Anaemia in Chronic Kidney Disease

Aetiology\(^{[1,2]}\)

In patients with chronic kidney disease, normochromic normocytic anaemia mainly develops from decreased renal synthesis of erythropoietin. The anaemia becomes more severe as the glomerular filtration rate (GFR) progressively decreases. No reticulocyte response occurs, red blood cell survival is decreased and there is an associated increased bleeding tendency due to uraemia-induced platelet dysfunction.

Iron deficiency is also common in patients with chronic kidney disease (CKD). The iron deficiency may be absolute, often due to poor dietary intake or sometimes occult bleeding, or functional, when there is an imbalance between the iron requirements of the erythroid marrow and the actual iron supply. Iron deficiency leads to a reduction in formation of red cell haemoglobin, causing hypochromic microcytic anaemia. Other causes for anaemia in chronic kidney disease include the presence of uraemic inhibitors (eg, parathyroid hormone, inflammatory cytokines), reduced half-life of circulating blood cells and deficiencies of folate or vitamin B12.

Epidemiology

- Studies of patients with CKD have shown that the prevalence of anaemia (defined as a haemoglobin level less than 12 g/dL in men and postmenopausal women and less than 11 g/dL in premenopausal women) is about 12%\(^{[3]}\).
- The National Health and Nutrition Examination Survey (NHANES) III study showed that the prevalence of anaemia increases as eGFR falls. Data collected in 2007-2010 showed that anaemia was twice as prevalent in people with CKD (15.4%) as it was in the general population (7.6%). The prevalence increased with the stage of CKD, from 8.4% at stage 1 to 53.4% at stage 5\(^{[1]}\).
- In patients with CKD, patients with diabetes are at a greater risk of developing anaemia earlier in the course of their disease (associated with inappropriately low levels of erythropoietin). Comparing patients with similar eGFR and erythropoietin levels, those with type 2 diabetes are generally more anaemic\(^{[3]}\).

Presentation

- It is often diagnosed by routine review blood tests.
- Renal anaemia may lead to the onset or aggravation of lethargy, cold intolerance and loss of stamina.
- Anaemia increases cardiac output, therefore contributing to the development of left ventricular hypertrophy and dilatation.

Differential diagnosis\(^{[3]}\)

Causes of anaemia in patients with CKD, other than renal failure itself, include:

- Chronic blood loss
- Iron deficiency
- Vitamin B12 or folate deficiency
- Hypothyroidism
- Chronic infection or inflammation
- Hyperparathyroidism
- Aluminium toxicity
- Malignancy
- Haemolysis
- Bone marrow infiltration
- Pure red cell aplasia

Investigations

Investigate patients with CKD if their haemoglobin falls to 11 g/dL or less, or they get symptoms due to anaemia, such as tiredness or breathlessness\(^{[3]}\).

This will involve ruling out other causes of anaemia, assessment of kidney function, assessment of any cardiovascular and other complications of anaemia or CKD.

- Kidney function, eGFR and electrolytes.
- FBC, blood film, iron studies (ferritin, transferrin saturation, iron), B12 and folate. Where ferritin is <100 µg/L there is iron-deficiency anaemia. If ferritin is above this level, a functional iron deficiency (and hence a requirement for iron supplementation) is defined by the percentage of hypochromic red cells >6% (if test is available) or otherwise a transferrin saturation <20%\(^{[3,4]}\).
- Other investigations will be determined by likely alternative diagnoses and cardiovascular effects of anaemia - eg, TFTs, renal ultrasound, echocardiography, investigations for gastrointestinal bleeding.
Management[3]

- Any patient with CKD presenting with anaemia:
  - Should be referred to the local specialist renal department for full assessment and management. Clinical assessment should include an assessment of nutrition, general well-being and other possible causes for anaemia (eg, occult blood loss).
  - Blood pressure should also be checked and any other factor suggesting acute on chronic kidney disease - eg, infection.
  - The basic blood test investigations as outlined above should be sent (ensuring the results are available at the renal department).

