Anaemia in Cats

Anaemia is a common presenting problem in cats and there are a wide range of potential causes that need to be considered. A logical approach to investigation is required as well as an early assessment of the severity of the anaemia and whether immediate emergency measures are required.

Interpreting the Feline Haemogram:

Anaemia is a reduction in the number of circulating red blood cells, or a reduction in haemoglobin concentration in the blood.

Measuring the Packed Cell Volume (PCV) in a microhaematocrit tube provides a rapid, in-house indication of anaemia but evaluation of the range of red cell parameters provided by a full blood count will then be needed to characterise the anaemia.

It is important to assess the severity of the anaemia and collect all appropriate samples BEFORE starting any supportive / emergency treatment as treatment may have a marked effect on the interpretation of results.

**NB:** Caution is required when interpreting red cell parameters generated by automated haematology analysers. Anomalous results can occur for a number of reasons:

- Feline red blood cells are smaller than canine red cells. Feline platelets are much larger than canine platelets and are very prone to clumping. Automated haematology analysers may mis-read large platelets or clumps of platelets as red blood cells, producing an anomalously low platelet count and an slightly elevated red cell count
- Feline red blood cells are prone to rouleaux formation (red cells sticking together). Automated haematology analysers may mis-read clumped red cells as white blood cells, producing an excessively high white cell count and a reduced red cell count

It is important to examine a fresh blood smears when interpreting results generated by in-house haematology analysers, especially when results fall outside the ranges expected from the clinical examination.
1) How Severe is the Anaemia?

There are three elements to consider when assessing the severity of anaemia:

- **Clinical Signs**: Is the cat showing any clinical evidence of anaemia?
  - Weakness, lethargy, tachypnoea, tachycardia and bounding or weak thready pulses are indicators of more severe anaemia and emergency treatment may be indicated.
  - Pallor is a less reliable indicator that reflects peripheral circulation / vasoconstriction as well as red cell concentration.

- **Level of reduction in PCV**:
  - PCV of 20-24% = mild anaemia
  - PCV of 15-19% = moderate anaemia
  - PCV of < 14% = severe anaemia

- **Rate of onset** of anaemia – a cat may cope well with severe anaemia if it has been gradual in onset but may be significantly compromised by an acute onset moderate anaemia.

As a rule of thumb a blood transfusion is indicated when:

- Anaemia is severe enough to cause clinical signs, e.g. weakness, dyspnoea
- There is acute anaemia with PCV < 15%
- There is chronic anaemia with PCV < 10%

2) Is the anaemia regenerative or non-regenerative?

**Regenerative anaemia** indicates haemorrhage or haemolysis followed by a normal up-regulation of red cell production from the bone marrow. However the bone marrow response will take up to 5 days to develop, so in the early stages there will be a “pre-regenerative” phase during which red cell parameters will be as for non-regenerative anaemia.

**Non-regenerative anaemia** indicates inability of the bone marrow to replace lost red blood cells due to chronic systemic disease or primary bone marrow disease.

**Identifying Regenerative Anaemia**

Regenerative anaemias are identified by the presence of increased numbers of circulating reticulocytes (immature red blood cells). Reticulocytes are identified by staining a blood smear with New Methylene Blue (see Box 1) – cats have two forms of reticulocyte:

- **Aggregate reticulocytes** contain large numbers of basophilic granules. They are an indication of recent activation of the bone marrow and are the hallmark of a regenerative anaemia. Aggregate reticulocytes appear in circulation within 3-5 days.
of the onset of anaemia and reach peak levels after 5-10 days, they mature into punctate reticulocytes within 24 hours of their release from the bone marrow.

- Absolute aggregate reticulocyte count > 6 x 10⁹/L is likely to reflect a regenerative response (but see below for calculation of the reticulocyte index).

- **Punctate reticulocytes** contain only sparse numbers of basophilic granules (< 6 per cell). They are a more mature form of reticulocyte and persist in the circulation for up to 10 days.

If both aggregate and punctate reticulocytes are present on a blood smear, it is the number of aggregate reticulocytes which determines the degree of regenerative response. However, in mild chronic anaemias which only cause mild bone marrow stimulation increased numbers of punctuate reticulocytes may be the only indication of regeneration.

