

# Feline Anemias – Peculiarities of Regenerative (Blood Loss and Hemolysis) and Non-regenerative Anemias

## Anemiile anemiei - particularități ale anemiilor regenerative (pierdere de sânge și hemoliză) și neregenerative

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Anemia is an extremely common clinical problem in cats and is associated with many different conditions. Despite severe anemia many cats may only show mild clinical signs particularly when chronic. In order to recognize the type, degree, and regeneration of anemia in cats, it is important to appropriately appreciate the hematological peculiarities of cats. When compared to dogs, the normal packed cell volume in cats is lower (Packed Cell Volume [PCV] 0.30-0.48/L; 30-48%), feline red blood cells are considerably smaller (MCV 38-50 fl), central red cell pallor is small (cannot see spherocytes), bone marrow iron stores are visually lacking, and there are mostly mild regenerative responses observed. There are aggregate reticulocytes (also reflected as polychromasia) which are short-lived in circulation (like in dogs), but cats also have punctate reticulocytes, which may linger around in circulation for a couple of weeks. The best parameter to assess a regenerative bone marrow response is the absolute reticulocyte count (normally <60,000/μl), which refers to the presence of aggregate reticulocytes and is equal to the degree of polychromasia. Note nucleated red blood cells may be proportionally increased with reticulocytes or may occur independently due to bone marrow endothelial damage as in lead poisoning, sepsis and myelodysplasia. While the evaluation of PCV, total protein, and blood smear are most valuable, a complete blood cell count and specific tests are generally required to reach classify the anemia, for a definitive diagnosis and to monitor the response to therapy. A complete blood cell count with reticulocyte count of modern hematology analyzers is ideal to best assess hematological disorders, but other tests are likely needed. These may include for instance chemistry screen, urinalysis, bone marrow cytology or core biopsy, hemostatic tests, iron parameters, infectious disease screen by serology and PCR, toxicological analysis, Coombs', and genetic/DNA tests.

Although kidney failure and some infections (flea infestation, FeLV infection and hemobartonellosis) are likely the most common causes of anemia, there are many other differential diagnoses to consider, such as bleeding disorders, toxicity, metabolic disturbances, hereditary defects, and immune-mediated hemolytic anemias. It is therefore crucial to carefully assess the feline patient by history taking, physical exam and routine laboratory tests in order to determine the cause and offer the most appropriate treatment.

In contrast to dogs, **blood loss anemias** are less commonly observed in cats, albeit they happen with trauma and surgery. In fact, many cats drop their PCV during and shortly after surgery which may in part be blood loss, but also unexplained lysis and sequestration. Moreover, external blood loss can rapidly result in iron deficiency particularly in the very young kitten (even with repeat phlebotomies for diagnostic purposes), however, the classic microcytosis and hypochromasia in iron deficiency may be very difficult to appreciate due to small feline red cells. The most common reason for blood loss is flea infestation, while maggots, ticks, and hookworms are less likely leading to major blood loss. Skin and other tumors may also cause local bleeding. Blood loss anemias are generally regenerative after 3-4 days and remain regenerative even when iron deficient. While in the above cases

hemorrhage was caused by vascular injury, there are also a variety of bleeding disorders to consider.

Thrombocytopenia is rare in cats but may be induced by drugs (methimazol) and rarely infection and cancer; immune-mediated thrombocytopenia also seems to occur rarely. Accurate platelet counts can be difficult to obtain due to their large size platelets and tendency to aggregate. Thus, any platelet count needs to be confirmed with an estimate from a blood smear examination (20,000 platelets/ $\mu$ l equals 1 platelet seen on a high power microscopic field). Thrombopathia – impaired platelet function - may be triggered by aspirin or similar drugs (cats appear particularly sensitive to platelet injury but less likely to aspirin or steroidal ulceration). Hereditary thrombopathias are extremely rare. Compared to dogs, anticoagulant rodenticide poisoning is less commonly observed in cats. However, coagulopathies due to hepatic failure are much more severe in cats than dogs; hence diagnostic liver biopsies are frequently associated with serious hemorrhage. Furthermore, there are several hereditary coagulopathies such as hemophilia A and B in domestic and Himalayan cats as well as a vitamin K-dependent coagulopathy in Devon Rex and Sphinx cats. Interestingly, domestic and exotic shorthair cats often have a coagulation factor XII deficiency; while this causes a markedly prolonged partial thromboplastin time, this is not associated with a bleeding tendency. Generally, the prothrombin and partial thromboplastin times provide sufficient information to differentiate the coagulopathies, although specific factor analyses may be needed.

