

APPROACH TO FELINE ANAEMIA CASES

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BACKGROUND

Anaemia is commonly encountered in our feline patients because cats are particularly prone to developing anaemia due to the shorter lifespan (70 days) of the feline red blood cell (RBC) and the lower blood volume of cats compared to other species. Feline haemoglobin is also sensitive to oxidative damage. A recent study¹ found that cats were significantly more likely to develop anaemia when hospitalized in ICUs than dogs. However cats have different types of haemoglobin that are thought to enable them to tolerate anaemia with relative ease, particularly chronic anaemia. Indeed cats may only exhibit clinical signs when anaemia becomes very severe.

TYPES OF FELINE ANAEMIA

Anaemia results in reduced oxygenation of the kidneys, which stimulates erythropoietin (EPO) release, which in turn stimulates the bone marrow to increase RBC production. This new RBC production indicates an appropriate regenerative response in the bone marrow, resulting in a **regenerative anaemia**. Regenerative anaemia arises due to blood loss or haemolysis. If the bone marrow response is insufficient a **non-regenerative anaemia** will result. Most anaemias in cats are non-regenerative in type and in a recent study of 180 cats referred to the Feline Centre at Langford with anaemia², 52.8% of cats had non-regenerative anaemias whereas 20.6% of cats had haemorrhage, and 10.6% of cats had haemolysis, both regenerative causes. Another recent study, looking at samples submitted to a diagnostic laboratory from first opinion vets³ also found that most anaemias (57.7%) were non-regenerative in nature (compared to 42.3% being regenerative). Regenerative anaemias have a tendency to be more severe than non-regenerative anaemia³, but obviously there is much variation.

LABORATORY INVESTIGATION OF ANAEMIA

1. **Packed Cell Volume (PCV) and Routine Haematology**

Spinning of a capillary microhaematocrit tube containing anticoagulated blood (3 mins at 12,500 rpm) is a simple and rapid way of determining PCV. It also allows crude in-house evaluation of the plasma; is it icteric, which could indicate the presence of acute severe haemolysis or liver disease, or is it red, consistent with haemoglobinaemia due to intravascular haemolysis?

Anaemia is defined by reduced numbers of RBCs or decreased haemoglobin content or decreased packed cell volume (PCV). Haemoconcentration due to dehydration can mask the degree of anaemia, so reassess haematological parameters after rehydration. *NB. Intravenous fluid therapy should be carefully administered in cats with chronic (severe) anaemia due to the relative hypervolaemia (increased intravascular volume occurring as a result of the haemodynamic compensatory responses) they have developed in adaptation to their anaemia; it has been shown that cats with PCVs $\leq 18\%$ have evidence of volume overload on echocardiography⁴ and are thus susceptible to congestive heart failure if intravenous fluid is given too rapidly.*

Haemoglobin (**Hb**) is a reliable parameter in routine haematology, which measures the oxygen carrying capacity of the blood. The mean cell volume (**MCV**) indicates the average size of the RBCs and is only abnormal if there are enough abnormal RBCs to pull the mean value out of a wide reference range. Normocytic cells have normal MCV, macrocytic cells have increased MCV and microcytic cells have reduced MCV. Regenerative anaemias can be macrocytic because reticulocytes have higher MCVs than RBCs, but a recent study found that most regenerative anaemias were actually normocytic³, as inadequate reticulocytes were present to affect the overall MCV. Macrocytosis is also seen with non-regenerative anaemias associated with FeLV infection or myelodysplasia. The mean cell haemoglobin concentration (**MCHC**) indicates the average concentration of Hb per RBC. A reduced MCHC reflects hypochromasia, and regenerative anaemias are usually hypochromic³ because reticulocytes have higher MCVs and lower Hb content than mature RBCs. Examination of other cell lines on haematology is important e.g. concurrent leukopenia or thrombocytopenia may indicate a bone marrow disorder, severe thrombocytopenia could be a cause (albeit rarely in cats) of bleeding (although some automated cell counting machines struggle to count feline platelets, as differentiating them from RBCs on size alone is difficult).

