

# Feline Nonregenerative Anemia: Diagnosis and Treatment\*

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**Abstract:** Anemia in cats is not a diagnosis but rather a sign of an underlying disease. The diagnostic work-up for an anemic patient is often extensive, starting with classification of the anemia as regenerative or nonregenerative. Once nonregenerative anemia is diagnosed, a number of tests may be required to determine its cause, including a close examination of the patient's blood and bone marrow. Although there are standard supportive measures for anemic cats, specific therapies can be implemented for certain etiologies of nonregenerative anemia.

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\*A companion article, "Feline Nonregenerative Anemia: Pathophysiology and Etiologies," is also available on [CompendiumVet.com](http://CompendiumVet.com).

Because anemia has many potential causes, arriving at a definitive diagnosis often requires a series of diagnostic steps. First, a thorough patient history should be obtained (**BOXES 1 AND 2**). Second, a complete physical examination should be performed. Third, a blood sample should be taken for laboratory testing. A minimum database for all cases of anemia should include a complete blood cell count (CBC; i.e., red blood cell [RBC] indices, platelet count, reticulocyte count), a blood smear, a biochemistry profile, chest radiography, and abdominal ultrasonography. Additional diagnostic tests may be warranted, depending on the individual case (**BOX 3**).

## Diagnosis

### Clinical and Hematologic Manifestations

As RBC numbers and blood viscosity decrease, so does the resistance to blood flow in peripheral blood vessels. At the same

time, hypoxia causes peripheral vasodilation. As less oxygen is carried by the blood per unit, the rate of blood flow must be increased to ensure adequate oxygen delivery to tissues, and the heart rate increases in an attempt to boost cardiac output. Any

## BOX 2

### Products That Can Cause Nonregenerative Anemia

#### Estrogen

#### Antibiotics

- ▶ Sulfonamides
- ▶ Trimethoprim
- ▶ Chloramphenicol

#### Anticonvulsants

- ▶ Phenobarbital

#### Chemotherapeutic drugs

- ▶ Alkylating agents: cyclophosphamide, melphalan, busulfan, chlorambucil
- ▶ Antibiotics: doxorubicin, mitoxantrone, actinomycin D
- ▶ Antimetabolites: methotrexate, cytarabine
- ▶ Others: carboplatin, nitrosureas, hydroxyurea

#### Other

- ▶ Albendazole
- ▶ Propylthiouracil
- ▶ Methimazole
- ▶ Griseofulvin

## BOX 1

### History Considerations for Anemic Cats

- ▶ Indoor/outdoor status
- ▶ Exposure to medications or toxins
- ▶ FeLV/FIV status
- ▶ Dietary history
- ▶ Nature and duration of clinical signs
- ▶ Medical history
- ▶ Flea and tick exposure

subsequent rise in tissue demand for oxygen associated with activity may exceed the heart's ability to compensate, resulting in cardiac failure.<sup>1</sup> Other compensatory mechanisms include the redistribution of blood to the vital organs (e.g., heart, brain) and, in regenerative anemia, an increase in erythropoiesis.

The clinical signs associated with anemia include pale mucous membranes, weakness, collapse, lethargy, exercise intolerance, tachypnea, and tachycardia. Many of these are attributable to hypoxia. A systolic heart murmur may be appreciated on auscultation as a direct result of turbulent blood flow related to decreased blood viscosity. The severity of observed clinical signs may correlate with the duration of anemia; signs of acute anemia are typically more severe than those of chronic anemia (BOX 4).

A CBC with a reticulocyte count and blood smear can be helpful in determining the etiology of anemia. Most cases of nonregenerative anemia have normal RBC indices and

are normocytic and normochromic. However, microcytosis can occur with iron-deficiency anemia, and macrocytosis may accompany FeLV-induced anemia. In contrast, most cases of regenerative anemia are macrocytic and hypochromic due to the abundance of reticulocytes in circulation. Classification schemes for feline reticulocytes divide these cells into two or three types (BOX 5). Reticulocyte counts in cats may show a "false" increase due to elevated epinephrine levels if the cat struggles during the blood draw<sup>2</sup>; however, the aggregate reticulocyte count can be a fairly good indicator of the degree of bone marrow response to anemia when considered in conjunction with the hematocrit.<sup>3</sup> Blood smear analysis allows

## QuickNotes

**Healthy cats may not have visible iron stores in their bone marrow, but if iron deposits are identified on a bone marrow sample, iron deficiency can be ruled out as a cause of anemia.**

### BOX 3

## Diagnostic Testing for Anemic Cats

### Minimum database

- ▶ CBC
  - ▶ RBC indices
  - ▶ Reticulocyte count
  - ▶ Platelet count
  - ▶ Total plasma protein
  - ▶ Blood smear (RBC morphology, parasites, autoagglutination)
- ▶ Serum biochemical profile
- ▶ FeLV/FIV
- ▶ Urinalysis (presence of blood, bilirubin)
- ▶ Fecal analysis (presence of occult blood, gastrointestinal parasites)
- ▶ Thoracic radiography
- ▶ Abdominal ultrasonography
- ▶ Coagulation profile
- ▶ Body fluid analysis

### If nonregenerative:

- ▶ Bone marrow aspiration ± core biopsy
- ▶ Iron assays (serum iron, serum ferritin, total iron-binding capacity)
- ▶ Immune testing (Coombs test) if hemolysis is suspected

### BOX 4

## Clinical and Physical Findings in Anemic Cats

### Nonspecific findings

- ▶ Pale mucous membranes
- ▶ Weakness
- ▶ Exercise intolerance
- ▶ Collapse
- ▶ Lethargy
- ▶ Anorexia
- ▶ Tachycardia
- ▶ Systolic heart murmur
- ▶ Bounding femoral pulses
- ▶ Tachypnea

### Findings suggesting blood-loss anemia

- ▶ Melena or hematochezia
- ▶ Hematuria
- ▶ External bleeding
- ▶ Petechiation
- ▶ Ecchymoses
- ▶ Hematemesis
- ▶ Epistaxis
- ▶ Hemoabdomen
- ▶ Hemothorax
- ▶ Hemarthrosis
- ▶ Hyphema

### Findings suggesting hemolysis

- ▶ Icterus
- ▶ Bilirubinemia
- ▶ Bilirubinuria
- ▶ Fever
- ▶ Splenomegaly

identification of RBC morphologic abnormalities (e.g., Heinz bodies) and other indicators of oxidant damage, autoagglutination, methemoglobinemia, or blood parasites.

