

## CLINICAL PRACTICE GUIDELINES

# Post-operative Care of the Kidney Transplant Recipient

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### **Bibliography**

## **Acknowledgements**

## Introduction

This document is intended for those engaged in the care of renal transplant recipients (RTR) who are non-experts. With increasing efforts to deliver healthcare locally many renal transplant recipients are followed up in centres remote from the main surgical transplant unit. At the same time transplantation medicine has evolved into an increasingly complex and specialised field of nephrology. The following guidelines reflect this alteration in clinical practice and are intended for those healthcare professionals who look after renal transplant patients. They are also intended to be useful to both medical and surgical trainees as well as nurse specialists and other associated healthcare professionals involved in the care of renal transplant patients.

These guidelines cover the period after renal transplantation, specifically from initial hospital discharge until graft failure or patient death. The management of KTR can be divided into two phases: (a) an early post-operative phase when prevention of acute rejection, optimization of graft function and prevention of opportunistic infection are paramount, and (b) a later phase when the aims are to preserve good graft function and prevent the long-term consequences of immunosuppression – malignancy, infection and premature cardiovascular disease. The transition between these two phases occurs around 3-6 months at the time when the progressive, protocolised, reduction in immunosuppression following transplantation reaches long-term maintenance levels. Management of early and late phase complications of transplantation requires monitoring at reducing frequency, awareness of the complications, access to investigation and monitoring, and strategies for the prevention and treatment of complications (ranging from early acute rejection, to late cardiovascular disease). We recognise that there are regional differences in demographics, risk and services and that the leading priority is the agreement of local strategies for post-transplant management.

These guidelines are designed to complement those previously published by Dudley and Harden relating to pre-transplant care:

[www.renal.org/Guidelines/GuidelinesSection/Guidelines.aspx](http://www.renal.org/Guidelines/GuidelinesSection/Guidelines.aspx)

It should be noted that other comprehensive guidelines have recently been published and reference will be made to these as appropriate <sup>1,2</sup>.

The evidence for these recommendations has been assessed using the modified GRADE system. The modified GRADE system defines both the strength of the recommendations of the guideline authors and the level of evidence upon which each of the recommendations is based. This grading system classifies expert recommendations as “strong” (Grade 1) or “weak” (Grade 2) based upon the balance between the benefits and risks, burden and cost. The quality or level of evidence is designated as high (Grade A), moderate (Grade B), low (Grade C) or very low (D) depending on factors such as study design, directness of evidence and consistency of results. Grades of recommendation and quality of evidence may range from 1A to 2D.

The GRADE system has been developed by an international group of guideline developers and methodologists to improve the usefulness of clinical practice guidelines in the management of typical patients.

## **Summary of clinical practice guidelines for Post-operative Care of the Kidney Transplant Recipient**

### **1. Kidney Transplant Recipient (KTR): Organisation of outpatient follow-up (Guidelines 1.1 – 1.4)**

#### **Guideline 1.1 – KTR: Clinic infrastructure**

We suggest that the following infrastructure should be in place for KTR follow up. (2D)

- A consultant-level health care professional should be available for every transplant clinic.
- KTRs should be reviewed in a dedicated outpatient area.
- The results of blood tests (including drug levels if possible) should be available within 24 hours.
- A formal mechanism should exist for results review by healthcare professionals within 24 hours of a clinic appointment.
- There should be access to a multidisciplinary renal team including pharmacist, dietician, social worker and psychologist.
- Patient care should be planned along principles set out in the National Service Framework.

#### **Guideline 1.2 – KTR: Clinic frequency**

We suggest that uncomplicated patients, as a general rule, may be reviewed progressively less frequently in clinic. (2C)

- 2-3 times weekly for the first month after transplantation.
- 1-2 times weekly for months 2-3.
- Every 1-2 weeks for months 4-6.
- Every 4-6 weeks for months 6-12.
- 3-6 monthly thereafter.

#### **Guideline 1.3 – KTR: Patient access**

We suggest that all patients should have ready access to support services and results. (2C)

- All patients should have on-line access to their results via the “Renal Patient View” service if they wish.
- All patients should have open access to the renal transplant outpatient service and have an established point of contact for enquiries.
- Patient information should be available in both written and electronic formats.

## **Guideline 1.4 – KTR: Chronic transplant care review**

We suggest that a detailed review should be performed annually post-operatively. (2C)

- A process should exist for patient review on an annual basis in a different format of clinic according to the “Care plan model”
- This should be a patient-centred clinic, facilitated by a healthcare professional
- It should address concerns in medical, social, psychological and sexual domains
- Open access to a renal dietician, social worker, specialist renal pharmacist or psychologist should be readily available from this clinic
- This process should proceed in parallel with formal medical review

## **2. Kidney Transplant Recipient (KTR): Non-adherence**

### **(Guideline 2.1)**

#### **Guideline 2.1 – KTR: Recognising non-adherence**

We suggest that it is important to prevent and detect non-adherence in kidney transplant recipients. (2C)

- Factors associated with non-adherence should be identified.
- An established interventional pathway should be in place for those at high risk of or with proven non-adherence.
- Pathways should be in place for paediatric KTRs in transition and for adolescent KTRs.

## **3. Kidney Transplant Recipient (KTR): Immunosuppressive treatment (Guidelines 3.1-3.12)**

### **Guideline 3.1 – KTR: Induction immunosuppression**

We recommend induction therapy should take into account the following:

- Immunosuppressive drugs should be started before or at the time of renal transplantation. (1B)
- Induction therapy with biological agents should be administered to all KTRs. (1B) In patients at low immunological risk this will generally involve an interleukin-2 receptor antagonist (IL2-RA). Recipients at higher immunological risk may be considered for T-cell (lymphocyte) Depleting Antibodies (TDAs; e.g. anti-lymphocyte preparations [ALG, ATG], alemtuzumab or OKT3).
- Induction therapy with TDAs may also be useful for lower immunological risk patients with the intention of either steroid or CNI avoidance. (1C)

### **Guideline 3.2 – KTR: Induction immunosuppression**

We suggest that a CNI should be started at the time of transplantation and not delayed until the graft is functioning. (2C)

### **Guideline 3.3 – KTR: Maintenance immunosuppression**

We recommend that maintenance immunosuppression should normally consist of a calcineurin inhibitor (CNI) and an anti-proliferative agent, with or without corticosteroids in low and medium immunological risk KTRs. (1B)

### **Guideline 3.4 – KTR: Maintenance immunosuppression**

We suggest that low dose tacrolimus (trough target 3-7ng/ml) is recommended as the CNI of choice in patients also taking steroids who are low and medium immunological risk and are not at high risk of developing NODAT. (2C)

### **Guideline 3.5 – KTR: Maintenance immunosuppression**

We suggest that MPA-based drugs should be the first-line antiproliferative agent, in preference to azathioprine. (2B)

### **Guideline 3.6 – KTR: Maintenance immunosuppression**

We suggest that mycophenolate mofetil (Cellcept<sup>®</sup>) and enteric coated mycophenolate sodium (Myfortic<sup>®</sup>) provide equivalent maintenance immunosuppression. (2B)

### **Guideline 3.7 – KTR: Maintenance immunosuppression**

We suggest that vigilant steroid avoidance or steroid withdrawal can generally be used during the first week after transplantation in low immunological risk kidney transplant recipients. (2B)

### **Guideline 3.8 – KTR: Maintenance immunosuppression**

We suggest aiming for minimum target levels for CNIs in uncomplicated renal transplantation after 3 months. (2C)

### **Guideline 3.9 – KTR: Maintenance immunosuppression**

We suggest that CNIs should be continued rather than withdrawn. (2B)

### **Guideline 3.10 – KTR: Maintenance immunosuppression**

We suggest if steroids are not withdrawn within the first month then they should be maintained at low dose (Prednisolone - 5mg per day or less). (2C)

### **Guideline 3.11 – KTR: Monitoring of immunosuppression**

We suggest that long-term monitoring of immunosuppression levels is required as follows:

- Tacrolimus and ciclosporin levels should be monitored. The initial frequency should be three times a week. Levels should also be checked when any medication with possible interactions is prescribed, the dosage is changed, the formulation is changed or when there is unexplained graft dysfunction. (2C)
- Tacrolimus should be monitored by the C<sub>0</sub> trough level, while ciclosporin can be monitored by either C<sub>0</sub> or C<sub>2</sub> level. (2C)
- Tacrolimus and ciclosporin levels should be available within 24 hours of taking blood samples in the first three months after transplantation. (2D)
- The utility of monitoring MMF C<sub>0</sub> levels is uncertain. (2D)
- Sirolimus should be monitored by the C<sub>0</sub> trough level. (2C)

### **Guideline 3.12 – KTR: Prescribing and the use of generic agents**

We suggest that generic compounds should not be used unless they have been shown to be bioequivalent to branded products and have been approved by the European Agency for the Evaluation of Medicinal Products (EMA). (2D)

### **Guideline 3.13 – KTR: Prescribing and the use of generic agents**

We suggest that KTRs should be made aware of the existence of generics and the dangers of indiscriminate usage. (2D)

### **Guideline 3.14 – KTR: Prescribing and the use of generic agents**

We suggest that drugs should be prescribed by brand name where unproven generic substitutes are available. (2D)

### **Guideline 3.15 – KTR: Prescribing and the use of generic agents**

We suggest that KTRs should be followed closely after switching to a generic preparation until a new steady state is established. (2D)

## **4. Kidney Transplant Recipient (KTR): Acute rejection**

### **(Guidelines 4.1-4.10)**

#### **Guideline 4.1 – KTR: Diagnosis of acute rejection**

We recommend that a transplant renal biopsy should be carried out before treating an acute rejection episode unless this will substantially delay treatment or pose a significant risk to the patient. (1C)

#### **Guideline 4.2 – KTR: Diagnosis of acute rejection**

We suggest that two cores of renal tissue should be obtained if possible since this will increase the sensitivity of the investigation. (2C)

#### **Guideline 4.3 – KTR: Diagnosis of acute rejection**

We suggest that routine C4d and SV40 staining should be performed upon transplant biopsies. (2C)

#### **Guideline 4.4 – KTR: Treatment of acute rejection**

We suggest that borderline acute cellular rejection should be treated. (2D)

#### **Guideline 4.5 – KTR: Treatment of acute rejection**

We recommend that high dose intravenous corticosteroids should be the first line treatment for acute cellular rejection. (1D)

#### **Guideline 4.6 – KTR: Treatment of acute rejection**

We suggest that maintenance steroids should be added or restarted in steroid-free patients undergoing acute rejection of any type. (2D)

#### **Guideline 4.7 – KTR: Treatment of acute rejection**

We suggest that lymphocyte depleting agents may be considered for refractory acute cellular rejection or aggressive vascular cellular rejection (i.e. BANFF category 4 Type II and III). (2C)

#### **Guideline 4.8 – KTR: Treatment of acute rejection**

We suggest that antibody mediated rejection (AMR) should be treated with one or more of the following modalities: steroids; plasma exchange; intravenous immunoglobulin; anti-CD20 antibody; or lymphocyte-depleting antibody. (2C)

#### **Guideline 4.9 – KTR: Treatment of acute rejection**

We suggest after an episode of rejection (unless associated with low CNI levels) that azathioprine should be switched to MPA-based immunosuppression, MPA should be started or the existing dose of MPA maximised. (2D)

#### **Guideline 4.10 – KTR: Treatment of acute rejection**

We suggest that a serum sample should be sent at the time of renal biopsy (for graft dysfunction) to look for HLA-specific antibodies. (2C)

## **5. Kidney Transplant Recipient (KTR): Chronic Allograft Injury (Guidelines 5.1-5.7)**

### **Guideline 5.1 – KTR: Diagnosis of Chronic Allograft Injury (CAI)**

We recommend that early identification of graft injury is desirable to maximise the potential to intervene. A proactive and systematic approach should be employed to identify graft dysfunction. (1C)

### **Guideline 5.2 – KTR: Detection of Chronic Allograft Injury (CAI)**

We suggest that renal function should be monitored at each clinic visit by assessment of serum creatinine and qualitative evaluation of urine protein excretion by dipstick supplemented by spot PCR or ACR if positive. (2C)

### **Guideline 5.3 – KTR: Diagnosis of Chronic Allograft Injury (CAI)**

We suggest that renal biopsy is the optimal investigation for parenchymal causes of graft dysfunction. (2C)

### **Guideline 5.4 – KTR: Diagnosis of Chronic Allograft Injury (CAI)**

We suggest that renal biopsies in patients with chronically deteriorating function should routinely be stained for C4d and SV40. (2C)

### **Guideline 5.5 – KTR: Diagnosis of Chronic Allograft Injury (CAI)**

We suggest that a serum sample should be sent at the time of renal biopsy (for graft dysfunction) to look for HLA-specific antibodies. (2C)

### **Guideline 5.6 – KTR: Treatment of chronic allograft injury**

We suggest that chronic allograft injury should be treated:

- By withdrawal of calcineurin inhibitors (CNIs) if there is either histological evidence of CNI toxicity or non-specific interstitial fibrosis and tubular atrophy. (2C)
- By intensification of immunosuppression if there is evidence of ongoing immune injury (cellular rejection and/or humoral rejection). (2C)
- In a similar fashion to other patients with CKD following similar preventative strategies and with timely referral to low clearance services. (2D)

### **Guideline 5.7 – KTR: Renal biopsy in chronic allograft injury**

We suggest that a renal transplant biopsy is indicated:

