How do I approach....anaemia in feline CKD
Sarah M. A. Caney BVSc PhD DSAM(Feline) MRCVS
RCVS Specialist in Feline Medicine

Anaemia is an acknowledged potential complication of chronic kidney disease (CKD) and it is estimated that between 30 and 60% of patients develop anaemia as their renal disease progresses. The mechanism behind anaemia development is multifactorial with mechanisms including:

- Decreased red cell production
  - Reduced production of erythropoietin by diseased kidneys is the main cause of anaemia associated with CKD. Erythropoietin is produced in the peritubular interstitial cells of the inner renal cortex and outer medulla and the main stimulus for erythropoietin production is renal hypoxia. As renal disease progresses, there are fewer and fewer erythropoietin-producing cells in the kidney.
  - Other factors which have a negative impact on erythropoiesis include inflammatory cytokines, iron deficiency, uraemic toxins and hyperparathyroidism
  - Some renal medications, including ACE inhibitors and angiotensin receptor blockers, are thought to have some effects to reduce erythropoietin release and reduce red cell production by the bone marrow
  - Aluminium-containing phosphate binders can contribute to anaemia through interfering with iron metabolism leading to development of a microcytic anaemia

- Reduced survival of red blood cells
  - Uraemic toxins reduce the lifespan of red blood cells and this can contribute to development of anaemia through haemolysis and premature clearance by the reticuloendothelial system

- Increased blood loss
  - Patients with CKD are vulnerable to blood loss via gastrointestinal ulcers
  - Excessive blood sampling may contribute to anaemia development

Anaemia can contribute to reduced quality of life, for example leading to lethargy and reduced appetite. Assessment of all CKD patients should therefore include attention to the possibility of anaemia. Clinical signs of anaemia are often subtle and may not be obvious to carers since they are insidious in onset and gradual in progression. Lethargy and reduced appetite are most commonly reported in anaemic CKD patients but are not specific signs since these can be associated with other complications of CKD.

Physical examination may reveal clues of anaemia such as pallor, however, assessment of mucous membrane colour is notoriously insensitive as an indicator of anaemia in cats unless they are ‘deathly’ pale. A complete blood count (CBC) is therefore essential in general monitoring of CKD patients, even when there is no clinical suspicion of anaemia, and of especial importance in CKD patients where anaemia is suspected. The anaemia associated
with CKD is typically normocytic, normochromic and poorly regenerative. Where iron deficiency is a feature, there may be microcytic and pale (hypochromic) red cells.

Treatment of anaemia is generally recommended once the haematocrit falls to wards or below 20%. If sequential CBCs show a gradual decline then it may be worthwhile intervening at an earlier stage (eg haematocrit 20 – 25%). Where possible, the author finds it helpful to assess iron status in renal patients. In the UK the most practical way of assessing iron status involves a panel which includes iron saturation, total iron binding capacity (TIBC) and iron levels. Whilst having low/normal serum iron and saturation with a low TIBC is generally considered compatible with an anaemia of chronic disease, in a patient with iron deficiency iron levels and saturation are low whereas TIBC is normal (Table 1). Where available, assessment of serum ferritin (a storage form of iron) can be helpful. Iron deficient patients have low serum ferritin levels whereas in patients with anaemia due to chronic inflammation, ferritin levels are normal or high. Ferritin is a species specific assay, currently only available in Kansas, USA, so often not practical to run from the UK.

Table 1. Iron deficiency or anaemia of chronic inflammation? (adapted from Naigamwalla et al, 2012)

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<th>Typical reference range</th>
<th>Iron deficiency</th>
<th>Chronic inflammation</th>
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<tr>
<td>Haematocrit</td>
<td>25 – 40%</td>
<td>↓ to ↓↓↓</td>
<td>↓ to ↓</td>
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<tr>
<td>MCV</td>
<td>38 – 50 fl</td>
<td>↓ to ↓↓↓</td>
<td>Normal to ↓</td>
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<tr>
<td>MCHC</td>
<td>28 – 36 g/dl</td>
<td>↓</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum iron</td>
<td>12 – 39 umol/l</td>
<td>↓ to ↓↓↓</td>
<td>Normal to ↓</td>
</tr>
<tr>
<td>Total iron binding capacity (TIBC)</td>
<td>40 – 90 umol/l</td>
<td>Normal to ↑</td>
<td>Normal to ↓</td>
</tr>
<tr>
<td>Percent iron saturation</td>
<td>&gt; 25%</td>
<td>↓ to ↓↓↓</td>
<td>Normal to ↓</td>
</tr>
<tr>
<td>Reticulocytes</td>
<td>&lt; 50 × 10⁹/L</td>
<td>Normal to ↓</td>
<td>↓</td>
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In genuinely iron deficient patients, injectable iron supplementation is recommended as the most efficient way to return iron levels to normal. Iron dextran at a dose of 50 mg can be given by intramuscular injection. Care should be taken not to over-supplement when using the injectable route. The iron dextran can be repeated after one month, if needed. Oral supplementation with iron tends to be much less effective and is often very unpalatable for patients. The author has had some success with oral supplements in mild/borderline deficient patients and best success in terms of tolerance has been with ferrous fumarate (eg Galfer capsules, these contain 100 mg elemental iron in enteric coated beads and a dose of 0.2 capsules per cat per day is generally sufficient).