The number of aggregate reticulocytes should be proportional to the severity of the anaemia; this can be assessed by calculating the reticulocyte index (RI).

- **A reticulocyte index** > 0.4 indicates an adequate regenerative response; RI > 0.6 indicates a strong regenerative response
  - RI = (% reticulocytes x current PCV)/35
  - % reticulocytes = (Absolute reticulocyte count/total red cell count) x 100

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**Box 1 New Methylene Blue Stain for Reticulocytes**

- Mix equal volumes of EDTA blood and 5% New Methylene Blue
- “Incubate” at 37°C for 20 minutes (in absence of incubator, keep as close to body temp as possible – e.g. keep in an inside pocket).
- Blood Smear: Count 100-200 RBCs and note the number of them that are aggregate reticulocytes
  - Aggregate reticulocytes have > 6 dots per cell
  - Punctate reticulocytes have < 6 dots per cell and must not be counted
- Then calculate Reticulocyte Index:
  - Observed % Reticulocytes x (PCV/35)

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A reticulocyte count is essential to determine whether anaemia is regenerative or non-regenerative. Other features of the haemogram that may suggest (but do not prove) a regenerative response are:

- **Polychromasia:** Reticulocytes appear bluish-purple when they are stained with a Wright’s / Romanowsky stain (e.g. Diff-Quick) but in cats the appearance can be subtle. Polychromasia is an indicator of bone marrow activity but a reticulocyte count is required to categorise the degree of regeneration.
- **Macrocytosis:** In regenerative anaemia there is in overall increase in Mean Cell Volume (MCV) because reticulocytes are larger than red blood cells.
Non-regenerative anaemias can also be macrocytic e.g. FeLV induced anaemia; myelodysplastic anaemia

- **Hypochromia:** Reticulocytes have lower haemoglobin content than mature red cells so the Mean Cell Haemoglobin Content (MCHC) is reduced
  - Iron deficiency anaemia is uncommon in cats but can occur (see later), and is an example of a hypochromic non-regenerative anaemia

- **Anisocytosis / Increased Red Cell Distribution Width (RDW):** The difference in size between a mature red cell and a reticulocyte is visible on blood smear and causes an increase in RDW.
  - Increased RDW can also be an indication of the presence macrocytes and/or microcytes in the absence of reticulocytes
  - Normal feline blood cells have a greater degree of anisocytosis than canine red cells

**NB:** Nucleated red blood cells may appear in the circulation during a regeneration response but can also be an indication of non-regenerative anaemias e.g due to myelodysplasia
Causes of Anaemia in Cats

1) Causes of Regenerative Anaemia

In regenerative anaemias there is an increased loss of red cells from the circulation, caused by either haemorrhage or haemolysis.

a) Haemorrhage

In the immediate aftermath of an episode of haemorrhage the PCV will be normal due to loss of whole blood, anaemia occurs when circulatory volume recovers and red cell numbers remain low.

| If anaemia is due to haemorrhage the serum total protein is also usually low |

External haemorrhage is usually apparent from the clinical history and/or clinical examination. Treatment is aimed at stopping further blood loss and supporting circulatory volume with crystalloid, colloid or a blood transfusion depending on the severity of the loss and the condition of the cat.

Internal Haemorrhage is most commonly due to acute blood loss into the abdomen or thorax, or chronic blood loss via the GI tract and is usually secondary to another disease or pathology e.g. a coagulopathy, a bleeding neoplasm, ulcerative gastritis secondary to uraemia or NSAID etc. Accurate history taking and careful physical examination are required to identify the primary disorder.

If internal haemorrhage has been mild but very chronic, iron deficiency may develop and the anaemia will become non-regenerative. Iron deficiency anaemia is rare in cats (see later) and must be distinguished from anaemia of chronic inflammation, which is much more common and for which iron supplement is not indicated.

Differential Diagnoses for Internal Haemorrhage

1) Coagulopathies: Potential causes include (but are not limited to):

- **Toxin Induced:** Rodenticide poisoning
- **Drug Induced:** Adverse reaction to methimazole or carbimazole
- **Secondary to chronic liver disease:** Acquired vitamin K deficiency
- **Disseminated Intravascular Coagulation:** e.g. due to acute pancreatitis

- Inherited coagulopathies: Rare in cats

2) Haemothorax: Most commonly associated with neoplasia or coagulopathy

3) Haemoperitoneum: Intra-abdominal bleeding is most commonly associated with neoplasia and/or liver disease:
In a review of 65 cats presenting with haemoperitoneum (Culp et al, 2010. JAVMA):

- 46% (30 cases) had abdominal neoplasia, but only 5 had a palpable mass:
  - Haemangiosarcoma was the most common neoplasm (18/30)
    - 9 splenic; 4 hepatic; 3 intestinal; 2 other
  - 7 cats had hepatic or biliary tumours of a type other than haemangiosarcoma
    - 4 had hepatic carcinoma
  - Other tumours involved the spleen (2), kidneys (2) and pancreas (1)
- 54% had non-neoplastic disease: The most common causes were:
  - Hepatic bleeding (17/35) due to:
    - Hepatic necrosis (8); Hepatic amyloidosis causing liver rupture (4); Inflammatory liver disease (3); Hepatic Haematoma (2)
    - Coagulopathy (8/35)
    - Ruptured bladder (5/35)
    - Gastrointestinal Ulcers (3/35) of which Gastric (2); Duodenal (1)
- The outcome was almost always fatal

4) Gastrointestinal blood loss: Chronic GI bleeding can occur in cats with gastric or intestinal neoplasia, inflammatory bowel disease, gastric ulcers secondary to renal disease or use of NSAIDs. Mild chronic blood loss is most common causing chronic progressive anaemia which may eventually lead to iron deficiency. An acute more severe haemorrhage can also occur presenting as shock, hypothermia, hypovolaemia and then anaemia, or there may be pre-existing chronic anaemia that becomes rapidly more severe.

Treatment is aimed at controlling the underlying disease with the additional use of gastric protectants:

- Ranitidine: Can be given i/v or as a constant rate infusion in acute cases
- Famotidine: 1.25 mg p/o once daily for longer term use
- Sucralfate: 0.25 – 0.5 g p/o two or three times daily
  - Antepsin suspension is strongly flavoured and often difficult to dose. The tablet form is large, but the dose of ¼ or ½ a tablet can be crushed into water to dose by syringe.

b) Haemolysis:

Haemolytic anaemia is common in cats but is usually secondary to another disease or toxin. Investigation to find the underlying cause is essential.

In severe acute haemolytic anaemia there is an increase in serum bilirubin (jaundice) but serum total proteins normal. However if haemolysis is mild and chronic there may be no accompanying increase in bilirubin as the increased production of bile pigments may not exceed the liver’s ability to clear them.

Haemolysis may be intravascular or extravascular (liver, spleen). In cats extravascular haemolysis is more common and there may be splenomegaly.

1) Immune Mediated Haemolysis: Auto-antibodies are raised against mature red cells. Cats present with anaemia and jaundice, they may also have fever, lymphadenopathy and/or
splenomegaly. In cats IMHA is usually secondary to some other disease or toxin - potential causes include:

- Adverse drug reaction e.g. anti-thyroid medications, trimethoprim-sulphonamides, β-lactam antibiotics
- Neoplasia
- Infectious diseases e.g. FIP, FeLV, *Mycoplasma haemofelis*
  - In the UK *M. Haemofelis* is an uncommon cause of haemolytic anaemia in otherwise healthy cats

Idiopathic or primary auto-immune haemolytic anaemia can occur, but is uncommon, so an underlying pre-disposing cause should always be sought.

Examination of a blood smear may show:

- **Spherocytes:** Presence of spherocytes indicates haemolysis, but in cats these can be difficult to identify since normal cat red cells are small and lack central pallor.
- **Auto-agglutination:** Spontaneous clumping of the red cells may occur when making a fresh blood smear. True agglutination is an indication of secondary or primary haemolysis, but great care must be taken to distinguish auto-agglutination from rouleaux formation:
  - Rouleaux formation is common in normal cat blood smears – the red cells form themselves into stacks described as “a pile of coins”. When this is marked it can be difficult to distinguish from auto-agglutination.