- If there is a persistent unexplained elevation of creatinine or failure to return to baseline after an episode of BPAR. (1C)
- Every 7-10 days during DGF. (2C)
- If expected renal function is not achieved within 4-8 weeks. (2D)
- If sustained new onset proteinuria develops (PCR>50 or ACR>35). (2C)

## **6. Kidney Transplant Recipient (KTR): Cardiovascular disease (Guidelines 6.1-6.7)**

### **Guideline 6.1 – KTR: Hypertension**

We suggest that the management of hypertension take into account that:

- Blood pressure should be recorded at each clinic visit. (1C)
- Clinic blood pressure should be less than 130/80mmHg in clinic (125/75mmHg if PCR>50 or ACR>35). (2C)
- Home blood pressure recordings and 24-hour ambulatory recordings may be helpful in some instances but lower targets should be set. (2D)
- There is no evidence that any antihypertensive agent is better than any other and effort should be focused on achieving absolute levels rather than the use of individual agents. (2D)
- Inhibitors of the renin-angiotensin system may be more effective in the minimisation of proteinuria but they should be used with caution in the first 3 months post transplant. (2C)
- Resistant hypertension may be due to transplant renal artery stenosis and should be investigated according to local practice. (2D)

### **Guideline 6.2 – KTR: Dyslipidaemia**

We suggest that the management of dyslipidaemia take into account that:

- Fasting lipid levels should be measured on an annual basis in all renal transplant recipients. (2C)
- Treatment targets should be the same as in the general population. (2C)
- KTRs at increased primary or secondary CV risk receive statin therapy to reduce the risk of coronary artery disease. (2C)
- The choice and dose of statin should take into account concurrent immunosuppression. (2D)

### **Guideline 6.3 – KTR: Diabetes mellitus**

We suggest that the detection and treatment of diabetes should consider:

- Screening for the development of post transplant diabetes by dipstick urinalysis and measurement of blood sugar level at each clinic visit. (2C)
- Post transplant immunosuppression should take into account risk factors for the development of diabetes. (2C)
- Post-transplant diabetes should be managed in collaboration with specialists in diabetic medicine. (2D)

- All units should have a protocol for the management of post-transplant diabetes. (2C)

#### **Guideline 6.4 – KTR: Ischaemic heart disease**

We suggest that KTRs receive standard treatment for ischaemic heart disease, including thrombolysis, revascularisation, and secondary prevention. (2C)

#### **Guideline 6.5 – KTR: Smoking cessation**

We recommend that smoking should be discouraged in transplant recipients (see guideline 6.4). (1A)

#### **Guideline 6.6 – KTR: Lifestyle measures**

We suggest that advice on healthy lifestyle forms a routine part of post-transplant care:

- Maintenance of a healthy diet should be encouraged. (2C)
- An active lifestyle should be encouraged. (2D)
- An ideal weight should be targeted ( $BMI \leq 25$ ). (2C)
- Weight management services should be available. (2C)
- Alcohol consumption should be within national guidelines. (2D)
- Recreational drug use should be avoided. (2D)
- The use of over-the-counter medications (without discussion with clinical staff) and non-proprietary medications (e.g. herbal medicines) should be discouraged. (2D)

## **7. Kidney Transplant Recipient (KTR): Neoplasia (Guidelines 7.1-7.4)**

#### **Guideline 7.1 – KTR: Screening for cancer**

We suggest that the organisation of screening for neoplasia in KTRs take into account:

- Screening should be similar to the general population for cervical, breast, colon and prostate cancer. (2C)
- Screening is not recommended for renal cell carcinoma. (2C)
- Breast and testicular self-examination should be encouraged. (2D)
- An annual examination of skin by a healthcare professional. (2C)
- Patients with cirrhosis should undergo an annual hepatic ultrasound and determination of serum alpha feto-protein. (2C)

#### **Guideline 7.2 – KTR: Non-Melanoma Skin Cancer (NMSC)**

We recommend that KTRs should be educated about the adverse effects of solar exposure. (1C)

### **Guideline 7.3 – KTR: Non-Melanoma Skin Cancer (NMSC)**

We suggest that KTRs that an individualised assessment of hazard should be made according to risk factors. (2C)

### **Guideline 7.4 – KTR: Non-Melanoma Skin Cancer (NMSC)**

We recommend that patients should be encouraged to cover their skin in direct sunlight and to use total sunblock (Sun Protection Factor  $\geq 50$ ). (1D)

### **Guideline 7.5 – KTR: Non-Melanoma Skin Cancer (NMSC)**

We suggest that self examination should be encouraged and should be supplemented by annual review by a trained healthcare professional. (2C)

### **Guideline 7.6 – KTR: Non-Melanoma Skin Cancer (NMSC)**

We suggest that acitretin should be prescribed to those with previous NMSC if there are no contraindications. (2B)

### **Guideline 7.7 – KTR: Immunosuppression in cancers**

We suggest that the overall level of immunosuppression should be reduced if neoplasia develops. (2C)

### **Guideline 7.8 – KTR: Immunosuppression in cancers**

We suggest that m-TORis are considered as an alternative immunosuppressive agents in KTRs who develop *de novo* malignancy. (2C)

### **Guideline 7.9 – KTR: Immunosuppression in Kaposi's sarcoma**

We suggest that m-TORis has specific anti-tumour effects in Kaposi's sarcoma and switching to this medication should be considered. (2C)

## **8. Kidney Transplant Recipient (KTR): Infection Complications (Guidelines 8.1-8.7)**

### **Guideline 8.1 – KTR: Vaccination**

#### **Guideline 8.1.1 – KTR: Vaccination**

We recommend that KTRs:

- Should be vaccinated with inactivated viruses as per the normal population except for HBV. (1D)
- Should receive annual influenza vaccination unless contraindicated. (1C)

### **Guideline 8.1.2 – KTR: Vaccination**

We suggest that KTRs:

- Should have HBsAb levels rechecked annually and revaccination carried out if antibody titres fall below 10mIU/ml. (2D)
- Should not receive live attenuated vaccines. (2C)
- Should receive pneumococcal vaccine and one booster after five years. (2D)

### **Guideline 8.2 – KTR: Cytomegalovirus disease**

#### **Guideline 8.2.1 – KTR: prophylaxis and treatment of CMV disease**

We recommend:

- Prophylaxis should be continued for 3-6 months, until immunosuppression has been reduced to long-term maintenance level; 6 months has proven benefit in sero-negative recipients of kidneys from CMV positive donors. (1B)
- Treatment should be administered for 6 weeks after treatment with a TDA. (1C)

#### **Guideline 8.2.2 – KTR: prophylaxis and treatment of CMV disease**

We suggest:

- All transplant units should have the ability to measure CMV serological status and the detection and quantification of viral load. (2D)
- Donor and recipient CMV sero-positivity should be recorded at the time of transplantation. (2D)
- A written protocolised strategy based either on prophylaxis, or pre-emptive therapy, or both should be implemented. (2D)
- For the treatment of mild and moderate CMV disease, oral valganciclovir and intravenous ganciclovir are of equivalent efficacy. (2C)
- Treatment of life-threatening CMV disease should be initiated with intravenous ganciclovir. (2D)
- Treatment duration should be determined by monitoring viral load. (2C)

### **Guideline 8.3 – KTR: Epstein Barr Virus infection**

#### **Guideline 8.3.1 – KTR: EBV infection**

We recommend that immunosuppression should be reduced or stopped following the development of PTLD. (1C)

#### **Guideline 8.3.2 – KTR: EBV infection**

We suggest:

- Both donor and recipient should have their EBV serology recorded at the time of transplantation. (2D)
- All high risk (D<sup>+</sup>/R<sup>-</sup>) patients (including adults) should have EBV viral load measured immediately after transplantation, monthly for six months, and three monthly to one year. (2C)
- EBV viral load should be monitored after the treatment of rejection. (2C)
- Total immunosuppression should be reduced when EBV titres rise significantly. (2C)

## **Guideline 8.4 – KTR: Varicella Zoster Virus infection**

### **Guideline 8.4.1 – KTR: VZV infection**

We recommend:

- Primary infection (chickenpox) should be treated with intravenous aciclovir or oral valaciclovir until the lesions scab over. (1C)
- Uncomplicated shingles should be treated with oral acyclovir or valaciclovir until the lesions scab over. (1D)
- Disseminated (>2 dermatomes), ocular or invasive shingles should be treated with intravenous aciclovir until the lesions scab over, together with a reduction in immunosuppression. (1B)
- Varicella-susceptible KTRs (i.e. VZV IgG -ve) with primary exposure to VZV should receive intravenous immunoglobulins, ideally within 96 hours, but up to a maximum of 10 days following exposure. If unavailable or after 10 days, oral aciclovir should be administered for seven days, starting one week after exposure. (1D)

### **Guideline 8.4.2 – KTR: VZV infection**

We suggest:

- Patients on the waiting list who are VZV IgG negative should be vaccinated prior to transplantation. (2D)
- Immunosuppression should be reduced during primary infection. (2D)

## **Guideline 8.5 – KTR: Herpes Simplex Virus infection**

### **Guideline 8.5.1 – KTR: HSV infection**

We recommend:

- Superficial HSV infection should be treated with appropriate oral agents until the lesions have resolved. (1D)
- Systemic HSV infections should be treated with intravenous aciclovir and a reduction in immunosuppression until a response occurs and oral medication continued for at least 14 days. (1C)

### **Guideline 8.5.2 – KTR: HSV infection**

We suggest that KTRs suffering frequent recurrent HSV infection should consider oral prophylaxis. (2D)

### **Guideline 8.6 – KTR: BK nephropathy**

#### **Guideline 8.6.1 – KTR: BK nephropathy**

We recommend that confirmed BK nephropathy should be treated by reduction in immunosuppression. (1D)

#### **Guideline 8.6.2 – KTR: BK nephropathy**

We suggest:

- KTRs should be screened for BKV viral load by performing urine microscopy for decoy cells or by PCR on urine or serum. (2C)
- Screening should be monthly for the first six months, then every three months until the end of the first year. (2D)
- Screening should also be carried out when renal function deteriorates in an unexplained fashion or when immunosuppression is intensified. (2D)
- Suspected BK nephropathy should be confirmed by renal biopsy which should be stained for SV40. Two cores containing medullary tissue should ideally be examined. (2D)
- Immunosuppression should be reduced when the serum BKV load exceeds  $10^4$  copies/ml. (2C)
- There is no established specific treatment for BK nephropathy. (2D)
- Re-transplantation can safely be considered in patients who have BK nephropathy diagnosed in an earlier graft. (2C)

### **Guideline 8.7 – KTR: Post-transplant infection prophylaxis**

We suggest:

- All patients should receive 3-6 months of treatment with co-trimoxazole 480mg daily. (1B)
- Oral antifungal prophylaxis should be administered for three months after transplantation. (2C)
- In selected patients, prophylaxis against mycobacterium tuberculosis with daily isoniazid (supplemented with pyridoxine) should be instituted for six months after transplantation. (2C)

## **9. Kidney Transplant Recipient (KTR): Bone and joint disease (Guidelines 9.1-9.4)**

### **Guideline 9.1 – KTR: Osteoporosis**

We suggest:

- KTRs suffering from osteoporosis or at high potential risk should be considered for steroid-avoiding immunosuppression. (2D)
- KTRs on longterm steroids or at high risk for osteoporosis should undergo DEXA scanning if eGFR>30 ml/min/1.73m<sup>2</sup>. (2D)
- Treatment should be according the RCP guidelines for steroid-induced osteoporosis. (2D)

### **Guideline 9.2 – KTR: Tertiary hyperparathyroidism**

We suggest:

- Severe hyperparathyroidism should be treated prior to transplantation. (2D)
- Cinacalcet can be used in KTRs. (2C)
- Treatment should be the same as for other patients with CKD. (2D)

### **Guideline 9.3 – KTR: Gout**

#### **Guideline 9.3.1 – KTR: Treatment of gout**

We recommend that allopurinol should not be administered with azathioprine. (1B)

#### **Guideline 9.3.2 – KTR: Treatment of gout**

We suggest:

- Hyperuricaemia should be treated when associated with gout, tophi or uric acid stones. (2D)
- Non steroidal anti-inflammatory drugs (NSAIDs) should be avoided in KTRs. (2D)
- Episodes of gout may be treated with brief courses of oral prednisolone. (2D)
- Colchicine is an effective treatment for gout in KTRs. (2D)

### **Guideline 9.4 – KTR: Calcineurin inhibitor bone pain**

We suggest:

- Reducing or withdrawing CNIs should be considered in KTRs with intractable bone pain. (2D)
- Dihydropyridine calcium antagonists also may be beneficial. (2D)

## **10. Kidney Transplant Recipient (KTR): Haematological complications (Guidelines 10.1-10.4)**

### **Guideline 10.1 – KTR: Anaemia**

We suggest that anaemia should be managed in the same way as other patients with CKD. (2D)

### **Guideline 10.2 – KTR: – Polycythaemia**

We recommend that initial treatment should be with angiotensin converting enzyme inhibitors (ACEIs) or with angiotensin receptor blockers (ARBs). (1C)

### **Guideline 10.3 – KTR: – Polycythaemia**

We suggest:

- Haemoglobin levels should be monitored at every clinic visit. (2D)
- Treatment should be initiated if the haematocrit or packed cell volume exceeds 52% in men and 49% in women. (2D)
- Aminophylline and venesection may be used in refractory cases. (2D)

