ANEMIA: Cause or Effect

Elizabeth Rozanski, DVM, DACVIM (SA-IM), DACVECC
Tufts University, North Grafton, MA

Anemia may be defined as a decreased red cell mass resulting in insufficient oxygen delivery to the tissues. It is a clinical finding, not a final diagnosis.

Anemias may be classified into regenerative, with increased red cell production to compensate for increased losses, and nonregenerative, with decreased production. In regenerative anemias, young enucleate red cells (reticulocytes) are released into the circulation in numbers, which correlate with the rate of effective erythropoiesis in the marrow. The reticulocyte count is the most important means for classification. Red cell morphology is expressed as macrocytic, normocytic, and microcytic with increased normal or decreased cell size (mean corpuscular volume, MCV), and normochromic or hypochromic with a normal or decreased hemoglobin level (mean corpuscular hemoglobin concentration, MCHC).

Regenerative anemia results when red cells are lost through hemorrhage or hemolysis. The marrow can expand its output up to ten times the normal rate, so that low-grade blood loss or hemolysis may be associated with reticulocytosis without anemia. Anemia results only when the rate of loss exceeds production.

KEY POINT- NRBC are not a marker of regeneration!

KEY POINT- Distinguish between normo and hypovolemic anemias.

BLOOD LOSS ANEMIA

Acute blood loss results in loss of both red cells and plasma, so the major problem is hypovolemia, and the hematocrit (Hct) remains normal initially. For this reason the Hct is not an accurate indicator of severity of ongoing bleeding. If fluid resuscitation is pursued, the PCV/TS will drop quickly.

Reticulocyte counts do not increase significantly for 3-4 days after acute blood loss.

Chronic blood loss results in depletion of red cells and iron with circulatory volume remaining normal. A microcytic, hypochromic anemia results but reticulocytosis usually persists. Occult blood loss may occur with blood sucking external parasites in pups or kittens or with intestinal loss from parasites, tumors or ulcers. Internal hemorrhage may be harder to detect. Some red cells will be reabsorbed and those that are damaged will give rise to a clinical picture more closely resembling hemolysis than hemorrhage. Iron is conserved so deficiency does not occur. Some causes of internal bleeding are trauma or tumors such as hemangiosarcomas. Coagulopathies can cause either internal or external blood loss. Platelet abnormalities cause petechiae or mucosal bleeding. Factor deficiencies are more likely to cause hematomas or bleeding into body cavities or joints.

HEMOLYTIC ANEMIA

Hemolytic anemia is associated with premature death of red cells and may be caused by a defect in the red cell itself (intrinsic) or by external factors acting upon the red cell (extrinsic). To understand hemolysis it is important to remember the normal mechanism of destruction of old red cells. The spleen is the major site of removal of senescent red cells and those with minor defects. The liver or bone marrow may also clear severely injured cells. Senescent red cells normally are phagocytized and hemoglobin is released. The heme is converted to bilirubin, iron, and globin. The iron is bound by transferrin and returned to the liver and marrow for storage. The globin is degraded to individual amino acids. Bilirubin is bound to albumin and transported to liver as unconjugated (indirect) bilirubin. In the liver bilirubin is dissociated from the albumin and conjugated to form bilirubin-diglucuronide. This complex is secreted

into the bile canaliculi. If it is not secreted (bile stasis), conjugated bilirubin (direct bilirubin) accumulates in the plasma. Some of the bilirubin in the intestine is reabsorbed into the enterohepatic circulation. A small amount will normally be excreted in the urine as urobilinogen, and the rest is re-excreted in the bile. When red cells are destroyed at a rate more rapid than normal, bilirubin can accumulate in the blood and cause icterus. Certain alterations occur in red cells, which predispose them to destruction. These are listed below:

Decreased surface area/volume ratio

Decreased surface area - loss of cell membrane, e.g. spherocytes.
Increased cytoplasmic volume, e.g. water intoxication.

Altered membrane structure

Decreased elasticity of membrane proteins e.g. decreased ATP (old cells).
Altered antigenic status - exposure of new "senescent antigens" causes cells to be coated with immunoglobulin and removed by the spleen.
Change in membrane lipids making cells rigid, e.g. liver disease.
Disruption of membrane integrity, e.g. lysis by complement, toxins, parasites, or trauma.
Oxidant Stress - Heme iron in the oxidized form (3^{+}) will not carry oxygen.
Oxidation will lead to methemoglobinemia and Heinz body formation - precipitates of denatured hemoglobin, which attach to the erythrocyte membrane, and are removed by the spleen leaving the cells more prone to lysis.

Hemolysis can occur in the intravascular space (intravascular hemolysis), or the red cells may be phagocytized by macrophages primarily in the spleen (extravascular hemolysis). Intravascular hemolysis is usually an acute, severe phenomenon. The free hemoglobin is bound to haptoglobin, an alpha- globulin, and any excess hemoglobin may be excreted intact in the urine. This can be detected by a red-brown color and a positive test for blood without intact red cells in the urine sediment. This is an important differentiation because urinary tract hemorrhage also gives a positive test. Urinalysis should be done soon after collection. Hemoglobinemia and hemoglobinuria are seen only with intravascular hemolysis. Icterus can occur with either intravascular or extravascular hemolysis.

Reticulocyte counts are higher after internal than external blood loss because of availability of iron. They are highest in hemolytic anemia, particularly intravascular hemolysis. The practical value in determining whether hemolysis is intravascular or extravascular is that diseases are more likely to be associated with one or the other. Knowing which is present may narrow a list of possible diagnosis. Intravascular hemolysis also tends to be more serious with decreased chance for recovery.

Changes in red cell morphology indicative of regenerative anemia include macrocytosis, anisocytosis, and polychromasia. Laboratory findings suggestive of hemolysis are spherocytosis, increased serum bilirubin concentration, and increased urinary urobilinogen or hemoglobin. The plasma may appear red from free hemoglobin.

Spherocytes are formed when the red cell membrane is partially phagocytized. If the cell escapes from the spleen, it repairs the defect but the lack of membrane causes the cell to lose its biconcave shape and become smaller and spherical. Cells become rigid and unable to squeeze through the microcirculation where they are destroyed. The spleen may remove some lesions or inclusions by pitting or plucking the abnormality from the cell and leave the cell intact. These cells are not removed as efficiently if the spleen has been removed or if it has been rendered ineffective in phagocytosis by adrenal corticosteroid administration. Increased numbers of nucleated red cells, Howell-Jolly bodies, or other red cell inclusions in the circulation may also follow splenectomy.

Immune Mediated Hemolysis (IMHA)

Premature loss of red cells by immune mediated destruction is one of the most common causes of severe anemia in the dog. It does occur in cats, but is less common. Immune reactions most commonly lead to extravascular hemolysis. Complement-mediated red cell lysis can also occur within the vasculature. When activated by interaction with immunoglobulin, complement produces small holes in the red cell membrane. Water then passes into the cell causing it to rupture intravascular hemolysis also results in the formation of vasoactive and chemotactic substances that can be harmful.

Monocytes and monocyte-derived tissue macrophages have been called reticuloendothelial (RE) cells, although they neither produce reticulum nor are derived from endothelial cells. These cells of the mononuclear phagocytic system are especially prevalent in the spleen, liver, lung and marrow. Macrophages process antigen, participate in the immune response, and by means of receptors for complement and the FC portion of IgG, they remove cells coated by antibody or complement.

The spleen is the primary site of removal of red cells that are coated with IgG, are abnormally shaped, or have decreased deformability. Splenic tissue from patients with IMHA contains increased numbers of lymphocytes and phagocytic cells, as well as trapped normal red cells and spherocytes. If the spleen is removed, the clearance of red cells coated by IgG or partially activated complement decreases, but the rate of intravascular hemolysis mediated by fully activated complement is unchanged. With increasing numbers of IgG molecules bound to the cell more complement activation occurs and the survival of sensitized red cells is progressively shortened. The clearance of IgM sensitized red cells occurs primarily in the liver and is entirely complement dependent.

Causes of IMHA – The causes are not well understood, but may be associated with other autoimmune disorders, or with other diseases, infectious agents, drugs or toxins. Abnormal helper T cell function and interactions between T cells and B cells have been suspected. Some humans may be genetically predisposed to develop IMHA as demonstrated by the association of autoimmune disorders with specific histocompatibility types. The antigens toward which the antibodies are directed are usually not specific to the patient, but are also present on red cells of normal individuals of the same species. With the decrease in normal immunologic function caused by aging, cancer or other disease mechanisms, self-reactive cells may be permitted to proliferate. A change in red cell membrane by an exogenous cause such as a virus might expose antigens that trigger IMHA. Increased antibody titers to viral antigens in some dogs with IMHA, and the occasional appearance of clinical disease shortly after vaccination with modified live viruses suggest that viruses may be implicated in some way in the etiology. Study results vary as to whether recent vaccination is a predisposing cause, or if a seasonal increase occurs in the summer and fall months. Infectious agents may share antigenic determinants with red cell membrane proteins and cause a cross reacting antibody response since normal red cells transfused into patients with IMHA are usually destroyed as quickly as the patient's own cells. The passive adherence of immune complexes to the red cell may also predispose the cell to hemolysis.

Coombs-positive hemolytic anemia has been seen in dogs with dirofilariasis, lymphoma, histiocytic sarcoma, and hemangiosarcoma implying an immune-mediated mechanism. Occasionally antibodies directed primarily against certain drugs may cause IMHA. In most cases, the antibody and drug complex are passively adhered to the red cell. This is a relatively common cause of IMHA in humans, but appears to be rare in dogs. Despite that, any medications being given to a dog that subsequently develops IMHA should be viewed with suspicion and stopped if possible.

Clinical and laboratory findings - Although either gender may be affected, most of the cases occur in middle aged females. A higher incidence has been reported in cocker spaniels and poodles, and in this author's experience, Lhasa apsos, Maltese, shih tzus, and Rottweilers.

When a dog is presented with signs of hemolytic anemia, a careful history must be taken so that causes of hemolysis other than IMHA are considered. Questions should address the following:

1. Travel to or living in areas endemic for such diseases as ehrlichiosis, anaplasmosis (formerly granulocytic ehrlichiosis), and babesiosis. [Risky areas like North Carolina ;)]
2. Recent exposure to modified live virus vaccines, drugs or toxins. Especially to be considered are antibiotics, such as cephalosporins, penicillins and trimethoprim-sulfa, zinc (ingestion of pennies), nonsteroidal anti-inflammatory drugs and onions.
3. Concurrent diseases such as hematopoietic (especially histiocytic) neoplasia, hemangiosarcoma, or splenic torsion.
4. Immunosuppression or prior splenectomy that could predispose to mycoplasmosis (formerly hemobartonellosis).
5. Hereditary causes such as pyruvate kinase deficiency in young dogs or phosphofructokinase deficiency in English springer spaniels should be considered.

The onset of anemia may be acute or gradual. Signs may be vague such as weakness, lethargy and anorexia, but if hemolysis is acute, fever, hemoglobinuria, icterus or vomiting may be present. Splenomegaly and mild lymphadenopathy are sometimes present. A minimum database should include a complete blood count (CBC) with platelet and reticulocyte counts, Coombs test, chemistry profile and urinalysis. A bone marrow aspirate does not routinely provide useful information, unless the anemia is non-regenerative. Abdominal radiographs can rule out metallic foreign bodies. Coagulation tests are indicated in severe cases.
Typical laboratory findings are autoagglutination, macrocytic, hypochromic or normochromic anemia, reticulocytosis, spherocytosis, anisocytosis, polychromasia, and leukocytosis with neutrophilia and sometimes a left shift. Thrombocytopenia is present in approximately two thirds of dogs with IMHA. Platelets can be decreased because of concurrent ITP or disseminated intravascular coagulation (DIC). Massive hemolysis, especially intravascular, can cause such a severe granulocyte and febrile response so as to be confused with an infection or leukemia. Circulating nucleated red cells may be present but are not an indicator of regenerative anemia. In fact, nucleated red cells in the absence of reticulocytosis are a negative prognostic sign and may indicate primary marrow disease. Anisocytosis and increased red cell distribution width (RDW) may be seen because of the presence of large reticulocytes and small spherocytes. The finding of spherocytosis strongly supports a diagnosis of IMHA even if the Coombs test is negative.

Not all dogs or cats with IMHA will have reticulocytosis. Those with a nonregenerative IMHA usually do not have spherocytosis or autoagglutination, and are Coombs-negative. In most cases, the clinical presentation is that of nonregenerative anemia with no clues in the blood as to the underlying cause. Those with a very acute onset of hemolysis (less than 3-4 days) may not yet show a response. In other cases, erythroid precursors may be destroyed in the marrow. An aspirate of the marrow may show maturation arrest at any stage. Erythrophagocytosis and an increase in plasma cells are seen in some cases. The myeloid to erythroid ratio may be increased, decreased or normal depending upon the stage of maturation that is affected. If very early precursors are destroyed, the appearance will be that of red cell aplasia.

The MCV may be falsely increased and the Hct falsely decreased if autoagglutination is present. The MCHC may be decreased if significant reticulocytosis is present, normal in some cases, or artifactually increased if hemoglobinemia is present. Spontaneous autoagglutination of red cells may occur when blood is placed in an EDTA tube or on a slide. Either antibody or increased rouleaux formation usually secondary to elevated serum protein levels can cause this. Rouleaux tend to disperse when the blood is diluted or washed in equal volumes of saline, whereas antibody-mediated agglutination remains. Autoagglutination is not caused by cold agglutinins but rather by high titers of warm antibodies, usually complement fixing IgG. Despite this, dogs with autoagglutination sometimes are Coombs-negative. Antibody may elute when cells are washed, or antibody may be more active at room temperature than at

37°C. The presence of autoagglutination in a dog with signs of hemolytic anemia can be considered to be diagnostic of IMHA; a Coombs test is not necessary.

Direct antiglobulin (Coombs) test - Approximately 70% of dogs with IMHA are Coombs-positive, meaning that antibody is detected on the red cell membrane. No correlation seems to exist between the strength of the reaction and the severity of clinical disease. The reagent is species-specific; thus laboratories routinely testing human blood cannot be used unless they have the correct reagent. Most standard canine reagents are pooled antisera directed against canine IgG, IgM and complement so that cells with either immunoglobulin and/or complement will be positive. The blood should be anticoagulated with EDTA.

Antibodies involved in canine IMHA are primarily IgG with varying degrees of complement fixation. In a Netherlands study, anemic dogs with only complement on red cells did not have hemolysis, but did have other underlying inflammatory, parasitic, granulomatous or malignant diseases. A positive Coombs test is not always associated with IMHA and the Coombs test may be negative in dogs that have signs compatible with IMHA.

Other tests - Increased alanine aminotransferase (ALT), hyperbilirubinemia, bilirubinuria, proteinuria, and hemoglobinuria may be present. Relative concentrations of conjugated (direct) and unconjugated (indirect) bilirubin are of little significance because they are so variable. The ALT may increase in anemic dogs from hypoxic damage to the liver. Abnormalities in coagulation tests such as thrombocytopenia, prolonged prothrombin (PT) and activated partial thromboplastin (APTT) times, decreased fibrinogen, and increased fibrin degradation products (FDP) are frequently present in dogs with severe hemolysis, even in the absence of clinical signs of hemorrhage. Thromboembolism and DIC are common complications of IMHA, and may significantly increase the morbidity and mortality. It may be difficult to determine if thrombocytopenia represents concurrent ITP or consumption by early DIC. A very low platelet count less than 40,000/ul is consistent with a diagnosis of ITP if other coagulation tests are normal, although mild to moderate thrombocytopenia may be the first abnormality that occurs in DIC.