**Hemolytic anemias** in cats are often hard to recognize as the degree of bone marrow regeneration and the evidence of bilirubinuria and hyperbilirubinemia are often mild (any bilirubinuria is important in a cat). In fact, icterus in cats is much more likely due to hepatic failure. While the normal feline spleen is very small, it can get fairly enlarged in cases of hemolytic anemia. Furthermore there is a syndrome of increased erythrocytic osmotic fragility seen in Abyssinian, Somali and other domestic house and purebred cats with massive splenomegaly. Pyruvate kinase deficiency is a common hereditary disease causing intermittent hemolytic anemia in Abyssinian, Somali and other purebred and even domestic house cats. There is also porphyria, a heme synthesis defect, which causes hemolysis but most remarkably erythrodontia with fluorescing teeth. Porphyria may dominantly or recessively inherited and cats may live for years with this condition requiring no specific treatment. In contrast to dogs, primary (auto-) immune-mediated hemolytic anemia seems rare in cats, but may be seen with other triggers such as infections, drugs, and cancer (secondary IMHA). Their species-specific Coombs' test is positive. In addition, some show autoagglutination that may break up when adding saline (Rouleaux) and after washing with saline when caused by unspecific agglutination such as by EDTA. More important than primary IMHA is alloantibody associated hemolysis. Neonatal type A and AB kittens nursing from a type B queen will frequently develop acute hemolysis of the newborn during the first hours to days of life. Classic signs are acute death, massive pigmenturia due to hemoglobinuria and occasionally they may develop icterus and a tail tip necrosis and survive. Similarly important are A-B mismatched (first transfusion due to preformed antibodies and rarely others like Mik and only after prior sensitizing) acute hemolytic transfusion reactions. Thus AB typing is critical prior to breeding and transfusing cats. Transfusing canine blood to cats (xenotransfusion) causes always severe hemolytic reactions and is not recommended.

### **Feline hemolytic anemias**

- **Infections**
  - Mycoplasma hemofelis, (also hemominutum, turicesis)
  - Cytauxzoon felis
  - Feline Leukemia Virus infection (A type)
  - Feline Infectious Peritonitis
- **Immune**

- Alloimmune – neonatal isoerythrolysis and acute transfusion reactions
- Autoimmune or primary hemolytic anemia (rare compared to dogs)
- Secondary (drugs [methimazol], infection, cancer)
- **Toxic**
  - Drugs - acetaminophen, lidocaine spray, propofol, etc.
  - Onions
- **Metabolic**
  - Hypophosphatemia (D. mellitus, hepatopathy, hyperalimantation)
- **Hereditary**
  - Pyruvate kinase deficiency (Abyssinian, Somali, other purebred and DSH cats)
  - Increased osmotic fragility (Abyssinian, Somali, other purebred and DSH cats)
  - Porphyria (Siamese and DSH cats)

There are several important differential diagnoses for hemolytic anemias and thus treatment options depend on the cause of hemolysis. Various triggers such as drugs and chemicals can be rapidly removed. However, other diagnoses may require tests at reference laboratories, such as for serology and real-time PCR for infectious diseases and genetic tests for hereditary diseases. It is therefore not unusual to start with a combination of prednisolone (fortunately even at high doses well tolerated) and doxycycline as initial treatment of hemolytic anemias to cover the bases until test results are back and specific and proper therapy can be instituted. For hereditary hemolytic anemias it is most important to avoid harmful treatments and offer a safe (indoor) environment.

Lastly, **non-regenerative anemias** due to decreased erythro- or overall hematopoiesis can be associated with a variety of disorders. Indeed, mild non-regenerative normochromic normocytic anemia is commonly seen with many organ diseases and is mostly well tolerated. However, many middle-aged to older cats with chronic renal failure develop a moderate to severe anemia. The main cause is a lack of renal production of erythropoietin, but uremic toxins affecting red cell stability and bone marrow production as well as blood loss from ulcers also play a role. Transfusion or human recombinant erythropoietin (darbepoetin) can reverse the anemia and associated clinical signs. However, repeat transfusions are generally needed and cats may become refractory, as they develop alloantibodies against the transfused red cells. Moreover, cats can develop antibodies against the recombinant human erythropoietin, which leads to a severe and hardly reversible pure red cell aplasia. Renal transplantation from a carefully selected donor cat has effectively reversed not only the anemia but also restored kidney function. While rarely truly deficient, iron, folate, and cobalamin may be replenished as needed. FeLV infections may end in a pure red cell aplasia (C type) or myelodysplasia to aplasia, while FIV exhibits less effects on the bone marrow. Cancer associated anemias may have many causes but may result in aplastic or myelophistic bone marrows.

Finally, many anemic cats need transfusion support during the initial management. There is no specific trigger PCV, but rather the overall clinical picture with a PCV of <20% is used. It should be noted that cats need to be AB blood typed before the first and crossmatched before the second transfusion (>4 days from first transfusion).

Author's studies were supported in part by grants from the National Institutes of Health (OD010939) and the AKC Canine Health and other Foundations. The author is scientific advisor to various companies and the director of the non-for-profit PennGen Laboratory offering genetic and hematological testing.