## **11. Kidney Transplant Recipient (KTR): Reproductive issues**

### **(Guidelines 11.1-11.3)**

#### **Guideline 11.1 – KTR: Conception and contraception (female)**

We recommend that MPA-containing immunosuppressant drugs should be stopped prior to conception and replaced appropriately. (1A)

#### **Guideline 11.2 – KTR: Conception and contraception (female)**

We suggest:

- KTRs should wait for one year after transplant and have stable function before attempting conception. (2C)
- Counselling regarding fertility and reproduction should be offered to female KTRs and their partners either prior to transplantation or soon afterwards. (2D)
- m-TORi should be stopped prior to conception and replaced as appropriate. (2D)
- Pregnancy should be managed jointly with an Obstetrics department. (2D)
- The risks and benefits of breastfeeding should be discussed. (2D)
- Contraception advice should be similar to the general population. (2D)

#### **Guideline 11.3 – KTR: Conception (male)**

We recommend that KTRs should be advised that m-TORi reduce the male sperm count and counselled accordingly. (1C)

#### **Guideline 11.4 – KTR: Conception (male)**

We suggest:

- All immunosuppressive drugs other than m-TORi can be used in male KTRs. (2D)
- Men on m-TORi who wish to conceive should discontinue these agents prior to conception and replace them as appropriate (2D)
- Men who wish to maintain fertility should avoid m-TORi or bank sperm prior to starting these drugs. m-TORi reduce the male sperm count and KTRs should be counselled accordingly. (2D)
- Men should be counselled about the possible risks of impotence following transplantation surgery that involves the internal iliac artery. (2D)

#### **Guideline 11.5 – KTR: Sexual dysfunction**

We suggest:

- Specific enquiry should be made regarding sexual dysfunction, preferably at an annual review clinic. (2D)
- Care pathways for dealing with sexual dysfunction should be established. (2D)
- Close liaison with the local andrology service is recommended. (2D)
- Sildenafil is safe and effective in male KTRs not taking nitrates. (2D)

## **Summary of audit measures for Post-operative Care of the Kidney Transplant Recipient**

1. Proportion of blood results available for review, and reviewed, within 24 hours.
2. Proportion of units with a written follow-up schedule available to all staff and patients.
3. Percentage of patients accessing their results through Renal Patient View.
4. Percentage of total patients assessed in an annual review clinic.
5. Percentage of total patients receiving induction with ILRAs and TDAs
6. Percentage of de novo KTRs receiving tacrolimus.
7. Percentage of de novo KTRs receiving MPA based immunosuppression.
8. Percentage of de novo KTRs receiving corticosteroid maintenance therapy.
9. Use of generic agents.
10. Severity of biopsy proven acute rejection (BPAR) recorded by BANFF criteria.
11. Percentage of KTRs with BPAR in first 3 months and first 12 months.
12. Percentage of KTRs requiring TDAs to treat rejection in first year.
13. Complication rates after renal transplant biopsy.
14. Proportion of patients receiving a target blood pressure of 130/80mmHg or 125/75mmHg in the presence of proteinuria (PCR>100 or ACR>70).
15. Proportion of patients receiving an ACE inhibitor or angiotensin receptor blocker.
16. Proportion of patients with proteinuria assessed by dipstix and, if present, quantified at each clinic visit.
17. Proportion of renal transplant recipients with an annual fasting lipid profile.
18. Proportion of RTR taking statins (including the type of statin) for primary and secondary prevention of premature cardiovascular disease.
19. Proportion of patients on other lipid lowering agents.
20. Proportion of patients achieving dyslipidaemia targets.
21. Incidence of new onset diabetes after transplantation (NODAT) at three months and at annual intervals thereafter.
22. Proportion of patients who require insulin, and in whom remedial action is undertaken – minimisation of steroids and switching of CNIs.
23. Proportion of patients with ischaemic heart disease.
24. Proportion of patients suffering myocardial infarction.
25. Proportion of patients undergoing primary revascularisation.
26. Proportion of patients receiving secondary prevention with a statin, anti-platelet agents and RAS blockers.
27. Proportion of patients who are obese.
28. Proportion of patients having screening procedures for neoplasia at the annual review clinic.
29. Incidence of CMV disease.
30. Rate of EBV infection and PTLD.
31. Completeness of records for EBV donor and recipient serology.
32. Rates of primary VZV and shingles infection.
33. Completeness of records for VZV recipient serology.
34. Rates and outcomes of HSV infections.
35. Rates of BK viral infection in screening tests.

36. Rates and outcomes of BK nephropathy.
37. Frequency of bisphosphonate use.
38. Incidence of fractures.
39. Incidence of hyperparathyroidism.
40. Incidence of parathyroidectomy.
41. Use of cinacalcet.
42. Frequency of hyperuricaemia and gout.
43. Prevalence of anaemia.
44. Prevalence of polycythaemia.
45. Pregnancy rates and outcomes.
46. Prevalence of sexual dysfunction.

## **Rationale of clinical practice guidelines for Post-operative Care of the Kidney Transplant Recipient**

### **1. Kidney Transplant Recipient (KTR) : Organisation of Outpatient Follow-up (Guidelines 1.1 – 1.4)**

#### **Guideline 1.1 – KTR: Clinic infrastructure**

**We suggest that the following infrastructure should be in place for KTR follow up. (2D)**

- **A consultant-level healthcare professional should be available for every transplant clinic.**
- **KTRs should be reviewed in a dedicated outpatient area.**
- **The results of blood tests (including drug levels if possible) should be available within 24 hours.**
- **A formal mechanism should exist for results review by health care professionals within 24 hours of a clinic appointment.**
- **There should be access to a multidisciplinary renal team including pharmacist, dietician, social worker and psychologist.**
- **Patient care should be planned along principles set out in the National Service Framework.**

#### **Audit Measure**

The proportion of blood results available for review, and reviewed, within 24 hours.

#### **Rationale**

All KTRs should have ready access to a senior clinical opinion; and a senior clinician should be available at renal transplant clinics. In some centres this may be a consultant-level nurse, in others a medical or surgical consultant. The exact type of healthcare professional is not important but KTRs and junior staff should have access to an individual with appropriate knowledge and experience. This will also benefit the training of junior medical staff. A dedicated outpatient area is beneficial to patients and clinical staff, as it provides a familiar environment and staff experienced in the management of patients on renal replacement therapy.

Prompt availability and formal review of test results is desirable since most complications can be resolved more easily if recognised at an early stage, particularly in the first few weeks after renal transplantation. It is recommended that patient care is carried out according to the principles laid out in the DoH leaflet, “Achieving Excellence In Kidney Care”<sup>3</sup>.

#### **Guideline 1.2 – KTR: Clinic frequency**

**We suggest that uncomplicated patients, as a general rule, may be reviewed progressively less frequently in clinic. (2C)**

- **2-3 times weekly for the first month after transplantation.**
- **1-2 times weekly for months 2-3.**
- **Every 1-2 weeks for months 4-6.**
- **Every 4-6 weeks for months 6-12.**
- **3-6 monthly thereafter.**

### **Audit Measure**

Proportion of units with a written follow-up schedule available to all staff and patients

### **Rationale**

Freedom from regular hospital attendance is an important benefit of renal transplantation balanced against the risks and prevention of complications. These risks (specifically of surgical complications) are highest in the immediate postoperative period and during the first few weeks following hospital discharge, when the burden of immunosuppression is greatest. For typical patients monitoring should therefore be most frequent during this period and then diminish with time. The use of virtual renal clinics should be explored as a complementary form of KTR review since it might be more convenient to some patients.

### **Guideline 1.3 – KTR: Patient access**

**We suggest that all patients should have ready access to support services and results. (2C)**

- **All patients should have on-line access to their results via the “Renal Patient View” service if they wish.**
- **All patients should have open access to the renal transplant outpatient service and have an established point of contact for enquiries.**
- **Patient information should be available in both written and electronic formats.**

### **Audit Measure**

Percentage of patients accessing their results through Renal Patient View

### **Rationale**

Patients should be encouraged to take an active role in their own care according to principles embodied in the National Service Framework<sup>3</sup>. Interest in their own blood results should be welcomed and KTRs should be encouraged to use Renal Patient View (<https://www.renalpatientview.org/>). Patient education is a crucial element in the success of renal transplantation and easy access to information should be provided for all patients in different formats (e.g. paper-based and electronic).

### **Guideline 1.4 – KTR: Chronic transplant care review**

**We suggest that a detailed review should be performed annually post-operatively. (2C)**

- **A process should exist for patient review on an annual basis in a different format of clinic according to the “Care plan model”**
- **This should be a patient-centred clinic, facilitated by a healthcare professional**
- **It should address concerns in medical, social, psychological and sexual domains**
- **Open access to a renal dietician, social worker, specialist renal pharmacist or psychologist should be readily available from this clinic**
- **This process should proceed in parallel with formal medical review**

### **Audit Measure**

Percentage of total patients assessed in an annual review clinic

### **Rationale**

Since KTRs experience considerable late morbidity which is unlikely to be managed properly in a traditional clinical setting (e.g. skin lesions, sexual dysfunction and psychological morbidity) it seems sensible to facilitate periodic follow up in a different and more holistic environment <sup>4,5</sup>.

## **2. Kidney Transplant Recipient (KTR): Non-adherence**

### **(Guideline 2.1)**

#### **Guideline 2.1 – KTR: Recognising non-adherence**

**We suggest that it is important to prevent and detect non-adherence in kidney transplant recipients. (2C)**

- **Factors associated with non-adherence should be identified.**
- **An established interventional pathway should be in place for those at high risk of or with proven non-adherence.**
- **Pathways should be in place for paediatric KTRs in transition and for adolescent KTRs.**

### **Audit Measures**

1. Recording “Did Not Attend” (DNA) rates for all patients
2. Recording sub-therapeutic drug levels.

### **Rationale**

Non-adherence with immunosuppressive medication is an important factor in graft loss and up to a third of patients report regularly missing tablets <sup>6</sup>. Clinical parameters associated with non-adherence are well recognised and should be used to assessing risk e.g. erratic or low immunosuppression levels, clinic non-attendance, psychiatric illness, low belief in the need for medication, adolescence and early adulthood <sup>7-9</sup>.

### **3. Kidney Transplant Recipient (KTR) : Immunosuppressive treatment (Guidelines 3.1-3.12)**

#### **General concepts**

The starting point for renal transplantation is comparison with other forms of renal replacement therapy (RRT). Renal transplantation provides a superior quality of life, an increased sense of well being and a superior life span when compared to other forms of RRT. Therefore minor differences in clinical outcome between different immunosuppressive regimes should be placed in context with the much greater difference in outcome between transplantation and other forms of RRT, for those fit enough to be wait listed (c. 30% of those with ESRD).

Almost all renal transplants are allogeneic (i.e. not from identical twins) and will provoke a powerful immunological rejection response in the recipient. Rejection will destroy renal tissue and so the primary aim of immunosuppression is to avoid rejection. In general, more potent immunosuppressive regimes will reduce the risk of all forms of rejection but at the expense of increased side effects. Side effects comprise generic immunosuppressive side effects (e.g. increased risk of infections and malignancy) or specific to the particular drug used (e.g. gingival hypertrophy with ciclosporin).

Immunosuppressive management may be divided into three phases – induction, early (<3-6 months post transplant) and late (>3-6 months). More intensive immunosuppression is required in the early post-operative period to prevent acute rejection episodes, while long-term immunosuppression should balance the risk of rejection against the adverse effects of immunosuppressive therapy. Effective immunosuppression is best achieved by combination therapy that minimises the side effects of individual agents. Overall, the aim of immunosuppression is to maximise patient and graft survival following transplantation and to maximise the quality-of-life and economic benefits of transplantation.

When planning immunosuppressive treatment it is essential to consider the risks to the recipient. The risks of immunosuppressive therapy are largely predictable and should be balanced against the risk of harm to the individual patient from under-immunosuppression and resulting rejection, and the benefits of a well functioning transplant<sup>10</sup>. Assessment of different risks in the potential recipient is less precise but Table 1 illustrates some broad categories. Many units employ such a policy but there is very little scientific evidence to support such strategies since most studies have excluded high-risk patients.

<b>Risk Type</b>	<b>Low</b>	<b>Medium</b>	<b>High</b>	<b>Possible strategy</b>
<b>Immunological</b>	0-DR mismatch First graft Unsensitised Recipient > 60	1-DR mismatch Afro-Caribbean recipient Historical DSAs DGF Older donor <sup>10</sup>	2-DR mismatch Previous early immunological graft loss DSAs ABO incompatible Sensitised (High PRA)	<b>Increase total immunosuppressive load</b>
<b>Metabolic</b>	Low BMI Age <40 Normal Pre-Tx GTT	Positive family history	Impaired GT BMI>35 HCV positive Age > 60 Previous CVD Race	<b>Avoid/minimise steroids and tacrolimus</b>
<b>Neoplastic</b>	Age < 40	Pre-malignant lesion	Previous cancer Hereditary syndrome e.g. VHL	<b>Consider low immunosuppression load or sirolimus</b>
<b>Ischaemia-reperfusion injury</b>	Living donor	CIT > 12 hours Donor aged 50 -60	DCD CIT > 24hours Extended Criteria Donor	<b>Reduce CNI exposure</b>
<b>Non-adherence</b>			Poor RRT compliance Age <20 Transition from paediatric to adult	<b>Education Simple drug regime alemtuzumab or belatacept</b>

For the purpose of these guidelines immunosuppression has been broadly divided into induction and maintenance phases; the maintenance phase can be further divided into early and late. While the distinction between these periods is largely arbitrary, here the induction period is considered as the peri-transplant period, the early maintenance period is the 3-6 month period after transplant when immunosuppression is tapered, and the late maintenance phase is the period beyond 3-6 months when immunosuppression has been tapered to long-term levels. It is recognised that the renal allograft is more immunogenic during the early post-transplant period and thus more potent immunosuppression is required to prevent rejection of any type. In the later maintenance phase the allograft becomes less immunogenic and more consideration can be given to minimisation of side effects from immunosuppressive.

