Proceedings of the
World Small Animal Veterinary Association
Mexico City, Mexico – 2005

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BASIC APPROACH TO ANEMIA DIAGNOSIS

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Abstract

Anemia is very common among dogs and cats. All veterinarians should have a basic approach to diagnosing the causes of anemia. This approach will vary with each veterinarian’s situation. One approach is provided here. One first needs to document an anemia is present and determine how severe the anemia is. Then one determines if the bone marrow is functioning as expected or whether the bone marrow is the cause of the anemia. Anemia in which the bone marrow is functioning well (regenerative anemias) is caused by loss of erythrocytes from the body (external blood loss) or destruction of erythrocytes within the body (hemolytic anemia or internal blood loss). Erythrocyte morphology is important in diagnosis of regenerative anemia. Anemia with poor bone marrow function is termed nonregenerative and has many causes. Nonregenerative anemia is more difficult to diagnose and the approach varies with the pattern of presenting signs. Common causes of nonregenerative anemia are inflammation, renal or hepatic disease, endocrine disease and neoplasia. The more severe types of nonregenerative anemia may be caused by aplastic pancytopenia, myelodysplasia, leukemia, pure red cell aplasia and various infections.

Recommended Reading


Author's references

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Proceedings of the WSAVA Congress, Mexico City, Mexico 2005
Diagnostic Approach

One documents the presence and severity of an anemia with a hematocrit (Hct), hemoglobin concentration (Hgb) or erythrocyte count (RBC). Any one of these will usually be equally effective in showing an animal has anemia and how severe it is. Each test has advantages and disadvantages and exceptions occur where one will not be equally reflective of the severity of an anemia. The microhematocrit method is recommended because it is simple, consistent and reveals additional information such as the presence of icterus, hemolysis and lipemia in the plasma portion, which aid in diagnosis of hemolytic anemia. One may also determine plasma protein concentration in the plasma portion with a refractometer. Plasma protein in diagnosis of external blood loss is discussed later. Guidelines for classifying the severity of anemia with the hematocrit are given in Table 1.

Anemia is defined by a hematocrit (or hemoglobin concentration or RBC count) below the reference values for that species, age and even breed. Recall that reference intervals include a predicted 95 % of normal patients, so 5 % (one of 20 patients) will be outside the reference values, usually slightly outside those values. Thus one is more confident the animal has anemia if the patient's hematocrit is prominently under the lower value for hematocrit. Puppies have noticeably lower hematocrit than adult dogs (even under 30 %). This plus lower plasma protein concentration and slightly higher reticulocyte percentages can make a puppy's results look like a blood loss anemia compared to adult reference values. Breed values also vary with for example Greyhounds having a higher hematocrit (52-60 %) than "non-greyhounds". Saint Bernard dogs often have low hematocrit (35-40 %). Other factors such as hydration status and splenic contraction during fear can affect the hematocrit (and Hgb and RBC). Mistakes in performing lab tests do occur. Thus there are non-anemia type factors to consider, but Hct is usually effective in showing how anemic an animal is.

Moderate to severe anemia is more likely to be a primary or at least major problem, which one needs to solve. Mild anemia is often a secondary problem (such as anemia of inflammation), which is not life threatening and will likely resolve with correction of the primary problem such as treating an infection. Many mild anemias are nonregenerative anemias discussed later.

In diagnosis of the moderate to severe anemias, one determines if the bone marrow appears to be functioning (that is, producing RBC) as expected. In blood loss and hemolytic anemias one expects good evidence of bone marrow function. This erythropoiesis is called regeneration or responsive anemia. A reasonable increase in the absolute number of reticulocytes (more immature stage of the erythrocyte) is the usual evidence for a normal/expected increase in erythropoiesis. Table 2 gives guidelines for interpreting the degree of bone marrow activity based on reticulocyte numbers. Other factors to consider include the severity of anemia. A hematocrit of 30 % or more in a dog causes little tissue hypoxia and thus little stimulus on the bone marrow. So one expects little regeneration with an anemia with a hematocrit of 30 % compared to one with a hematocrit of 15 %. The maximum reticulocyte increase is expected about 4-6 days after onset of the hypoxic stimulus. No increase in reticulocytes is expected during the first 1-2 days after stimulus (preregenerative anemia) and reticulocyte numbers reduce to more normal numbers after 10-14 days, if the anemia does not worsen.

Feline reticulocytes need special criteria for evaluation because they may have very large numbers of a long-lived reticulocyte (punctate reticulocyte), which can greatly confuse diagnosis. Because punctate reticulocytes live quite longer (10-12 days) than the 1-2 days for canine reticulocytes, they can accumulate in large numbers in the blood despite that the bone marrow is not producing them as rapidly as their numbers suggest. Note in table 2 that if one had 200 x10^9/L feline reticulocytes (type not given), one could interpret this as no increase (if they were all punctate) or a maximal increase (if all were aggregate reticulocytes). Thus a reticulocyte report from a lab that does not indicate what type of reticulocyte they counted is worthless. Aggregate reticulocytes have many ribosomes ("reticulum"), look canine reticulocytes with an aggregate or
clump of ribosomes, and have a time span in blood more like canine reticulocytes. Punctate reticulocytes have few and individualized ribosomes that look like dots in the cell. Most labs require the cell to have more than 2 ribosomes to call it a reticulocyte. Punctate reticulocytes mature over 10-12 days and lose ribosomes (mRNA) with time. The peak aggregate reticulocyte response is about 4-6 days like the dog’s reticulocyte. The peak reticulocyte response is at 1-2 weeks after onset of an anemia.