### Bone Marrow Evaluation

If the anemia appears to be nonregenerative based on the CBC and the lack of reticulocytes after at least 4 to 7 days of anemia, and the

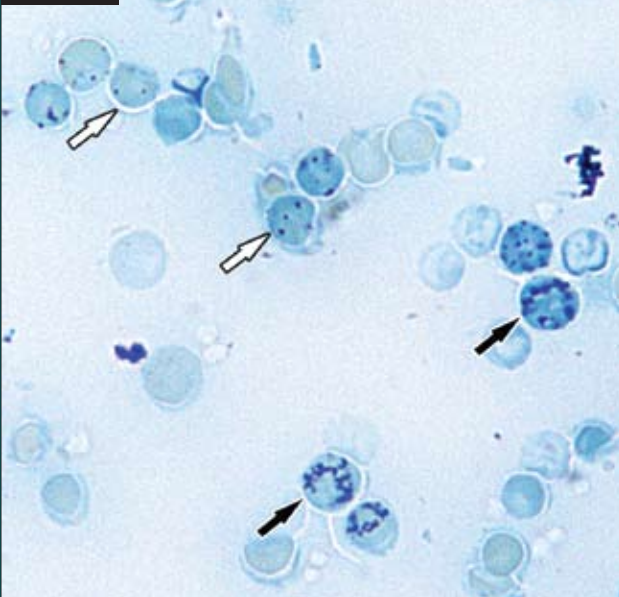
**BOX 5**

## Feline Reticulocytes and Reticulocyte Counts

Reticulocytes are immature RBCs in which hemoglobin is distributed over a larger volume. The two main types of reticulocytes in cats are differentiated by the amount of precipitate they contain (FIGURE A). Aggregate (class I) reticulocytes have linear aggregates of precipitate. They tend to be the largest and least mature of the circulating reticulocytes. Aggregate reticulocytes are polychromatophilic when treated with Romanowsky-type stain. They mature into punctate (class II) reticulocytes within 12 hours. Punctate reticulocytes have a smaller amount of RNA that appears as dots or granules, and they do not appear polychromatophilic with Romanowsky staining. They circulate for up to 10 days before all RNA is gone and they become mature RBCs.<sup>3</sup>

Certain classification schemes recognize a third class of feline reticulocytes (class III).<sup>a</sup> Class III reticulocytes are the most heavily reticulated of the three types. They have blue-green cytoplasm, with a heavy, dark blue granular network occupying a large portion of the cell on new methylene blue staining.<sup>b</sup> Class III reticulocytes are larger than mature RBCs; thus, their presence causes macrocytosis (increased mean corpuscular volume) and anisocytosis.

**FIGURE A**



**Photomicrograph of a cytologic preparation of blood from a cat with regenerative anemia. Note the punctate reticulocytes (white arrows) and aggregate reticulocytes (black arrows). (New methylene blue stain, 100x)**

In a healthy cat, reticulocytes require 2 to 3 days in the bone marrow to mature. They then enter the peripheral circulation via diapedesis through the sinusoids of the bone marrow. This process is stimulated by erythropoietin. If erythropoietin production and reticulocyte release are increased, as occurs with severe anemia or hypoxia, then the cells may be released prematurely into the circulation, sometimes with a few nucleated RBCs. These reticulocytes mature in the peripheral blood or in the spleen over the next 24 to 48 hours.<sup>c</sup>

Punctate reticulocyte counts are more difficult to interpret than aggregate reticulocyte counts, as concentrations may vary from 1% to 10% in nonanemic cats. Additionally, punctate reticulocytes can persist in the blood of cats with nonregenerative anemia for up to 4 weeks.<sup>d</sup> Many laboratories report only the aggregate reticulocytes as a percentage. The percentage of aggregate reticulocytes can be corrected for the degree of anemia using a formula extrapolated from humans:

$$\text{Corrected reticulocyte percentage} = \text{Reticulocyte percentage} \times \frac{\text{Hematocrit}}{35}$$

An absolute reticulocyte count can also be obtained:

$$\text{Absolute reticulocyte count} = \text{Reticulocyte percentage} \times \text{RBC count (RBCs} \times 10^6)$$

Ideally, the reticulocyte count should be conducted 4 to 7 days after the onset of anemia.

An absolute reticulocyte count exceeding 50,000/ $\mu$ L is considered to be evidence of regeneration.<sup>d</sup> A major increase in aggregate reticulocytes relative to a minor increase in punctate reticulocytes may indicate an early regenerative response (likely 3 to 6 days after the onset of anemia).<sup>e,f</sup> In contrast, a major increase in punctate reticulocytes relative to aggregate reticulocytes can indicate a later stage in the regenerative process (likely 9 to 20 days after the onset of anemia).<sup>g</sup>

<sup>a</sup>Clinkenbeard KD, Meinkoth JH. Normal hematology of the cat. In: Feldman BF, Zinkl JG, Jain NC, eds. *Schalm's Veterinary Hematology*. 6th ed. Philadelphia: Williams & Wilkins; 2000:1064-1068.