Strategies may be pre-emptive or reactive. For example, steroid avoidance is a strategy pursued by some units with the objective of avoiding steroid-related side effects. It also permits the widespread usage of tacrolimus with a reduced risk of New Onset Diabetes after Transplantation (NODAT).

When considering evidence in the literature it is essential to look at long-term data. However, long-term data from adequately powered clinical trials is frequently not available and we are reliant on data from large registries with their inherent limitations of data collected and bias. It is also important to focus on intention-to-treat analysis to limit bias associated with intolerance of therapy (which is common in this population).

### **Guideline 3.1 – KTR: Induction Immunosuppression**

**We recommend induction therapy should take into account the following:**

- **Immunosuppressive drugs should be started before or at the time of renal transplantation. (1B)**
- **Induction therapy with biological agents should be administered to all KTRs. (1B) In patients at low immunological risk this will generally involve an interleukin-2 receptor antagonist (IL2-RA). Recipients at higher immunological risk may be considered for T-cell (lymphocyte) Depleting Antibodies (TDAs; e.g. anti-lymphocyte preparations [ALG, ATG], alemtuzumab or OKT3).**
- **Induction therapy with TDAs may also be useful for lower immunological risk patients with the intention of either steroid or CNI avoidance. (1C)**

### **Guideline 3.2 – KTR: Induction Immunosuppression**

**We suggest that a CNI should be started at the time of transplantation and not delayed until the graft is functioning. (2C)**

#### **Audit Measure**

Percentage of total patients receiving induction with ILRAs and TDAs

#### **Rationale for 3.1 and 3.2**

Following allogeneic renal transplant there is an intense period of immunological activity whereby recipient lymphocytes respond to allogeneic material. Induction therapy aims to minimise this response and the risk of early graft rejection, at a time when oral agents may not have reached effective concentrations.

There is good evidence that IL2-RAs reduce the risk of early rejection when compared to placebo, although there is no definitive evidence of improved graft survival at three years, nor are there trials of adequate statistical power to answer the question of long-term benefits. Pharmacoeconomic analysis has shown that these agents are cost effective in the early post-transplant period, and this is embodied in the NICE guidelines (<http://guidance.nice.org.uk/TA85>)

There is moderate evidence that TDAs reduce the risk of acute rejection in high-risk immunological recipients. However, this benefit is generally gained at the expense of increased side effects in particular an increased incidence of malignancy, cytopenias and infections.

There is limited evidence to suggest that the clinical profile of alemtuzumab differs from that of other T cell depleting antibodies, with a lower incidence of Post Transplant Lymphoproliferative Disease (PTLD) <sup>11</sup>. Preliminary evidence suggests

that that B lymphocyte depleting antibodies, such as anti-CD20, rituximab, are not suitable as routine induction agents <sup>12</sup>.

A more detailed discussion of these data is available in the KDIGO guidelines <sup>1,2</sup>.

### **Guideline 3.3 – KTR: Maintenance immunosuppression**

**We recommend that maintenance immunosuppression should normally consist of a calcineurin inhibitor (CNI) and an anti-proliferative agent, with or without corticosteroids in low and medium immunological risk KTRs. (1B)**

### **Guideline 3.4 – KTR: Maintenance immunosuppression**

**We suggest that low dose tacrolimus (trough target 3-7ng/ml) is recommended as the CNI of choice in patients also taking steroids who are low and medium immunological risk and are not at high risk of developing NODAT. (2C)**

### **Guideline 3.5 – KTR: Maintenance immunosuppression**

**We suggest that MPA-based drugs should be the first-line antiproliferative agent, in preference to azathioprine. (2B)**

### **Guideline 3.6 – KTR: Maintenance immunosuppression**

**We suggest that mycophenolate mofetil (Cellcept<sup>®</sup>) and enteric coated mycophenolate sodium (Myfortic<sup>®</sup>) provide equivalent maintenance immunosuppression. (2B)**

### **Guideline 3.7 – KTR: Maintenance immunosuppression**

**We suggest that vigilant steroid avoidance or steroid withdrawal can generally be used during the first week after transplantation in low immunological risk kidney transplant recipients. (2B)**

### **Guideline 3.8 – KTR: Maintenance immunosuppression**

**We suggest aiming for minimum target levels for CNIs in uncomplicated renal transplantation after 3 months. (2C)**

### **Guideline 3.9 – KTR: Maintenance immunosuppression**

**We suggest that CNIs should be continued rather than withdrawn. (2B)**

### **Guideline 3.10 – KTR: Maintenance immunosuppression**

**We suggest if steroids are not withdrawn within the first month then they should be maintained at low dose (Prednisolone - 5mg per day or less). (2C)**

## Audit Measures

1. Percentage of de novo KTRs receiving tacrolimus.
2. Percentage of de novo KTRs receiving MPA based immunosuppression.
3. Percentage of de novo KTRs receiving corticosteroids maintenance therapy.

### Rationale for 3.3-3.10

Immunosuppressive drugs are generally used in combination to balance effective total immunosuppression with minimisation of drug-specific side effects. Since the graft is most immunogenic in the early post-transplant period it is important to use higher doses of these drugs during this period. Thereafter dosages and thus blood levels can be reduced. High, medium and low  $C_0$  levels for tacrolimus are >10, 5-10 and <5 ng/mL respectively. Comparable  $C_0$  levels for ciclosporin are >200, 100-200 and <100 ng/ml respectively.

The risk of acute rejection is minimised by early achievement of target CNI levels and so there is no reason to delay the initiation of a CNI. Specifically there is no evidence that delaying the introduction of a CNI prevents or ameliorates delayed graft function.

Trial evidence demonstrates that tacrolimus reduces the risk of acute rejection and improves graft survival during the first year of transplantation compared to ciclosporin<sup>13</sup>. Protocol biopsy studies also suggest that subclinical rejection is less prevalent in regimes containing tacrolimus as opposed to ciclosporin<sup>14</sup>. However, NODAT is significantly more common with tacrolimus even accounting for variation in concomitant steroid usage<sup>15</sup>. Low blood levels of tacrolimus minimise the risk of new onset diabetes after transplantation (NODAT) compared to higher levels. It should be recognised that there are important pharmacogenetic variations in tacrolimus metabolism and some centres reduce doses in black recipients<sup>16</sup>.

A large recent RCT suggested that low dose tacrolimus, combined with MMF and steroids with an IL2-RA as induction was superior at 12 months in terms of graft function, graft survival and acute rejection rate to either standard or low dose ciclosporin in low immunological risk KTRs<sup>17, 18</sup>. There are concerns over the early nephrotoxic effects of CNIs but whether these observations extend to lower doses and levels is unknown. To date no alternative to CNIs has been shown to improve either early or late graft outcomes.

Induction therapy plus low-dose tacrolimus, MMF and corticosteroids, have produced the lowest rates of acute rejection, best graft function, and best graft survival<sup>17</sup>. Compared with placebo and azathioprine, MMF reduces the risk of acute rejection<sup>19, 20</sup>.

The evidence comparing MMF to placebo consistently demonstrates lower rates of acute rejection on MMF but at the expense of increased bone marrow suppression and increased opportunistic infection rates. There is limited evidence comparing MMF to azathioprine. Despite conflicting results there is significant evidence for reduced rejection rates but not for improved graft survival or graft function<sup>21</sup>. Absolute

numbers of patients with gastrointestinal side effects are higher with MMF though this is not significant. There is limited evidence that mycophenolate sodium (Myfortic<sup>®</sup>) leads to a reduced incidence of GI side effects compared to Mycophenolate Mofetil<sup>22</sup>.

Steroids have a well-documented adverse event profile, which has heightened interest in steroid withdrawal and avoidance regimes. Whether low dose prednisolone (e.g. 5mg daily) is associated with a similar adverse profile is unknown. The majority of accumulated trial evidence in renal transplantation has involved steroid-containing regimes, and there is a relative paucity of data in steroid withdrawal/avoidance. Steroid withdrawal studies later than one month after transplantation generally show increased rejection rates. Early withdrawal and avoidance studies show increased acute rejection rates but without an effect on graft survival<sup>23-25</sup>. Long-term follow up is required to fully assess these effects. It is clear that close vigilance is required with steroid-avoidance regimes since acute rejection rates will probably be higher. Patients who do reject should probably be maintained on long-term oral steroids<sup>26</sup>. There are no differences in graft survival between patients treated with or without maintenance corticosteroids beyond the first week after kidney transplantation and avoidance beyond the first week after kidney transplantation reduces adverse effects.

Higher doses of CNIs are required during the first three months when the recipient's immune response is receiving the most allostimulation. There is theoretically a good reason to reduce the immunosuppressive load after this time to reduce the incidence of drug-related adverse effects (i.e. reduce CNI target levels). Analysis of RCTs has shown that CNI withdrawal leads to higher rejection rates without any improvement in graft survival. Comparison of lower dose CNI regimes with higher doses have generally shown little difference in outcomes<sup>27</sup> but in some cases better renal function has been attained. Those seeking a fuller discussion of these studies are referred to the 2009 KDIGO guidelines<sup>1</sup>.

While there is some evidence that m-TORi can allow reduced doses of CNIs and better graft function at one year after transplantation there are problems with tolerability of these agents and higher rejection rates<sup>28</sup>. The exact role of m-TORi use in the early stages after transplantation requires further study, but higher rates of lymphocoele, poor tolerability and poor wound healing are reported<sup>29</sup>

### **Guideline 3.11 – KTR: Monitoring of immunosuppression**

**We suggest that long-term monitoring of immunosuppression levels is required as follows:**

- **Tacrolimus and ciclosporin levels should be monitored. The initial frequency should be three times a week. Levels should also be checked when any medication with possible interactions is prescribed, the dosage is changed, the formulation is changed or when there is unexplained graft dysfunction. (2C)**
- **Tacrolimus should be monitored by the C<sub>0</sub> trough level, while ciclosporin can be monitored by either C<sub>0</sub> or C<sub>2</sub> level. (2C)**
- **Tacrolimus and ciclosporin levels should be available within 24 hours of taking blood samples in the first three months after transplantation. (2D)**
- **The utility of monitoring MMF C<sub>0</sub> levels is uncertain. (2D)**

- **Sirolimus should be monitored by the C<sub>0</sub> trough level. (2C)**

### **Rationale**

Therapeutic drug monitoring is advisable for drugs with a narrow therapeutic index. For tacrolimus and ciclosporin the absorption may vary in the early stages after transplantation but usually stabilises within a month. Both drugs may exhibit both inter-patient and intra-patient variability. Tacrolimus and ciclosporin are traditionally monitored by 12 hour C<sub>0</sub> trough levels, but in the case of ciclosporin there is some evidence that C<sub>2</sub> levels may also be used although target ranges are less well established and the logistics of sample collection are more complex. There is little evidence directly comparing different target levels of the same drug in a controlled fashion.

Drug monitoring of MMF is best carried out by measuring the AUC but clinical studies have not been conclusive<sup>27, 30</sup>. C<sub>0</sub> levels correlate poorly with AUC and remain unproven in clinical practice.

Sirolimus levels should be monitored since toxic effects correlate with high drug levels and C<sub>0</sub> levels correlate well with AUC<sup>31, 32</sup>.

### **Guideline 3.12 – KTR: Prescribing and the use of generic agents**

**We suggest that generic compounds should not be used unless they have been shown to be bioequivalent to branded products and have been approved by the European Agency for the Evaluation of Medicinal Products (EMA). (2D)**

### **Guideline 3.13 – KTR: Prescribing and the use of generic agents**

**We suggest that KTRs should be made aware of the existence of generics and the dangers of indiscriminate usage. (2D)**

### **Guideline 3.14 – KTR: Prescribing and the use of generic agents**

**We suggest that drugs should be prescribed by brand name where unproven generic substitutes are available. (2D)**

### **Guideline 3.15 – KTR: Prescribing and the use of generic agents**

**We suggest that KTRs should be followed closely after switching to a generic preparation until a new steady state is established. (2D)**

### **Audit Measure**

The use of generic agents should be monitored and audited.

### **Rationale for 3.12 – 3.15**

The introduction of many generic preparations of tacrolimus, ciclosporin and MPA is anticipated in the next decade. These offer potential cost savings but at the risk that these medications are not truly bioequivalent, due to the limitations of the regulatory process. This has led to differences in both pharmacokinetic and clinical outcomes, compared with the original agents<sup>33</sup>.

Immunosuppressive drugs in common use have narrow therapeutic windows, with significant risk of under- and over-immunosuppression and, with CNIs, risk of nephrotoxicity due to over-exposure. Plasma CNI levels are carefully measured in practice, with narrow therapeutic ranges. Assessment of generic agents requires only that time-averaged plasma concentrations (area-under-the-curve) fall between 80-125% of the original preparation in normal subjects. Differences in bioavailability due to food or other factors are not assessed. For ciclosporin the bioavailability of generic agents extends across this range and is influenced by food, thus switching between generic agents may result in major differences in drug exposure. This may be minimised by careful measure of drug exposure after switching between agents and generic preparations (“named” generics). When the choice of generic is left to the dispenser this is likely to result in variable exposure. The same issues may apply to tacrolimus but the bioavailability of this agent is less variable, and to other generic immunosuppressants such as MPA, although monitoring of this agent is not usually undertaken in clinical practice. For these reasons a local protocol for the use of generic agents should be available to all involved in the care of transplant recipients, specifically those who write and dispense prescriptions.

#### **4. Kidney Transplant Recipient (KTR): Acute rejection (Guidelines 4.1-4.10)**

##### **Guideline 4.1 – KTR: Diagnosis of acute rejection**

**We recommend that a transplant renal biopsy should be carried out before treating an acute rejection episode unless this will substantially delay treatment or pose a significant risk to the patient. (1C)**

##### **Guideline 4.2 – KTR: Diagnosis of acute rejection**

**We suggest that two cores of renal tissue should be obtained if possible since this will increase the sensitivity of the investigation. (2C)**

##### **Guideline 4.3 – KTR: Diagnosis of acute rejection**

**We suggest that routine C4d and SV40 staining should be performed upon transplant biopsies. (2C)**

##### **Guideline 4.4 – KTR: Treatment of acute rejection**

**We suggest that borderline acute cellular rejection should be treated. (2D)**

#### **Guideline 4.5 – KTR: Treatment of acute rejection**

**We recommend that high dose intravenous corticosteroids should be the first line treatment for acute cellular rejection. (1D)**

#### **Guideline 4.6 – KTR: Treatment of acute rejection**

**We suggest that maintenance steroids should be added or restarted in steroid-free patients undergoing acute rejection of any type. (2D)**

#### **Guideline 4.7 – KTR: Treatment of acute rejection**

**We suggest that lymphocyte depleting agents may be considered for refractory acute cellular rejection or aggressive vascular cellular rejection (i.e. BANFF category 4 Type II and III). (2C)**

#### **Guideline 4.8 – KTR: Treatment of acute rejection**

**We suggest that antibody mediated rejection (AMR) should be treated with one or more of the following modalities: steroids; plasma exchange; intravenous immunoglobulin; anti-CD20 antibody; or lymphocyte-depleting antibody. (2C)**

#### **Guideline 4.9 – KTR: Treatment of acute rejection**

**We suggest after an episode of rejection (unless associated with low CNI levels) that azathioprine should be switched to MPA-based immunosuppression, MPA should be started or the existing dose of MPA maximised. (2D)**

#### **Guideline 4.10 – KTR: Treatment of acute rejection**

**We suggest that a serum sample should be sent at the time of renal biopsy (for graft dysfunction) to look for HLA-specific antibodies. (2C)**

#### **Audit Measures**

1. Severity of biopsy proven acute rejection (BPAR) recorded by BANFF criteria.
2. Percentage of KTRs with BPAR in first 3 months and first 12 months
3. Percentage of KTRs requiring TDAs to treat rejection in first year
4. Complication rates after renal transplant biopsy

#### **Rationale for 4.1-4.10**

Historically, unresolved acute rejection episodes invariably led to graft loss so it is rational to treat such episodes unless the treatment is likely to do more harm than good. Rejection episodes are characteristically associated with loss of graft function but diagnosis is best established by a percutaneous biopsy since it differentiates rejection clearly from other causes of graft dysfunction. Recognition of different forms of rejection may inform different treatment regimes (e.g. AMR). Two cores of tissue should be obtained since this approach increases the sensitivity for diagnosis of

rejection by approximately 10%<sup>34</sup>. Biopsies should be examined by an experienced renal histopathologist and graded according to the recognised BANFF criteria<sup>35-39</sup>.

Subclinical rejection is defined as histological rejection in the absence of clinical evidence of altered graft function. The utility of treating subclinical rejection seems to depend on the underlying SCAR rate at any given time point and with modern immunosuppression regimes has not proven as yet to be worthwhile<sup>40-42</sup>.

Most acute cellular rejection responds to treatment with corticosteroids. The optimal regime for steroid administration has not been determined but intravenous methylprednisolone on three consecutive days is commonly used. The use of T cell depleting antibodies (TDAs) in milder grades of cellular rejection (BANFF category 4 type I) may be more effective in restoring renal function but results in significantly greater side effects<sup>43</sup>. There is some evidence that adding an MPA product after such episodes or substituting azathioprine with MPA will result in fewer subsequent rejection episodes<sup>44</sup>. Treating more severe cellular rejection (BANFF category 4 Type IIa,IIb or III) and steroid unresponsive episodes with TDAs often improves graft function although a thorough risk- benefit assessment of such treatment should be undertaken<sup>43</sup>.

Intensifying immunosuppression after a rejection episode may help prevent further rejection. The treatment of borderline acute rejection is controversial and there is little evidence to guide therapy<sup>45,46</sup>.

If renal function does not return to baseline, or if there is a new decline in function after successful treatment of an acute rejection episode, a biopsy should be considered to rule out additional rejection or other causes of graft dysfunction (e.g. BK nephropathy)

It is recommended to stain all biopsies for C4d and to send serum samples for HLA-specific antibodies to facilitate the diagnosis of acute antibody-mediated rejection (AMR) according to joint BSHI/BTS guidelines<sup>47</sup>. Consideration of this possibility is important since light microscopic findings may be similar to those associated with acute tubular necrosis<sup>37</sup>. If AMR is diagnosed then there is limited evidence that treatment with alternative modalities such as plasma exchange, infusion of immunoglobulins or the administration of monoclonal antibodies that target B cell function may be beneficial (rituximab, orthiclizumab or bortiluzimab)<sup>48,49</sup>.

## **5. Kidney Transplant Recipient (KTR): Chronic Allograft Injury (CAI) (Guidelines 5.1-5.7)**

### **Guideline 5.1 – KTR: Diagnosis of Chronic Allograft Injury (CAI)**

**We recommend that early identification of graft injury is desirable to maximise the potential to intervene. A proactive and systematic approach should be employed to identify graft dysfunction. (1C)**

### **Guideline 5.2 – KTR: Detection of Chronic Allograft Injury (CAI)**

**We suggest that renal function should be monitored at each clinic visit by assessment of serum creatinine and qualitative evaluation of urine protein excretion by dipstick supplemented by spot PCR or ACR if positive. (2C)**

### **Guideline 5.3 – KTR: Diagnosis of Chronic Allograft Injury (CAI)**

**We suggest that renal biopsy is the optimal investigation for parenchymal causes of graft dysfunction. (2C)**

### **Guideline 5.4 – KTR: Diagnosis of Chronic Allograft Injury (CAI)**

**We suggest that renal biopsies in patients with chronically deteriorating function should routinely be stained for C4d and SV40. (2C)**

### **Guideline 5.5 – KTR: Diagnosis of Chronic Allograft Injury**

**We suggest that serum samples should be sent at the time of renal biopsy (for graft dysfunction) to look for HLA-specific antibodies. (2C)**

### **Rationale for 5.1-5.5**

Unfortunately there are currently no good markers of early allograft injury. Graft damage can be detected by protocol biopsy but the clinical utility of this approach is unproven. Studies show that at least moderate chronic damage is prevalent on protocol biopsies in a quarter of patients by one year and over 90% patients by ten years<sup>50</sup>. Therefore current best practice consists of vigilant monitoring of simple clinical markers of allograft function such as serum creatinine and proteinuria<sup>51</sup>. More complex and expensive approaches such as monitoring serum anti-HLA antibodies also remain unproven.

Deterioration in graft function is a heterogeneous entity with multiple causes, both immunological and non-immunological<sup>52</sup>. Treatment may entail diametrically opposite strategies and therefore deterioration of allograft function should be investigated by percutaneous biopsy if possible. Tissue samples should be examined by an experienced renal histopathologist and classified according to the BANFF criteria. Staining for C4d deposition and SV40 antigen should be routinely available since positive staining will affect the treatment strategy.

Although there is not yet any proven therapy, it is important to recognise chronic humoral rejection diagnosed according to the BANFF criteria<sup>37,49</sup>. The detection of anti-HLA antibodies and C4d staining on transplant biopsy are associated with worse clinical outcomes<sup>53-58</sup>. Routine post transplant screening for post transplant antibodies has been recommended but there is not yet a solid evidence base with which to recommend it routinely<sup>47</sup>.

### **Guideline 5.6 – KTR: Treatment of chronic allograft injury**

**We suggest that chronic allograft injury should be treated:**

- **By withdrawal of calcineurin inhibitors (CNIs) if there is either histological evidence of CNI toxicity or non-specific interstitial fibrosis and tubular atrophy. (2C)**
- **By intensification of immunosuppression if there is evidence of ongoing immune injury (cellular rejection and/or humoral rejection). (2C)**
- **In a similar fashion to other patients with CKD following similar preventative strategies and with timely referral to low clearance services. (2D)**

### **Rationale**

There is some evidence that withdrawal of CNIs following chronic deterioration of graft function is beneficial<sup>1, 59, 60</sup>. The role of mTOR-inhibitors as replacements for CNIs is uncertain but this approach should be avoided in patients with eGFRs < 40ml/min/1.73m<sup>2</sup> and/or significant proteinuria (PCR>0.5 or ACR>0.35)<sup>61</sup>.

There is no proven therapy for chronic humoral rejection although studies are ongoing. However if there is evidence of an ongoing immunological process it seems logical consider increased immunosuppression after weighing up the risks and benefits.

It seems sensible to employ measures used in other non-transplant patients with CKD. Some studies have shown that anaemia is more prevalent in transplant patients and is associated with poor outcomes<sup>62</sup>.

### **Guideline 5.7 – KTR: Renal biopsy in chronic allograft injury**

**We suggest that a renal transplant biopsy is indicated:**

- **If there is a persistent unexplained elevation of creatinine or failure to return to baseline after an episode of BPAR. (1C)**
- **Every 7-10 days during DGF. (2C)**
- **If expected renal function is not achieved within 4-8 weeks. (2D)**
- **If sustained new onset proteinuria develops (PCR>50 or ACR>35). (2C)**

### **Rationale**

It is common practice during episodes of delayed graft function to perform regular biopsies of the renal graft since the usual clinical markers of rejection (urine output and serum creatinine) are unhelpful. Proteinuria is associated with poor outcome and should be investigated for a treatable cause<sup>63-65</sup>.

## **6. Kidney Transplant Recipient (KTR): Cardiovascular disease (Guidelines 6.1-6.5)**

## **Guideline 6.1 – KTR: Hypertension**

**We suggest that the management of hypertension take into account that:**

- **Blood pressure should be recorded at each clinic visit. (1C)**
- **Clinic blood pressure should be less than 130/80mmHg in clinic (125/75mmHg if PCR>50 or ACR>35). (2C)**
- **Home blood pressure recordings and 24-hour ambulatory recordings may be helpful in some instances but lower targets should be set. (2D)**
- **There is no evidence that any antihypertensive agent is better than any other and effort should be focused on achieving absolute levels rather than the use of individual agents. (2D)**
- **Inhibitors of the renin-angiotensin system may be more effective in the minimisation of proteinuria but they should be used with caution in the first 3 months post transplant. (2C)**
- **Resistant hypertension may be due to transplant renal artery stenosis and should be investigated according to local practice. (2D)**

The aim of blood pressure reduction is to prevent cardiovascular complications of hypertension (stroke, myocardial infarction, heart failure and arrhythmias) and to slow progressive decline in renal transplant function. Blood pressure targets should be individualised to minimise proteinuria and prevent, or regress left ventricular hypertrophy.

### **Audit Measures**

1. The proportion of patients receiving a target blood pressure of 130/80 or 125/75 in the presence of proteinuria PCR>100 or ACR>70).
2. The proportion of patients receiving an ACE inhibitor or angiotensin receptor blocker.
3. Proportion of patients with proteinuria assessed by dipstick and, if present, quantified at each clinic visit.

### **Rationale**

Hypertension is associated with impaired graft and patient survival following renal transplantation<sup>66-69</sup>. Many patients require polypharmacy and for most patients immunosuppressive therapy (specifically corticosteroids and CNI) contributes to the severity of hypertension and the resistance to treatment<sup>70</sup>. There are no large-scale interventional trials of any specific agent to support the use of one specific agent, nor any CV outcome trials of antihypertensive therapy or targets in this population. It is considered unlikely that the necessary trials will be performed, and targets are dependent on extrapolation of data from other populations, and published guidelines<sup>1</sup>. The use of blockers of the renin-angiotensin system has been associated with improved patient and graft survival in retrospective studies<sup>71</sup>, and effectively reduces proteinuria in KTRs<sup>72</sup>. The use of inhibitors of the renin-angiotensin system may thus have specific benefits but at the expense of lowering haemoglobin, raising potassium levels and decreasing GFR<sup>73</sup>. The use of dihydropyridine calcium antagonists may have benefits in the control of hypertension, and regression of associated left ventricular hypertrophy, due to calcineurin inhibitors<sup>74</sup>. Switching from ciclosporin to tacrolimus, minimisation of calcineurin inhibitors, switching to CNI-free

immunosuppression and withdrawal of corticosteroids may all be associated with lower blood pressure <sup>75, 76</sup>. Thus, modification of immunosuppression may be considered to lower blood pressure, particularly in cases of resistant hypertension not associated with allograft rejection <sup>77</sup>.

