Review Article

Management of Non-Regenerative Anaemia in Cats

Selin Sinem Sümbül LACİN[1*], Mustafa Sinan AKTAS[2], Sümeyye BAYSAL[3]

[1] Sağlık Bilimleri Enstitüsü, İç Hastalıkları Anabilim Dalı, Atatürk Üniversitesi, Erzurum, Türkiye
[2] İç Hastalıkları Anabilim Dalı, Atatürk Üniversitesi, Erzurum, Türkiye
[3] İç Hastalıkları Anabilim Dalı, Atatürk Üniversitesi, Erzurum, Türkiye

ORCID : 0000-0002-8680-5402
ORCID : 0000-0002-7206-5757
ORCID : 0000-0003-1464-4993

***Corresponce:**
Selin Sinem Sümbül Laçin
Atatürk Üniversitesi, Veteriner Fakültesi, İç Hastalıkları Anabilim Dalı, Erzurum, Türkiye

Phone : 0544 320 25 07
E- mail : selinsinemsum@gmail.com
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Abstract

Non-regenerative anemia is a common condition in cats. Non-regenerative anemia in cats is a condition caused by insufficient erythrocyte production or impaired erythropoiesis. Non-regenerative anemia occurs in cats of all ages , which is characterized by a low number of erythrocytes in the blood and, as a result, a decrease in oxygen-carrying capacity. The etiology of non-regenerative anemia in cats is a complex issue and includes a variety of conditions such as acute blood loss, infectious diseases such as Feline leukemia virus (FeLV), Feline infectious peritonitis, and immune hemolytic anemia. It is usually associated with a variety of causes, such as iron deficiency, chronic diseases, toxin exposure, or genetic factors. Symptoms include fatigue, pale gums, loss of appetite, and weakness. The diagnosis is made by laboratory tests and a complete blood count. Treatment varies depending on the underlying cause and may include iron supplements, blood transfusions, immunosuppressive agents, or specific drug therapies, primarily with the elimination of the underlying cause. Non-regenerative anemia is a very serious condition and requires timely intervention. Non-regenerative anemia in cats is an important issue in clinical practice and it is important for veterinarians to maintain their knowledge and skills in this area.

Keywords: Anemia, cat, non-regenerative anemia

Introductıon

Anaemia is a condition characterized by a decrease in haemoglobin (Hb), haematocrit (HCT), or red blood cell (RBC) count. It is caused by an underlying condition and can be classified into macrocytic, microcytic or normocytic subgroups based on morphology (Turner and Parsi, 2024). Anaemia is categorised If the bone marrow is functioning normally, this is regenerative anaemia. This type of anaemia is due to the removal of red blood cells from the body, for example in trauma, or the degradation of red blood cells in the system, for example in haemolytic anaemia or internal haemorrhage. Regenerative anaemia is in general easier to diagnose than non-regenerative anaemia (Tvedten, 2022). The incapacity of the bone marrow to react adequately to peripheral erythrocyte deprivation results in non-regenerative anaemia in cats. The causes of non-regenerative anaemia include both primary bone marrow diseases and

systemic diseases with secondary involvement of the bone marrow. Prognosis varies, with some conditions being short-lived while others may become chronic or fatal (White and Reine, 2009). Non-regenerative anaemia occurs when the bone marrow responds ineffectively to the increasing demand for red blood cells. Anaemias that result from a decrease in the hormone that stimulates red blood cell production or an abnormality in the bone marrow are called non-regenerative anaemias. Non-regenerative anaemia is a common condition in cats (Winzelberg Olson and Hohenhaus, 2019). The cause of feline non-regenerative anaemia is unknown, but it is probably due to the fact that cats become anaemic more often than dogs, and cats are susceptible to a number of chronic diseases that lead to predisposition to anaemia (Lynch et al., 2016).

Etiology ff Non-Regenerative Anaemia

Non-regenerative anaemia in cats can have various causes. The most commonly occurring are acute blood loss, infectious diseases, renal failure and immune mediated haemolytic anaemia (Winzelberg Olson and Hohenhaus, 2019).

Acute Blood Loss

During the early phase of the loss of blood, before there is a peripheral reticulocyte reaction, the anaemia may not be regenerative (White and Reine, 2009).