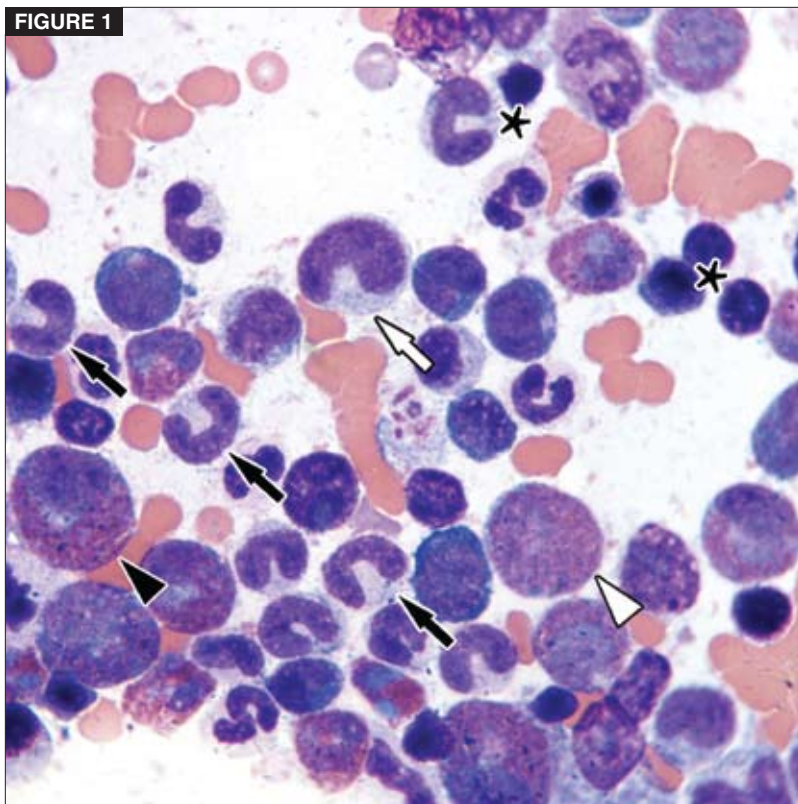
<sup>b</sup>Schalm OW. Normal values in blood morphology. In: Schalm OW, Jain NC, Carroll EJ, eds. *Schalm's Veterinary Hematology*. 3rd ed. Philadelphia: Lea & Febiger; 1975:113.

<sup>c</sup>Fernandez FR, Grindem CB. Reticulocyte response. In: Feldman BF, Zinkl JG, Jain NC, eds. *Schalm's Veterinary Hematology*. 5th ed. Philadelphia: Williams & Wilkins; 2000:110-113.

<sup>d</sup>Kociba GJ. Feline anemia. In: Kirk RW, ed. *Current Veterinary Therapy X: Small Animal Practice*. Philadelphia: WB Saunders; 1989:425-429.

<sup>e</sup>Tvedten H, Weiss DJ. Classification and laboratory evaluation of anemia. In: Feldman BF, Zinkl JG, Jain NC, eds. *Schalm's Veterinary Hematology*. 5th ed. Philadelphia: Williams & Wilkins; 2000:143-150.

<sup>f</sup>Dunn CDR, Legendre A. Humoral regulation of erythropoiesis in cats: preliminary report. *Am J Vet Res* 1980;41(5):779-780.



**FIGURE 1**  
Photomicrograph of a cytologic preparation of feline bone marrow showing erythroid hypoplasia and myeloid hyperplasia. Note the presence of large numbers of myeloid hematopoietic precursors, including myeloblasts (white arrowhead), promyelocytes (black arrowhead), metamyelocytes (white arrow), and bands (black arrows). A few erythroid hematopoietic precursor cells are present (asterisks). (Wright–Giemsa stain, 100x)

etiology of the anemia is not apparent based on an initial minimum database (BOX 3), then evaluation of the bone marrow is warranted. Bone marrow aspiration allows for examination of the activity of the erythroid, myeloid, and megakaryocyte series and can help to identify neoplastic cells or infectious organisms. Bone marrow cytology can aid in the diagnosis of primary bone marrow disorders such as erythroid hypoplasia, pure red cell aplasia, myelo-

dysplastic syndromes (MDS), aplastic anemia, and leukemia. A peripheral nonregenerative anemia may be accompanied by erythroid hypoplasia and relative myeloid hyperplasia in the bone marrow (FIGURE 1). Bone marrow examination for iron stores using Prussian blue or other staining may be helpful in ruling out iron deficiency as the cause of anemia (FIGURE 2). Healthy cats typically do not have visible iron stores in their bone marrow, so the absence of these stores is not diagnostic. However, if iron deposits are identified in the marrow, iron deficiency can be excluded.<sup>4</sup> Cats with anemia of inflammatory disease may have normal to increased bone marrow iron stores because macrophages of the bone marrow tend to sequester iron.<sup>5</sup>

If bone marrow aspiration yields a poorly cellular or nondiagnostic sample, a core biopsy may be beneficial. A core biopsy allows for improved evaluation of bone marrow cellularity, iron stores, and bone marrow stroma. This may be particularly helpful in the diagnosis of conditions that alter the stroma of the bone marrow, such as myelofibrosis.<sup>6</sup> A current CBC should always be reviewed in conjunction with bone marrow evaluation.

