Anaemia in dogs and cats (part 2)

In the second part of this article, RCVS recognised and European veterinary specialist in small animal medicine, Polly Frowde MAVetMB DipECVIM MRCVS examines the causes and management of regenerative anaemia

Regenerative anaemia is often acute in onset and causes more marked clinical signs for a given drop in haematocrit (Hct) compared to non-regenerative anaemia. However, some forms of regenerative anaemia can be mild/insidious (eg. low-grade haemolysis or gastrointestinal bleeding). Confirmation of a regenerative response was discussed in part 1. Regenerative anaemia is caused by either red blood cell (RBC) destruction (haemolysis) or haemorrhage.

HAEMOLYSIS: IMMUNE-MEDIATED HAEMOLYTIC ANAEMIA

Immune-mediated haemolytic anaemia (IMHA) is a common cause of regenerative anaemia in dogs and can be primary (idiopathic) or secondary to a variety of underlying diseases/drug therapy. Definitive diagnosis requires fulfilment of the following criteria:

- Regenerative anaemia;
- Evidence of haemolysis (eg. bilirubinaemia/bilirubinuria, haemoglobinuria, spherocytosis); and
- Evidence of immune-mediated red blood cell (RBC) destruction (eg. spherocytosis, in-saline agglutination, Coombs test positive, flow cytometry).

The pathogenesis involves a type II hypersensitivity reaction targeting antibody-bound RBCs, leading to direct complement-mediated haemolysis (intravascular haemolysis) or phagocytosis (extravascular haemolysis). Various mechanisms for auto-antibody formation have been proposed, eg. RBC damage-exposing antigens that have escaped immune tolerance; cross-reacting antibody targeting foreign RBC-bound antigen (eg. mycoplasma); or non-specific lymphocyte activation during inflammation. Anti-RBC IgG is more common than IgM but the latter is associated with intravascular haemolysis and greater disease severity.

Predisposed breeds include Cocker and Springer Spaniels, Bichon Frise, Old English Sheepdogs, Poodles, Irish Setters and Dachshunds. Disease is more common in young, middle-aged dogs and possibly neutered females (there may be minimal gender/neuter-status bias once breed/age is taken into account). Secondary IMHA can be triggered by the following: infection (with specific pathogens or any infectious focus, eg. abscess); neoplasia (especially haematopoietic neoplasms); drug therapy; inflammation or necrosis (especially in cats); or multi-systemic immune-mediated disease eg. systemic lupus erythematosus (SLE). Secondary IMHA is considered more common than primary disease in cats. An association with vaccination remains controversial – many clinicians avoid repeating any vaccinations given within one month of IMHA onset.

Clinical signs include: pallor, weakness, tachypnoea (hypoxia, pulmonary thromboembolism), anorexia, jaundice, pigmenturia, hepatosplenomegaly and, less commonly, petechiae, vomiting, diarrhoea, pica, pyrexia and lymphadenomegaly. The anaemia is usually regenerative (macrocytic, hypochromic with polychromasia), although can be non-regenerative in peracute disease (ie. pre-regenerative) or non-regenerative IMHA (precursor destruction – discussed in part 1). Reticulocytosis can be marked (more so than with haemorrhage, due to differences in iron availability). Spherocytosis (see Figure 1) may be difficult to appreciate (especially in cats) and can occasionally be seen in other types of anaemia, eg. pyruvate kinase (PK) deficiency. Auto-agglutination (which occurs with intravascular or severe extravascular IMHA) confirms the presence of anti-RBC Ab.

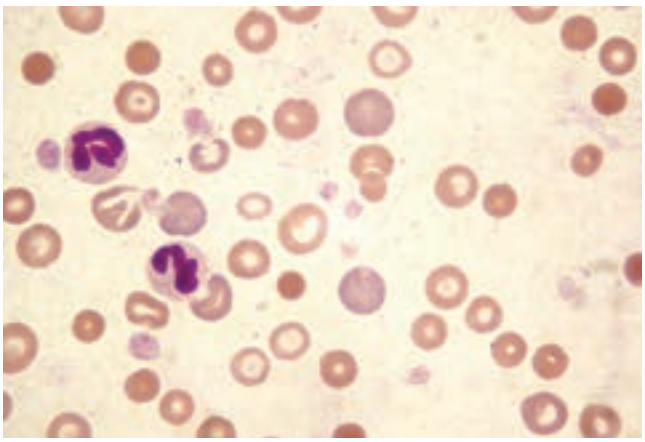

Figure 1: Spherocytes and reticulocytes. Photo: Roger Powell.