- Management of anaemia should be considered in people with anaemia of CKD when the haemoglobin level is less than or equal to 11 g/dL (or 10 g/dL if under 2 years of age).
- In people with anaemia of CKD, treatment should aim to maintain stable haemoglobin levels between 10 and 12 g/dL for adults and children aged over 2 years and between 9.5 and 11.5 g/dL in children aged under 2 years.
- Treatment with erythropoiesis-stimulating agents should be offered to patients with anaemia of CKD who are likely to benefit in terms of quality of life and physical function. There are few studies comparing the efficacy of the various agents. One study reported that darbepoetin alfa weekly or every two weeks was more efficient in achieving target haemoglobin than those on weekly epoetin alfa, with fewer dose changes and minor vascular access complications.
- The time taken for erythropoietin treatment to be effective will depend on individual patient factors, such as degree of anaemia, degree of kidney disease and presence of other adverse factors - eg, iron deficiency.
- Contra-indications for erythropoietin treatment include uncontrolled hypertension.
- Potential side-effects of erythropoietin include increase in blood pressure or aggravation of hypertension, headache, increase in platelet count, influenza-like symptoms (may be reduced if intravenous injection is given over five minutes), thromboembolic events, pure red cell aplasia, hyperkalaemia and skin reactions.
- Increasing concerns over the risk of cardiovascular events have led to a reduction in the use of erythropoetins as a group in recent years.

There have been very rare reports of pure red cell aplasia in patients treated with epoetin alfa. The Commission on Human Medicines has advised that in patients developing epoetin alfa failure with a diagnosis of pure red cell aplasia, treatment with epoetin alfa must be discontinued and testing for erythropoietin antibodies considered. Patients who develop pure red cell aplasia should not be switched to another erythropoietin.[7]

- Monitoring: in people with anaemia of CKD, haemoglobin should be monitored:
  - Every 2-4 weeks in the induction phase of erythropoiesis-stimulating agent therapy.
  - Every 1-3 months in the maintenance phase of erythropoiesis-stimulating agent therapy.
  - More actively after dose adjustment of the erythropoiesis-stimulating agent.

  - Epoetin alfa:
    - Epoetin (recombinant human erythropoietin) is used for the anaemia associated with erythropoietin deficiency in CKD. The clinical efficacy of epoetin alfa and epoetin beta is similar.
    - It is also used to increase the yield of autologous blood in normal individuals and to shorten the period of anaemia in patients receiving cytotoxic chemotherapy.
    - Epoetin beta is also used for the prevention of anaemia in preterm neonates of low birth weight.

  - Darbepoetin:
    - Is a hyperglycosylated derivative of epoetin which has a longer half-life and may be administered less frequently than epoetin.

  - Methoxy polyethylene glycol-epoetin beta:[9]
    - Is a continuous erythropoietin receptor activator. It is licensed for the treatment of anaemia associated with CKD in patients who are symptomatic. It has a longer duration of action than epoetin.

- Other factors which contribute to the anaemia of CKD (eg, iron or folate deficiency) should be corrected before treatment and monitored during therapy.
- Aluminium toxicity, concurrent infection or other inflammatory disease may impair the response to erythropoietin.[7]
- People receiving erythropoiesis-stimulating agent maintenance therapy should be given iron supplements (often requires intravenous iron) to keep their:
  - Serum ferritin between 200 and 500 μg/L and either:
    - The transferrin saturation level above 20% (unless ferritin is >800 μg/L); or
    - Percentage hypochromic red cells less than 6% (unless ferritin is >800 μg/L).

- In view of the concerns about the adverse effects of erythropoetins, other therapeutic options are being explored. These include hypoxia inducible factor-1 alpha (HIF-1α) stimulators. HIF-1α is known to be associated with oxygenation of the kidney tubule.
- Clinically relevant hyperparathyroidism should be treated in order to improve anaemia management in patients with anaemia of CKD.
- Where possible, blood transfusions should be avoided in patients in whom kidney transplant is a treatment option.

Prognosis
Untreated anaemia of CKD is strongly associated with cardiovascular and renal complications, resulting in increased hospitalisations and mortality. Therefore, correcting anaemia is considered an important part of slowing or even stopping the progression of CKD. [10]

Treatment with recombinant human erythropoietin in pre-dialysis patients corrects anaemia, avoids the requirement for blood transfusions and also improves quality of life and exercise capacity. [11, 12]

**Prevention**

Restricting the progression of CKD - eg, smoking cessation, optimal control of diabetes. [13]

**Further reading & references**

- Anaemia management in people with chronic kidney disease; NICE Guidelines (June 2015)

3. Anaemia Management in People with Chronic Kidney Disease; NICE Clinical Guideline (February 2011)
7. British National Formulary

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**Author:**
Dr Laurence Knott

**Peer Reviewer:**
Dr Adrian Bonsall

**Document ID:**
2961 (v25)

**Last Checked:**
23/04/2014

**Next Review:**
22/04/2019

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