### Serum Iron Evaluation

Laboratory findings for patients with iron-deficiency anemia can closely resemble those for patients with anemia of inflammatory disease. An iron panel, which is used to evaluate iron levels and availability, can aid in making the distinction between these conditions (TABLE 1). Because processes other than iron deficiency can decrease iron values, a serum iron level is a nonspecific measurement. Total iron-binding capacity (TIBC) is a measure of serum transferrin content relative to iron content. The TIBC in a healthy cat is between 169 and 325 µg/dL.<sup>7</sup>

TABLE 1

### Hematologic Findings in Iron-Deficiency Anemia and Anemia of Inflammatory Disease

Measurement	Iron Deficiency	Anemia of Inflammatory Disease
Serum iron	Decreased	Decreased
Total iron-binding capacity	Normal to increased	Normal to increased
Percent saturation	Decreased	Normal to increased
Serum ferritin	Decreased	Normal to increased

The difference between serum iron levels and the TIBC indicates the unsaturated iron-binding capacity, or the amount of iron-binding capacity still remaining on transferrin. The normal unsaturated iron-binding capacity for cats is 105 to 205  $\mu\text{g}/\text{dL}$ .<sup>7</sup> The percentage of transferrin saturation can be calculated by dividing the serum iron value by the TIBC value.<sup>8</sup>

With iron deficiency, the TIBC is generally increased, while serum ferritin levels tend to be decreased. However, in addition to being an iron-binding protein, ferritin is also an acute-phase inflammatory protein. Thus, ferritin levels may be increased in conditions involving an inflammatory response, particularly in interleukin-1 production.<sup>9</sup>

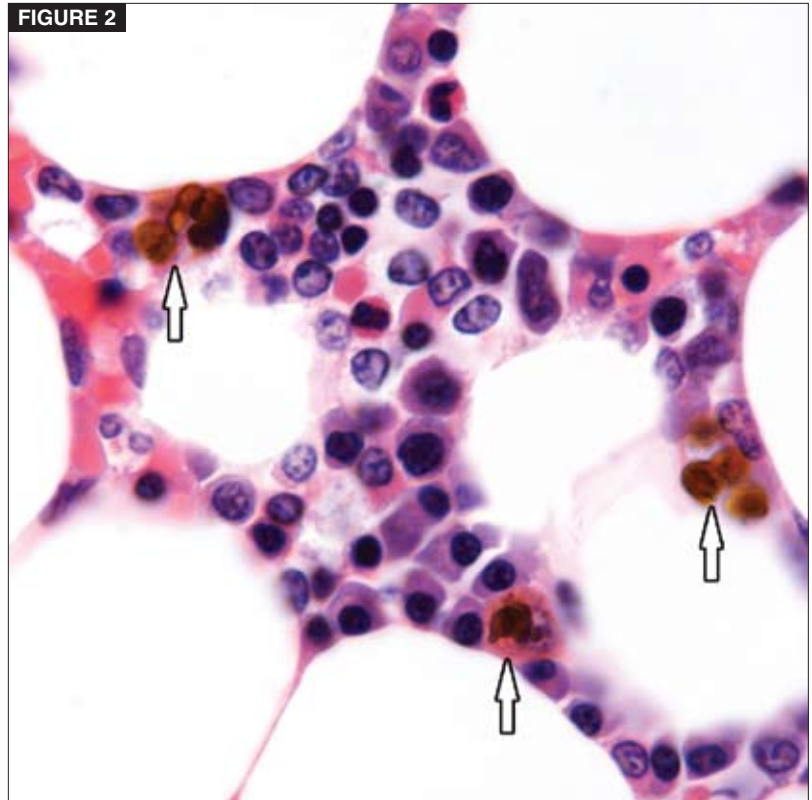
### Treatment

#### Transfusion

Currently, there is no established threshold hematocrit below which a cat requires a blood transfusion. Rather, the decision to transfuse an anemic patient is based on the hematocrit in conjunction with the clinical picture. Clinical signs such as tachycardia, tachypnea, poor pulse quality, lethargy, weakness, or pale mucous membranes may indicate that a transfusion is warranted. Results of two retrospective studies of blood transfusions in cats revealed that cats were most often transfused because of anemia as a result of blood loss, followed by erythropoietic failure (most commonly due to renal failure).<sup>10,11</sup>

Three naturally occurring blood types have been described in cats: A, B, and AB. Unlike dogs, the presence of natural isoantibodies is common. The prevalence of cats with type A blood is much greater than those with type B in the United States, and cats with type AB blood are rare. A survey of more than 9000 cats in the United States and Canada revealed that only 0.14% had type AB blood.<sup>12</sup> There is a higher frequency of type B blood, sometimes exceeding 50%, in some purebred cats, such as the Cornish rex, Devon rex, British shorthair, Abyssinian, and Himalayan.<sup>13</sup> Type AB blood has been found in breeds in which type B blood has been detected.<sup>12</sup>

Approximately 70% of all cats with type B blood have anti-A antibodies in amounts sufficient to cause an acute hemolytic or anaphylactic reaction to as little as 1 mL of type A blood.<sup>13</sup> In contrast, 35% of all cats with type



**FIGURE 2**  
**Photomicrograph of a histologic section of bone marrow from a cat with erythroid hyperplasia, indicating a regenerative response to anemia. Note the presence of increased stores of iron, represented by coarse clumps of golden-brown hemosiderin pigment within bone marrow macrophages (arrows). Although many healthy cats do not have visible iron stores in the bone marrow, the presence of these stores helps to exclude iron deficiency as a cause of anemia. (Hematoxylin–eosin stain, 100x)**

A blood have anti-B antibodies, but usually in low enough amounts that a transfusion of type B blood results only in reduced RBC survival time and minor transfusion reactions.<sup>13,14</sup> Cats with type AB blood are best transfused with type AB or type A blood.<sup>12</sup> Based on the potential for the presence of preformed antibodies, all donors and recipients should have their blood type confirmed before transfusion; it is not appropriate to administer a “test” dose of blood to determine compatibility.

Blood typing can be performed by a reference laboratory or in-house using a card typing system (Rapid Vet-H Feline blood-typing cards, DMS Laboratories). Ideally, both blood typing and crossmatching should be performed before a blood transfusion.<sup>15</sup> Blood typing alone may be adequate for a first transfusion. However, if at least 4 days have elapsed since a previous transfusion, crossmatching must be performed.<sup>16</sup> Crossmatching determines the

compatibility between the donor and recipient for the sample being transfused but does not predict the compatibility of future transfusions between the same donor and recipient.

