

# Medical Management of the Renal Transplant Patient

## Cardiovascular disease

- Renal transplant patients have a 10 fold increased risk of death from CVD
- Increased prevalence of traditional risk factors:
  - Diabetes
  - Hypertension
  - Hyperlipidaemia
- Non traditional risk factors include
  - Immunosuppression induced endothelial injury
  - Hyperhomocysteinaemia
  - Hypomagnesaemia
  - Vitamin D deficiency
  - Hyperparathyroidism / Coronary calcification
- New onset diabetes after transplantation
  - Approx 13% of transplant patients
  - Approx 16% patients on tacrolimus vs 9% on CsA
  - Risk factors
    - Older age
    - Black recipients
    - Obesity
    - Family history of DM
    - Hepatitis C infection
    - Tacrolimus and Steroids
  - Most common early post transplant when steroid and CNI levels are high
  - Patients with increased risk should be considered for steroid avoidance using tac/MMF
  - Steroid withdrawal should only be considered in those with low immunological risk
  - Treatment
    - Dietary modification
    - Oral therapy
      - Sulfonylurea
      - Meglitinides
      - Biguanides if creatinine <200
    - Oral + insulin
    - Insulin
- Hypertension
  - Pathogenesis
    - Preexisting hypertension
    - CNI (CsA > Tac) / Steroids

- Chronic allograft nephropathy
- Transplant artery stenosis

- Treatment goal

- BP 135/85 (no proteinuria)
- BP 120/80 (proteinuria)

- Treatment

- Loss of weight / salt restriction

- The choice of antihypertensive depends on comorbid conditions
  - Generally first line should be calcium antagonist (?protects against CNI nephrotoxicity)
  - Avoid ACEI / ARB within first 3 months
  - See table on antihypertensives

| Compelling indication             | Recommended drugs |                  |               |     |     |                        |
|-----------------------------------|-------------------|------------------|---------------|-----|-----|------------------------|
|                                   | Diuretic          | $\beta$ -blocker | ACE inhibitor | ARB | CCB | Aldosterone antagonist |
| Heart failure                     | ●                 | ●                | ●             | ●   | ●   |                        |
| Postmyocardial infarction         |                   | ●                | ●             |     |     | ●                      |
| High coronary artery disease risk | ●                 | ●                | ●             |     |     | ●                      |
| Diabetes                          | ●                 | ●                | ●             | ●   |     |                        |
| Chronic kidney disease            |                   |                  | ●             | ●   |     |                        |
| Recurrent stroke                  | ●                 |                  | ●             |     |     |                        |

- Hyperlipidaemia
  - Associated with increased risk of CVD
  - Independent risk factor for CAN and graft loss
  - JBS guidelines recommend total cholesterol <4 and LDL <2
- Treatment ladder
  - Diet
  - Simvastatin 40
  - Rosuvastatin 10
  - Either of above + ezetimibe 10mg od

## Infectious Disease

- Bacterial and fungal infections most common in the first few weeks
- Opportunistic infections such as CMV, Pneumocytis, mycobacteria, nocardia, aspergillosis occur later ( 1month +)
- Immunosuppression should be reduced during acute illness if patient is very unwell/ septic. Usually the antimetabolite is stopped temporarily
- Recurrent infections suggests over immunosuppression and should lead to small / gradual reductions in immunosuppression in the clinic
- Most common bacterial infection is UTI. Caution if stent present  
Mostly prevented by cotrimoxazole prophylaxis during first 3-6 months
- CMV infection
  - Most important viral infection in renal transplant patients
  - CMV replication is associated with increased
    - Acute cellular rejection
    - Chronic allograft nephropathy
    - Cardiovascular disease
    - Diabetes
    - Post transplant lymphoproliferative disease
    - Predisposition to other infections
  - CMV infection defined as detection of CMV DNA or protein in blood
  - CMV disease defined as above + fever / lethargy
  - CMV disease may be associated with organ specific involvement:
    - Bone marrow (low WBC)
    - Hepatitis
    - Pneumonitis
    - Colitis (Often late onset / CMV DNA may not be present in blood)
    - Retinitis: Rare
  - CMV disease prevalence depends on serology of donor / recipient
    - Donor pos / Recipient neg: 50-80%
    - Donor pos / Recipient pos: 25-35%
    - Donor neg / Recipient pos: 15%
    - Donor neg / Recipient neg: <10%
  - Use of ATG and/or high levels of immunosuppression for history of ACR is associated with increased CMV disease
  - Management
    - Prophylaxis with valganciclovir if patient has received ATG
    - Preemptive treatment based on CMV DNA
    - Treatment if CMV DNA log >3.6
      - Valganciclovir 900mg bd
      - Dose of valganciclovir reduced with renal impairment
      - Treatment continued until CMV DNA neg

