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CHRONIC NONREGENERATIVE ANEMIA: A CHALLENGE?
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The diagnosis and treatment of nonregenerative anemia are usually more challenging than the regenerative ones. It’s a common condition that does not represent a diagnosis by itself, but a manifestation of several diseases and conditions. Reticulocyte count is the most reliable noninvasive method to access bone marrow erythroid production. Reticulocyte counts lower than 60.000/µL or 1% (absolute count) for dogs and lower than 15.000/µL or 0,4% (absolute count) of aggregate reticulocytes for cats are expected in nonregenerative anemias.
Since erythrocytes have a long life span it may take several weeks to months to the establishment of anemia, especially if there is not any concurrent blood loss, hemolysis or shortening of the red cell life span. Once feline erythrocytes have a shorter life span, cats will develop an anemic state quicker than dogs in a situation of decreased erythrocyte production. Although most diseases do not stop erythrocyte production completely, they also cause a shorter erythrocyte life span which can lead to a quicker development of anemia.
The persistence of a moderate to severe nonregenerative anemia for five days or more excludes the possibility of a short time for an adequate response from a normal bone marrow. This transitory situation can be seen in acute blood loss or in acute hemolytic anemia. The major causes of a true non regenerative anemia are decreased erythrocyte production or, less commonly, a defective erythropoiesis which can be caused by many diseases and conditions (Table 1).

Table 1. Diseases and conditions that cause nonregenerative anemias

<table>
<thead>
<tr>
<th>Decreased erythrocyte production</th>
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<tbody>
<tr>
<td>Inflammatory disease (infectious or not)</td>
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<tr>
<td>Chronic renal disease</td>
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<tr>
<td>Marrow hypoplasia or aplasia (infections, drugs, toxins, irradiation, myelophthisis, myelofibrosis, osteopetrosis)</td>
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<tr>
<td>Selective erythroid hypoplasia or aplasia (PRCA, FeLV, endocrine, liver disease)</td>
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<table>
<thead>
<tr>
<th>Defective erythropoiesis</th>
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<tbody>
<tr>
<td>Nutritional anemia (Iron, copper, vitamin B12, folate or cobalamin)</td>
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<tr>
<td>FeLV (causing dyserythropoiesis or erythroid neoplasia)</td>
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<tr>
<td>Immune-mediated destruction of erythroid progenitors</td>
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<td>Myelodisplastic syndrome - MDS</td>
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PRCA - Pure Red Cell Aplasia

Anemia of inflammatory disease (AID) is the most common nonregenerative anemia in dogs and cats. It’s typically a mild to moderate normocytic normochromic anemia that can be caused by inflammatory, infectious (bacterial, viral, fungal, protozoal), neoplastic, toxic or immune-mediated disorders. The pathogenesis of AID is multifactorial and involves reduced erythrocyte production (inadequate production of Erythropoietin – Epo and diminished responsiveness to Epo); lowered iron disponibility; and shortened erythrocyte life span (erythrocyte removal by immunologic mechanisms or oxidative damage). Treatment must be focused in the primary disease since iron supplementation will not be effective.
Anemia in patients with chronic renal disease may be mild to severe and is mainly caused by decreased Epo production. Epo replacement therapy can be effective in these cases. Damage to erythrocytes by toxic substances accumulated during kidney insufficiency and the blood loss through mucosal ulcers or vascular damage may also contribute to the anemia.
Marrow hypoplasia or aplasia of multiple cell lineages may be associated with neutropenia or thrombocytopenia which can be noticed earlier than the regenerative anemia due to the shorter life span of neutrophils and platelets. Some antineoplastic and immunosuppressive drugs, like
doxorubicin, cyclophosphamide, vincristine, azathioprine and hydroxyurea cause a reversible damage do the stem cells. The discontinuation of their use may be effective in these cases, but some animals may present an irreversible state. Estrogen, phenylbutazone and phenobarbital in dogs and griseofulvin in cats also can cause aplastic anemia or pancytopenia. Infectious agents like *Ehrlichia canis* and *Leishmania* sp are among the most commonly associated to marrow hypoplasia. The mechanisms involved in the damage to the stem cells are multiple, including progenitor cells infection and immune-mediated processes. Other cells like fibrocytes, fat, endothelial and reticular cells may also be a target to drug or infectious agents damage. Myelophthisis, caused by the neoplastic cell infiltration in bone marrow like those seen in leukemias, multiple myeloma and malignant histiocytosis, myelofibrosis and osteopetrosis can also result in pancytopenia due to the replacement of hematopoietic cells in the marrow.