Hypertension is associated with risk of graft loss, and CV disease: specifically stroke, and cardiac death <sup>67, 78-80</sup>. LVH is common in renal transplantation, is dependent on hypertension, and linked to CV death <sup>78, 81</sup>. For these reasons LV structure and function should be assessed in transplant recipients, particularly in the presence of resistant hypertension. An ECG and CXR may be performed annually and if LVH, or cardiomegaly, is present the cause investigated. Echocardiography should be readily available for the investigation of patients with resistant hypertension or suspected LVH. Ambulatory, or home, blood pressure monitoring may be used in the assessment of patients where “white coat” hypertension is suspected. Target blood pressure readings on ABPM in transplant recipients have not been established but are likely to be 10/5mmHg below clinic readings.

## **Guideline 6.2 – KTR: Dyslipidaemia**

**We suggest that the management of dyslipidaemia take into account that:**

- **Fasting lipid levels should be measured on an annual basis in all renal transplant recipients. (2C)**
- **Treatment targets should be the same as in the general population. (2C)**
- **KTRs at increased primary or secondary CV risk receive statin therapy to reduce the risk of coronary artery disease. (2C)**
- **The choice and dose of statin should take into account concurrent immunosuppression. (2D)**

### **Audit Measures**

1. The proportion of renal transplant recipients with an annual measure of fasting lipids.
2. The proportion of RTR taking statins (including the type of statins) for primary and secondary prevention of premature cardiovascular disease.
3. The proportion of patients on other lipid lowering agents.
4. The proportion of patients achieving dyslipidaemia targets.

### **Rationale**

KTRs have a high prevalence of dyslipidaemia, characterised by elevations in total cholesterol, HDL and LDL cholesterol, and triglycerides <sup>1, 82</sup>. This reflects the effects of immunosuppressive therapy (specifically, corticosteroids, m-TORi and CNI – ciclosporin to a greater degree than tacrolimus <sup>70</sup>). Large scale trials have shown that statin therapy has similar short-term effects on the secondary dyslipidaemia associated with transplantation in patients with ESRD as it does in other populations with primary or secondary dyslipidaemia, or who are at elevated CV risk <sup>83, 84</sup>. In long-term studies the use of fluvastatin has been shown to reduce the incidence of CV events, specifically cholesterol-dependent effects and myocardial infarction <sup>85</sup>. Statins are

metabolised by the cytochrome P450 microsomal enzyme system resulting in higher statin exposure and as a consequence, there is a higher risk of adverse effects with statins<sup>86</sup>. Fibrates also have a high risk of side effects, and careful monitoring of lipid lowering therapy is necessary. Ezetimibe can be used safely in KTRs and reduces both total cholesterol and LDL fractions. It should not be used with fibrates and hypothetically it may interfere with ciclosporin levels though in practice these effects seem to be insignificant<sup>87-89</sup>. Lipid lowering targets, and specific subfractions, have been adopted from the general population in the absence of specific transplant targets<sup>1, 90</sup>.

### **Guideline 6.3 – KTR: Diabetes mellitus**

**We suggest that the detection and treatment of diabetes should consider:**

- **Screening for the development of post transplant diabetes by dipstick urinalysis and measurement of blood sugar level at each clinic visit. (2C)**
- **Post transplant immunosuppression should take into account risk factors for the development of diabetes. (2C)**
- **Post-transplant diabetes should be managed in collaboration with specialists in diabetic medicine. (2D)**
- **All units should have a protocol for the management of post-transplant diabetes. (2C)**

#### **Audit Measures**

1. The incidence of new onset diabetes after transplantation (NODAT) at three months and at annual intervals thereafter
2. The proportion of patients who require insulin, and in whom remedial action is undertaken – minimisation of steroids and switching of CNIs.

#### **Rationale**

New onset diabetes after transplantation (NODAT) is a common consequence of renal transplantation, a reflection of increased dietary intake, weight gain and the use of immunosuppressive agents – specifically corticosteroids, CNIs (tacrolimus more than cyclosporine) and m-TORi<sup>91-93</sup>. National and International guidelines are available for the management of patients with NODAT<sup>1, 94</sup>. In patients who develop NODAT, the guidelines recommend consideration of minimisation of steroids and/or switching from tacrolimus to ciclosporin, in addition to the conventional use of diet, oral hypoglycaemic agents and insulin. Preventive use of steroid minimisation, early withdrawal or avoidance and the use of ciclosporin, rather than tacrolimus may be used in patients at high risk of developing diabetes – specifically those with previous stress induced diabetes, a family history of diabetes, and who are elderly or overweight prior to transplantation<sup>1, 94</sup>. Long-term follow-up and surveillance of patients with NODAT is the same as for patients with diabetes in the general population, and is best conducted in collaboration with a specialist in diabetic medicine.

## **Guideline 6.4 – KTR: Ischaemic heart disease**

**We suggest that KTRs receive standard treatment for ischaemic heart disease, including thrombolysis, revascularisation, and secondary prevention. (2C)**

### **Audit Measures**

1. The proportion of patients with ischaemic heart disease.
2. The proportion of patients suffering myocardial infarction.
3. The proportion of patients undergoing primary revascularisation.
4. The proportion of patients receiving secondary prevention with a statin, anti-platelet agents and RAS blockers.

### **Rationale**

Coronary artery disease is common in patients with ESRD, including transplant recipients, and is a major contributory factor to CV mortality and morbidity. It is known that patients with ESRD, including transplant recipients, are less likely to undergo cardiac intervention (thrombolysis or per-catheter therapies), possibly because of higher complication rates, and are less likely to receive secondary prevention. There is no reason to believe that transplant recipients will benefit less than patients in the general population, many of whom have renal impairment. Patients with renal transplants should have equal access to cardiac investigations and surgery as patients without CKD.

## **Guideline 6.5 – KTR: Smoking cessation**

**We recommend that smoking should be discouraged in transplant recipients (see guideline 6.4). (1A)**

## **Guideline 6.6 – KTR: Lifestyle measures**

**We suggest that advice on healthy lifestyle forms a routine part of post-transplant care:**

- **Maintenance of a healthy diet should be encouraged. (2C)**
- **An active lifestyle should be encouraged. (2D)**
- **An ideal weight should be targeted (BMI $\leq$ 25). (2C)**
- **Weight management services should be available. (2C)**
- **Alcohol consumption should be within national guidelines. (2D)**
- **Recreational drug use should be avoided. (2D)**
- **The use of over-the-counter medications (without discussion with clinical staff) and non-proprietary medications (e.g. herbal medicines) should be discouraged. (2D)**

### **Audit Measure**

The proportion of patients who are obese (BMI $>$ 30).

## **Rationale**

Cigarette smoking is associated with reduced life expectancy, increased cardiovascular disease, malignancy and respiratory disorders in the general population. Although detailed information is limited in KTRs, there is strong evidence that cigarette smoking is associated with increased cardiovascular risk in this population<sup>88-90</sup>. The long-term benefits of smoking cessation have not been proven in transplant recipients, nor are long-term studies likely to be performed. However, strategies for smoking cessation are safe and likely to produce the same benefits seen in other populations or public health studies. A local strategy should be available and record made of advice given and available (See Guideline 6.4).

Transplant recipients have often been subjected to dietary restriction associated with advanced CKD, removal of which after transplantation is one of the factors contributing to weight gain, the metabolic syndrome, diabetes and their sequelae. KTR should have access to dietary advice, and to weight management services if necessary. Pharmacological intervention for obesity has not been assessed in a clinical trial in KTR and may interfere with the metabolism and absorption of immunosuppressive agents. Bariatric surgery is similarly unproven in this population and likely to have a higher incidence of side effects and potential interactions. Dose reduction or withdrawal of corticosteroids helps weight loss but more intensive monitoring is essential around the time of dose changes.

Alcohol excess and recreational drug use are common in KTR and have particular risks in this population with regard to adherence with prescribed medication and drug interaction. Access to counselling, addiction services and rehabilitation should be available.

There are potential interactions with non-prescribed (OTC) and “herbal medications” (e.g. St. John’s Wort). Patients should be aware of the increased risk and potential sequelae of drug interactions, and encouraged to discuss with clinical staff or an expert renal pharmacist.

## **7. Kidney Transplant Recipient (KTR): Neoplasia (Guidelines**

### **7.1-7.3)**

#### **General concepts**

Neoplasia is more common in KTRs due to impaired immunosurveillance. As a result virally driven cancers in particular are more prevalent e.g. HPV-induced cervical cancer (see Table 2).

The relative risk of cancer is higher in younger patients (relative risk of neoplasia 20x) than older patients (2x for over 65s)<sup>95,96</sup>. KTRs with neoplasia have worse outcomes than members of the general population probably due to increased toxicity from treatment. Preventative strategies are therefore paramount in management, which may involve screening and the minimisation or modification of immunosuppressive therapy. If cancer develops then part of the treatment will involve reducing and/or modifying immunosuppression therapy. This is likely to be

more beneficial and therefore clinically more important in those cancers with higher relative risks in KTRs (e.g. more likely to have a clinical impact in non-melanoma skin cancer than pancreatic cancer). Emerging evidence supports the notion that low-dose immunosuppression and the use of mTORi may reduce the incidence and recurrence of some cancers<sup>97-99</sup>.

Table 2

Relative risk - KTR	Common cancers
High RR >5	Kaposi's sarcoma Eye Lymphoma Kidney Non-melanoma skin Lip Thyroid
Medium RR 1-5	Melanoma Cervix Vulvovaginal Bladder Colon Lung Stomach Oesophagus Oropharynx and Larynx Myeloma Anus Leukaemia Hepatobiliary
No increase	Breast Prostate Ovary Uterus Pancreas Brain Testis

### Guideline 7.1 – KTR: Screening for cancer

**We suggest that the organisation of screening for neoplasia in KTRs take into account:**

- **Screening should be similar to the general population for cervical, breast, colon and prostate cancer. (2C)**
- **Screening is not recommended for renal cell carcinoma. (2C)**
- **Breast and testicular self-examination should be encouraged. (2D)**
- **An annual examination of skin by a healthcare professional. (2C)**
- **Patients with cirrhosis should undergo an annual hepatic ultrasound and determination of serum alpha feto-protein. (2C)**

## **Audit Measure**

Proportion of patients having screening procedures for neoplasia at the annual review clinic

## **Rationale**

The merits of any screening programme must balance the individual's risk of developing the disease, their prognosis if detected and the risk of harm from screening. Screening should be individualised and reflect co-morbidities and other competing risks (e.g. vascular disease). Some authors have advocated more frequent screening (e.g. annual cervical screening) but there is little evidence to support these assertions<sup>95</sup>. Thus screening should follow the pattern in the general population for most common cancers<sup>95</sup>. The national cancer screening protocols are described on the NHSCSP website<sup>96</sup> Smoking cessation should be encouraged in all KTRs. A formal protocol for the management of smoking cessation should be available in each transplant centre (see Guidelines 6.4 and 6.5)

### **Guideline 7.2 – KTR: Non-Melanoma Skin Cancer (NMSC)**

**We recommend that KTRs should be educated about the adverse effects of solar exposure. (1C)**

### **Guideline 7.3 – KTR: Non-Melanoma Skin Cancer (NMSC)**

**We suggest that KTRs that an individualised assessment of hazard should be made according to risk factors. (2C)**

### **Guideline 7.4 – KTR: Non-Melanoma Skin Cancer (NMSC)**

**We recommend that patients should be encouraged to cover their skin in direct sunlight and to use total sunblock (Sun Protection Factor  $\geq$  50). (1D)**

### **Guideline 7.5 – KTR: Non-Melanoma Skin Cancer (NMSC)**

**We suggest that self examination should be encouraged and should be supplemented by annual review by a trained healthcare professional. (2C)**

### **Guideline 7.6 – KTR: Non-Melanoma Skin Cancer (NMSC)**

**We suggest that acitretin should be prescribed to those with previous NMSC if there are no contraindications. (2B)**

### **Rationale for 7.2 – 7.6**

Certain patient groups are at higher risk of non-melanoma skin cancer, particular the fair-skinned living in a sunny climate. Other risk factors include occupation, behaviour, previous skin cancer, childhood solar exposure and family history. It is sensible to minimise exposure and use sun block. Acitretin (0.2-0.4 mg/kg/day) may prevent recurrence in those with previous skin cancer. There is some evidence that

sirolimus reduces incidence of second tumours but at the expense of increased side effects and possibly adverse effects on graft function<sup>98-100</sup>. Registry data suggest that mTOR inhibitors may be associated with fewer NMSC, particularly cutaneous Kaposi's sarcoma and recent data suggests that switching KTRs to sirolimus may reduce new NMSC<sup>99</sup>. The role of HPV vaccination in KTRs is unclear, but it is an inactivated vaccine that could be administered safely either before or after transplantation.

**Guideline 7.7 – KTR: Immunosuppression in cancers**

**We suggest that the overall level of immunosuppression should be reduced if neoplasia develops. (2C)**

**Guideline 7.8 – KTR: Immunosuppression in cancers**

**We suggest that m-TORis are considered as an alternative immunosuppressive agents in KTRs who develop *de novo* malignancy. (2C)**

**Guideline 7.9 – KTR: Immunosuppression in Kaposi's sarcoma**

**We suggest that m-TORis has specific anti-tumour effects in Kaposi's sarcoma and switching to this medication should be considered. (2C)**

**Rationale for 7.7-7.9**

There is no evidence that any particular immunosuppressant agent is linked to a particular cancer other than the association of TDAs and PTLD<sup>11,97</sup>. It is generally agreed that the overall level of immunosuppression should be decreased when cancer occurs. This decision should be individualised according to; the stage of the cancer at diagnosis; the likely impact of a reduction in immunosuppression; the availability of treatment for the tumour; and potential drug interactions between the chemotherapy agents and immunosuppressive agents. In general the effect of reducing the overall level of immunosuppression is more likely to be beneficial where the relative risk of the tumour in KTRs is higher. There is retrospective evidence that m-TORis are associated with lower rates of *de novo* malignancy and a recent prospective study demonstrated a benefit of sirolimus in preventing recurrence of NMSC<sup>98,99</sup>. m-TORis are also indicated in the treatment of Kaposi's sarcoma as well as reduced levels of overall immunosuppression<sup>100</sup>.