Whole blood and packed RBCs (pRBCs) can both be used in the treatment of anemia. Whole blood contains RBCs, serum proteins, clotting factors, and platelets. Platelets are lost after 2 to 4 hours, and the function of factors V and VIII is lost after 24 hours.<sup>17</sup> Whole blood transfusions are generally indicated for anemia as a result of hemostatic disorders or with concurrent hypoproteinemia. The advantage of using pRBCs is that they provide the same degree of oxygen-carrying capacity as whole blood, but in a significantly smaller volume. Therefore, it is desirable to use pRBCs in normovolemic patients that are anemic from blood loss, hemolysis, or ineffective erythropoiesis.<sup>18</sup> If volume overload is a concern (e.g., patients with cardiac conditions), pRBCs are preferable. The life span of a normal transfused RBC is 21 to 48 days.<sup>17</sup>

All blood transfusions should be administered through a filter to remove particles and blood clots. The transfused blood should be run through a dedicated IV line or combined with 0.9% sodium chloride.<sup>17</sup> Blood can be given intravenously or intraosseously. The volume transfused depends on the size of the animal, the degree of anemia, and the overall clinical status. As a guideline, the administration of 20 mL/kg of whole blood or 10 mL/kg of pRBCs will raise the packed cell volume (PCV) by 10%, assuming that there is no ongoing hemorrhage or hemolysis.<sup>18,19</sup> The volume to be transfused can be calculated using the following equation<sup>17</sup>:

$$\text{Body weight (kg)} \times 70 \times \frac{(\text{Desired PCV} - \text{Recipient PCV})}{\text{Donor PCV}}$$

The donor PCV of pRBCs is 70% to 80%; for RBCs in nutritive medium, it is 50% to 60%.

All transfusions should be started slowly, at approximately 2 to 3 mL over the first 5 minutes, to watch for transfusion reactions.<sup>18</sup> The rate of transfusion thereafter depends on physiologic and hemodynamic factors. For a normovolemic animal, the rate of transfusion is 10 mL/kg/hr.<sup>15</sup> In cats with heart failure or cardiac disease, the infusion rate should not

exceed 2 to 4 mL/kg/hr.<sup>18</sup> In contrast, animals with hypovolemic anemia may tolerate receiving the transfusion as fast as it can be given. The entire transfusion should be completed in 4 hours to prevent bacterial contamination.

During blood transfusion, the patient should be closely monitored with frequent evaluation of attitude, vital signs, capillary refill time, and pulse quality. Any unexpected changes in these parameters could suggest a transfusion reaction. Transfusion reactions may be acute or delayed, as well as immunologic or nonimmunologic. The PCV should be checked 1 to 2 hours after the blood transfusion is complete.

The use of hemoglobin-based oxygen-carrying solutions (e.g., Oxyglobin, Biopure, Cambridge, MA) has been investigated as an alternative to blood products in anemic cats. Such solutions contain no RBCs, but rather rely on bovine hemoglobin polymers to transport oxygen and improve blood flow. They can be a valuable option for anemic cats in settings where feline blood is not readily available. However, these solutions do not affect the hematocrit, so if they are used, the patient's hemoglobin status must be monitored. Other advantages include a long shelf life (36 months) the elimination of blood typing and crossmatching. A disadvantage is a shorter half-life (days to weeks) in circulation.<sup>20</sup>

## Specific Etiologies

### *Inflammatory Disease*

Specific treatment for anemia of inflammatory disease is not necessary or helpful, and iron deficiency is not recommended.<sup>21</sup> If the underlying cause for the anemia is reversible, treatment of the condition will reverse the anemia.

### *Renal Disease*

Human recombinant erythropoietin (r-HuEPO) has become a common treatment choice for anemic patients with chronic renal disease. It is a genetically engineered protein that contains 165 amino acids. The administered product consists of r-HuEPO in 0.25% human serum albumin buffered by sodium citrate and sodium chloride.<sup>22</sup> The erythropoietin molecule is generally similar among species, allowing for cross-species biologic activity. r-HuEPO is not currently licensed for use in companion animals, so its use in veterinary patients is strictly extralabel. Although the most common indication for r-HuEPO is anemia associated

## QuickNotes

**An aggregate reticulocyte count of more than 50,000/ $\mu$ L generally indicates the presence of a regenerative anemia.**

with renal insufficiency, its use has also been studied for other causes of nonregenerative anemia, with varying results.<sup>23,24</sup> The use of r-HuEPO in cases of feline nonregenerative anemia unrelated to renal insufficiency needs further examination.

Anemia is a significant contributor to the morbidity associated with renal failure in cats. Because r-HuEPO administration is not without risk, its use in companion animals should be limited to cases in which anemia significantly affects quality of life. In many cats, this happens when the hematocrit level falls below 20%.

Anemia associated with renal insufficiency is usually nonregenerative, with a lack of peripheral reticulocytes and erythroid hypoplasia of the bone marrow. r-HuEPO acts on the bone marrow to stimulate RBC precursor proliferation and differentiation. The result is a decreased myeloid:erythroid (M:E) ratio and peripheral reticulocytosis. The clinical response may be slow, as it takes time for this process to occur in the bone marrow. However, once peripheral reticulocytosis is observed, the hematocrit may rise by 0.5% to 1% per day and may normalize within the first month. r-HuEPO does not seem to affect leukocyte production, but a transient increase in platelet count may be observed.<sup>25</sup>

The recommended dose of r-HuEPO is 100 U/kg SC three times weekly.<sup>22,26–28</sup> This is continued for the first 12 weeks of therapy, or until the lowest limit of the target hematocrit range is reached (30% to 40% in cats). The dosage should then be reduced to twice weekly, using the lowest possible maintenance dose. If polycythemia occurs, the dosage can be decreased to once weekly. If anemia persists at twice-weekly dosing, the dosage can be increased to three times weekly. If the patient is still anemic, the dose can be increased to 125 to 150 U/kg three times weekly. Although the maintenance dose must be individualized, dosages of 75 to 100 U/kg 2 to 3 times weekly are usually sufficient.<sup>22</sup> If the patient fails to respond or the response decreases, a thorough diagnostic work-up for other causes of anemia should be performed.