Treatment - Canine IMHA varies from a relatively mild disease, which responds rapidly to corticosteroids to one that is rapidly fatal despite aggressive therapy. Most deaths occur within the first few days of illness, and are associated with renal, hepatic, or cardiac failure or pulmonary thromboembolism or DIC. Of dogs with fulminating disease, the mortality is probably 75-80%. Signs of fulminating disease include hemoglobinemia, hemoglobinuria, autoagglutination, severe icterus, or DIC. In one group of dogs treated at Tufts with IMHA severe enough to require transfusion, the survival rate was close to 70%.

The initial objective is to decrease the rate of destruction of red cells and allow recovery of the red cell mass. Corticosteroids are the first line treatment for most cases of IMHA. They increase red cell survival by decreasing FC receptors for IgG sensitized cells on monocytes, thus decreasing erythrophagocytosis. Corticosteroids are most effective in reducing clearance of IgG sensitized cells, moderately effective in the presence of IgG plus complement, and least effective in the presence of IgM and complement. In most cases initial treatment should consist of prednisone at a dose of 1 mg/kg twice daily. There is no evidence that higher doses of prednisone or dexamethasone are more effective, and in fact higher doses may increase the risk for thromboembolism. The initial dose is continued until the Hct begins to rise. Treatment is then continued at 2 mg/kg once daily in the morning for one to two weeks, and then decreased to 1 mg/kg daily for an additional one to two weeks. If improvement continues, treatment is then reduced to a maintenance dose of 1 mg/kg every other day, and eventually be tapered and discontinued. In some cases complete resolution of anemia can take weeks to months. So long as enough red cells are present for adequate tissue oxygenation (Hct > 20-25%), one can continue maintenance prednisone for 6-8 weeks before deciding that stronger immunosuppressive drugs are needed to obtain an adequate response. A change in the Coombs test from positive to negative during treatment is a favorable prognostic sign.

Cyclosporine is not myelosuppressive. It suppresses primarily cell-mediated immunity. Because absorption from the GI tract can be variable, blood levels should be monitored. Adverse effects include trembling, anorexia, vomiting, diarrhea, gingival hyperplasia, papillomatosis and hirsutism.

Mycophenolate mofetil inhibits purine synthesis and decreases antibody production. It has been used primarily in humans to prevent rejection of organ transplants, but anecdotal reports suggest efficacy in treatment of IMHA in dogs.

Human intravenous immunoglobulin (IVIG) is used to treat ITP and IMHA in humans that fail to respond to corticosteroids. The IVIG binds to and inactivates FC receptors on macrophages and also down regulates antibody production. At Tufts, IVIG was evaluated in a blinded randomized trial where prednisone alone was compared with prednisone plus IVIG. No added benefit of IVIG was found.

In addition to immunosuppressive drugs, intravenous fluids and transfusions are given as needed. Oxygen therapy is of minimal value since hemoglobin saturation is already maximal. What is needed is more hemoglobin. Although whole blood can be used, packed red cells are the preferred treatment for anemia. Transfusions should not be withheld for fear of worsening the hemolysis. Although the transfused cells may be destroyed by circulating autoantibody, they are no more likely to be destroyed than are the patient's own red cells, and the net result is that the transfusion provides at least temporary benefit. Concurrent immunosuppressive treatment may prolong survival of transfused cells. The volume of transfused red cells should be enough to alleviate clinical signs of hypoxia. If transfusion is withheld when signs of hypoxia are present, the risk of progressive damage to the heart, liver and kidneys increases. Ventricular arrhythmias, hepatic centrilobular necrosis and renal tubular necrosis can all be caused by hypoxia. The condition of the dog should determine the need for transfusion, rather than a specific Hct. Essentially, all dogs with IMHA should be transfused at a minimum Hct of 12-15%, but those in critical condition or with coexisting heart or lung disease will benefit from red cell transfusion in the 15-20% range. Typing and crossmatching can be difficult or impossible if autoagglutination is present in which case DEA 1.1-negative donors should be used. Bovine hemoglobin is sometimes used, because no RBC antigens are present, and red cell transfusion may be averted or at least delayed until immunosuppressive treatment has begun.