- Valganciclovir may cause neutropaenia. However If neutropenic on valganciclovir reduce MMF / Aza in preference to valganciclovir
  - CMV DNA should fall by 1 log per week
  - If no response think about ganciclovir resistant CMV
  - Resistance usually seen with short courses and low doses of valganciclovir
  
- Polyoma virus nephropathy
  - More common in patients on TAC / MMF combination. (approx 5% prevalence).
  - Up to 70% of patients with established polyoma virus nephropathy lose the transplant from the infection.
  - BK viuria is the first sign of active viral replication and progression to viraemia appears to be a prerequisite for the development of BK nephropathy.
  - Gold standard for diagnosis is biopsy.
  - Light microscopy alone is usually sufficient to make the diagnosis (large, “washed out” nuclei in tubular epithelial cells but special immunohistochemical stains (SV40) are available.
  - Treatment involves reducing immunosuppression (some favour stopping antimetabolite) and consideration of either low dose cidofovir or leflunomide treatment.
  - Brennan reported success with monitoring viraemia and preemptive reduction of immunosuppression (stopping antimetabolite first followed by reduction in CNI if persisting viraemia 4 weeks after stopping antimetabolite).
  - This preemptive approach completely prevented BK nephropathy.

## Preemptive protocol

- Monitor BK virus DNA in blood (purple top tube : send out test to Bristol)
- BK virus DNA assessed fortnightly from 1 month to 4 then at month 5, 6, 9 and 12
- Stop MMF if BK virus DNA >10,000 copies per ml
- Reduce CNI dose if BK virus DNA > 10,000 copies per ml for >4 weeks after stopping MMF

## Bone Disease

- Fracture rate is 5-10 X higher than general population
- Mainly appendicular fractures (contrary to axial fractures in postmenopausal women)
- Most common in elderly, females, diabetics and those with hyperparathyroidism
- Aetiologic factors
  - Preexisting bone disease
    - Osteitis fibrosa
    - Osteomalacia
    - Adynamic bone disease
    - Osteoporosis
  - Corticosteroids
    - Major cause of osteonecrosis
  - Hypophosphataemia
  - Gonadal dysfunction

- Treatment
  - Prevention
    - Elemental Calcium 1g / day
    - Vitamin D 800iu/day
    - Above in the form of Adcal D3 1 tab bd
  - Established Osteoporosis
    - Alendronate 70mg q week if established
    - Steroid withdrawal (if low immunological risk)

## Post transplant gout

- Common post transplant
- CsA is hypouricosuric leading to increased uric acid levels
- This effect is not seen with Tacrolimus
- Allopurinol can not be given with Azathioprine
- Patient may have to be switched to MMF to allow allopurinol therapy
- Acute gout best managed by
  - Colchicine 0.6ug q 2 hrs
  - Increase prednisolone to 30mg for 1 week
  - Avoid NSAIDS

## Malignancy

- Mechanisms
  - Reduced immune surveillance of tumour cells
  - Enhanced viral mediated oncogenesis
  - Direct oncogenic potential of immunosuppressive drugs particularly CN
- The tumours most increased in incidence are virally mediated
  - Skin cancer (Squamous cell CA: HPV mediated)
  - Post transplant lymphoproliferative disease (EBV mediated)
  - Cervical CA (HPV mediated)
  - Anal / Vulval CA (HPV mediated)
  - Kaposi sarcoma (HHV 8 mediated)
- Renal cell CA is increased in incidence mainly because of its association with ESRD
- Prevention
  - Regular skin checks
  - Avoid sun exposure
  - Cancer screening as per regular population
  - Minimize immunosuppression whenever possible
  - Caution in patients who are EBV negative (mainly paediatric population) prior to transplantation

- Treatment
  - Multiple skin lesions respond well to sirolimus therapy
  - PTLD is managed by
    - Reduction in immunosuppression
    - Rituximab treatment

## Anaemia post transplant

- Causes
  - Allograft dysfunction
  - Immunosuppressives
    - Sirolimus > MMF > azathioprine
  - ACEI / ARB
  - Other drugs eg valganciclovir, Bactrim
  - Parvovirus B19
  - Hemolysis
    - CNI induced thrombotic microangiopathy
    - Bactrim induced haemolysis in G6PD deficiency
- Other causes
  - Iron deficiency etc

## Gastrointestinal disorders

- Heart burn
  - All patient should be on PPI for first 4-6 months
  - Think about candida oesophagitis
- Diarrhoea
  - MMF induced
    - Related to peak level
    - Split dose into tds / qds
    - Change to enteric coated MMF (Myfortic)
  - Usual hospital pathogens
    - Viral
    - C. difficile
  - CMV colitis
    - Pathology required
    - CMV DNA may be negative
  - PLTD
    - Rare
    - Pathology required