Causes of nonregenerative anemia may be categorized by a mnemonic using the letter D: Detection, Delay, Destruction, Deficiency, Deep-Development-Dam, Diversion, Displacement, Depression, Dilution and Drugs. The categories are not mutually exclusive and anemia may be multifactorial in etiology. A pathophysiologic mechanism common to many of the causes is defective development of erythroid cells in the BM, which is reflected in a BM (BM) biopsy quantitatively as altered absolute and relative numbers of developing RBCs, and qualitatively as altered appearance of these cells (dysplasia). Cats with chronic anemia may develop reversible cardiomegaly and heart failure, multifocal retinal bleeding, and pica.

1. Detection of regeneration
Regeneration may not be detected because of clerical or laboratory errors. Polychromasia is not as intense using in-house quick stains, and experience is needed for accurate counting of reticulocytes using new methylene blue stain.

Mild regeneration may be difficult to detect when there is only low-grade hemolysis or hemorrhage, especially with a chronic problem because of adaptation to anemia. Counting of polychromatophilis is less precise than reticulocyte counting, and also mildly underestimates regeneration, so the latter is recommended to confirm poor regeneration. Increases in MCV and RDW are supportive of regeneration. It is also possible that a cat is not presented during an episode of acute anemia, and that the anemia is diagnosed after regeneration has abated. An increase in punctate reticulocytes will help identify a previous or ongoing regenerative response. BM biopsy may be necessary to examine for erythroid hyperplasia.

Many “nonregenerative” anemias are actually minimally regenerative, where a regenerative response is present, but is inappropriate for the degree of anemia. If it is not recognized, then complicating factors limiting erythropoiesis and contributing to the anemia may be overlooked. As anemia becomes more chronic and regeneration becomes less intense, it becomes more difficult to judge the adequacy of regeneration.

2. Delay in regeneration (preregenerative anemia)
A dog or cat with acute anemia may be presented before regeneration can be seen on a CBC. Because acute anemia is due to hemorrhage or hemolysis, other clinical signs will often help differentiate an acute preregenerative anemia from a chronic nonregenerative one. Although a dog or cat with a chronic nonregenerative anemia may present for acute clinical signs when the Hct falls below a critical level, most will have some chronic signs, unlike acute anemia, where peracute signs prompt rapid presentation by the owner. Causes in the cat where acute anemia itself is responsible for the presenting clinical signs include hemotropic mycoplasma infection and cytauxzoonosis. Less common causes include internal hemorrhage due to vitamin-k antagonist poisoning, and hemoabdomen due to bleeding tumours or peliosis hepatis.

Distinguishing acute pre-regenerative, from chronic non-regenerative, anemia, becomes more difficult as the anemia becomes less severe. Fortunately the clinical urgency also becomes less, and serial CBCs may be examined to observe for regeneration.

3. Destruction of bone marrow

Cytotoxic drugs and toxins
Cytotoxic drugs used to treat neoplasia and immune-mediated diseases kill mitotically active cells, thereby causing transient injury to BM progenitor cells. The result is predictable, dose-dependent, myeloid, megakaryocytic, and erythroid hypoplasia in the BN, and pancytopenia in the peripheral blood. The changes in peripheral blood are a reflection of mature cell lifespan: neutropenia appears prior to, and is more severe than, thrombocytopenia, which appears prior to, and is more severe than, anemia. Dogs and cats with cytotoxic BM suppression will be presented for lethargy and fever due to infection secondary to neutropenia. Anemia due to chemotherapy is usually mild in dogs, but cats may develop more severe anemia because of shorter RBC lifespan. The anemia is initially normocytic normochromic, but later some macrocytosis and anisocytosis may develop because of regeneration.

Unexplained transient BM suppression sometimes occurs - it is assumed that the BM received an unidentified toxic insult. If a BM biopsy is obtained during BM recovery, an exuberant response of progenitor cells, which occurs before the increase in mature BM and peripheral blood cells, may be mistaken for leukemia. Early myeloid hyperplasia is characterized by proliferation of normal blast cells, while myeloid leukemia is characterized by proliferation of mutant blast cells.4 Distinguishing the two is difficult, and serial CBCs and BM biopsies may be necessary to confirm a diagnosis.

Infectious diseases
Feline parvovirus damages intestinal crypt cells with resulting diarrhea and sepsis. The virus is also cytopathic to BM progenitor cells and may cause dysplasia. The salient hematologic findings are neutropenia and lymphopenia, but anemia may also occur, due to blood loss, malnutrition, and erythroid infection by the virus.
4. Deficiency of nutrients required for erythropoiesis
   Iron deficiency and other causes of microcytic hypochromic anemia
Portosystemic shunts may also cause microcytosis and hypochromia due to defects in iron metabolism, although changes are not as marked in cats as in dogs. Cats are usually presented for clinical signs of liver dysfunction and not anemia. Sideroblastic anemia is characterized by iron deposits in mature red cells in blood and in nucleated red cells in BM. It is a result of a defect in Hb synthesis and has been seen in cats with myelodysplastic syndrome (MDS).