Integrity of the coagulation system should monitored periodically during the critical stage of illness. The finding of dyspnea that cannot be explained by pneumonia or cardiac disease should raise suspicion of pulmonary thromboembolism, which is a problem in approximately 30% of dogs with IMHA. Arterial blood gases show hypoxemia and normocapnea. Coagulation tests may be normal, although a thromboelastogram may detect a hypercoagulable state. Radiographs in anemic dogs with pulmonary thromboembolism show a pronounced interstitial pattern and slight pleural effusion. Even at necropsy the diagnosis is difficult to make because thrombi often spontaneously dissolve within a few hours of death. Prevention and treatment of DIC will be discussed later.

The nonregenerative form of IMHA usually has a more gradual onset than does the form associated with acute hemolysis. The response to treatment is also slower since erythroid precursors must mature before the Hct can rise. In nonregenerative IMHA both the patient's red cells and those transfused may survive longer, allowing time for response to treatment. The addition of azathioprine or cyclophosphamide may accelerate recovery in some dogs that do not respond to corticosteroids. The nonregenerative form of IMHA is an exception to the general rule that regenerative anemias have a better prognosis than non-regenerative anemias.

After the Hct has improved to a stable level, one may begin to taper medication slowly. Unless the cause is known and has been removed, the taper should continue with frequent checking of the Hct over several months. It may take weeks or even months for the Hct to return to normal, so patience is needed to stay the course and not jump to other treatments too quickly in the chronic phase of the disease. Signs may or may not recur after initial treatment.

Hemolytic Anemia from Other Causes

Toxins - Oxidant toxins cause hemolysis primarily in the cat, and less commonly in the dog. Heinz bodies and/or methemoglobinemia are the classic findings. These drugs or toxins include acetaminophen, methylene blue, benzocaine, lidocaine, propofol, hydroxyurea and propylene glycol. In addition to anemia, acetaminophen may cause hepatic necrosis in cats. Methemoglobinemia may be suspected initially if the mucous membranes become cyanotic and the blood appears brown when drawn. Treatment includes acetylcysteine to replenish glutathione, transfusions and supportive care. To be effective, treatment must be started within the first 24 hours after Ingestion of the toxin since its major effect is to replenish stores of reduced glutathione. Once oxidative damage has occurred, treatment is unlikely to reverse it. Cimetidine is also given in cases of acetaminophen toxicity to inhibit the cytochrome oxidase system which produces toxic byproducts.

Zinc toxicity is most commonly encountered in young dogs with zinc-containing foreign bodies (e.g. pennies) or from ingestion of zinc oxide ointments. Removal of the zinc usually results in recovery. Other drugs, vaccines, and ingestion of onions or garlic have been associated with hemolytic anemia. Signs usually resolve when the exposure is eliminated.

Infections - Babesiosis is endemic in parts of the southern US, and other tropical climates. Greyhounds are especially likely to be infected with *B canis* while pit bulls appear to be predisposed to *B. gibsoni.* Several species of *Mycoplasma* (formerly *Haemobartonella*) may cause hemolysis in cats and in splenectomized dogs. Ehrlichiosis may cause anemia by blood loss from thrombocytopenia, through hemolysis or through suppression of the marrow. Babesiosis can be treated with aromatic diamidines such as imidocarb. Doxycycline is the treatment of choice for mycoplasmosis and ehrlichiosis.

Other causes of hemolysis – In cases of microangiopathic anemia the cause must be removed. This includes manual removal of heartworms occluding the vena cava or splenectomy for splenic torsion or hemangiosarcoma. Severe hypophosphatemia, usually <2 mg/dl can cause hemolysis. This is seen most often in diabetic cats during initial treatment with insulin.

NONREGENERATIVE ANEMIA

Nonregenerative anemia results from decreased production of red cells which usually have a normal appearance and lifespan. This may be caused by an extramedullary cause such as renal failure or an infection such as feline leukemia virus or ehrlichiosis, or any chronic debilitating disease. The other major cause is primary marrow disease.