Neutrophilia is common due to tissue hypoxia/necrosis and cytokine induction – this can be dramatic with toxic changes/a left shift. Concurrent thrombocytopenia can occur due to co-existing ITP ('Evans-like' syndrome) or consumption, eg. thromboembolic disease, disseminated intravascular coagulation ([DIC]; aPTT/PT and D-dimers can aid assessment). In cats, IMHA seems to be more insidious and less inflammatory, with patients often only showing clinical signs once anaemia is severe.

Biochemistry can reveal hyperbilirubinaemia, especially with intravascular haemolysis or concurrent hepatic dysfunction/hypoxia, however a healthy liver is very efficient at clearing excess bilirubin so this may not be present. Hepatic hypoxia secondary to anaemia is common, and liver enzymes are therefore often mildly elevated. There may be other consequences of inappetance/malaise and hypoxia, eg. azotaemia. Protein levels are usually normal (to help differentiate from many forms of haemorrhage). Bilirubinuria can occur with intra or extravascular disease, whereas, haemoglobinuria is an indicator of intravascular haemolysis (and severe disease).

ADDITIONAL LABORATORY TESTS

Coombs (direct antiglobulin test) is indicated if there is insufficient evidence for immune-mediated RBC destruction, (eg. in-saline auto-agglutination is negative). Recent studies have challenged previous concerns regarding false negative results with prior immunosuppressive therapy or transfusions,[1] however, false-positive results can occur, eg. with neoplasia infection. Flow cytometry is sensitive/specific at identifying anti-RBC antibody, but expense/availability limits its clinical use in IMHA. Osmotic fragility tests are occasionally used, but are also affected by hereditary RBC disorders.

As soon as IMHA is suspected, the search should begin for possible underlying triggers.

INFECTIOUS DISEASE SCREENING

Tick-borne disease testing should be indicated post-travel to mainland Europe, eg. for babesia, ehrlichia and leishmania, depending on geographical exposure. An endemic profile for non-travelled dogs should also be considered, especially if tick exposure is likely. In the UK, this could include borrelia, bartonella, anaplasma +/- ehrlichia and babesia, however, a recent review of tick-borne diseases specific to Ireland showed only evidence for borrelia in cats/dogs.[2] It might still be worthwhile screening for possible emerging diseases, especially if the patient is responding poorly to standard therapy. Feline immunodeficiency virus (FIV)/feline leukaemia virus (FeLV) and mycoplasma screening should be performed in cats. Since many pathogens are theoretically capable of triggering 2° IMHA, appropriate screening should be performed if clinical features raise suspicion for a specific infection.

DIAGNOSTIC IMAGING

Thoracic radiographs and abdominal radiographs/ultrasound are an essential part of the screening process for potential secondary causes, (eg. inflammatory focus, neoplasia), but also help rule out some non-immune mediated causes of haemolysis, eg. zinc foreign body (see Figure 2). Imaging should be performed before starting immunosuppressive treatment in case further sampling is required prior to steroids, or steroids are contraindicated/treatment needs to focus on the underlying disease.

TREATMENT

Regardless of whether IMHA is primary or secondary (or even confirmed), the first treatment decision is whether a blood transfusion is indicated. This depends on clinical signs more than lab values – the rate of decline in red cell mass will influence the patient's ability to compensate. Tachycardia, weakness, and decreased mentation attributable to anaemia are definite indications; commonly adopted PCV thresholds are <15-20% for acute IMHA (dogs) or <10-15% for chronic/NR-IMHA (or acute IMHA in cats), but clinical parameters should be the main guide. Fluid therapy is indicated in most cases (unless eating, well hydrated, no azotaemia and no suspicion of thromboembolic disease) since dehydration is common and exacerbates tissue hypoxia/poor perfusion. Rates of 1-2x maintenance are unlikely to dilute the PCV dramatically. Oxygen is not indicated unless there is concurrent respiratory compromise (eg. pulmonary thromboembolism [PTE], aspiration pneumonia) since hypoxia is due to reduced oxygen content (RBC count), rather than oxygen saturation (often already maximal).

