in figure 2. Patients with established osteoporosis should be referred to the bone clinic for further investigation and management.
Renal Bone Disease Clinic
A multi-disciplinary renal bone disease clinic is held on a monthly basis on a Friday afternoon. Although we are willing to see any renal patient with a metabolic bone problem, usual indications for referral include transplant patients with established osteoporosis or a low trauma fracture.

Evidence Base

Contributors: Dr S.D. Roe, Consultant Nephrologist; Dr M.J.D. Cassidy, Consultant Nephrologist; Dr D.J. Hosking, Consultant Physician, Dr I. Pande, Consultant Rheumatologist and Mrs. C.J. Porter, Senior Scientist Renal Unit
Management of newly transplanted patients

At transplant: Ca, P, Alk Phos, PTH
Baseline DXA scan (spine, hip, whole body) and MXA

3 months post transplant: Ca, P, Alk Phos, PTH, 25(OH) vit D, CTX
Male patients: Testosterone, LH, SHBG

Review baseline BMD result and investigations

#1: T score above 0
- General measures
  - Start calcichew D3 forte or ergocalciferol
  - General measures
  - Repeat BMD in 1 year

#2: T score between 0 and -2.0
- Treat hypogonadism
  - Is 25(OH) PTH >
    - Yes
      - Start calcichew D3 forte or ergocalciferol
    - No
      - General measures
      - Repeat BMD in 1 year

#3: T score -2.0 and lower or previous fragility fracture
- Treat hypogonadism
  - Is PTH >
    - Yes
      - Start calcitriol 0.25mcg nocte
    - No
      - Start bisphosphonate if no contraindications

Repeat BMD in 1-2 years

T score above 0
- No further BMD assessments unless clinical circumstances change

T score between 0 and -2.0
- Go to #2

T score -2.0 and lower or incident fragility fracture
- Go to #3

BMD fall >8% (fast looser)
- Correct hypogonadism, vit D deficiency and ↑PTH
  - Consider bisphosphonate depending on BMD
  - Repeat DXA 1-2 years

General measures:
- Reduce corticosteroid use to minimal dose possible
- Good nutrition and adequate calcium intake
- Regular weight bearing exercise
- Avoid tobacco use and excess alcohol

Figure 1
Management of established transplant patients

Baseline DXA: Spine, hip and whole body and spinal MXA
Check Ca, Phos, Alk phos, PTH, 25(OH) vit D, CTX
Male patients: Testosterone, LH, SHBG

Review BMD result and investigations

- T score above 0
  - General measures
  - No further BMD assessments unless clinical circumstances change

- T score between 0 and -2.0
  - General measures

- T score -2.0 and lower or previous fragility fracture
  - Treat hypogonadism
  - Is PTH > target?
    - Yes
      - GFR: PTH
        - >30: 35-70
        - 15-29: 70-110
    - No

- Is 25(OH) Vit D
  - Yes
    - Start calcichew D3 forte or ergocalciferol
  - No
    - Start calcitriol 0.25mcg nocte

- Start bisphosphonate if no contraindications

- Repeat BMD in 1-2 years

General measures:
- Reduce corticosteroid use to minimal dose possible
- Good nutrition and adequate calcium intake
- Regular weight bearing exercise
- Avoid tobacco use and excess alcohol consumption

Figure 2
In the case of post-transplant erythrocytosis, first line treatment should be the administration of an ACE-inhibitor (e.g. ramipril 1.25mg) or angiotensin II receptor antagonist (e.g. losartan 50mg). Patients who are unable to tolerate drug treatment will require regular venesections. The goal of treatment is to reduce the haematocrit to ~0.45, a level at which the risk of complications is minimized.

Erythrocytosis (defined as a haematocrit >51%; corresponding to a haemoglobin of >170g/l) affects 8-22% of renal transplant recipients. Risk factors include male gender, long duration of dialysis, acquired cystic disease, ciclosporin treatment, adult polycystic kidney disease, smoking and diabetes. Recent studies have failed to confirm the previous suggestion of an association with renal artery stenosis. The red cell production appears to be stimulated in many cases by either excess erythropoietin produced by the native kidneys, an over production of IGF-1 (an important regulator of erythropoiesis), activation of the renin-angiotensin system or endogenous androgens.

Erythrocytosis may also be associated with an underlying malignancy (particularly renal, breast and hepatocellular) and COPD, along with rarer causes such as cerebellar haemangiomas and phaeochromocytomas. The rarer causes should have been excluded in the pre-transplant workup and erythrocytosis occurring in the early post transplant period is likely to be due to post-transplant erythrocytosis. Underlying malignancy should be considered in patients developing erythrocytosis in the late post transplant period and diagnostic evaluation based on clinical findings/suspicion.

Treatment options include:
1. ACE inhibitors.
   - Low dose ACE inhibitors have proved to be effective\(^1\). The effect begins within 6 weeks and is complete in 3-6 months.

2. Angiotensin II receptor antagonists.
   - Post transplant erythrocytosis can be effectively treated with Losartan\(^2\). The response is dose dependent. Angiotensin II receptor antagonists are in general associated with fewer side effects than ACE inhibitors (in particular a reduction in the incidence of cough).

3. Venesection.

4. Theophylline\(^3\).
   - Theophylline (dose 300mg bd) is not as predictably effective as ACE inhibitors but can be used as an alternative to regular venesection in those who are unable to tolerate ACE inhibitors or AT-II receptor antagonists. Remember to consider drug interactions when prescribing theophylline.
Due to the increased risks of thrombotic complications a Hb of >185g/l should be treated with venesection initially, prior to drug treatment.

Hyperkalaemia induced by ACE inhibitors or AT-II receptor antagonists may be a particular problem in ciclosporin treated patients and these drugs should be used with caution in those with a potassium of >5.0 mmol/l. Although a small rise in serum creatinine (up to 25%) may occur following the introduction of an ACE inhibitor or AT-II receptor antagonist, a significant rise in serum creatinine may indicate underlying transplant renal artery stenosis.

References


Audit Plans:
Although no formal audit plans are in place for this guideline, the following would be suitable audit topics:
- Proportion of patients with functioning transplants with Hct >51% and/or Hb >170g/l.
- Number of patients requiring venesection for post-transplant erythrocytosis. Reasons why these patients not treated with medical therapy (ACE-I, AT2RA or theophylline).
- Number of patients starting treatment for post-transplant erythrocytosis (prospective audit).
PCV > 0.55 and/or Hb >185g/l

Venesect

PCV 0.51 – 0.55

Diagnostic evaluation:
Ultrasound native kidneys + ultrasound Doppler transplant
Breast examination +/- mammography in females
If risk factors for hepatocellular carcinoma – liver ultrasound & αFP
Long standing smoking history/ clinical suspicion of COPD:
Chest xray, PFT’s, capillary blood gases

Clinical picture suggestive of Post-transplant Erythrocytosis?