Reported adverse effects of r-HuEPO include the development of cross-reacting antibodies against the medication and, potentially, against endogenous erythropoietin. This development is associated with an acute onset of severe nonregenerative anemia. Bone marrow cytology

reveals an increased M:E ratio. Anti-r-HuEPO titer antibodies can be measured, which may aid in diagnosing this side effect.<sup>29</sup> This reaction has been detected in 20% to 50% of patients receiving therapy.<sup>22</sup> Antibody formation occurs with greater frequency in patients receiving higher doses of r-HuEPO, generally after at least 4 weeks of treatment. This condition is usually reversible after cessation of the drug and supportive care with blood transfusions, and patients generally return to pretreatment status.

Researchers have also looked at the use of recombinant feline erythropoietin in the treatment of cats with anemia resulting from chronic renal failure and red cell aplasia induced by r-HuEPO therapy. Their findings suggest that recombinant feline erythropoietin is effective at increasing hematocrits secondary to both conditions. However, some cats developed severe nonregenerative anemia, suggesting antibody formation to the feline-specific preparation.<sup>30</sup>

Another potential complication of r-HuEPO therapy is systemic hypertension. The patient's blood pressure should be measured before therapy is initiated and monitored throughout treatment. Hypertension is thought to result from increased peripheral vascular resistance caused by reversal of the vasodilatory state induced by anemia.<sup>25</sup>

The erythropoietic response to r-HuEPO causes a large amount of iron to be mobilized from tissue stores and can cause iron deficiency. Therefore, even if iron levels are normal before therapy, they should be monitored 3 to 4 weeks after initiation and monthly to bimonthly thereafter. Iron levels should be normal before starting treatment, and all patients should receive iron supplementation during therapy.

Seizures have been infrequently reported in patients with severe azotemia or hypertension that are receiving r-HuEPO. However, it is not certain whether this is a result of the underlying disease process or of drug therapy.<sup>25,29</sup> Although rare, hypersensitivity reactions to the drug at the administration site (e.g., inflammation, pain, discoloration) can occur.<sup>28</sup> Additionally, vomiting and uveitis following administration have been reported.<sup>29</sup> Although r-HuEPO may significantly improve the quality of life of patients with renal failure, these risks must be weighed against the benefit and discussed in detail with the owner.

### QuickNotes

**Between 20% and 50% of feline patients receiving human recombinant erythropoietin develop cross-reacting antibodies, resulting in a severe, nonregenerative anemia.**

### *Feline Leukemia Virus*

Cats that are anemic due to FeLV infection may present with nonspecific findings such as weight loss, fever, GI signs, or signs related to anemia or other cytopenias (if other cell lines are affected). Cats with FeLV may also have a regenerative, hemolytic anemia. In these cases, blood parasites, such as *Mycoplasma haemofelis* or “*Candidatus Mycoplasma haemominutum*” (previously named *Hemobartonella felis*),<sup>31</sup> or other causes of immune-mediated hemolytic anemia (IMHA) should be ruled out. Cats with FeLV may have an increased susceptibility to *M. haemofelis* or “*Candidatus Mycoplasma haemominutum*” infection and thus should be tested for these diseases.<sup>32</sup> Studies have shown that cyclic hematopoiesis may be observed in cats with FeLV.<sup>33,34</sup>

Treatment of anemia associated with FeLV infection involves supportive care, including blood transfusions, antibiotics in the presence of infectious disease, and immunosuppressive agents if immune-mediated hemolysis is a factor. Currently, no specific therapies have proved effective for treating FeLV, but protocols using antibody, immunomodulatory, and antiviral drugs are under study.<sup>35</sup>

### *Immune-Mediated Hemolytic Anemia*

The clinical signs associated with IMHA in cats are usually caused by the anemia and include weakness, lethargy, and inappetence. The onset of signs tends to be acute to subacute and may be triggered by a stressful event. Patients may also present with fever, hepatosplenomegaly, tachycardia, tachypnea, pale or icteric mucous membranes, and lymphadenopathy. Hemoglobinemia and hemoglobinuria are not observed due to extravascular hemolysis.

Laboratory findings in addition to anemia may include leukocytosis, lymphocytosis, hyperbilirubinemia, hyperglobulinemia, and increased liver enzyme values. Increased RBC osmotic fragility may also be seen.<sup>36</sup> Varying degrees of autoagglutination may be observed, but studies conflict as to the prevalence of this finding.<sup>36,37</sup> The Coombs test may have some use in diagnosing primary or secondary IMHA in cats but cannot be conducted if severe agglutination is present.

Treatment of cats with IMHA involves therapy for any underlying condition as well as immunosuppressive doses of glucocorticoids

(e.g., prednisolone, 2 to 4 mg/kg/day).<sup>36</sup> If there is a favorable response, indicated by a rise in the hematocrit and the reticulocyte count, the dose can be tapered slowly to prevent recurrence of hemolysis. Steroids are often combined with doxycycline to treat potential *Mycoplasma* infection. Cats that either do not respond to glucocorticoid therapy or experience relapse may require additional immunosuppressive medications, although the use of cytotoxic drugs needs further evaluation in feline IMHA patients.