Figure 2: Zinc-gastric foreign body causing haemolytic anaemia in a dog. Photo: Dr Nat Whitley.

IMMUNOSUPPRESSIVE THERAPY

Immunosuppressives are indicated in all 1° and some 2° IMHA, however 2° IMHA may resolve with treatment of the underlying disease alone (and immunosuppression may be detrimental, eg. infectious focus).

STEROIDS

Steroids are the first drug of choice (unless contraindicated) and there is insufficient data to compare their efficacy with any alternative agent monotherapy. Therapeutic actions include inhibition of RBC phagocytosis, giving them a rapid speed of onset (unlike certain cytotoxics that only inhibit lymphocytes/antibody production). Prednisolone 1mg/kg bid is used initially in dogs (<2mg/kg bid in cats); there is no additional benefit to using higher doses, only a greater incidence of side effects. Alternatively, parenteral dexamethasone 0.2mg/kg sid can be given if anorexia or vomiting prevents oral therapy, but switch to oral as soon as possible.

There is no evidence that co-administration of additional immunosuppressives improves outcome, however, most would agree that they are indicated in IMHA refractory to steroids alone (eg. after one week), or when 'steroid-sparing' is necessary (ie. severe side effects). Steroids unfortunately contribute to the risk of thrombosis.

AZATHIOPRINE

Azathioprine is a purine synthesis inhibitor (inhibits lymphocytes), used in dogs only. Adverse effects include myelosuppression, hepatotoxicity and pancreatitis, making regular monitoring (haematology and biochemistry) essential, since myelosuppression and hepatotoxicity are

often picked up on blood tests prior to causing clinical signs. Maximal efficacy may take less than weeks. The starting dose (2mg/kg sid) is given for a maximum of six weeks before dropping to 2mg/kg eod to reduce the risk of side effects.

CICLOSPORIN

Ciclosporin inhibits T-cell activity, macrophage function and antibody production, theoretically giving it a faster mechanism of action than azathioprine. The most common side effects are transient vomiting and diarrhoea – often managed with symptomatic treatment or temporary dose reduction. The standard immunosuppressive dose is 5mg/kg bid (NB higher than licensed atopy dose). Commercial pharmacodynamic testing (available via Mississippi State University) is more reliable for guiding efficacy/dose adjustments than monitoring serum levels. Ciclosporin can also be pro-thrombotic.[3]

CYCLOPHOSPHAMIDE

Cyclophosphamide has largely fallen out of favour – studies have failed to show convincing efficacy, sometimes suggesting a poorer prognosis with its use. As an alkylating agent, its main action is to reduce antibody production (ie. delayed efficacy), and side effects are common (myelosuppression, haemorrhagic cystitis, gastroenteritis).

MYCOPHENOLATE MOFETIL

Mycophenolate mofetil is a purine synthesis inhibitor with fewer side effects than azathioprine (IV preparation available as well as oral and gastrointestinal [GI] side effects are common).

LEFLUNOMIDE

Leflunomide is a pyrimidine synthesis inhibitor (inhibits B and T cells). Side effects are rare (myelosuppression, hepatotoxicity), but periodic monitoring is recommended.

CHLORAMBUCIL

Chlorambucil is the most popular adjunctive agent used in feline IMHA. Side effects include anorexia, nausea and (uncommonly) myelosuppression. Ciclosporin, mycophenolate or leflunomide could also be considered in cats.

There is insufficient evidence to recommend one second agent over another. Selection is often based on personal preference, relative risk of side effects, perceived speed of action, availability for parenteral administration, cost and patient size or convenient dosing.