2. **Blood Smear Examination**

Blood smear examination can provide rapid in-house assessment of anaemia. In-house staining (e.g. Diff-quick, Leishmann's) can be performed. Basic features are easy to recognise e.g. polychromasia and anisocytosis in regenerative anaemias, and nucleated RBCs (NRBCs). NRBCs usually reflect active regeneration but are also seen

with splenic dysfunction, shock or bone marrow disorders. Non-regenerative anaemias typically consist of RBCs which are of uniform size and staining. The white blood cells can also be evaluated. An *estimated* platelet count can also be derived from blood smear examination, which may be of use if thrombocytopenia is suspected as a cause of the anaemia (although rare in cats). Each platelet visible per X 1000 field (i.e. using the X 100 lens with oil) represents $20 \times 10^9/l$ platelets in the peripheral blood. Normal feline platelet counts range from 200 to $700 \times 10^9/l$, equivalent to around 10–35 platelets per X1000 field. If platelet clumps are present this is usually a sign that platelet numbers are adequate, although they preclude accurate platelet count estimation. Platelet clumps, when visible, are usually found in the feathered edge of the blood smear. However, a specialist haematologist should always be consulted to obtain the maximum information from a blood smear.

3. **Reticulocyte Count**

The reticulocyte count quantifies the bone marrow response to determine if the anaemia is regenerative or non-regenerative, helping to determine possible causes of the cat's anaemia by differentiating regenerative (blood loss or haemolytic causes) from non-regenerative anaemias. Reticulocytes are only identifiable with vital stains such as new methylene blue (NMB), which clump material in reticulocytes allowing them to be visualised. Reticulocytes correspond to the polychromatic cells on a routinely-stained blood smear. Cats have punctate and aggregate reticulocytes. Aggregate reticulocytes have multiple (> 6) small dark blue cytoplasmic granules, in lines, chains or clumps whereas punctate reticulocytes have only a few (2 to 6) cytoplasmic dots. Aggregates last in the circulation for about a day before maturing into punctate forms which then survive in the circulation for up to 10 days. Only aggregates reflect recent bone marrow RBC production so these are the reticulocytes included in feline reticulocyte counts, especially when evaluating cats with moderate to marked anaemia. Reticulocyte counts are routinely performed in commercial diagnostic laboratories, but can be done in-house too.

Performing feline reticulocyte counts in-house?

- Mix equal parts (volume or drops) of EDTA blood and NMB stain
- Leave to stand for 15-20 minutes
- Mix again gently and make a blood smear and rapidly air dry
- Count % of aggregate reticulocytes in 500-1000 RBCs. This is the % reticulocytes present
- Use this % in the equation below to calculate the absolute aggregate reticulocyte count, which takes into account the degree of anaemia present by incorporating the RBC count in the equation. This count can be used to quantify any degree of regeneration present

Absolute aggregate reticulocyte count ($\times 10^9/l$) = % aggregate reticulocytes \times RBC count ($\times 10^{12}/l$) $\times 10$

Regenerative response	Absolute reticulocyte count ($\times 10^9/l$)
Negligible	< 50
Mild	50-100
Moderate	100-200
Substantial	>200

4. **Biochemistry Including Total Serum Protein (TSP)**

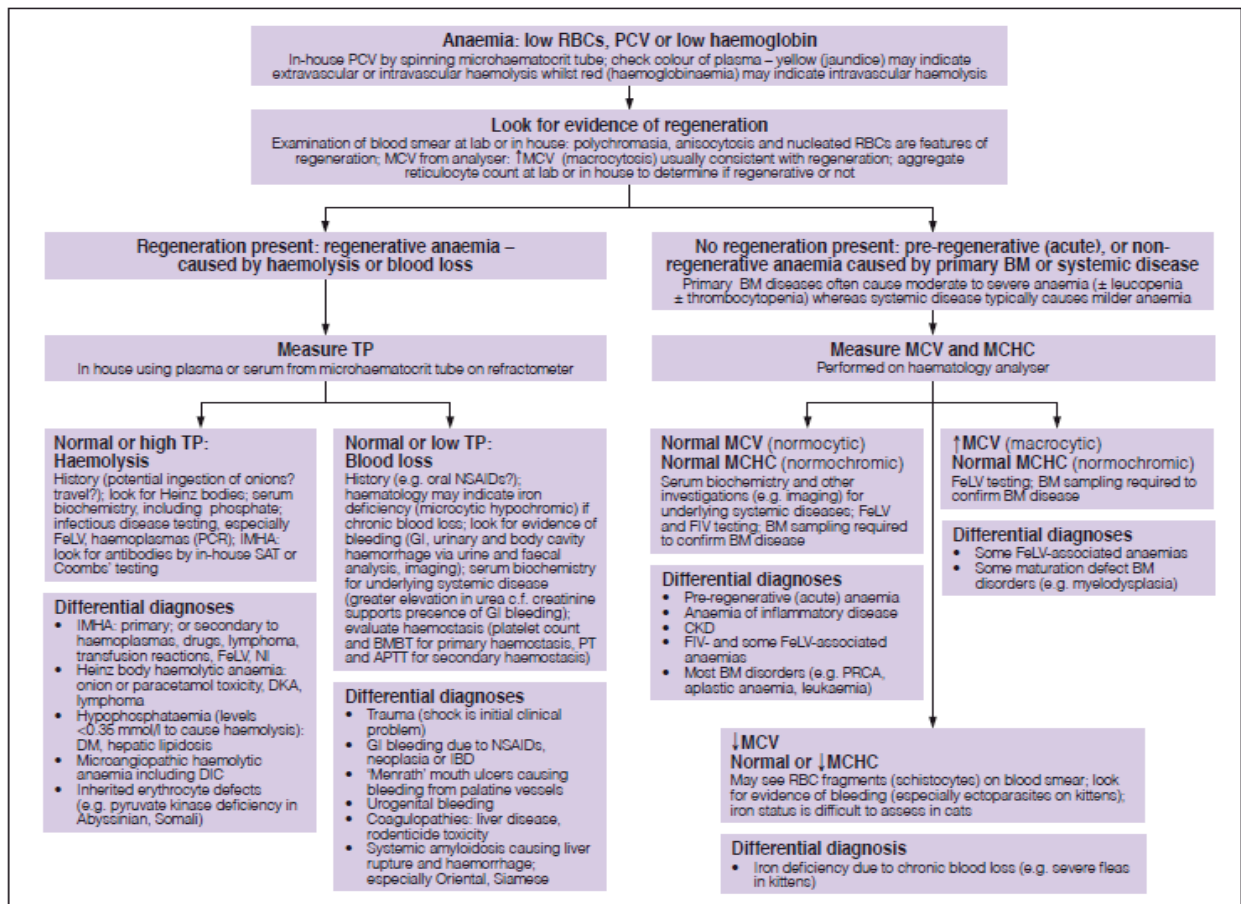
This is usually performed by submitting blood for a biochemistry profile. It evaluates for underlying systemic disease which may be associated with anaemia e.g. renal parameters, electrolytes. Liver parameters can be elevated due to hypoxic damage. Bilirubin may be elevated due to concurrent liver disease or if acute severe haemolysis has occurred. Total plasma protein (TPP) can also be measured rapidly in-house using a refractometer. Measurement of TPP can be helpful in differentiating blood loss anaemia (protein usually low or low-normal) from haemolysis (protein usually normal or high).

5. **Retroviral Testing**

Haemolytic and non-regenerative anaemias may be associated with FeLV or FIV infection, although anaemia is more commonly a feature of FeLV infection than FIV infection⁵. Anaemia, especially non-regenerative, occurs in 25-50% FeLV-infected cats, and is seen in 18-36% FIV-infected cats.

DIAGNOSTIC APPROACH TO FELINE ANAEMIA

An algorithm outlining the diagnostic possibilities for cases of feline anaemia can be seen below, kindly reproduced from the BSAVA Manual of Feline Practice: a Foundation Manual⁶.

**5.4.6**

A diagnostic approach to feline anaemia. APTT = activated partial thromboplastin time; BM = bone marrow; BMBT = buccal mucosal bleeding time; CKD = chronic kidney disease; DIC = disseminated intravascular coagulation; DKA = diabetic ketoacidosis; DM = diabetes mellitus; GI = gastrointestinal; IBD = inflammatory bowel disease; IMHA = immune-mediated haemolytic anaemia; MCHC = mean cell haemoglobin concentration; MCV = mean cell volume; NI = neonatal isoerythrolysis; PCV = packed cell volume; PRCA = pure red cell aplasia; PT = prothrombin time; RBCs = red blood cells; TP = total protein.

CLASSIFICATION OF FELINE ANAEMIA**1. Regenerative: haemorrhagic/blood loss****2. Regenerative: haemolytic****3. Non-Regenerative**

The above classification is the basis used for the diagnostic approach to anaemia. However, in cats multiple mechanisms and diseases often contribute to the development of anaemia, so simple classification of the anaemia may not always be possible. Also important factors that can make regenerative causes of anaemia appear non-regenerative must always be considered e.g. pre-regenerative anaemia, concurrent disease.

1. Regenerative: haemorrhagic/blood loss**Acute Blood Loss**

Acute blood loss is common in cats, particularly after major trauma. Haemostatic disorders are less common but are seen with liver disease and rodenticide toxicity. Systemic amyloidosis, an uncommon condition seen most often in young to middle-aged Siamese and related breeds, but also in non-pedigrees, can cause spontaneous liver rupture and fatal abdominal haemorrhage. Gastroduodenal ulceration and bleeding, due to neoplasia (mast cell tumours, gastrinoma, lymphoma), NSAID toxicity and inflammatory bowel disease, can also result in significant acute blood loss. Oral haemorrhage due to a Menrath ulcer eroding the palatine artery is occasionally seen in cats with severe pruritus; the excessive licking leads to the lingual papillae eroding the roof of the mouth and repeatedly cause bleeding from palatine vessels. Recently⁷, anaemia in association with urethral obstruction has been reported; this was presumed to be due to bladder haemorrhage. A recent study¹ found that cats that developed anaemia when hospitalized in ICUs underwent more frequent blood sampling than cats that did not develop anaemia; thus blood loss due to blood sampling should be considered as a potential factor in the development or severity of anaemia in hospitalised cats. Hypovolemic shock, rather than anaemia, is the most worrying initial consequence of acute severe blood loss. Cats with ongoing blood loss (such as during major surgery) that are receiving intravenous fluids are protected from hypovolaemia, and if bleeding continues such patients can rapidly become anaemic.

Chronic Blood Loss

Chronic blood loss is less common in cats, but can occur with severe flea or lice infestation in kittens, or chronic gastrointestinal (GI) (or more rarely urogenital) blood loss.

Diagnostic Features of Blood Loss

A rising reticulocyte count is not evident for 3-5 days (this is the pre-regenerative phase) and the reticulocyte count then peaks at 5-7 days, although PCV may take up to 2-3 weeks to return to normal after bleeding. Regeneration is also evidenced by anisocytosis, polychromasia and sometimes NRBCs on blood smears. Hypoproteinaemia may occur in the first week after bleeding, but persistent anaemia and hypoproteinaemia suggest ongoing blood loss. Chronic external blood loss may eventually lead to iron deficiency and a non-regenerative/poorly regenerative anaemia. This is uncommon in adult cats but kittens have low body iron stores and are therefore sometimes susceptible to iron deficiency. Iron deficiency anaemias are typically microcytic and sometimes hypochromic although these features are not as commonly seen in cats compared to dogs.

Further Investigation of Blood Loss

Blood loss is usually suspected based on clinical examination and standard diagnostic tests. Potential GI, urinary and body cavity haemorrhage can be evaluated via parasitology, urine analysis and thoracic and abdominal imaging. Haemostasis (platelet count and buccal mucosal bleeding time for primary haemostasis, prothrombin time and activated partial thromboplastin time for secondary haemostasis) may be indicated. If chronic blood loss with iron deficiency anaemia is suspected, ideally iron status should be evaluated although interpretation is difficult in cats. Since cats do not normally have storable iron stores in the bone marrow, bone marrow samples cannot be evaluated for iron status although the presence of iron in bone marrow does rule out iron deficiency. An iron profile may be helpful in that iron deficiency anaemia is characterized by a normal total iron binding capacity (TIBC) and low serum ferritin (soluble iron stores), as well as low serum iron, whereas anaemia of inflammatory disease (AID) is characterized by a low TIBC, high serum ferritin in the presence of low serum iron. Unfortunately it is difficult to get serum ferritin testing done in cats and so mostly serum iron and TIBC are performed. Faecal occult blood testing, to test for GI bleeding, is also difficult since cats need to be maintained on a meat free diet for 3-5 days prior to sampling, but e.g. Purina HA can be used for this purpose. Raised urea levels relative to creatinine may indicate GI bleeding, together with a thrombocytosis. Total protein may be helpful in differentiating blood loss anaemia (protein low or low-normal) from haemolysis (protein normal or high).