If red cell clumping is seen on a fresh blood smear mix 1 drop of EDTA blood with 1 large drop of 0.9% saline. Place on clean glass slide, cover with a cover slip and examine under high power – rouleaux should be dispersed by this method but auto-agglutination will persist.

A feline specific **Coombs test** can be used to try to confirm the presence of haemolysis, but false positive and false negative results can occur. A positive result does not distinguish between secondary or primary haemolytic anaemia.

Less commonly auto-antibodies will be directed against red cell precursors within the bone marrow – this will produce a **non-regenerative** blood picture and bone marrow biopsy will be required to reach a diagnosis (see later).

**Treatment of immune-mediated haemolytic anaemia** involves identifying and treating the underlying cause where possible and also inhibiting the auto-immune response. For the latter immunosuppressive doses of prednisolone (2-4 mg/kg/day) are usually the first-line treatment. In severe acute cases and initial dose of dexamethasone (1 mg/kg i/v) may be helpful and a blood transfusion may be indicated.

Where long term treatment is required and there are prednisolone induced adverse effects (e.g Diabetes) chlorambucil or cyclosporine may be considered.
2) Microangiopathic Haemolytic Anaemia: Red cells are physically damaged as they pass through abnormal blood vessels; the damaged red cells are subsequently haemolysed, usually in the spleen.

Diseases that can cause microangiopathic haemolytic anaemia include haemangiosarcomas and inflammatory diseases that lead to DIC (e.g. FIP, acute pancreatitis).

There may be schistocytes on examination of a fresh blood smear.

3) Heinz Body Anaemias - Oxidative Damage: Feline red blood cells are highly vulnerable to oxidant damage resulting in formation of Heinz bodies (precipitates of damaged haemoglobin). Affected red cells are removed from the circulation by haemolysis.

Potential causes include:
- Toxins: Paracetamol, Onions and garlic, Propylene glycol, Phenolic antiseptics or disinfectants
- Drug induced - xylocaine, prolonged propofol infusion
- Secondary to other disease – e.g. pancreatitis, hepatotoxicity, lymphoma, diabetic ketosis

In severe cases (e.g. paracetamol toxicity) the blood appears brown due to methaemoglobinemia.

Increased numbers of Heinz bodies will be seen:
- Heinz Bodies (HBs) are spherical red cell inclusions that stain pink with Diff-quick (pale blue with New Methylene Blue) and may appear to project from the red cell membrane.
  - HBs must be distinguished from Howell-Jolly bodies, which are similar in size and shape but stain dark blue with both Diff-quick and New Methylene Blue.
  - Small numbers of Heinz bodies are a normal finding in cats (single HB in up to 5% of cells)

Treatment is needed in severe cases and involves removing the inciting cause, supportive treatment as needed and additional use of anti-oxidants:
- S-adenosyl methionine (e.g. Hepatosyl, Zentonil, Denamarin etc)
- Vitamin E

For cats with paracetamol toxicity:
- N-acetyl cysteine (NAC) - 140 mg/kg p/o, then 70 mg/kg repeated every 4 hours until methaemoglobinemia is resolved.
- Cimetidine - inhibits cytochrome P450 limiting the metabolism of paracetamol into its toxic metabolites.
  - Dose 5-10 mg/kg p/o, i/m or i/v, repeated every 6-8 hours
  - NB: Ranitidine and famotidine do not have this effect.
5) Infectious Causes – Feline Haemoplasmas: Haemoplasma infection is uncommon in cats in the UK especially those with adequate immune system function.

- *Mycoplasma haemofelis* and *cMycoplasma turicensis* can cause severe haemolytic anaemia especially in immunosuppressed cats
- *Mycoplasma haemominutum* causes mild anaemia, unless the cat is immunosuppressed in which case haemolysis may be more severe

Confirmation of diagnosis is by PCR test on an EDTA blood sample – the sample must be collected before starting treatment, otherwise false negative results are likely.

*M. haemofelis* also causes auto-antibody production so may produce auto-agglutination and a positive Coomb’s test.

The organisms may be visible on a fresh stained blood, but absence of organisms does not rule out disease, and many other artefacts and red cell inclusions can easily be mistaken for mycoplasma organisms leading to a false positive result. Confirmation of the diagnosis by PCR is recommended in all cases.

Treatment is with a 6 week course of doxycycline. *M haemofelis* has also been shown to be sensitive to fluoroquinolones.

6) Pyruvate Kinase Deficiency: An inherited disorder that is found in Abyssinian, Somali and Bengal cats. An autosomal recessive gene defect causes lack of pyruvite kinase, an essential metabolic enzyme of the red blood cell. Homozygotes suffer episodes of haemolytic anaemia which may be mild or sub-clinical but can occasionally be severe and even life threatening.

A gene test is available to identify the defective gene and to distinguish between affected homozygote cats and unaffected heterozygotes. (Langford Veterinary Diagnostics)

Treatment is difficult, but most cats suffer only mild intermittent episodes of anaemia and their quality of life remains good. In severely affected cats splenectomy may reduce the rate of haemolysis but does not address the underlying enzyme defect.

2) Non-Regenerative Anaemia

In non-regenerative anaemias the bone marrow fails to replace the red cells that are removed from circulation at the end of their life-span.

In cats non-regenerative anaemia is more common than regenerative anaemia, and in most cases it is a secondary complication of other systemic disease. In these cases anaemia is usually mild but can become debilitating if it progresses, or if it further compromises a cat whose underlying disease is advanced.

Primary bone marrow disorders are less common but can be severe and often the prognosis is guarded or poor. Distinguishing primary bone marrow disease from secondary disease is therefore important with regards to the treatment choices and prognosis.
In non-regenerative anaemia reticulocytes are sparse or absent, and the red cell population is a uniform mature population so there is no anisocytosis and no polychromasia. Most will produce a normocytic and normochromic anaemia but bone marrow dysplasia may result in release of immature red cells causing a macrocytic non-regenerative anaemia. In rare cases iron deficiency may be inhibiting red cell production (see later) and some of the red cells will be hypochromic and microcytic.

a) Secondary Bone Marrow Suppression

1) Anaemia due to Chronic Renal Failure
Anaemia is a common complication of CRF and is caused by a number of factors:
- Uraemia damages red cell membranes reducing the circulating life span
- Uraemia may also lead to GI ulcers, causing chronic low-grade bleeding.
  - Initially the lost red cells are replaced but in the longer term iron deficiency can develop (see Box 3), especially if the cat has poor food intake
- Reduced erythropoietin secretion from the damaged kidney leads to inability to replace red blood cells as they reach the end of their life span.
- Poor food intake, leading to a negative protein and energy balance contributes to the problem.

The anaemia is usually non-regenerative, slowly progressive, and difficult to reverse:
- Poor nutrition and iron deficiency (if present) should be addressed in the first instance.
- Controlling azotaemia will prolong red cell lifespan – encourage increased oral fluid intake, feed a low protein diet and in more severe cases use sub-cutaneous fluids
- Androgens have been suggested as a means of treating CRF induced anaemia, but response is often poor.
- Maintain adequate vitamin B12 levels
- Recombinant human erythropoietin (rHuEPO) can be effective but must be used with care as it may induce anti-erythropoietin antibodies which will ultimately make the anaemia worse.
  - Consider using EPO if the PCV is consistently < 20%
  - See Box 2 for a suggested dosing protocol.
- Iron dextran injection(s)
  - ONLY if serum Total Iron and % Transferrin Saturation have been measured and are low – see Box 3
  - 50 mg i/m every 3-4 weeks
    - Oral iron supplement is poorly tolerated by most cats
- Blood transfusions provide only short term improvement.
2) Anaemia of Inflammatory Disease / Chronic Disease:
Mild to moderate non-regenerative, normocytic, normochromic anaemia secondary to inflammatory processes, chronic infections, neoplasia or post-trauma. The onset of anaemia is generally within 1-2 weeks but occasionally is even quicker than that.

The major mechanisms are:
- Decreased iron availability
- Reduced red cell lifespan
- Diminished bone marrow response to EPO.

Total body iron stores are not depleted but the iron is sequestered in macrophages so is unavailable for haemoglobin synthesis and serum total iron assay will appear low (see Box 3).

Treatment is aimed at controlling the underlying disease. Iron supplementation and erythropoietin are not indicated and will not be helpful, indeed iron has oxidizing effects so may promote additional inflammation.