Erythrocyte stimulating agents (ESAs) such as recombinant human erythropoietin (rHuEPO) have been used for many years in cats. rHuEPO has an 83% homology with feline EPO. A number of different forms of rHuEPO are available for use in people and include epoetin alpha (eg Epogen, Procrit), epoetin beta and darbepoetin alpha (eg Aranesp). These different preparations vary in their degree of glycosylation which affects the speed of renal
clearance (and hence frequency of administration needed) but not the efficacy of anaemia treatment. Table 2 summarises the dose recommendations for the most frequently recommended ESAs. An induction protocol is followed until the packed cell volume (PCV) has reached target levels of 25% or higher, after which the maintenance protocol is followed. A response to treatment is generally seen within 2-4 weeks although not all cats respond to this medication. The long-term aim is for the PCV to remain between 25 and 35% and the dose and frequency of ESA can be adjusted to achieve this, for example reducing the dose by 20% and reducing the frequency of administration once the target PCV is achieved (Table 2). ESAs are not effective in all patients and side-effects have been described with these medications, as outlined later.

Table 2. Doses and protocols for ESAs in cats

<table>
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<tr>
<th>ESA</th>
<th>Induction dose (typically 2-4 weeks)</th>
<th>Initial suggested maintenance dose</th>
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<tr>
<td>Epoetin</td>
<td>100 iu/kg s/c three times a week</td>
<td>50 – 100 iu/kg s/c twice weekly</td>
</tr>
<tr>
<td>Darbepoietin</td>
<td>1 mcg/kg s/c once a week</td>
<td>1 mcg/kg s/c every 2-3 weeks</td>
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Epoetin was the first rHuEPO to become available and has been used with great success in cats. More recently darbepoietin has become very popular since it has a longer half life and therefore does not need to be administered as frequently. Recombinant feline EPO has been developed but is not available commercially.

Weekly monitoring of PCV and reticulocyte count is recommended until the PCV and dosing regime stabilise, after which the frequency of monitoring can be reduced to monthly.

Side effects to ESAs are well documented and although the overall response to treatment can be excellent it is important to have an awareness of potential side-effects. Most common is development of systemic hypertension (up to 50% of patients), hence the importance of monitoring blood pressure. Blood pressure should be monitored whenever the cat is given their ESA treatment (ie initially on a weekly basis). Uncontrolled systemic hypertension can cause seizures in some cats. Pure red cell aplasia (PRCA) is another important potential adverse effect and is encountered in up to one third of treated cats. PRCA arises due to induction of neutralising antibodies that cross-react with the ESA and the cat’s endogenous EPO. PRCA results in a severe non regenerative anaemia. PRCA appears to be much less common in cats receiving darbepoietin versus epoetin (<10% v 30% cases) which is another reason for the current popularity of darbepoietin. When PRCA develops, ESA treatment must be stopped and the patient becomes dependent on blood transfusions. As expected, development of PRCA is usually followed by euthanasia within a short period of time. Interestingly, PRCA appears to develop in a similar proportion of cats treated with recombinant feline EPO which may be one reason why this has not been developed commercially.

Where a poor response to ESA treatment is found, clinicians should consider possible causes such as:
- Iron deficiency – check iron status and supplement as necessary
- Poor compliance to ESA and/or iron
- Dose or frequency of ESA inadequate
- Continued blood loss eg gastrointestinal blood loss
- Concurrent infection or inflammatory process contributing to the anaemia – look for other clinical problems and treat these if possible
- Bone marrow disease eg PRCA, fibrosis or neoplasia (bone marrow aspirate and/or biopsy may be needed to confirm these)

Consideration to other factors such as B vitamin deficiency, adverse effects of ACEI, ARB or aluminium hydroxide may be relevant in some cases.

Iron therapy is recommended in all cats receiving ESAs. Iron status should ideally be assessed before starting treatment and thereafter on a monthly basis. In patients eating a commercial renal diet and where appetite is reasonable, vitamin deficiency should not be a concern. In those where appetite is poor, supplementation with B vitamins may be prudent to mitigate potential B vitamin deficiency which could have an adverse effect on erythropoiesis and lead to apparent failure to respond to ESA treatment.

Anabolic steroids have been proposed as a treatment for anaemia associated with CKD but have dubious efficacy and potential adverse effects, therefore are not recommended. Blood transfusion and/or use of synthetic haemoglobin-based products such as oxyglobin (where available) can be helpful for short term support of patients pending other therapies or allowing the owner some time to come to terms with their cat’s reduced clinical status prior to euthanasia.

In conclusion, anaemia is a common complication associated with CKD and can have a deleterious effect on quality of life. Treatment including ESAs can make a big impact on quality of life although attention needs to be paid to potential side-effects such as systemic hypertension and PRCA.

References and Further Reading