If an anemia is adequately regenerative for the severity and duration of the anemia, then it is due to blood loss or hemolysis. Diagnosis of blood loss anemia is often helped by the history of trauma or bleeding. If bleeding is not obvious, because it is, for example, into the gut lumen, then plasma protein is helpful. In external blood loss one expects loss of plasma protein with blood loss to cause a low plasma protein or at least lower total protein than the mean value. Plasma protein is replaced faster than erythrocytes so anemia can be present without hypoproteinemia in external blood loss. Internal blood loss mimics hemolytic anemia because plasma protein is retained in the body so hypoproteinemia is not expected. Iron and other nutrients in hemoglobin are also retained so regeneration is on average greater with internal blood loss than external blood loss.

Regeneration varies with time through external blood loss. During the first 1-3 days after bleeding, there is not time for reticulocyte production so the pattern in the blood is nonregenerative (better called preregenerative) and is normocytic normochromic. At 4-7 days after bleeding, maximal reticulocyte release should cause a regenerative (macrocytic hypochromic) anemia. Chronic bleeding may cause iron deficiency anemia, which becomes increasingly less regenerative to nonregenerative and microcytic hypochromic.

Hemolytic anemia is often diagnosed best with a blood smear evaluation. Morphologic changes leading to diagnosis include spherocytes, autoagglutination, Heinz bodies, eccentricocytes and blood parasites. Other tests may be indicated based on the history and clinical picture. These include zinc, copper or phosphate concentration or tests for hereditary hemolytic anemias like pyruvate kinase deficiency or phosphofructokinase deficiency.

Nonregenerative anemia diagnosis is quite varied based on the clinical presentation. Anemia of chronic inflammation (ACI) is likely the most common cause. It is usually mild and is best ignored in animals with a disease with inflammation or neoplasia as the primary disease. Anemia in renal and hepatic failure is also a secondary problem that does not merit much diagnostic work or treatment unless the anemia becomes severe. Anemia in endocrine disease is often mild and diagnostic work and treatment is aimed at the endocrine disease.

Severe to moderate nonregenerative anemia should be evaluated. This often requires bone marrow evaluation and many types of diseases and patterns may be identified by bone marrow examination. Bone marrow problems include aplastic pancytopenia, pure red cell aplasia, myelodysplasia, neoplasia and dyserythropoiesis (ineffective hematopoiesis). A common and confusing pattern is that an animal can have low cell counts in 1, 2 or 3 cell lines (nonregenerative anemia; bicytopenia or pancytopenia) and yet have normal to increased erythroid cells, myeloid cells and/or megakaryocytes in the bone marrow.

Infections, medications and toxins commonly affect bone marrow function. Their effect may be seen as morphologic changes in the bone marrow or "hidden" effects where bone marrow morphology is normal and even more active, but effective release of cells into the blood is too low to maintain normal cell counts. FeLV and FIV viruses in cats are a first rule out. Ehrlichia canis, other rickettsial infections, Leishmania can cause cytopenias yet the bone marrow may have increased cell counts. Estrogen is a potent bone marrow toxin in the dog. Cytopenia in an animal being treated should warn the clinician to consider the drug as a cause of the reduced cell counts.

In summary, a low hematocrit (hemoglobin concentration or RBC count) has many causes. One should have a basic approach to diagnosis of anemia, which is effective in most situations to give a reasonable conclusion. The best diagnosticians have, however, an open mind and a flexible response to each situation. Enjoy each day we help our patients and their owners.
Table 1 Guidelines for Classification of Severity of Anemia

<table>
<thead>
<tr>
<th></th>
<th>Dog</th>
<th>Cat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>0.30-0.37*</td>
<td>0.20-0.26</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.20-0.29</td>
<td>0.14-0.19</td>
</tr>
<tr>
<td>Severe</td>
<td>0.13-0.19</td>
<td>0.10-0.13</td>
</tr>
<tr>
<td>Very Severe</td>
<td>&lt; 0.13</td>
<td>&lt; 0.10</td>
</tr>
</tbody>
</table>

* Values are Hematocrit or Packed Cell Volume in L/L.

TABLE 2. Reticulocyte Guidelines*

<table>
<thead>
<tr>
<th>DEGREE OF REGENERATION</th>
<th>CANINE RETICULOCYTES</th>
<th>FELINE AGGREGATE RETICULOCYTES</th>
<th>FELINE PUNCTATE RETICULOCYTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>60</td>
<td>&lt;15</td>
<td>&lt; 200</td>
</tr>
<tr>
<td>Slight</td>
<td>150</td>
<td>50</td>
<td>500</td>
</tr>
<tr>
<td>Moderate</td>
<td>300</td>
<td>100</td>
<td>1,000</td>
</tr>
<tr>
<td>Marked</td>
<td>&gt; 500</td>
<td>&gt; 200</td>
<td>1,500</td>
</tr>
</tbody>
</table>

*Cells reported in cells x10⁹/L

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