   Folate and cobalamin deficiency
Metabolism of folate and cobalamin are intricately related, and deficiency of one or both may cause megaloblastic anemia by interfering with DNA synthesis. Naturally-occurring megaloblastic anemia in cats responding to folate and cobalamin supplementation has been reported infrequently. The anemia is normocytic-to-macrocytic. Serum levels of folate and/or cobalamin may be reduced with various gastrointestinal, pancreatic and hepatic disorders, and in hyperthyroidism. Anemia or macrocytosis are not common. Presumptive cobalamin deficiency resulting from a genetic disorder of intestinal malabsorption has been reported.

5. Development dam deep in the bone marrow
   Nonregenerative immune-mediated hemolytic anemia
Immune-mediated hemolytic anemia (IMHA), with peripheral destruction of RBCs and strong regeneration, is uncommon in cats. However, the immune attack on erythropoiesis may occur “deeper” in the BM instead of, or in addition to, the peripheral blood. This is the more frequent form of IMHA in cats. The attack may occur at several levels of erythropoiesis and act as a “dam” in the BM preventing maturation.

   Feline leukemia virus infection
FeLV is not cytopathic but infection of erythroid cells alters their development causing a normocytic normochromic or macrocytic anemia (pure red cell hypoplasia). FeLV-positive cats may also develop anemia secondary to hemotropic mycoplasma infections, hematopoietic and non-hematopoietic neoplasia, and possibly IMHA. Endogenous EPO levels are elevated and in principle rHuEPO therapy should not help, but there are anecdotal reports of benefit.

   Porphyria
Erythropoietic porphyria is a rare genetic defect in heme synthesis in which heme precursors accumulate in cells and body fluids, resulting in anemia and discolored teeth.

6. Diversion of hematopoietic cells
   Acute myeloid (myelogenous) leukemia (AML)
“Myeloid” leukemia refers to neoplasia arising from any hematopoietic cell in the BM. (The term “myeloid” in the context of leukemia is used to distinguish such leukemias from lymphoid ones, while in the context of normal hematopoiesis “myeloid” refers to granulocyte and monocyte cells as distinct from erythroid cells.) Hematopoiesis is diverted into production of neoplastic cells, decreasing normal cell production. Any AML may cause anemia, but the most profound tend to be with leukemias arising from erythropoiesis, i.e. erythroleukemia and erythremic myelosis. Cats are presented for inappetence and lethargy. The main physical examination finding in a cat with erythroid leukemia is pale mucous membranes. Petechiation may be present if there is concurrent thrombocytopenia. Fever may be present, especially if the cat is neutropenic. Leukemic cell infiltration may cause splenomegaly, hepatomegaly and lymphadenopathy, but the latter is not typically as marked as with lymphoma.

   A CBC may reveal many combinations of leukemic cells and low normal cell counts. It is important not to misinterpret the presence of nucleated red blood cells (rubricytes and metarubricytes) as a sign of regeneration. BM biopsy is needed for diagnosis if only anemia ± other cytopenias are present. If leukemic cells are present in the blood, BM biopsy is not strictly necessary but may further characterize the disorder. BM biopsy of a cat with erythremic myelosis will reveal marked erythroid hyperplasia with maturation arrest and erythrodysplasia. Following on the previous discussion of nonregenerative IMHA, it is difficult to distinguish malignant from non-malignant causes of erythroid hyperplasia with dyserythropoiesis. How may AML, which carries a poor prognosis, be distinguished from similar appearing nonregenerative IMHA, which carries a relatively good prognosis? First, a positive test for FeLV supports a diagnosis of AML. Second, the greater the percentage of blast cells in the BM the greater the likelihood of AML, but there is no specific cut-off value. Third, the greater the presence of abnormal cells on the CBC, the greater the likelihood of leukemia. Fourth, aspiration of enlarged spleen, liver or lymph nodes may reveal neoplastic cell infiltration. Fifth, concurrent immune-mediated disorders, and positive ANA or Coomb’s tests support nonregenerative IMHA. Finally, FeLV-negative AML is uncommon in cats. Because it is difficult to confirm a diagnosis of AML, and cats with this diagnosis are often euthanized, the clinician is strongly encouraged to treat for IMHA in an FeLV-negative cat.

   Myelodysplastic syndrome (MDS)
MDS is characterized by low blood cell counts but normal-to-increased BM cell counts, myelodysplasia, and a risk of progression to AML. It may also be caused by FeLV. The key problem is an abnormal clone of progenitor cells that may suppress, displace and progressively replace normal marrow cells. The hematologic and clinical pictures are highly variable, and it may be even more
difficult to distinguish MDS from a nonregenerative IMHA. There are also other causes of dysplastic changes in the marrow, and work-up should include investigation for infections, drugs, toxins, nutritional deficiencies and non-AML neoplasia. Treatment of MDS has historically relied on transfusions. If MDS is a differential diagnosis based on CBC and BM biopsy, but the cat is FeLV-negative, then as with AML, immunosuppression and observation of response is the most practical course.