2. Regenerative: haemolytic

Extravascular (RBCs removed by macrophages in the spleen, liver and bone marrow) and intravascular (RBCs destroyed within the vascular system) haemolysis occur in cats, but extravascular haemolysis is more common. Immune-mediated haemolytic anaemia (IMHA) can also occur, mediated by RBC-bound antibodies.

Causes of Haemolysis in Cats

- Primary IMHA; in some cases no underlying causes of IMHA can be identified and such cases are called primary IMHA. This is common in dogs, and was thought to be rare in cats, but recent reports^{8,9} suggest otherwise
- Secondary IMHA; can arise secondary to FeLV, haemoplasmas, feline infectious peritonitis (FIP), drugs (e.g. methimazole, trimethoprim-sulphonamides), neoplasia (e.g. lymphoma, myeloproliferative disorders), cholangitis, pancreatitis⁹, blood transfusion reactions and neonatal isoerythrolysis (NI: intravascular haemolysis common in NI)
- Infections; FeLV, haemoplasmosis (particularly *Mycoplasma haemofelis*), *Babesia* spp., cytauxzoonosis, FIV
- Oxidant injury such as exposure to chemicals e.g. onions, and some disease states e.g. ketoacidosis, lymphoma, can result in a Heinz body haemolytic anaemia
- Hypophosphataemia can cause intravascular haemolysis if severe (<0.65, and often <0.35, mmol/l; reference interval 0.95-1.55 mmol/l), due to depletion of RBC energy supply. Occurs with diabetes mellitus, hepatic lipidosis and refeeding syndrome
- Microangiopathic haemolytic anaemia results from RBC damage due to abnormal vascular endothelium or fibrin deposition within vessels (schistocytes [fragmented RBCs] may be visible on blood smears)
- Inherited RBC defects; osmotic fragility syndrome and pyruvate kinase (PK) deficiency are both reported in Abyssinians and Somalis, and more recently in other breeds (PK deficiency in Bengals and Singapuras)

Diagnostic Features of Haemolysis

As with blood loss, a rising reticulocyte count occurs with haemolysis, but is not evident for 3-5 days (the pre-regenerative phase) and then peaks at 5-7 days. Regeneration is evidenced by anisocytosis, polychromasia and sometimes NRBCs on examination of stained blood smears. Some IMHAs, however, are non-regenerative in nature

due to immune targeting of bone marrow precursors. Unlike anaemia due to haemorrhage, serum protein concentrations remain normal, or are high, with haemolysis, unless concurrent disease affects these. Hb, released from haemolysed RBCs, is metabolized to unconjugated bilirubin which is then very efficiently taken up by hepatocytes, conjugated and excreted into bile. Only massive, acute haemolysis overwhelms this process leading to jaundice (icterus) with bilirubinaemia with or without bilirubinuria, and this is quite uncommon in the cat. Jaundice can occur with both extravascular and intravascular haemolysis whereas haemoglobinaemia and haemoglobinuria are features only of intravascular haemolysis, where massive release of haemoglobin directly into the circulation overwhelms plasma binding of the haemoglobin. Fever may indicate an infectious cause of haemolysis such as *Mycoplasma haemofelis*. Pica is occasionally reported with immune-mediated haematology disorders². Splenomegaly, and possibly hepatomegaly, may be evident, reflecting haemolytic activity, but these may also occur with extramedullary haematopoiesis or RBC sequestration. In the dog, the presence of spherocytes on examination of a stained blood smear specifically indicates that the haemolysis is immune-mediated, but spherocytes are difficult to recognize in cats as normal feline RBCs lack central pallor, making diagnosis of IMHA more difficult in the cat. Cats also lack the typical strong leukocytosis and left shift seen usually in IMHA dogs. Large numbers of Heinz bodies suggests exposure to oxidant damage; Heinz bodies are clumps of precipitated haemoglobin that are colourless with routine stains (e.g. Wright-Giemsa or Diff-Quik) but blue-green on slides stained with NMB. In cats Heinz bodies tend to be single and uniform in size and can become very large.

Further Investigation of Haemolysis

Potential causes of haemolytic anaemia may be apparent on the history e.g. potential ingestion of onions in baby food or soup, travel to areas where infectious causes of haemolysis such as *Babesia* spp. are endemic. Serum biochemistry is helpful to screen for underlying systemic diseases and hypophosphataemia. Other investigations can include FeLV/FIV testing, polymerase chain reaction (PCR) testing for feline haemoplasma infection and performing thoracic and abdominal imaging to assess for neoplasia or other underlying diseases. Tests to investigate feline IMHA include the slide agglutination test (SAT) and Coombs' test. The SAT is a simple test that detects severe agglutinating IMHA; the RBCs of cats suffering from this form of IMHA are coated so heavily with antibodies and complement that they spontaneously agglutinate, forming clumps visible to the naked eye.

Slide Agglutination Test: SAT

4 to 10 drops of normal (0.9%) saline and 1 drop of whole EDTA-anticoagulated blood are mixed on a glass microscope slide and the mixture is gently swirled by moving the slide and looking at the blood mixture against a white background. The SAT is positive if distinct red speckles become visible within a few minutes; this is gross macroscopic agglutination. Examination of the blood under the microscope, by adding a coverslip, is strongly recommended to further confirm the agglutination (random disorganized clumping of RBCs) compared to rouleaux (organized stacking of RBCs). Rouleaux formation occurs naturally in some cats and can occur in the presence of high levels of total serum protein, and is macroscopically identical to true agglutination (although the saline in the SAT should disperse these).

The diagnosis of IMHA with a negative SAT may be supported by Coombs' testing¹⁰. Coombs' testing detects the presence, and can describe the nature, of erythrocyte-bound antibodies, although positive results may occur with hyperglobulinaemia, pancreatitis and myelodysplastic syndromes.

Bone marrow examination may be useful to help diagnose cases of non-regenerative or poorly-regenerative IMHA; features include dysmyelopoiesis, myelofibrosis, haemophagocytic syndrome, lymphocyte aggregation, and lymphocyte or plasma cell hyperplasia¹¹.

3. Non-Regenerative

Non-regenerative anaemias usually develop gradually as the diseased bone marrow fails to replace ageing erythrocytes. Compensatory mechanisms are well established, enabling cats to cope despite severe anaemia in many cases, so outward clinical signs can be minimal. The major causes of non-regenerative anaemias are primary bone marrow disorders or systemic suppression of the bone marrow. Primary marrow disorders often cause moderate to severe anaemia whilst systemic disorders tend to produce mild subclinical anaemia, although exceptions occur.

Causes of Non-regenerative Anaemia in Cats

- Pre-regenerative anaemia due to acute haemolysis or haemorrhage
- AID [previously known as anaemia of chronic disease but we know this can develop quickly, even within three to four days^{5,12}]
- Chronic kidney disease
- Retroviral associated anaemias

- Bone marrow disorders e.g. pure red blood cell aplasia, non-regenerative IMHA, aplastic anaemia, myeloproliferative diseases e.g. leukaemias, myelodysplastic diseases where RBC maturation is abnormal
- Chronic iron deficiency anaemia will become non-regenerative