**8. Kidney Transplant Recipient (KTR) : Infection Complications  
(Guidelines 8.1-8.7)**

**Guideline 8.1 – KTR: Vaccination**

**Guideline 8.1.1 – KTR: Vaccination**

**We recommend that KTRs:**

- **Should be vaccinated with inactivated viruses as per the normal population except for HBV. (1D)**
- **Should receive annual influenza vaccination unless contraindicated. (1C)**

### **Guideline 8.1.2 – KTR: Vaccination**

#### **We suggest that KTRs:**

- **Should have HBsAb levels rechecked annually and revaccination carried out if antibody titres fall below 10mIU/ml. (2D)**
- **Should not receive live attenuated vaccines. (2C)**
- **Should receive pneumococcal vaccine and one booster after five years. (2D)**

#### **Rationale**

Ideally vaccination for KTRs and their household members should be completed prior to transplantation. A minimum of 4 weeks between vaccination with live attenuated vaccines and transplantation is recommended.

After transplantation there is no evidence to link vaccination with rejection episodes<sup>1</sup>. After transplantation it is safe to administer inactivated vaccines but live attenuated vaccines should be avoided (see Table 3 below). Vaccination should probably be carried out at least 3 months and preferably six months after transplantation when the maximal levels of immunosuppression have declined. Consideration should be given to vaccination of close household contacts where appropriate e.g. Varicella vaccination for children of VZV seronegative KTRs.

Table 3

<b>Inactivated Vaccines</b>	<b>Live Attenuated Vaccines</b>
Inactivated Influenza	Measles
Hepatitis A	Mumps
Hepatitis B	Rubella
Inactivated Polio	Varicella
Diphtheria	BCG
Tetanus	Smallpox
Pneumococcal	Yellow Fever
Meningococcal	Oral Salmonella
Human Papilloma Virus	Oral Polio
Rabies	
Anthrax	
Intramuscular Salmonella	
Japanese encephalitis	

The HPV vaccine has never formally been tested in KTRs but there is a strong link between HPV and anogenital and non-melanoma skin cancer. Some authors have recommended vaccination for all female KTRs aged between 9 and 26<sup>101</sup>.

Malaria prophylaxis should consist of chloroquine in sensitive areas, but it may increase levels of ciclosporin. Prophylaxis should therefore start two weeks prior to departure to permit monitoring of drug levels. In areas of chloroquine-resistance three options can be used; atovaquone and proguanil; mefloquine; or doxycycline. The choice of agent will be dictated by local preference and side effect profile but drugs should be started a few weeks prior to departure to allow blood tests to check renal and hepatic function, full blood count and immunosuppression levels. More extensive guidance for KTRs who are travelling overseas is available<sup>102, 103</sup>.

## **Guideline 8.2 – KTR: Cytomegalovirus disease**

### **Guideline 8.2.1 – KTR: prophylaxis and treatment of CMV disease**

**We recommend:**

- **Prophylaxis should be continued for 3-6 months, until immunosuppression has been reduced to long-term maintenance level; 6 months has proven benefit in sero-negative recipients of kidneys from CMV positive donors. (1B)**
- **Treatment should be administered for 6 weeks after treatment with a TDA. (1C)**

### **Guideline 8.2.2 – KTR: prophylaxis and treatment of CMV disease**

**We suggest:**

- **All transplant units should have the ability to measure CMV serological status and the detection and quantification of viral load. (2D)**
- **Donor and recipient CMV sero-positivity should be recorded at the time of transplantation. (2D)**
- **A written protocolised strategy based either on prophylaxis, or pre-emptive therapy, or both should be implemented. (2D)**
- **For the treatment of mild and moderate CMV disease, oral valganciclovir and intravenous ganciclovir are of equivalent efficacy. (2C)**
- **Treatment of life-threatening CMV disease should be initiated with intravenous ganciclovir. (2D)**
- **Treatment duration should be determined by monitoring viral load. (2C)**

## **Audit Measure**

The incidence of CMV disease.

## **Rationale**

CMV infection is the most common serious viral infection affecting renal transplant recipients<sup>104, 105</sup>. It occurs most commonly in CMV naïve recipients of a kidney from a CMV positive donor. However, seropositive transplant recipients may be affected by reactivation of CMV infection, and by primary infection with a new genotype. CMV infection is associated with more intensive immunosuppression, treatment of acute rejection episodes and the use of TDAs. For CMV disease there is clear evidence that prophylaxis reduces the severity, delays the onset and prevents CMV infection in CMV negative recipients of CMV positive kidneys<sup>106, 107</sup>. CMV infection is also associated with concomitant infection by other herpes viruses, the significance of which is uncertain but prevention of which may be an added benefit of prophylaxis over pre-emptive strategies<sup>108</sup>. CMV prophylaxis is therefore recommended in CMV negative KTRs from a CMV positive donor (D<sup>+</sup>/R<sup>-</sup>), and for seropositive KTRs (D<sup>-</sup>/R<sup>+</sup> or D<sup>+</sup>/R<sup>+</sup>) exposed to more intensive immunosuppression, in particular TDAs.

In CMV negative recipients of a CMV positive kidney the use of oral antiviral therapy – specifically valaciclovir, acyclovir, ganciclovir, or valganciclovir – is proven to delay the onset of CMV disease, to prevent CMV disease in a proportion of patients and limit the severity of disease. It is important to recognise that a proportion of patients will develop CMV disease following discontinuation of prophylaxis and will require clinical and virological monitoring for at least three months following discontinuation of prophylactic therapy<sup>109</sup>. At present, evidence exists for the use of valaciclovir and valganciclovir<sup>105, 106</sup>. In clinical practice valaciclovir is not widely available or used, and valganciclovir is the agent of choice. The dose of valganciclovir should be adjusted according to renal transplant function. Most commonly, and based on the available evidence, antiviral prophylaxis is continued for 90 days following transplantation. The rationale is that reduction of immunosuppressive therapy over this period will allow the immune system to combat viral replication once prophylactic therapy is withdrawn. However, it is likely that longer prophylaxis may have additional beneficial effects, most likely until immunosuppression has been reduced to long-term maintenance levels<sup>110, 111</sup>.

Treatment of CMV disease is equally effective with either oral valganciclovir or intravenous ganciclovir<sup>112, 113</sup>. However this landmark study excluded patients with life-threatening CMV infection and it is probably advisable to initiate treatment with intravenous therapy in such circumstances<sup>114</sup>.

### **Guideline 8.3 – KTR: Epstein Barr virus infection**

#### **Guideline 8.3.1 – KTR: EBV infection**

**We recommend that immunosuppression should be reduced or stopped following the development of PTLD. (1C)**

#### **Guideline 8.3.2 – KTR: EBV infection**

**We suggest:**

- **Both donor and recipient should have their EBV serology recorded at the time of transplantation. (2D)**
- **All high risk (D<sup>+</sup>/R<sup>-</sup>) patients (including adults) should have EBV viral load measured immediately after transplantation, monthly for six months, and three monthly to one year. (2C)**
- **EBV viral load should be monitored after the treatment of rejection. (2C)**
- **Total immunosuppression should be reduced when EBV titres rise significantly. (2C)**

### **Audit Measures**

1. Rates of EBV infection and PTLD amongst KTRs
2. Completeness of records for EBV donor and recipient serology

### **Rationale**

After transplantation primary EBV infection may be manifest by a broad spectrum of disorders ranging from asymptomatic infection to high grade non-Hodgkin lymphoma (PTLD). EBV seronegative KTRs are up to 50 times more likely to develop PTLD compared to their seronegative counterparts. The EBV genome is found in more than 90% of PTLD occurring during the first year after transplantation<sup>115</sup>. Vigilance is therefore essential especially since EBV viraemia usually precedes the development of PTLD by 4-16 weeks<sup>116</sup>. However assays for EBV viral load can often be positive in asymptomatic patients (false positives) and so clinical correlation and attention to changes in viral load are essential. Risk factors for early PTLD include primary EBV infection, young donor age, CMV infection and induction with TDAs. The use of antiviral agents (e.g. valacyclovir or valganciclovir) or immunoglobulins in response to rising viral loads is unproven and cannot be recommended. Since the immune response to EBV infected tissue is thought to depend on EBV-specific T cell responses it is logical to reduce immunosuppressive treatment in the face of clinical EBV infections and PTLD.

### **Guideline 8.4 – KTR: Varicella Zoster Virus infection**

#### **Guideline 8.4.1 – KTR: VZV infection**

##### **We recommend:**

- **Primary infection (chickenpox) should be treated with intravenous aciclovir or oral valaciclovir until the lesions scab over. (1C)**
- **Uncomplicated shingles should be treated with oral acyclovir or valaciclovir until the lesions scab over. (1D)**
- **Disseminated (>2 dermatomes), ocular or invasive shingles should be treated with intravenous aciclovir until the lesions scab over, together with a reduction in immunosuppression. (1B)**
- **Varicella-susceptible KTRs (i.e. VZV IgG -ve) with primary exposure to VZV should receive intravenous immunoglobulins, ideally within 96 hours, but up to a maximum of 10 days following exposure. If**

**unavailable or after 10 days, oral aciclovir should be administered for seven days, starting one week after exposure. (1D)**

#### **Guideline 8.4.2 – KTR: VZV infection**

**We suggest:**

- **Patients on the waiting list who are VZV IgG negative should be vaccinated prior to transplantation. (2D)**
- **Immunosuppression should be reduced during primary infection. (2D)**

#### **Audit Measures**

1. Annual rates of primary VZV and shingles infection
2. Completeness of records for VZV recipient serology in KTRs

#### **Rationale**

Acquired by 90% of the population before adulthood, VZV causes chickenpox during a primary infection. Thereafter the virus remains latent in the cranial nerve and dorsal root ganglia. Secondary reactivation results in shingles and typical dermatomal blistering skin lesions. Primary infection can be acquired by direct skin contact and by airborne droplet transmission<sup>117, 118</sup>. Primary disease in KTRs can be devastating with severe skin lesions, widespread visceral involvement and disseminated intravascular coagulation<sup>119</sup>. It seems sensible to vaccinate VZV naïve patients on the waiting list since the vaccine has been shown to be safe<sup>118</sup>.

#### **Guideline 8.5 – KTR: Herpes Simplex Virus infection**

##### **Guideline 8.5.1 – KTR: HSV infection**

**We recommend:**

- **Superficial HSV infection should be treated with appropriate oral agents until the lesions have resolved. (1D)**
- **Systemic HSV infections should be treated with intravenous aciclovir and a reduction in immunosuppression until a response occurs and oral medication continued for at least 14 days. (1C)**

##### **Guideline 8.5.2 – KTR: HSV infection**

**We suggest that KTRs suffering frequent recurrent HSV infection should consider oral prophylaxis. (2D)**

#### **Audit Measure**

Rates and outcomes of HSV infections

## **Rationale**

There is an increased potential for superficial HSV infections to become disseminated or invasive in KTRs. Reactivation most commonly occurs in the first few weeks after transplantation and complicated disease can become life threatening. Since treatment is safe and effective it seems sensible to treat early infections<sup>120, 121</sup>. Due to their gravity complicated infections should be treated with intravenous therapy and reduction in immunosuppression.

### **Guideline 8.6 – KTR: BK nephropathy**

#### **Guideline 8.6.1 – KTR: BK nephropathy**

**We recommend that confirmed BK nephropathy should be treated by reduction in immunosuppression. (1D)**

#### **Guideline 8.6.2 – KTR: BK nephropathy**

**We suggest:**

- **KTRs should be screened for BKV viral load by performing urine microscopy for decoy cells or by PCR on urine or serum. (2C)**
- **Screening should be monthly for the first six months, then every three months until the end of the first year. (2D)**
- **Screening should also be carried out when renal function deteriorates in an unexplained fashion or when immunosuppression is intensified. (2D)**
- **Suspected BK nephropathy should be confirmed by renal biopsy which should be stained for SV40. Two cores containing medullary tissue should ideally be examined. (2D)**
- **Immunosuppression should be reduced when the serum BKV load exceeds  $10^4$  copies/ml. (2C)**
- **There is no established specific treatment for BK nephropathy. (2D)**
- **Re-transplantation can safely be considered in patients who have BK nephropathy diagnosed in an earlier graft. (2C)**

#### **Audit Measures**

1. Rates of BK viral infection in screening tests
2. Rates and outcomes of BK nephropathy

## **Rationale**

The human polyoma BK virus is linked to two major clinical syndromes in KTRs, namely BK nephropathy (BKN) and transplant ureteric stenosis<sup>122-124</sup>. BKN occurs in up to 10% of KTRs and is responsible for a significant number of allograft losses. 90% of young adults have serological evidence of prior infection and the DNA virus remains latent in the uroepithelium. Under the influence of immunosuppression the virus becomes active and replicates. BK virus is cytolytic and so epithelial cells are shed in the urine as decoy cells and free virus can be detected in the urine. With increased viral replication BKV spills into the blood and can be detected as BK

viraemia by PCR. Approximately half of patients with high level viruria ( $>10^7$  copies/ml) will develop significant BK viraemia ( $10^4$  copies/ml) and half of these will develop histological BKN<sup>125</sup>. This sequence justifies screening for either high level urinary BKV shedding (alternatively the presence of decoy cells) or BK viraemia. Risk factors for BKV include not only both donor and recipient characteristics but also high immunosuppressive burden and intensification of immunosuppression. Definitive diagnosis requires demonstration of the virus in renal tissue usually stained with the antibody for large T antigen of SV40. Since the infection can be focal and preferentially affects the renal medulla, two cores including medulla should be examined<sup>126</sup>. The mainstay of treatment is reduction of immunosuppression and but there is no evidence that reducing any particular immunosuppressive agent is particularly beneficial<sup>127</sup>. Common approaches include stopping anti-proliferative agents or reducing CNI levels in the face of rising viral replication<sup>128</sup>. Specific agents such as intravenous immunoglobulin, quinolones, cidofovir and leflunomide have been shown to have antiviral activity but there is no definitive evidence to show that they offer any advantage over simply reducing the total immunosuppressive burden<sup>129-133</sup>. Prospective trials are urgently required to explore this question. If a first graft is lost due to BKN there is no evidence that this will adversely affect the outcome of subsequent grafts and no special precautions are necessary (e.g. allograft nephrectomy) prior to re-listing<sup>134</sup>.