Yes

Previous side effects with ACE inhibitors?

Yes

Losartan
50mg daily

No

ACE inhibitor
(e.g. Ramipril 1.25mg daily)

Tolerated?

No

Yes

Monitor PCV and creatinine

If no effect on PCV after 4 weeks increase dose of ACE-I / Losartan

Drug treatment effective and tolerated?

Yes

Aim PCV ~ 0.45

No

Regular venesections to maintain PCV ~ 0.45

No

Treat underlying problem

Yes

Venesect
Take a history and examine the patient. Particularly check for dyspepsia, weight loss, change of bowel habit. Take a menstrual history and dietary history.

Iron deficiency anaemia
(blood film,
Ferritin <20,
Fe + TIBC,
% HRC's

< 45 yrs
Upper GI endoscopy
duodenal biopsy and colonoscopy

> 45 yrs
Upper GI endoscopy
duodenal biopsy and barium enema

If negative treat iron deficiency for 6 to 12 weeks stop iron and monitor FBC, ferritin, Fe TIBC and %HRC.

If iron deficiency recurs then formal referral for GI opinion
1. Background

BK virus is a polyoma virus. Polymavirus has a worldwide prevalence of 60-80% in general population. Reactivation of virus in transplant patients can cause interstitial nephritis (BK nephropathy). BK virus interstitial nephritis (nephropathy) occurs in approximately 3 to 8% of renal allografts. One year graft loss is 35 - 67% and there is no therapy of proven efficacy. The clinical features of BK virus nephropathy mimic acute rejection although peak incidence is 10 to 13 months post transplant. It has however been reported as early as 8 weeks and as late as 5 years post transplant. Allograft dysfunction may be acute or slowly progressive.

Risk factors include: heavy immunosuppression (but no association with a particular drug has been identified), older age, diabetes mellitus, white ethnicity, male gender. Previous acute rejection and pulse methylprednisolone treatment are associated with future development of BK virus nephropathy.

**Urinalysis** may reveal low grade proteinuria and pyuria/microscopic haematuria. Urine cytology may identify “decoy cells”. These are not specific for BK virus nephropathy (CMV and adenovirus infection) and their absence does not rule out BK nephropathy.

**Quantitative PCR** of blood for BK virus DNA with viral loads of >10000 copies/ml is 100% sensitive and 88% specific for BK virus nephropathy. Urine BKV PCR has a very low positive predictive value (27%) and its use is not cost effective. Hence do not test urine for BKV using PCR.

**Renal histology:** Features are very similar to those seen in acute cellular rejection ie interstitial mononuclear cell infiltrate, tubular injury and tubulitis. However the presence of intranuclear basophilic inclusions in tubular epithelial cells on light microscopy, viral inclusion bodies on electron microscopy and positive SV40 large T antigen staining on immunohistochemistry help to differentiate it from rejection. Clearly differentiating BK virus nephropathy from acute rejection is important since inappropriate additional immunosuppression for acute rejection may precipitate accelerated graft loss in BK virus nephropathy. Late diagnosis of BKVN and chronic damage on allograft biopsy is associated with poor allograft survival. Resolution of histological findings of BKVN can occur if BKVN is diagnosed early.

The cornerstone of treatment for BK Virus nephropathy is reduction in immunosuppressive therapy. Pre-emptive reduction in immunosuppressive therapy guided by screening has been shown to be effective. The cost and logistics of a screening program is a challenge. Other adjunct therapies such as cidofovir or leflunomide are used in resistant cases but the evidence base for such treatment is poor. A systematic review had shown no benefit on graft function by adding adjunct therapies. Further trials are ongoing.

Modification of the immunosuppressive protocol with minimisation according to immunological risk has been proposed and may reduce the burden of cumulative immunosuppressive therapy.
2. Case identification

Screening

Routine screening of asymptomatic patients is not considered necessary. This is based on low level incidence of BK infection found on local audit data. This will remain under review and be re-considered if the incidence is found to increase.

Indication testing

Patients who have received more intense immunosuppression should be considered at particular risk.

Check a BK virus PCR on a serum sample if:

1. There is an unexplained rise in the creatinine
2. There is an unexplained ureteric obstruction

A definitive viral load cut off associated with BKVN has not been established and as such interpretation of PCR level may not correlate with histological change at an individual level. Never the less the PCR copy count does allow some stratification of diagnostic certainty.

- > 10,000 – presumptive diagnosis of BKVN
- 5000 – 10,000 and rising trend – likely BKVN
- <5,000 – BKVN possible

Urine BK Virus PCR should not be used for monitoring.

Indication for renal transplant biopsy

A renal biopsy is usually performed to assess transplant dysfunction. The result is often available before a BK virus PCR is reported and can therefore be the first means of identifying the BK infection. A renal biopsy can classify level of histological change and exclude concomitant rejection.

Samples should be stained for the SV40 antigen. Two cores containing medullary tissue should ideally be examined.

Biopsy should be considered for patients with

- Unexplained renal dysfunction
- Intermediate or high level viraemia to confirm diagnosis and assess histological grade
- Renal dysfunction, BK viraemia and failure to improve after immunosuppression reduction. This is to assess for concomitant BK nephropathy and rejection.
- Renal dysfunction after reduction in immunosuppressive therapy. This is to exclude new rejection.

3. Treatment recommendations:

The management plan should always be discussed with a consultant.

If BKV PCR positive

- Reduce anti-proliferative (MMF or Azathioprine) dose by 25-50%
- Reduce tacrolimus dose if levels above target range
- Monitor renal function every 1-2 weeks
- Monitor BK PCR monthly
- Further adjustments of immunosuppression based on response of BKV PCR level and renal function
High grade BK nephropathy

- Reduce anti-proliferative (mycophenolate or azathioprine) dose by 50%
- Consider stopping anti-proliferative altogether if high grade nephropathy and significant renal dysfunction.
- Ensure CNI levels not higher than target
- Monitor renal function every 1-2 weeks
- Monitor BK PCR monthly

Further adjustments of immunosuppression based on response of BKV PCR level and renal function. If BK PCR remains elevated or rises consider the following options:

- Discontinue the anti-proliferative (mycophenolate or azathioprine) if not already done so
- Reduce calcineurin inhibitor
- Switch Tacrolimus to cyclosporin
- Switch calcineurin inhibitor to sirolimus
- Maintain low-dose prednisolone (<10mg/day)

Stabilisation of renal function may take up to 3-6 months to achieve with immunosuppression reduction alone. It is unusual to see renal function improvement back to baseline levels even when viral replication is suppressed (i.e., renal impairment is irreversible). In addition, between one to two thirds of patients have progressive allograft dysfunction in spite of immunosuppression reduction (and virological improvement).