Infectious Diseases

Non-regenerative anaemia can be caused by infectious diseases. Feline leukaemia virus (FeLV) is one such disease (Gleich and Hartmann, 2009), Feline Immunodeficiency Virus (FIV) (Shelton et al., 1990; Gleich and Hartmann, 2009), Feline Infectious Peritonitis (FIP) (Paltrinieri et al., 2001), *Cytauxzoon felis* (MacNeill et al., 2015), Haemotrophic *Mycoplasma species* (Weingart et al., 2016), *Leishmania infantum* (Pennisi et al., 2015), and *Ehrlichia canis* (Braga et al., 2013). There are many causes of infection-related anaemia, but the most important is hepcidin, a type 2 acute phase protein which is produced by the liver (Verga Falzacappa and Muckenthaler, 2005). Hepcidin synthesis is induced by interleukin-6, which is produced early in host defence (Ganz, 2006). Hepcidin interferes with iron uptake by duodenal enterocytes and macrophages, which results in reduced iron uptake and iron deposition in macrophages (Verga Falzacappa and Muckenthaler, 2005). Hypoxia or iron deficiency reduces hepcidin production (Pietrangelo and Trautwein, 2004). Erythropoietin levels rise or fall depending on the severity of anaemia in infectious diseases. (White and Reine, 2009). Cats may develop anaemia within 2 to 3 days of the beginning of the infectious process and the haematocrit drops by up to 8% on average (Waner and Harrus, 2000).

Kidney Failures

Erythropoietin is predominantly secreted by the kidney into the peritubular interstitial cells of the inner renal cortex and outer medulla. Renal failure impairs the kidneys' ability to increase erythropoietin secretion in responding to hypoxia (White and Reine, 2009). Both acute and chronic etiologies of renal failure reduce erythropoietin secretion, and chronic renal failure is known to a primary cause of non-regenerative anaemia in cats (Furman et al., 2014). Renal failure commonly leads to normocytic, normochromic, non-regenerative anaemia (White and Reine, 2009).

Immune Mediated Haemolytic Anaemia (Imha)

IMHA is less frequent in cats than in dogs. The disease can be primary (idiopathic) or secondary to infections including Feline Leukemia Virus (FeLV), toxin, medication, blood parasite, neoplasia and systemic scleroderma (Little et al., 2018). Complement-mediated and extravascular haemolysis is observed in cats with IMHA. To date, no cases of intravascular haemolysis have been reported in cats (Kohn et al., 2006).

Pure Red Cell Aplasia (Prca)

Pure red cell aplasia (PRCA) is a unique syndrome that is characterised by severely nonregenerative anaemia with a deficit of erythrocyte precursors in the bone marrow in spite of normal leukocyte and platelet counts. PRCA can be either primary, or secondary to FeLV infection (White and Reine, 2009).

Myeloproliferative Syndromes

Myeloproliferative conditions are a group of associated neoplasms which result from the clonal

transformation of non-lymphoid stem cells and their derivatives (Feldman et al., 2000). Dysmyelopoiesis is a term used to describe bone marrow disorders that originate from haematopoietic stem cells and result in a decrease in one or more species of circulating blood cells. It is not known whether FeLV infection causes myeloproliferative syndrome in cats; an estimated 80% of cats with myeloproliferative syndrome test positive for FeLV (Feldman et al., 2000).

Iron Deficiency

Iron is naturally present in the body as haemoglobin (the most abundant form), myoglobin, labile iron, tissue iron and transport iron. A haemoglobin molecule carries four iron atoms, representing 0.34% of its total weight. Every millilitre of red blood cells carries 1.1 mg of iron (Feldman et al., 2000). Iron depletion is typically linked to chronic blood loss in the cat (gastrointestinal, parasitic through heavy flea infestation, or noted on anecdotal evidence in cases of chronic haematuria) (Winzelberg Olson and Hohenhaus, 2019). Iron measurement can also help to differentiate between anaemia resulting from iron deficiency and anaemia due to inflammation, but the difference can still be difficult to make. In both situations, serum iron levels are depressed. Ferritin, the tissue soluble form of iron storage, is typically reduced in iron deficiency anaemia and elevated in inflammatory anaemia (Winzelberg Olson and Hohenhaus, 2019).

Inadequate Nutrition

Nutritional deficit anaemia is now uncommon in veterinary practice as a result of the improved nutritional quality of commercial pet foods and the greater knowledge. These anaemias are typically caused by errors such as feeding an incorrectly formulated homemade diet, or by a digestive problem that inhibits nutrient absorption (White and Reine, 2009). Malnourished cats may exhibit normocytic, normochromic, non-regenerative anaemia resulting from protein, calorie, vitamin or mineral depletion (Watson and Canfield, 2000).

