Haematological Abnormalities in Renal Transplant Recipients	University Hospitals of Leicester NHS NHS Trust C125/2016

1. Introduction and Who Guideline applies to

Following renal transplantation there are several haematological abnormalities that can typically arise and require further investigation and treatment

2. Guideline Standards and Procedures

This guideline is intended for clinical staff involved in the management of Renal Transplant patients

3. Education and Training

3.1 Post-transplant erythrocytosis

3.1.1 Post renal transplant there is an initial increase in serum erythropoietin which subsequently falls back to a baseline level. This increase is followed by a reticulocytosis and a rise in haematocrit.

The aetiology of post-transplant erythrocytosis remains uncertain but it may be due to an over-secretion of erythropoietin by native kidneys, the transplanted kidney or the liver (however, some patients have low EPO levels). Other factors can include IGF-1

Erythrocytosis occurs in around 20% of transplant patients. It usually occurs within the first 2 years of transplantation, especially in hypertensive males or those with ADPKD; most patient still have their native kidneys *in situ*; other patients include those who have received a simultaneous pancreas and kidney transplant.

Erythrocytosis is an important condition which if untreated, is associated with increased incidence of vascular and thromboembolic disorders or excesive bleeding.

3.1.2 Evaluation and treatment are required when the haematocrit is > 50% on 2 consecutive occasions in a 6-month window.

Investigations are oriented to other potential causes in selected population:

- Blood film to detect bone marrow abnormalities (primary polycythaemia and myeloproliferative disorders
- To rule out other causes polycythaemia: use of SGLT-2 inhibitors, surreptitious use of EPO, smoking, obstructive sleep apnoea, COPD and, if concerned, cancer (breast, renal cell and hepatocellular carcinomas), haemangioblastomas, etc. If appropriate, imaging can be requested (Doppler and ultrasound; CT CAP) along with other tests (spirometry, polysomnography

The mechanism by which certain medications affect erythropoiesis, like ACEi/ARB and SGLT-2 inhibitors is not well understood, but it could involve effects on hypoxia-inducible factor (HIF), abnormal function of EPO producing fibroblasts in peritubular capillaries and proximal convoluted tubule.

3.1.3 Most patient will get medical treatment, rarely they might rely only on phlebotomy:

- Where haemoglobin is less than 170 g/L or haematocrit >51%:
    - ACE inhibitors (ACEi) or Angiotensin receptor blockers (ARB):

- Mechanism of action is still unknown but may be due to a reduction in erythropoiesis as a consequence of suppression of angiotensin-driven EPO production in native kidneys. These agents alter renal haemodynamics and may improve oxygenation of EPO producing cells; before starting these drugs:
    - Ensure blood pressure is adequate to tolerate introduction of ACEi or ARB (consider whether other BP treatment should be reduced)
    - Consider possibility of transplant renal artery stenosis. Imaging (doppler scan) is not mandatory unless other clinical features point to stenosis, but serum creatinine must be checked within 1-2 weeks of starting ACEi or ARB
- Ramipril 2.5 – 10 mg daily or
- Losartan 50 – 100 mg daily (if patient is intolerant of ACE inhibitor e.g. cough)
- Other ACE/ARB can be used too

- When haemoglobin 170 g/L or higher, where there is a contraindication to medical therapy or when medical therapy is ineffective
    - Phlebotomy (venesection): 2-3 occasions one month apart, followed by medical therapy as above
- Other therapies would need discussion with the Transplant lead for approval. This includes Theophylline, which is effective but has significant side effects and narrow therapeutic range
- The goal is to achive Haemoglobin <17 (haematocrit <51%)

3.2 Bone marrow suppression including pancytopaenia

- Bone marrow suppression - anaemia, leucopaenia, thrombocytopaenia – after transplant is most often due to drugs; it can be presented as pancytopaenia or as a combination of the above. Most common culprits are:
    - Azathioprine/Mycophenolate
    - Sirolimus
    - Co-trimoxazole/dapsone
    - Valgalciclovir/ganciclovir
    - Use of a lymphocyte depleting agent (ATG/alemtuzumab)
    - There are always other possibilities – review medications in detail
- Mycophenolate and azathioprine also cause macrocytosis, and the latter profound leucopenia in combination with allopurinol [reduce azathioprine dose by 75% if allopurinol is needed, and azathioprine cannot be avoided]
- Opportunistic infections: CMV, EBV, VZV, Tuberculosis
- Depending on the clinical picture, patients might benefit from the following:
    - Reduction/switching to other drugs
    - Use of stimulating agents like EPO or filgrastim (this requires discussion with consultant and treatment effectivity constantly monitored)

3.3 Persistent anaemia post-transplantation

- Good graft function is necessary for spontaneous correction of anaemia post-transplant. With serum creatinine in normal range, Hb will typically return to normal post-transplant in 4-8 weeks

- Anaemia in early post-transplant period, consider
    - Iron deficiency anaemia; B12/folic acid deficiency
    - Parvovirus B19 infection (check for DNA PCR, not serology)
    - Haemolytic anaemia
    - Recurrent or *de novo* HUS/TTP
- Anaemia due to chronic graft failure
    - Exclude causes above.
    - Check: haematinics, PTH, CRP

- If all normal, consider EPO therapy (discuss with nephrology consultant)

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Incidence of Haematocrit >55%	Proton data	Transplant lead	Bi-annually	To Q&S lead

5. Supporting References (maximum of 3)

If None say NONE

6. Key Words

Kidney transplant, erythrocytosis, anaemia

CONTACT AND REVIEW DETAILS	
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Details of Changes made during review:	