Chronic Renal Failure

Anemia occurs in dogs and cats with chronic renal failure because of decreased erythropoietin. Human recombinant erythropoietin has been used with some success in reversing the anemia when the Hct drops below 20-25% and other signs of uremia are minimal. Supplemental iron may be needed. The Hct begins to rise after 2-3 weeks, and when it reaches approximately 30%, the dose is reduced to once or twice weekly. The Hct must be monitored to prevent polycythemia.

Allergic reactions such as skin rash, fever, arthralgia, and mucocutaneous ulcers occur in some patients. Antibodies to both human and autologous erythropoietin may develop over time, and cause the Hct to fall abruptly. This occurs in 20-30% of treated cases, and treatment must be stopped.

Primary Bone Marrow Disease

If primary marrow failure is present, all hematopoietic cell lines are usually suppressed resulting in pancytopenia. Granulocytopenia and thrombocytopenia occur before anemia because red cells have the longest lifespan. Causes include idiopathic aplasia, fibrosis, or necrosis of the marrow or immune-

mediated destruction of stem cells. No specific treatment has been shown to be effective for primary marrow failure. Response to immunosuppressive drugs in a few dogs and cats suggests an immune-mediated cause. Hematopoietic growth factors have sometimes been advocated for short term benefit if the underlying cause is gone. Some animals will recover with supportive care. A syndrome of pancytopenia in young dogs has been recognized. Many of these dogs will recover eventually, either spontaneously or because of immunosuppressive treatment.

Drugs, such phenylbutazone, chloramphenicol or some chemotherapeutic drugs may suppress the marrow. Endogenous (e.g. Sertoli cell tumor) or exogenous (e.g. estradiol cyclopropionate) estrogen, or a toxin such as benzene are other possible causes of aplastic anemia. Marrow failure from hyperestrogenism may be irreversible. Rarely decreased folate or B_{12} levels secondary to chronic intestinal disease may cause anemia.

Myelodysplasia causes cytopenias because of abnormal maturation and cell death in the marrow. In dogs, myelodysplasia may occur secondary to hemotopoletic malignancy or immune mediated causes. If the underlying disease is treated, the myelodysplasia may resolve. In cats, myelodysplasia is more often a primary preleukemic disease. Erythropoietin has been transiently effective in raising the Hct in some of these cats. Acute leukemia can cause suppression of any or all normal hematopoietic cell lines because of inhibitory effects of infiltrating malignant blasts. These malignant cells may or may not appear in the blood. Acute myelogenous leukemia (AML) is rarely treated successfully in dogs and cats. Acute lymphoblastic leukemia (ALL) in dogs and cats sometimes responds to aggressive therapy.

Anemia of Chronic Disease

A mild nonregenerative anemia may occur with any chronic infection or debilitating disease. Cats, because of their normally short red cell lifespan are more at risk and the anemia more severe than in dogs. Anemia of chronic disease is associated with sequestration of adequate iron stores primarily in the marrow. The serum iron and total iron binding capacity may both be decreased. Iron supplementation is not necessary because the anemia resolves if the underlying disease improves.

OUTCOME AND SUMMARY

The prognosis for recovery in anemic animals varies with cause. In general the prognosis is better in regenerative than in nonregenerative anemias. Acute and chronic blood loss can be treated successfully if the cause is removed. Hemorrhage from coagulopathies varies as to prognosis.

Immune mediated hemolytic anemia may respond readily to immunosuppressive therapy, or the disease may be rapidly progressive and refractory to all therapy. Hemolysis from exogenous causes such as parasites and toxins has a relatively favorable prognosis after removal of the cause. Microangiopathic hemolysis is a sign of serious disease such as vascular tumor, splenic torsion, or DIC. The prognosis depends upon the underlying disease.

Nonregenerative anemias from infections, nutritional deficiencies, or secondary to toxins or treatable chronic diseases are most likely to be correctable. A systematic approach to the anemic patient will allow for proper classification, an accurate diagnosis, treatment, and prognosis.