Nonregenerative anemia can also be caused by selective erythroid hypoplasia or aplasia. Immune-mediated destruction of erythroid precursors appears to be associated to some cases of pure red cell aplasia (PRCA). Anti-Epo antibodies following human recombinant Epo therapy for chronic kidney disease have been detected in some dogs with PRCA. Other forms of nonregenerative immune-mediated anemia (IMA) have been recognized in dogs. They can be differentiated from PRCA by the evidences of an immune-mediated destruction of intermediate to latest stages of erythroid progenitor cells. These evidences are the presence of phagocytosis of erythroid precursors and a maturation arrest with or without erythroid hyperplasia. Response to immunosuppressive therapy in PRCA and nonregenerative IMA may take longer than the classic forms of regenerative IMAs since earlier stages of erythroid cells must be replaced in marrow till the resolution of the anemia. Spherocytosis and red blood cell agglutination may be observed in some cases. Similarly to the regenerative forms of IMA, this immune-mediated destruction can be caused by infectious agents, drugs, neoplasia or can be idiopathic.

Nutrient deficiencies causing nonregenerative anemias are rare nowadays but iron deficiency is the most common reported cause. Chronic external blood loss through ulcers or by parasites (intestinal or cutaneous) is the main mechanism of iron deficiency in small animals. Iron spoliation caused by hemodialysis may contribute to the anemia in chronic renal disease. Iron can also be supplemented along with Epo replacement in order to improve its efficiency. The classic morphology of iron deficiency anemia is microcytic hypochromic. Other types of nutrient deficiency (copper, pyridoxine, cobalamin or folate) are rare in dogs and cats, but they need to be considered in the differential diagnosis.

Endocrine diseases, especially hypothyroidism and hypoadrenocorticism, and liver disease can cause a mild to moderate nonregenerative anemia but hyperestrogenism usually causes a severe anemia associated with other cytopenias (pancytopenia).

FeLV infection may cause a selective erythroid hypoplasia or aplasia or a dysplastic or neoplastic transformation. Subgroup C of FeLV is constantly associated to erythroid neoplasia or myelodysplastic syndrome (MDS) with erythroid predominance in cats, resulting in a defective erythropoiesis. In these cases an inappropriate presence of erythroid precursors in the peripheral blood may be noticed.

A guideline for the diagnosis of nonregenerative anemia must include a search for an inflammatory, infectious, endocrine, metabolic or neoplastic underlying disease, chronic blood loss and a bone marrow aspiration to search for immune-mediated destruction of erythroid progenitors, infiltrative or neoplastic bone marrow disease.

The treatment and prognosis of these conditions are closely related to the primary disease. The resolution of the primary condition can bring the animal to the normality, which is the case of anemia of inflammatory, disease and some infectious, endocrine and metabolic diseases. In some situation, drug therapy like erythropoietin replacement, iron supplementation, immunosuppressive or antineoplastic therapy may be necessary. In others, the only effective alternative would be a bone marrow transplant, but it is not an available procedure yet, due to, among other factors, the lack of a data bank to find a compatible donor.

In conclusion, the first step in the diagnosis of non regenerative anemia is to distinguish a truly nonregenerative from those with anemia of per acute onset. A follow up of the case and a complete history will answer this question. Recognizing the primary cause of severe, nonregenerative anemia is crucial, since many of them are treatable.
References: