

Hematology and Immune-Related Disorders

Edward Javinsky

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Blood and immune diseases are relatively common in cats and often caused by infectious agents. Many of the presenting signs are nonspecific, requiring a detailed and logical investigation into their cause. Understanding normal physiology is important in recognizing disease. This chapter covers some diagnostic techniques useful in evaluating cats with blood disease. Important, non-neoplastic blood and systemic immune dysfunction is discussed, with an emphasis on diagnosis and treatment. Specific immune disorders of the skin and joints are covered in Chapters 22 and 26, and neoplastic diseases are discussed in Chapter 28.

DIAGNOSTIC TECHNIQUES

Bone Marrow Collection

Bone marrow evaluation is an underutilized technique in veterinary medicine. Any veterinarian with the easily obtained proper supplies can collect bone marrow. For a diagnostic technique so full of potential rewards, the risks are minimal. As with any other diagnostic test, proper patient selection is important to avoid performing an unnecessary procedure.

Indications

Indications for obtaining a sample of bone marrow include the presence of an unexplained nonregenerative anemia, neutropenia, thrombocytopenia, or combination of cytopenias (Box 25-1). Bone marrow collection can be

used to stage neoplasia or determine the etiology of hypercalcemia or hypergammaglobulinemia that may be caused by lymphosarcoma or multiple myeloma. Although most healthy cats do not have visible iron stores in the bone marrow, the presence of iron here will eliminate iron deficiency as a cause of anemia.³⁴ Additional indications for collecting bone marrow include the inappropriate presence of immature hematopoietic cells in the circulation, unexplained leukocytosis or thrombocytosis, and dysplastic changes in the circulating blood cells. Routine evaluation of the bone marrow is not helpful in sorting out the causes of absolute erythrocytosis (polycythemia) because the erythroid morphology of the marrow appears the same in all cases (erythroid hyperplasia).⁴⁷

Contraindications

There are few contraindications for collecting a sample of bone marrow when it is warranted. Most of these relate to the severity of the cat's condition and its ability to tolerate sedation or general anesthesia. Hemorrhage as a result of the bone marrow collection is uncommon even in situations of severe thrombocytopenia. The veterinarian should not hesitate to collect bone marrow when it is indicated.

Equipment and Supplies

Most hospitals will have, or can easily obtain, the supplies required to collect a bone marrow sample. These supplies include a bone marrow biopsy needle, chemical restraint, surgical scrub, sterile fenestrated surgical

BOX 25-1**Indications for Sampling Bone Marrow****Abnormal Peripheral Blood Findings**

- Unexplained anemia, leukopenia, or thrombocytopenia
- Unexplained leukocytosis or thrombocytosis
- Myeloproliferative disease
- Lymphoproliferative disease
- Abnormal blood cell morphology
- Rubricytosis (increased nucleated erythrocytes) without polychromasia
- Neutrophilic left shift without inflammatory disease

Historical or Physical Findings

- Fever of unknown origin
- Occult disease
- Unexplained lymphadenopathy
- Drug toxicity
- Neoplasia

Therapeutic Monitoring

- Hematopoietic disorders
- Neoplasia

Abnormal Serum Biochemical Changes

- Unexplained hypercalcemia
- Monoclonal gammopathy
- Polyclonal gammopathy
- Proof of adequate iron stores (normal cats may have no identifiable stored iron)

drape, slides, anticoagulant, a 12-mL syringe, a dozen glass microscope slides, sterile gloves, and a scalpel blade. If a core biopsy will be performed, tissue fixative such as 10% formalin will be required. Local anesthesia will be used for patients in which chemical restraint is contraindicated. Other supplies that may be useful, but are not required, include pipettes and microhematocrit tubes.

Several types of bone marrow needles are available (Figure 25-1). An 18-gauge needle is an appropriate size for collecting marrow from a cat. The Jamshidi and Rosenthal needles are made of stainless steel and can be heat sterilized. The Illinois needle contains plastic and requires gas or cold sterilization. The presence of a stylet in the needle keeps the lumen from becoming plugged with a core of cortical bone at the beginning of the procedure. The stylet must be completely in place until the actual sample is collected, or a frustrating obstruction of the needle will occur. For hospitals without a bone marrow needle, an 18-gauge venipuncture needle may



FIGURE 25-1 Bone marrow biopsy needles. *Left to right*, Jamshidi disposable core-aspiration biopsy needle (11-gauge, 4 inches), stylet for the Jamshidi biopsy needle, Rosenthal reusable core-aspiration biopsy needle (16-gauge, 1½ inches), stylet for the Rosenthal needle.

be substituted. Because there is no stylet to keep the lumen open, an obstruction of the venipuncture needle is likely. This means a second needle will be needed, and dexterity will be required to find the hole in the cortical bone made by the first needle.

Bone marrow collection is a painful procedure. The struggling of an uncooperative and anxious patient makes collecting a diagnostic sample difficult. It may also be unethical to put a cat through unnecessary pain and anxiety when chemical restraint is available; trauma to assistants can also be avoided. If chemical restraint is not appropriate, a local anesthetic can be used to minimize the pain of passing the needle through the skin to the periosteum. Cortical bone itself has no pain receptors. Unfortunately, the endosteum cannot be anesthetized, and most of the pain of this procedure occurs when the endosteum is torn during sample collection.

Bone marrow clots readily when collected. The use of an anticoagulant is recommended so that there is no rush to process the sample after collection. A 2.5% solution of ethylenediaminetetraacetic acid (EDTA) can be made by injecting 0.35 mL of sterile saline into a 3-mL lavender-top EDTA blood collection tube. The contents are withdrawn and injected into a second EDTA tube.⁷¹ The resulting 0.5 mL volume is placed in a 12-mL syringe and should be adequate for preventing coagulation of the collected marrow sample.

Collection Sites

Bone marrow can be collected from one of three sites: the proximal humerus (Figure 25-2), the iliac crest, or the femur (Figure 25-3). The proximal humerus is easily accessible, has little overlying tissue, and offers a large

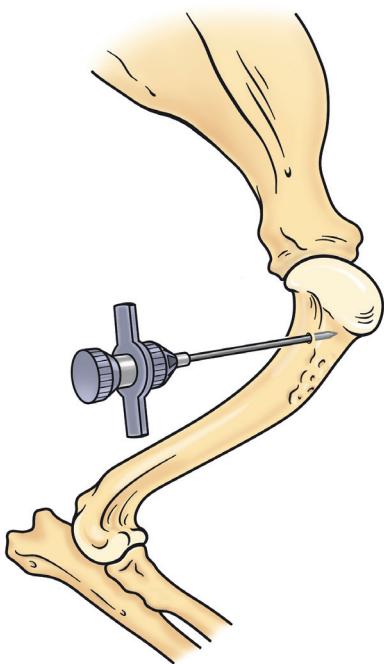


FIGURE 25-2 Bone marrow collection site from the proximal humerus. (Redrawn from Grindem CB: *Bone marrow biopsy and evaluation*, Vet Clin North Am 19:674, 1989.)

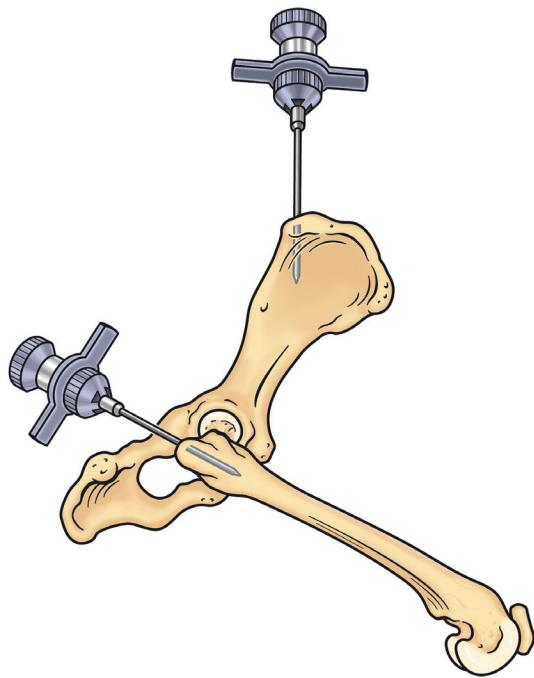


FIGURE 25-3 Bone marrow collection sites from the iliac crest and the proximal femur. (Redrawn from Grindem CB: *Bone marrow biopsy and evaluation*, Vet Clin North Am 19:673, 1989.)

surface for needle placement. The greater tubercle is palpated, and the needle inserted into the flat surface of the craniolateral humerus just distal to the tubercle. The needle is inserted in a craniomedial direction perpendicular to the long axis of the bone.

The iliac crest may be wide enough only in large cats and is difficult to palpate in obese patients. The needle is directed ventrally and slightly medially into the most dorsally palpable portion of the ilium, where the bone is widest. Occasionally, the needle will come to rest against the opposing cortical wall. If aspirating a sample from the iliac crest is difficult, the clinician should withdraw the needle slightly before concluding that the procedure is a failure.

The proximal femur is an easily accessed site for collecting marrow from cats. The greater trochanter is palpated and the needle inserted into the trochanteric fossa medial to the trochanter. The needle is directed parallel to the long axis of the femur. A potential, but uncommon, complication with using this site is damage to the sciatic nerve running medial and caudal to the greater trochanter. There should be plenty of room, however, to obtain the sample while leaving the nerve untouched.

Aspiration Biopsy

Before preparing the patient, the veterinarian should place all the materials in easy reach. A surgical tray is an excellent choice. Once the cat is anesthetized, it is placed in lateral recumbency with the side to be sampled facing up. The area is shaved, surgically prepared, and draped. While wearing sterile gloves, the veterinarian makes a small incision in the skin and superficial subcutaneous tissue. The incision need only be large enough for the needle to pass through. The veterinarian holds the needle between the thumb and middle finger with the index finger along the shaft for stabilization. The top of the stylet should rest against the palm of the hand so that it does not become displaced during the passage through the cortical bone. The grip is more like holding a screwdriver than a pen and allows for more force to be placed on the needle during the procedure. The veterinarian firmly holds the limb with one hand while advancing the needle through the incision down to the bone.

After ensuring the proper orientation of the needle, the veterinarian begins advancing through the cortical bone with firm clockwise and counterclockwise rotations while maintaining proper orientation. When the needle is properly placed, it will feel solidly seated. For example, if the veterinarian is collecting from the proximal femur, the cat's whole leg should move when the needle is fanned. If the seating does not feel proper or the needle slides down the side of the bone into the soft tissue, the veterinarian should withdraw it to the level of the cortical bone, reposition if necessary, and try again. When the needle is in the soft tissue, it is freely movable.

Once the needle is firmly in the bone, the stylet is removed. If an 18-gauge blood collection needle is being used, it should be removed and a second needle placed in the same hole in the cortical bone. The anticoagulated 12-mL syringe is placed on the end of the needle, and

the plunger of the syringe is pulled rigorously to aspirate the marrow. A sample may be obtained with the first aspiration, or several attempts may be required. If no marrow is aspirated, the stylet is replaced. If it does not go all the way in, there may be a bony plug at the end of the needle. If the stylet resumes its normal position, the veterinarian should continue advancing the needle for a short distance and try again.

Once a sample appears in the syringe, no more than 1 or 2 mL of marrow is required. The syringe is removed from the needle and rocked gently to mix the sample with the anticoagulant. The marrow is then expelled onto a glass microscope slide. It should look like blood with small particles in it. The slide is then tilted to allow blood to run off onto a paper towel. What remains on the slide are the whitish to gray bone marrow spicules. These can be collected with a pipette, a microhematocrit tube, or the end of another glass slide. The sample is transferred to a slide and covered with a second slide. The sample is allowed to spread a small amount, and then the two slides are rapidly but gently slid apart. Little, if any, pressure should be applied because this may damage the cells. If a sufficiently large sample is collected, about 12 slides should be made in this manner; if not, as many slides should be made as the sample allows. These slides should be air dried and submitted to the laboratory along with a sample of peripheral blood in a lavender-top tube. The interpretation of a bone marrow sample should always be made in the light of a complete blood cell count (CBC). If the patient suffers from severe thrombocytopenia, direct pressure should be applied to the wound once the needle is removed.

Aspiration of marrow allows for a cytologic evaluation, but architecture cannot be assessed. It is recommended to perform both an aspiration and a core biopsy of the bone marrow so that the procedure does not have to be repeated at a later date. A core biopsy is also recommended if there is a dry tap. Potential causes for a dry tap include myelofibrosis, myelophthisis, marrow necrosis or aplasia, and operator error. The only additional supply required for a core biopsy is tissue fixative. The veterinarian must remember to remove any cytology preparations away from the area when working with formalin. The fumes released when the vial is opened can fix the prepared slides, preventing proper staining of the cells.

Core Biopsy

If an aspiration of the bone marrow has been performed, the needle should still be in place. If not, the veterinarian should follow the instructions for performing an aspiration of bone marrow without aspirating any bone marrow. Collecting a core sample of bone marrow from a separate site may increase the likelihood of identifying metastatic neoplasia.⁷¹

Once the needle is seated firmly in the bone, or if it is still in place after aspiration, it is advanced another 1 to 1.5 cm, with the stylet removed, using the same rotational pressure as before. This maneuver should cut a core out of the marrow. At this point the needle need no longer be advanced. The core is broken off by several clockwise revolutions of the needle followed by several counterclockwise twists. The needle is withdrawn a short distance and advanced slightly again, this time at an angle slightly off axis. It should be twisted in both directions several times so that the bevel of the needle cuts the core off at the endosteum. The needle is removed by again rotating in both directions. The core sample should be gently pushed out of the top of the needle using the stylet. Bone marrow biopsy needles are tapered at the beveled end, and forcing the core sample through the tip will damage the sample. Once removed, the core can be rolled on a glass microscope slide for cytology if an aspirate has not been obtained. The veterinarian then places the sample into tissue fixative, remembering to remove any cytology preparations from the area before opening a jar of formalin to avoid having the fumes fix the cells on the slide. Direct pressure is placed on the wound to prevent hematoma formation in cats with severe thrombocytopenia.

With a little practice and the proper supplies, which all clinics can obtain easily, the cause of unexplained changes in circulating cells may be elucidated. More specific therapy may then be possible. Other than the risks involved with an anesthetic, there are few, if any, contraindications to the procedure.

Cross-Match

A crossmatch test can identify compatibility or incompatibility between the blood donor and transfusion recipient. It tests for the presence of alloantibodies, induced or naturally occurring, for which blood typing does not test. At the present time, typing for the *Mik* erythrocyte antigen is not readily available. Other, unknown erythrocyte antigens may be present and cause blood incompatibility. Because of the potential presence of unknown alloantibodies in feline blood, a cross-match should be performed before any transfusion, even if both donor and recipient are blood typed and a prior cross-match has indicated compatibility.

The major cross-match tests for alloantibodies in the plasma of the recipient that may hemolyze the donor's red cells. The minor cross-match tests for alloantibodies in the plasma of the donor that may attack the recipient's erythrocytes. Autoagglutination in the major cross-match predicts that antibodies in the recipient's plasma will attack the donor's red cells, likely eliciting a transfusion reaction. A minor cross-match incompatibility suggests that antibodies in the donor's blood will attack the

recipient's red cells. Incompatible blood should not be used for transfusions.

A quick means of performing a major cross-match is to mix 2 drops of plasma from the recipient with 1 drop of anticoagulated blood from the donor on a slide at room temperature.³⁵ The opposite will be a minor cross-match. Development of macroscopic agglutination within a minute suggests the presence of anti-A alloantibodies in the plasma sample of the recipient (major cross-match) or donor (minor cross-match). In either case the blood is incompatible. Autoagglutination can make interpretation of the test difficult. Running a control test using saline instead of plasma may help with interpretation.

For hospitals performing frequent transfusions, a standardized gel agglutination test is available for in-hospital use. Although more time consuming than the previously described method, the gel test is less vulnerable to operator interpretation error. Because it is stable, the test result can be saved and reviewed at a later time if needed.¹¹⁸ Two commercially available products include the DiaMed-ID cross-match gel (DiaMed, Switzerland) and the Rapid Vet-H companion animal cross-match gel (DMS Laboratories, Flemington, New Jersey). More rigorous and time-consuming methods involving washing, centrifuging, and incubating samples have been published.^{25,42}

Slide Agglutination Test

A positive, properly performed slide agglutination test suggests the presence of antibody-coated erythrocytes and negates the need for performing a direct Coombs' test. It is important to differentiate erythrocyte clumping caused by autoagglutination from that caused by rouleaux formation. These types of erythrocyte clumping are differentiated by washing the cells with saline, which will reliably break up clumps formed by rouleaux. A quick method of performing the test is to mix a drop of EDTA anticoagulated blood on a slide with 2 to 5 drops of 0.9% NaCl followed by a gross and microscopic examination of the sample.⁵⁴ The "stacked coins" appearance characteristic of rouleaux formation (Figure 25-4) will disperse, whereas the random or rosette clumping of autoagglutination will not (Figure 25-5). If the test is negative, a direct Coombs' test should be requested. An important limitation to this test is its inability to separate primary from secondary immune-mediated disease.

ERYTHROCYTE PHYSIOLOGY AND DIAGNOSTIC EVALUATION

The erythrocyte is a unique cell with a singular function: to carry oxygen to the tissues. Decreased numbers of red blood cells results in decreased tissue oxygenation;

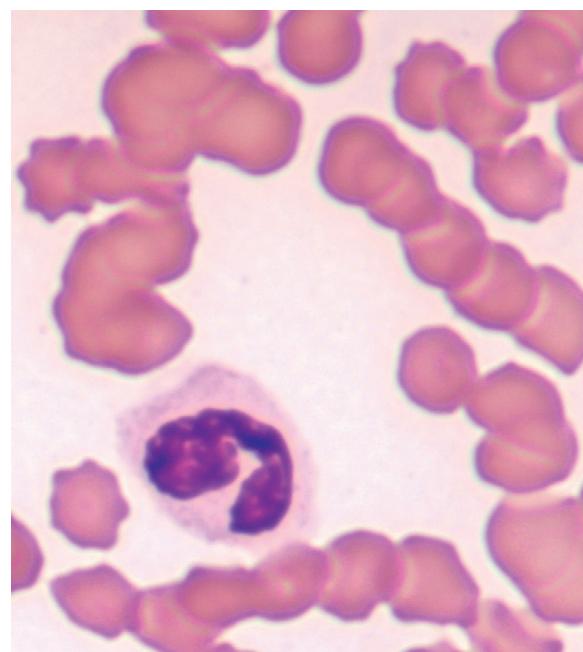


FIGURE 25-4 The "stack of coins" arrangement associated with rouleaux formation. (Courtesy Rick Cowell.)

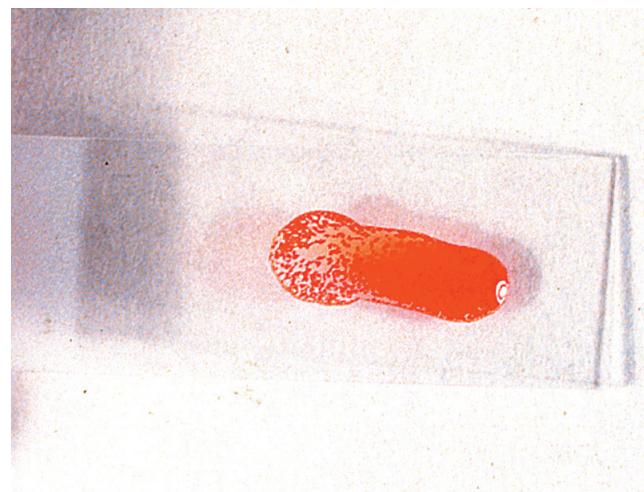


FIGURE 25-5 Macroscopic agglutination is apparent on the slide. If clumping remains after proper washing, autoagglutination would be the conclusion. (From Fry MM, McGavin MD: Bone marrow, blood cells, and lymphatic system. In McGavin MD, Zachary JF, editors: Pathologic basis of veterinary disease, ed 4, St Louis, 2007, Mosby.)

however, an excessive number of erythrocytes make blood more viscous, potentially resulting in less than optimal oxygenation. Changes in the visual appearance of erythrocytes yield clues as to the underlying disease. A change in red blood cell numbers is a sign of disease, not a disease itself. Therefore a change in erythrocyte numbers or appearance requires investigation of the etiology.

The production of erythrocytes by the bone marrow is influenced by the hormone erythropoietin (EPO),

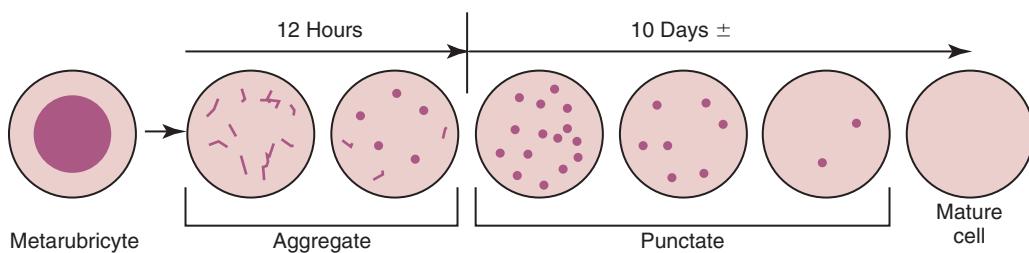


FIGURE 25-6 Diagram depicting the progressive maturation of feline reticulocytes. Aggregate reticulocytes lose their inclusions and mature into punctate reticulocytes in approximately 12 hours. The punctate reticulocytes slowly lose their inclusions over a period of around 10 days. (From Weiser MG: Disorders of erythrocytes and erythropoiesis. In Sherding RG, editor: The cat: diseases and clinical management, ed 2, Philadelphia, 1994, Saunders.)

which is produced by fibroblasts adjacent to the renal tubules near the corticomedullary junction in response to decreased local oxygen tension.¹²⁹ Increased EPO production begins within minutes of onset of hypoxia, with maximal production occurring 24 hours later. Colony-forming-unit erythrocytes in the bone marrow respond to increased concentrations of EPO by increasing production, maturation, and release into circulation of new red cells. Increasing numbers of new circulating erythrocytes will not be apparent for at least 2 or 3 days.

When hypoxia is caused by anemia, immature erythrocytes are released early to the circulation. The immaturity of the released cells is proportional to the severity of the anemia. Reticulocytes are immature erythrocytes that still contain ribosomes, are larger than mature red cells, and have lower concentrations of hemoglobin. The ribosomes stain a bluish color, giving reticulocytes their characteristic blue-gray color. Their presence in circulation is responsible for the variation in cell size and color observed on a blood smear examination in regenerative anemias.

Two types of feline reticulocytes are recognized: aggregate and punctate. Aggregate reticulocytes have long, linear chains of ribosomes; are larger and bluer than mature red cells; and are the less mature of the two types of reticulocytes. The ribosomes appear dark blue after staining with new methylene blue. Most of the ribosomes are removed within 12 hours as the cell matures into a punctate reticulocyte. Punctate reticulocytes have a few small dots representing the remaining ribosomes and are the color of a mature red cell. It takes up to 10 to 14 days for the remaining ribosomes to be removed and the cell to become a mature erythrocyte. Some punctate reticulocytes are present in healthy cats, and punctate reticulocytes may be present in the circulation for up to 1 month after an anemic event.

It is important to realize that these two types of reticulocytes are not different cells but rather a progression in the maturation of the erythrocyte (Figure 25-6). As the anemia becomes more severe, younger reticulocytes are released in an attempt to increase the number of oxygen-carrying red cells. The result is an increase in the number of aggregate reticulocytes in the circulation. Because

they mature so quickly to punctate reticulocytes, the presence of increased numbers of circulating aggregate reticulocytes suggests ongoing hypoxia. An important concept regarding feline anemia is that an increase in the numbers of aggregate reticulocytes (above the reference range for the laboratory) is required before a moderate to severe anemia is considered regenerative. Unless the anemia is mild, and the more immature aggregate reticulocytes are not required, the presence of punctate reticulocytes alone is not evidence of regeneration. In cats the absolute number of aggregate reticulocytes is a more reliable indicator of regeneration than the corrected reticulocyte percentage or the reticulocyte production index.⁵⁴

EPO also stimulates hemoglobin synthesis. Feline hemoglobin is unique in that it has less affinity for oxygen than the hemoglobin found in other species; consequently, oxygen is more easily released to the tissues. This may be one explanation for why the packed cell volume (PCV) and hemoglobin concentration in the normal cat are lower than those of normal dogs.⁵⁴ In a healthy cat the production and removal of erythrocytes is balanced. The life span of the normal, mature feline erythrocyte is approximately 73 days, after which they are removed from circulation by macrophages in the spleen, and the heme and iron recycled.

Quantitative Erythrocyte Parameters

Erythrocytes can be classified by their size and hemoglobin concentration on the basis of quantitative parameters such as the mean corpuscular volume (MCV, the average cell size), the red cell distribution width (RDW), and the mean corpuscular hemoglobin concentration (MCHC). *Macrocytosis*, *normocytosis*, and *microcytosis* refer to cell size above, within, or below the reference range, respectively. The RDW is derived from the cell numbers versus cell volume histogram (Figure 25-7); an increase in RDW indicates a greater than normal variation in cell size. The RDW may be artificially affected by the overlap in size between feline platelets and red cells. *Normochromia* and *hypochromia* refer to MCHC within or below the reference range, respectively. Hemoglobin makes up

approximately 33% of the volume of the cell. Erythrocytes cannot carry more hemoglobin in their cytoplasm than normal, so they cannot be hyperchromic. An increased MCHC is usually associated with hemolysis, either a result of disease or of improper venipuncture or sample handling. A change in any of these parameters requires a review of a blood smear for an explanation.¹²⁶

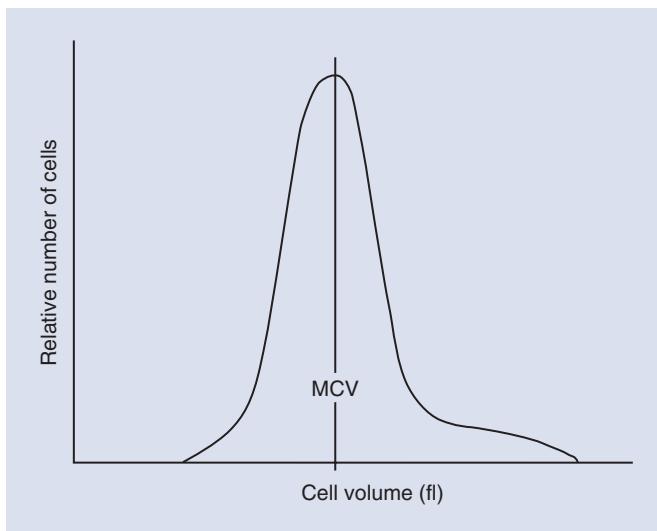


FIGURE 25-7 The erythrocyte volume distribution histogram. The mean cell volume is represented by the vertical bar. Increased variation in cell volume (anisocytosis) causes the curve to widen, increasing the red cell distribution width (RDW). (From Weiser MG: Disorders of erythrocytes and erythropoiesis. In Shering RG, editor: The cat: diseases and clinical management, ed 2, Philadelphia, 1994, Saunders.)

Qualitative Erythrocyte Parameters

Qualitative erythrocyte parameters are based on a blood smear evaluation. Increased variations in cell size, color, and shape are known as *anisocytosis*, *polychromasia*, and *poikilocytosis*, respectively. Anisocytosis is present if there is a combination of normal-size cells along with an appreciable number of larger or smaller cells. Anisocytosis may result in an increased RDW. The larger cells are often reticulocytes, although infection with the feline leukemia virus (FeLV) can result in larger cells without increased reticulocyte numbers. Polychromasia is usually due to the presence of increased numbers of aggregate reticulocytes and indicates regeneration.¹²⁶ Lack of polychromasia, however, does not rule out regeneration.¹⁸ Variations in cell shape may be artifactual or due to disease (Figure 25-8). Echinocytes are crenated red cells with uniform, often pointy, projections. They are usually artifacts but are important to recognize; when the projections are viewed end on, they may appear as small rings and mimic the ring form of hemoplasmosis (e.g., *Mycoplasma haemofelis*). Acanthocytes are similar to echinocytes but have fewer and more rounded projections. They are frequently present in cats with hepatic disease. Erythrocyte fragments, such as schistocytes or keratocytes, are the result of cell trauma. When there are many fragments, the presence of turbulent blood flow or microangiopathic disorders such as hemangiosarcoma or disseminated intravascular coagulation (DIC) should be considered. Iron deficiency may also cause increased fragmentation.¹⁸ Spherocytes are smaller cells that are

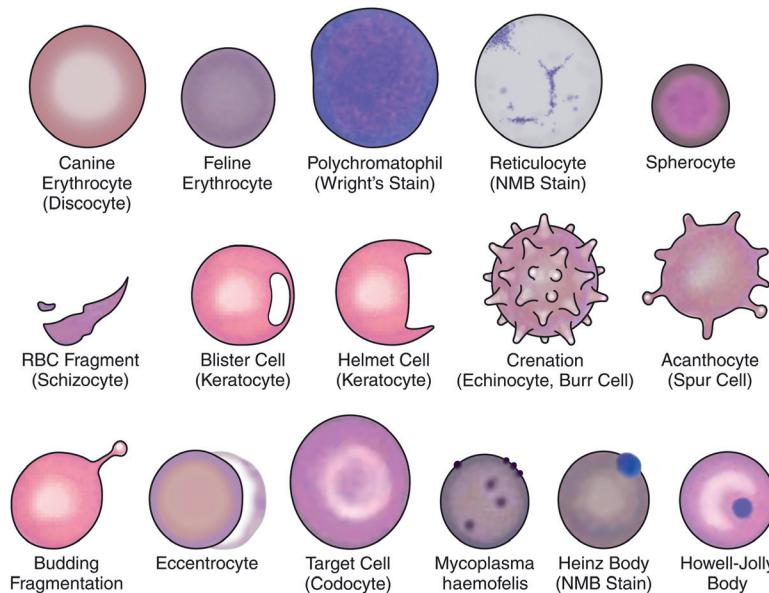


FIGURE 25-8 Some common terms and synonyms are given beneath a drawing of selected morphologic changes in red blood cells. These illustrations are of the cell as it appears on a Wright-stained smear, except for reticulocytes and Heinz bodies, which are preferentially stained with new methylene blue. A canine erythrocyte is included for comparison purposes. (From Weiss D, Tvedten H: The complete blood cell count and bone marrow examination: general comments and selected techniques. In Willard MD, Tvedten H, editors: Small animal diagnosis by laboratory methods, ed 4, St Louis, 2004, Saunders.)

the product of immune-mediated removal of antibody-coated parts of the erythrocyte membrane, after which the cell is reconfigured into a sphere. Because normal feline erythrocytes are small and lack central pallor, spherocytosis in this species is difficult or impossible to appreciate and identification is best left to an experienced veterinary hemocytologist.

Microagglutination and rouleaux formation may be visible on blood smears. Agglutination appears as a random, disorganized clumping of cells not dispersed by the addition of saline. True autoagglutination indicates an immune-mediated disease affecting the erythrocyte. Rouleaux formation looks similar to a stack of coins (see [Figure 25-4](#)) and will disperse after the addition of saline (see [Figure 25-5](#)). Circulating monocytes may phagocytose antibody-covered red cells; this is called *erythrophagocytosis*. Although not observed very often, erythrophagocytosis also suggests the presence of immune-mediated red cell damage. Heinz bodies are areas of oxidatively denatured hemoglobin within the cell (discussed later). The altered hemoglobin is pushed off to one side and often seen as a projection off the surface of the cell membrane. Heinz bodies stain dark with new methylene blue stain, somewhat clear with Diff-Quik, and the same as the cytoplasm with Wright's stain¹⁸ ([Figures 25-9 and 25-10](#)). Howell-Jolly bodies are intracytoplasmic remnants of nuclear material found in erythrocytes that may mimic red cell parasites. Blood smear examination is an essential part of a CBC, particularly when it comes to evaluating the erythron. There is no other way to identify the morphologic changes in red cells that can yield clues to the etiology of erythrocyte disease. Without a blood smear evaluation, a CBC is incomplete.

Blood Types

There are three well-known, clinically important blood groups in cats: A, B, and AB. Another potentially important group called *Mik* has recently been identified.¹²⁴ The blood groups are genetically determined erythrocyte surface antigens. The *A*-allele is dominant over the *b*-allele so that cats with genotypes *A/A* and *A/b* will be type A, whereas only the homozygous *b/b* will have the type B phenotype. A third allele, *Ab*, occurs rarely and is said to be recessive to the *A*-allele and dominant to the *b*-allele, although controversy exists regarding the exact inheritance. A and B antigens are produced on the same red cell only in cats with the genotypes *Ab/b* or *Ab/Ab*.³⁵ A more in-depth discussion of feline blood types has recently been published.⁷ Blood typing can be performed by a diagnostic laboratory using various methods or in the hospital with a card typing system (DMS RapidVet-H [feline], DMS Laboratories). If the card-typing system is used, type AB and type B results should be confirmed by a referral laboratory because some cross-reactions

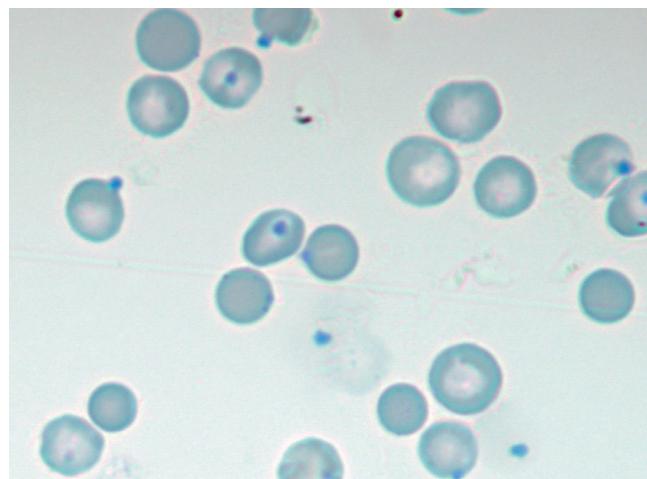


FIGURE 25-9 Heinz bodies appear as dark-stained structures in this new methylene blue-stained smear of feline blood. (Courtesy Rick Cowell.)

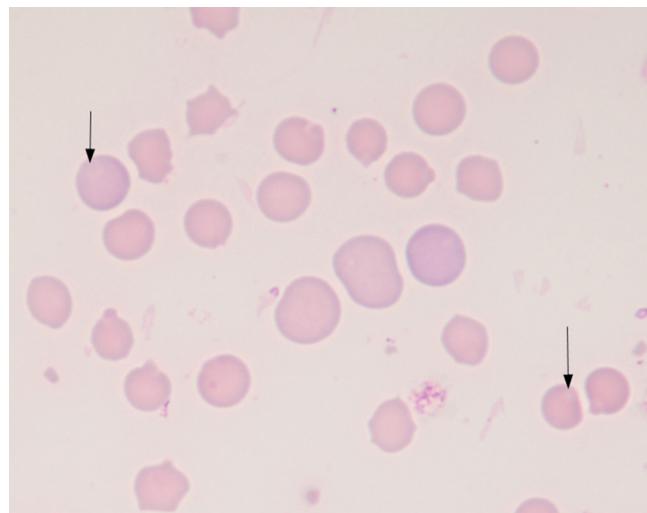


FIGURE 25-10 Heinz bodies stain pale on a Wright-stained feline blood smear. They may be seen projecting from some erythrocytes, whereas others appear as pale areas in the erythrocyte, as shown by the arrows. (Courtesy Rick Cowell.)

have been known to occur.¹⁰⁴ A recently introduced option for patient-side blood typing is the gel column agglutination test (DiaMed-Vet feline typing gel, DiaMed, Switzerland). This test is easier to interpret than the card method, although it requires a specially designed centrifuge that may be cost prohibitive in some settings.¹¹⁸ An evaluation of various blood typing methods for the cat concluded that the gel column test is reliable compared with the gold standard, the Penn tube assay.¹⁰⁴

Genetic blood typing using buccal mucosal swabs is available from certain labs and may allow breeders to identify heterozygous type A cats (*A/b*). Breeding two of these cats together would be expected to produce 25% type B kittens (*b/b*) and 50% heterozygous type A kittens (*A/b*). However, genetic typing cannot distinguish between type A and type AB.

Understanding feline blood groups is important because, unlike other mammals, cats produce naturally occurring antibodies, called *alloantibodies*, against the erythrocyte antigens not present on their own cells. The kitten produces these alloantibodies at approximately 2 to 3 months of age, as a result of exposure to antigens on plants, bacteria, or protozoa that are structurally similar to red cell antigens. No alloantibodies are produced against antigens that are similar to self-antigens, and no previous exposure to blood products (transfusions) is necessary to produce the alloantibodies.

Knowledge of this system is important in the prevention of transfusion reactions and neonatal isoerythrolysis. Cats with type B blood have anti-A antibodies with strong hemolytic potential. Even a small volume of type A or AB blood administered to a type B cat can cause potentially life-threatening hemolysis within minutes of the transfusion.³⁶ Hemolysis of type B blood administered to a type A cat will result in a reduced life span of the transfused erythrocytes, but severe reactions are uncommon.⁴² Ingestion of colostrum from a type B queen by a type A newborn results in absorption of anti-A alloantibodies and subsequent rapid hemolysis of the kitten's erythrocytes. This is known as *neonatal isoerythrolysis* and occurs only when type A or AB kittens are born to a type B queen.

The distribution of blood types varies by geographic region and breed (Tables 25-1 and 25-2). Type A is the most common type among cats. There is, however, a geographic variation in the number of type B domestic shorthair cats. More than 10% of the domestic shorthair cats in Australia, France, Greece, India, Italy, Japan, Turkey, and some regions of England are type B. Distribution of blood types among pedigree breeds does not vary as much by location because of the international exchange of breeding cats. More than 30% of British Shorthair cats, Cornish and Devon Rex cats, and Turkish Angora or Vans have type B blood. In contrast, Siamese and related breeds are almost exclusively type A. Ragdoll cats appear to be unique with regard to blood types. Approximately 3% of Ragdoll cats are discordant when genotyping is compared to serology, necessitating further investigation in this breed.⁷ The AB blood type is very rare, and the frequency of the Mik blood type is unknown. The presence of erythrocyte antigens in addition to the A and B groups may explain why transfusion compatibility is not guaranteed by blood typing; cross-matching is recommended before any transfusion.¹²⁴ Breeding queens, along with blood donors and, if possible, blood recipients, should be blood typed.

Clinical Evaluation of Cats with Anemia

Anemia is defined as a decrease in the number of circulating red blood cells, the PCV, or the hemoglobin concentration. Because anemia is a sign of disease, making

TABLE 25-1 Geographic Distribution of Blood Type Frequencies in Domestic Cats

Region	Number of Cats	A%	B%	AB%
US (British Virgin Island)	32	100	0	0
US (New England)	69	100	0	0
Finland	61	100	0	0
Hungary (Budapest area)	73	100	0	0
US	432	99.77	0.23	0
US (82% Philadelphia area)	1072	99.72	0.28	0
Switzerland	1014	99.6	0.4	0
Japan	238	89.9	0.9	9.2
US (Northeast)	1450	99.7	0.3	0
US (North Central)	506	99.4	0.4	0.2
US (Southeast)	812	98.5	1.5	0
US (Southwest)	483	97.5	2.5	0
US (West Coast)	812	94.8	4.7	0
Germany (Berlin and Brandenburg area)	372	98.7	1.1	0.3
Denmark (Copenhagen area)	105	98.1	1.9	0
Argentina (Buenos Aires area)	76	96.1	2.6	1.3
Brazil (Rio de Janeiro area)	172	94.8	2.9	2.3
Scotland	70	97.1	2.9	0
Austria	101	97	3	0
England (Manchester)	477	97	3	0
Portugal (North)	147	89.1	4.1	6.8
Netherlands	95	94.8	4.2	0.1
Spain (Barcelona area)	100	94	5	1
Germany (Gieben area)	404	94.1	5.9	0
Gran Canaria	97	88.7	7.2	4.1
Italy (Piedmont region)	122	86.9	7.4	5.7
UK (Edinburgh area)	139	87.1	7.9	5
Italy (Lombardy region)	57	89.5	8.8	1.7
Japan (Tokyo)	207	90	10	0
Italy (Tuscany region)	363	87.1	12.9	0
France (Paris area)	350	85	15	0
Greece	207	78.3	20.3	1.4
Turkey	301	73.1	24.6	2.3
Australia (Brisbane area)	1895	73.3	26.3	0.4
England (Southeast)	105	67.6	30.5	1.9
Australia (Sydney region)	187	62	36	1.6

US, United States; UK, United Kingdom.

From Bighignoli B, Owens S, Froenicke L, et al: Blood types of the domestic cat. In August JR: *Consultations in feline internal medicine*, ed 6, St Louis, 2010, Elsevier.

TABLE 25-2 Worldwide Frequencies of Blood Types A, B, and AB in Different Breeds

Breed	Country	Number of Cats	A%	B%	AB%
Abyssinian	US	230	86.5	13.5	0
Abyssinian	US	194	79.9	20.1	0
Birman	US	216	82.4	17.6	0
British Shorthair	UK	121	39.7	58.7	1.6
British Shorthair	US	85	41.2	58.8	0
British Shorthair	Germany	33	54.5	45.5	0
British Shorthair	Germany	35	71.4	28.6	0
British Shorthair	Denmark	30	66.7	33.3	0
Burmese	Australia	30	93	3	3
Burmese	US	25	100	0	0
Chartreux (Kartäuser)	Germany	27	77.8	18.5	3.7
Devon Rex	US	288	50.3	49.7	0
Devon Rex	US	100	57	43	0
Devon Rex*	Australia	71	45	54	1.4
Himalayan	US	35	80	20	0
Maine Coon	Germany	25	96	4	0
Persian	US	230	90.4	9.6	0
Persian	US	170	75.9	24.1	0
Persian	Germany	157	91.7	7.6	0.6
Persian	Denmark	56	96.4	3.6	0
Persian	Italy	38	97.4	2.6	0
Ragdoll	Italy	36	72.2	8.3	19.4
Scottish Fold	US	27	85.2	14.8	0
Siamese	US	99	100	0	0
Siamese	Germany	46	100	0	0
Siamese	Italy	26	96.2	3.8	0
Somali	US	27	77.8	22.2	0
Tonkinese	US	31	100	0	0
Turkish Angora	Turkey	28	53.6	46.4	0
Turkish Van	Turkey	85	40	60	0

US, United States; UK, United Kingdom.

*Also includes hybrids.

From Bighignoli B, Owens S, Froenicke L, et al: Blood types of the domestic cat. In August JR: *Consultations in feline internal medicine*, ed 6, St Louis, 2010, Elsevier.

appropriate therapeutic decisions depends on identifying the underlying etiology. As with any disease, the first, most important steps include taking a thorough history and performing a detailed physical examination. The signs associated with anemia are often nonspecific. They are the result of decreased oxygen-carrying capacity of the blood, decreased blood volume, or the underlying disease. The severity of the signs is related to the rate of onset of the disease and

the severity of the anemia. Most anemic cats are presented for evaluation of weakness, lethargy, or anorexia. Bleeding may or may not be obvious, depending on its location. The owner should be asked about previous illnesses in addition to the duration and course of the present illness. Exposure to drugs or toxins, such as acetaminophen or onions, as well as the outdoors is important to ascertain. Cats that go outside have a greater risk of trauma and increased exposure

to other cats and thus infectious diseases such as retroviral infections. Outdoor cats are also more likely to be exposed to fleas or ticks, possible vectors for important infectious causes of anemia. Discolored urine from hemoglobinuria must be distinguished from hematuria. The geographic location of the cat and its travel history may provide clues as to the cause of the disease. The blood type of a neonate's parents may be critical information if an ill day-old kitten exhibits signs of neonatal isoerythrolysis. Other signs, such as polyuria and polydipsia, can indicate the presence of chronic diseases. Gastrointestinal signs may lead to the consideration of chronic blood loss or inflammatory disease. Recent surgery or trauma may result in blood loss anemia.

Mucous membrane pallor is a common physical finding. If hemolysis is present, the mucous membrane color may be icteric. Decreased peripheral perfusion from causes such as shock or congestive heart failure may also cause pallor, whereas hepatic failure can result in icterus. Evidence of volume contraction, such as tacky mucous membranes or prolonged skin tenting, may be present. Remember that older cats lack skin elasticity and may have a prolonged skin tent even if well hydrated. A moderate decrease in erythrocyte numbers leads to decreased blood viscosity and tissue hypoxia. A soft murmur may be present because turbulent blood flow is directly related to decreased blood viscosity. Hypoxia leads to vasodilation, resulting in an increased heart rate in an attempt to increase cardiac output and oxygen delivery to the tissues. Tachypnea is also a common finding. Fleas or ticks may be found during a detailed examination of the skin, particularly in young animals. Fever may be present in cats with infectious causes of anemia, and splenomegaly is a common finding in cats with hemolysis of any etiology. Small kidneys may be appreciated in a cat with chronic renal disease. Any abdominal mass should be noted for further evaluation. Petechial or ecchymotic hemorrhages indicate bleeding from hemostatic disorders, whereas bleeding wounds may be evidence of recent trauma. Discolored urine may stain the perineum of a longhaired white cat. The severity of the clinical signs shown by anemic cats is more often related to the chronicity than degree of anemia. Chronic anemia allows the cat to adapt physiologically and behaviorally to decreased tissue oxygenation, whereas acute anemia does not allow this adaptation to take place.

When presented with a pale cat, the first diagnostic step is to measure the PCV and total plasma protein concentration. If the PCV is normal, the veterinarian should look for other causes of pallor. If the PCV is low, the next step is to determine if the anemia is regenerative or nonregenerative (Figure 25-11). The single, best indicator of regeneration is an increase in the absolute aggregate reticulocyte count.¹²⁶ The severity of anemia should

not be assessed until any volume deficits have been corrected. A CBC with a platelet and aggregate reticulocyte count and a blood smear examination will provide evidence of regeneration as long as sufficient time has elapsed since the initial insult. If the protein content is low, acute bleeding should be suspected. Additional tests to consider include a slide agglutination test, a direct Coombs' test, testing for retroviral infection, and a polymerase chain reaction (PCR) test for hemotropic *Mycoplasma*. Other tests to consider include thoracic and abdominal radiography and abdominal ultrasonography, a serum biochemical profile, urinalysis, and coagulation profile. If the anemia is nonregenerative, evaluation of the bone marrow may be required to make an etiologic diagnosis. An attempt should be made to biopsy any masses identified during the evaluation. Examination and sampling of the gastrointestinal mucosa may be required to diagnose causes of blood loss from this system. To differentiate anemia of inflammatory disease from iron deficiency anemia, serum iron, ferritin, and transferrin (total iron-binding capacity) will have to be measured. By following a logical, ordered diagnostic approach to anemia, the veterinarian can often make an etiologic diagnosis, allowing specific therapy to be instituted.

SUPPORTIVE CARE FOR CATS WITH ANEMIA

Specific treatment for an anemic cat can be attempted only after the cause has been identified. Until that time, supportive care is essential. Bleeding should be controlled to prevent further blood loss. Home care while awaiting test results may be adequate if the anemia is mild. Avoiding stressful situations, such as excessive handling, barking dogs, or fractious cats, will help reduce oxygen requirements. Correction of volume contraction may improve the patient's attitude and appetite. Intravenous fluids may be necessary if volume depletion is significant. Concerns regarding reduction of oxygen-carrying capacity by reducing the PCV with fluid therapy are probably unfounded. The total body hemoglobin and oxygen-carrying ability remains unchanged. However, cats with low plasma protein levels are at risk of edema formation as a result of dilution by aggressive fluid administration. Cats with severe signs related to the anemia, such as respiratory distress or extreme weakness, may require a transfusion. Oxygen administration adds little to the ability to improve tissue hypoxia in anemic patients.³⁵ The low solubility of oxygen in plasma results in a very small increase in the dissolved oxygen content when 100% oxygen is inhaled. In addition, the stress a cat may experience during oxygen administration may be deleterious.

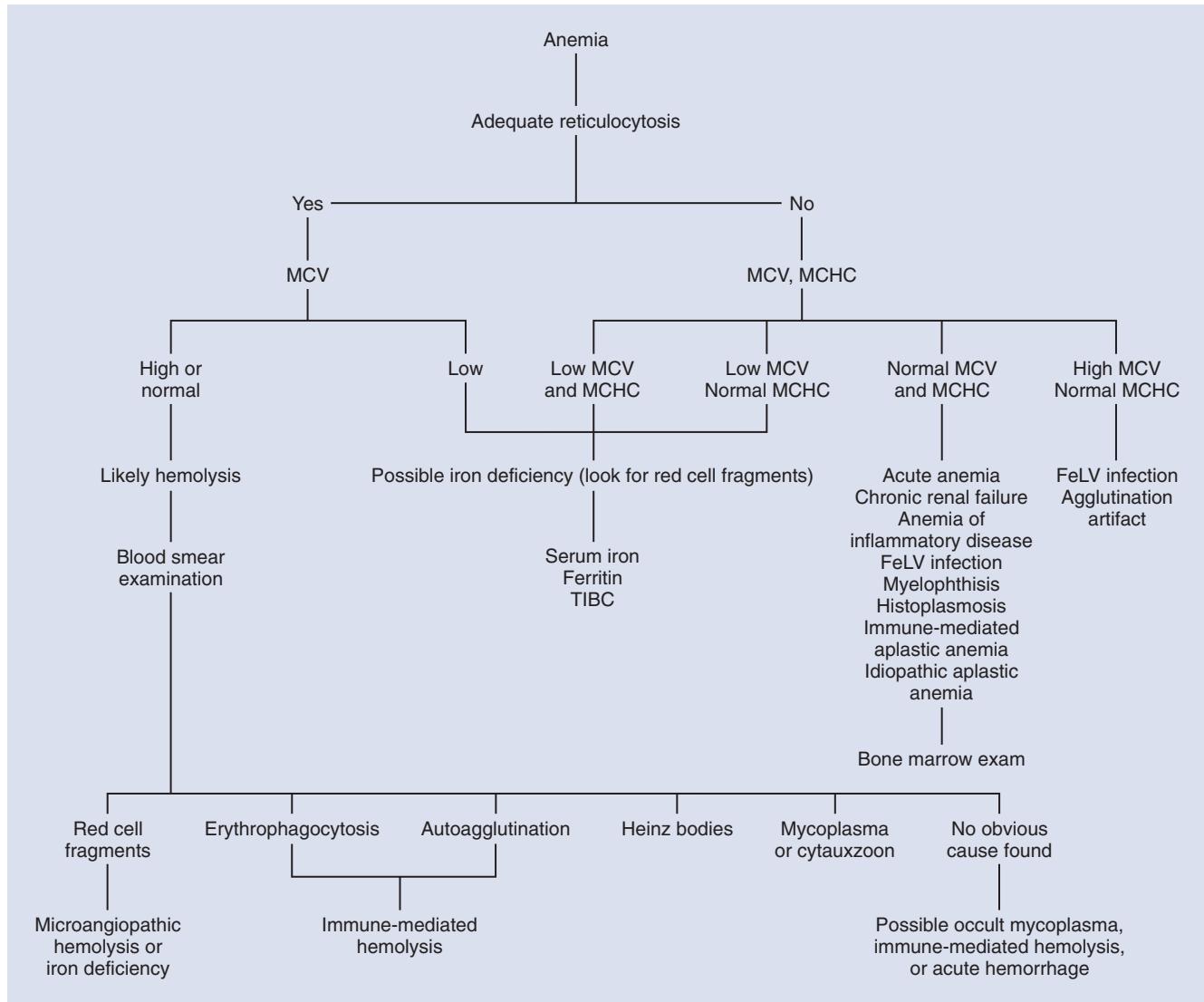


FIGURE 25-11 An algorithm that may be useful in evaluating a cat with anemia. Clinical judgment should be used when following any algorithm because an individual cat may not follow the rules. Further testing should be performed as needed.

Basic Feline Transfusion Medicine

The indications for the use of blood products are many and include hemorrhage, anemia, hemostatic defects, and hypoproteinemia.⁴² Many blood products are available or may be prepared, although most veterinary hospitals have hospital cats to use as needed for whole blood donation.

Many blood products are available and have specific uses. Fresh, whole blood contains erythrocytes, platelets, clotting factors, and serum proteins. Storage of whole blood results in the loss of platelets in 2 to 4 hours and clotting factors V and VIII within 24 hours of collection.⁴² Packed red cells maintain the oxygen-carrying capacity of whole blood in a smaller volume. This product may be used when volume expansion is unwanted, such as anemic cats with heart disease. Fresh frozen plasma

contains albumin and all the clotting factors and is used in cats hemorrhaging from coagulation disorders such as liver failure, DIC, or anticoagulant rodenticide toxicity. The use of plasma products to treat hypoalbuminemia is beneficial only in the short-term because transfused albumin rapidly equilibrates with the extravascular space.²⁵ The addition of synthetic colloids may prolong the oncotic effects of a plasma transfusion in these cats.⁴² Platelet-rich plasma is indicated for cats bleeding from platelet deficiency or dysfunction. Sources for products other than fresh whole blood include a local emergency or referral hospital or a regional veterinary blood bank. Oxyglobin (Biopure, Cambridge, Mass.) is a bovine hemoglobin product containing 130 g/L of hemoglobin that has been licensed for use in dogs. Because no cell membranes are present, there is no antigenicity and the product can be used when compatible

blood is unavailable. However, availability of the product has been erratic, and at the time of this writing, it is not available.

Donor cats should be healthy larger cats with a PCV above 35% and fully vaccinated.⁴² Donors should be blood typed before blood is collected. No abnormal morphologic cell types should be present, and platelet numbers should be in the reference range. The American College of Veterinary Internal Medicine (ACVIM) consensus statement on screening blood donors recommends testing donor cats for *M. haemofelis*; *Candidatus Mycoplasma haemominutum*; FeLV antigen; feline immunodeficiency virus (FIV) antibody; and, possibly, *Bartonella* infections.¹²² Cats that test positive for FIV antibody should be excluded even if vaccinated against the disease because development of reliable tests to discriminate between antibodies present from a natural infection versus vaccination has been difficult. Heartworm disease cannot be transmitted by blood donation, insofar as the larvae require passage through the mosquito to become infective. Screening for cytauxzoonosis is unnecessary because most cats with the disease are ill. Toxoplasmosis and feline infectious peritonitis have not been documented to be transmitted by transfusion.¹²² Donor cats should be kept indoors to reduce the risk of exposure to infectious diseases. Healthy cats can donate 10% to 20% of their total blood volume without adverse effects. A cat's total blood volume is approximately 66 mL/kg. For example, approximately 50 mL of blood (10 mL/kg) can be collected from a 5-kg cat no more often than every 4 to 6 weeks. Subcutaneous fluids should be administered at 2 to 3 times the volume of donated blood. Collection of more than 70 mL of blood from a 5-kg cat can lead to hypovolemia, and the volume should be replaced with intravenous fluids. Many donors resent sitting still long enough to have this volume of blood removed and may require sedation or general anesthesia.

For the treatment of anemia, there are no established levels of PCV below which a cat requires a blood transfusion. The decision to transfuse is instead based on the condition of the patient and assessment of the potential benefits weighed against the risks. Indications that an anemic cat may require a transfusion include respiratory distress, weak pulses, or severe weakness.¹²⁶ Both the donor and recipient should be blood typed. Even if the blood types are known, cross-matching should be performed before blood administration to prevent incompatible transfusions caused by untested or unknown erythrocyte antigens such as *Mik*. The half-life of appropriately matched red blood cells in the cat is 29 to 39 days, but for mismatched transfusions the half-life may be a matter of hours. When type B blood is transfused to a type A cat, the life span of transfused red blood cells is only 2 days. When type A blood is transfused to a type B cat, in addition to a potentially severe and fatal

reaction, the life span of the transfused cells is only a few hours. A cross-match should be performed again if more than 4 days have elapsed since the last transfusion from the same donor or if another donor is used.

Blood collected for immediate use can be anticoagulated with heparin. Heparin has no preservative properties, and heparinized blood should be used within 8 hours.⁴² If blood is to be stored for a longer period, citrated anticoagulants should be used. The required blood volume can be collected into a large syringe. If stored blood is used, it should be warmed to room temperature. Blood is administered through a filter connected to a dedicated intravenous line or a line without the presence of calcium-containing fluids. The transfusion is usually administered using gravity flow, although an infusion pump can be used if the manufacturer has stated that it can be used for this purpose. Bacterial contamination is a potential risk, and aseptic techniques for blood collection should be followed. Blood products can be administered intravenously or intraosseously in small patients.

For severely anemic cats the goal of transfusing whole blood is to ameliorate life-threatening decreases in PCV. This can be accomplished by attempting to raise the PCV to over 20%.⁴² The volume of whole blood required to increase the PCV to a desired level can be calculated by using the following formula:

$$70 \times \text{recipient's body weight in kg} \times \left[\frac{\text{desired PCV} - \text{recipient PCV}}{\text{donor PCV}} \right]$$

The volume to be delivered is equal to 70 times the recipient cat's weight in kilograms times the difference between the desired and the patient's PCV divided by the donor's PCV. Administer 2 to 3 mL of typed and cross-matched blood over 5 minutes and watch for evidence of adverse reaction, such as an increased body temperature, increased heart or respiratory rate, or a prolongation of the capillary refill time. Whole blood can be administered at 10 mL/kg/hour in a normovolemic cat or 2 to 4 mL/kg/hour in a cat with heart disease. The recipient should be constantly monitored for increased heart and respiratory rate, fever, and any signs of adverse reaction (e.g., vomiting) until the transfusion is complete. The transfusion should be completed within 4 hours to avoid bacterial contamination and the PCV measured 1 to 2 hours after completion.

For cats with incompatible cross-matches or in cases when blood products are unavailable, Oxyglobin (Biopure, Cambridge, Mass.) may be administered at a dose of 5 to 15 mL/kg at a rate of 5 mL/kg/h. Because the product contains no red cells, the hemoglobin concentration is measured to assess the effectiveness of the treatment. Oxyglobin has high colloidal properties, and cats are prone to volume overload with its use. Adverse reactions in cats included vomiting, pulmonary edema,

and pleural effusion. In one study of cats receiving Oxyglobin, 20% of cats developing respiratory signs required furosemide or supplemental oxygen during or after treatment. Most of these cats had preexisting heart disease.³² The lower dose should be used cautiously in cats with cardiac disease. The oxygen-carrying effects of Oxyglobin last up to 3 days in circulation.⁴²

Adverse effects of blood transfusions can be immunologic reactions to incompatible blood or nonimmune events and may occur within 1 or 2 hours after the transfusion begins. Occasionally, they may be seen up to 48 hours later.⁴² In a study of 126 cats that received blood transfusions, 11 cats (8.7%) suffered acute reactions.⁵³ Multiple red blood cell transfusions (either whole blood or packed red blood cells) are also well tolerated in cats and may be critical for survival of some severely ill patients.⁹⁸ Immune-mediated reactions can include hemolysis, allergic reactions, fever, or graft-versus-host reactions. Bacterial contamination of the blood product, hemolysis, hypocalcemia (from citrate toxicity), hypothermia, hyperammonemia, and volume overload are examples of nonimmune adverse reactions. In either case, the life span of the transfused erythrocytes may be shortened. Some reactions are severe enough to cause death. Despite the best efforts to prevent them, transfusion reactions may still occur. Depending on the severity, therapy may include glucocorticoids, epinephrine, crystalloid intravenous fluids, and discontinuation of the transfusion. Fever is usually mild, requiring no treatment. Furosemide should be administered if volume overload occurs. To prevent hypothermia, the blood product can be warmed to no more than 37° C. If the reaction is relatively mild, the transfusion can be restarted at a slower rate. Cross-matching blood is the best means of preventing immune-mediated transfusion reactions even if the blood type is known for both cats. It is also imperative that blood be collected and administered as aseptically as possible and that cats receiving blood products be carefully monitored.

ERYTHROCYTE DISORDERS

Regenerative (Responsive) Anemia

Definition

Regenerative anemia is recognized by a decrease in the PCV, erythrocyte count, and hemoglobin concentration, along with evidence of bone marrow production of new erythrocytes. The presence of polychromasia or increased reticulocyte numbers (or both) is evidence that the bone marrow has increased production of new cells. Regenerative anemia is recognized in a cat with blood loss of longer than 4 to 7 days or with destruction (hemolysis) of erythrocytes faster than they can be replaced. Blood loss anemia can be caused by gastrointestinal bleeding;

bleeding secondary to vessel damage from trauma or surgery; bleeding associated with hemostatic defects such as platelet or coagulation disorders; or the early stages of flea or tick infestations. Red cell destruction has myriad potential causes, including primary immune-mediated mechanisms; immune-mediated destruction secondary to infectious disease or drug administration; direct damage from hemoglobin oxidation or blood parasites; congenital defects resulting in erythrocyte membrane fragility; or exposure to alloantibodies from incompatible transfusions or neonatal isoerythrolysis. An anemia is regenerative if there are adequate numbers of circulating aggregate reticulocytes for the degree of anemia. An anemia may not appear regenerative for 4 to 7 days, the time it takes the bone marrow to produce and release new aggregate reticulocytes.

History and Physical Examination

The signs associated with anemia are often nonspecific and have been covered in a previous section of this chapter ([Clinical Evaluation of Cats with Anemia](#)).

Diagnostic Plans

A regenerative anemia of greater than 5 days' duration would be expected to show specific changes in a CBC. All cats suspected of being anemic on the basis of the history and clinical signs should have blood drawn for a CBC to include erythrocyte indices, a reticulocyte count, and a blood smear evaluation. The presence of pinpoint hemorrhages (petechiae) should prompt a platelet count. A CBC from a cat with a regenerative anemia should reveal evidence of a reduced erythrocyte mass such as a decreased PCV, red blood cell count, and hemoglobin concentration. The presence of reticulocytes, which are larger and have less hemoglobin than mature erythrocytes, should result in an increased MCV and decreased MCHC. This is why regenerative anemias are classified as macrocytic (increased MCV) and hypochromic (decreased MCHC). Examining a properly made blood smear is very important. The blood smear evaluation may reveal populations of cells of different sizes (anisocytosis) and colors (polychromasia). Morphologic changes may also be present that may give clues as to the cause of the anemia. Blood parasites and Heinz bodies may be seen on a blood smear. Because of the small size of feline erythrocytes, recognizing spherocytes in this species is difficult and is best left to an experienced veterinary cytopathologist. Microscopic agglutination and rouleaux formation can be appreciated when looking at a blood smear. The presence of a population of immature erythrocytes will increase the RDW, and a histogram of cell size versus numbers may contain two peaks representing two populations of cells—mature and immature. If the anemia has not been present long enough, few reticulocytes will be in the circulation and the red cell indices are likely to be within

the reference range for the laboratory. It may be necessary to repeat a CBC at a later date to reveal regeneration.

After recognizing a regenerative anemia, the veterinarian must decide if the anemia is due to hemorrhage or to hemolysis. Coagulation parameters and, if not part of the initial CBC, a platelet count may illuminate the cause of unknown bleeding. Endoscopic examination may be required to identify causes of gastrointestinal blood loss. Radiography of the thorax and an abdominal ultrasound examination should be performed to look for the presence of an effusion or mass. Congenital or acquired coagulopathy or trauma may result in a hemorrhagic effusion. A mass lesion may indicate the presence of neoplasia that could result in a secondary immune-mediated event. An abdominal radiograph may reveal the presence of a metallic foreign body in the gastrointestinal tract. Such a foreign body may be a zinc-containing coin, suggesting a possible nonimmune cause for the hemolytic anemia. A slide agglutination test should be performed on a washed or saline diluted EDTA blood sample. If there is no obvious agglutination on gross examination of the slide, a microscopic exam should be performed. Because both test for the presence of antibodies coating the erythrocyte, a direct Coombs' test is unnecessary if the slide agglutination test is positive. If the slide agglutination test is negative, a direct Coombs' test should be performed. Occasionally, FeLV will cause immune-mediated hemolysis. Testing for FeLV antigen is recommended in cats with a regenerative anemia, as is a PCR test for hemotropic mycoplasma DNA.

Acute Blood Loss

Early in the course of blood loss, before reticulocytes can be produced and released, the anemia may appear nonregenerative. The physiologic response to volume loss is to shunt blood away from the skin and spleen to protect the heart, brain, and viscera.³⁴ Pallor seen in this situation is not due to anemia but to decreased blood flow to the mucosa. During and immediately after significant blood loss, the PCV may remain normal, insofar as there is loss of both erythrocytes and plasma. A shift of fluid from the interstitial to intravascular space occurs within 12 to 24 hours, diluting the erythrocytes.¹²⁹ The result is a decrease in the PCV and total protein concentration. These decreases occur earlier if intravenous fluids have been administered. Erythrocyte morphology at this point will be normal, as will the MCV and MCHC. For 3 to 5 days, the anemia will appear nonregenerative and the diagnosis of a blood loss anemia is made on the basis of suspicion, history, physical findings, and a decreased total protein concentration. Once sufficient time has elapsed, reticulocytes appear and the anemia becomes regenerative. If the bleeding is controlled, the transient increase in aggregate reticulocyte numbers is followed by a rise in the number of punctate reticulocytes as

the aggregate ones mature.³⁴ If clinical signs are sufficiently severe, a whole blood transfusion should be considered.

If the cause of the bleeding is not determined or controlled, loss of iron stores will lead to an iron deficiency anemia. Gastrointestinal bleeding should be considered if a cause for the blood loss is not obvious. Bleeding gastrointestinal tumors, inflammatory bowel disease, gastric ulcers from overzealous use of nonsteroidal anti-inflammatory drugs (NSAIDs), and gastrointestinal parasitism are all potential causes of external blood loss.³⁴ Urinary blood loss is unlikely to cause depletion of iron stores.¹²⁹ Young kittens infested with fleas can experience significant blood loss, insofar as 100 fleas can consume approximately 1 mL of blood daily.³⁴ This represents about 10% of a 1-kg kitten's blood volume over a 1-week period.

Immune-Mediated Hemolysis

Immune-mediated hemolytic anemia (IMHA) occurs when an immune response is directed against antigens on erythrocytes, leading to their removal by the mononuclear phagocyte system of the spleen (extravascular hemolysis) or complement-mediated lysis (intravascular hemolysis). If the immune-mediated event is associated with another disease, it is a secondary IMHA. Infectious or inflammatory disease may lead to secondary IMHA, as might neoplasia or drug administration. When no underlying cause can be discerned, it is termed *primary* IMHA.

Dysregulation of the immune system results in a loss of self-tolerance. Antibodies may be formed against erythrocyte antigens (type II hypersensitivity), against a non-erythrocyte antigen attached to the red cell surface (type III hypersensitivity), or an antibody may be produced against an unassociated antigen that is similar to an erythrocyte antigen. Alloantibodies present in transfused blood or in colostrum from a type B queen ingested by a type A kitten may lead to immune-mediated hemolysis. Some erythrocyte antigens are hidden and exposed to the immune system only after the cell membrane has been damaged. New antigens that cross-react with red cell antigens or attach to the red cell membrane may be released into circulation by infection or inflammation.³⁴

The antibodies involved in the immune process are usually IgG, although IgM can be present alone or with IgG. Macrophages of the mononuclear phagocyte system have receptors for the Fc portion of the IgG antibody but not for IgM. Fc receptors are proteins on the surfaces of cells such as macrophages and neutrophils that contribute to the protective functions of the immune system. Fc receptors bind to the Fc portion of antibodies attached to pathogens or infected cells and stimulate the activity of phagocytic or cytotoxic cells. The antibody-coated cells are removed after antibody binds to the receptor on the macrophage, mostly in the red

pulp of the spleen. The result is extravascular hemolysis. Complete phagocytosis may not occur, and only a portion of the membrane may be removed. The cell's volume-to-surface-area ratio is reduced, and the cell becomes spherical. Spherocytes are less able to deform, making passage through the spleen more difficult. Because of the nonsinusoidal nature of the feline spleen (see the section on splenic diseases later in this chapter), less cell deformability is required for cells to pass through, and decreased numbers of spherocytes are trapped and destroyed than in dogs. Splenic macrophages also have receptors for complement. If a sufficient quantity of IgG antibodies coat the cell membrane, complement may also bind to the erythrocyte. The presence of complement on the cell membrane increases the efficiency of erythrocyte removal. If a sufficient number of the antibodies are IgM, complement-mediated lysis can occur, resulting in intravascular hemolysis. However, none of the 19 cats with primary IMHA in one study had intravascular hemolysis despite the presence of IgM in 8 of the cats.⁵⁷

Cats with IMHA, whether primary or secondary, will exhibit signs related to the anemia. These can include anorexia, lethargy, weakness, or respiratory difficulties. Additional signs as a result of the underlying disease may be present in cats with secondary IMHA. Most of the cats with primary IMHA are young adults. In the previously mentioned report of 19 cats with primary disease, six were younger than 2 years old; the median age for all 19 cats was 2 years.⁵⁷ Eleven of the cats were male, and eight female. Cats with secondary disease will have a signalment related to the underlying disease. Physical changes that might be present include pale or icteric mucous membranes, tachycardia, tachypnea, or splenomegaly as a consequence of increased processing of damaged erythrocytes. Tachypnea and tachycardia are attempts at compensating for the decreased oxygen-carrying capacity of the anemic patient; pulmonary thromboembolism, so common in dogs with IMHA, is rare in cats.⁵⁷ Splenomegaly occurs in many nonimmune disorders causing hemolysis as the organ attempts to deal with the increased numbers of damaged red cells. Body temperature is likely to be normal unless the patient is moribund, in which case hypothermia may be noted. A systolic murmur may be heard during auscultation of the thorax.

Diagnosis of IMHA can be frustrating. There are many mechanisms causing hemolysis that do not involve the immune system. Distinguishing primary from secondary IMHA is important because therapy may be different. With aggressive diagnostic investigation, an underlying cause is often found. Two sources state that primary IMHA is rare in cats.^{34,75} However, Kohn and coworkers⁵⁷ found that of 23 anemic cats with a positive Coombs' test or persistent erythrocyte agglutination, an underlying cause was identified in only four patients

after an extensive workup. Put another way, 19 of the 23 Coombs'-positive cats had primary IMHA.

To make a diagnosis of primary IMHA, other causes of hemolysis must be eliminated. A CBC with reticulocyte and platelet counts, serum biochemical profile, and urinalysis should be performed. The cat's retroviral status should be ascertained and a PCR test for *M. haemofelis* DNA should be run. Thoracic radiography and an abdominal ultrasound examination should be performed to rule out the presence of potential bronchial infections, or thoracic or abdominal masses. A bone marrow evaluation may be useful when a regenerative response to the anemia is equivocal. Specific immunodiagnostic tests such as a slide agglutination test and a direct Coombs' test should be performed.

If the hemolysis is severe enough and the anemia is not peracute, there should be evidence of regeneration in the CBC report. Increased numbers of aggregate reticulocytes should be present. Polychromasia and rubricytosis (nucleated red blood cells) may be present. The hallmark of IMHA in dogs, spherocytosis, is unlikely to be identified. The PCV may be surprisingly low for the condition of the patient; cats seem to tolerate a lower PCV than dogs.⁵⁷ The lower the PCV, the higher the aggregate reticulocyte count should be. If the reticulocyte count is not appropriate for the degree of anemia, it may be nonregenerative. In this case an immune response directed at erythrocyte precursors in the bone marrow might be considered. Another difference from dogs is the lack of leukocytosis or neutrophilia with left shift in cats with primary IMHA. In the aforementioned study by Kohn and coworkers⁵⁷ 17 of the 19 cats with primary IMHA had a white cell count within the reference range. The platelet count should be within the reference range, too. Evans syndrome, a combination of immune-mediated damage to both erythrocytes and platelets, is rare in cats. Although evidence of DIC is common in dogs with IMHA, it is uncommon in cats. Before convicting a cat with anemia of also having thrombocytopenia on the basis of an automated cell count, a blood smear should be examined to determine whether platelet clumping is present. The smear examination will also allow identification of intraerythrocytic parasites or morphologic changes in the erythrocyte that may suggest causes of anemia other than IMHA.

There are no pathognomonic changes for IMHA in the biochemical profile. Anemia may cause hepatic centrilobular hypoxia, hepatocyte injury, and subsequent increases in serum alanine transferase (ALT) activity. Hyperbilirubinemia and hyperproteinemia may be present. Volume contraction may be reflected by azotemia, which is likely prerenal in cats with primary IMHA. Other changes may be present if there is an underlying disease (secondary IMHA). Any thoracic or abdominal masses should be biopsied. An airway wash with

cytology and culture might be attempted in cats with peribronchial thickening.

The direct Coombs' test detects the presence of antibodies or complement on the red cell surface. A positive test is consistent with, but not necessarily diagnostic for, IMHA. However, a diagnosis of IMHA should include a positive direct Coombs' test.³⁴ False-negative tests are unlikely. In the study by Kohn and coworkers, 78 cats with anemia had a direct Coombs' test performed and 55 were negative, all of which had nonimmune etiologies identified as causing the anemia; an additional 14 cats without anemia were also direct Coombs' test negative.⁵⁷ The direct Coombs' test may become negative after a patient with IMHA enters remission, although a few days of immunosuppressive therapy is unlikely to cause a negative test.³⁴ A limitation of the test is the inability to differentiate between primary and secondary IMHA. A properly performed slide agglutination test may detect anti-erythrocyte IgM or large quantities of anti-erythrocyte IgG coating the erythrocytes. Autoagglutination must be distinguished from rouleaux formation by proper washing or dilution of the blood on the slide. A direct Coombs' test is unnecessary if the slide agglutination test is positive because they both test for anti-erythrocyte antibodies; autoagglutination is considered indicative of IMHA.⁵⁷ Autoagglutination may artifactually increase the MCV because clumps of cells are counted as one.

Therapy for IMHA depends on the cause and severity of the anemia and must be tailored to the individual. Removal of an underlying cause or trigger will help bring secondary IMHA under control. If an infection, such as *M. haemofelis*, is thought to be contributing to the disorder, use of appropriate antibiotics is required. Surgical drainage of any fight-wound abscesses or removal of potentially neoplastic masses may be necessary. Removal of nonessential drugs, particularly those known to induce an immune response, may eliminate a potential trigger for the immune-mediated process.

Supportive measures should not be forgotten. Volume expansion in a severely ill cat will improve organ

perfusion. Concerns regarding exacerbating hypoxia by decreasing the PCV with intravenous fluids are unwarranted. Although the PCV may decrease, the total amount of hemoglobin in the body does not. However, rehydration will reveal the true severity of the anemia. Depending on the cat's condition and PCV, a blood transfusion may be required. A major cross-match before collecting and administering blood is imperative, even if the blood type of the donor and recipient is known. Unfortunately, autoagglutination may make interpretation of the cross-match difficult. Alternatively, a hemoglobin-containing solution, Oxyglobin, may be used to improve oxygen-carrying capacity. Stressful situations while in hospital, such as frequent handling or exposure to barking dogs, should be minimized in severely ill cats.

Reduction of the immune-mediated destruction of erythrocytes is the goal of drug therapy. The optimal drug protocol will decrease phagocytosis of antibody or complement coated red cells, reduce complement activation, and eliminate the production of anti-erythrocyte antibodies (Table 25-3). Glucocorticoids are the initial drug of choice. These drugs are both antiinflammatory and immunosuppressive, although higher doses are required to accomplish the latter. Oral prednisone is the most commonly used glucocorticoid, but it requires conversion by the liver to the active form, prednisolone.¹⁰⁰ There is some evidence that intestinal absorption or hepatic conversion of prednisone to prednisolone may be poor in cats,¹¹⁹ thus prednisolone is thought by some to be a better initial choice in this species. The pharmacologic effects are due to interference with cellular communication and interaction among cells of the immune system. Glucocorticoids also inhibit production of cytokines used to amplify the immune response.⁷⁵ Decreased production of IL-2 leads to decreased T_h1 helper cell proliferation and cytotoxicity.²⁷ Glucocorticoids stimulate maturation of T-suppressor cells and inhibit antibody-dependent cytotoxicity by natural killer cells,²⁷ resulting in inhibition of the cellular arm of the immune system. They are beneficial in reducing binding of the Fc component of the attached IgG to the Fc receptors on

TABLE 25-3 Immunosuppressive Drugs

Drug	Trade Name	Dose	Preparation
Prednisone/prednisolone		2-4 mg/kg/day	
Dexamethasone		0.25-1 mg/kg/day	
Chlorambucil	Leukeran	0.1-0.2 mg/kg q24h or 2 mg/cat q48-72h	2-mg tablets
Cyclophosphamide	Cytoxan	2-4 mg/kg q24h 4 days/week	25- and 50-mg tablets
Cyclosporine	Atopica, Neoral	1-5 mg/kg q12-24h use ideal body weight for obese cats	10-, 25-, 50-, and 100-mg capsules (Atopica) 25- and 100-mg capsules, 100-mg/mL oral suspension (Neoral)
Leflunomide	Arava	2-4 mg/kg q24h	10- and 20-mg tablets

splenic macrophages. In addition, they may decrease antibody binding to the red cell membrane and complement activation.³⁴ There are few direct effects on B-lymphocytes, and therefore there is little effect on antibody production.^{27,90} Cats have fewer and less sensitive cytoplasmic glucocorticoid receptors than dogs.¹⁶ This may explain why cats typically have less pronounced side effects; for instance, polyuria and polydipsia and steroid hepatopathy are not typical side effects of glucocorticoid use in cats.²⁷ Cats receiving immunosuppressive doses of glucocorticoids may have difficulty eliminating infections on their own, and some infections may be inapparent because the inflammation associated with the infection may be blunted by the antiinflammatory effect of the glucocorticoid.

An initial immunosuppressive dose of prednisone or prednisolone is 2 to 4 mg/kg orally every 24 hours. The biological duration of action of these drugs is 24 to 36 hours, which is longer than the plasma half-life. Therefore there is little advantage in dividing the daily dose in two other than to reduce the gastric irritation some patients experience at very high doses.¹⁶ If oral medication is contraindicated because of vomiting or severe oral cavity or esophageal disease, injectable dexamethasone may be substituted at 0.25 to 1 mg/kg every 24 hours subcutaneously, intramuscularly, or intravenously. Repository glucocorticoids such as methylprednisolone acetate (Depo-Medrol, Pfizer) prevent accurate titrating of the dose, and their use is not recommended.¹⁶ Response is indicated by a stable or rising PCV and can be expected within a week. Appropriately treated secondary IMHA may respond more quickly. The Coombs' test will remain positive, possibly for months, despite a normal PCV. Once the PCV has reached and remains in the low part of the reference range for at least 1 week, consideration may be given to slowly decreasing the glucocorticoid dose. A rapid response may allow for a more rapid reduction in dose. The dose may be reduced by 25% to 50% every 2 to 4 weeks. Once the dose of prednisolone has reached 0.5 mg/kg, alternate-day therapy may begin. It is imperative to ensure the maintenance of remission before each dose reduction. There is no sense in reducing the dose in a cat that is deteriorating. Once a physiologic dose (0.25 mg/kg) of prednisolone has been reached, an attempt can be made to discontinue the drug. Whether this is possible depends on the individual cat. Relapses are to be expected and should be treated by increasing to the last effective dose.

Additional immunosuppressive drugs may be required if the response to prednisolone is inadequate, if control occurs only at high doses of prednisolone, or if side effects are unacceptable. Chlorambucil is an acceptable additional drug to use in cats. Although not as potent as cyclophosphamide, it is well tolerated by cats and is the preferred first choice when an additional drug is required. Dosages range from 2 mg/cat orally

every 48 to 72 hours¹¹⁹ to 0.1 to 0.2 mg/kg orally every 24 hours.⁸⁸ Hemorrhagic cystitis has not been reported in cats, and myelosuppression is uncommon¹¹⁹; however, myelotoxicity may result in neutropenia, with a nadir occurring 7 to 14 days after starting the drug. A white blood cell count should be performed at that time. If the neutrophil count is less than $0.5 \times 10^9/L$, the veterinarian should administer prophylactic antibiotics and reduce the dose by 25%.⁸⁵

Other immunosuppressive drugs include cyclophosphamide, cyclosporine, and leflunomide. An alkylating agent similar to chlorambucil, cyclophosphamide may have a more rapid onset of action.⁸⁷ Cats seem more resistant to the adverse effects of this medication than dogs⁸⁷; however, gastrointestinal signs such as vomiting, diarrhea, nausea, and anorexia are possible. Although it is metabolized in the liver to active metabolites, production of substances toxic to the bladder epithelium do not seem to be produced as they are in dogs,⁸⁷ and sterile hemorrhagic cystitis has not been reported in cats receiving cyclophosphamide. The drug is cytotoxic and decreases the production of white blood cells and antibodies. As with chlorambucil, a white blood cell count should be performed 7 to 14 days after starting the drug. The dose is 2 to 4 mg/kg orally every 24 hours for 4 consecutive days per week.²⁹ The tablet is not homogeneous and therefore should not be split; compounding may be required to enable accurate dosing.

Cyclosporine acts by suppressing cytokine release from T cells, particularly IL-2.¹¹⁹ This, in turn, prevents early activation of T_h1 helper cells and cytotoxic T cells. Cyclosporine has little effect on nonstimulated T cells, is not cytotoxic or myelosuppressive,⁵⁸ and spares other rapidly dividing cells.⁴⁰ Common adverse effects include anorexia and vomiting, which respond to a decrease in the dose. It has a bitter taste that may cause refusal to eat if mixed with food.⁸⁷ Hepatotoxicity is not a problem except at extremely high blood levels,⁴⁰ but reversible nephrotoxicity, although not as common as in people, can occur in cats at any blood level.⁴⁰ Monitoring of renal function in cats receiving cyclosporine is warranted. The gingival lesions seen in dogs receiving cyclosporine have not been reported in cats.¹¹⁹ Patients receiving cyclosporine may also have an increased risk of developing neoplasia, particularly lymphosarcoma.⁴⁰ This effect may be due to decreased surveillance for neoplastic cells by the cellular arm of the immune system. Only the modified formulations of cyclosporine are recommended. A veterinary preparation of the emulsified form, Atopica (Novartis Animal Health), is available in capsules, allowing more accurate dosing in cats. This formulation is administered orally at 1 to 5 mg/kg of ideal body weight every 12 to 24 hours, and routine drug monitoring is generally unnecessary⁸⁷ unless the patient is not responding as expected. Measuring 2-hour postadministration cyclosporine concentrations is more

closely correlated with the drug's area under the curve than trough blood levels and more accurately predicts clinical response.⁸⁷ Because cyclosporine is extensively bound to erythrocytes, whole blood levels are higher than plasma concentrations.⁵⁸

Leflunomide (Arava, Sanofi Aventis) is a prodrug that is metabolized into the active form by the intestinal mucosa.⁴⁰ The active form inhibits a lymphocyte growth factor receptor⁴⁰ and mitochondrial enzymes, leading to inhibition of T cell proliferation.^{40,92} It is particularly effective in inhibiting B cell proliferation and antibody production. The drug is metabolized by the liver and excreted in the urine.⁹² The gastrointestinal problems experienced by dogs do not seem to occur in cats,⁴⁰ insofar as the metabolite causing the gastrointestinal distress is less toxic to cats.¹³⁰ Cats with inadequate renal function may, however, accumulate enough of the metabolite to cause gastrointestinal upset.¹³⁰ Leflunomide is administered orally at 2 to 4 mg/kg every 24 hours. Once remission is achieved, the dose can be reduced to once or twice weekly to maintain adequate blood levels.⁴⁰ Leflunomide orally at 10 mg per day has been used along with methotrexate to induce remission of refractory rheumatoid arthritis in cats. Once control is achieved, the dose is reduced to 10 mg twice weekly.

Because of the severe myelosuppression that occurs in cats, azathioprine is not recommended. When weaning off treatment using multiple drugs, the veterinarian should start by reducing the cytotoxic drugs. Once they are discontinued, reduction in glucocorticoid doses can begin. In the rare instance that combination therapy is ineffective, splenectomy may be required.

The prognosis for cats with IMHA depends on response to therapy, the prognosis associated with any underlying disease, and the occurrence of complications. The mortality rate for cats with primary IMHA is thought to be much lower than in dogs. Kohn and coworkers⁵⁷ reported a mortality rate of 23.5% compared with much higher rates in dogs. Life-threatening complications such as DIC or pulmonary thromboembolism also occur at a much lower rate in cats.

In summary, primary IMHA may be more common in cats than previously thought. Diagnosis remains an exclusionary one; elimination of other disorders by comprehensive investigation is required before making a diagnosis of primary IMHA. Therapy depends on whether an underlying condition exists but usually involves the use of immunosuppressive drugs. Fortunately, the prognosis for cats with primary IMHA is better than for dogs.

Inherited Erythrocyte Abnormalities Causing Hemolysis

The erythrocyte membrane is composed of a lipid bilayer attached to the membrane skeleton. Numerous glycoproteins act as receptors or transporters. The membrane

sodium/potassium (Na/K) ATPase is lost during maturation, and, subsequently, the cytoplasmic sodium and potassium concentrations are similar to plasma. Because erythrocytes lack mitochondria, energy generation is exclusively anaerobic. Pyruvate kinase (PK) is involved in the last step in energy production and catalyzes the production of pyruvate from phosphoenolpyruvate, yielding a high-energy ATP molecule.⁵⁵ Some of this energy is responsible for maintaining the pliability of the cell membrane, which allows the cell to squeeze through small capillaries. Two inherited defects in the feline erythrocyte occur in the related Abyssinian and Somali breeds of cat. Both defects affect erythrocyte survival time. One involves a PK deficiency; the other an idiopathic increase in red cell osmotic fragility. Both are inherited in an autosomal recessive manner and are identified in young cats with Coombs'-negative hemolytic anemia. Other, more common causes of hemolysis must be eliminated as possible causes of anemia before considering inherited defects. This requires an exhaustive effort to find other causes of regenerative anemia. A CBC, including an aggregate reticulocyte count and measurement of red cell indices, serum biochemical profile, and a urinalysis, should be performed. The patient should be screened for retroviral and hemoplasma infection and have a direct Coombs' test run.

Abyssinian and Somali cats with PK deficiency are usually young adults when presented for evaluation, although cats younger than 1 year old may be affected. These cats exhibit the common signs associated with anemia, including lethargy, weakness, pale mucous membranes, and anorexia. The signs are often intermittent and mild, even in cats with severe anemia. Physical findings are not specific for PK deficiency and may include pallor, lethargy, icterus, or weight loss. Mild to moderate splenomegaly is common. At presentation, most, but not all, cats are anemic, with a PCV between 13% and 29% (median of 25%) reported in one study.⁵⁵ The anemia in most is regenerative with macrocytosis, polychromasia, and an aggregate reticulocytosis. Some cats have a lymphocytosis and a polyclonal hyperglobulinemia, possibly as a result of nonspecific immune system stimulation. A genetic test is available for PK deficiency and might be useful in all breeding Abyssinian and Somali cats, particularly those related to cats with anemia. Affected cats are homozygous for the causative mutation and have very low PK activity.³³ Heterozygotes have intermediate PK activity and, because they are asymptomatic carriers, can transmit the defect unknowingly. Therapy is limited for cats with PK deficiency. They are often misdiagnosed with IMHA or hemoplasmosis and receive prednisolone, doxycycline, or both. Prednisolone may be beneficial in reducing the number of hemolytic crises by delaying phagocytosis by macrophages in the spleen. Splenectomy should be considered when recurrent hemolytic episodes occur or if

the spleen becomes so large that it restricts expansion of the stomach, leading to anorexia.⁵⁵ Stressful events can lead to a life-threatening hemolytic crisis and should be avoided. The prognosis for a cat with PK deficiency is variable. Most cats that die do so during a hemolytic crisis. In contrast to dogs, cats do not develop progressive osteosclerosis.³³ Some cats can live to an older age; according to one source,³⁴ the oldest PK-deficient cat lived to 13 years of age.

A population of Somali and Abyssinian cats has been identified with increased fragility of the erythrocyte membrane.⁵⁶ The cause for the increased fragility has not been elucidated, but an inherited defect in the cell membrane is suspected with a likely autosomal recessive mode of inheritance. The disorder has also been identified in Siamese and domestic shorthair cats.³⁴ All of the cats had normal PK activity. The age at the initial visit was between 6 months and 5 years (mean of 2 years). The most common presenting complaints included lethargy, anorexia, weight loss, and pale mucous membranes—signs typical of anemia. In some cats the signs were episodic. Physical examination revealed the presence of pallor and splenomegaly. As these cats age, the splenomegaly appears to become more profound. As with PK deficiency, the initial presentation may be misinterpreted for some other cause of hemolysis. Most blood samples were severely hemolyzed after an overnight stay in refrigeration. Although the PCV was most often in the range of 15% to 25%, during a hemolytic crisis it dropped to as low as 5%. The anemia was usually mildly to moderately regenerative with macrocytosis, anisocytosis, polychromasia, and an aggregate reticulocytosis. Macroscopic agglutination was present in 50% of the cats but disappeared after proper washing. The agglutination may have artifactually increased the MCV as aggregates of cells passed through the cell counter. Many cats had a lymphocytosis and polyclonal hyperglobulinemia. Retroviral tests were negative, as was a direct Coombs' test. Microscopic examination for hemoplasma infection was negative; because of the insensitivity of this test in detecting the bacteria, cats were treated with doxycycline anyway. Osmotic fragility testing is performed by placing the patient's red cells in serial dilutions of a saline solution. Because mature erythrocytes have no Na/K ATPase, the amount of water inside the cell rapidly equilibrates with that of the solution and the cell increases in volume. Hemolysis of patient erythrocytes occurs at much higher concentrations of saline than control samples. Affected erythrocytes are osmotically fragile even when there are no clinical signs. Whereas some of the cats responded to glucocorticoid administration, others improved without treatment. Splenectomy was performed in cats that did not respond or had recurrent hemolytic events. This effectively removed the organ responsible for phagocytosis of the damaged erythrocytes.

In summary, cats with PK deficiency and increased erythrocyte fragility have many clinical and hematologic similarities, such as the young age of onset, character and chronicity of the hemolytic anemia, splenomegaly, and treatments available. Because of the similarity of the two diseases, testing for both in a patient in whom the disease is suspected may be wise. A DNA test for PK deficiency is available for Abyssinian and Somali cats. Osmotic fragility testing requires an EDTA blood sample from both the patient and a control. Cats with PK deficiency have relatively normal osmotic fragility, and those with severe osmotic fragility have normal PK activities.

Neonatal Isoerythrolysis

The strong hemolytic characteristics of the anti-A alloantibodies found in the serum of type B cats is responsible for the often fatal hemolysis that occurs in very young kittens. When the pathologic basis for neonatal isoerythrolysis is understood, it is easy to see how it can be prevented. Treatment of the disorder is often unrewarding.

The *A* and *Ab* alleles in cats are dominant to the *b* allele. Type B queens mated to type A or AB toms may have kittens that have expressed type A (or AB) antigens on their erythrocytes. Because the placenta in cats is impermeable to the passage of immunoglobulins, in utero hemolysis does not occur. Once the kitten is born, however, passive absorption of proteins from colostrum, including anti-A antibodies, occurs for the first 12 to 24 hours. Exposure to the strongly hemolyzing anti-A antibodies leads to massive, often fatal erythrocyte destruction in type A and AB kittens. The severity of signs is related to the amount of colostral antibody absorbed before closure of the kitten's intestinal tract to passive immune transfer. Once gut closure occurs, the kitten is no longer at risk for neonatal isoerythrolysis. The time at which this occurs varies among individuals.

Kittens at risk are born healthy and become ill only after consuming anti-A antibodies in the colostrum. Clinical signs appear within the first few hours to days of life and may range in severity from sudden death to development of tail-tip necrosis from vessel obstruction by agglutinating erythrocytes. Some kittens develop dark-colored urine. These kittens may also stop nursing, fail to thrive or gain weight, and develop anemia and icterus; they usually die within the first week after birth. The diagnosis is confirmed by blood typing the queen and affected kittens.

Because of the acute nature of the disease, therapy is usually unsuccessful. The kitten should be removed from the queen for the first 24 hours after birth, and the body temperature should be well controlled. Between 2 and 3 mL of type B blood may be transfused through an intraosseous catheter. Type B blood is used because the only alloantibodies present in the sick newborn kitten

are the anti-A antibodies from the queen's colostrum; the kitten has not yet made any of its own alloantibodies. Ideally, the blood would come from the queen because she has no antibodies directed against her own red cells. Kittens start to produce their own anti-B alloantibodies soon after birth. If a further transfusion is necessary 3 days after birth, type A blood should be used.

Preventing the disorder, however, is much more successful than treating it. Blood typing of breeding individuals in breeds known to have a high percentage of type B cats will identify matings at risk of producing neonatal isoerythrolysis (see **Tables 25-1 and 25-2**). If mating a type B queen with a type A or AB tom is desired, plans should be made to foster the kittens to a type A queen for the first 24 hours of life. Alternatively, these kittens can be fed with kitten milk replacer for the first 24 hours. If there is concern about lack of passive transfer of maternal immunity in kittens fed milk replacer, 5 mL of serum from a type A cat can be administered subcutaneously or intraperitoneally every 8 hours for the first 24 hours.⁶⁰ Type B kittens receiving anti-B antibodies from the colostrum of type A queens are not known to be at risk of developing isoerythrolysis.

Because blood typing is readily available, preventing kitten death from neonatal isoerythrolysis is rather easy. It is recommended that cats of breeds with high frequency of type B blood, whether intended for breeding or as pets, have their blood typed at the earliest opportunity in case the information is needed in an urgent situation in the future.

Cytauxzoonosis

Cytauxzoonosis is a tick-borne blood disease of cats caused by the protozoal organism *Cytauxzoon felis*. The reservoir for the organism is the North American bobcat (*Lynx rufus*). Infection in domestic cats is usually rapidly fatal, insofar as they are a terminal host.⁹ The only proven vector for the organism is the tick *Dermacentor variabilis*. Cytauxzoonosis presently has a limited geographic distribution in the central, south-central, southeastern, and mid-Atlantic areas of the United States. This is also the geographical area where *D. variabilis* is encountered.

After the tick ingests parasitized erythrocytes from an infected host, the parasite is released into the gut, undergoes reproduction, and migrates to the salivary glands. When the tick feeds on a domestic cat, the parasite enters the circulation and infects mononuclear phagocytes. Massive replication in the phagocytes (tissue phase) causes the cells to swell and burst. Freed parasites are found in erythrocytes 1 to 3 days later (erythrocyte phase).³⁹ Interestingly, inoculation of infected red cells results in a chronic erythrocyte parasitemia without the severe illness normally seen in domestic cats. In order for the parasite to cause virulent disease, it must develop

in the tick.⁹ There is no evidence the parasite can infect humans.

The prepatent period for the disease is between 2 and 3 weeks. The tissue phase is responsible for many of the clinical signs because the swollen macrophages obstruct vessels, resulting in decreased organ perfusion. Damage to the lungs, liver, spleen, bone marrow, and brain account for many of the clinical signs. Erythrocyte infection and destruction occur 2 to 3 days before death, not enough time for the hemolytic anemia to become regenerative. Surviving cats may have a regenerative anemia if a sufficient number of erythrocytes are destroyed. If the hemolysis is severe enough, the resulting hypoxia will exacerbate organ damage. By-products of the parasite may be cytotoxic, pyrogenic, and vasoactive.³⁹ Once clinical signs are present, death follows in less than 1 week.

There is no age or gender predilection, although younger cats seem to represent many of the cases. Cats that go outside have an increased risk of tick exposure. Most infections are identified during early spring to early fall, when the ticks are most active. Cats infected with *C. felis* exhibit vague, nonspecific signs such as lethargy, anorexia, pallor, icterus, or respiratory distress. Physical examination of an infected cat may reveal fever, hepatosplenomegaly, tachycardia, tachypnea, and pale or icteric mucous membranes. Alterations in mentation, seizures, and vocalizing may be seen in cats in the later stages of the disease. Recumbency, hypothermia, and coma are seen in terminally ill cats. Death usually occurs a few days after the temperature peaks.

Diagnostic plans entail a CBC, including a platelet and aggregate reticulocyte count and blood smear evaluation; serum biochemical profile, and urinalysis. The cat's retrovirus status should be determined. If hepatosplenomegaly is palpated, an abdominal ultrasound examination is warranted. The goal of testing is to logically eliminate potential causes of the clinical signs. Diagnosing a *C. felis* infection requires an index of suspicion for the disease. Cats in an endemic area with acute onset of vague signs of disease should be considered candidates for this infection. Finding a tick on the cat's body can be an enormous clue. Anemia is not present until later in the course of illness and is usually normocytic and normochromic, with no increase in the number of aggregate reticulocytes. A neutrophilic leukocytosis may be present; however, if parasite-laden macrophages fill up the bone marrow, myelophthisis may lead to neutropenia. Thrombocytopenia may be present as a result of consumption, possibly from DIC. Hepatic infiltration with parasite-loaded macrophages may cause hyperbilirubinemia and increases in liver enzyme activities.

A definitive diagnosis involves identifying the parasite in macrophages or red blood cells. Because erythrocyte infection takes place later in the course of disease, aspiration of liver, spleen, lymph nodes, lung or bone

marrow is more likely to produce a diagnosis. Infected monocytes may be identified at the feathered edge of a blood smear. The organism is recognized as a basophilic, possibly lobulated area taking up much of the cytoplasm of the phagocyte (Figure 25-12). The parasite can be demonstrated in the erythrocyte as a characteristic round signet ring form (Figure 25-13). Other forms found in the

red cells include small dots and an ovoid safety-pin shape. There is usually only one parasite per red cell, but pairs and tetrads are seen occasionally.³⁹ Because erythrocyte infection occurs later in the disease, parasitemia may not be present early; a repeated smear examination should reveal the parasite.

Even though infection with *C. felis* is usually fatal, cats have survived, including some that received only aggressive supportive care. A population of 18 cats from the Arkansas–Oklahoma border area survived, suggesting the presence of a less virulent strain of the parasite.⁷² Goals of therapy include preventing DIC and bacterial septicemia, promoting perfusion, and improving tissue oxygenation. Aggressive intravenous fluid administration will help preserve intravascular volume, maintain tissue perfusion, and consequently improve tissue oxygenation and help prevent DIC. The prophylactic use of heparin to prevent DIC has been suggested.⁹ Even though antibiotics are not able to directly control the protozoa, they have been used in most cats that have survived.⁹ Effective drugs able to eradicate *C. felis* are not yet available. In fact, many cats that survived infection did so without the benefit of antiprotozoal drugs.

Therapy is often unrewarding; most cats die despite aggressive treatment. Until effective protocols for treating *C. felis* infections are developed, prevention of the initial infection should be the goal of the veterinarian and owner. Tick control is mandatory in preventing infection, as is confinement indoors during the tick season to minimize exposure to the protozoal parasite. Daily grooming to remove ticks is also helpful. Preliminary data have been published regarding the use of oral atovaquone 15 mg/kg every 8 hours in combination with oral azithromycin 10 mg/kg every 24 hours for 10 days along with aggressive supportive care. The protocol resulted in the survival of 14 of 22 infected cats.⁸ It is possible that some of these cats were infected with the less virulent strain of *C. felis*.

Heinz Body Anemia

Heinz bodies are indicative of oxidative injury to the erythrocyte. They are clumps of irreversibly denatured hemoglobin attached to the erythrocyte cell membrane (see Figures 25-9 and 25-10). Feline hemoglobin is quite sensitive to oxidative injury because there are more targets on the molecule to oxidize than in other mammals and cats have reduced capacity for scavenging oxidative substances. Feline hemoglobin also dissociates more readily than other species.¹⁴ Because of the nonsinusoidal nature of the feline spleen, rigid bodies such as erythrocytes with Heinz bodies are not forced to squeeze their way through the red pulp. Therefore the feline spleen is inefficient in removing Heinz bodies, and they accumulate. Still, the result is decreased erythrocyte survival time. Oxidation of the iron in the hemoglobin can occur without denaturing the hemoglobin. The Fe⁺² is oxidized

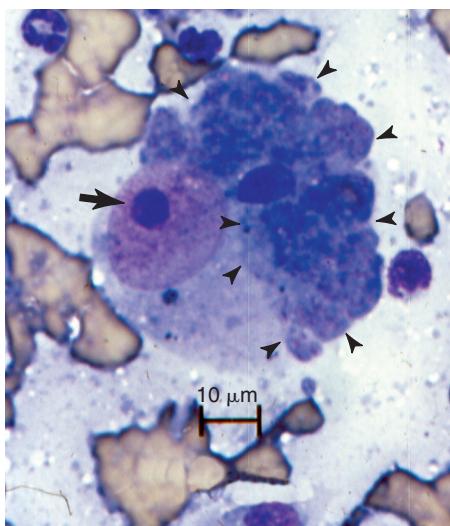


FIGURE 25-12 A macrophage from a feline liver contains a developing *Cytauxzoon* schizont. The early schizont is outlined by arrowheads and appears as a lobulated basophilic area within the cytoplasm of the cell. A large prominent nucleolus in the host nucleus is indicated by the long arrow (Wright-Giemsa, $\times 165$). (From Greene CE, Meinkoth J, Kocan A: *Cytauxzoonosis*. In Greene CE, editor: Infectious diseases of the dog and cat, ed 3, St Louis, 2006, Saunders/Elsevier.)

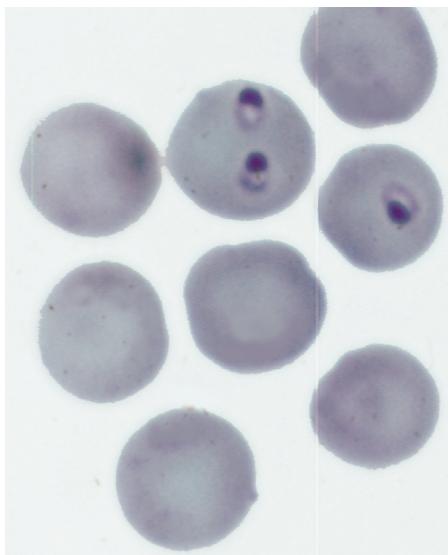


FIGURE 25-13 Feline erythrocytes infected with the characteristic signet-ring shaped *Cytauxzoon* piroplasms. The clear nuclear area in the parasite allows the organism to be differentiated from hemotropic *Mycoplasma* organisms (Wright-Giemsa, $\times 330$). (From Greene CE, Meinkoth J, Kocan A: *Cytauxzoonosis*. In Greene CE, editor: Infectious diseases of the dog and cat, ed 3, St Louis, 2006, Saunders/Elsevier.)

BOX 25-2**Substances and Diseases Associated with Oxidative Damage to Erythrocytes****Foods**

- Onions
- Propylene glycol
- Broccoli
- Garlic
- Salmon-based food

Drugs

- Acetaminophen
- Benzocaine
- Propofol
- DL-methionine
- Vitamin K₃

Metals

- Zinc
- Copper

Disease

- Diabetes mellitus (especially with ketoacidosis)
- Hyperthyroidism
- Hepatic lipidosis
- Lymphosarcoma

Cats are more susceptible to damage from oxidative drugs than other species. A number of drugs can produce oxidative damage to the red blood cell. In cats acetaminophen is particularly dangerous. Cats cannot metabolize the drug through glucuronidation, and oxidative metabolites are formed that damage the erythrocyte and the hemoglobin. Several diseases can produce substances that cause oxidative injury. Ketoacidotic cats may have up to 70% large Heinz bodies.¹⁴ Diabetic cats without ketosis have a lesser degree of Heinz bodies. Owners should refrain from feeding onion-containing baby food to diabetic cats.

Signs of Heinz body anemia are similar to those found in most anemic cats: lethargy, anorexia, pale mucous membranes, tachycardia, and tachypnea. The addition of the lowered oxygen-carrying capacity of methemoglobin caused by iron oxidation can make the signs of hypoxia appear worse than the lowered PCV would suggest. If over 15% of the hemoglobin is in the form of methemoglobin, the color of the mucosa and blood can be altered to appear darker red or brownish in color. Significant methemoglobin is rarely associated with diet or diseases that produce Heinz bodies.¹⁴

The development and degree of anemia depends on the size, number, and rate of formation of Heinz bodies. Heinz bodies are produced at a slower rate by diet or disease compared with oxidative drugs and are less likely to be associated with acute hemolysis. Anemia is more likely when the Heinz bodies are large and affect over 30% of the erythrocytes. Heinz bodies appear dark when stained with new methylene blue stain. Ghost cells may appear on the slide if the erythrocytes are seen to be extruding the Heinz body. These cells look like empty circular rims with an attached Heinz body. As opposed to dogs, cats often have single, large Heinz bodies. The presence of many large Heinz bodies can artifactually increase the MCHC and automated leukocyte count. Once Heinz body anemia has been discovered, the veterinarian should carefully evaluate the cat for drug or onion ingestion or diabetes mellitus. It is important to search for an underlying cause for anemia even if Heinz bodies are present; they are a sign of disease, not the disease itself. Thoracic and abdominal radiography and abdominal ultrasonography may help identify any malignancies or metallic foreign bodies. Offending dietary substances may be identified on the food's package label. Owners sometimes unwittingly administer acetaminophen to cats that seem to be in pain.

Therapy for Heinz body anemia should first be directed at removing the cause of the oxidative damage (e.g., eliminating onion-containing foods or treating the underlying disease). As with any anemia-causing disease, supportive care based on the cat's condition is important. Intravenous fluid therapy to correct volume contraction is always important in dehydrated cats. If the clinical signs warrant, a blood transfusion may

to Fe⁺³, which is unable to bind oxygen. The result is methemoglobinemia.

Oxidative substances are free radicals that damage cell structures. They may accumulate when there is increased production or decreased detoxification of the free radical, which can be produced spontaneously from oxygen. They may also be the result of drugs, plants, or chemicals with oxidative properties.¹⁴ Many substances or diseases can produce Heinz bodies (Box 25-2).

Heinz bodies are reported as the percentage of red cells containing Heinz bodies. Because of the nature of the feline spleen, up to 10% of erythrocytes in healthy cats may have Heinz bodies.¹²⁶ Any amount over this percentage should generate questions for the owner regarding diet and drug exposure. Owners who give their cats homemade diets or meat-based baby food may be inadvertently feeding enough onion powder to cause up to 50% Heinz bodies.¹⁴ Cats ingesting an oxidative diet may be more susceptible to oxidative drugs. Cats with diseases generating increased numbers of Heinz bodies should not be given foods with Heinz body-producing potential insofar as the effects can be additive.

become necessary. Lastly, antioxidant therapy may be required if the disorder is severe. N-acetylcysteine is used to treat acetaminophen toxicity (see Chapter 31). Methylene blue can be administered intravenously to cats at 1 to 1.5 mg/kg once; however, additional doses may exacerbate the Heinz body anemia. Once the oxidative substance is removed from the cat, the Heinz bodies should disappear over the next 1 to 4 weeks.

Acute Hemolysis Secondary to Severe Hypophosphatemia

Phosphorus exists in the body as organic and inorganic phosphates. Organic phosphate is an important component of many cellular structures and molecules in the cat such as adenosine-5'-triphosphate (ATP), cyclic adenosine monophosphate (cAMP), the electron transport chain, and cell membranes. These, in turn, are important in maintaining the integrity of the cell. Inorganic phosphate is present mostly in the extracellular space and is an important substrate for oxidative phosphorylation and glycogenolysis.⁷⁴ Acute hemolysis due to hypophosphatemia has been recognized in cats treated for diabetes mellitus and hepatic lipidosis.¹ Cats with these diseases may already have low serum phosphate concentrations; treatment of the disease may result in a further decrease as exogenous insulin is administered to diabetic patients or endogenous insulin increases when chronically anorexic cats are refed. Insulin results in an intracellular shift of phosphate as it follows glucose into cells. The intraerythrocytic phosphate concentration is dependent on the serum phosphate concentration.

Severe hypophosphatemia leads to decreased erythrocyte phosphate and consequently depletion of ATP. The resultant loss of the high-energy phosphate leads to an inability to maintain the cell's biconcave shape,¹ a reduction in membrane deformability, increased osmotic fragility, and increased susceptibility to oxidative stress.³⁴ The result is a rigid, oxidatively stressed, fragile cell. The macrophages in the spleen remove these cells, and anemia develops. The presence of Heinz bodies in diabetic cats can exacerbate the anemia caused by hypophosphatemia.

Anemia caused by acute hemolysis develops within 1 to 2 days of documentation of a serum phosphate concentration less than 0.65 mmol/L. Because of the acute nature of the hemolysis, the anemia will be normocytic and normochromic and appear nonregenerative. In one report the PCV dropped between 9 and 18 percentage points.¹ Increased numbers of Heinz bodies may be found when examining a blood film. Cats that survive are expected to develop an aggregate reticulocytosis during recovery.

Supplementation is recommended when the serum phosphate is less than 0.65 mmol/L. Intravenous sodium phosphate or potassium phosphate is administered at 0.01 to 0.06 mmol/kg per hour in calcium-free

solutions.⁴⁹ Serum calcium and phosphate concentrations should be monitored every 6 hours because hypocalcemia is a common complication (it is treated with intravenous calcium gluconate).³⁴ Once serum phosphate is over 0.65 mmol/L, the dosage can be decreased by half and discontinued shortly thereafter. Oral supplementation is started at this time.

Hypophosphatemia-associated acute hemolytic anemia is a complication of treating a diabetic cat or can result from refeeding syndrome. It is important to remember to evaluate the serum phosphate levels in these cats because the development of anemia can complicate recovery. Prophylactic use of phosphate supplementation for these patients may be considered if proper monitoring is available.

Feline Hemoplasmosis (*Hemobartonellosis*)

Feline hemoplasmas are epicellular gram-negative organisms causing anemia and illness in cats around the world. In one study 27% of 310 cats with acute or regenerative anemia tested positive for hemoplasmosis.¹⁰⁹ Another investigation found that 14% of all anemic cats were positive for hemoplasmosis.⁸³ Four distinct hemoplasmas have been detected in cats by PCR testing: *M. haemofelis*, *Candidatus Mycoplasma haemominutum*, *Candidatus Mycoplasma turicensis*, and *Candidatus Mycoplasma haematoparvum*. The most common hemoplasma found in cats is *Candidatus M. haemominutum*; mixed infections are not unusual.¹⁰⁹ *M. haemofelis* is the most pathogenic of the hemoplasmas and can cause potentially fatal hemolytic anemia. *Candidatus M. haemominutum* usually causes little to no illness in cats,³¹ unless there is FeLV co-infection or co-infection with another hemoplasma. *Candidatus M. turicensis* has caused anemia when inoculated into specific-pathogen free cats.¹⁰⁸ The pathogenicity of *Candidatus M. haematoparvum* is as yet undetermined.

Erythrocyte cell membrane damage occurs as a result of attachment of the organism. Consequently, cell survival time is affected. The damaged membrane can also reveal antigens previously hidden from the immune system. Antibodies directed against these antigens (type II immune reaction) as well as the organism itself (type III immune reaction) can lead to Coombs'-positive immune-mediated hemolysis. The spleen removes these damaged cells, leading to a reduction in the PCV. Macrophages in the spleen may also remove the bacteria from the surface of the red cell and, if it is not too severely damaged, return the erythrocyte back into the circulation.¹¹¹ Despite appropriate therapy, cats that recover can remain subclinically infected for a period of time. PCR remains positive in these cats while the bacteria disappears from the erythrocytes and the PCV reaches the reference range. Cats that become carriers have reached a steady state between organism replication and macrophage phagocytosis and removal of

erythrocytes. Carriers are more likely to occur after infection with *Candidatus M. haemominutum* than with *M. haemofelis*.¹¹¹

The mode of transmission is poorly understood. Traditionally, it was thought that transmission of hemoplasmas occurred by fleas (*Ctenocephalides felis*). Although PCR tests have documented the presence of hemoplasma DNA in flea larvae, feces, and eggs, ingestion of these did not result in transmission to cats under experimental conditions.¹³³ Transmission of infection has been found after fleas infected with hemoplasma fed on cats in an experimental setting. Experimental ingestion of infected blood, but not infected feline saliva,⁷⁹ also resulted in transmission of infection. Whether these results translate to the clinical setting is unknown, but this research leads to speculation that aggressive interactions between cats may also play a role in the transmission of the organism.⁸³

Cats infected with hemoplasmas can be males or females of any age and are brought to the veterinarian for reasons similar to those of most other cats with anemia. They are often lethargic, pale, not eating well, and losing weight. The course may be waxing and waning as circulating parasite numbers fluctuates. The severity of the clinical signs depends on the species involved, the rate of development, and the degree of anemia. Cats infected with *M. haemofelis* or *Candidatus M. turicensis* are more likely to become anemic than cats infected with *Candidatus M. haemominutum*. The presence of FeLV co-infection results in a more severe illness; however, concurrent infection with FIV is not associated with more severe disease.¹⁰⁸ Physical findings include fever, pale mucous membranes, splenomegaly, and icterus. Cats infected with *Candidatus M. haemominutum* may have no physical abnormalities at all.¹⁰⁸ An ill cat infected with *Candidatus M. haemominutum* and no co-infection should be evaluated for other causes of anemia.

Evaluation of a cat experiencing the aforementioned clinical signs should include a CBC with a blood smear examination, an aggregate reticulocyte, and a platelet count; a Coombs' test; and retroviral testing. The anemia caused by feline hemoplasma infection should be macrocytic, normochromic to hypochromic and regenerative if enough time has elapsed to allow production of new erythrocytes. Increases in aggregate reticulocyte numbers should be present if the anemia is moderate to severe. If the anemia is mild, only punctate reticulocytes may be observed. The Coombs' test is often positive.¹¹¹ The cat should be evaluated for other causes of regenerative anemia as warranted by other clinical signs, such as bleeding.

Specific tests for hemoplasmosis include close inspection of erythrocytes on the blood smear for evidence of the organism and PCR tests for organism DNA. Occasionally, the organisms may appear on the blood smear

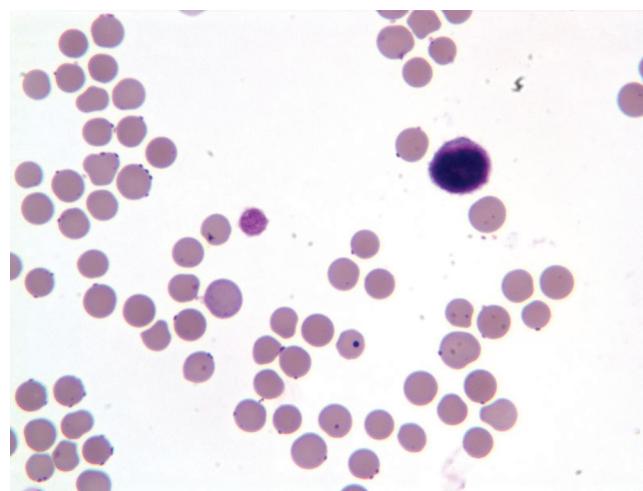


FIGURE 25-14 Giemsa-stained blood smear from a cat with *Mycoplasma haemofelis* infection. The organisms are attached to the surface of the erythrocytes. Anisocytosis (variation in cell size) is present on the slide. (From Tasker S, Lappin MR: Update on hemoplasmosis. In August JR, editor: Consultations in feline internal medicine, ed 5, St Louis, 2006, Elsevier.)

(Figure 25-14). The likelihood of finding organisms in this manner is affected by the cyclic nature of the parasitemia and, possibly, by sample handling issues. Slides should be made within 1 hour of collection to prevent the unlikely possibility that the organism will dislodge from the red cells.¹¹¹ Infected erythrocytes must be differentiated from Howell-Jolly bodies, stain precipitate, and ribosome-containing reticulocytes. PCR is a more sensitive test and is considered the test of choice for the infection. Cats undergoing antibiotic treatment are often PCR negative and should not be tested with this technique. A positive test result indicates the presence of organism DNA and may not correlate with clinical disease. Carriers of the infection are identified with this test.

Traditionally, cats with hemoplasma infections have been treated with tetracycline. Oral doxycycline at 10 mg/kg every 24 hours can be effective in treating the illness caused by hemoplasmosis. Courses longer than 21 days may be required for elimination of the organism. Esophageal strictures are a possible complication of doxycycline administration in tablet or capsule form and can be prevented by ensuring passage of the drug into the stomach by syringing a small amount of food or water after administering the pill to the cat. Doxycycline can also be compounded into a suspension. Applying a small amount of butter or margarine to the nose may accomplish the same thing. Fluoroquinolone antibiotics have been shown to be effective in treating cats with hemoplasma infections. Enrofloxacin (Baytril, Bayer HealthCare) at 5 mg/kg orally every 24 hours was associated with improvement in clinical signs, although elimination of the infection was uncommon.²¹ Daily doses higher than this may cause retinal degeneration in cats. Other fluoroquinolones may be effective.

Marbofloxacin (Zeniquin, Pfizer Animal Health) at 2 mg/kg orally every 24 hours is effective at treating illness but may not result in clearance of the infection.¹¹⁰ Retinal toxicity has not yet been identified in cats receiving marbofloxacin. Pradofloxacin (Veraflox, Bayer AG) at 5 mg/kg orally every 24 hours appears to be safe and effective in treating illness caused by hemoplasma infections. It also appears to be more effective in clearing the organism than doxycycline.²² Prednisolone, initially dosed at 2 mg/kg orally every 24 hours, before dose tapering has been used to control the immune-mediated component of the disease. However, this drug may be unnecessary because some cats recover without the use of glucocorticoids.¹¹¹ If the illness and anemia are severe, a transfusion may be required.

Cats with anemia caused by hemoplasmosis have an excellent prognosis for recovery.⁸³ The prognosis may not be as good for cats with concurrent disease, such as co-infection with FeLV. Prevention of the disease may include flea control and preventing aggressive interactions with other cats. The efficacy of these tactics is unknown insofar as the mode of transmission of the infection is still not clear. Cats with a positive PCR test should not be used as blood donors.

Nonregenerative (Nonresponsive) Anemia

Definition

Nonregenerative anemia is defined as a decreased erythrocyte mass (decreased PCV, red cell count, and hemoglobin concentration) without evidence of increased bone marrow production of new red blood cells. Lack of regeneration can be caused by decreased EPO production, decreased responsiveness of the bone marrow to EPO, decreased erythroid precursors in the bone marrow, or iron deficiency. Numerous disorders can lead to a nonregenerative anemia, including chronic renal disease, liver disease, inflammatory disease, FeLV infection, immune-mediated destruction of erythrocyte precursors, and primary bone marrow disease such as neoplasia and myelodysplasia. An anemia is nonregenerative if there are inadequate numbers of circulating aggregate reticulocytes for the degree of anemia. It is important to remember that an acute onset of anemia may also appear nonregenerative if there has not been enough time (4 to 7 days) for the bone marrow to produce and release aggregate reticulocytes.

History and Physical Examination

The signs associated with anemia are often nonspecific and have been covered in a previous section of this chapter ([Clinical Evaluation of Cats with Anemia](#)).

Diagnostic Plans

A CBC, along with measurement of erythrocyte indices, a blood smear evaluation, and a reticulocyte count,

should be performed in all cats in which anemia is a suspected cause of the clinical signs. Nonregenerative anemias are most often normocytic and normochromic. As with regenerative anemias, the PCV, erythrocyte count, and hemoglobin concentration are all decreased. However, because there is no increase in reticulocyte production, the MCV is usually within the reference range. The RDW is also in the reference range because most of the erythrocytes are similar in size. These parameters may lie outside the reference range in disorders such as iron deficiency and infection with FeLV. Most of the erythrocytes will have their normal allotment of hemoglobin, so the MCHC is also in the reference range.

Once a nonregenerative anemia has been identified, the goal of further diagnostic procedures is to identify extramarrow causes of the anemia before pursuing intramarrow disorders. A serum biochemical profile, urinalysis, and retroviral tests should be performed.¹⁸ If the duration of illness is shorter than 5 days, the cat's bone marrow may not have had enough time to increase erythrocyte production. Another CBC and reticulocyte count should be performed to ensure that the anemia is nonregenerative. Other diagnostic procedures that may be useful include thoracic radiographs and abdominal imaging. If these steps have not identified a cause for the anemia, evaluation of the bone marrow should be performed.

Iron Deficiency

Iron exists in the body in the form of hemoglobin, myoglobin, labile iron, tissue iron, and transported iron.¹²⁹ Hemoglobin concentrations inside the maturing erythrocyte help determine when cell division stops; erythrocytes undergo extra divisions, resulting in smaller cells when decreased hemoglobin is available. In most species the anemia of iron deficiency is microcytic (decreased MCV) and hypochromic (decreased MCHC), but cats are less likely to develop these changes.¹⁸ Early in the course of iron deficiency, the anemia is likely to be regenerative. Sufficient polychromasia and reticulocytosis may be present.¹⁸ As iron stores are depleted, polychromasia and reticulocytosis decrease and the anemia becomes nonregenerative. The degree of anemia ranges from mild to life threatening.¹²⁹ Variations in red cell shape (poikilocytosis)¹²⁹ and fragmented erythrocytes (schistocytosis)¹⁸ are commonly observed on the blood smear. Poikilocytosis is also common in cats with liver disease.¹²⁶

Kittens are at risk of developing iron deficiency anemia as a result of endoparasitism or ectoparasitism. Repeated blood sampling from kittens can also lead to iron depletion. Severe flea-bite anemia occurs in young kittens as a result of iron loss.¹²⁹ Anemia from total body iron depletion is unusual in adult cats.¹²⁹ Chronic blood loss caused by gastrointestinal ulceration or neoplasia may result in an iron deficiency anemia. If the amount of blood lost at any one time is small, there will not be

TABLE 25-4 Anemia of Inflammatory Disease Versus Iron-Deficiency Anemia

	Anemia of Inflammatory Disease	Iron-Deficiency Anemia
Erythrocyte indices	Normocytic, normochromic	Microcytic, hypochromic
Serum iron concentration	Low	Low
Total iron-binding capacity (transferrin)	Often decreased	Often normal
Bone marrow iron	May be increased	Absent (also a finding in normal cats)
Serum ferritin	High	Low
Inflammatory disease	Present	Need not be present

evidence of regeneration; the anemia will be caused by chronic iron loss. Careful evaluation of the gastrointestinal tract may be required insofar as there may be no overt evidence of gastrointestinal disease (e.g., vomiting, melena).⁹³ Loss through the urinary tract from bleeding transitional cell carcinoma or cystitis is unlikely to lead to iron loss sufficient to cause anemia.¹²⁹

Diagnosis of an iron deficiency anemia can be difficult. The changes in the erythron can be similar to anemia of inflammatory disease (AID; see later discussion). Sometimes the diagnosis can be made on the basis of the history and physical examination because there will be evidence of blood loss or active inflammation. Often, more information is required. Healthy cats typically do not have visible iron stores in their bone marrow. Although the presence of iron in the bone marrow rules out iron deficiency, its absence does not prove it.^{34,128} An iron profile can prove useful (Table 25-4). Serum iron concentrations alone are too nonspecific.¹²⁸ Assessing the total iron-binding capacity (TIBC) and serum ferritin concentrations can be helpful. The TIBC is a measure of the concentration of transferrin, a plasma protein that functions in iron transport. In an iron-deficient cat, transferrin (and TIBC) would be expected to be normal to slightly increased³⁴ in an attempt to offer more capacity for transport of iron to the cells. Because serum iron is low, the saturation of transferrin is decreased. Iron sequestration and decreased iron transport are a consequence of inflammatory disease so that transferrin concentrations (and TIBC) are decreased.¹²⁶ Ferritin is a cytoplasmic protein that stores iron in a soluble phase inside the cell.³⁴ In states of iron deficiency, cytoplasmic iron stores are decreased, resulting in decreased ferritin requirements and decreased plasma concentrations. Ferritin also

happens to be an acute phase inflammatory protein. In conditions involving inflammation, ferritin concentrations are expected to be elevated.¹²⁸ In summary, transferrin (TIBC) is increased and ferritin decreased in iron deficiency, whereas the reverse may be true for AID.

When a cat with iron deficiency is being treated, it is imperative that the cause of blood loss be identified and addressed. If the cat's clinical signs warrant it, a transfusion may be required. Iron replacement therapy involves administering ferrous sulfate at 50 to 100 mg/cat orally every 24 hours. If gastrointestinal upset occurs, the dose may be divided. The dose should be decreased by 50% once the PCV is in the reference range. If intestinal absorption is questionable, iron dextran should be administered intramuscularly at 50 mg every 3 to 4 weeks until the gastrointestinal disease is under control. Occasionally, hypersensitivity reactions will occur with iron dextran injections. Evidence of regeneration, such as polychromasia and reticulocytosis, should be apparent within several days¹⁸ as hemoglobin synthesis and erythropoiesis accelerate.

Anemia of Inflammatory Disease

Inflammatory conditions cause mild to moderate nonregenerative anemia.^{43,126} The PCV is often greater than 20% and is generally associated with an inflammatory leukogram¹⁸ and fever.¹²⁶ Cytokines released by inflammatory cells in response to infection, cell damage, or malignancy cause iron sequestration by macrophages. Because iron is an essential growth factor for microorganisms,⁸⁶ this is thought to be a protective mechanism against infection. It also leaves less iron for erythropoiesis. The inflammatory environment leads to decreased erythrocyte survival, decreased EPO secretion in response to anemia, and decreased bone marrow response to existing EPO.⁸⁶ This process has been known as anemia of chronic disease; however, cats in one study had a decreased PCV within 2 days of onset of an inflammatory disease.⁸⁶ Many of the cats developed hyperglobulinemia as a result of the inflammation.

The diagnosis of AID is one of exclusion. Other causes of nonregenerative anemia must first be eliminated.⁸⁶ Evidence for this mechanism of anemia may be found in the history or physical examination. Decreases in serum iron concentrations may mimic iron deficiency and are not confirmatory for either disease. Measuring serum ferritin concentrations may be helpful. In addition to being an iron-carrying protein, it is also an acute phase protein and may be elevated in inflammatory disorders.¹²⁸ Bone marrow cytology is nonspecific because changes such as myeloid hyperplasia and erythroid hypoplasia are common. This results in an increased myeloid to erythroid (M:E) ratio.¹⁸

Therapy for AID involves treating the underlying disease. When treated successfully, the anemia should resolve within several weeks.⁸⁶ Because the anemia is

usually mild to moderate, specific therapy, such as blood transfusions, is usually not required. Supplementation with iron products is not recommended because the increased iron may promote the growth of pathogenic bacteria or tumor cells.⁸⁶ Occasionally, the anemia is severe, and a blood transfusion is needed. In a retrospective study, only 3 of 21 cats with nonregenerative anemia associated with inflammatory disease required a transfusion.⁸⁶

Chronic Renal Disease

Anemia is an expected consequence of chronic renal disease (CRD) in cats and contributes significantly to their lack of well-being.⁹¹ Marked azotemia and an inappropriate urine specific gravity are usually present by the time CRD causes a significant anemia.¹⁸ The cause of anemia is multifactorial and may be exacerbated by concurrent illness.⁹³ There are four major causes of the anemia:

1. Uremic toxins may suppress the maturation of erythroid precursors in the bone marrow.
2. Erythrocyte life span may be shortened in animals with CRD.
3. Blood loss is often overlooked as a cause of anemia in CRD patients. Uremia can lead to platelet dysfunction and to gastrointestinal ulceration.¹²⁹ Evidence of gastrointestinal blood loss can be difficult to find because melena may not be present.⁹³
4. The most important contributing factor to the anemia of CRD is EPO deficiency. EPO is produced in the peritubular fibroblasts deep in the renal cortex in response to hypoxia. Decreasing renal mass results in decreased numbers of EPO-producing cells.

The anemia of CRD is normocytic, normochromic, and hypoproliferative.⁹⁷ Poikilocytes may be noted during examination of a blood smear.⁹³ Initially, the anemia is mild, but as renal disease progresses, the anemia becomes correspondingly more severe.¹²⁹ Occasionally, a transfusion becomes necessary. Bone marrow cytology may reveal erythroid hypoplasia and an increased myeloid to erythroid (M:E) ratio.

Specific therapy directed at treating anemia of CRD includes EPO replacement and minimizing blood loss. An overlooked but obvious consideration is minimizing the number and volume of blood samples obtained when a patient is hospitalized. Repeated blood monitoring should be limited to that which is essential to manage the patient.⁹³ Occult gastrointestinal blood loss can lead to significant anemia in patients that would otherwise have enough EPO to maintain the PCV in an acceptable range. Because of the difficulty in proving gastrointestinal blood loss, empirical use of H₂ receptor blockers along with sucralfate should be considered.⁹³

Recombinant human EPO (rhEPO) is a genetically engineered protein used to treat anemia in humans.¹⁹ The structure of EPO is relatively well conserved across species, allowing for biological activity of rhEPO in cats.¹²⁸ Hormone replacement using rhEPO is the treatment of choice for anemia associated with erythropoietic failure in cats with chronic renal failure.⁹³ Consideration for use of rhEPO should be limited to patients with severe anemia that affects quality of life. The initial dose is 100 units/kg subcutaneously three times weekly. This dose may be modified if the anemia is particularly severe without requiring a transfusion. If the PCV is less than 14%, 150 U/kg may be administered subcutaneously three times weekly. Should the patient be hypertensive or if the anemia is not particularly severe (yet still causing clinical signs), a dose of 50 U/kg may be effective in increasing the PCV while preventing a further increase in blood pressure.⁹³ The initial dose is continued for 8 to 12 weeks until the target PCV of 30% is reached.¹⁹ The PCV should be measured weekly so the dose can be altered when the target is reached.⁷⁰ At that point, dosing frequency is reduced to once or twice weekly to maintain the PCV above 30%. The dosage and dosing interval must be individualized for each patient.¹²⁸ Changes in dose should be made infrequently because there is a lag between a dosage change and its effect on the PCV. Generally, the dose should not be changed more than once monthly.⁹³ If iatrogenic erythrocytosis occurs, the dose or dosing interval (or both) should be decreased. A cat that does not respond should be evaluated for iron deficiency, external blood loss, AID, or the development of antibodies directed against rhEPO.¹⁹ Improper storage, handling, or administration by the owner should also be considered.⁹³ The drug vial should be refrigerated, and care should be taken not to vigorously shake the vial to prevent protein denaturation.

Potential adverse effects of rhEPO administration include iron deficiency, hypertension, erythrocytosis, anaphylaxis, local reactions to the injection,⁹⁴ and most important the development of anti-EPO antibodies.¹²⁸ The rapid increase in erythropoiesis can lead to the use of large amounts of iron. If iron is not supplemented, iron deficiency will develop. All cats receiving rhEPO should also receive ferrous sulfate at 50 to 100 mg/cat per day orally. Chronic anemia leads to vasodilation¹⁹ to facilitate delivery of blood to the tissues. Once the anemia is corrected by using rhEPO, total peripheral resistance increases, although clinical hypertension is uncommon. In a study of cats receiving recombinant feline EPO (rfEPO), only 2 of 26 cats that responded developed hypertension requiring antihypertensive therapy.⁹⁴

Although the rhEPO molecule is very similar to the cat's endogenous EPO, it is not identical. There is enough structural variation for the immune system of some cats to recognize rhEPO as a foreign protein and mount an

immune response against it.⁹⁴ Approximately 20% to 50% of cats receiving rhEPO will develop antibodies against the protein.^{91,128} These antibodies usually develop in cats receiving rhEPO for longer than 4 weeks.¹²⁸ Unfortunately, these antibodies block the biological effects not only of rhEPO but also of the cat's endogenous EPO.⁹⁴ This can lead to a life-threatening red cell aplasia as the patient's PCV drops to below pretreatment levels. This condition is reversible with cessation of the drug, but it may be months before the PCV recovers.⁷⁰ Until that time transfusions may be necessary to support the cat. After developing antibodies against rhEPO, its use is contraindicated. Because of the development of these antibodies, rhEPO should be reserved for patients most in need. Proper client education and communication are important when making decisions regarding the use of this therapy.

Evaluation of an rfEPO has been reported. Although the product is not available, it seems to be effective in reversing the anemia of chronic renal failure.⁹⁴ It also reversed the red cell aplasia caused by antibodies against rhEPO in some cats. Unexpectedly, 8 of the 26 cats receiving rfEPO redeveloped a nonregenerative anemia after an initial response. It was postulated that perhaps there are variations in the endogenous EPO in the cat population, allowing immune response against the molecule. Other possible targets of an immune reaction are the carbohydrate moiety on the molecule or some additive in the rfEPO preparation.⁹⁴

Darbepoietin is a longer acting form of rhEPO. Anecdotally, it seems to have similar efficacy and safety as rhEPO.⁹⁷ It can be administered as a weekly injection and may be less immunogenic in animals, but this has not been documented. Darbepoietin acts similarly to EPO by stimulating erythropoiesis in the bone marrow. Adverse effects in animals are unknown but are likely similar to rhEPO because darbepoietin causes increased erythropoiesis and improved oxygen delivery to tissues. This may result in hypertension, erythrocytosis, and iron deficiency. Until proven otherwise, darbepoietin should be considered potentially immunogenic.

With the availability of rhEPO, the ability to control anemia caused by chronic renal failure has improved. Careful patient selection, proper patient monitoring, and constant client communications are crucial to successful management of these patients. Supplementation with ferrous sulfate and control of gastrointestinal bleeding are also essential.

Feline Leukemia Virus Infection

Various hematologic abnormalities are common in cats infected with FeLV. Anemia can be caused by bone marrow suppression, myelodysplasia, myelophthisis due to lymphosarcoma or leukemia, or immune-mediated hemolysis.¹²⁹ Most of the anemias caused by FeLV are nonregenerative. The anemia can be

normocytic, normochromic, and nonregenerative or macrocytic, normochromic, and nonregenerative. If there is immune-mediated hemolysis, a regenerative anemia may occur.¹⁸ Hemolysis may be a direct result of the virus or due to co-infection with *M. haemofelis*.

The virus causes nonregenerative anemia by infecting erythroid precursors in the bone marrow and the stromal cells supporting the marrow.⁵⁹ Integration of proviral DNA into the marrow cell may cause marrow dysfunction by altering regulatory mechanisms or inducing the expression of an unknown antigen on the surface of the erythrocyte precursor or stromal fibroblast, leading to immune-mediated destruction of these cells.¹⁰⁷ The result is depletion and maturation arrest of erythrocyte precursors in the bone marrow.⁵⁹ Granulocyte precursors and megakaryocytes may also be affected, causing leukopenia and thrombocytopenia or thrombocytosis.¹²⁵ Cats with macrocytic nonregenerative anemias are often FeLV antigen positive.¹⁸ Macrocytosis is thought to result from a skipped mitosis during erythropoiesis; reticulocyte numbers are not increased.¹²⁹

Some FeLV-infected cats will have normocytic nonregenerative anemias with anisocytosis but no polychromasia. Anisocytosis results from a subpopulation of mature cells that are larger than the others but are not reticulocytes.²⁶ These cats may have an increased RDW reported on a hemogram. If a histogram of red cell size is provided, two peaks may be present, reflecting the two populations of cells: one of normal size and one a bit larger. Macrocytosis without anemia may be seen in some cats with hyperthyroidism.¹⁴ A spurious macrocytosis may result from the agglutination of erythrocytes as they pass through automated cell counters.

A cat with hematologic changes that is negative for circulating FeLV antigen may still be infected with the virus. Latent FeLV infections are defined as circulating antigen negative and bone marrow positive. The provirus is present in a nonreplicating form in myelomonocytic precursors in the marrow.¹⁰⁷ The viral particles may be identified by performing an indirect fluorescent antibody test on marrow smear or by using a PCR test. A study of a population of cats with various types of nonregenerative cytopenias of unknown origin was performed to assess the role of latent FeLV infections. All the cats had a negative test for circulating FeLV antigen. Only 2 of the 37 cats had a positive PCR test for FeLV proviral DNA in the bone marrow. The researchers concluded that FeLV latency does not play an important role in cats with nonregenerative cytopenias.¹⁰⁷

Any cat with anemia without obvious cause (e.g., trauma, blood loss) should be checked for the presence of FeLV antigen. If the anemia is regenerative, additional testing for blood parasites such as *M. haemofelis* is indicated. Therapy for cats with FeLV-associated anemia is supportive. Concurrent infection with blood parasites should be treated appropriately. Immunosuppressive

doses of prednisolone should be used if immune-mediated hemolysis is a factor.¹²⁸ Blood transfusions will be useful in ameliorating clinical signs of anemia. Some cats may respond to the administration of rhEPO, although most cats already have high circulating concentrations of EPO.⁵⁹

Pure Red Cell Aplasia

Pure red cell aplasia (PRCA) is characterized by a severe normocytic, normochromic, nonregenerative anemia along with erythroid hypoplasia and increased lymphocyte numbers in the bone marrow.¹²⁵ Granulocytes and megakaryocytes are left intact. This is a rare syndrome¹²⁹ thought to be caused by immune-mediated response against erythrocyte precursors in the marrow. Infection with FeLV subgroup C has also been implicated in the pathogenesis of the disease. It appears to be a disease of younger cats.¹²⁵ A Coombs' test may be positive, and other causes of anemia are absent. The PCV is often lower than 20%.²⁶ Aggressive combination immunosuppressive therapy with prednisolone and another drug (such as chlorambucil) is often required to control the immune-mediated damage (see the previous section on treating immune-mediated hemolytic anemia). Response to treatment may not be apparent for several weeks.

Acute Blood Loss or Hemolysis

Acute loss of sufficient erythrocytes either by hemorrhage or hemolysis leads to hypoxia and increased production of EPO by the kidneys. If the cat is evaluated before aggregate reticulocytes are released by the bone marrow, the circulating red cell morphology will appear nonregenerative. Immediately upon bleeding, both red cells and plasma are lost and no decrease in PCV is detected. Within 12 to 24 hours of acute hemorrhage, interstitial fluid shifts into the intravascular space. The increase in plasma volume dilutes the red cells and is recognized as anemia. Acute hemolysis will also lead to decreased erythrocyte numbers. In both situations the anemia may be evaluated before the appearance of aggregate reticulocytes in the circulation. A CBC performed at this time will reveal the presence of a normocytic, normochromic, nonregenerative anemia without polychromasia or increased aggregate reticulocyte numbers. The anemia will not be recognized as regenerative until aggregate reticulocytes are released 4 or 5 days after the initial event. A second CBC should be performed 5 days after onset of illness before the conclusion is reached that an anemia is nonregenerative.

Bone Marrow Disease

Numerous types of bone marrow disorders can cause nonregenerative anemia in cats, although they are very uncommon. Disorders include aplastic anemia, myelofibrosis, myelodysplasia, and myelophthisis secondary to inflammatory diseases or neoplasia. Many are associated

with FeLV. The etiologic diagnosis of bone marrow disease requires a cytologic or histopathologic evaluation of a bone marrow sample.

Aplastic anemia is defined as the presence of bycyopenia or pancytopenia. Most of the hematopoietic space of the marrow is replaced by adipose tissue. Cats most commonly have a nonregenerative anemia along with leukopenia, thrombocytopenia, or both. Although it may be idiopathic in cats, aplastic anemia is also associated with chronic renal disease, FeLV infections, and methimazole and griseofulvin toxicity.¹²⁵ Starvation and emaciation appear to have a role in the pathogenesis of the disorder in association with chronic renal disease and those with idiopathic aplastic anemia.¹²⁷ Some cats may survive for prolonged periods despite the presence of hypocellular bone marrow.¹²⁷

Myelofibrosis is defined as proliferation of fibroblasts or collagen in the bone marrow. It can be primary or secondary. Primary or idiopathic myelofibrosis is a disorder of dysplastic megakaryocytes, which produce cytokines that induce proliferation of fibroblasts.⁵² Secondary myelofibrosis in cats is associated with immune-mediated anemia, myelodysplasia, acute myelogenous leukemia, CRD,¹²⁵ and FeLV infection.⁵² Most commonly, a moderate to severe nonregenerative anemia is found in cats.¹²⁵ Myelofibrosis should be suspected when repeated bone marrow aspirates are unsuccessful, and definitive diagnosis is based on finding excessive fibroblasts on histopathologic examination of a bone marrow core biopsy.⁵²

Myelodysplastic syndrome (MDS) comprises a group of proliferative hematologic disorders originating from a mutation in a hematopoietic stem cell.¹²⁵ Most cats are anemic, and many have other cytopenias. The anemia is commonly macrocytic, normochromic, and nonregenerative. Almost 80% of cats with MDS are FeLV positive.¹²⁹ MDS is thought to be a preneoplastic condition and may be lethal without progression to leukemia.¹²⁹ Therapy for cats with MDS is supportive and may include blood transfusions, antibiotics for those with severe leukopenia, and corticosteroids. Survival time for a cat with MDS is likely to be measured in days to weeks from the time of diagnosis. However, some cats may survive for longer than 1 year.

By definition, *myelophthisis* is the replacement of hematopoietic space of the bone marrow by neoplastic, inflammatory, or collagen-producing cells.⁵² Acute and chronic leukemia may infiltrate the bone marrow, leading to a nonregenerative anemia. Acute inflammatory lesions in the marrow have been associated with immune-mediated hemolytic anemia, bacterial sepsis, and infection with the coronavirus responsible for feline infectious peritonitis. Pyogranulomatous inflammation has been observed in cats with disseminated histoplasmosis. The anemia in cats with myelophthisis is often moderate to severe.¹²⁵

Unfortunately, nonregenerative anemia can be a frustrating problem to solve and sometimes unrewarding to treat. A lack of increased numbers of aggregate reticulocytes in the face of a decreased PCV is indicative of this type of anemia. Extensive testing is often required to achieve a diagnosis. Some cats remain a diagnostic dilemma and must be treated symptomatically with blood transfusions, antibiotics, and corticosteroids. Frequent monitoring is often required to detect changes that may affect the cat's well-being.

Feline Erythrocytosis

Definition

Erythrocytosis, also known as *polycythemia*, is defined as an increase in the red blood cell mass as measured by an increase in the PCV, red blood cell count, and hemoglobin concentration. Like anemia, erythrocytosis is a sign of disease, not a disease in itself. Erythrocytosis is an uncommon finding in cats. EPO is a hormone produced by fibroblasts adjacent to proximal convoluted tubules deep in the renal cortex.⁴⁷ These cells are subject to negative feedback based on systemic or local oxygen tension. They respond to hypoxia by increasing the production of EPO. Red blood cell precursors in the bone marrow respond to EPO by dividing and maturing into cells capable of carrying oxygen to the tissues. Optimal oxygen delivery in normovolemic cats occurs at a PCV between 35% and 45%.⁸⁴ When hypoxia resolves, EPO production decreases, and production of new erythrocytes slows.

Clinical Signs and Physical Findings

The signs associated with erythrocytosis are due to increased blood viscosity. This leads to a decrease in the rate of blood flow in the microcirculation followed by distention and possibly thrombosis of these vessels. Hyperemia, bleeding, and central nervous system signs are the result of these changes. With increased hemoglobin concentration comes a greater chance of exceeding the 50 g/L level of deoxygenated hemoglobin, above which cyanosis becomes evident, making the detection of hyperemia difficult. Bleeding occurs because of rupture of the distended small vessels. Vessel obstruction and bleeding may result in central nervous system hypoxia and subsequent alterations in mentation, seizures, weakness, ataxia, and blindness. Approximately 25% of cats will have splenomegaly.⁴⁷ Other clinical signs may be present if there is an underlying disease.

Classification and Pathophysiology

Erythrocytosis can be classified into categories, each with its own unique underlying pathophysiology (Figure 25-15). The disorder can be relative or absolute. Relative erythrocytosis is caused by decreased plasma volume

and a "relative" increase in the red blood cell volume as measured by the PCV. Whereas the PCV is mildly increased, the total erythrocyte mass is not. Any disease leading to fluid loss and volume contraction may result in a relative erythrocytosis. Common causes include diarrhea and burns. EPO concentrations and reticulocyte numbers would be expected to be low to normal. Splenic contraction does not significantly elevate erythrocyte numbers in cats.⁸⁴

Absolute erythrocytosis, characterized by an actual increase in the red blood cell mass, is further categorized into primary and secondary absolute erythrocytosis. Primary erythrocytosis is a neoplastic disease seen in young to middle-aged cats in which autonomous erythrocyte precursors in the bone marrow divide and mature in the absence of EPO.⁸⁴ The other cell lines in the bone marrow remain unaffected.

Secondary absolute erythrocytosis is associated with increased EPO production and is divided further into physiologically appropriate or inappropriate. Appropriate secondary erythrocytosis occurs as a normal response to systemic hypoxia and is an appropriate, compensatory response. The most common causes include congenital cardiac disease with right-to-left shunting of blood, a high-altitude environment, chronic pulmonary parenchymal disease, and severe obesity (Pickwickian syndrome).^{47,84} Serum EPO would be expected to be normal to high.

Inappropriate secondary erythrocytosis is defined as increased erythrocyte mass without evidence of systemic hypoxia. The most common cause in cats is renal disease, including solid tumors or diffusely infiltrative neoplasia, polycystic kidney disease, amyloidosis, or pyelonephritis.⁴⁷ Locally reduced renal parenchymal blood flow due to compression or infiltration leads to focal hypoxia in the cortex, resulting in increased production of EPO.⁸⁴ Tumors of other body systems may produce EPO or EPO-like substances as a paraneoplastic syndrome. As with appropriate secondary erythrocytosis, EPO levels would be expected to be normal to high.

Diagnostic Plans

A logical approach to the diagnosis of erythrocytosis is important, insofar as treatment depends on the underlying cause. A thorough history and detailed physical examination, along with a CBC with a reticulocyte count, serum biochemical profile, and urinalysis is the recommended minimum database.⁸⁴

Relative erythrocytosis should be evident at this phase of the workup; the history and physical examination should reveal evidence of disease causing volume contraction. Along with an elevated PCV, the reticulocyte count should be low because erythropoiesis is not increased. The total plasma protein concentration should be elevated, along with the presence of azotemia and an appropriate increase in urine specific gravity. A

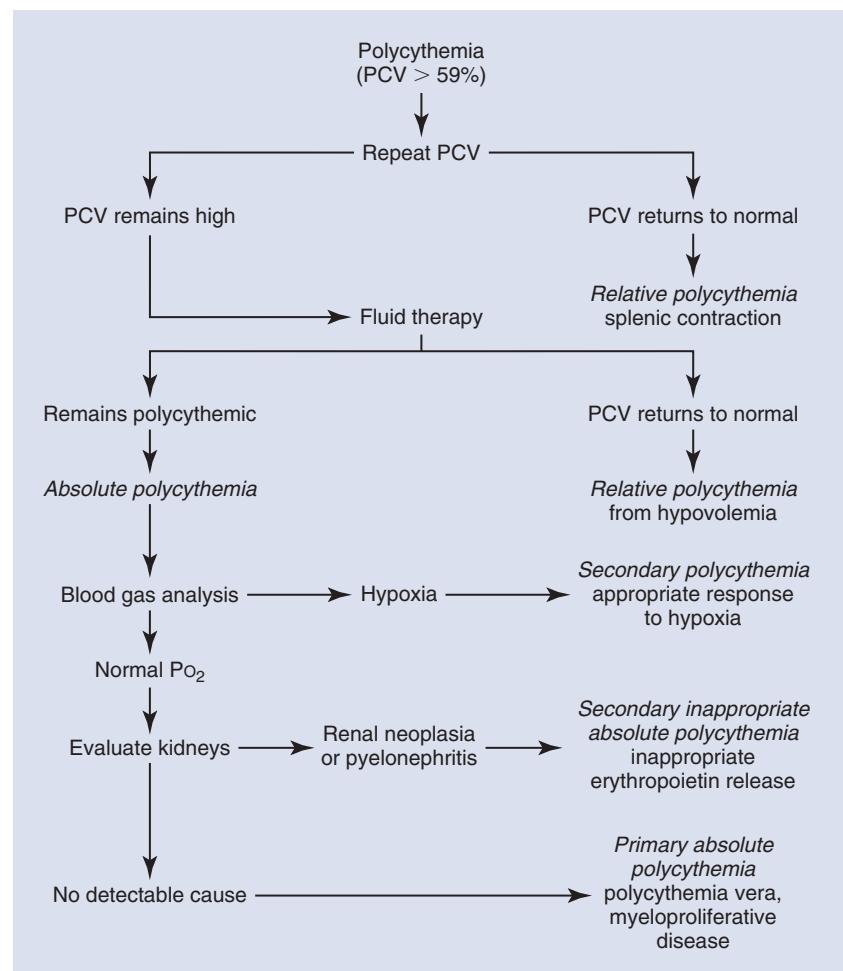


FIGURE 25-15 An algorithm that may be useful in deciding the classification of erythrocytosis. A diagnosis of primary erythrocytosis is made only when all other potential causes have been eliminated. The veterinarian should use clinical judgment when following an algorithm because an individual cat may not follow the rules. PCV, Packed cell volume. (Modified from Figure 3-6; Weiss D, Tvedten H: *Erythrocyte disorders*. In Willard MD, Tvedten H, editors: *Small animal diagnosis by laboratory methods*, ed 4, St Louis, 2004, Saunders.)

reduction in PCV after volume expansion confirms the diagnosis.

If the erythrocytosis is not relative, the next step is to look for evidence of hypoxia and accelerated erythropoiesis. An increased reticulocyte count in the face of an increased PCV suggests increased erythropoietic activity.⁴⁷ Severe obesity causing decreased pulmonary function may be present.⁸⁴ Cats with hypoxia often show evidence of respiratory distress and possibly cyanosis. Pulse oximetry and arterial blood gas assessment should confirm hypoxia. An etiologic diagnosis should be pursued by obtaining thoracic radiographs and performing an echocardiogram. Mild bronchointerstitial changes in the lungs and mild left ventricular hypertrophy may be found in cats with hyperviscosity from any cause.⁴⁷ Rarely, methemoglobinemia in cats can lead to erythrocytosis.

If no evidence of hypoxia is found, a diligent search for disorders causing an inappropriate production of

EPO should be performed. Because renal neoplasia (both carcinoma and lymphosarcoma) is the most common cause, imaging of the kidneys is prudent.⁸⁴ Abdominal radiography, intravenous pyelography, and abdominal ultrasonography may identify structural abnormalities of the kidneys. These procedures may also reveal tumors of other organs that may be producing EPO or EPO-like substances.

Primary erythrocytosis is a diagnosis made by exclusion.⁸⁴ Most cats with this disease will have normal laboratory parameters, other than the hemogram, and normal imaging results. EPO concentrations would be expected to be low to normal⁸⁴; if not, the veterinarian should reconsider the likelihood of inappropriate secondary erythrocytosis. Bone marrow examination is not helpful in the diagnosis, insofar as there are no markers for abnormal erythrocyte precursors, and absolute erythrocytosis leads to marrow erythroid hyperplasia, no matter the cause.⁴⁷

Therapeutic Plans

Phlebotomy should be the initial treatment for symptomatic cats with absolute erythrocytosis from any cause. The goal is to maintain the PCV such that clinical signs are alleviated. This is usually in the range of 50% for cats, unless they have hypoxia causing an appropriate secondary erythrocytosis.⁴⁷ No more than 10 to 20 mL/kg should be removed daily to reduce the PCV to the target level, and when it is safe to do so, the veterinarian should administer an equal volume of intravenous fluids or re-infuse the patient's removed plasma to further reduce viscosity. This should be repeated as needed to maintain the PCV at that range.

Phlebotomy is a generally safe procedure. However, phlebotomy is more physically demanding for the operator when dealing with erythrocytosis because of the increased viscosity of the blood being removed. Potential unwanted sequelae include hypovolemia and hypoproteinemia.⁸⁴ Frequent blood removal may also lead to iron deficiency, and iron supplementation may be required.

Therapy for relative erythrocytosis involves volume expansion with appropriate intravenous fluids or blood products and correction of the underlying cause. Successful treatment of inappropriate secondary erythrocytosis resulting from EPO-secreting tumors involves surgical removal of the offending neoplasm after stabilization of the cat's clinical status and PCV.⁸⁴ Presurgical phlebotomy may reduce the risk of bleeding or thrombosis during surgery. Drainage of large cysts and antimicrobial therapy may be useful in cats with polycystic kidney disease or pyelonephritis, respectively.

Appropriate secondary erythrocytosis is a compensatory mechanism to combat hypoxia; therefore removing too much blood by phlebotomy may exacerbate the hypoxia experienced by the cat. Systemic oxygenation declines with a PCV over 60%, so the veterinarian should attempt to maintain a PCV in the range of 55% to 60%.^{47,84} Treating the underlying cause is imperative. Severely obese cats should have a proper weight loss program instituted, and cats with heart disease and those with chronic bronchial disease should be treated appropriately. Because cats with cardiac disease may already be volume expanded, crystalloid replacement of the volume of blood removed by phlebotomy may result in volume overload and pulmonary edema.

Cats with primary absolute erythrocytosis will require phlebotomy for the rest of their lives. If the procedure needs to be performed too frequently or is ineffective in maintaining the PCV at an appropriate level, the addition of hydroxyurea should be considered. Hydroxyurea is an alkylating chemotherapeutic agent that suppresses production of erythrocytes. The dose should be individualized to maintain an acceptable PCV. The regimen begins with 10 to 15 mg/kg orally every 12 hours until

the target PCV is met, then continues every other day at the lowest dose needed to maintain that PCV. The dose is increased if the PCV starts to climb.¹²⁰

Hydroxyurea may cause reversible myelosuppression,⁴⁷ so a CBC with platelet count should be performed periodically to assess white blood cell and platelet numbers. If cell numbers decrease significantly, the medications should be discontinued until cell counts become normal, and the drug is restarted at a lower dose. Other potential side effects include vomiting, anorexia, and methemoglobinemia at high doses.

Prognosis

The prognosis for cats with erythrocytosis depends on the underlying cause. Removal of a renal tumor in a patient with secondary inappropriate erythrocytosis may be curative as long as metastasis has not occurred. Animals with primary erythrocytosis have lived for many years with appropriate treatment.⁴⁷

SELECTED LEUKOCYTE DISORDERS

Evaluation of White Blood Cell Changes

Interpretation of the leukogram seems straightforward, and often it is. As with investigating any other body system, evaluation of white blood cells involves integration of the signalment, history, and physical findings with the numbers reported on the CBC. Abnormal cell numbers in a healthy cat may be normal for that particular cat. A thorough white blood cell evaluation is both quantitative (cell numbers) and qualitative (smear examination). Interpretation of absolute cell numbers for each of the different cell types is essential; relative cell percentages are often inaccurate and should be ignored. It is also important to look at the value reported for each cell, not just those flagged as abnormal. An important aspect of a CBC is examining a well-made smear for changes in cell appearance. White blood cells are short lived in the circulation, and changes can be rapid. It is important to remember a CBC is an evaluation at a set point in time, and repeated CBCs may be necessary to identify important trends.

Neutrophilia

Physiologic Leukogram

This increase in leukocyte count is transient and nonpathologic (Box 25-3). The fear or excitement a cat experiences during a trip to the veterinarian results in an increase in epinephrine secretion with subsequent increases in heart rate, blood pressure, and blood flow. Neutrophils and lymphocytes are mobilized out of the marginated pool next to the vessel wall and into the

BOX 25-3**Some Causes of Neutrophilia in Cats****Physiologic Leukocytosis**

- Stress
- Illness
- Glucocorticoid administration

Inflammatory

- Tissue trauma
- Pancreatitis
- Surgery
- Burns
- Immune-mediated tissue injury

Infection

- Pyothorax
- Pyometra
- Abscesses
- Peritonitis
- Mycotic

Metabolic

- Uremia
- Diabetic ketoacidosis

Acute Hemolysis

- Drug induced
- Immune-mediated (uncommon)
- Hemoplasmosis

Neoplasia

- Lymphosarcoma
- Granulocytic leukemia
- Adenocarcinomas
- Ulcerated or necrotic masses

circulating pool. Because many of the neutrophils in cats are in the marginated pool, the increase in neutrophil numbers can be significant, up to three to four times the upper level of the reference range. The same degree of increase may be expected in the lymphocyte count.¹⁰ The changes are immediate and usually last 20 to 30 minutes. A physiologic leukocytosis is, then, mature neutrophilia with lymphocytosis. There should not be an increase in immature neutrophils.

Stress Leukogram

Chronic pain and illness cause secretion of glucocorticoids, leading to a change in the leukocyte count known as a *stress leukogram*, which is also recognized in cats receiving exogenous glucocorticoids for disease

management. The increased glucocorticoid concentration results in decreased diapedesis of neutrophils into the tissues, increased mobilization of neutrophils out of the marginated pool and into the circulating pool, and increased production and release of neutrophils by the bone marrow. The stress leukogram is characterized by a mature neutrophilia (no bands), lymphopenia, and eosinopenia. Unlike in dogs, monocytosis is an uncommon finding in cats with a stress leukogram. Resolution of a stress leukogram may take days after cessation of glucocorticoid administration.

Inflammatory Leukogram

The number of neutrophils in the blood represents balances among bone marrow production and release, physiologic changes in blood flow, diapedesis, and tissue demands. Inflammation from many different causes increases demands for neutrophils, and the bone marrow responds through increased release of stored mature neutrophils and accelerated production of new neutrophils. If the bone marrow can supply enough neutrophils to meet the needs of the inflamed tissue, there should be increases in the number of mature and immature neutrophils in the circulation. This is called a *regenerative left shift* and is characterized by a neutrophilia with an increased number of band neutrophils. A left shift should not be thought of as just the result of a bacterial infection, although this is a common cause. Immature neutrophils representing greater than 10% of the neutrophils in a cat with neutropenia is also called a *regenerative left shift*.

When tissue requirements for neutrophils outpaces the bone marrow's ability to replace them, most of the mature neutrophils will be in the tissues and the circulating neutrophils will be composed mostly of immature cells. If the number of bands (or other immature neutrophils) is greater than the number of mature neutrophils, a *degenerative left shift* is present and is often associated with a guarded to poor prognosis.

Severe inflammation can cause changes in the morphology of the maturing neutrophil, leading to the presence of what are known as toxic changes. Döhle bodies are small, retained accumulations of grey-staining cytoplasmic endoplasmic reticulum. They represent mild toxic changes. Retention of ribosomes in the cytoplasm causes basophilia and, along with vacuolization, suggests more severe inflammation. In one study the presence of toxic neutrophils was associated with longer hospitalization.¹⁰² This same study also found that, unlike dogs, toxicity was not associated with increased mortality in cats. Toxic granules represent severe inflammation and, in Birman cats, must be differentiated from the nonpathologic neutrophil granulation anomaly seen in this breed.

Extreme neutrophilic leukocytosis is defined as a white blood cell count over $50 \times 10^9/L$ with more than 50% of

the cells identified as neutrophils.⁶⁴ This finding is associated with a grave prognosis; 76 of the 104 cats in a study of extreme neutrophilic leukocytosis died as a result of the underlying disease.⁶⁴ Surprisingly, only 29 of the cats were febrile. Categories of disease causing this extreme white blood cell count included various types of infections, malignancies, immune-mediated diseases, and severe tissue necrosis. The highest risk of death associated with extreme neutrophilic leukocytosis was in cats with neoplasia.⁶⁴

Neutropenia

A neutrophil count below the reference range for the laboratory may be caused by overwhelming tissue needs, decreased production or abnormal release of neutrophils by the bone marrow, or immune-mediated destruction (Box 25-4). Deficient neutrophil production

is caused by infection with FeLV, FIV, or feline parvovirus (panleukopenia); drug administration; or myelophthisis. Because the half-life of circulating neutrophils, at 7 to 10 hours, is shorter than that for erythrocytes or platelets, neutropenia is often the first evidence of bone marrow disease.

Approximately half of cats with FeLV-related disease have neutropenia.⁴³ Mild neutropenia appears to be the most common change and is associated with mild lymphopenia and normal hematopoiesis. Moderate neutropenia is associated with hypoplastic bone marrow and must be differentiated from infection with feline parvovirus.⁴³ Severe neutropenia is caused by ineffective maturation and release of neutrophils by the bone marrow and is associated with a paradoxical marrow granulocyte hyperplasia because the cells produced are not released to the circulation effectively. FeLV can also cause a cyclic neutropenia, with the lowest neutrophil count occurring every 8 to 18 days.⁴³

Occasionally, a healthy cat will be identified with neutropenia after a CBC is performed as part of wellness or preanesthetic testing. It is often difficult to know how aggressively this finding should be pursued. The history and physical examination should be revisited in a more thorough manner. The veterinarian should ensure that a blood smear has been examined to confirm the neutropenia. A new blood sample of adequate volume should be collected for a repeated CBC to eliminate laboratory or blood collection errors.¹³ If the cat is easygoing, the sample may be collected after exposure to a mild stressful event such as running tap water. Epinephrine secretion will mobilize neutrophils from the marginated pool into the circulating pool for sampling. If the neutrophil count is over $2 \times 10^9/L$, monitoring the cat's temperature and attitude at home is probably sufficient.⁸⁵ Another reason for an apparently healthy cat to have a mild neutropenia is the manner in which laboratory reference ranges are determined. The reference range is designed to catch 90% of normal patients, meaning that 5% of normal cats will fall below the reference range for neutrophil counts and be considered neutropenic despite being normal for that individual. Sometimes the neutrophil count will persist below $1 \times 10^9/L$, necessitating further investigation. A serum biochemical profile and urinalysis should be performed if not already done. Urine can also be collected for culture. The cat's retroviral status should be ascertained and imaging of the chest and abdomen performed to look for abnormalities. If the neutropenia persists for more than 1 week, the veterinarian should consider performing a bone marrow examination in an attempt to catch bone marrow disease early.¹³

An afebrile cat with a neutrophil count below $0.5 \times 10^9/L$ has an increased risk of infection with normal gastrointestinal, nasal cavity, or skin bacteria. Broad-spectrum antibiotics should be administered when

BOX 25-4

Some Causes of Neutropenia in Cats

1. Increased tissue demand or destruction
 - a) Severe bacterial infections
 - b) Drug induced
 - c) Immune mediated
 - d) Paraneoplastic
2. Neutrophil shift from circulating to marginated pool
 - a) Endotoxic shock
3. Decreased bone marrow production
 - a) Myelophthisis
 - i. Neoplasia
 - ii. Myelofibrosis
 - b) Drug-induced (idiosyncratic)
 - i. Chloramphenicol
 - ii. Trimethoprim-sulfa
 - iii. Griseofulvin (especially in FIV-positive cats)
 - iv. Methimazole
 - v. Propylthiouracil
 - vi. Albendazole
 - vii. Anticancer drugs
 - viii. Immunosuppressive drugs (e.g., azathioprine)
 - c) Infectious disease
 - i. FeLV
 - ii. FIV
 - iii. Feline parvovirus (panleukopenia)
 - iv. Histoplasmosis
 - d) Idiopathic
4. Defects in neutrophil precursor maturation and release from bone marrow
 - a) Drug-induced (as above)
 - b) FeLV/FIV infection
 - c) Myelodysplasia
 - d) Cyclic neutropenia

FIV, Feline immunodeficiency virus; FeLV, feline leukemia virus.

neutrophil counts drop below 0.5×10^9 cells/L and continue until the neutrophil count is over 2×10^9 /L.⁸⁵ These cats should be isolated at home to decrease the risk of infection. They should be kept indoors, and the owner should monitor the cat's appetite, attitude, and temperature. The owner should refrain from giving the cat table scraps.¹³ Constant communication between the veterinarian and owner is essential.

A cat with a neutrophil count below 0.5×10^9 /L, fever, and an unconfirmed bacterial infection should be hospitalized, preferably in isolation, for investigation into the cause of the neutropenia and supportive care. The evaluation would be similar to the workup mentioned previously. Additional tests, depending on physical findings, might include arthrocentesis, cerebrospinal fluid collection, airway wash, echocardiography, and blood cultures.¹³ The cat should be closely monitored while hospitalized. Parameters to monitor include temperature, respiratory rate, body weight, urine output, blood pressure, and central venous pressure. Hands should be thoroughly washed and laboratory coats changed before handling these cats. One thermometer should be designated for use in this particular cat. Broad-spectrum bactericidal antibiotics should be administered through an aseptically maintained intravenous catheter. Antibiotic administration should continue for 1 to 7 days past the return of the neutrophil count to above 1×10^9 /L and resolution of the fever.⁸⁵ Cats with confirmed pulmonary, urinary tract, or soft tissue infections require antibiotics for a minimum of 7 days past return of the neutrophil count to above 1×10^9 /L and resolution of clinical signs and radiographic changes.⁸⁵ A reduction in fever would be expected 72 hours after appropriate antibiotic administration.⁸⁵ Potential causes for apparent treatment failure include infection with something other than bacteria, a bacteria not sensitive to the chosen drug, or poor host defenses.

Changes in the Numbers of Other Leukocytes

A significant eosinophilia may be seen in cats with endoparasitism or ectoparasitism, certain neoplasms such as mast cell tumors, hypersensitivity reactions such as asthma and eosinophilic gastritis, hypereosinophilic syndrome, or hyperthyroidism.⁴³ An increased eosinophil count by itself should not be used to confirm eosinophilic disease, and the degree of eosinophilia is not helpful in differentiating among the various eosinophilic disorders. Non-neoplastic lymphocytosis in cats can be seen along with a mature neutrophilia in a physiologic leukocytosis or after antigenic stimulation. Lymphopenia is a nonspecific finding in many ill cats. Monocytosis is also a nonspecific finding in cats and has little diagnostic value. A decreased number of monocytes is insignificant. Basophilia is interpreted in a manner similar to eosinophilia.

Hypereosinophilic Syndrome

Hypereosinophilic syndrome is a disease characterized by a mature eosinophilia and eosinophilic infiltration into many organs and is usually fatal. Clonal expansion of type 2 helper T ($T_{h}2$) cells secreting eosinopoietic factors such as interleukin-5 (IL-5) result in increased eosinophil survival.¹³⁴ The eosinophils infiltrate the liver, spleen, lymph nodes, bone marrow, and the gastrointestinal tract and result in organ failure. Almost three times as many female cats are affected as male cats.¹¹ Clinical signs depend on the organ affected. Vomiting, diarrhea, anorexia, fever, weight loss, and pruritus have been reported. Diagnosis depends on demonstrating excessive eosinophilic infiltration into numerous organs. Often, a fine-needle aspiration biopsy of the liver, spleen, or an affected lymph node will suffice. Although glucocorticoids have been used, no therapy has proved effective in cats. Imatinib mesylate (Gleevec, Novartis), a signal inhibitor, has been used successfully in humans.¹⁰ Other promising treatments include the use of anti-IL-5 antibodies, IL-5 receptor blockers, and eosinophil chemotaxis inhibitors.¹³⁴

Birman Hypotrichosis and Thymic Atrophy

A severe combined immunodeficiency has been identified in Birman kittens born hairless. These kittens are T cell deficient as a result of thymic atrophy and die within a few days of birth. Necropsy findings include a lack of a thymus and aplastic lymph nodes. The disorder has an autosomal recessive mode of inheritance.²⁸

Birman Neutrophil Granulation Anomaly

Birman neutrophil granulation anomaly is a hereditary trait in Birman cats. The trait is transmitted in an autosomal recessive manner. Neutrophil function is unaffected, and no treatment is necessary. The increased granularity of the cytoplasm of the abnormal neutrophils resembles the cytoplasm of immature cells. The main concern is to differentiate the anomaly from toxic granulation found in severely ill cats.¹⁰

Chédiak–Higashi Syndrome

Although light blue smoke-colored Persian cats with yellow-green eyes may be attractive, they also may have Chédiak–Higashi syndrome (CHS). Homozygous cats affected by CHS are prone to bleeding and infections and usually die at an early age. They also tend to have abnormal brain stem auditory evoked responses.¹¹ The disease is an autosomal recessive inherited trait. Decreased bone marrow release of neutrophils leads to neutropenia. The neutrophils that do make their way into circulation have defects of intracellular killing and

motility.¹⁰ The large granules found in the neutrophils are friable and rupture spontaneously, causing tissue damage such as cataracts noted in cats with this disease.¹¹⁵ Impaired natural killer (NK) cell and cytotoxic lymphocyte function has also been identified. Abnormal platelet granule release results in impaired platelet aggregation and an increased buccal mucosal bleeding time. Diagnosis is based on signalment, history, and physical findings. A few large, eosinophilic granules can be found in the neutrophils, and comparison of the hair shafts of affected animals to those of normal cats reveals large melanin granules in the affected cat.¹⁰ At present, there is no cure for the disease. Care should be taken to avoid and control hemorrhage in affected cats. Use of drugs known to cause platelet dysfunction is contraindicated. Administration of recombinant canine granulocyte colony-stimulating factor (rcG-CSF) or IL-2 has been shown temporarily to improve neutrophil function. A bone marrow transplant may resolve the neutrophil and platelet dysfunction, but the neurologic and renal changes will remain.¹⁰ Affected cats should not be bred, and their unaffected parents, who are obligate carriers, should be removed from breeding programs.

Pelger–Huët Anomaly

Pelger–Huët anomaly is an uncommon, benign congenital defect of leukocyte development found in domestic shorthair cats that is transmitted in an autosomal dominant manner.¹⁰ Affected cats are heterozygous because the homozygous defect is lethal in utero. The disorder is characterized by hyposegmentation of granulocytes and monocytes. Cell function is normal, and no treatment is necessary. Affected neutrophils resemble immature band cells; affected cells, however, have mature, clumped chromatin. A healthy cat with this anomaly may be reported as having a degenerative left shift without toxic change. It is important to differentiate a true left shift associated with sick cats from healthy cats with this anomaly to avoid unnecessary, potentially expensive, and possibly invasive testing and treatment.

Pseudo Pelger–Huët anomaly is a transient condition caused by various illnesses and administration of drugs such as ibuprofen or anticancer agents.¹⁰ The changes resolve after resolution of the disease or withdrawal of the offending drug. Drug-associated changes are idiosyncratic.

DISORDERS OF HEMOSTASIS

Hemostasis is a complex and coordinated system, with a balance between clot formation and dissolution. Its sole purpose is to seal the defects in vessel walls that occur in health and disease until they can be mended. Disorders of this system can lead to clinically significant

bleeding. Fortunately, abnormalities of hemostasis are rare in cats, and spontaneous bleeding is uncommon in patients with these abnormalities. Normal hemostasis comprises primary and secondary hemostasis and fibrinolysis. Primary hemostasis involves interactions among the vessel wall, platelets, and von Willebrand factor (vWF), whereas secondary hemostasis results in the formation of a fibrin mesh. Fibrinolysis is the process of dissolving previously formed clots. It is important to realize that hemostasis (primary and secondary) and fibrinolysis, along with the various inhibitory and amplification steps, are all happening at the site of vascular injury simultaneously, and not in a stepwise fashion.

Primary Hemostasis

Platelets are small anucleate cells formed in the bone marrow by fragmentation of megakaryocytes. A single megakaryocyte may produce thousands of platelets, with thrombopoiesis taking approximately 4 days. The survival time of platelets in circulation is 1 to 2 days, after which they are removed by macrophages of the mononuclear phagocyte system in the spleen.

Vascular damage leads to local vasoconstriction and exposes subendothelial collagen, to which platelets adhere by way of a membrane receptor. Adhesion to collagen is made more efficient by the presence of vWF. After adhesion platelets undergo shape change (to increase their surface area) and activation (release of granular contents), with the subsequent recruitment of more platelets that adhere to the wound and one another. Platelet-to-platelet adhesion is known as *aggregation*. Platelet adhesion to the vessel wall and aggregation to one another form a temporary and unstable plug in the damaged vessel that is sufficient to stem bleeding from the minor defects associated with daily life.

Secondary Hemostasis

Mediators of secondary hemostasis are produced in the liver (clotting factors) and cells in and surrounding the vessel wall (tissue factor). Clotting factors are released into circulation in inactive form and require activation to become functional. For the hepatocyte to produce factors II, VII, IX, and X, vitamin K₁ must be present in adequate quantities.

Vascular damage exposes tissue factor to the circulation, which combines with circulating activated factor VII (VIIa) to activate factor X (Xa), the extrinsic pathway of coagulation. Factor Xa activates and combines with factor V (Va). Factors Xa and Va combine with ionized calcium (Ca^{2+}) and phospholipid on the platelet membrane, which localizes the formation of thrombin from prothrombin to the area of the platelet plug. The formation of thrombin is the beginning of the common pathway. Thrombin catalyzes the conversion of

fibrinogen to soluble fibrin and amplifies the coagulation process by activating other procoagulant factors, particularly those of the intrinsic pathway. Finally, after activation by thrombin, factor XIIIa catalyzes the cross-linking of the fibrin strands into an insoluble mesh that stabilizes the platelet plug produced by primary hemostasis.

Classically, the intrinsic and extrinsic pathways were thought to be equally important in initiating the coagulation process. However, in live animals the beginning of the intrinsic pathway, activation of factor XI, is catalyzed by thrombin generated by the extrinsic pathway. Therefore it is more appropriate to consider the extrinsic pathway as the initiator of coagulation and the intrinsic pathway as the sustainer or amplifier of coagulation.¹⁰³

Inhibition of coagulation prevents excessive and uncontrolled clot formation. Antithrombin (AT), previously known as *antithrombin 3*, is produced by the liver and inhibits the actions of thrombin, IXa, Xa, and XIa. The presence of heparin on the surface of the vascular endothelial cell augments the function of AT and helps control clot formation at the edges of the damaged vessel localizing the clot to the damaged area.¹⁰³ Like factors II, VII, IX and X, synthesis of protein C and protein S is vitamin K₁ dependent, and they are released in inactive form by the liver. After binding to thrombomodulin on the endothelial cell, thrombin loses its coagulant activity and activates protein C, which combines with protein S to inactivate factors V and VIII.¹⁰³

Fibrinolysis

Clot dissolution is mediated by plasmin produced by the liver as plasminogen. Tissue plasminogen activator (tPA) is produced by endothelial cells and, as its name suggests, activates plasminogen. Plasmin degrades fibrinogen and soluble and insoluble fibrin into fibrin degradation products (FDPs), which also have inhibitory actions on platelets and various clotting factors. Degradation of cross-linked or insoluble fibrin also results in the production of D-dimers. Inhibition of fibrinolysis occurs by way of inhibition of tPA or plasmin by various proteins.

Etiology of Hemostatic Disorders

Primary hemostatic defects result from vasculopathy, thrombocytopenia, platelet dysfunction, or a combination of these (Box 25-5). They may be congenital or acquired. Ehlers–Danlos syndrome is an uncommon inherited defect of collagen. Cats with this condition typically have hyperelastic skin. Because normal subendothelial collagen is required for platelet adhesion to the damaged vessel, cats with Ehlers–Danlos syndrome have a propensity to bleed, similar to cats with platelet dysfunction. Acute, traumatic bleeding may result in

thrombocytopenia as the platelets are consumed in an attempt to control the bleeding. However, the decrease is usually mild insofar as thrombopoiesis ramps up quickly and the spleen releases sequestered platelets. Very low platelet counts in bleeding cats are usually the cause of the bleeding, not caused by bleeding.⁶⁶

Reduced activity or concentrations of clotting factors can be congenital or acquired and result in secondary hemostatic disorders (Table 25-5). Factor XII deficiency is the most common congenital coagulopathy in cats.⁸⁹ This is an autosomal recessive disorder resulting in prolongation of the partial thromboplastin time (PTT) or activated clotting time (ACT). Because *in vivo* generation of fibrin does not require activated factor XII, no spontaneous bleeding is associated with this defect. It is most often identified in the course of a preoperative evaluation before an elective surgery or invasive diagnostic procedure such as a liver biopsy.¹² Factor IX deficiency (hemophilia B) also results in prolongation of the PTT and ACT.³⁸ This is an X-linked recessive disorder that may lead to bleeding in severely affected male cats. As with all bleeding from factor deficiencies, hematomas and cavitary bleeding are most likely. A definitive diagnosis is based on identification of decreased factor IX activity. Once the gene encoding the feline factor IX protein is sequenced, a genetic test may become

TABLE 25-5 Secondary Hemostatic Defects

Inherited Factor Deficiency	Comments
Factor I (fibrinogen)	DSH, DLH
Factor VII	DSH
Factor VIII (hemophilia A)	DSH, DLH, Persian, Havana brown, Siamese, Himalayan
Factor IX (hemophilia B)	DSH, DLH, British Shorthair, Siamese
Factor X	DSH
Factor XII	DSH, DLH (does not cause bleeding)
Acquired Factor Deficiency	
Hepatic disease	Factors II, VII, IX, and X
DIC	FDPs also inhibit the function of multiple factors
Vitamin K ₁ Antagonism or Deficiency	
Anticoagulant rodenticide	
Severe cholestasis	Decreased bile-associated fat-soluble vitamin absorption
Phenobarbital	Decreased activities of factors II and VII

DSH, Domestic shorthair; DLH, domestic longhair; FDPs, fibrin degradation products.

BOX 25-5 Selected Primary Hemostatic Disorders

Thrombocytopenia

A—Decreased Bone Marrow Production

Infection

- Retroviral infections
- Systemic mycosis involving the marrow
- Feline infectious peritonitis
- Cyttauxzoonosis

Neoplasia

Drugs

- Methimazole
- Propylthiouracil
- Griseofulvin
- Cytotoxic drugs such as chlorambucil
- Chloramphenicol
- Trimethoprim-sulfa
- Albendazole

Myelodysplasia

B—Increased Destruction

Immune mediated

Primary

Secondary

- Drugs
 - Penicillins
 - Cephalosporins
 - Sulfonamides
 - Methimazole
 - Propylthiouracil
- Infection
 - Retroviral infections
 - *Mycoplasma haemofelis*
 - Bacterial
- Neoplasia
- Modified-live vaccines
- Inflammatory disorders such as pancreatitis

C—Increased Use/Consumption

DIC

- Liver disease
- Neoplasia
- Sepsis
- FIP
- Shock

Hemorrhage (mild decrease only)

D—Sequestration in the Spleen

Infiltrative disease

Splenitis

NSAIDs, Nonsteroidal antiinflammatory drugs; *IMTP*, immune-mediated thrombocytopenia; *DIC*, disseminated intravascular coagulation; *FIP*, feline infectious peritonitis.

Platelet Functional Defects

A—Inherited

- von Willebrand disease
- Chédiak-Higashi syndrome

B—Acquired

Drugs

- NSAIDs
- Clopidogrel
- Penicillins
- Diazepam
- Acepromazine
- Ketamine
- Propofol

Uremia

Antiplatelet antibodies from IMTP

Fibrin degradation products from DIC

Liver disease

Myeloproliferative disease

Vessel (Endothelial) Disorders

Ehlers–Danlos syndrome

Vasculitis

- FIP

available. Cats with less than 1% of the normal activity often die at birth from umbilical bleeding. Cats with greater than 5% activity may have no clinical signs until challenged by trauma or surgery.³⁸ Clinically affected cats are treated with appropriately typed and

cross-matched fresh frozen plasma or, if sufficiently anemic, whole blood transfusions. It must be remembered that hemostatic abnormalities in cats are very uncommon, and spontaneous bleeding associated with them is even more unusual.⁸⁹

A combination of primary and secondary disorders may be found in cats with DIC. In one retrospective study, 21 of 69 cats with hemostatic abnormalities had laboratory evidence of DIC, the most common hemostatic abnormality. Most of these cats did not have clinically significant bleeding. Neoplasia, feline infectious peritonitis, and hepatic disease were the most common causes of DIC in this study.⁸⁹ Another study identified neoplasia and pancreatitis as the most common diseases associated with DIC.²⁴ Only 7 of the 46 cats with DIC in this study had evidence of hemorrhage. DIC consists of excessive thrombin formation combined with the loss of inhibitory control and stimulation of inflammation.¹⁰⁵ Normally kept out of circulation by the vascular endothelium, intravascular production of tissue factor by neoplastic cells or inflammatory cytokine-stimulated monocytes initiates DIC.¹⁰⁵ The initial phase of DIC is hypercoagulable, with inhibitors counterbalancing the formation of thrombin. This is the non-overt or compensated stage of DIC. Although difficult to detect clinically, treatment at this stage may prevent progression to the next stage. When coagulation inhibitors are overwhelmed, widespread microthrombosis occurs, leading to tissue hypoxia and death. This overt or decompensated phase is clinically important in the deterioration of the patient's condition. In the study by Estrin and coworkers,²⁴ 43 of 46 cats with DIC died or were euthanized. The thrombotic stage is much more common than the hemorrhagic stage of DIC, as demonstrated by the few cats in DIC that bleed.²⁴ The late stage occurs when there is consumption of clotting factors and platelets. Neoplasms can also cause hemostatic abnormalities by causing thrombocytopenia or platelet dysfunction or by producing procoagulants. Inhibition of clotting factors and intrinsic anticoagulants are also potential mechanisms by which substances produced by neoplasms can affect the clotting system.