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**Box 2: Low Dose Erythropoeitin Protocol:**

This protocol aims to reduce the risk of anti-EPO antibody production by minimizing the amount of exogenous EPO that is given. It only produces a slow, gradual rise on PCV.

1) Inject 250 μg Vitamin B12 and 0.5ml iron dextrans i/m (NB: Stings!!)

2) Erythropoietin: 100 iu/kg s/c once a week until the PCV reaches 25-28%; then every 14-28 days until the PCV is > 28%, then cease, and monitor. If the cat is now stable the PCV will often be maintained, but if it drops to < 20%, restart weekly EPO injection.

3) Repeat the 0.5ml B12 injection once a month, but the iron is given once only.

**AntiEPO antibodies:** Rare when using this protocol. If they do occur they cause a rapid and marked drop in PCV = e.g. 30% to 13% within 1 week. If this occurs need to STOP erythropoietin, and either use blood transfusion, or PTS.

A mild drop in PCV over several weeks is not consistent with antibody induction, so can increase the EPO frequency to weekly (if on less than weekly) or twice weekly (if already on weekly injections).
3) Retroviral Induced Anaemia:
FeLV and FIV can both cause non-regenerative anaemia. In the case of FeLV the anaemia may be macrocytic despite being non-regenerative. Prognosis is poor but supportive treatment may be indicated. Anti-viral treatment e.g. with Virbagen Omega may be helpful.

4) Toxin or Drug Induced:
- **Anti-thyroid medications**: methimazole, carbimazole. Both drugs can cause a range of blood dyscrasias including leucopenia, thrombocytopenia or non-regenerative anaemia. Bone marrow suppression usually arises within the first 4 – 6 weeks of treatment but delayed onset can occur.
  - In most cases changes are mild and not of clinical significance
  - Less commonly severe changes occur which can be life threatening if not identified. Changes are reversible on ceasing treatment and cell counts recover within 2 -4 weeks, but in the interim supportive treatment and a blood transfusion may be required in cats with severe anaemia or thrombocytopenia
- **Other drugs which cause bone marrow suppression** include chemotherapy agents, grizeofulvin, azathrioprine, chloramphenicol and oestrogen supplements
b) Primary Bone Marrow Diseases
Primary bone marrow disease is a less common cause of non-regenerative anaemia, but can be due to a number of underlying diseases. If systemic disease is not evident examination of a peripheral blood sample and retrovirus testing may indicate the cause, otherwise a bone marrow aspirate may be required.

1) Myeloproliferative Disorders / Myelophthisis:
Proliferation of a neoplastic cell line in the bone marrow inhibits haematopoiesis resulting in non-regenerative anaemia. There may be associated leukaemia, or a population of abnormal blastic lymphocytes in the circulating blood, but these white cell changes can be absent in some cases.

Some myeloproliferative disorders are associated with retroviral infection, others will arise in retrovirus negative cats.

Attempted treatment depends on the cell line involved, but the prognosis is universally poor.

2) Myelodysplastic Syndromes:
Abnormal marrow cell maturation in one or more of the haemopoietic cell lines produces a hypercellular marrow but peripheral cytopoenias. Abnormal cells are released into the circulation and there may be a macrocytic non-regenerative anaemia. Some cases are associated with FeLV infection but in recent times FeLV negative cases are more common.

Treatment options are limited, cytosine arabinoside or Vitamin K2 analogues may help in some cases but prognosis remains poor. Progression to leukaemia can occur.

3) Pure Red Cell Aplasia:
Selective loss of red cells due to failure of maturation. This can be caused by FeLV infection in which case prognosis is poor. Other cases arise due to immune-mediated destruction of a red cell precursor stage – some of these cats can respond well to immunosuppressive therapy as described for other immune-mediated haemolytic anaemias.

4) Aplastic Anaemia / Pancytopenia:
Loss of all blood cell lines due to failure of all the haematopoietic lines. Potential causes include:

- Infections: FeLV, FIV, FIP, Feline Panleukopenia Virus, Canine Parvovirus, Toxoplasmosis
- Drug Induced: Chemotherapy agents, grizeofulvin
- Idiopathic

Prognosis is poor except for those drug-induced cases in which the drug can be ceased and an alternative treatment of the primary disease exists.