Although the prognosis for cats with IMHA has been considered guarded, a recent study involving primary IMHA revealed a mortality of 23% (compared with 70% in dogs).<sup>34,38,39</sup> This may be because (unlike dogs) cats with IMHA rarely have thromboembolic complications.<sup>40</sup>

### *Pure Red Cell Aplasia*

Information regarding the treatment of primary pure red cell aplasia in cats comes from a study of nine cats with this disease.<sup>41</sup> These cats had severe normocytic, normochromic to hypochromic anemia; hematocrits ranging from 6% to 15%; and leukocyte and platelet counts within the normal reference range.<sup>40</sup> Six of the seven cats for which follow-up information was available responded to immunosuppressive therapies, as indicated by the appearance of reticulocytes in the bone marrow and a rise in hematocrit. The response was fairly rapid in most cases, ranging from 1.5 to 5 weeks. However, all cases required aggressive and prolonged treatment, and most needed a combination of prednisolone and another immunosuppressive agent (e.g., cyclophosphamide). Erythropoietin levels were measured in one cat and were found to be increased. r-HuEPO was administered in four cats and did not prove beneficial.

### *Myelodysplastic Syndromes*

The presenting signs of MDS (tachypnea due to anemia, recurrent infection due to leukopenia, abnormal primary hemostasis due to thrombocytopenia) tend to result from cytopenia. Enlargement of the spleen, liver, or lymph nodes may be seen in patients with a leukemic form of MDS.<sup>42</sup>

Although multiple cytopenias are common with MDS, it is possible for a single cell line to be decreased while other lines remain normal

## QuickNotes

**Iron-deficiency anemia can closely resemble anemia of inflammatory disease, necessitating a serum iron panel to help distinguish between the conditions.**



or increase. This usually occurs with the erythroid cell line, with anemia present in almost all cases of feline MDS. RBC abnormalities may include increased nucleated RBCs, megaloblastic rubricytes, nuclear fragmentation, abnormal nuclear shape, ringed sideroblasts, and circulating rubricytes without polychromasia.<sup>43</sup> Some patients have positive Coombs test results and autoagglutination.<sup>42,44</sup>

Bone marrow samples may be normocellular to hypercellular but can also be hypocellular or patchy, with morphologic abnormalities of cells in one or multiple cell lines.<sup>42,44</sup> Hemosiderin and increased numbers of small lymphocytes may be found in the bone marrow as well.<sup>42</sup> Core biopsy samples from the marrow may reveal myelonecrosis or fibrosis.<sup>44</sup>

Treatments for MDS involve symptomatic therapy, including blood transfusions in anemic patients and antibiotics in leukopenic patients. Prednisolone was given to cats with MDS in one study<sup>43</sup> and was found to be effective in five of 13 cats. The same researchers also tried chemotherapeutic agents, including cytarabine, cyclosporine A, vincristine, and daunorubicin, but no statistical advantage was described. Human MDS patients have found some benefit from combinations of r-HuEPO, recombinant granulocyte-colony-stimulating factor, and recombinant granulocyte-macrophage-colony-stimulating factor.<sup>23,42</sup>

The survival time in patients with MDS ranges from a few days to a few months after diagnosis. Although many factors are involved in the prognosis, high blast counts in the bone marrow and multiple, severe cytopenias tend to confer a shorter survival time and an increased incidence of progression to acute myelogenous leukemia.<sup>42</sup> However, some cats with MDS that present with less severe clinical signs can survive for 1 year or longer.<sup>44</sup>

### Infectious Diseases

**Mycoplasmosis.** Historically, diagnosis of *M. haemofelis* or “*Candidatus Mycoplasma haemominutum*” required demonstration of the organism in a blood or organ sample. This can be difficult, however, as parasites tend to be present in the blood in cycles, corresponding to parasitemic episodes. A polymerase chain reaction assay to detect infection is commercially available and has shown higher sensitivity and specificity than previous diagnostic

methods.<sup>31,45</sup> Many cats with clinical disease have a history of an abscess a few weeks before presentation.<sup>46</sup> This may act as a source of compromise and stress, allowing for an opportunistic infection to develop.

An increased relative risk of infection with *Mycoplasma* spp has been documented in FeLV-positive cats.<sup>32</sup> Additionally, cats coinfecting with FeLV and *Mycoplasma* spp have been found to develop a more severe anemia than cats infected with *Mycoplasma* spp alone.<sup>47</sup> It is possible that cats with *Mycoplasma* infection are more susceptible to FeLV infection, or FeLV may cause a latent *Mycoplasma* infection to progress to clinical disease.

Doxycycline is an effective antibiotic in the treatment of *Mycoplasma* infections; enrofloxacin can be used if doxycycline is not tolerated.<sup>48</sup> The recommended dose is 2.5 to 5 mg/kg twice daily for 21 days for doxycycline<sup>48,49</sup> and 5 mg/kg for 14 days for enrofloxacin.<sup>48</sup> Immunosuppressive agents are recommended if severe hemolytic anemia is present.<sup>46,49</sup>

Without therapy, 33% of cats with uncomplicated *Mycoplasma* infection die as a result of anemia. Survival rates are higher for cats that can mount an adequate immune response and develop a regenerative anemia.<sup>46</sup>

**Cytauxzoonosis.** Parasitemia results in a mild to moderate nonregenerative anemia as well as neutropenia, thrombocytopenia, and icterus that is often profound. Clinically infected cats often present with a fever that progresses to hypothermia.

Diagnosis of cytauxzoonosis requires demonstration of merozoites in RBCs (piroplasms) or of schizonts or merozoites in macrophages of the bone marrow, spleen, liver, or lymph nodes.<sup>48</sup> Because the tissue phase of infection precedes the erythrocytic phase, parasites may not be visible on a blood smear in cats with clinical disease.