Clinical Findings

The clinical findings that indicate a need for the cat owner to visit the clinic include symptoms such as malaise, muscle weakness, pale mucous membrane colour, icterus, haemoglobinuria, or haematuria (Tvedten, 2022) A study was conducted on 15 cats with IMHA disease, which found that all cats experienced malaise for a duration ranging from 5 days to 3 months (mean 7 days). Other clinical signs reported were decreased appetite (n=12), weight loss (n=4) and pica (n=3). Pallor of mucous membranes was observed in all cats. Clinical exam findings were: tachypnea (n=13), galloping heart rhythm (n=9) and grade II-III/VI systolic murmur (n=9) (Black et al., 2016). In our clinic, pale mucous membrane is a common clinical sign in cats with IMHA (Figure 1-a and Figure 1-b).

Figure 1-a, b: Anemia seen in the eye mucosa of a cat with IMA

Diagnosis And Classification of Anaemias

When diagnosing and classifying anaemia in cats, it is important to primarily assess RBC, HGB, HCT, MCH and MVHC. A HCT less than 29% is seen in cats with anaemia. Differential diagnosis of anaemia is performed on the bases of RBC size and haemoglobin capacity. The classification of anaemias is based on the parameters of mean corpuscular volume (MCV) and reticulocytes. To identify anaemia, different tests are carried out on blood samples. These tests are normally carried out as part of the complete blood count (CBC). The most widely used test to diagnose anaemia is the packed cell volume (PCV), also called the haematocrit. In a healthy cat, 25-45% of the blood is red blood cells. If the HCT falls below 25%, the cat is considered anaemic (Weir, 2024).

Reticulocyte Count

A count of reticulocytes is required to distinguish regenerative anaemia from non-regenerative anaemia, and a high reticulocyte count is suggestive of regenerative anaemia. The cat definition of reticulocytosis varies between values >0.045 x 1012/l and >0.060 x 1012/l. (Fielder, 2024). Feline WBCs can be counted by manual and automated techniques. WBC count by automated techniques

(blood counting machines) is slightly higher, but correlates with manual total reticulocyte count (Fujino et al., 2013).

Mcv

RBC markers are MCV and mean corpuscular haemoglobin concentration (MCHC). These can help to identify the type of anaemia by examining cell volume and haemoglobin concentration, e.g. microcytic hypochromic anaemias (regenerative or otherwise) are generally caused by iron deficiency (Eclinpath, 2024).

Other Tests

If the cause of non-regenerative anaemia cannot be determined through haematology, biochemistry, or infectious disease testing, additional tests such as blood smear, bone marrow cytology, or organ aspiration cytology may identify cytopenias, abnormal blood cells, Heinz bodies, organ hypertrophy, or diagnostic imaging abnormalities (Winzelberg Olson and Hohenhaus, 2019).

Treatment

Non-regenerative anaemia should be managed by identifying the underlying condition and developing an appropriate treatment plan. Supportive therapies are also commonly used to treat non-regenerative anaemia. (Winzelberg Olson and Hohenhaus, 2019).

Supportive Treatment

Agents Stimulating Erythropoiesis

In cats, these drugs are used to manage non-regenerative anaemia due to chronic renal failure. Studies have shown that these drugs, used in aplastic anaemia, FIP and FIV-related non-regenerative anaemia, cause an increase in HCT (Tanaka et al., 2015). Several recombinant human erythropoiesis-stimulating products are currently on the market, such as epoetin alfa, epoetin beta and darbepoetin alfa. Darbepoetin alfa is hyperglycosylated compared to epoetin alfa, which results in a three time longer circulating half-life and a reduction in mean elimination rate of over 70% (ml/kg x h) (Tanaka et al., 2015). Darbepoetin is given only once a week. initial dose of 1.0 µg/kg in cats (Marks, 2023). As the target HCT is achieved, the dosing interval is decreased every 2-3 weeks and the dose is adapted to maintain the HCT within the target range (25-35%). It is important to note that epoetin should be dosed three times a week (Chalhoub et al., 2012). For cats, the suggested starting dose is 100 units/kg subcutaneously three times per week. Once the target hematocrit (HCT) level of 30-40% is achieved, the dosing frequency can be reduced to twice a week for ongoing treatment (Chalhoub et al., 2012).