A multifactorial clotting factor defect has been identified in Devon Rex cats involving a decrease in the vitamin K₁-dependent activity of the enzyme gamma-glutamyl carboxylase.⁶² Without the function of this enzyme, vitamin K₁ is not properly recycled, resulting in decreased activation of clotting factors II, VII, IX, and X. An autosomal recessive mode of inheritance is suspected.^{62,67} Affected cats may present for spontaneous intracavitary bleeding or uncontrolled postoperative hemorrhage. There may be a history of similar episodes in related cats. Both the prothrombin and activated partial thromboplastin times are significantly prolonged.⁶⁷ Severe liver failure, intestinal malabsorption, and exposure to anticoagulant rodenticide toxins must be ruled out. Treatment involves transfusion with appropriately typed and cross-matched blood because there are many individuals with blood type B in this breed. Intravenous or subcutaneous administration of vitamin K₁ at 5 mg/cat every 24 hours is also required.

Long-term normalization of the laboratory and clinical abnormalities is accomplished by using oral vitamin K₁ at 2.5 to 5 mg/cat every 24 hours.^{62,67} Treatment may be required for the life of the patient. This disorder should be suspected in any Devon Rex cat presenting with a history of unexpected bleeding.

Clinical Evaluation

Cats with hemostatic abnormalities are often brought to see the veterinarian for reasons other than spontaneous bleeding. Unlike dogs, cats with hemophilia rarely develop detectable spontaneous bleeding; the disease is suspected after prolonged intraoperative bleeding is noted, often during elective surgery such as ovariohysterectomy or castration. Cats tolerate thrombocytopenia and lower concentrations of clotting factors better than dogs do.^{66,89} This may be partially due to a cat's more sedentary lifestyle. Many platelet disorders are secondary to other diseases, and the patient may exhibit signs related to that disease. The patient may be volume contracted or have signs of anemia such as weakness, lethargy, pallor, or respiratory distress. Cats with severe hereditary hemostatic disorders may exhibit bleeding at a young age before elective surgery. Owners should be questioned about potential exposure to anticoagulant rodenticides or drugs known to cause platelet dysfunction. Evidence of hemostatic problems such as melena, bruising, or petechiation may not be recognized by the owner as bleeding. Excessive or prolonged bleeding from previous traumatic events, surgery, dental procedures, or nail trims should be queried.

Spontaneous bleeding resulting from severe thrombocytopenia or platelet dysfunction usually arises from small breaks in capillaries that cannot be plugged by platelets. These pinpoint hemorrhages in the skin, mucosa, or conjunctiva are known as *petechiae*. Coalescence of petechiae into a larger area of bruising is known as *ecchymosis*. A cat presenting with either of these two abnormalities likely suffers from severe platelet disease. However, cats with platelet disorders may also have epistaxis, hematemesis, melena, hyphema, or hematuria, signs often associated with clotting factor abnormalities. Cats with congenital factor XII deficiency rarely bleed spontaneously. A palpably enlarged spleen may be present if there is excessive immune-mediated destruction of platelets.¹³²

Diagnostic Plans

Most hemostatic abnormalities in cats are identified unexpectedly because they are usually subclinical. Once trauma has been ruled out, diagnostic evaluation of a bleeding cat revolves around deciding if the abnormality is with primary or secondary hemostasis or both. The initial step is to perform a CBC with a platelet count

and blood smear examination. Additional tests to consider, depending on clinical signs and results of the CBC, include a serum biochemical profile and urinalysis to identify potential systemic diseases (e.g., hepatic or renal failure) that may result in bleeding diathesis. Retroviral testing is imperative because FeLV is a common cause of thrombocytopenia. Thoracic radiography and abdominal ultrasonography might identify evidence of bacterial bronchitis or abdominal masses or organomegaly that may be responsible for immune-mediated thrombocytopenia or DIC. Sampling the bone marrow may yield clues as to the cause of unidentified thrombocytopenia. Because *M. haemofelis* infection occasionally causes thrombocytopenia, PCR testing for hemoplasmosis is suggested. If anemia is present, a positive Coombs' test may help prove the presence of Evans syndrome (primary immune-mediated anemia and thrombocytopenia).⁴⁴

Laboratory Evaluation of Primary Hemostasis

Primary hemostasis consists of interactions between vascular endothelial cells, platelets, and vWF. A buccal mucosa bleeding time (BMBT), along with a platelet count, is performed before evaluating the levels of vWF. A BMBT should be performed using a standardized stylet rather than a scalpel blade or a hypodermic needle; however, the latter instruments will suffice if the stylet is unavailable. The BMBT is difficult to perform in nonsedated cats and should be less than 4 minutes.⁶⁶ Longer times suggest an abnormality in any of the components of primary hemostasis. A normal BMBT eliminates primary hemostatic defects as a cause of the bleeding.¹⁰³

Platelet counting can be performed by an automated cell counter or manually using a hemacytometer, or it can be estimated by examination of the blood smear. The most common cause of thrombocytopenia when reported from a laboratory is artifact caused by platelet clumping. Clumped platelets cannot be counted separately by automated cell counters, which also have difficulty differentiating between the rather large feline platelet and the small feline erythrocyte. The following handling factors are among those that predispose feline platelets to clump:

- Traumatic venipuncture
- Slow sampling from a peripheral vein
- Refrigeration
- Use of EDTA for anticoagulation
- Sampling from a recently used vein or through catheters

A smear made from fresh blood should accompany any sample to the laboratory in case it is needed for estimation of platelet numbers. Smears made by the laboratory will be from blood refrigerated before making

the smear. Using sodium citrate as an anticoagulant can reduce, but not eliminate, the amount of clumping. A normal platelet count reported by the laboratory is probably normal and can be trusted. A low platelet count reported by an automated cell counter should always be confirmed by a manual count or by examination of a fresh blood smear. Estimation of platelet numbers is performed by examining the monolayer of a smear (which is an essential part of a CBC anyway) under oil immersion and counting the number of platelets in 5 to 10 fields. The average number of platelets per oil field is multiplied by 20 to get the number of platelets $\times 10^9/L$.⁶⁶ Many clumps suggest a normal number of platelets. A smear examination also allows for identification of shift platelets, evidence of increased marrow production of platelets. The presence of shift platelets precludes the necessity for collecting bone marrow. FeLV infection, a common cause of thrombocytopenia, is also associated with increased platelet volume.⁴⁴

Spontaneous bleeding caused by thrombocytopenia in cats usually occurs only when the platelet count is lower than $30 \times 10^9/L$.⁵¹ If bleeding occurs in a cat with a platelet count above this, the veterinarian should consider a concurrent platelet function defect or a secondary hemostatic problem. Because the BMBT evaluates hemostatic abnormalities resulting from platelet disorders in addition to problems with the vascular endothelium, it is unnecessary to perform this test when platelet counts are severely depressed. A prolonged BMBT in a cat with a platelet count over $30 \times 10^9/L$ suggests a vessel problem such as vasculitis or an inherited collagen defect, congenital or acquired platelet dysfunction, or von Willebrand disease. A detailed history should eliminate the possible exposure to drugs that can cause platelet dysfunction. Platelet function testing is usually performed only by special hemostasis laboratories and often requires freshly drawn blood samples.

Laboratory Evaluation of Secondary Hemostasis

Tests evaluating secondary hemostasis include those that test the extrinsic, intrinsic, and common pathways of secondary hemostasis and tests of fibrinolysis. The prothrombin time (PT) evaluates the extrinsic (the initiating pathway) and the common pathway by using tissue factor to activate factor VII and initiate clot formation. The test is rather insensitive insofar as it will be normal until more than 65% of the factor activity is lost¹⁰³ and is not affected by thrombocytopenia. The activated partial thromboplastin time (aPTT) evaluates the intrinsic (amplification pathway) and common pathways by activating factor XII to initiate clotting. Prolongation of this test also occurs only when over 65% of factor activity is lost. Thrombocytopenia does not affect the test results. The ACT essentially mimics the aPTT in that it also initiates clotting by activating factor XII. Accuracy is affected

by variations in the temperature at which the test is performed and by the experience of the operator in recognizing the endpoint of the test, which is the formation of a clot. The ACT is very insensitive insofar as it is not prolonged until more than 90% of the factor activity is lost. Severe thrombocytopenia will erroneously prolong the test as platelet cell membranes provide the phospholipids required by the test. An abnormal PT in the face of a normal aPTT suggests an abnormality in factor VII activity, because of either an inherited deficiency or early vitamin K₁ antagonism. An abnormal aPTT with a normal PT will occur if there are abnormalities in factors VIII (hemophilia A), IX (hemophilia B), XI, or XII. A patient with a prolonged aPTT is not predisposed to spontaneous bleeding.¹⁰³ If both the PT and aPTT are prolonged, a common pathway defect, multiple factor involvement, or late vitamin K₁ antagonism should be considered. Testing for hepatic failure would be appropriate in this situation. Specific factor activities can be assessed depending on the test results. A low platelet count in association with a prolonged PT and aPTT is consistent with DIC, and an evaluation of fibrinolysis is warranted.

Laboratory Evaluation of Fibrinogen and Fibrinolysis

Measurement of the thrombin time evaluates the conversion of fibrinogen to fibrin, and prolongation is suggestive of fibrinogen deficiency, abnormal fibrinogen structure, or inhibition of thrombin by FDPs or heparin. Low fibrinogen concentrations are due to an inherited deficiency, decreased production by the liver, or increased utilization from DIC. FDPs are formed by the plasmin-mediated dissolution of fibrinogen, soluble (not cross-linked) fibrin or insoluble (cross-linked) fibrin. Increased FDPs are indicative only of plasmin activation because they can be produced by breakdown of fibrinogen without the presence of a clot. D-dimers are the result of plasmin dissolution of cross-linked fibrin found in clots, and increases in this substance truly represent active thrombosis and fibrinolysis. Controversy exists regarding the sensitivity of the D-dimers test for the detection of DIC in cats.^{105,112} A combination of prolonged PT and aPTT, thrombocytopenia, and elevations in D-dimers is consistent with a diagnosis of consumptive coagulopathy, particularly if there are signs compatible with DIC or a disease known to cause DIC (e.g., neoplasia) is present.

Supportive Care for Cats with Hemostatic Disorders

Although most cats with hemostatic disorders do not present with spontaneous bleeding, supportive care for those that do is important in preventing serious

consequences. It is important to identify and control underlying disease; this may remove any triggers for secondary thrombocytopenia, platelet dysfunction, or DIC. Gentle handling is essential in preventing further damage to vessels. Cage rest in the hospital or at home, if possible, is imperative until the cause of the bleeding is isolated and brought under control. Pressure bandages may be required to control bleeding from surgical sites. Fractious cats may require sedation. Offering soft food may prevent gingival bleeding.¹³² Unnecessary trauma such as elective surgery or intramuscular injections should be avoided. However, should collection of bone marrow be required, the veterinarian should not hesitate to perform the procedure because bleeding is rarely a problem.

Drugs that affect platelet function, particularly NSAIDs, should be avoided. If the cat is thrombocytopenic, interfering with function of the remaining platelets will make the situation worse. Blood should be collected as atraumatically and infrequently as possible using small bore needles and preferably sampling from the jugular vein. Several minutes of compression after blood collection may be necessary to prevent hematoma formation. Cats requiring additional fluid support should receive fluids intravenously through a small-gauge catheter. Thoracocentesis or abdominocentesis is not recommended unless respiratory distress is present. Cats suspected of ingesting anticoagulant rodenticides should receive vitamin K₁. Cats with bleeding disorders related to biliary obstruction may also benefit from parenteral vitamin K₁.

A blood transfusion using fresh whole blood may supply needed clotting factors; platelets; and, if the patient is anemic, erythrocytes to cats with DIC. Blood administered to patients with DIC is more effective in controlling clotting factor consumption if heparin is used at the same time. Because cats usually tolerate thrombocytopenia without excessive bleeding, platelet transfusion should be considered when the count is less than $5 \times 10^9/L$, which is rarely encountered in this species. However, the veterinarian should always use clinical judgment and not base treatment solely on a number. Administration of platelets to cats with destructive or consumptive causes of thrombocytopenia is usually ineffective because the transfused platelets are quickly lost. Platelets administered to cats with bone marrow failure will last a few days, the normal life span of a platelet.

Thrombocytopenia

A genuine decrease in platelet numbers is an uncommon finding in cats. The most common cause of thrombocytopenia is clumping of platelets. If it is determined that the low platelet count is real, a concerted effort should be made to identify the underlying cause. One study of

41 cats with thrombocytopenia identified only one cat with primary immune-mediated platelet destruction.⁵¹ Even in cats with documented presence of platelet-bound antibodies, 17 of the 19 cats had identifiable underlying causes for the immune-mediated disease.¹³² The most commonly identified causes of feline thrombocytopenia are infectious. In the previously mentioned study of 41 cats with thrombocytopenia, 19 (46%) had infectious diseases identified as the cause of the thrombocytopenia. Of those 41 cats, 37 were tested for FeLV antigen and 11 (30%) of them were positive. The next most common cause was various types of malignancy, which affected 16 (39%) of the cats.⁵¹

Immune-mediated thrombocytopenia (IMTP) is caused by the removal of antibody-coated platelets by macrophages in the spleen. Similar to IMHA, these antibodies may be directed against antigens on the surface of the platelet or against antigens similar in structure to platelet antigens. Disease may reveal hidden antigens on the platelet surface. Antigen-antibody complexes may deposit on the platelet membrane and elicit a type 3 hypersensitivity response (innocent bystander destruction). Platelets also have Fc receptors on their surface and may bind the Fc portion of an antibody to these receptors. Antiplatelet antibodies may also contribute to platelet dysfunction.¹³² Because primary IMTP is rare in cats, it is important not to immediately administer immunosuppressive doses of glucocorticoids to cats with thrombocytopenia. Laboratory proof of the presence of antiplatelet antibodies is difficult to obtain. Specialized laboratories may be able to perform a flow cytometric assay for platelet-bound antibodies. In most veterinary hospitals the diagnosis of primary IMTP is made by the elimination of secondary etiologies of platelet destruction and response to immunosuppressive therapy.

Once secondary causes of IMTP have been eliminated, primary IMTP may respond well to oral prednisolone at 2 to 4 mg/kg every 24 hours.⁶⁶ In a report of four cats with presumed primary IMTP, two of the three survivors required either administration of a different glucocorticoid or the addition of another immunosuppressive drug to control the disease.⁶ More information on the use of additional immunosuppressive drugs is found in the section on treating IMHA. The immunosuppressive regime is continued until the platelet count has reached and remains above 75 to $100 \times 10^9/L$ for at least 1 to 2 weeks. Attempts at reducing the dose should not be made unless the platelet count is acceptable and stable. The veterinarian should start by reducing the dose of any drug added to the glucocorticoid. There is no sense in reducing the dose if the patient is not in remission, as defined by a stable platelet count at a reasonable level and a cat that is not bleeding. It may not be possible, and indeed is unnecessary, to have the platelet count reach the reference range for the laboratory. Once the

prednisolone dose reaches 0.5 mg/kg every 24 hours, alternate-day dosing may be attempted. If the platelet count starts to decrease at any point, the veterinarian should return to the last effective dose. Frequent monitoring is necessary because relapses are common.⁶

The etiology of hemostatic disorders is often difficult to identify, insofar as hemostasis is complex and difficult to fully understand. Lack of experience in dealing with these disorders contributes to the difficulty. Fortunately, hemostatic diseases in cats are rare, and significant spontaneous bleeding is even more uncommon.

DISORDERS OF THE SPLEEN

The spleen has long been recognized as inessential for life. It is not, however, unimportant; its function in maintaining homeostasis is slowly being recognized. Understanding the microanatomy of the spleen is necessary to understand its function in health and disease. The functions of the spleen include storage of erythrocytes and platelets, extramedullary hematopoiesis, and blood filtration. It is also an important immune organ. Disorders of the feline spleen are uncommonly diagnosed.²⁰

Microanatomy and Circulation

The splenic parenchyma is made mostly of white and red pulp. White pulp is composed of lymphoid nodules and loose collections of lymphocytes surrounding small arterioles. Red pulp consists of venous spaces into which arteriolar blood empties along with the macrophage-populated structural framework of the spleen. In addition to the macrophages, there are increased numbers of lymphocytes and megakaryocytes in the red pulp. Blood enters at the hilus and makes its way through small arterioles to capillaries terminating in the lymphoid nodules of the white pulp or to capillaries leading into the red pulp. Some of the arterioles entering the white pulp continue on to the venous side of the circulation. Venous blood exits the spleen at the hilus and enters the portal circulation. The path an erythrocyte takes between the arterioles and the venous circulation varies by species. In dogs the circulation is sinusoidal; to enter the red pulp, cells have to squeeze through splenic cords and vessel endothelial cells. Cats, however, have nonsinusoidal microcirculation.⁶⁸ Most erythrocytes pass into the red pulp and flow directly into the venous circulation unimpeded by endothelial cells and unscrutinized by immune cells.⁴⁴

Function

The four major functions of the spleen are storing blood, filtering blood, serving as a site for hematopoiesis, and acting as an organ of immunity. The spleen can store

between 10% and 20% of the circulation erythrocyte mass and up to 30% of the platelets.^{68,113} There are three patterns of blood flow through the spleen. Under normal conditions most (90%) of the blood enters the rapid pool and flows through the spleen in 30 seconds. The remainder flows through in approximately 8 minutes (the intermediate pool) or 60 minutes (the slow pool). Blood can be shunted in and out of these pools as needed during times of stress. Because of the nonsinusoidal nature of the feline spleen, splenic contraction does not result in the movement of as many erythrocytes into the circulation as it does in dogs.⁸⁴ Most of the stored platelets are in the slow pool. Iron from recycled erythrocytes is stored in the spleen while awaiting transport to the bone marrow for use in the production of hemoglobin for incorporation into new erythrocytes.

The spleen functions as an organ of filtration. As erythrocytes squeeze through the parenchyma, they come into contact with macrophages whose function is to remove rigid particulate matter from the cell. These particles include parasites, nuclear remnants (Howell-Jolly bodies), and denatured hemoglobin (Heinz bodies). The high metabolic activity in the spleen results in areas with a slightly anaerobic environment.¹¹³ The decreased oxygen content causes the cell membrane of old, badly damaged, or abnormal erythrocytes to stiffen. This renders them unable to undergo the deformation required to pass through the sinuses, and they are removed from circulation.¹¹³ These cells, and those coated in antibodies, are phagocytosed by nearby macrophages, which process the hemoglobin and recycle the iron. Owing to the nonsinusoidal nature of the feline spleen, the cat is less efficient at removing these cells than is the dog and is one reason that normal cats have higher numbers of Heinz bodies present in the circulation. In addition to obsolete erythrocytes, the spleen also removes bacteria from the blood.⁶⁸

The fetal hematopoietic function of the spleen in cats ceases at birth.⁶⁸ In situations of increased need overwhelming the bone marrow, the adult spleen can resume these functions. These conditions can include infiltrative bone marrow disease, immune-mediated hemolysis or thrombocytopenia, inflammatory or infectious diseases, and malignancy. Splenic extramedullary hematopoiesis results in either generalized or nodular splenomegaly and is less common than in dogs.

The spleen serves as a major site for clearing microorganisms and is important in the immune response to circulating antigens.¹¹³ The spleen is the principle site of IgM production and is therefore important in the early immune response. The many macrophages act in the phagocytosis and processing of antigens. Various cytokines are produced in the spleen to both improve neutrophil function and activate complement. Soluble antigens are sent to the lymphoid centers of the white pulp, whereas particulate antigens lodge in the red pulp,

where they are phagocytosed and sent by macrophages to the lymphoid follicles in the white pulp for further processing.¹¹³ The spleen also removes antibody-coated erythrocytes (extravascular hemolysis) and platelets during immune-mediated events.

Clinical Signs and Physical Findings

Historical findings in cats with splenic disorders are often vague and usually relate to an underlying disorder. Common complaints include anorexia, vomiting, diarrhea, weight loss, and an enlarged, sometimes painful abdomen. Most of these signs relate to a mass effect in the abdomen with organ displacement. Polyuria and polydipsia may occur; the pathogenesis is unclear, and it resolves after splenectomy.² The most reliable physical finding in cats with splenic disease is splenomegaly. The enlargement may be generalized or focal. However, not all enlarged spleens are abnormal, nor are they always palpable. Gentle palpation is important because a diseased spleen is often friable and may rupture with rough handling. Other physical changes may be present depending on the primary disease. Peripheral or abdominal lymph node enlargement may be present. At times, it is difficult to differentiate splenomegaly from enlargement of the liver.

Diagnostic Plans

When splenomegaly is identified in a patient, a search should begin for an underlying cause. Blood should be obtained for a CBC. Splenic disease is a possible cause for the presence of nucleated red blood cells in the face of a normal PCV. Hypercalcemia may be due to lymphosarcoma. If malignancy is suspected, radiographic views of the chest should be obtained to look for evidence of metastasis. Morphologically abnormal cells or a proliferation of normal cells in the circulation may suggest leukemia. A bone marrow biopsy may be required in this situation. All cats with splenic enlargement should also be checked for retroviral infection.

Compiling a list of differentials may be facilitated by classifying the enlargement as generalized or focal. Generalized enlargement (or splenomegaly) can be caused by congestion or by infiltration with neoplastic or inflammatory cells and is the most common type found in cats.¹¹³ Focal enlargement can be caused by neoplastic or non-neoplastic lesions. The nonsinusoidal nature of the feline spleen decreases its susceptibility to the formation of nodular hyperplasia and hematomas.¹¹³

Visualizing the spleen is important in determining the type of enlargement. Abdominal radiography allows for easy visualization of the spleen, although the location varies owing to its mobility within the abdomen. The head of the spleen is located caudal to the stomach and cranial to the left kidney and appears triangular on a

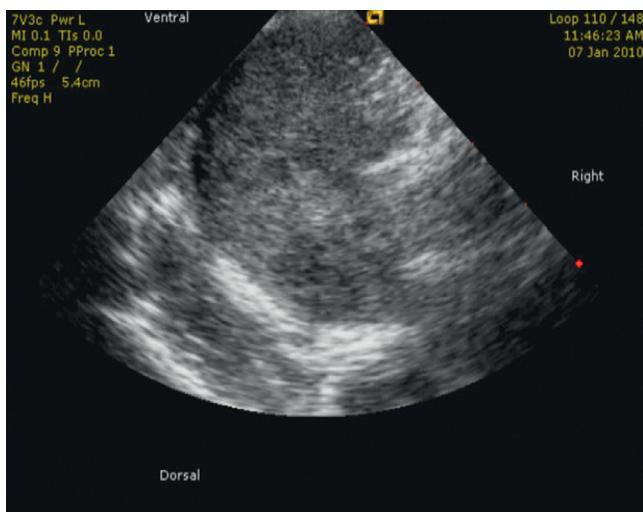


FIGURE 25-16 A transverse sonogram of the spleen of a cat with mast cell infiltration. Note the irregular hypoechoic (darker) area in the middle of the image.

ventrodorsal projection. The tail of the spleen is uncommonly seen in cats,² so visualizing the tail on an abdominal radiograph is supportive of splenomegaly. Lesions rarely alter the radiodensity of the spleen. Ultrasonography allows assessment of the parenchymal architecture and the surface contour (Figure 25-16). Ultrasonography is sensitive in detecting splenic lesions, but a definitive diagnosis requires sampling the lesion.⁴ Focal changes in the parenchyma and irregularities in the surface are criteria for lesions in the spleen. Nodular changes within the parenchyma are easily identified as hypoechoic or hyperechoic to the rest of the parenchyma. Benign nodules are difficult to differentiate from malignant masses without using contrast ultrasonography or splenic biopsy techniques. Fine-needle aspiration biopsies can be guided by the ultrasound image. Unfortunately, there are no objective criteria for evaluating the size of the organ in cats.

Sampling the splenic parenchyma is crucial in establishing an etiologic diagnosis. A fine-needle aspiration biopsy of a lesion may be sufficient because most diseases of the spleen exfoliate readily.² In a study evaluating the correlation of the sonographic appearance of splenic lesions to cytologic and histologic diagnoses in 29 dogs and 3 cats, 19 of the aspirated samples matched the histologic diagnosis.⁴ Carefully performed fine-needle biopsies of the spleen are safe in cats with thrombocytopenia or coagulopathy.² If ultrasound is unavailable for guidance, an enlarged spleen can be immobilized manually. A 22-gauge needle can be used to obtain cells by moving the needle in and out multiple times. Minimal blood contamination can be achieved by not applying suction with a syringe. The veterinarian must take care not to reposition the needle while it is in the spleen because this may result in laceration of the

capsule and potentially catastrophic bleeding. If a mass is palpable in the spleen, fine-needle aspiration should be avoided until an ultrasound examination can verify that the lesion is not cavitated. Cavitated lesions, while uncommon in cats, are best dealt with by splenectomy. Aspiration biopsies may be unnecessary in cats with diffuse homogeneous splenomegaly without clinical signs.² Normal cell types collected from a splenic biopsy include medium and large lymphocytes. Neutrophils are rare.

Generalized Splenomegaly

Congestion of the spleen can occur after administration of a sedative or general anesthetic (Box 25-6). The capsule relaxes and allows for an increase in the storage capacity of the parenchyma. Portal venous or caudal vena caval obstruction or congestion from right-sided heart failure will infrequently cause splenic congestion. Infarcts may occur secondary to hepatic or renal disease and may obstruct the efferent blood supply.

Infiltrative lesions of the spleen are the result of neoplasia, hyperplasia of normally occurring cell types, or inflammation. The most common splenic abnormalities in a report of 101 cats with splenic disease were lymphosarcoma ($n = 30$), mast cell tumor ($n = 27$), and extramedullary hematopoiesis and/or lymphoid hyperplasia ($n = 27$).⁴⁵ Hyperplasia may occur in response to an increased workload. Massive hemolysis (whether immune mediated or caused by some other mechanism) or the presence of bloodborne antigens increases the number of mononuclear phagocytes and lymphocytes required to do the work. Extramedullary hematopoiesis requires an increase in blood-forming cells in the spleen. Eosinophilic infiltrates may be present in cats with hypereosinophilic syndrome. Different inflammatory cell types are associated with different types of infection. Infectious agents can cause splenomegaly by direct injury or by chronic antigenic stimulation. Potential infectious causes of splenomegaly in cats include retroviral infection, feline infectious peritonitis, hemotropic *Mycoplasma* infections, ehrlichiosis, and cytauxzoonosis.² Patients with peripheral neutrophilia or eosinophilia may have splenic aspirates with increases in those cell types because of the increased numbers in the circulation, not from neutrophilic or eosinophilic inflammatory disease.²

Localized Lesions

Focal enlargements in the spleen of cats are less common than generalized splenomegaly.⁶⁸ Non-neoplastic lesions are more common than neoplastic lesions, but these types are indistinguishable from each other at the time of surgery. Neoplastic lesions can be malignant, benign, or metastatic. Hematomas, nodular hyperplasia,

BOX 25-6**Causes of Splenomegaly****Focal Enlargement****Infectious Inflammation**

Bacterial abscess

Neoplastic

Lymphosarcoma

Hemangiosarcoma

Hemangioma

Sarcomas arising from other splenic cell types

Metastatic lesions

Non-neoplastic

Extramedullary hematopoiesis

Hematoma

Myelolipoma

Hyperplastic lymphoid nodules

Diffuse Enlargement**Infectious Inflammation**

Bacterial:

- Mycobacteriosis
- Salmonellosis
- Hemoplasmosis
- Other various organisms

Mycotic:

- Sporotrichosis
- Histoplasmosis

Protozoal:

- Toxoplasmosis

Viral:

- Feline leukemia virus
- Feline immunodeficiency virus
- Feline infectious peritonitis

Neoplastic

Mast cell tumor

Lymphosarcoma

Multiple myeloma

Myelolymphoproliferative disorder

Malignant histiocytosis

Non-neoplastic

Amyloidosis

Extramedullary hematopoiesis

Pyruvate kinase deficiency

Excessive osmotic fragility

Other noninflammatory hemolysis

Noninfectious Inflammation

Plasmacytic-lymphocytic enteritis

Hypereosinophilic syndrome

Immune-mediated hemolytic anemia

Congestive

Portal hypertension

Drug induced (sedation, anesthesia)

Right-sided heart failure

abscesses, and foreign bodies may present as focal lesions.

Therapy

Treatment of generalized splenomegaly is focused on treating the underlying disorder. Splenectomy may be considered in cats with immune-mediated anemia or thrombocytopenia refractory to aggressive immunosuppressive therapy.² Splenectomy should be performed in all cats with mass lesions of the spleen because it is difficult to tell neoplastic lesions from non-neoplastic ones. The outcome of this mode of therapy depends on the underlying disease and the patient's preoperative condition. In a report of 19 cats undergoing splenectomy for various reasons, only weight loss had any prognostic significance.³⁷ The median survival time following splenectomy for the three cats with weight loss was 3 days compared with 293 days for those without. The loss of the filtration function of the spleen can predispose the cat to infections.² The loss of the filter may lead to increases in morphologically abnormal erythrocytes such as those with Heinz bodies.¹¹³ Because the spleen plays a major role in the removal of erythrocyte parasites, splenectomized cats may be more susceptible to infections with hemotropic mycoplasma. Before performing splenectomy to treat cytopenias, it is important to be certain that the bone marrow is functioning properly. If splenic extramedullary hematopoiesis is the primary source of the missing blood cells, its removal could prove fatal.¹¹³

LYMPHADENOGRAPHY**Definition**

Diseases of lymph nodes are almost always recognized by enlargement. The enlargement may be solitary, regional, or generalized. Solitary lymphadenopathy, as its name suggests, is enlargement of a single lymph node, whereas regional lymphadenopathy is enlargement of lymph nodes draining an anatomic area. *Generalized lymphadenopathy* refers to enlargement of lymph nodes draining multiple anatomic areas. The enlargement is due to infiltration of cells into the node; the cell types may be normal lymph node constituents, inflammatory cells, or neoplastic infiltrates.

Anatomy and Function

Lymph nodes are kidney-shaped structures located throughout the body (Figure 25-17). Afferent and efferent blood vessels enter and exit at the hilus. Afferent lymphatic vessels enter at various points of the periphery. Lymph flows toward the hilus, percolating through cortical, paracortical, and medullary regions of the

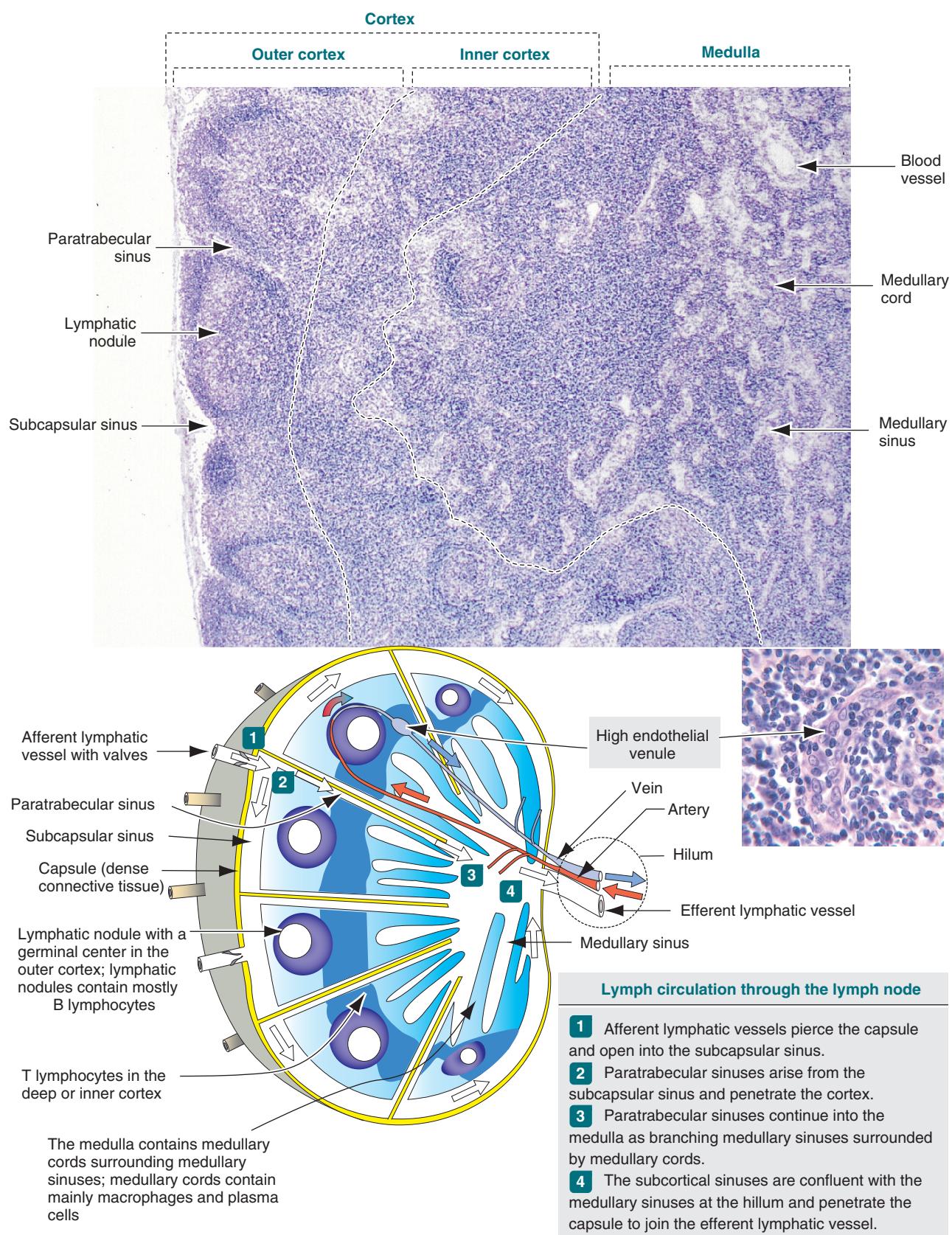


FIGURE 25-17 Anatomic and histologic structure of a lymph node. (From Kierszenbaum AL: Histology and cell biology: an introduction to pathology, St. Louis, 2002, Mosby).

BOX 25-7**Causes of Generalized Lymphadenopathy****Infectious**

Bacterial

Viral:

- Feline leukemia virus
- Feline immunodeficiency virus
- Feline infectious peritonitis
- Postvaccinal

Noninfectious

Immune mediated:

- Chronic progressive polyarthritis

Idiopathic:

- Distinctive lymph node hyperplasia of young cats
- Generalized lymphadenopathy resembling lymphosarcoma

Neoplastic:

- Lymphosarcoma
- Myelolymphoproliferative disease
- Myeloma
- Mast cell tumor

Non-neoplastic:

- Hypereosinophilic syndrome

lymph node, and exits at the hilus through the efferent lymphatic vessel. Lymph then flows to other lymph nodes or into the venous circulation.

The cortex of the lymph node is primarily composed of follicles of B cells surrounded by a rim of T cells. The medullary area is made of cords of macrophages, lymphocytes, and plasma cells. The endothelium in the medulla is discontinuous, allowing for exposure of fluid and particles to the immune cells. Between the cortex and medulla is the paracortical area containing small T cells and macrophages acting as antigen-presenting cells.⁴⁶

The lymph node functions as a filter of interstitial fluid. It retains particles, cells, and antigens brought to it by the afferent lymphatics. The best known function of the lymph node is as an immune organ. All the cell types (B cells, T cells, macrophages, and plasma cells) required for an immune response are brought together in the lymph node.⁸¹ These functions form the basis for explaining why a lymph node enlarges. Proliferation of the normal population of immune cells in response to antigens presented to the lymph node will cause it to enlarge, as will neoplastic proliferation of the resident cells. Enlargement will also occur when there is infiltration by inflammatory or neoplastic cells from processes in the region drained by the lymph node. Etiologies causing lymphadenopathy can be found in Boxes 25-7 and 25-8. Neoplastic enlargement is discussed in Chapter 28.

BOX 25-8**Causes of Single or Regional Lymphadenopathy****Infectious**

Bacterial:

- Mycobacteriosis
- Hemoplasmosis
- Various other organisms

Mycotic:

- Histoplasmosis
- Blastomycosis
- Cryptococcosis
- Sporotrichosis
- Phycomycosis

Viral:

- Feline leukemia virus
- Feline immunodeficiency virus
- Feline infectious peritonitis

Noninfectious

Idiopathic:

- Plexiform vascularization
- Distinctive lymph node hyperplasia of young cats

Local inflammation

Neoplastic:

- Hemolymphatic neoplasms
- Metastatic neoplasia

Non-neoplastic:

- Eosinophilic granuloma complex

Clinical Signs and Physical Findings

The discovery of an enlarged lymph node is often unexpected. The owner may be concerned about a lump found while petting the cat or enlarged lymph nodes may be discovered during a physical examination for a vague illness or during a wellness visit. Questions should be directed at identifying potential underlying illness, as well as the duration of the changes. It is also important to find out how fast the lump is growing.

Normally palpable lymph nodes include the mandibular, superficial cervical (prescapular), and popliteal. The ileoceccocolic lymph node is sometimes palpable in normal cats. All these nodes are more difficult to palpate in cats than in dogs.⁸¹ The fat surrounding a lymph node in an obese cat may give the impression of increased size; however, with more careful palpation the firmer node can be felt in the middle of the fat. If there is significant inflammation, the enlarged lymph node may be painful and the area warm to the touch. Clinical signs in other areas may be

present if the locally enlarged lymph node is acting as a space-occupying lesion:

- Dysphagia may be present if a retropharyngeal node is enlarged.
- Swelling of the head, neck, and cranial sternal areas (precaval syndrome) may be present if a mediastinal or cervical lymph node is enlarged.
- Intrathoracic lymphadenopathy may cause pleural effusion and subsequent respiratory distress.
- Horner's syndrome may be present if there is mediastinal lymphadenopathy.
- The cat may have tenesmus if the sublumbar lymph node is large.

Diagnostic Plans

Numerous diagnostic procedures are available to evaluate a cat with lymphadenopathy. The easiest, fastest, and most noninvasive means of obtaining information about a palpably enlarged lymph node is a fine-needle biopsy. In some cases the results provide an etiologic diagnosis; in others the results lead to the selection of additional tests that may be helpful. Retroviral testing should be performed on all cats with generalized lymphadenopathy. Thoracic radiographs and thoracic and abdominal ultrasound examination may reveal an enlarged lymph node in these areas. An exploratory laparotomy should be considered if a lymph node presents as a large abdominal mass.

The cytologic appearance of the normal lymph node is a heterogeneous population of small lymphocytes. Any enlarged lymph node with normal cytology should be considered reactive (hyperplastic) because normal nodes do not enlarge.⁴⁶ Increased numbers of medium and large lymphocytes and plasma cells are also to be expected in a reactive lymph node. Lymphadenitis is either suppurative, pyogranulomatous, or eosinophilic. Suppurative lymph nodes should be cultured. If a fine-needle biopsy is inconclusive (as it often is in cats), an excisional biopsy should be performed. Other tests to contemplate depending on the results of the fine-needle biopsy include a CBC, serum biochemical profile, urinalysis, bone marrow biopsy, and infectious disease serology.⁸¹

Therapy

Treatment of a cat with lymphadenopathy involves treating any identified underlying disease. If an underlying cause cannot be identified, the temptation to use glucocorticoids in an attempt to shrink the size of the lymph node should be resisted. Idiopathic lymphadenopathies have been reported in cats that either require only patience or can be treated surgically.

Distinctive Lymph Node Hyperplasia of Young Cats

There is a report of 14 cats with peripheral lymphadenopathy with microscopic architecture of the lymph nodes similar to cats with experimental feline leukemia viral infections.⁷⁷ The 14 cats were young (5 months to 2 years of age) with no gender predilection. Eight of the 14 cats were healthy aside from the lymphadenopathy. The others had a combination of signs such as lethargy, anorexia, fever, or hepatosplenomegaly. Vaccines had not been administered for at least 4 months and were not considered responsible for the lymph node enlargement. Generalized peripheral lymphadenopathy was present in 13 of the 14 cats; the other had only an enlarged mandibular lymph node. The nodes were judged to be 2 to 3 times the normal size. Some of the cats had abnormalities such as anemia, neutrophilia, and lymphocytosis, and 6 of 9 cats tested were positive for FeLV antibodies. The outcome was known for 10 of the 14 cats. Two were euthanized because of the positive FeLV status; the other eight were followed for 5 years. One cat developed mediastinal lymphosarcoma, and six experienced complete resolution of the lymphadenopathy over a 2- to 28-week period. The remaining cat had episodic lymphadenopathy. The cause of the spontaneous lymph node hyperplasia in these young cats was not determined. The similarities of the lesions to those found in cats with experimental FeLV infections and the exposure to the feline leukemia virus in six of the cats suggest that the virus may be involved in the pathogenesis of the disease.

Generalized Lymphadenopathy Resembling Lymphosarcoma

There is a report of six young cats with generalized lymphadenopathy with lesions similar to those of lymphosarcoma.⁷⁶ The cats were 1 to 4 years of age and were either Maine Coons (three) or domestic shorthairs (three). Four of the cats were initially seen for urinary or upper respiratory disease. The other two were from FeLV-positive homes. The only significant physical finding was generalized lymphadenopathy. One cat was euthanized after an initial diagnosis of lymphosarcoma. Of the other five cats, four had a persistent leukocytosis with two of them having atypical lymphocytes or a lymphocytosis. FeLV antigen tests were negative in the five cats. Histopathologic evaluation of the lymph nodes revealed some features consistent with lymphosarcoma; however, some of the findings were not compatible with malignancy, such as a lack of high-grade anaplastic changes, no capsular invasion, a mix of infiltrating cell types, and the presence of normal follicles. None of the cats was treated because the clinical and histopathologic features of their disease were equivocal for neoplasia.

Surprisingly, all went on to experience regression of the lymphadenopathy within 1 to 17 weeks. All the cats were still alive and doing well 1 to 7 years after the initial examination for lymphadenopathy, supporting the diagnosis of nonmalignant lymphadenopathy.

Plexiform Vascularization of Lymph Nodes

An unusual cause of lymphadenopathy in cats has been reported,⁸¹ specifically in adult cats ranging in age from 3 to 14 years. All cats were clinically normal except for one or two enlarged lymph nodes. Two cats with inguinal lymphadenopathy were affected bilaterally. The disease was characterized by replacement of the follicles by a plexiform proliferation of small blood vessels. The cause of this change was unknown, but removal of the affected gland(s) was curative.

Because lymphadenopathy has many potential causes, a cat presenting with generalized lymphadenopathy should not automatically be convicted of having malignant disease. Many cats may prove to have curable diseases when approached with a systematic, logical evaluation.

CYTOKINES

Currently, there is great interest in exploring the use of cytokines in feline medicine. Imbalances in cytokine profiles are associated with a wide range of diseases in cats. Potential uses include use as tools for investigating the underlying pathogenesis of disease and for the diagnosis, monitoring, and therapy of disease. Efforts are hampered by the lack of specifically cloned feline molecules, the complexity of the cytokine regulatory system, and the paucity of cats available for evaluation. Individual cytokines may have actions in cats that are not predicted by their effects in humans and mice.⁹⁵

Definition

Cytokines are small glycoproteins secreted by many different cells, including dendritic cells, lymphocytes, macrophages, monocytes, endothelial cells, and fibroblasts in response to specific stimuli. Interleukins, interferons, lymphokines, tumor necrosis factors, and hematopoietic growth factors such as EPO are examples of cytokines. They act locally in intercellular communication to regulate cell growth and maturation, regulate immune and inflammatory responses, and modify hematopoiesis. They affect multiple cell types and are important enough that the effects often overlap those of other cytokines, acting as a natural backup system. Some cytokines have different effects depending on the concentration; for example, interferon (INF)-alpha has immunostimulating properties at low concentrations but immunoinhibitory

properties at high concentrations. Cytokine structure is not well preserved across mammalian species so that administration of a nonfeline cytokine to a cat often elicits an antibody response, resulting in loss of function.⁶³

Physiology

Production of cytokines is induced by alteration in gene expression and is usually transient. Cytokines act by binding to specific receptors on the surface of the target cell, with a subsequent modification of gene expression in that cell. This changes cell proliferation, differentiation, or function, often in concert with other mediators. Circulating non-cell-associated receptors for the cytokines may be present to prevent systemic actions if some should reach the circulation.²³

Normal embryonic development may be affected by alterations in cytokine concentrations, leading to birth defects.²³ Hematopoiesis is modified by the presence or absence of EPO, thrombopoietin (TPO), or colony-stimulating factors (Figure 25-18). Cytokines are active in immunoregulation through a complex interaction among the various cytokines, which activate or suppress helper T cells (T_h cells) (Figure 25-19). The outcome of these interactions is an alteration in the balance of cell-mediated and humoral immunity. Activated macrophages elaborate various cytokines important in the acute inflammatory response by altering vascular permeability, increasing endothelial leukocyte adhesion and leukocyte chemotaxis (Box 25-9). The acute phase inflammatory response is, in part, mediated by cytokines secreted by these macrophages. Nonspecific effects of chronic inflammation such as cachexia and tissue destruction may be due to the presence of cytokines. Growth factors have a role in wound healing by stimulating the migration of fibroblasts into the wound and increasing angiogenesis.

Therapeutic Uses

Manipulation of cytokines for use in treating disease can involve administration of the cytokine itself in one form or another. Presently, cytokines are primarily used to treat hematocytopenias. The best-known example is the use of EPO to treat hypoproliferative anemia. Cytokines may also be used to treat tumors. Intralesional injections of IL-2 may be beneficial as an adjunctive therapy for fibrosarcoma.²³ In the future it may be possible to use cytokines to augment the immune response to disease or alter tissue repair. Inhibiting cytokine activity may modulate the immune response and result in novel methods of treating immune-mediated and allergic disease. Glucocorticoids and cyclosporine are examples of drugs that inhibit production of proinflammatory cytokines such as IL-2. Glucocorticoids also stimulate

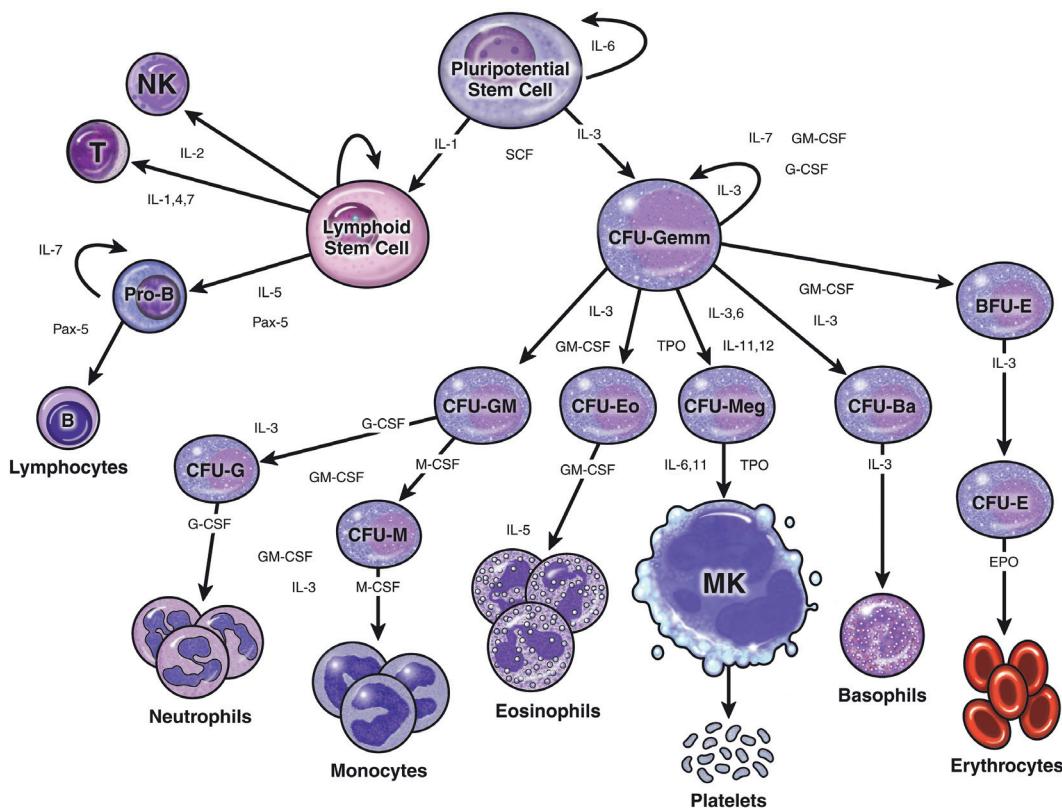


FIGURE 25-18 Cytokines important in proliferation and differentiation of cell types during hematopoiesis. *B*, B-lymphocyte; *BFU-E*, burst-forming unit-erythrocyte; *CFU-Ba*, colony-forming unit-basophil; *CFU-E*, colony-forming unit-erythrocyte; *CFU-Eo*, colony-forming unit-eosinophil; *CFU-G*, colony-forming unit-granulocyte; *CFU-Gemm*, colony-forming unit-granulocyte-erythroid-monocyte-megakaryocyte; *CFU-GM*, colony-forming unit-granulocyte-monocyte; *CFU-M*, colony-forming unit-monocyte; *CFU-Meg*, colony-forming unit-megakaryocyte; *EPO*, erythropoietin; *G-CSF*, granulocyte colony-stimulating factor; *GM-CSF*, granulocyte-monocyte colony-stimulating factor; *IL*, interleukin; *M-CSF*, macrophage-monocyte colony-stimulating factor; *MK*, megakaryocyte; *NK*, natural killer cell; *Pax-5*, transcription factor produced by expression of PX-5 gene in B-lymphocyte development; *T*, T-lymphocyte; *TPO*, thrombopoietin.

BOX 25-9

Important Cytokines Released from Stimulated Macrophages

Interleukin-8

- Induces inflammation by stimulating leukocytes
- Chemotactic for neutrophils
- Serves as principle secondary mediator of inflammation

Interleukin-6

- Stimulates hepatocytes to synthesize acute phase proteins
- Serves as principle growth factor for B cells

Interleukin-1

- Enhances proliferation of helper T cells
- Enhances growth and differentiation of B cells
- Stimulates interleukin-2 production by T_h1 cells
- Stimulates nearby macrophages to produce interleukin-6 and interleukin-8

Tumor Necrosis Factor

- Causes vascular endothelium to become adhesive for leukocytes
- Activates inflammatory leukocytes
- Stimulates nearby macrophages to produce interleukin-1, interleukin-6, and interleukin-8

Interferon-alpha

- Inhibits viral replication in adjacent cells
- Inhibits cell proliferation in adjacent cells
- Increases class I major histocompatibility complex (MHC) expression in adjacent cells
- Increases lytic potential of natural killer (NK) lymphocytes

Interleukin-12

- Enhances interferon-gamma production by T_h1 cells and further activation of macrophages
- Inhibits T_h2 cell proliferation and activation

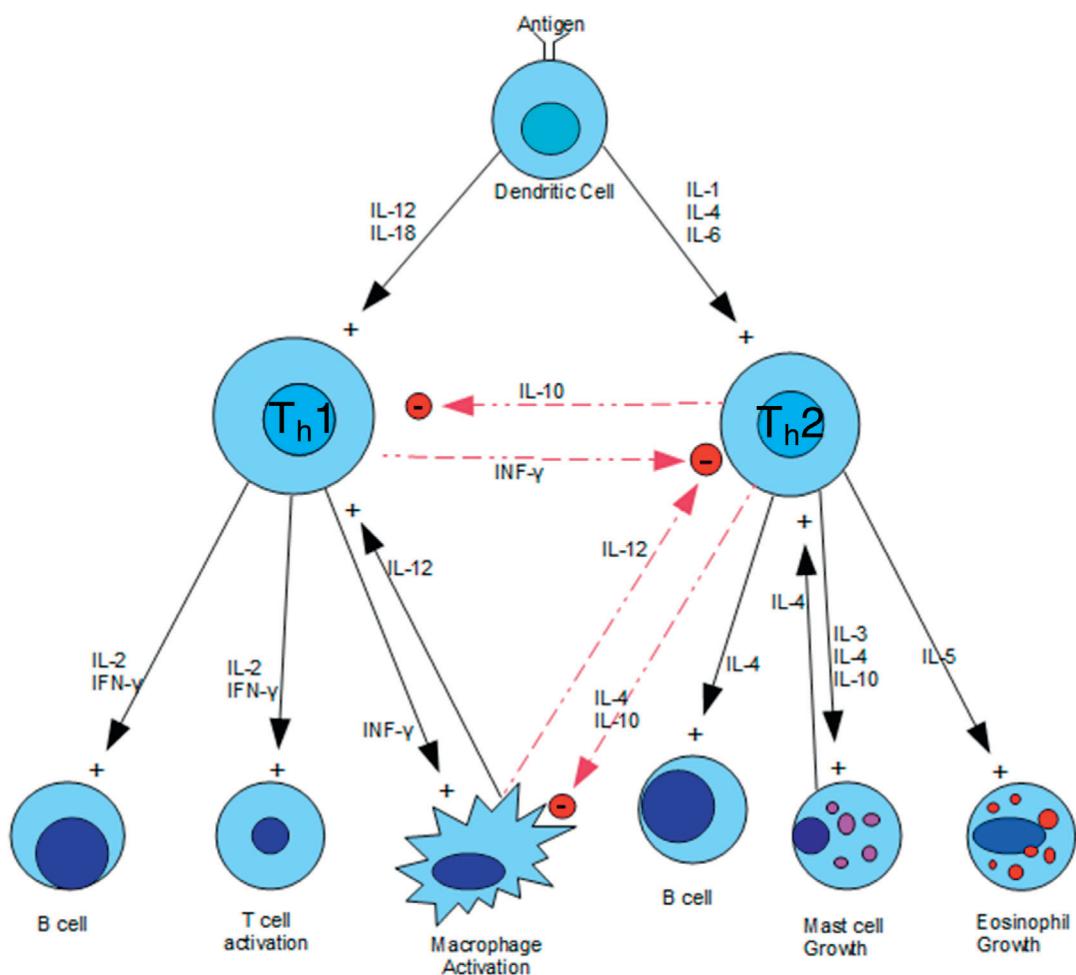


FIGURE 25-19 Regulatory effects of interleukins secreted by macrophages and T_{h1} and T_{h2} lymphocytes on the cell-mediated and humoral immune response after antigen presentation by dendritic cells. Red, dashed lines represent inhibitory effects. Solid black lines represent stimulatory effects. IL, interleukin; INF, interferon.

the production of IL-10, an immunosuppressive cytokine. Antibodies against the cytokine or its receptor may help reduce its activity. Inactivation may also be accomplished by the use of direct cytokine antagonists or administration of their receptors in soluble form. IL-2 receptor antagonist protein (IRAP) has shown promise in reducing the severity of inflammatory bowel disease.²³ Manipulation of a single cytokine may trigger mechanisms that control its activity and neutralize or enhance its effect.¹¹⁴ No treatment is without potential adverse effects, and cytokine therapy is no exception. Systemic use of cytokines has resulted in fever, anorexia, nausea, pain, anemia, shock, pulmonary edema, coma, or death.

Interleukins

Interleukins are cytokines produced by antigen-activated dendritic cells, lymphocytes, and macrophages (see Figure 25-19). As with all cytokines, they act by binding to specific receptors on the effector cell. In health fewer than 15% of immune cells have

interleukin receptors on the surface. This guards against an overzealous immune response.⁴⁸ Bacterial and viral infections stimulate T_{h1} cells to produce interleukins such as IL-2, interferon (INF)-gamma, and tumor necrosis factor-alpha that are responsible for enhancing cell-mediated immunity. These interleukins activate natural killer (NK) cells, cytotoxic lymphocytes, and macrophages. IL-12 is secreted by activated macrophages with subsequent activation and recruitment of new T_{h1} cells, thereby acting as a positive feedback loop to amplify the cell-mediated immune response. IL-12 is also a potent stimulator of NK cell and cytotoxic lymphocytes. Large, extracellular parasites activate T_{h2} cells to secrete interleukins that result in augmentation of the humoral arm of the immune system.⁴⁸ Increases in B lymphocytes, eosinophils, and mast cells follow. T_{h2} cells also release the antiinflammatory interleukins, IL-4 and IL-10. These potent inhibitors of INF-gamma secretion by T_{h1} cells act to reduce cell-mediated immune activity. These two interleukins also stimulate activation of B lymphocytes and

mast cells.⁴⁸ Of course, there is never stimulation or inhibition of only T_h1 or T_h2 cells; a balance must be maintained, or illness ensues.

IL-2, part of cell-mediated immunity, may be useful in the treatment of malignancy. For example, IL-2 activates the tumocidal effects of pulmonary alveolar cells.⁴⁸ Animals with depressed cell-mediated immunity may have derangements in IL-2 production. Dogs with generalized demodicosis have decreased expression of IL-2 and decreased numbers of lymphocytes with IL-2 receptors. Production of IL-2 by feline lymphocytes infected with retroviruses is decreased. IL-8 is a potent neutrophil activator and may be useful in disorders characterized by neutrophil dysfunction. Antagonists of IL-8 may have a role in combating asthma. IL-12 is a potent inhibitor of tumor angiogenesis and has potent antitumor effects that may be used to treat neoplasia. IL-12 may also have a role in the development of autoimmune diseases.

Hematopoietic Growth Factors

Differentiation, proliferation, and maturation of the different types of stem cells in the bone marrow are stimulated by various cytokines. EPO and TPO stimulate increases in production and release of erythrocytes and platelets, respectively. A number of cytokines mediate similar activities on leukocytes. Granulocyte colony-stimulating factor (G-CSF) is produced by bone marrow stroma, neutrophils, and endothelial cells. The receptor for G-CSF is found on both immature and mature neutrophils and stimulates proliferation and maturation of neutrophils. G-CSF also enhances neutrophil chemotaxis and antibody-dependent cell-mediated cytotoxicity and increases the expression of Fc receptors on the neutrophil surface.⁶³ A neutrophilia reliably occurs 24 hours after administration of recombinant human (rh)-G-CSF to healthy cats and is useful in preventing chemotherapeutic neutropenia. Using G-CSF to reverse an established neutropenia, such as seen in cats with FeLV infection, is unrewarding. The action of rh-G-CSF in cats ends when the patient starts making antibodies against the cytokine. The recombinant canine product, however, retains its efficacy, suggesting that antibodies are not produced.⁶³

Granulocyte monocyte (GM)-CSF is made in fibroblasts, endothelial cells, T lymphocytes, and monocytes. The targeted cells are neutrophils, eosinophils, monocytes, and their respective progenitor cells. GM-CSF prolongs the survival of the target cells and enhances their function. GM-CSF-activated macrophages recognize and kill tumor cells and present their antigens to T_h cells as a part of tumor immune surveillance.⁶³ Macrophage-CSF promotes the survival and functions of macrophages and may be useful in treating fungal infections.⁶³ Stem cell factor is produced by bone marrow support cells and

endothelial cells and may find uses in treating aplastic anemia, myelofibrosis, or bone marrow toxicity.

Investigational Use

Cytokine profiles and individual cytokines are being used by researchers investigating many different disorders in cats. The cytokine profile information can elucidate the extent to which each arm of the immune system is involved in the pathogenesis of the disease. Are the increases or decreases in the various cytokines measured consistent with activation of T_h1 or T_h2 cells? Is the response stimulatory or inhibitory? Assessment of individual cytokines may present opportunities for intervention in the disease process. Many different body systems and individual infectious diseases have been examined with regard to cytokines. Tumor necrosis factor-alpha is produced by cardiac myocytes in response to ventricular pressure overload in cats with cardiomyopathy and has been implicated in the pathogenesis of cardiac cachexia, ventricular dysfunction, and the development of congestive heart failure.⁷³ Evaluations of the cytokine profiles of the nasal and oral cavities in cats suggest that a T_h1 profile of cytokines is present to protect against bacterial and viral infections of these tissues. An increase in T_h1 cytokines is associated with progression of the signs and histologic changes of nasal cavity disease. Humans with allergic rhinitis have T_h2 profiles.⁵⁰ IL-4-producing lymphocytes have been found in lesional and nonlesional skin from cats with allergic dermatitis, but not from the skin of healthy control cats, which suggests a role for IL-4 in allergic skin disease in this species.⁹⁶ IL-5, thought to be a major regulator for eosinophils, was not correlated with the number of eosinophils in cats with suspected allergic dermatitis, whereas IL-2 was.⁸⁰ This is an example of an investigation with a conclusion that steers therapeutic intervention away from what theory suggests should be effective. Antibodies against IL-5 and IL-5 receptor blockers are under investigation for the treatment of hypereosinophilic syndrome.¹³⁴

Inflammatory disease in other body systems would seem to be reasonable areas of investigation. Indeed, cytokine evaluation in cats with inflammatory bowel disease (IBD) is an ongoing area of interest. Nguyen Van and coworkers found a statistically significant increase in both proinflammatory and regulatory cytokine expression in cats with inflammatory lesions of the intestine compared with those without inflammation. They concluded that the pathogenesis of IBD involves aberrations in both regulatory and inflammatory aspects of the immune system.⁸² The ACVIM consensus statement on gastrointestinal inflammation suggests that a role for decreased immunoregulation is predicted in the pathogenesis of IBD in cats based on the cytokine profile from humans and rodents.¹²³ The pathogenesis and response to treatment of allergic airway disease in cats involves

alterations in cytokine profiles. An imbalance in cytokine production favoring T_h2 cell products in response to environmental aeroallergens is thought to be a major part of the pathogenesis of this disease.¹⁰¹ These T_h2-derived cytokines lead to increased production of allergen-specific IgE. Investigators are evaluating different substances for their efficacy in altering or inhibiting the activity of these cytokines.¹⁰¹ Even behavior can be affected by cytokines. Increased IL-2 in certain areas of the brain has been found to potentiate defensive rage behavior in cats.⁵

Perhaps the most important area of study of cytokines is in the pathogenesis and treatment of infectious diseases. This area of study may be important in designing prevention and therapies for infections with FIV. Increased IL-10, an immunosuppressive T_h2 cytokine, was found in the early stages of FIV infection corresponding to high viral replication. This was followed by an increase in IFN-gamma levels to bring the ratio back into balance. The increase in IFN-gamma was associated with a decreased tissue viral load.³ In a challenge study, cats infected with FIV and then challenged with *Toxoplasma gondii* infections produced significantly lower amounts of T_h1 (proinflammatory) cytokines compared with challenged FIV-negative controls. The FIV-positive cats also maintained the elevated levels of IL-10 found before the challenge with *T. gondii*.⁶¹ Imbalances in T_h1 versus T_h2 cytokines were also suggested as a cause for the development of lesions in the neurologic form of FIP. It was also thought that a failure to increase IFN-gamma concentrations in the infected tissues might be an important reason these cats succumbed to the FIP infection.³⁰ Another example of using a cytokine for the treatment of infectious disease is the use of rhIFN-alpha to treat cats with FeLV infections.²³ Although the use of cytokines holds great promise for feline medicine, much research must still be performed to fully understand the complexity of the system and the implications of manipulating it and to develop new strategies for using cytokines to intervene in the management of sick cats.

SYSTEMIC LUPUS ERYTHEMATOSUS

Definition

Systemic lupus erythematosus (SLE) is a rare disease characterized by autoimmune damage to multiple tissues and organ systems. The most commonly affected tissues in cats include synovial joints, glomeruli, skin, blood cells, and the central nervous system (Box 25-10). The syndrome mimics many other disorders, and diagnosis can be difficult because diseases including infectious and neoplastic causes must first be eliminated.

BOX 25-10

Disorders Consistent with Systemic Lupus Erythematosus

Major Signs

Immune-mediated hematologic disease

- Immune-mediated hemolytic anemia
- Immune-mediated thrombocytopenia
- Immune-mediated leukopenia

Polymyositis

Glomerulonephritis

Non-erosive immune-mediated polyarthritis

Vesicobullous dermatitis

Minor Signs

Oral ulceration

Fever of unknown origin

Central nervous system disturbances

- Seizures
- Dementia
- Coma

Pleuritis

Myocarditis

Pericarditis

Peripheral lymphadenopathy

Signalment

Young to middle-aged cats are most commonly affected,⁶⁵ and unlike in humans, there is no gender predilection.⁶⁹ Purebred cats are more likely to be affected than domestic cats.¹⁰⁶

Clinical Signs and Physical Findings

Clinical signs depend on the body system affected. These can include fever; lameness; muscle pain; lymphadenopathy; ulcerative stomatitis; skin lesions such as crusts, erythema, and ulceration; depigmentation around the head and paws; pale mucous membranes; and central nervous system signs ranging from subtle behavioral changes to alterations in mentation and seizures. These signs may be exacerbated by ultraviolet radiation from the sun or concurrent infection.¹⁰⁶

Pathophysiology

The changes resulting from SLE are due to inflammation of the affected body part. Dysregulation of the immune system (possibly the result of abnormal function of T suppressor cells) leads to an attack against the body's self-antigens and is responsible for the inflammation. Circulating antigen-autoantibody complexes deposit in the vessel walls of the synovium, glomerulus, or choroid plexus (type 3 hypersensitivity). Complement is

activated, and neutrophils and macrophages are recruited, resulting in vasculitis and damage to tissues. Less commonly, antibodies against nuclear, cytoplasmic, and membrane antigens (type 2 hypersensitivity) alter cell function. Direct T cell damage of tissues (type 4 hypersensitivity) is also possible.¹⁰⁶

Diagnostic Plans

Diagnosis of SLE requires an increased index of suspicion for a cat with apparent multisystemic disease. Various criteria have been proposed for the diagnosis of SLE in dogs and cats based on those used for the diagnosis in people. One such proposal requires evidence for autoimmune injury to at least two organ systems, along with a positive antinuclear antibody (ANA) test, or three affected organ systems with a negative ANA titer. A positive ANA titer is neither sufficient nor required for a diagnosis.¹⁰⁶ Most commonly, a combination of the following occurs:

- IMHA
- IMTP
- Immune-mediated skin disease
- Glomerulonephritis
- Central nervous system signs
- Non-erosive immune-mediated polyarthritis¹⁰⁶

No single test is available to diagnose SLE. A CBC, serum biochemical profile, ANA test, and urinalysis should be performed along with thoracic radiographs to rule out potential bronchial infections. The ANA test is relatively sensitive in identifying anti-self antibodies. The results are reported as a titer along with an immunofluorescence pattern that is clinically insignificant.¹⁰⁶ Many false-positive and false-negative tests occur. False-positive tests may occur in cats with infectious, neoplastic, or chronic inflammatory diseases. About 10% of healthy cats will have a low titer for ANA.¹⁰⁶ Therefore a high ANA titer is more consistent with SLE than is a low titer. A lupus erythematosus (LE) cell preparation identifies neutrophils with phagocytosed nuclei in the cytoplasm. Interpretation depends on the experience of the technician, and many false-negatives occur.¹⁰⁶ Because of the difficulty in performing the test and problems with sensitivity, it has largely been replaced with the ANA test. If there is evidence of a regenerative anemia, the veterinarian should perform a Coombs' test and a PCR test for hemotropic mycoplasmosis. The cat's retroviral status should also be ascertained. If there is joint pain or effusion, synovial fluid should be obtained for cytology; the synovial neutrophils should be well preserved in a cat with SLE. If the neutrophils are lytic or if bacteria are present, a culture of the fluid should be performed.⁶⁹ Cats with azotemia and proteinuria should have the urine protein to creatinine (UPC) ratio measured. A

renal biopsy should be performed if the UPC ratio is high because the elevated protein may be due to glomerulonephritis. One cat was identified with coagulation defects because of the presence of a circulating lupus anticoagulant, an antibody against phospholipid that interferes with function of the common coagulation pathway and platelets (see the section on hemostasis). This cat had prolongation of both PT and aPTT. No overt bleeding was reported.⁶⁵ Any skin lesions should be biopsied in an appropriate manner.^{69,106} To make a diagnosis of SLE, infectious and neoplastic causes must be eliminated as possible explanations for the cat's clinical signs.

Therapeutic Plans

Control of tissue inflammation and addressing organ failure are the goals of therapy for SLE. In situations where there is mild pain, NSAIDs may suffice.^{69,106} If not, or if the signs are more severe, immunosuppressive doses of corticosteroids should be started. Prednisolone at 2 to 4 mg/kg daily should be effective. If there is no improvement in 1 week, consideration should be given to a change in therapeutic plans such as the addition of cytotoxic immunosuppressants. Ultraviolet light can be a trigger for some cats with SLE, and they should be kept out of the sun.

Additional immunosuppression can be achieved by adding cytotoxic drugs such as chlorambucil. Chlorambucil is well tolerated, with minimal side effects; however, the dose must be individualized to the particular patient. A good starting point is 0.25 to 0.5 mg/kg orally every 24 to 48 hours.⁶⁹ Side effects include anorexia and myelosuppression. Constant communication between owner and veterinarian is essential.

Once remission has been achieved, a reduction in drug dose can begin. Remission is defined as resolution of clinical signs and initial radiographic and laboratory changes.¹⁰⁶ If combination therapy has been used, the chlorambucil should be reduced first. The dose is reduced by 50% for 4 weeks. As long as clinical remission continues, further reductions can take place every month. Usually a minimum of 6 months of therapy is required.¹⁰⁶ If a relapse occurs, the veterinarian should return to the previous effective dosage until remission is accomplished. Further attempts at reducing drug dosages should be made more slowly. Some cats will require lifelong therapy.

Prognosis

Because SLE in cats is rare, the natural course of the disease is unknown. Many cats will achieve remission, and drug doses can be tapered; however, relapses should be expected to occur. Frequent follow-up examinations and laboratory evaluations may be necessary.

SYSTEMIC ANAPHYLAXIS

Systemic anaphylaxis is a life-threatening allergic event resulting in massive, generalized mast cell degranulation. The inflammatory mediators released by mast cells result in grave consequences if not treated promptly. Because time is of the essence, recognizing the signs of anaphylactic shock is essential if the veterinarian is to institute appropriate therapy.

Pathophysiology

An anaphylactic reaction is mediated by interactions among antigens, IgE antibodies, and mast cells. This type I hypersensitivity reaction requires previous exposure to an antigen and production of IgE against that antigen. Many different substances can play the role of antigen, including drugs such as NSAIDs and antibiotics, insect or reptile venom, food, vaccines, and inhaled allergens. Most animals produce IgA or IgG when exposed to an environmental allergen, whereas others have an exaggerated T_h2 response and produce excessive amounts of IgE.¹¹⁶ Once the cat is re-exposed to the antigen, it can be bound to IgE molecules on the mast cell surface. Cross-linking occurs when the antigen is bound to two IgE molecules at the same time. Once the two antibodies are cross-linked, IgE receptors signal the mast cell to degranulate, produce increased quantities of phospholipase A₂, and begin production of new inflammatory cytokines.

Degranulation of mast cells results in the release of preformed mediators of inflammation. This occurs rapidly, with evidence of their effects appearing within seconds to minutes of exposure to the antigen. These mediators, which include but are not limited to histamine, heparin, kallikrein, and inflammatory cell chemotactic factors, result in physiologic changes responsible for many of the clinical signs recognized as anaphylactic shock. Histamine bound to H₁ receptors causes smooth muscle contraction in the intestinal tract and in the airways and pulmonary vasculature. H₁ activation also results in increased vascular permeability and neutrophil and eosinophil chemotaxis. Binding to the H₂ receptor is followed by increased production of airway mucus and bronchodilation. The balance between H₁ and H₂ stimulation results in hypotension, bronchospasm, airway obstruction, hyperperistalsis, increased vascular permeability, and pruritus.¹¹⁵ Chemotactic factors amplify the inflammatory reaction by recruiting neutrophils and eosinophils. Consequences of the release of other mast cell mediators include complement activation, enhanced smooth muscle contraction, increased vascular permeability, and stimulation of pain sensors.¹²¹

Phospholipase A₂ acts on the phospholipids in the cell membranes to form arachidonic acid. Although

not as immediate as degranulation, this process still occurs within minutes of exposure to the antigen. Production of secondary inflammatory mediators such as prostaglandins, leukotrienes, thromboxane, and platelet-activating factor augments inflammation, bronchoconstriction, and vascular permeability.