Attempts to treat cytauxzoonosis have included supportive treatment with IV fluids, antibiotics to prevent sepsis, and heparin to prevent the onset of disseminated intravascular coagulation.<sup>50</sup> Although cytauxzoonosis is usually fatal in domestic cats, a recent study revealed that two of 34 cats with this disease survived.<sup>51</sup> One of the surviving cats was treated with imidocarb dipropionate, heparin, amoxicillin, and intravenous fluids, while the other cat was treated with ampicillin and subcutane-

ous fluids.<sup>51</sup> Another study reported that 18 cats survived natural infection with *C. felis*.<sup>52</sup> All cats were from a limited geographic area in northwestern Arkansas and northeastern Oklahoma, and four cats were asymptomatic. One of the surviving cats was treated with imidocarb dipropionate, and four cats received no treatment. These findings may suggest the existence of a less virulent strain of *C. felis*. The use of anti-protozoal drugs (e.g., imidocarb dipropionate, diminazene aceturate) is controversial, as these drugs have not been shown to improve patient survival and their use in cats is not approved by the US Food and Drug Administration.<sup>51</sup>

### Iron Deficiency

In treating iron-deficiency anemia, it is most important to identify and address any source of chronic blood loss. Iron replacement therapy provides sufficient iron to enable hemoglobin synthesis, correct the anemia, and replenish iron stores. Iron-deficiency anemia does not develop in animals until the body's iron stores have been depleted. Thus, when iron replacement therapy is initiated, iron is first used by the hematopoietic tissues to synthesize hemoglobin. Once there is adequate iron for erythropoiesis, the replacement iron is deposited into storage reservoirs.<sup>53</sup>

Iron should be administered as ferrous sulfate at 50 to 100 mg PO once daily.<sup>54</sup> The dosage

should be decreased by 50% once the hematocrit normalizes. If severe gastrointestinal disease (e.g., hemorrhage, malabsorption) is the cause of the iron deficiency, supplementation may be given parenterally until oral therapy can be tolerated. Iron dextran can be given at a dosage of 50 mg IM q 3–4 weeks.<sup>55</sup> Blood transfusions are rich in iron that is readily bioavailable, with 1 mL of blood containing 0.5 mg of iron.<sup>18</sup> However, this method of iron supplementation is only temporary, and the cause of the iron deficiency must still be addressed.

### Conclusion

In some cases of feline nonregenerative anemia, a diagnosis can be obtained early in the course of disease with few diagnostic tests. However, these patients more often follow a chronic course and require extensive testing. Treatment with blood products is necessary in some cases before a primary etiology can be determined. Despite the best efforts, some cases of feline nonregenerative anemia remain a diagnostic mystery. In these cases, the clinician must rely on supportive care and perhaps therapy for a presumptive diagnosis. **C**

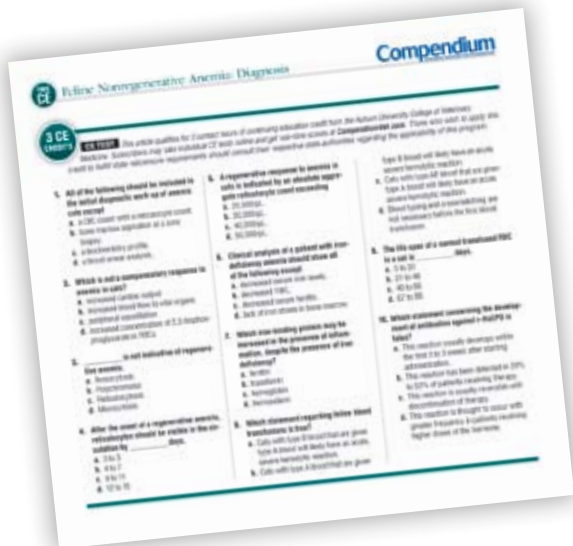
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# Feline Nonregenerative Anemia: Diagnosis and Treatment

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- All of the following should be included in the initial diagnostic work-up of anemic cats except**
  - a CBC count with a reticulocyte count.
  - bone marrow aspiration or a core biopsy.
  - a biochemistry profile.
  - a blood smear analysis.
- Which is not a compensatory response to anemia in cats?**
  - increased cardiac output
  - increased blood flow to vital organs
  - peripheral vasodilation
  - increased concentration of 2,3-bisphosphoglycerate in RBCs
- \_\_\_\_\_ is not indicative of regenerative anemia.**
  - Anisocytosis
  - Polychromasia
  - Reticulocytosis
  - Microcytosis
- After the onset of a regenerative anemia, reticulocytes should be visible in the circulation by \_\_\_\_\_ days.**
  - 0 to 3
  - 4 to 7
  - 8 to 11
  - 12 to 15
- A regenerative response to anemia in cats is indicated by an absolute aggregate reticulocyte count exceeding**
  - 20,000/ $\mu$ L.
  - 30,000/ $\mu$ L.
  - 40,000/ $\mu$ L.
  - 50,000/ $\mu$ L.
- Clinical analysis of a patient with iron-deficiency anemia should show all of the following except**
  - decreased serum iron levels.
  - decreased TIBC.
  - decreased serum ferritin.
  - lack of iron stores in bone marrow.
- Which iron-binding protein may be increased in the presence of inflammation, despite the presence of iron deficiency?**
  - ferritin
  - transferrin
  - hemoglobin
  - hemosiderin
- Which statement regarding feline blood transfusions is true?**
  - Cats with type B blood that are given type A blood will likely have an acute, severe hemolytic reaction.
  - Cats with type A blood that are given type B blood will likely have an acute, severe hemolytic reaction.
  - Cats with type AB blood that are given type A blood will likely have an acute, severe hemolytic reaction.
  - Blood typing and crossmatching are not necessary before the first blood transfusion.
- The life span of a normal transfused RBC in a cat is \_\_\_\_\_ days.**
  - 5 to 20
  - 21 to 48
  - 49 to 66
  - 67 to 88
- Which statement concerning the development of antibodies against r-HuEPO is false?**
  - This reaction usually develops within the first 2 to 3 weeks after starting administration.
  - This reaction has been detected in 20% to 50% of patients receiving therapy.
  - This reaction is usually reversible with discontinuation of therapy.
  - This reaction is thought to occur with greater frequency in patients receiving higher doses of the hormone.