Further deterioration in renal function following reduction in immunosuppression should prompt a follow-up biopsy to look for evidence of acute rejection.

Treatment of concomitant acute rejection and BK Virus Nephropathy

The treatment of recipients whose biopsy shows rejection with concurrent BKV nephropathy or rejection early after reduction of immunosuppression to treat BKV nephropathy remains problematic. An urgent SV40 Ag staining of the biopsy should be requested to differentiate interstitial nephritits from BKVN from acute rejection.

A short course of pulse methylprednisolone is suggested. If it is steroid resistant, IVIg can be considered.

Treatment of resistant cases of BK Virus Nephropathy:

If immunosuppression reduction does not lead to a fall in viral load within 12 weeks, or if renal function is rapidly deteriorating in the absence of any other identifiable cause, additional treatment may be considered.

It should be noted that this therapy is not licensed for this indication and the evidence supporting its use is derived from small case series at best. The decision to commence this treatment must be discussed with a transplant consultant or at the transplant MDT meeting. The patient must be fully informed of the rationale behind the treatment.

Novel and experimental therapy

**Intravenous immunoglobulin (IV-Ig)**
IV-Ig has been used alongside other treatments for patients with BK nephropathy. The evidence of benefit is based on case series and case control studies. It may permit treatment with no increased risk of rejection and may also be useful in cases of concomitant BKVN and rejection.

Dosing 100mg/kg per dose for 10 weeks (totalling 1 g/kg), using 1 L normal saline prehydration.

Predose enoxaparin 1 mg/kg subcutaneously to prevent thrombosis, unless contraindicated.

**Cidofovir**

Cidofovir is a cytosine analogue DNA polymerase inhibitor licensed as 3rd line treatment for CMV retinitis. Case reports of benefit in patients with progressive multifocal leucoencephalopathy have suggested that it may have some activity against polyoma viruses.

It is nephrotoxic and induces proteinuria and renal failure in 20% of treated patients. Recently a low-dose regimen has been described that may be effective (stable renal function in all 8 patients treated with reduced immunosuppression and low-dose cidofovir (after mean 24 months) compared to 9/13 graft losses in those treated by immunosuppression reduction alone after mean of 8 months) and free of significant nephrotoxicity.

**Regimen:**

Immunosuppression reduction as above
0.5 mg/kg cidofovir IV over 1 hour weekly for total of 4 to 10 doses depending on response. The dose can be increased to 1mg/kg/week if response is lacking.

Before giving cidofovir, volume expand with 1L saline intravenously (after careful volume assessment of patient) over 1 hour. Probenecid pre-treatment is not necessary.

Cidofovir can induce neutropenia, and iritis/uveitis. Check FBC before each dose and monitor for development of ocular abnormalities.

**Leflunomide**

Leflunomide is an anti-inflammatory drug approved for the treatment of rheumatoid arthritis. Leflunomide has considerable immunosuppressive potency in human renal and liver transplant recipients. Its active form has substantial antiviral activity against cytomegalovirus (CMV), herpes and BKV *in vitro* and in experimental animals. The rationale for the use of leflunomide in BK Virus nephropathy rests on these combined immunosuppressive and antiviral actions.

In two large case series, the same research group reported on 26 and 17 patients, respectively, who developed BKVN on triple therapy with tacrolimus, MMF and steroids. In all patients, MMF was withdrawn and leflunomide was administered at a loading dose of 100 mg daily for 3-5 days followed by a maintenance dose of 20-60 mg daily, aiming a trough level of 50-100ug/ml. Clearance or a progressive reduction in viral load and a stabilization or improvement of graft function was achieved in 84 and 88% of patients, respectively. The patients who deteriorated had leflunomide plasma levels <40 µg/ml.

**Regimen:**

Immunosuppression reduction as above
Loading dose of 100 mg daily for 3 days followed by maintenance dose of 20mg daily.

Side effects due to leflunomide are diarrhoea and rash, with potential for severe reactions including hepatotoxicity, pneumonitis, neurotoxicity, and bone marrow suppression in rare cases. Higher levels of leflunomide are associated with haemolysis, thrombotic microangiopathy.
4. Audit measures:
   a) Number of new cases of BKVN per year
   b) Immunosuppressive regimen at the time of diagnosis of BKVN
   c) Number of patients with previous therapy for acute rejection
   d) Adherence to protocol for immunosuppression reduction following diagnosis of BKVN
   e) Number of patients with BKVN receiving adjunct therapies
   f) Number of cases with BKVN who develop acute rejection following modification of IS regimen.
   g) Five year graft survival of cases with BK Virus Nephropathy

5. References

5 Keywords (up to six)
Kidney; transplant; BK virus; immunosuppression; cidofovir, Leflunomide
Assessment

All prospective transplant recipients should have their varicella-zoster serology tested.

Vaccination

Non-immune patients should receive 2 doses of 0.5mL of varicella vaccine. The outer aspect of the upper arm (deltoid region) is the preferred site of injection. Either of these vaccines are acceptable.

Varilrix®: Subcutaneous injection only. Interval between doses 4 - 8 weeks but in no circumstances less than 4 weeks.

Varivax®▼: Subcutaneous or intramuscular injection. Interval between doses 4 - 8 weeks. If the interval between doses exceeds 8 weeks, the second dose should be given as soon as possible. Some individuals may not be protected until after the second dose has been administered.

The vaccines are live attenuated virus. Be aware that patients can be infective to other non-immune patients.

Contraindications to vaccination

- History of hypersensitivity to any varicella vaccine, to any of the excipients or to gelatin or neomycin
- Blood dyscrasias, leukaemia, lymphomas of any type, or other malignant neoplasms affecting the hemic and lymphatic systems.
- Individuals receiving immunosuppressive therapy (including high doses of corticosteroids).
- Individuals with humoral or cellular (primary or acquired) immunodeficiency, including hypogammaglobulinemia and individuals with HIV infection with CD4 <200 on HAART or CD4 <400 if not on HAART.
- Individuals with a family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated.
- Active untreated tuberculosis.
- Any illness with fever >38.5°C; however, low-grade fever itself is not a contraindication to vaccination.
- Pregnancy.

NOTE The Zostavax® vaccine used to reduce the incidence of varicella zoster (shingles) is also a live attenuated vaccine and is contraindicated in transplant patients.

Assessment of vaccination response

Patients should have their immunity checked at least 4 weeks after the second vaccination.

Those with positive serology, i.e. responded to vaccination, can be listed for transplantation.
Those with negative serology, ie non-responders to vaccination, can still be listed for transplantation but they should be counselled about the risks associated with a varicella infection if they were to be immunosuppressed. They should also receive advice to avoid individuals with chickenpox or shingles.

If patients with negative serology get exposed when they are immunosuppressed they should receive Varicella zoster immunoglobulin, VZIg (as detailed in the British National Formulary) within 10 days of exposure and ideally as soon as possible. If they present more than 10 days after the exposure then consider giving aciclovir as prophylaxis for at least the incubation period (3 weeks). This should be discussed with the microbiology or infectious diseases team.

In working hours VZIg is obtained on discussion with Virology, extension 63524, or by contacting the Microbiology duty room, extension 64103. Out of hours the Microbiologist on call should be contacted via QMC switchboard.
Hepatitis B and Kidney Transplantation

Transplantation from Hepatitis B +ve donors has traditionally been avoided however it is now recognised that they in certain circumstances the risks and benefits of transplanting such organs can be justified.

In addition potential recipients may have previously had hepatitis B which could be reactivated in the post transplant period as a consequence of their immunosuppression.

This document details the important background information about hepatitis B infection in relation to transplantation and details the assessment and management of patients to

1. Minimise the risk of hepatitis B transmission from a Hepatitis B donor
2. Minimise the risk of reactivation in recipients who are already Hepatitis B +ve

Hepatitis B virus and the serological response

Hepatitis B is a viral infection which can cause varying degrees of liver injury from transient LFT abnormalities to cirrhosis and liver failure. Many patients may be unaware that they have the infection. It is caused by a DNA virus that primarily infects hepatocytes but can also infect other cell types. The viral DNA persists in the nucleus as an episome and multiple copies can exist in each cell. The virus utilises the cells transcriptional machinery to produce new virus particles which are then shed from the cell into the blood stream.

The first serologically detectable response to the infection is a positive Hepatitis core antibody (Anti-HBc) and this probably persists life long. The presence of hepatitis surface antigen (HBsAg) indicates active infection which can be confirmed and quantitated by a Hepatitis B DNA PCR. In those individuals who have controlled their infection Hepatitis surface antibody (Anti-HBs) will become +ve, and usually stay +ve.

Hepatitis B vaccine contains purified HBsAg. Patients who have been vaccinated and had an immunological response should be Anti-HBs +ve but Anti-HBc -ve.

To complicate matters it has become increasingly recognised that some patients infected with Hepatitis B do not follow the classic pattern described above.

1. Patients who have had an appropriate serological response with clinically resolved infection (Anti-HBc +ve, HBsAg –ve and Anti-HBs +ve) can still reactivate at a later date, usually when immunosuppressed. This is because ‘dormant’ viral DNA present within the hepatocyte nucleus can reactivate the infection and cause subsequent liver injury.

2. Patients who have had an appropriate serological response with clinically resolved infection (Anti-HBc +ve, HBsAg –ve and Anti-HBs +ve) can still have viral DNA detected in their blood periodically. They are therefore still potentially infective to other individuals.

3. Patients can be Anti-HBc +ve but have no detectable surface antigen or surface antibody. These individuals are considered to have unresolved infection with viral DNA integrated into the hepatocyte but with minimal, if any, viral replication.
Transplantation of kidney from a Hepatitis B positive donor

Standard donor serological tests

Potential organ donors have their Anti-HBc and HBsAg status tested. Organs from Anti-HBc +ve, HBsAg –ve donors are offered to transplant centres willing to accept such kidneys.

Assessment of risks and benefits

Transplantation from Anti-HBc +ve donors has traditionally been avoided because of the risk viral transmission however the demand for transplants has steadily increased. This has been a major issue in countries where the prevalence of hepatitis B is high. In the UK most patients are vaccinated against hepatitis B (although not all respond). In addition anti-viral therapy is available as a means of prophylaxis. As a result of these developments, and the pressure to transplant more patients, practitioners have now utilised such organs in selected individuals and reported a low incidence of transmission.

The use of an Anti-HBc +ve kidney for any individual recipient needs a joint decision between the consultant transplant surgeon, the consultant nephrologist and the patient. Advice may also need to be obtained from the on-call microbiologist or virologist. The risk of viral transmission needs to be balanced against a variety of factors which determine the patient’s risk of staying on dialysis and their need for a transplant eg age, co-morbidity, dialysis access and complications, transplant number, level of sensitization and length of wait.

Recipient risk stratification when receiving an organ from a core antibody positive donor.

<table>
<thead>
<tr>
<th>Recipient Anti-HBc status</th>
<th>Recipient Anti-HBs status</th>
<th>Risk of Hep B viral transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>Low</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>Low</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>Intermediate</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>Higher</td>
</tr>
</tbody>
</table>

Patient information and consent

A patient who is being considered as a potential recipient of a kidney from Anti-HBc +ve donor obviously needs to be informed of this fact. They need to know they will require additional anti-viral therapy to minimise the risk of transmission and be made aware of the duration of this therapy. They also need to know that they could develop hepatitis B in the future although we would consider the risk to be small (< 5 %). This discussion needs to be clearly documented in the patient’s notes and the risk of viral transmission should be included on the patient’s consent form.

Lamivudine prophylaxis

Lamivudine should be used as prophylaxis against viral transmission for all patients who receive an Anti-HBc +ve kidney.

A single stat dose should be prescribed pre-operatively and once a day dosing thereafter. This should be adjusted according to the patients GFR.
**Dose based on GFR**

<table>
<thead>
<tr>
<th>GFR Range</th>
<th>Dose Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>100mg od</td>
</tr>
<tr>
<td>30-50 mls/min</td>
<td>100mg first dose then 50mg od</td>
</tr>
<tr>
<td>15-30 mls/min</td>
<td>100mg first dose then 25mg od</td>
</tr>
<tr>
<td>5-15 mls/min</td>
<td>35mg first dose then 15mg od</td>
</tr>
<tr>
<td>&lt;5 mls/min</td>
<td>35mg first dose then 10mg od</td>
</tr>
</tbody>
</table>

Haemodialysis or Peritoneal dialysis – dose as in GFR <5

**Important interactions**

Trimethoprim – inhibits excretion of lamivudine – avoid concomitant use with high dose co-trimoxazole.

Antivirals – avoid concomitant use with IV ganciclovir, foscarnet and emtricitabine.

**Discontinuation**

Lamivudine should be continued for at least 12 months. Prior to stopping the patient should have Hepatitis serology and Hepatitis B DNA PCR checked.

If the serology or PCR indicates active infection/reactivation then this should be discussed with the hepatologists.

If it is negative then the lamivudine can be stopped. The patients should then have Hepatitis serology and Hepatitis B DNA PCR checked every 3 months to look for evidence of reactivation. If it is negative 12 months after stopping lamivudine then no further testing is required unless there is subsequent clinical suspicion of a viral hepatitis.

**Transplantation of a kidney into a Hepatitis B positive recipient**

**Recipient assessment.**

All patients who are assessed for transplantation should have their Anti-HBc and HBsAg status tested.

Those who are HBsAg +ve should be referred to see a hepatologist.

Those who are Anti-HBc +ve, HBsAg –ve and Anti-HBs positive ie controlled or ‘dormant’ infection should have:

1. Liver ultrasound
2. Liver fibroscan

This is to look for evidence of hepatocellular carcinoma and/or liver cirrhosis.

If either scan is abnormal then the patients should be referred to see a hepatologist. If both scans are normal then patients can proceed to transplant listing.

**Lamivudine Prophylaxis**

Lamivudine prophylaxis should be used for uncomplicated patients with controlled or ‘dormant’ infection to reduce the risk of reactivation.
This should be for 12 months after transplantation and this should follow the dosing schedule, monitoring and discontinuation protocol which is detailed above.

References


1. Introduction

1.1 Scope and purpose
The transplant of organs from an Rh-D positive donor to an Rh-D negative recipient may result in the release of Rh-D positive red cells into the recipient’s circulation, which may cause Rh-D sensitisation and the production of anti-D alloantibodies. This would require the recipient to receive only Rh-D negative blood components for all subsequent transfusions. This should be of no further clinical significance except for premenopausal females in whom the presence of immune anti-D in the maternal circulation may result in Haemolytic Disease of the Fetus and Newborn should the recipient go on to conceive a Rh-D positive infant.

The use of Rh-D immuno-prophylaxis for the prevention of immune sensitisation to the Rh-D antigen is a well established and proven procedure used extensively in the obstetric setting. This protocol outlines the procedure to be followed in the case of solid organ transplants to prevent Rh-D alloimmunisation and has been produced following guidance from the British Committee for Standards in Haematology “BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn” (2013)

1.2 Responsibility
It is the responsibility of the medical team managing the transplant to identify those patients for whom Rh-D sensitisation may present an obstetric or transfusion support risk in the future and to provide suitable and timely samples for testing to meet this guideline.

It is the responsibility of the transfusion laboratory team to respond to notification of any at risk transplant and to support the testing and prophylaxis procedures for each individual case.

2. Identification of ‘at risk’ transplants

2.1 All Rh-D negative premenopausal females who are to be recipients of donor organs from Rh-D positive donors should be classed as ‘at risk’ unless there is unequivocal evidence to ensure that the individual will not conceive at any date after the transplant (for instance, if the patient is post-hysterectomy).

2.2 The transplant team must have a robust system for the identification of ‘at risk’ transplants and for the prompt notification of the transfusion laboratory.

2.3 The transplant team must have robust procedures for obtaining and sending appropriately timed and labelled samples as identified in this procedure.

3. Pre-transplant testing

3.1 Prior to transplant, all patients should be tested for ABO, Rh-D and red cell alloantibody screen, which may be performed at any date prior to the transplant.
4. At the time of transplant

4.1 Within 24hrs of the transplantation of a Rh-D positive organ to a Rh-D negative ‘at risk’ recipient, the transfusion laboratory must be notified so that preparations can be made for the testing of subsequent samples (see below) and issue of prophylaxis.

4.3 A system must be in place on the transplant unit to ensure all subsequent sampling and prophylaxis are completed as described below.

5. Anti-D Prophylaxis

5.1 As soon as possible after transplant, and within 72 hours of the procedure, give anti-D 500 I.U. IM, which will cover a 4 ml exposure. This will be the standard dose that the transfusion laboratory will issue.

5.2 The transplant units must arrange for the collection and administration of Anti-D Prophylaxis

5.3 The form accompanying the anti-D must be completed and returned to the transfusion laboratory. This is documentation of the “fate” of the anti-D.

5.4 Subsequent doses will depend on the result of flow cytometry quantitation (see below).

5.5 The patient’s (or guardian’s) informed consent MUST be documented in the hospital case notes by the doctor responsible for the decision to administer anti-D. This is a legal requirement.

5.6 Prophylactic anti-D should be administered within 72 hours after the surgery but can be administered up to 10 days afterward if there are exceptional circumstances (see below).

6. 24 hours post transplant

6.1 At least 24 hours after transplant—to allow donor cells to wash off the organ and enter the circulation—send an EDTA sample (purple top) to the transfusion laboratory for flow cytometric quantitation of RhD positive cells.

6.2 If the exposure is 0 ml, no further action, including sampling, needs to be taken.

6.3 If the exposure is >4 ml, give an additional dose of anti-D: 125 I.U. for each additional 1 ml of D+ cells. This will be guided by the Transfusion Department. This is very rare and will usually be unnecessary in renal transplants.

7. 72 hour post prophylaxis

7.1 Send repeat samples for flow cytometry every 72 hours until no D+ cells are present. Give additional doses of anti-D as required (125 I.U./ml) until D+ cells are cleared from the circulation.

8. "Missed" at risk transplants

8.1 If an at risk transplant is “missed” and prophylactic anti-D is not administered within 72 hours after the surgery, it can still be given up to 10 days afterward
8.2. An EDTA sample for flow cytometry should still be sent. The transfusion laboratory will need to be informed.

8.3. If there is a delay >72 hours, this is classed as a delayed anti-D event. An incident form must be completed, and the incident must be reported to the Serious Hazards of Transfusion Haemovigilance scheme (SHOT).

References:

**Introduction**

All patients with, or approaching ERF should be considered for transplantation. It is important that there are written guidelines for the selection of patients deemed suitable for transplantation that are clear and transparent. This should take into account both equity of access and a risk-benefit analysis. If the patient is not deemed suitable by the consultant nephrologist or surgeon the reason should be documented in the notes. These guidelines should be used in conjunction with the:
1. NHSBT policy, ‘Patient Selection for Deceased Donor Kidney Only Transplantation’; and
2. East Midlands ‘Assessment Guidelines for Potential Renal transplant Recipients.’

Pre-emptive renal transplantation should be encouraged for all patients. Whenever a living donor is available and in order to facilitate pre-emptive transplantation, donor evaluation should start sufficiently early to allow time for more than one donor to be assessed if necessary. Information should be provided at an early stage and discussion with potential donors and recipients should be started when the recipient’s eGFR is approximately 20 ml/min. Thereafter, recipient and donor assessment should be tailored according to the rate of decline in recipient renal function, taking into account disease specific considerations and individual circumstances.