A late-phase inflammatory reaction occurs after newly produced cytokines are released by the mast cell. This occurs between 2 and 24 hours after exposure to the antigen. Cytokines produced by mast cells include IL-4, IL-5, IL-6, IL-13, IL-16, tumor necrosis factor-alpha, and macrophage inflammatory protein 1-alpha. These are either proinflammatory or promote a T_h2 response with increased IgE antibody production.¹¹⁶ They also augment vasodilation and stimulate the production of cell adhesion proteins on endothelial cell membranes, which increases the ability of circulating inflammatory cells to stick to and then move through the vessel wall into the tissues.¹⁵

An anaphylactoid reaction is the result of mast cell degranulation without an immune component.¹¹⁶ IgE is not involved, and previous exposure to the antigen is not required; mast cells are activated directly or, more commonly, indirectly by complement activation. Other than the initial stimulus, the two processes are virtually the same. Anaphylactoid reactions can be caused by drugs such as NSAIDs or opioids, iodinated radiographic contrast materials, or dextrans. Ingestion of certain types of spoiled fish can cause an anaphylactoid reaction. Bacterial contamination of tuna, mackerel, or mahi-mahi converts the abundant histidine in the fish to histamine.⁴¹ Anaphylactic and anaphylactoid reactions have the exact same clinical signs and treatment, so differentiating between the two is immaterial in the emergency situation.

Clinical Evaluation

The major shock organ in the cat is the lung, with the intestinal tract involved to a lesser degree. The signs of anaphylaxis are the result of the actions of all the different inflammatory mediators released by the mast cells. Respiratory distress is the major sign of anaphylactic shock in cats. Increases in respiratory rate and effort are consequences of laryngeal edema, bronchoconstriction, and increased production of airway mucus; open-mouth breathing may be noticed. Pruritus about the face and head may be present, and increased salivation may be noted along with vomiting, pale mucous membranes, poor pulse quality, and a prolonged capillary refill time. Hypovolemia owing to increased vascular permeability and vasodilation leads to decreased tissue oxygenation. Progression to collapse, coma, and death may follow rapidly. Diagnosis of anaphylactic shock is based on recognizing the presenting signs and the acute nature of illness. A cursory initial examination of the cat is often

all that time will allow, insofar as many are life-threateningly ill. A detailed history and physical examination of less severely affected cats may yield clues to the cause of the anaphylaxis. An insect stinger in the tongue of a cat with open-mouth breathing is suggestive of an allergic reaction to a bee sting.

Therapy

Once anaphylaxis is recognized, rapid and aggressive treatment may be life saving. Following the precepts of basic emergency medicine gives the veterinarian the best chance at success. The veterinarian must first ensure that the airway is patent and be ready to intubate if laryngeal edema is causing an airway obstruction. Tracheotomy may be necessary if intubation is not possible. If the upper airway is not obstructed and the cat is having respiratory difficulties, administration of oxygen may be required. Cardiovascular and respiratory dysfunction can be addressed with intravenous fluids and drugs.

Intravenous access should be established early on so that volume contraction can be corrected. Intravenous fluids at 50 to 60 mL/kg over the first hour should be administered to cats with severe anaphylaxis. After the first hour the cat should be reassessed and fluids continued. Fluid rates will likely need to be greater than maintenance rates but should be tailored to the individual patient. Monitoring the central venous pressure (CVP) is an excellent means of assessing fluid requirements. Fluids can be administered until the CVP reaches 3 to 5 cm of water. Otherwise, the pulse quality and rate, capillary refill time, and mucous membrane color are used as clinical guides to fluid therapy after the initial shock rates are completed. If DIC is present,

blood products may be used to replace clotting factors consumed in the process. The addition of heparin alone to augment the effectiveness of the transfusion is controversial. In humans a combination of antithrombin and heparin has shown promise in reducing mortality, as has administration of activated protein C.⁹⁹ Use of these modalities has not yet been reported in cats or dogs.

Many of the pathophysiologic derangements that occur with anaphylactic shock can be ameliorated by the administration of epinephrine (Table 25-6). Stimulation of the alpha-adrenergic receptors results in vasoconstriction, thereby decreasing blood pooling in the splanchnic circulation, increasing venous return to the heart, and improving cardiac contractility. Beta-adrenergic receptor stimulation decreases bronchoconstriction and impedes further mast cell degranulation while also improving cardiac output through positive inotropic and chronotropic effects. Epinephrine is used as a 1:10,000 dilution and administered intravenously at 0.02 mg/kg, which is 0.2 mL/kg or 1 mL for a 5-kg cat. To create 10 mL of a 1:10,000 dilution of epinephrine, 1 mL of the 1:1,000 solution is mixed with 9 mL of sterile saline. If venous access cannot be established, the volume can be doubled and administered through a urinary catheter passed through an endotracheal tube and wedged in a small bronchus.¹³¹ Alternatively, epinephrine can be administered in the sublingual vein. If the patient's condition is not serious, the epinephrine can be administered intramuscularly or subcutaneously. The cat's heart rate and rhythm should be monitored because epinephrine can precipitate cardiac dysrhythmias. Epinephrine should be readministered in 15 to 20 minutes.

A positive response to parenteral fluid and epinephrine administration should be noticed within minutes of

TABLE 25-6 Drugs Useful for the Treatment of Anaphylaxis

Drug	Dose	Use
Epinephrine (intravenous)	0.2 mL/kg of a 1:10,000 dilution repeat in 15 minutes	Initial treatment along with intravenous fluids
Epinephrine (intratracheal or intrabronchial)	0.4 mL/kg of a 1:10,000 dilution repeat in 15 minutes	Initial treatment along with intravenous fluids; administer through a urinary catheter
Aminophylline	5 mg/kg IV slowly	Respiratory distress refractory to epinephrine
Atropine	0.02-0.04 mg/kg IV or IM	Bradycardia refractory to epinephrine
Dopamine	4-10 µg/kg/min constant-rate infusion	Refractory hypotension
Dexamethasone sodium phosphate	1-4 mg/kg IV	After correction of volume contraction
Prednisone sodium succinate (Solu-Delta-Cortef)	10-25 mg/kg IV slowly	After correction of volume contraction
Diphenhydramine (Benadryl)	0.5-1 mg/kg IV slowly	H ₁ receptor blockade After correction of volume contraction
Tripelennamine	1 mg/kg IV or IM	H ₁ receptor blockade After correction of volume contraction

IV, Intravenously; IM, intramuscularly.

beginning therapy. If not, additional drugs should be considered. If respiratory distress is still present, aminophylline 5 mg/kg administered slowly and intravenously may help reduce bronchoconstriction and strengthen contraction of the respiratory muscles.¹²¹ If additional cardiovascular support is required, infusions of dopamine or dobutamine may be considered. Atropine at 0.02 to 0.04 mg/kg intravenously or intramuscularly may be used if bradycardia is refractory to epinephrine.

Once the life-threatening crisis is dealt with, glucocorticoids and antihistamines can be administered. They are not useful for the acute treatment of anaphylaxis.¹²¹ Glucocorticoids cause vasodilation and decreased cardiac contractility and are detrimental if administered before correction of hypovolemia with intravenous fluids. Rapid-acting glucocorticoids such as dexamethasone sodium phosphate at 1 to 4 mg/kg intravenously may be beneficial by enhancing beta-receptor sensitivity and decreasing phospholipase A₂ activity. H₁-receptor-blocking antihistamines such as diphenhydramine (Benadryl, McNeil PPC) at 0.5 to 1 mg/kg administered slowly and intravenously or tripelennamine 1 mg/kg intravenously or intramuscularly may reduce the further effects of histamine on the target tissues. This may be of limited benefit insofar as histamine is only one of many mediators released by mast cells. H₂-receptor-blocking antihistamines may be used if gastric ulceration is suspected.

The cat experiencing anaphylactic shock should be monitored closely for the next 24 hours, the time period over which new cytokine synthesis and release occurs. Parameters to follow include respiratory rate and effort, heart rate and rhythm, pulse quality, capillary refill time, the patient's attitude, urine output, systemic blood pressure, and oxygen saturation as measured by pulse oximetry. Bloody diarrhea may signal the presence of DIC. Preparations should be made to act on significant changes in any of these parameters.

Prognosis

The effectiveness of therapeutic interventions in cats with anaphylactic shock depends on timely and aggressive action on the part of the veterinarian and support staff. The prognosis for these patients varies with the individual and the individual's response to initial therapy. The sooner appropriate therapy can begin, the better chance the cat has of surviving. However, some patients will die despite the best efforts of the veterinarian.

Prevention

Once the acute crisis is over, the owner can be questioned regarding recent vaccination and exposure to

insects, drugs, reptiles, and new foods. Any intravenous injections in the future should be administered slowly. Avoidance of any triggers is advisable. If this is not possible, as may be the case with vaccinations, pretreatment with antihistamines or glucocorticoids may help minimize the severity of any reaction. Any cat experiencing anaphylaxis after vaccination should remain at the hospital for 20 to 30 minutes after subsequent vaccinations to allow for immediate intervention should anaphylaxis recur. If a severe reaction has not begun within that time frame, it is unlikely to happen.¹⁷ Although they are uncommon, anaphylactic and anaphylactoid reactions can occur at any time. Anticipating the needs of a cat experiencing this frightening reaction is essential to a successful outcome.

Vaccine-Associated Adverse Events

Vaccination represents a common scenario in which cats are exposed to foreign proteins. Fortunately, the chance of a vaccine-associated adverse event (VAAE) occurring, although slightly higher than in dogs, is quite low.^{78,117} Vaccine reactions are usually mild and transient.¹¹⁷ In a report of almost 500,000 vaccinated cats, VAAEs were reported in approximately 0.5% of these cats. The most common adverse event was lethargy followed by localized vaccine-site reactions, vomiting, facial edema, and generalized pruritus.⁷⁸ Only four cats died within 48 hours of vaccine administration; two of them fit the description of anaphylaxis. The chances of developing a VAAE increased with the number of agents vaccinated against at one time.⁷⁸ A reduction in the number of vaccinations administered at one time might reduce the chances of VAAE development. Localized swellings appear 24 hours after vaccination, may be painful and hot, and usually last about 1 week.¹¹⁷ These localized swellings occur two to five times more frequently in cats than in dogs.⁷⁸ Although this has not been studied in cats, there is limited evidence supporting an association between vaccine administration and the development of immune-mediated disorders in dogs.¹¹⁷ Vaccination against calicivirus has been associated with polyarthritis and postvaccination lameness in cats.¹¹⁷ Injection-site sarcomas are covered in Chapter 28.

References

- Adams LG, Hardy RM, Weiss DJ et al: Hypophosphatemia and hemolytic anemia associated with diabetes mellitus and hepatic lipidosis in cats, *J Vet Intern Med* 7:266, 1993.
- Autran de Moraes H, O'Brien R: Non-neoplastic diseases of the spleen. In Ettinger S, Feldman E, editors: *Textbook of veterinary internal medicine*, ed 6, St Louis, 2005, Elsevier/Saunders, p 1944.
- Avery PR, Hoover EA: Gamma interferon/interleukin 10 balance in tissue lymphocytes correlates with down modulation of mucosal feline immunodeficiency virus infection, *J Virol* 78:4011, 2004.

4. Ballegeer EA, Forrest LJ, Dickinson RM et al: Correlation of ultrasonographic appearance of lesions and cytologic and histologic diagnoses in splenic aspirates from dogs and cats: 32 cases (2002-2005), *J Am Vet Med Assoc* 230:690, 2007.
5. Bhatt S, Siegel A: Potentiating role of interleukin 2 (IL-2) receptors in the midbrain periaqueductal gray (PAG) upon defensive rage behavior in the cat: role of neurokinin NK(1) receptors, *Behav Brain Res* 167:251, 2006.
6. Bianco D, Armstrong PJ, Washabau RJ: Presumed primary immune-mediated thrombocytopenia in four cats, *J Feline Med Surg* 10:495, 2008.
7. Bighignoli B, Owens S, Froenckle L et al: Blood types of the domestic cat. In August J, editor: *Consultations in feline internal medicine*, ed 6, St Louis, 2010, Elsevier/Saunders, p 628.
8. Birkenheuer A, Cohn L, Levy M et al: Atovaquone and azithromycin for the treatment of *Cytauxzoon felis*, *J Vet Intern Med* 22:703, 2008.
9. Bondy P, Cohn L, Kerl M: Feline cytauxzoonosis, *Compend Contin Educ Pract Vet* 27, 2005.
10. Brockus C: Interpreting the leukogram. In August J, editor: *Consultations in feline internal medicine*, ed 5, St Louis, 2006, Elsevier/Saunders, p 585.
11. Brockus C: Leukocyte disorders. In Ettinger S, Feldman E, editors: *Textbook of veterinary internal medicine*, ed 6, St Louis, 2006, Elsevier/Saunders, p 1937.
12. Brooks M, DeWilde L: Feline factor XII deficiency, *Compend Contin Educ Pract Vet* 28:148, 2006.
13. Brown R, Riogers K: Neutropenia in dogs and cats, *Compend Contin Educ Pract Vet* 23:534, 2001.
14. Christopher M: Disorders of feline red blood cells. In Bonagura J, editor: *Kirk's current veterinary therapy XIII small animal practice*, Philadelphia, 2000, Saunders, p 421.
15. Cohen R: Systemic anaphylaxis. In Bonagura J, editors: *Kirk's current veterinary therapy XII small animal practice*, Philadelphia, 1995, Saunders, p 150.
16. Cohn L: Glucocorticoid therapy. In Ettinger S, Feldman E, editors: *Textbook of veterinary internal medicine*, ed 6, St Louis, 2005, Elsevier/Saunders, p 503.
17. Cowell A, Cowell R: Management of bee and other hymenoptera stings. In Bonagura J, editor: *Kirk's current veterinary therapy XII small animal practice*, Philadelphia, 1995, Saunders, p 226.
18. Cowell R, Tyler R, Meinkoth J: Diagnosis of anemia. In August J, editor: *Consultations in feline internal medicine*, ed 5, St Louis, 2006, Elsevier/Saunders, p 565.
19. Cowgill L: CVT update: use of recombinant human erythropoietin. In Bonagura J, editor: *Kirk's current veterinary therapy XII small animal practice*, Philadelphia, 1995, Saunders, p 961.
20. Culp WT, Aronson LR: Splenic foreign body in a cat, *J Feline Med Surg* 10:380, 2008.
21. Dowers KL, Olver C, Radecki SV et al: Use of enrofloxacin for treatment of large-form *Haemobartonella felis* in experimentally infected cats, *J Am Vet Med Assoc* 221:250, 2002.
22. Dowers KL, Tasker S, Radecki SV et al: Use of pradofloxacin to treat experimentally induced *Mycoplasma hemofelis* infection in cats, *Am J Vet Res* 70:105, 2009.
23. Dunham SP: Cytokines and anti-cytokine therapy: clinical potential for treatment of feline disease, *J Feline Med Surg* 1:7, 1999.
24. Estrin MA, Wehausen CE, Jessen CR et al: Disseminated intravascular coagulation in cats, *J Vet Intern Med* 20:1334, 2006.
25. Feldman B: Blood transfusion guidelines. In Bonagura J, editor: *Kirk's current veterinary therapy XIII small animal practice*, Philadelphia, 2000, Saunders, p 400.
26. Feldman B: Nonregenerative anemia. In Ettinger S, Feldman E, editors: *Textbook of veterinary internal medicine*, ed 6, St Louis, 2005, Elsevier/Saunders, p 1908.
27. Feldman E, Nelson R: *Glucocorticoid therapy: canine and feline endocrinology and reproduction*, ed 3, St Louis, 2004, Saunders, p 464.
28. Felsburg P: Hereditary and acquired immunodeficiency diseases. In Bonagura J, editor: *Kirk's current veterinary therapy XIII small animal practice*, Philadelphia, 2004, Saunders, p 516.
29. Foley J: Feline infectious peritonitis and feline enteric coronavirus. In Ettinger S, Feldman E, editors: *Textbook of veterinary internal medicine*, ed 6, St Louis, 2005, Elsevier/Saunders, p 663.
30. Foley JE, Rand C, Leutenegger C: Inflammation and changes in cytokine levels in neurological feline infectious peritonitis, *J Feline Med Surg* 5:313, 2003.
31. George JW, Rideout BA, Griffey SM et al: Effect of preexisting FeLV infection or FeLV and feline immunodeficiency virus coinfection on pathogenicity of the small variant of *Haemobartonella felis* in cats, *Am J Vet Res* 63:1172, 2002.
32. Gibson GR, Callan MB, Hoffman V et al: Use of a hemoglobin-based oxygen-carrying solution in cats: 72 cases (1998-2000), *J Am Vet Med Assoc* 221:96, 2002.
33. Giger U: Hereditary erythrocyte disorders. In August J, editor: *Consultations in feline veterinary internal medicine*, ed 4, Philadelphia, 2001, Saunders, p 484.
34. Giger U: Regenerative anemias caused by blood loss or hemolysis. In Ettinger S, Feldman E, editors: *Textbook of veterinary internal medicine*, ed 6, St Louis, 2005, Elsevier/Saunders, p 1886.
35. Giger U: Blood-typing and crossmatching. In Bonagura J, Twedt D, editors: *Kirk's current veterinary therapy XIV*, St Louis, 2009, Saunders/Elsevier, p 260.
36. Giger U, Bucheler J: Transfusion of type-A and type-B blood to cats, *J Am Vet Med Assoc* 198:411, 1991.
37. Gordon SS, McClaran JK, Bergman PJ et al: Outcome following splenectomy in cats, *J Feline Med Surg* 12:256, 2010.
38. Goree M, Catalfamo JL, Aber S et al: Characterization of the mutations causing hemophilia B in 2 domestic cats, *J Vet Intern Med* 19:200, 2005.
39. Greene C, Meinkoth J, Kocan A: Cytauxzoonosis. In Greene C, editor: *Infectious diseases of the dog and cat*, ed 3, St Louis, 2006, Saunders, p 716.
40. Gregory C: Immunosuppressive agents. In Bonagura J, Twedt D, editors: *Kirk's current veterinary therapy XIV*, St Louis, 2009, Saunders/Elsevier, p 254.
41. Guilford W: The gastrointestinal tract and adverse reactions to food. In August J, editor: *Consultations in feline internal medicine*, ed 4, Philadelphia, 2001, Saunders, p 113.
42. Haldane S, Roberts J, Marks S et al: Transfusion medicine, *Compend Contin Educ Pract Vet* 26, 2004.
43. Hall R: Interpreting the leukogram. In August J, editor: *Consultations in feline internal medicine*, ed 2, Philadelphia, 1994, Saunders, p 489.
44. Hammer A, Couto C: Disorders of the lymph nodes and spleen. In Sherding R, editor: *The cat: diseases and clinical management*, ed 2, Philadelphia, 1994, Saunders, p 671.
45. Hanson JA, Papageorges M, Girard E et al: Ultrasonographic appearance of splenic disease in 101 cats, *Vet Radiol Ultrasound* 42:441, 2001.
46. Hardie R, Petrus D: Lymphatics and lymph nodes. In Slatter D, editor: *Textbook of small animal surgery*, ed 3, Philadelphia, 2003, Saunders, p 1063.
47. Hasler A: Polycythemia. In Ettinger S, Feldman E, editors: *Textbook of veterinary internal medicine*, ed 6, St Louis, 2005, Elsevier/Saunders, p 215.
48. Helfand S: Hematopoietic cytokines: the interleukin array. In Bonagura J, editor: *Kirk's current veterinary therapy XIII small animal practice*, Philadelphia, 2000, Saunders, p 408.
49. Holan K: Feline hepatic lipidosis. In Bonagura J, Twedt D, editors: *Kirk's current veterinary therapy XIV*, St Louis, 2009, Saunders/Elsevier, p 570.

50. Johnson LR, De Cock HE, Sykes JE et al: Cytokine gene transcription in feline nasal tissue with histologic evidence of inflammation, *Am J Vet Res* 66:996, 2005.
51. Jordan HL, Grindem CB, Breitschwerdt EB: Thrombocytopenia in cats: a retrospective study of 41 cases, *J Vet Intern Med* 7:261, 1993.
52. Kearns S, Ewing P: Causes of canine and feline pancytopenia, *Compend Contin Educ Pract Vet* 28, 2006.
53. Klaser DA, Reine NJ, Hohenhaus AE: Red blood cell transfusions in cats: 126 cases (1999), *J Am Vet Med Assoc* 226:920, 2005.
54. Knottenbelt S, Blackwood L: The blood. In Chandler E, Gaskell C, Gaskell R, editors: *Feline medicine and therapeutics*, ed 3, Oxford, 2004, Blackwell Publishing, p 235.
55. Kohn B, Fumi C: Clinical course of pyruvate kinase deficiency in Abyssinian and Somali cats, *J Feline Med Surg* 10:145, 2008.
56. Kohn B, Goldschmidt MH, Hohenhaus AE et al: Anemia, splenomegaly, and increased osmotic fragility of erythrocytes in Abyssinian and Somali cats, *J Am Vet Med Assoc* 217:1483, 2000.
57. Kohn B, Weingart C, Eckmann V et al: Primary immune-mediated hemolytic anemia in 19 cats: diagnosis, therapy, and outcome (1998-2004), *J Vet Intern Med* 20:159, 2006.
58. Langston C, Ludwig L: Renal transplantation. In Ettinger S, Feldman E, editors: *Textbook of veterinary internal medicine*, ed 6, St Louis, 2005, Elsevier/Saunders, p 1752.
59. Levy J, Crawford P: Feline leukemia virus. In Ettinger S, Feldman E, editors: *Textbook of veterinary internal medicine*, ed 6, St Louis, 2005, Elsevier/Saunders, p 653.
60. Levy JK, Crawford PC, Collante WR et al: Use of adult cat serum to correct failure of passive transfer in kittens, *J Am Vet Med Assoc* 219:1401, 2001.
61. Levy JK, Liang Y, Ritchey JW et al: Failure of FIV-infected cats to control Toxoplasma gondii correlates with reduced IL2, IL6, and IL12 and elevated IL10 expression by lymph node T cells, *Vet Immunol Immunopathol* 98:101, 2004.
62. Littlewood JD, Shaw SC, Coombes LM: Vitamin K-dependent coagulopathy in a British Devon rex cat, *J Small Anim Pract* 36:115, 1995.
63. London C: Hematopoietic cytokines: the myelopoietic factors. In Bonagura J, editor: *Kirk's current veterinary therapy XIII small animal practice*, Philadelphia, 2000, Saunders, p 403.
64. Lucroy MD, Madewell BR: Clinical outcome and diseases associated with extreme neutrophilic leukocytosis in cats: 104 cases (1991-1999), *J Am Vet Med Assoc* 218:736, 2001.
65. Lusson D, Billiemaz B, Chabanne JL: Circulating lupus anticoagulant and probable systemic lupus erythematosus in a cat, *J Feline Med Surg* 1:193, 1999.
66. Mackin A: Platelet disorders. In August J, editor: *Consultations in feline internal medicine*, ed 5, St Louis, 2006, Elsevier/Saunders, p 575.
67. Maddison JE, Watson AD, Eade IG et al: Vitamin K-dependent multifactor coagulopathy in Devon Rex cats, *J Am Vet Med Assoc* 197:1495, 1990.
68. Marino D: Diseases of the spleen. In Bonagura J, editor: *Kirk's current veterinary therapy XIII small animal practice*, Philadelphia, 2000, Saunders, p 520.
69. Marks S, Henry C: CVT update: diagnosis and treatment of systemic lupus erythematosus. In Bonagura J, editor: *Kirk's current veterinary therapy XIII small animal practice*, Philadelphia, 2000, Saunders, p 514.
70. May S, Langston C: Managing chronic renal failure, *Compend Contin Educ Pract Vet* 28, 2006.
71. McSherry L: Techniques for bone marrow aspiration and biopsy. In Ettinger S, Feldman E, editors: *Textbook of veterinary internal medicine*, ed 6, St Louis, 2005, Elsevier/Saunders, p 285.
72. Meinkoth J, Kocan AA, Whitworth L et al: Cats surviving natural infection with *Cytauxzoon felis*: 18 cases (1997-1998), *J Vet Intern Med* 14:521, 2000.
73. Meurs KM, Fox PR, Miller MW et al: Plasma concentrations of tumor necrosis factor-alpha in cats with congestive heart failure, *Am J Vet Res* 63:640, 2002.
74. Miller C, Bartges J: Refeeding syndrome. In Bonagura J, editor: *Kirk's current veterinary therapy XIII small animal practice*, Philadelphia, 2000, Saunders, p 87.
75. Miller E: Immune-mediated hemolytic anemia. In Bonagura J, Twedt D, editors: *Kirk's current veterinary therapy XIV*, St Louis, 2009, Saunders/Elsevier, p 266.
76. Mooney SC, Patnaik AK, Hayes AA et al: Generalized lymphadenopathy resembling lymphoma in cats: six cases (1972-1976), *J Am Vet Med Assoc* 190:897, 1987.
77. Moore FM, Emerson WE, Cotter SM et al: Distinctive peripheral lymph node hyperplasia of young cats, *Vet Pathol* 23:386, 1986.
78. Moore GE, DeSantis-Kerr AC, Guptill LF et al: Adverse events after vaccine administration in cats: 2,560 cases (2002-2005), *J Am Vet Med Assoc* 231:94, 2007.
79. Museux K, Boretti FS, Willi B et al: In vivo transmission studies of '*Candidatus Mycoplasma turicensis*' in the domestic cat, *Vet Res* 40:45, 2009.
80. Nakazato A, Momoi Y, Kadoya M et al: Measurement of feline serum interleukin-5 level, *J Vet Med Sci* 69:843, 2007.
81. Neer T: Splenomegaly and lymphadenopathy. In August J, editor: *Consultations in feline internal medicine*, ed 4, Philadelphia, 2001, Saunders, p 439.
82. Nguyen Van N, Taglinder K, Helps CR et al: Measurement of cytokine mRNA expression in intestinal biopsies of cats with inflammatory enteropathy using quantitative real-time RT-PCR, *Vet Immunol Immunopathol* 113:404, 2006.
83. Nibblett BM, Snead EC, Waldner C et al: Anemia in cats with hemotropic mycoplasma infection: retrospective evaluation of 23 cases (1996-2005), *Can Vet J* 50:1181, 2009.
84. Nitsche E: Erythrocytosis in dogs and cats: diagnosis and management, *Compend Contin Educ Pract Vet* 26, 2004.
85. Ogg A, Kruth S: Antimicrobial therapy for the neutropenic dog and cat. In Bonagura J, editor: *Kirk's current veterinary therapy XIII small animal practice*, Philadelphia, 2000, Saunders, p 267.
86. Ottenjann M, Weingart C, Arndt G et al: Characterization of the anemia of inflammatory disease in cats with abscesses, pyothorax, or fat necrosis, *J Vet Intern Med* 20:1143, 2006.
87. Papich M: Drug therapy in cats: precautions and guidelines. In August J, editor: *Consultations in feline internal medicine*, ed 5, St Louis, 2006, Elsevier/Saunders, p 279.
88. Paterson S: Diagnosis and management of pemphigus foliaceus. In August J, editor: *Consultations in feline internal medicine*, ed 5, St Louis, 2006, Elsevier/Saunders, p 261.
89. Peterson JL, Couto CG, Wellman ML: Hemostatic disorders in cats: a retrospective study and review of the literature, *J Vet Intern Med* 9:298, 1995.
90. Platt S, Abramson C, Garosi L: Administering corticosteroids in neurological disease, *Compend Contin Educ Pract Vet* 27, 2005.
91. Plotnick A: Feline chronic renal failure: long-term medical management, *Compend Contin Educ Pract Vet* 29, 2007.
92. Plumb D: Leflunomide. In *Plumb's veterinary drug handbook*, ed 6, Stockholm, WI, 2008, PharmaVet Inc.
93. Polzin D, Osborne C, Ross S: Chronic kidney disease. In Ettinger S, Feldman E, editors: *Textbook of veterinary internal medicine*, ed 6, St Louis, 2005, Elsevier/Saunders, p 1756.
94. Randolph JE, Scarlett JM, Stokol T et al: Expression, bioactivity, and clinical assessment of recombinant feline erythropoietin, *Am J Vet Res* 65:1355, 2004.
95. Rojko J, Hardy W: Feline leukemia virus and other retroviruses. In Sherding R, editor: *The cat: diseases and clinical management*, ed 2, Philadelphia, 1994, Saunders, p 263.
96. Roosje PJ, Dean GA, Willemse T et al: Interleukin 4-producing CD4+ T cells in the skin of cats with allergic dermatitis, *Vet Pathol* 39:228, 2002.

97. Roudebush P, Polzin DJ, Ross SJ et al: Therapies for feline chronic kidney disease. What is the evidence? *J Feline Med Surg* 11:195, 2009.
98. Roux FA, Deschamps JY, Blais MC et al: Multiple red cell transfusions in 27 cats (2003-2006): indications, complications and outcomes, *J Feline Med Surg* 10:213, 2008.
99. Rudloff E, Kirby R: Disseminated intravascular coagulation: diagnosis and management. In Bonagura J, Twedt D, editors: *Kirk's current veterinary therapy XIV*, St Louis, 2009, Saunders/Elsevier, p 287.
100. Sartor L, Trepanier L: Rational pharmacological therapy of hepatobiliary disease in dogs and cats, *Compend Contin Educ Pract Vet* 25, 2003.
101. Schooley EK, McGee Turner JB, Jiji RD et al: Effects of cyproheptadine and cetirizine on eosinophilic airway inflammation in cats with experimentally induced asthma, *Am J Vet Res* 68:1265, 2007.
102. Segev G, Klement E, Aroch I: Toxic neutrophils in cats: clinical and clinicopathologic features, and disease prevalence and outcome—a retrospective case control study, *J Vet Intern Med* 20:20, 2006.
103. Smith J, Day T, Mackin A: Diagnosing bleeding disorders, *Compend Contin Educ Pract Vet* 27, 2005.
104. Stieger K, Palos H, Giger U: Comparison of various blood-typing methods for the feline AB blood group system, *Am J Vet Res* 66:1393, 2005.
105. Stokol T, Brooks M: Diagnosis of DIC in cats: is it time to go back to the basics? *J Vet Intern Med* 20:1289, 2006.
106. Stone M: Systemic lupus erythematosus. In Ettinger S, Feldman E, editors: *Textbook of veterinary internal medicine*, ed 6, St Louis, 2005, Elsewhere/Saunders, p 1952.
107. Stutzer B, Muller F, Majzoub M et al: Role of latent feline leukemia virus infection in nonregenerative cytopenias of cats, *J Vet Intern Med* 24:192, 2010.
108. Sykes JE, Drazenovich NL, Ball LM et al: Use of conventional and real-time polymerase chain reaction to determine the epidemiology of hemoplasma infections in anemic and nonanemic cats, *J Vet Intern Med* 21:685, 2007.
109. Sykes JE, Terry JC, Lindsay LL et al: Prevalences of various hemoplasma species among cats in the United States with possible hemoplasmosis, *J Am Vet Med Assoc* 232:372, 2008.
110. Tasker S, Caney SM, Day MJ et al: Effect of chronic FIV infection, and efficacy of marbofloxacin treatment, on *Mycoplasma haemofelis* infection, *Vet Microbiol* 117:169, 2006.
111. Tasker S, Lappin M: Update on hemoplasmosis. In August J, editor: *Consultations in feline internal medicine*, ed 5, St Louis, 2006, Elsevier/Saunders, p 605.
112. Tholen I, Weingart C, Kohn B: Concentration of D-dimers in healthy cats and sick cats with and without disseminated intravascular coagulation (DIC), *J Feline Med Surg* 11:842, 2009.
113. Tillson D: Spleen. In Slatter D, editor: *Textbook of small animal surgery*, ed 3, Philadelphia, 2003, Saunders, p 1046.
114. Tizard I: Drugs and other agents that affect the immune system. In Tizard I, editor: *Veterinary immunology: an introduction*, ed 8, St Louis, 2009, Saunders/Elsevier, p 480.
115. Tizard I: Primary immunodeficiencies. In Tizard I, editor: *Veterinary immunology: an introduction*, ed 8, St Louis, 2009, Saunders/Elsevier, p 448.
116. Tizard I: Type I hypersensitivity. In Tizard I, editor: *Veterinary immunology: an introduction*, ed 8, St Louis, 2009, Saunders/Elsevier, p 329.
117. Tizard I: The use of vaccines. In Tizard I, editor: *Veterinary immunology: an introduction*, ed 8, St Louis, 2009, Saunders/Elsevier, p 270.
118. Tocci LJ, Ewing PJ: Increasing patient safety in veterinary transfusion medicine: an overview of pretransfusion testing, *J Vet Emerg Crit Care (San Antonio)* 19:66, 2009.
119. Trepanier L: Idiopathic inflammatory bowel disease in cats. Rational treatment selection, *J Feline Med Surg* 11:32, 2009.
120. Vail D, Thamm D: Hematopoietic tumors. In Ettinger S, Feldman E, editors: *Textbook of veterinary internal medicine*, ed 6, St Louis, 2005, Elsevier/Saunders, p 732.
121. Waddell L: Systemic anaphylaxis. In Ettinger S, Feldman E, editors: *Textbook of veterinary internal medicine*, ed 6, St Louis, 2005, Elsevier/Saunders, p 458.
122. Wardrop KJ, Reine N, Birkenheuer A et al: Canine and feline blood donor screening for infectious disease, *J Vet Intern Med* 19:135, 2005.
123. Washabau RJ, Day MJ, Willard MD et al: Endoscopic, biopsy, and histopathologic guidelines for the evaluation of gastrointestinal inflammation in companion animals, *J Vet Intern Med* 24:10, 2010.
124. Weinstein NM, Blais MC, Harris K et al: A newly recognized blood group in domestic shorthair cats: the MiK red cell antigen, *J Vet Intern Med* 21:287, 2007.
125. Weiss D: Nonregenerative anemias. In Bonagura J, Twedt D, editors: *Kirk's current veterinary therapy XIV*, St Louis, 2009, Saunders/Elsevier, p 272.
126. Weiss D, Tvedten H: Erythrocyte disorders. In Willard M, Tvedten H, editors: *Small animal clinical diagnosis by laboratory methods*, ed 4, St Louis, 2004, Saunders, p 38.
127. Weiss DJ: Aplastic anemia in cats—clinicopathological features and associated disease conditions 1996-2004, *J Feline Med Surg* 8:203, 2006.
128. White C, Reine N: Feline nonregenerative anemia: diagnosis and treatment, *Compend Contin Educ Pract Vet* 31, 2009.
129. White C, Reine N: Feline nonregenerative anemia: pathophysiology and etiologies, *Compend Contin Educ Pract Vet* 31, 2009.
130. Williams CR, Sykes JE, Mehl M et al: In vitro effects of the active metabolite of leflunomide, A77 1726, on feline herpesvirus-1, *Am J Vet Res* 68:1010, 2007.
131. Wohl J, Murtaugh R: Use of catecholamines in critical care patients. In Bonagura J, editor: *Kirk's current veterinary therapy XII small animal practice*, Philadelphia, 1995, Saunders, p 188.
132. Wondratschek C, Weingart C, Kohn B: Primary immune-mediated thrombocytopenia in cats, *J Am Anim Hosp Assoc* 46:12, 2010.
133. Woods JE, Wisnewski N, Lappin MR: Attempted transmission of *Candidatus Mycoplasma haemominutum* and *Mycoplasma haemofelis* by feeding cats infected *Ctenocephalides felis*, *Am J Vet Res* 67:494, 2006.
134. Young K, Moriello K: Eosinophils and eosinophilic diseases. In August J, editor: *Consultations in feline internal medicine*, ed 5, St Louis, 2006, Elsevier/Saunders, p 239.