7. Displacement of erythroid tissue (myelophthisis)

Erythroid cells may be crowded out by metastatic cancer cells, lymphoblasts, granulomatous inflammation (e.g. histoplasmosis), myelofibrosis, or osteopetrotic. As with other causes of generalized BM injury, neutropenia and thrombocytopenia may be more responsible for clinical signs than anemia. BM biopsy is diagnostic and usually lymphoid leukemia does not pose the same diagnostic dilemma as do AML and MDS.

Myelofibrosis is a non-specific finding: it may be idiopathic, the result of FeLV infection, chronic inflammation in the BM (including autoimmunity – it is a common finding in nonregenerative IMHA), secondary to a primary leukemia, or in some cases a primary tumour of BM stromal cells.13,19 Neutrophil and platelet numbers are often normal, and moderate-to-severe nonregenerative anemia is the salient finding. The anemia is typically normocytic normochronic. Idiopathic myelofibrosis is usually treated immunosuppression. Osteopetrosis may be a feature of FeLV subgroup C induced BM failure.15

8. Depression by disease (“anemia of chronic disease”)

Non-hematologic diseases depress erythropoiesis by various mechanisms. Diseases include infections, non-septic inflammation, neoplasia, liver diseases and chronic kidney disease. Some mechanisms of anemia are shared by the disorders, but there are enough differences in mechanisms and in onset of anemia that render “anemia of chronic disease” too broad a term.

Anemia of inflammatory disease (AID) and cancer-associated anemia

Anemia of inflammatory disease (AID) is caused by complex derangements of cytokines, which decrease EPO production and function, iron metabolism, and RBC lifespan. A key event is iron sequestration, which is believed to be an adaptive mechanism that makes it unavailable to infecting micro-organisms. These mechanisms are present in acute inflammation and Hb levels start decreasing in several days. In contrast to dogs, anemia may develop within 1 - 2 weeks in cats and become severe, in part because of the shorter red cell lifespan. The anemia is normocytic and normochromic. Serum iron should be low-normal to low, but in contrast to iron deficiency, AID is supported by documenting low-normal to decreased transferrin, and high-normal to elevated ferritin, although these changes are not always present. BM biopsy should reveal normal-to-mildly depressed erythropoiesis.

Cancer-related anemia is common in humans and is considered to be common in animals, but is not well-documented. The mechanisms of AID are involved in cancer-related anemia, and iron-sequestration in paraneoplastic AID may be protective. Correcting anemia with transfusion or rHuEPO improves quality of life, but the effect on tumour response, tumour progression, and overall patient survival in humans is not clear.21 The current recommendation in cats is to treat anemia in the oncology patient using the same transfusion triggers as with patients with non-neoplastic disorders. Treatment with rHuEPO has also been used for this purpose; It is not known if the risk for antibody formation is the same as with chronic kidney disease. Correcting anemia with transfusion or rHuEPO improves quality of life, but the effect on tumour response, tumour progression, and overall patient survival in humans is not clear.21 The current recommendation in cats is to treat anemia in the oncology patient using the same transfusion triggers as with patients with non-neoplastic disorders. Treatment with rHuEPO has also been used for this purpose; It is not known if the risk for antibody formation is the same as with chronic kidney disease.

Feline immunodeficiency virus (FIV)

Anemia was present in 36% of FIV-positive cats in one case series. Some of the anemias are due to secondary diseases including hemotropic mycoplasma infections and neoplasia, but anemia may occur without these. Anemia is likely due to alteration of the marrow inductive microenvironment and regulatory T-cells. Treatment with rHuEPO therapy may be beneficial, and with a low risk of anti-EPO antibody formation.

Chronic liver and kidney diseases

Mechanisms of anemia in liver diseases include AID, malnutrition, reduced RBC lifespan, and bleeding due to coagulopathy and hepatic rupture. Excluding a major bleed, the anemia is mild-to-moderate normocytic normochromic. Anemia in chronic renal failure is progressive and due to EPO deficiency (important mechanism), decreased RBC lifespan, and uremic bleeding. Benefits of EPO go beyond the correction of anemia, but side-effects may occur including aggravation of hypertension and red cell aplasia due to antibody formation. The risk for the latter is less with darbepoietin than erythropoietin. Currently the prognosis for acceptable correction of anemia is about 65%.

Critical illness

Anemia is common in critically ill cats because of repetitive blood sampling, surgery, AID, decreased red cell lifespan, and nutritional deficiencies. Transfusion has been associated with worse outcomes in humans in some situations; therefore rHuEPO is being used with increasing frequency. The current recommendation in cats is to transfuse using the same triggers as with anemia due to other causes, i.e. based on clinical status.
10. Drugs

Drugs may cause an idiosyncratic nonregenerative anemia, either by immunologic or toxic mechanisms.

References & suggested reading