ALTERNATIVE THERAPIES

HUMAN INTRAVENOUS GAMMA GLOBULIN

This inhibits macrophage Fc receptors. Current evidence for efficacy is limited (improved haematological parameters but no clear survival benefit) but studies are ongoing.

SPLENECTOMY

Splenectomy is occasionally performed as a salvage option for idiopathic IMHA cases refractory to medical

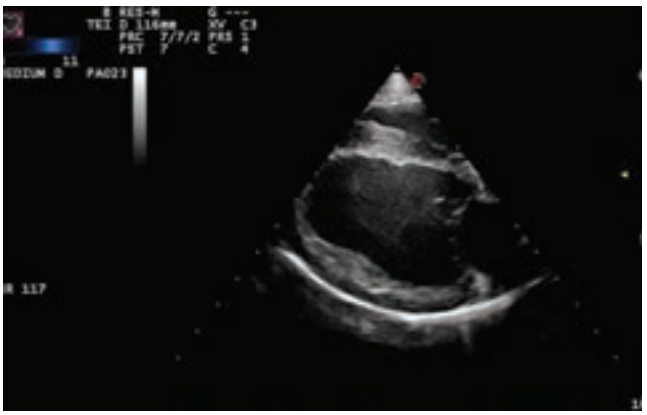

Figure 3: Spontaneous echocontrast within the left ventricle of a dog with primary IMHA: a hypercoagulable disease.

management,[4] however this remains controversial and larger studies are needed to assess safety and outcome. Proposed candidates are those with significant extravascular haemolysis, stable enough for anaesthesia and preferably not yet on cytotoxic drugs.

LIPOSOMAL CLODRONATE

Liposoma clodronat holds possible future potential (studies underway) – the bisphosphonate may inhibit splenic phagocytosis.

ADJUNCTIVE TREATMENT

Antacids are not essential in most cases – reserve for cases with additional ulcerogenic risk factors (eg. vomiting, gastritis) or perhaps with concurrent thrombocytopenia (when GI haemorrhage could be catastrophic).

Anti-thrombotic therapy is recommended during acute haemolysis (when the risk of thromboembolic disease is high (see Figure 3). Options include heparins and platelet inhibitors, but optimal protocols/dose rates remain controversial.

Clopidogrel has been proven more effective than aspirin in cats with thromboembolic disease (18.75mg/cat po sid).[5] Although we don't have the same evidence for Clopidogrel in dogs (2-4mg/kg po sid), it is at least not ulcerogenic, whereas latest recommendations for optimum aspirin dosing (1-2mg/kg sid) seem less confident of being risk-free with regards to increasing the risk of ulceration during concurrent steroid therapy. Heparins can be given by injection; low molecular weight heparins (LMWHs) eg. Dalteparin (150iu/kgscq eight hours) may be safer than unfractionated heparin, but drug monitoring is inconvenient (via 'anti-Xa activity'). Oral direct factor-Xa inhibitors (eg. rivaroxaban) have recently become available/affordable and may provide a more practical option for outpatients, although monitoring is still advised.[6]

MONITORING/TAPERING

PCV/TP is monitored daily until >20% (dogs) or >15% (cats), at which point patients can usually be discharged. A full haematology profile is then performed weekly until Hct near normal (eg. >30%). Gradual drug tapering can then start with ongoing monitoring (reduced to repeat for two weeks) to

ensure no relapse. Total treatment duration is usually at least three months. If on combination therapy, taper one drug at a time, starting with the drug perceived to be causing more side effects (usually steroids). Prednisolone is tapered by 25-33% every 10-14 days until on a maintenance dose (0.5mg/kg eod for four weeks). Any second agent is continued unchanged until on the maintenance steroid dose, then either this or the steroids stopped, with all therapy ceasing another two to four weeks later. Azathioprine is an exception – as discussed previously.

Regardless of drugs used, prolonged immunosuppression can predispose to opportunistic infection. In people, there is an increased risk of neoplasia with chronic immunosuppression – probably related to the degree of immunosuppression rather than any particular drug.