**Medical Assessment**

All patients who wish to be considered for transplantation should be formally assessed. This includes those who are pre-dialysis, as well as those on dialysis. Patients with the following conditions are not suitable for transplantation:
- Previous malignancy, excluding non-melanoma skin carcinoma, within last 2 years (For breast, melanoma may need to be five years)
- Active systemic infections
- Current IV drug abuser
- Any condition with a life expectancy <2 years

There are a number of other relative contraindications, which include:
- Active renal disease e.g. vasculitis or recurrent disease with predicted risk of graft loss greater than 50% at 1 year
- Other significant co-morbid conditions with a predicted patient survival of <5 years
- BMI >35 (Patients with a BMI of up to 40 will be considered depending on the distribution of body fat and result of a cardiac stress test)
- HIV infection not treated with Highly Active Anti-Retroviral Therapy (HAART) or already progressed to AIDS
- Patients unable or unlikely to adhere with immunosuppressant therapy requirements
- Immunosuppression predicted to cause life-threatening complications

Patients should be seen by a consultant nephrologist or their deputy, but in all cases discussed with the consultant. The assessment should include a thorough history and examination and consideration of psychosocial factors (desire to have a transplant and evidence of concordance). In addition to routine blood tests all normal risk patients require a CXR and ECG. Males aged>50
years old require PSA screening. Medically high risk patients will require further investigation as detailed in the East Midlands ‘Assessment Guidelines for Potential Renal transplant Recipients.’ If the patient is potentially suitable for transplantation then a written referral should be made to the transplant surgeons, using the referral letter template (available on request) which outlines the salient points and including the results of investigations. Simultaneous kidney/pancreas transplantation is the treatment of choice for carefully selected patients with end-stage renal failure with type 1 diabetes. These patients should be referred to the Nottingham transplant surgeons in the first instance and all will need an abdominal ultrasound, DSE and a lower limb Duplex scan (to include iliac vessels). If appropriate they will then be referred to the surgical team at Addenbrookes for further assessment, or if not, considered in Nottingham for kidney only transplantation.

**Surgical Assessment**

On receipt of the referral letter most patients will be given a date for an assessment clinic and a patient information session. The likely exceptions are those who have had a previous but recent transplant, or where there is a communication difficulty e.g. where a translator is required or where a patient has learning difficulties. At the information session and surgical assessment the following areas will be discussed:

- The process of getting on the list, staying on the list and suspensions
- DBD, DCD and living donor transplantation
- Use of higher risk organs and risk of disease transmission
- Allocation of kidneys
- Risks and benefits of transplantation, including short & long-term complications
- Immunosuppression with the general and specific side-effects

In addition the patient will be given written information. Patients who DNA a patient information session will be contacted and a new date given. If they DNA again a further appointment will not be given and the referring nephrologist informed. Patients requiring assessment, for whom an information evening is not appropriate, will be seen at a transplant assessment clinic. At this visit a consultant surgeon will see the patient and the assessment will include a history and examination, gaining consent for transplantation and the opportunity for the patient to ask any further questions. The possibility of live donor transplantation will always be explored and encouraged where appropriate. In most situations the patient will be suitable to be listed and the patient will be seen by the recipient co-ordinator for bloods for H&I assessment and further counselling. On rare occasions the patient will be deemed not suitable or will require further investigations. The outcome of this visit will be documented in the notes and a letter written to the referring consultant nephrologist with a copy to the patient, GP and pre-transplant nurses. If the patient is listed they will be discussed at the next listing MDT and given an appointment for a transplant list review clinic in 12 months. If the patient is not deemed suitable for transplant listing then there will be discussion at the listing MDT. If there is disagreement amongst other members of the MDT or with the patient, then the patient will be offered an independent opinion at another centre. This will usually be Leicester, but may be elsewhere depending on patient choice. Patients who DNA the transplant list review clinic on two successive occasions will have a phone call from the pre-transplant nurse, and if they still do not attend without reason will be taken off the list and the patient and their nephrologist informed. The outcome of the list review clinic visit will be documented in the notes and in a letter to the consultant nephrologist with a copy to the GP and the recipient co-ordinator.
Placing a patient on the transplant list

Once the tissue typing, virology and antibody status is known, and the patient is ready to be listed they will be informed by a member of the pre transplant team and put on the transplant list. Pre-emptive transplantation should be considered in all patients. Ideally this should not be considered until the patient is within six months of requiring dialysis although it is recognised that this can be difficult to judge. A GFR of <15 with a progressive decline in renal function is a reasonable guide. It should also be a joint decision between the nephrologist and surgeon.

- Patients will normally be listed for a 222 mismatch. In reality the patients who will usually receive a >0 DR MM kidney will be those who are:
  - Homozygous for DR
  - Aged >60 years old
  - Waiting more than 3 years and non-sensitised
  - Deemed clinically urgent.
  - Age matched DCD donor organ
- If live donor transplantation is a possibility the patient is given the contact details of the live donor coordinator and encouraged to contact them directly. Once this has been done the donor is sent a questionnaire and then referred by GP.
**East Midlands: Assessment guidelines for Potential Renal Transplant Recipients**

**Introduction**

The assessment of a patient’s suitability for a renal transplant can be complex and these guidelines have been developed to help clinicians investigate and refer patients appropriately. The evaluation is a joint process between nephrologists and transplant surgeons and will often include the opinion of other specialists. It should be emphasised that each patient must be assessed on an individual basis and difficult cases should be discussed at a dedicated multidisciplinary team meeting.

Each section of advice below deals with a specific problem but these are often interlinked.

Timely access to kidney transplant listing, ideally to enable pre-emptive transplantation, should remain a high priority of all concerned in the delivery of this service.

Patients should be actively involved in the discussions and decisions about transplant assessment and listing. This should include patients with advanced kidney disease where transplantation is clearly not a treatment option.

The guidelines should help support the delivery of a clear patient pathway and also enhance equity of access for transplant listing.

More detailed guidelines are available at

- [www.renal.org/guidelines](http://www.renal.org/guidelines)

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1 Prepared by Gavin McHaffie, Consultant Nephrologist, Nottingham & John Feehally, Consultant Nephrologist, Leicester
Referral pathway for renal transplant assessment

DSE = dobutamine stress echocardiography

Suggested eGFR timeline

- eGFR ≤ 23

All patients with, or approaching, CKD stage 5 should be formally considered for living and deceased donor transplantation by their consultant nephrologist. Process to start 12 months before expected start of RRT.

- If potential Living Donor - referral for living donor work-up process

Absolute Contra-indications to Transplantation

1. Uncontrolled Cancer
2. Active systemic infection or active systemic vasculitis
3. Current IV drug abuser
4. Any condition with life expectancy less than 2 years

Does patient wish to be considered?

- Yes

Is patient medically suitable?

- Yes

CXR, ECG, ECHO, cardiac stress test (DSE or perfusion scan)

Follow separate flow chart

- No

Document in notes/clinical IT system Review decision if and when appropriate

Higher CV risk

- No

Normal CV risk

- CXR & ECG

Written referral to Transplant Surgeon

Patient given appointments for information session and assessment clinic

Patient seen in transplant assessment clinic (within eight weeks from referral)

Is patient suitable to be listed?