Primary IMHA with immune-mediated destruction of erythrocyte precursors results in a non-regenerative anaemia. This occurs in two conditions; pure red cell aplasia (PRCA) and non-regenerative immune-mediated haemolytic anaemia (NRIMHA), which may reflect immune-mediated destruction of different stages of erythrocyte cell maturation. PRCA is characterised by bone marrow erythroid aplasia or hypoplasia whereas NRIMHA has bone marrow erythroid hyperplasia and/or erythroid maturation arrest. Recently we reported¹³ the outcome of 15 cats with PRCA (7) and NRIMHA (8); most (12/15) were <3 years old and volume overload was common (8/11) at presentation. Most (11/15) achieved remission 12-42 days after starting immunosuppressive treatment, primarily with prednisolone alone (remission in 6/7 cats) or glucocorticoids and chlorambucil (remission in 3/6 treated cats). Outcome (remission and survival) was not different between PRCA and NRIMHA; 4/15 (2 PRCA, 2 NRIMHA) cats failed to respond giving an overall mortality rate of 27%. Following clinical remission, gradual withdrawal of immunosuppressive treatments should be attempted with close monitoring for relapse; some cats require long-term treatment.

Diagnostic Features of Non-regenerative Anaemia

Non-regenerative anaemias have minimal anisocytosis and polychromasia, and a low reticulocyte count; RBCs are usually normal in size and staining i.e. normocytic and normochromic, with most of the causes of non-regenerative anaemia. FeLV infection and myelodysplasia, however, may cause a *macrocytic* non-regenerative anaemia, whilst iron deficiency will result in a *microcytic*, and sometimes a *hypochromic*, anaemia. Bone marrow disorders may cause concurrent leukopenia and thrombocytopenia, and may be associated with pica². AID is associated with a mild to moderate anaemia (PCV >17%).

Further Investigation of Non-regenerative Anaemia

Systemic illnesses causing secondary depression of erythrocyte production can usually be identified by history, physical examination, haematology and serum biochemistry. FeLV and FIV testing should be performed. Bone marrow aspiration cytology and/or core biopsy histopathology is essential for establishing a definitive diagnosis in cats with non-regenerative anaemia due to primary marrow disorders. Bone marrow samples should always be interpreted with a concurrent haemogram, requiring blood sampling at the time of bone marrow sampling. Measurement of serum EPO levels may help confirm the aetiology of anaemia in a cat with chronic kidney disease, but is rarely performed. Assessment of iron status may be helpful to differentiate iron deficiency anaemia (low serum ferritin and normal TIBC measurements) from AID disease (serum ferritin is high and TIBC is often low), although, as mentioned above, a feline serum ferritin assay is not currently available.

Bone Marrow Needles

At Langford, when manual bone marrow samples are obtained, we use Jamshidi disposable bone marrow aspirate or biopsy needles between 11 and 15 G, depending on patient size. A recent study compared the use of 15G bone marrow needles in the proximal humerus with 13G bone marrow needles in the iliac crest to obtain bone marrow core biopsies in cats¹⁴. The study found that both samples were of similar quality although the 15G samples were easier to collect and were associated with less post-biopsy limb swelling. However it is hard to compare the effect of size of needle alone as two different collection sites were used. Additionally the cats were healthy and large (3.4 – 8.4 kg, mean 5.4 kg), and only core biopsies were taken without aspirates first. Another recent study¹⁵ reported the use of a battery operated power device in obtaining bone marrow samples. This study collected both aspirate and core samples using an 11G bone marrow needle in 20 dogs and a 15G needle in 2 cats. The 2 feline core biopsy samples were of medium quality but enabled a diagnosis to be reached and it is noteworthy that both the aspirate and core samples were obtained from the same single site, which is advantageous and time-saving. Other authors¹⁴ have suggested that the better directional control one has during manual collection is an advantage over the use of a powered device. Powered devices are often used in humans now due to faster collection time and reduced pain. At Langford, we have been using a powered device for bone marrow collection for the past 11 months with great success, including in cats. The time taken to collect samples is extremely short, reducing anaesthesia time and samples collected have been diagnostic. We use the Arrow® OnControl® (<http://www.arrowoncontrol.com/>) collection system using 15G needles for aspirates and 11G needles for cores in cats. The stab incision has to be quite wide to avoid catching hair with the rotary device during ‘drilling’ and one must remember not to exert pressure during ‘drilling’ as the drill will move forward without pressure. The manufacturers provide blocks for practising which provide ‘give’ once you are through the cortical bone to help you learn when to stop drilling.

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