PROGNOSIS

Reported mortality rates have ranged between 20-70% (probably nearer to 30% with current standards of care), with the first two weeks carrying the highest risk of death. Thromboembolic disease (especially pulmonary thromboembolism) is a significant contributor. IMHA relapse can occur both during and after treatment but is most common in the first few weeks and usually necessitates a return to initial immunosuppressive doses.

Any potential trigger factors should be avoided (eg. medications +/- vaccinations). Negative prognostic factors include hyperbilirubinaemia, concurrent thrombocytopenia, prolonged clotting times, intravascular haemolysis or a left shift.[7,8]

HAEMOLYSIS: NON-IMMUNE-MEDIATED

INFECTION

BABESIA

Babesia canis is transmitted by the tick species Dermacentor (present in much of Europe, spreading north) and Rhipicephalus (Mediterranean). There are also reports of direct transmission (eg. blood transfusions +/- fighting dogs). Immunosuppressed dogs (including splenectomised) are more susceptible to infection. Babesia causes direct haemolysis of infected RBCs (and may also trigger 2' IMHA) +/- thrombocytopenia.

Diagnosis can be confirmed on a direct smear (more sensitive if collected from a peripheral, eg. ear vein); or with PCR (PCR/RLB). Anti-protozoal drugs, eg. imidocarb are the main treatment (+/- blood transfusions), with alternative drugs (atovaquone + azithromycin) being necessary for some smaller species, (eg. gibsoni) due to imidocarb resistance. Immunosuppression is generally advised against for European babesia species (or only used with great care if no response to initial therapy). Tick repellents are the main means of prevention.

MYCOPLASMA HAEMOFELIS

Mycoplasma is transmitted between cats via indirect (fleas are implicated) and direct mechanisms (eg. fighting and blood transfusions).

Disease predominantly involves extravascular haemolysis, and latent infection can recrudesce during times of stress/concurrent illness (eg. infection, trauma). Jaundice is uncommon, but other clinical signs of haemolytic anaemia may be accompanied by cyclic fever.

Although infection can sometimes be diagnosed on a fresh blood smear, PCR is more sensitive.

However, a positive result does not guarantee that mycoplasma is the current cause of anaemia (subclinical carriers exist) – although always warrants treating in an anaemic cat.[9] Doxycycline (10mg/kg sid) is the treatment of choice and usually resolves disease, although may not clear infection (chances are increased with prolonged therapy less than eight weeks).

Secondary IMHA is sometimes suspected, but often resolves with antibiotics alone – steroids are best reserved for cases with refractory signs of IMHA despite antibiotics.

OXIDATIVE DAMAGE

Common causes of oxidative RBC damage include: onion, garlic, propylene glycol, zinc, copper, cyanide, napthalene (mothballs), paracetamol and occasionally, (in cats), diabetes mellitus, hyperthyroidism, lymphoma, lipidosis.

Oxidative damage (OD) can manifest as methaemoglobinaemia and/or oxidative haemolytic anaemia.

Haemoglobin is oxidised from Fe2+ to Fe3+ forming methaemoglobin, which cannot bind oxygen. OD also causes haemoglobin aggregation/direct RBC membrane damage, forming Heinz bodies (see Figure 4) and eccentrocytes. This makes RBCs more fragile, resulting in predominantly extravascular/splenic destruction.

Altered RBC conformation occasionally triggers 2° IMHA.

Clinical signs of methaemoglobinaemia include cyanosis/muddy membranes, lethargy, dyspnoea.

Heinz body/eccentrocyte induced haemolysis presents similarly to IMHA but usually without immune-mediated features, ie. agglutination, spherocytes.

Most in-house analysers of oxygen saturation/content cannot detect reductions due to methaemoglobinaemia – external analysis is required. Paracetamol poisoning

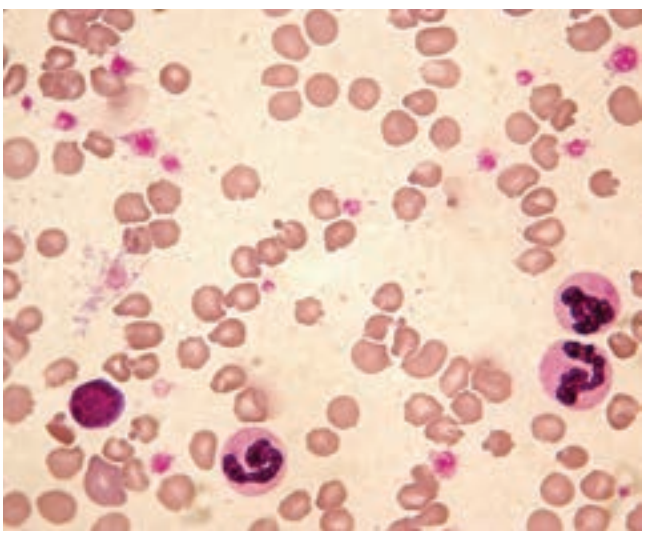

Figure 4: Heinz Bodies due to oxidative RBC damage in a cat. Photo: Roger Powell.

manifests as methaemoglobinaemia within hours, and haemolytic anaemia within days (+/- hepatic necrosis) – cats are particularly susceptible to haematologic toxicity. Treatment is supportive (blood transfusions, antioxidants eg. SAMe +/- methylene blue or vitamin C for methaemoglobinaemia), with some toxins warranting specific management, eg. N-acetylcysteine (paracetamol), foreign body removal (zinc).

HYPOPHOSPHATAEMIA

Significant hypophosphataemia (<0.8mmol/l) can cause haemolysis via increased RBC fragility and susceptibility to Heinz bodies. It is most commonly seen with re-feeding syndrome, treatment of DKA or excessive use of phosphate binders. Signs of anaemia may be accompanied by muscle weakness. Supplementation needs to be carefully titrated with close electrolyte monitoring to avoid hyperphosphataemia or hypocalcaemia.

HEREDITARY HAEMOLYTIC ANAEMIAS

Inherited membrane defects are more common in cats, eg. osmotic fragility – reported in Abyssinian, Somali, Siamese and even Domestic Short Hair cats.[10] Disease is often associated with hyperglobulinaemia and splenomegaly and diagnosis is confirmed by osmotic fragility testing. Transient improvement may be seen with steroids, however splenectomy seems to achieve better long-term disease control (but not cure). Hereditary spherocytosis has been documented in Golden Retrievers and appears to be associated with osmotic fragility. Stomatocytosis is seen in Alaskan Malamutes, Miniature Schnauzers and can cause mild, regenerative anaemia.

AUTSOMAL RECESSIVE ENZYME DEFECTS

Phosphofructokinase deficiency causes RBCs to become fragile in an alkaline environment (via reduced ATP/2-3, DPG). Haemolysis is therefore most commonly seen with alkalaemia (eg. respiratory alkalosis due to hyperventilation during barking/exercise) and may be accompanied by a myopathy (muscle weakness/cramps due to PFK deficiency in muscle). Affected breeds include Springer Spaniels, Cockers. The anaemia is often mild but regenerative (PCV may even be normal, but with a reticulocytosis maintaining it so) and accompanied by haemoglobinuria, hyperbilirubinaemia and elevated creatine kinase (CK). Genetic testing is available for certain breeds and a more convenient diagnostic tool than trying to arrange specific enzyme testing. Management focuses on avoiding triggers, eg. heat, exercise. Prognosis is good.

Pyruvate kinase deficiency causes more severe disease – moderate to severe regenerative anaemia and eventually myelofibrosis/osteosclerosis and liver disease due to chronic erythropoietic stimulation and iron absorption. Affected breeds include Basenjis, Beagles, Dachshunds, Miniature Poodles, Springer Spaniels and West Highland White Terrier (WHWTs) – genetic testing available in some breeds; specific enzyme testing required in others). There is no specific treatment and prognosis is guarded (survival <5 years due to 2° complications). PK deficiency in cats (documented in several pedigree breeds) tends to cause milder (often asymptomatic) anaemia and may improve with splenectomy if treatment is indicated.