### **Guideline 8.7 – KTR: Post-transplant infection prophylaxis**

**We suggest:**

- **All patients should receive 3-6 months of treatment with co-trimoxazole 480mg daily. (1B)**
- **Oral antifungal prophylaxis should be administered for three months after transplantation. (2C)**
- **In selected patients, prophylaxis against mycobacterium tuberculosis with daily isoniazid (supplemented with pyridoxine) should be instituted for six months after transplantation. (2C)**

#### **Rationale**

There is good evidence that co-trimoxazole provides effective prophylaxis against urinary tract infections after renal transplantation<sup>135</sup>. Alternatives include cephalosporins and fluoroquinolones. Co-trimoxazole is preferred since it also provides excellent cover against pneumocystis jirovecii. Alternative agents against pneumocystis jirovecii include dapsone, atovaquone or aerosolized pentamidine.

Candidal infection is common after renal transplantation and can cause considerable morbidity. It is usually acquired from colonisation of the oral mucosa and so topical oral preparations offer a simple form of prevention without the potential toxicity of systemic preparations.

Clinical tuberculosis in KTRs is usually due to reactivation of quiescent disease under the influence of immunosuppression. In other immunosuppressed populations treatment of latent TB prevents progression to clinically active TB<sup>136</sup>. Recent evidence suggests that prophylaxis with isoniazid in selected population is probably

effective and it should be prescribed with pyridoxine to prevent peripheral neuropathy<sup>137</sup>.

## **9. Kidney Transplant Recipient (KTR) : Bone and joint disease (Guidelines 9.1-9.4)**

### **Guideline 9.1 – KTR: Osteoporosis**

**We suggest:**

- **KTRs suffering from osteoporosis or at high potential risk should be considered for steroid-avoiding immunosuppression. (2D)**
- **KTRs on longterm steroids or at high risk for osteoporosis should undergo DEXA scanning if eGFR>30 ml/min/1.73m<sup>2</sup>. (2D)**
- **Treatment should be according the RCP guidelines for steroid-induced osteoporosis. (2D)**

### **Audit Measures**

1. Prevalence of KTRs on corticosteroids
2. Frequency of bisphosphonate usage amongst KTRs
3. Incidence of fractures amongst KTRs

### **Rationale**

All KTRs have a complex bone disorder whereby the effects of immunosuppression are superimposed on an underlying Chronic Kidney Disease Mineral and Bone Disorder (CKD-MBD). Any guidance should be used in conjunction with existing guidelines for CKD-MBD<sup>138</sup>. The risk of fractures after renal transplantation is high but there is no accurate way to predict fracture risk. Clinical tools have not been validated in KTRs. Bone Mineral Density may not reflect the future risk of fracture in KTRs particularly in those with eGFR < 30mls/min/1.73m<sup>2</sup><sup>139</sup>. In addition bisphosphonates are contraindicated in subjects with eGFR < 30mls/min/1.73m<sup>2</sup>. Corticosteroids seem to be the principal determinant of bone turnover and bone volume so it seems logical to target interventions towards reduction or withdrawal of these drugs<sup>140</sup>. There are numerous guidelines for corticosteroid induced osteoporosis including those of the Royal College of Physicians and it seems reasonable to follow them<sup>141, 142</sup>.

### **Guideline 9.2 – KTR: Tertiary hyperparathyroidism**

**We suggest:**

- **Severe hyperparathyroidism should be treated prior to transplantation (2D)**
- **Cinacalcet can be used in KTRs (2C)**
- **Treatment should be the same as for other patients with CKD (2D)**

## **Audit Measures**

1. Incidence of hyperparathyroidism in KTRs
2. Incidence of parathyroidectomy in KTRs
3. Usage of cinacalcet in KTRs

## **Rationale**

Post transplant hyperparathyroidism is a complex entity that may represent a true high bone turnover state but also low bone turnover<sup>143</sup>. In the latter case the suppression of PTH secretion may lead to adynamic bone disease and the only certain way to distinguish between the two types of mineral and bone disorder (MBD-CKD) is by bone biopsy. There is contradictory data on the effect of parathyroidectomy post transplantation but it seems sensible to treat severe hyperparathyroidism prior to transplantation<sup>144, 145</sup>. Cinacalcet may be used in KTRs but caution should be exercised with high doses<sup>146</sup>.

### **Guideline 9.3 – KTR: Gout**

#### **Guideline 9.3.1 – KTR: Treatment of gout**

**We recommend that allopurinol should not be administered with azathioprine.  
(1B)**

#### **Guideline 9.3.2 – KTR: Treatment of gout**

**We suggest:**

- **Hyperuricaemia should be treated when associated with gout, tophi or uric acid stones. (2D)**
- **Non steroidal anti-inflammatory drugs (NSAIDs) should be avoided in KTRs. (2D)**
- **Episodes of gout may be treated with brief courses of oral prednisolone. (2D)**
- **Colchicine is an effective treatment for gout in KTRs (2D)**

## **Audit Measure**

1. Frequency of gout and hyperuricaemia amongst KTRs

## **Rationale**

Gout is common after transplantation and may cause significant morbidity. Hyperuricaemia increases the risk of gout and may also be linked with increased rates of cardiovascular disease<sup>147</sup>. Important drug interactions alter the strategy for managing gout in KTRs. CNIs are associated with higher uric acid levels and may contribute to the development of gout.

### **Guideline 9.4 – KTR: Calcineurin inhibitor bone pain**

#### **We suggest:**

- **Reducing or withdrawing CNIs should be considered in KTRs with intractable bone pain. (2D)**
- **Dihydropyridine calcium antagonists also may be beneficial. (2D)**

## **Rationale**

It has become increasingly recognised that CNIs may cause bone pain which preferentially affects bones in the lower legs<sup>148, 149</sup>. Bone marrow oedema can be demonstrated on MRI scanning and treatment involves reducing CNI levels and the use of dihydropyridine calcium antagonists.

## **10. Kidney Transplant Recipient (KTR) : Haematological complications (Guidelines 10.1-10.4)**

### **Guideline 10.1 – KTR: Anaemia**

**We suggest that anaemia should be managed in the same way as other patients with CKD. (2D)**

#### **Audit Measure**

1. Prevalence of anaemia amongst KTRs

## **Rationale**

Anaemia is common in the KTR population and may be associated with poor outcomes<sup>62</sup>. It may be exacerbated by immunosuppressant therapy especially anti-proliferative agents and these may be tapered to improve haemoglobin levels. Management should be similar to other patients with CKD<sup>150</sup>.

### **Guideline 10.2 – KTR: – Polycythaemia**

**We recommend that initial treatment should be with angiotensin converting enzyme inhibitors (ACEIs) or with angiotensin receptor blockers (ARBs). (1C)**

### **Guideline 10.3 – KTR: – Polycythaemia**

**We suggest:**

- **Haemoglobin levels should be monitored at every clinic visit. (2D)**
- **Treatment should be initiated if the haematocrit or packed cell volume exceeds 52% in men and 49% in women. (2D)**
- **Aminophylline and venesection may be used in refractory cases. (2D)**

#### **Audit Measure**

1. Prevalence of polycythaemia amongst KTRs

### **Rationale for 10.2 and 10.3**

Polycythaemia is common after renal transplantation and may be associated with significant morbidity and mortality<sup>151, 152</sup>. Studies have shown that ACEIs and ARBs are associated with a drop in haematocrit of around 10% in KTRs<sup>1</sup>.

## **11. Kidney Transplant Recipient (KTR) : Reproductive issues (Guidelines 11.1-11.3)**

### **Guideline 11.1 – KTR: Conception and contraception (female)**

**We recommend that MPA-containing immunosuppressant drugs should be stopped prior to conception and replaced appropriately. (1A)**

### **Guideline 11.2 – KTR: Conception and contraception (female)**

**We suggest:**

- **KTRs should wait for one year after transplant and have stable function before attempting conception. (2C)**
- **Counselling regarding fertility and reproduction should be offered to female KTRs and their partners either prior to transplantation or soon afterwards. (2D)**
- **m-TORi should be stopped prior to conception and replaced as appropriate. (2D)**
- **Pregnancy should be managed jointly with an Obstetrics department. (2D)**
- **The risks and benefits of breastfeeding should be discussed. (2D)**
- **Contraception advice should be similar to the general population. (2D)**

#### **Audit Measures**

1. Pregnancy rates and outcomes should be monitored

## **Rationale for 11.1 and 11.2**

Female fertility returns rapidly after successful renal transplantation and KTRs and their partners need to be counselled about potential pregnancy. Pregnancies in KTRs should be deemed above average risk with increased rates of maternal hypertension, preeclampsia, prematurity, low birth weight and caesarean section<sup>153, 154</sup>. The risk of pregnancy to allograft function is probably small, particularly with good baseline function<sup>155</sup>. Immunosuppressive drugs can all have effects on the foetus and caution should be exercised. Sirolimus and MPA compounds are teratogenic and should be avoided completely<sup>156-158</sup>. Alternative immunosuppression should be planned prior to conception. All immunosuppressants are excreted in the breast milk albeit in tiny quantities and are usually contraindicated in guidelines. However toxicity has not been reported after breastfeeding with ciclosporin, prednisolone, azathioprine and tacrolimus<sup>155</sup>. There is very little data surrounding the use of contraception in KTRs and so it seems sensible to extrapolate from the general population with similar cautions and contraindications<sup>155, 159</sup>. A number of hypothetical risks associated with specific forms of contraception have not been confirmed in observational studies though the data quality is poor<sup>159</sup>.

### **Guideline 11.3 – KTR: Conception (male)**

**We recommend that KTRs should be advised that m-TORi reduce the male sperm count and counselled accordingly. (1C)**

### **Guideline 11.4 – KTR: Conception (male)**

**We suggest:**

- **All immunosuppressive drugs other than m-TORi can be used in male KTRs. (2D)**
- **Men on m-TORi who wish to conceive should discontinue these agents prior to conception and replace them as appropriate (2D)**
- **Men who wish to maintain fertility should avoid m-TORi or bank sperm prior to starting these drugs. m-TORi reduce the male sperm count and KTRs should be counselled accordingly. (2D)**
- **Men should be counselled about the possible risks of impotence following transplantation surgery that involves the internal iliac artery. (2D)**

### **Rationale**

Outcomes of pregnancies fathered by male KTRs are similar to the general population<sup>160</sup>. Sirolimus and presumably other m-TORi are associated with oligospermia which appears to be reversible on cessation of treatment<sup>161-163</sup>.

### **Guideline 11.5 – KTR: Sexual dysfunction**

**We suggest:**

- **Specific enquiry should be made regarding sexual dysfunction, preferably at an annual review clinic. (2D)**

- **Care pathways for dealing with sexual dysfunction should be established. (2D)**
- **Close liaison with the local andrology service is recommended. (2D)**
- **Sildenafil is safe and effective in male KTRs not taking nitrates. (2D)**

### **Audit Measures**

1. Prevalence of sexual dysfunction in the transplant clinic

### **Rationale**

Sexual dysfunction is very common in both men and women with advanced CKD and manifests with decreased libido and erectile dysfunction. These problems are often improved after successful renal transplantation but remain common<sup>164, 165</sup>. Sildenafil is safe and may be effective for erectile dysfunction in KTRs<sup>166</sup>.

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## Glossary

ACR	Albumin/creatinine ratio
BMI	Body mass index
BPAR	Biopsy proven acute rejection
CAI	Chronic allograft Injury
CKD	Chronic kidney disease
CNI	Calcineurin inhibitors
ESRD	End stage renal disease
IL-2RA	Interleukin-2 receptor antagonist
Induction period	Initial 3 months after transplant
KTR	Kidney transplant recipient
TDA	T-Lymphocyte depleting agent
LVH	Left ventricular hypertrophy
Maintenance period	Period greater than 3 months after transplant
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid
m-TORi	m-TOR inhibitor
NMSC	Non-melanoma skin cancer
PCR	Protein/creatinine ratio
PTLD	Post transplant lymphoproliferative disease
RRT	Renal replacement therapy
SCAR	Subclinical acute rejection

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