- Yes

Bloods for tissue typing, cytotoxic antibodies and virology

- No

Register with NHSB&T

Ensure regular review after listing to assess continued suitability

Suggested eGFR timeline

- eGFR ≤ 18

- eGFR ≤ 15
Contraindications to Renal Transplantation

Absolute contraindications

There are few absolute contraindications to renal transplantation. These include:

- Uncontrolled cancer
- Active systemic infections or active systemic vasculitis
- Current IV drug abuse
- Any condition with a life expectancy <2 years

Relative contraindications

Patients may have a number of co-morbidities that individually are not a contraindication to listing for transplantation, but when considered together may represent a clear contraindication to transplantation:

- Predicted patient survival of less than 5 years (despite renal transplantation).
- Malignant disease not amenable to curative treatment, or remission for greater than 5 years.
- HIV infection not treated with Highly Active Anti-Retroviral Therapy (HAART) or already progressed to AIDS.
- Cardiovascular disease – ischaemic heart disease, the prognosis of which cannot be improved by revascularisation and/or cardiac failure with a predicted risk of death greater than 50% at 5 years.
- Predicted risk of graft loss greater than 50% at 1 year.
- Patients unable or unlikely to adhere with immunosuppressant therapy requirements.
- Immunosuppression predicted to cause life-threatening complications.
**Assessment**

**Cardiovascular disease**

All patients should have an ECG and CXR. If these are normal in low risk, asymptomatic patients then they can be referred directly to the transplant surgical team. If these are abnormal further investigations should be pursued as appropriate.

Asymptomatic patients deemed at higher risk should have a cardiac stress test and echocardiogram. Some factors associated with higher risk are a spectrum and clinicians may need to make a judgement about the level of risk and the need for these additional investigations.

**Factors associated with higher risk**

- Increasing age
- Diabetes
- Abnormal ECG (other than LVH)
- Coronary heart disease (angina, previous MI, CABG or angioplasty) or CCF
- Peripheral vascular disease (claudication or arterial bypass surgery)
- Ischaemic cerebrovascular disease
- BMI >35

Patients with active cardiovascular disease or patients with a positive cardiac stress test should be referred to a cardiologist for an opinion about the need for coronary angiography.

If coronary angiography is proposed in pre-dialysis patients the timing of the procedure may be influenced by the level of residual renal function. Such a judgement needs to balance the risks of acute kidney injury with the potential benefit of timely transplant listing.

It should be noted that there is no current evidence supporting the use of coronary interventions where the sole indication is pre-operative optimisation prior to renal transplantation.

<table>
<thead>
<tr>
<th>Heart failure</th>
<th>Patient’s functional capacity as well as LV function both important determinants of outcome.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valvular heart disease</td>
<td>Consider seeking cardiology opinion. If surgical intervention predicted necessary over next few years consider operating pre-transplant.</td>
</tr>
<tr>
<td>Cerebrovascular disease Previous TIA, stroke</td>
<td>Reversible factors should obviously have been resolved, e.g. surgery for occlusive carotid disease. Cardiovascular risk prevention strategies need to be optimised. Consider listing 3-6 months after event.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Proceed if good control and left ventricular function satisfactory.</td>
</tr>
</tbody>
</table>
Cardiac assessment for renal transplantation

Assess CV risk

Factors associated with higher risk
Increasing age
Diabetes
Abnormal ECG (other than LVH)
IHD (angina, previous MI, CABG or angioplasty)
or CCF
PVD (claudication or arterial bypass surgery)
Ischaemic cerebrovascular disease
BMI >35

Normal

Abnormal ECG (except LVH)

CXR & ECG

ECHO + DSE or perfusion scan

Positive cardiac Stress test

Cardiology assessment

Coronary angiogram

Consider for revascularisation

Not successful or considered too high risk

Unsuitable

Negative cardiac stress test

Further interventions

Refer for surgical transplant

Transplant list if

Successful

Consider referral after

Yearly ECG. CXR as indicated. Cardiac stress test every 5 years (3 years for diabetics) unless clinical status, ECG or cardiology opinion dictate otherwise.

Factors associated with higher risk
Increasing age
Diabetes
Abnormal ECG (other than LVH)
IHD (angina, previous MI, CABG or angioplasty)
or CCF
PVD (claudication or arterial bypass surgery)
Ischaemic cerebrovascular disease
BMI >35
### Respiratory disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Usually proceed unless very severe and unstable. Respiratory and anaesthetic assessment if severe.</td>
</tr>
<tr>
<td>COPD</td>
<td>Spirometry, CXR and functional assessment important. Consider respiratory and anaesthetic opinion prior to listing.</td>
</tr>
<tr>
<td>Bronchiectasis [and other chronic suppurative lung disease]</td>
<td>Respiratory assessment of lung function and for opinion on expected infection pattern with immunosuppression.</td>
</tr>
<tr>
<td>Previous pulmonary TB or risk of TB</td>
<td>All patients should have individual risk assessment – including history of previous disease, treatment and contact history. In general all Black or Asian patients born outside the UK should be tested and considered for preventive anti-TB therapy prior to or after transplant. Testing with a TB interferon gamma release assay should be performed in high risk patients. Preventive therapy for latent TB should be detailed in local protocol.</td>
</tr>
</tbody>
</table>

### Gastrointestinal disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>Usually BMI &lt; 35 before proceeding, but case by case decision.</td>
</tr>
<tr>
<td>Dentition</td>
<td>Dental review to deal with chronic infection/inflammation.</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Proceed if disease suppressed and nutritional state good.</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>Symptomatic – intervene before proceeding [e.g. cholecystectomy]. Asymptomatic – transplant surgical assessment regarding intervention.</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>Proceed on long term PPI.</td>
</tr>
</tbody>
</table>
**Hepatic disease**

<table>
<thead>
<tr>
<th>Chronic viral hepatitis</th>
<th>Hepatology assessment. Usually require liver biopsy to assess disease extent, and active treatment of HBV or HCV before proceeding. See Trust hospital guidelines.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>Hepatology assessment of functional reserve before proceeding.</td>
</tr>
</tbody>
</table>

**Diabetes mellitus**

<table>
<thead>
<tr>
<th>Type 1 diabetes</th>
<th>If possible patients should be considered for simultaneous kidney-pancreas OR live donor renal transplant. Suitability for SPK Transplant [Oxford or Cambridge]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- typically age &lt;50, but older if cardiovascularly fit</td>
</tr>
<tr>
<td></td>
<td>- no major end organ compromise from macrovascular disease</td>
</tr>
<tr>
<td></td>
<td>- BMI &lt;30 kg/m$^2$</td>
</tr>
<tr>
<td></td>
<td>- neuropathy not causing severe CV compromise</td>
</tr>
<tr>
<td></td>
<td>- especially if brittle diabetic control</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>Decision to proceed usually dictated by severity of cardiovascular disease</td>
</tr>
</tbody>
</table>