Iron Supplementation

Cats being treated for iron deficiency anaemia or after the administration of erythropoietin-stimulating agents may require iron supplementation (Winzelberg Olson and Hohenhaus, 2019). Iron dextran, iron gluconate, and iron sucrose are all used for parenteral supplementation. In veterinary medicine, iron dextran is the most frequently used. The recommended dose for cats is 10 mg/kg, administered intramuscularly every 3-4 weeks. To minimize the risk of anaphylaxis, intramuscular administration is recommended rather than intravenous administration (Winzelberg Olson and Hohenhaus, 2019).

Vitamin B12

Anaemia due to hypocobalaminemia may require vitamin B12 supplementation (Winzelberg Olson and Hohenhaus, 2019). For parenteral administration, vitamin B12 is given as cyanocobalamin. Dosing protocols may vary, but the most recent recommendation is to administer 250 µg subcutaneously once a week for six weeks, followed by an initial dose 30 days later; serum cobalamin levels should be reassessed 30 days after the last injection (Kempf et al., 2017). Research indicates that oral cyanocobalamin supplementation can increase serum cobalamin levels in cobalamin-deficient cats, above the normal reference range. The recommended dose is 250 µg administered orally (PO) every 24 hours with continuous supplementation (Toresson et al., 2017).

Glucocorticoids

Glucocorticoids are the preferred initial treatment for immune-mediated haemolytic anaemia. They slow down the destruction of erythrocytes by altering Fc receptors (Wang et al., 2013). Long-term use of corticosteroids may result in several side effects, including gastrointestinal irritation, hyperadrenocorticism, repeated infections, sepsis, weight gain, polyuria/polydipsy, delayed wound healing and alopecia (Wang et al., 2013; Manev

and Marincheva, 2018).

Prednisolone and Prednisone

The immunosuppressive dose will vary between drugs, but for prednisolone and prednisone it is 2 mg/kg given twice daily for 2 weeks or until HTC is stabilised (McCullough, 2003).

Cyclosporine

Cyclosporine is the most studied and widely used supplement to glucocorticoids and is used in the treatment of IMHA in cats (Black et al., 2016). To obtain the desired clinical results, oral microemulsion cyclosporine is recommended at a dose of 5-20 mg/kg given at 24-hour cycles for 2-7 weeks (Swann et al., 2016).

Blood Transfusion

Blood transfusion is indicated for cats with severely anaemic conditions and HCT values between 12-14%. (Castellanos et al., 2004). Cats have three blood groups: A, B, and AB. Type A is the most widely used type in the world, particularly in shorthaired domestic cats, type B is less common and type AB is believed to be rare (Barfield and Adamantos, 2011). Blood group identification can be carried out in any standard laboratory from a whole blood sample anticoagulated with EDTA, or by using rapid diagnostic test kits (Barfield and Adamantos, 2011). Fresh whole blood is currently the most widely used product in cats, but transfusions also include stored whole blood, packed red cells and fresh frozen plasma (FFP) (Roux et al., 2008). It is preferable for the donor cat to weigh more than 4 kg (Castellanos et al., 2004). Cats that are on long-term medication, including non-steroidal anti-inflammatory agents, should not be used as donors. Cats should be fully vaccinated as required in your region (Castellanos et al., 2004). To draw a full unit of blood (50-60 ml), it is recommended to pre-fill three 20 ml syringes with 3 ml each of acid citrate dextrose or citrate phosphate dextrose anticoagulant. It is important to avoid heparin as an anticoagulant due to its potential to inhibit platelet aggregation and clotting factors. However, heparin can be used as an alternative anticoagulant in an emergency at a rate of 5-10 units of heparin/ml of blood (Dippenaar, 1999). The jugular vein is punctured using a 19-21G butterfly needle, and blood is collected over a period of 10-15 minutes. To ensure sufficient anticoagulant distribution in the collected blood, each syringe is slowly rotated during and after donation. A maximum of 10-12 ml/kg of blood can be transfused at one time (Castellanos et al., 2004). The primary objective of this procedure is to raise the patient's HCT levels adequately to alleviate the symptoms of anaemia. The target should be to achieve a 20% increase in HCT (Castellanos et al., 2004).

Conclusion

Non regenerative anaemia is common in cats. There are many different causes in the aetiology and differential diagnosis is of great importance in its treatment. Therefore, the underlying disease should be treated first. There are many options for supportive treatment of non-regenerative anaemia in cats. Blood transfusion is indicated depending on the haematocrit level.

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