MICROANGIOPATHIC ANAEMIA

Seen with mechanical RBC trauma, eg. due to DIC, splenic disease (including torsion), vascular neoplasms, vasculitis, heartworm and typically accompanied by signs of RBC shear injury, eg. schistocytes.

ENVENOMATION

Direct haemolysis can result from certain venom toxins, most commonly those produced by exotic snake/spider species. There have been occasional reports of haemolytic anaemia in dogs after bee stings, usually with a 2° immune-mediated component and spherocytosis.

HAEMOPHAGOCYTIC SYNDROME

This benign proliferative disorder of macrophages causes bone marrow invasion (+/- liver, spleen) and phagocytosis of haematopoietic cells, causing at least two cytopenias. Disease can primary (rare), or occurs secondary to immune-mediated disease, infection or neoplasia (especially histiocytic disease). The prognosis is poor unless there is treatable underlying disease, eg. infection.

HAEMORRHAGE

Although anaemia due to blood loss is often easily diagnosed, some forms of haemorrhage may be more occult. Gastrointestinal bleeding is not always accompanied by elevated urea or overt melaena (faecal occult blood tests can be useful). Chronic haematuria can sometimes cause significant anaemia (eg. idiopathic renal haematuria). Spontaneous thymic haemorrhage occasionally occurs in young dogs, causing acute anaemia/hypovolaemia as well as respiratory signs. Retroperitoneal or deep intramuscular haemorrhage can escape initial examination/survey imaging. As with haemolysis, the regenerative response may lag behind acute haemorrhage, ie. the anaemia can be 'pre-regenerative'. The true extent of anaemia may only be apparent once intra and extravascular fluids have re-equilibriated (do not be falsely reassured by a normal or even elevated PCV (splenic contraction) in the face of acute haemorrhage, especially if cardiovascular parameters suggest hypovolaemia). Hypoproteinaemia is supportive of blood loss but not always present (eg. internal bleeding). Chronic occult haemorrhage may progress to iron deficiency and eventually poor regeneration.

Haemorrhage into body cavities can be diagnosed via centesis (if safe to do so/clotting function normal) and fluid PCV/TP analysis – the PCV is less than or equal to that of a venous blood sample with acute haemorrhage, but may be greater with chronic haemorrhage (due to re-absorption of plasma), or accidental splenic aspiration (in which case the sample will clot). Haemophagocytosis also points towards chronicity in haemorrhagic effusions.

Decisions about blood transfusions are based on estimations of blood volume lost (if known); failure to improve after appropriate shock management with crystalloids/colloids; or follow-up PCV/TP monitoring. Most clinicians consider any acute, hypovolaemic drop in Hct to <20-25% in dogs, <15-20% in cats as an indication to transfuse.

CONCLUSION

We have approached anaemia in a systematic, logical way, however some cases will not fit neatly into a particular category and can pose a diagnostic challenge. For example, immune-mediated disease that apparently targets peripheral and marrow cells *simultaneously*; or poorly regenerative 'acute' anaemia requiring urgent transfusion therapy before allowing an opportunity to reassess reticulocyte response (following which there may not be the same drive for regeneration). Specialist advice/referral should be considered in challenging cases.

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READER QUESTIONS AND ANSWERS

TRUE OR FALSE?

1. **PYRUVATE KINASE DEFICIENCY CARRIES A GOOD PROGNOSIS IN BOTH DOGS AND CATS.**
2. **A POSITIVE MYCOPLASMA PCR RESULT IN AN ANAEMIC CAT CONFIRMS THIS AS THE CAUSE OF THE ANAEMIA.**
3. **FLUID THERAPY (EG. MAINTENANCE RATE CRYSTALLOIDS) IS FREQUENTLY INDICATED IN CASES OF IMHA, UNLIKE OXYGEN THERAPY.**
4. **THROMBOEMBOLIC DISEASE IS ONE OF THE MAIN CONTRIBUTORS TO MORTALITY IN CANINE IMHA.**
5. **UREA ELEVATION IS A VERY SENSITIVE MARKER OF GASTROINTESTINAL HAEMORRHAGE.**

1.FALSE 2. FALSE 3. TRUE 4. TRUE 5. FALSE