**Chronic infection**

<table>
<thead>
<tr>
<th>HBV</th>
<th>Hepatology or ID referral. Active treatment according to local guidelines to suppress or eliminate viraemia before proceeding. If disease seroconverted, ie Hep B core antibody positive and Hep B surface antigen negative, then need to ensure post transplant anti-viral prophylaxis plan established before listing.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td>Hepatology or ID referral. Active treatment according to local guidelines to suppress or eliminate viraemia before proceeding.</td>
</tr>
<tr>
<td>HIV</td>
<td>Active treatment – usually HAART. See British HIV Association and BTS HIV guidelines. Will need trial of immunosuppression prior to listing.</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Proceed if fully treated. Anti-TB prophylaxis according to local protocol.</td>
</tr>
</tbody>
</table>
**Malignancy**

**Cancer Screening**

Cancer screening should be advised according to national guidelines. Asymptomatic patients who decline screening should not be barred from transplantation listing.

Prostate cancer – there is no national screening programme for prostate cancer (although some patients may have had their PSA checked through the Prostate Cancer Management programme). The following advice is based on local consensus opinion.

- Men aged 50 and over – check PSA prior to transplant listing.
- PSA raised - refer patient to a urologist for further assessment.
- If the urologist wishes to continue a watch and wait because risk considered low then the patient can be listed for transplantation.
- If the urologist wishes to investigate the patient further then the outcome of these investigations should be completed prior to consideration of listing.
- Men age > 50 years active on the waiting list should have their PSA level checked every 3 years

**Waiting period between malignancy and listing for transplantation.**

Each patient's specific cancer should be considered based on its particular characteristics including its histological type, location, spread and response to treatment. Patient characteristics should also be considered.

The decision about listing should be discussed with the patient's specialist surgeon, physician and/or oncologist. The Israel Penn International Transplant Tumour registry may also be consulted for further advice - [http://www.ipittr.uc.edu](http://www.ipittr.uc.edu)

<table>
<thead>
<tr>
<th>Cutaneous malignancy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>Minimum 5 years disease free</td>
</tr>
<tr>
<td>Non-melanoma skin cancer</td>
<td>Usually proceed, but caution if already multiple cancers</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other epithelial malignancy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma in situ – cervix, vulva, or bladder</td>
<td>Proceed to listing</td>
</tr>
<tr>
<td>Non-in situ carcinoma of the uterus</td>
<td>Minimum 2 years disease free</td>
</tr>
<tr>
<td>Colorectal cancer – Stage A and B</td>
<td>Minimum 2 years disease free</td>
</tr>
<tr>
<td>Colorectal cancer – Stage C</td>
<td>Minimum 5 years disease free</td>
</tr>
<tr>
<td>Breast cancer – in-situ</td>
<td>Minimum 2 years disease free</td>
</tr>
<tr>
<td>Breast cancer – stage II</td>
<td>Minimum 5 years disease free</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Listing may be possible and should be considered on a case by case basis with appropriate counselling.</td>
</tr>
<tr>
<td>Renal Cell Carcinoma - Asymptomatic</td>
<td>Proceed to listing</td>
</tr>
<tr>
<td>Disease</td>
<td>Recurrence risk</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>60%</td>
</tr>
<tr>
<td>HSP nephritis</td>
<td>35%</td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>30%</td>
</tr>
<tr>
<td>FSGS</td>
<td>Overall 30%.</td>
</tr>
</tbody>
</table>

**Women of childbearing age**

- Ensure rubella immunisation
- Ensure discussion of
  - Risks of unplanned pregnancy in early post-transplant period
  - Appropriate contraception
  - Fetal, maternal and graft outcomes after transplant
  - Planning pregnancy and need to modify drug regimens

**Primary renal disease**

**Guidance on recurrence risk**

- High risk if
  - aggressive initial course (heavy proteinuria and renal failure within 3 years of onset)
  - < 15 years at onset
  - mesangial proliferation on biopsy
  - not known to be familial

- 75% if already
<table>
<thead>
<tr>
<th>Disease</th>
<th>Recurred Once</th>
<th>Recurred Once &amp; HCV Status</th>
<th>Recurred Once &amp; HCV Status</th>
<th>OK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesangiocapillary GN – type 1</td>
<td>40%</td>
<td>80% if already recurred</td>
<td>Depends on HCV status &amp; other factors</td>
<td>OK</td>
</tr>
<tr>
<td>Mesangiocapillary GN – type 2 [dense deposit disease]</td>
<td>80%</td>
<td>25% at 10 years</td>
<td>OK</td>
<td></td>
</tr>
<tr>
<td>ANCA-positive vasculitis</td>
<td>15%</td>
<td>Rare</td>
<td>OK</td>
<td></td>
</tr>
<tr>
<td>Anti-GBM disease</td>
<td>Very low if anti-GBM Ab negative</td>
<td>Very low if anti-GBM Ab negative</td>
<td>OK</td>
<td></td>
</tr>
<tr>
<td>Alport syndrome</td>
<td>Zero</td>
<td>Rare – unless early development of anti-GBM antibodies &lt;10% of Alport transplants</td>
<td>Evaluate potential carriers carefully</td>
<td></td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>1-30% reported!</td>
<td>Very low</td>
<td>OK</td>
<td></td>
</tr>
<tr>
<td>D+ HUS</td>
<td>Rare</td>
<td>Rare</td>
<td>OK</td>
<td></td>
</tr>
<tr>
<td>D- HUS</td>
<td>Overall 30% Variable but very high with some complement mutations Evaluation of suitability for transplantation must follow national guidance including liaison with Prof T Goodship (Newcastle)</td>
<td>Overall 80% Variable but very high with some complement mutations</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Primary hyperoxaluria</td>
<td>Very high</td>
<td>Very high</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Consider combined liver-kidney transplant</td>
<td></td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>AA amyloid</td>
<td>10% at 5 years</td>
<td></td>
<td>OK</td>
<td></td>
</tr>
<tr>
<td>AL amyloid</td>
<td>Uncertain – discuss on case by case basis</td>
<td></td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

**Re-evaluation of listed potential recipients**

All patients active on the transplant waiting list should be assessed annually by the consultant nephrologist in charge of their care to determine their continuing suitability for transplantation. This will include cardiac assessment according to the algorithm above. Re-referral to the transplant surgical assessment clinic will be made at the discretion of the nephrologist in line with local protocol.
References


