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CHAPTER 65

Disorders of White Blood Cells

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GENERAL CONSIDERATIONS

Leukogram Evaluation

I. The complete blood count (CBC) evaluates white blood cells (WBCs [leukocytes]), red blood cells (RBCs [erythrocytes]), and platelets.
II. The leukogram is composed of total, relative, and absolute differential leukocyte counts and morphology evaluation.
  A. Absolute differential leukocyte counts (total WBC × WBC type relative percent) are the preferred evaluation method and result in fewer interpretation errors.
  B. Canine and feline leukocytes are present in the following numeric order of prevalence in healthy animals: neutrophils, lymphocytes, monocytes, eosinophils, and basophils.
III. Published total leukocyte counts in health are 6000 to 17,000/μL in dogs and 5500 to 19,500/μL in cats (Mahaffey, 2003).
  A. These numbers are provided as guidelines; use the reference ranges provided by each laboratory to interpret the leukogram.
  B. Interpretation of the leukogram is based on the absolute leukocyte count (reported as numbers/μL) rather than the relative percentages.
  C. The absolute numbers of the various WBCs are altered by physiological, pathologic, or pharmacological processes.
  D. Increased numbers of leukocytes are denoted by the addition of the suffix "ilia" or "osis."
    1. *Neutrophilia* is defined as absolute neutrophil counts >12,000/μL in dogs and >12,500/μL in cats; it is the most common contributor to leukocytosis.
    2. *Monocytosis* is defined as absolute monocyte counts >1400/μL in dogs and >850/μL in cats.
    3. *Lymphocytosis* is defined as absolute lymphocyte counts >2900/μL in dogs and >7000/μL in cats.
    4. *Eosinophilia* is defined as absolute eosinophil counts >1300/μL in dogs and >750/μL in cats; it generally occurs with hypersensitivity reactions or parasitic infections.
    5. *Basophilia* is defined as absolute basophil counts >140/μL in dogs and >200/μL in cats.
    6. Basophilia is rare, is often accompanied by eosinophilia, and is associated with parasitic diseases (particularly dirofilariasis); hypersensitivity reactions; inflammation; neoplasia (basophilic leukemia, mast cell tumor/mastocytosis, lymphomatoid granulomatosis, essential thrombocythemia); and drug reactions (heparin, penicillin).
  E. Decreased numbers of leukocytes are denoted by the addition of the suffix "penia" or "cytopenia."
    1. *Neutropenia* is defined as absolute neutrophil counts of <2900/μL in dogs and <2500/μL in cats.
    2. *Lymphopenia* is defined as absolute lymphocyte counts <400/μL in dogs and <1500/μL in cats.
    3. Monocytopenia and basopenia occur infrequently and are of no clinical importance.
    4. Eosinopenia and basopenia are difficult to define, because the lower limit of normal in dogs and cats typically extend to 0/μL.
      a. Eosinopenia may occur with acute inflammation or infection.
      b. Eosinopenia also may follow endogenous corticosteroid release secondary to stress, trauma, or hyperadrenocorticism, and may be associated with exogenous corticosteroid or adrenocorticotropic hormone (ACTH) administration.
IV. Assessment of WBC morphology is extremely important.
  A. Altered WBC morphology and the presence of cytoplasmic inclusions are important indicators of physiological abnormalities or disease (Tables 65-1 and 65-2).
  B. Abnormal morphology does not always indicate abnormal or compromised cell function; normal morphology does not guarantee normal cell function.
  C. Characteristic and cyclical patterns of changes in WBC numbers over time are unique to certain disorders (e.g., canine cyclic hematopoiesis).

Peripheral Blood Neutrophil Pools

I. Neutrophils in peripheral blood randomly disperse into two interchangeable populations—the circulating and the marginated pools.
II. The circulating pool includes neutrophils located within the vasculature that are sampled with routine blood collection and quantified in the CBC.
III. The marginated pool is composed of neutrophils that are loosely attached to capillary and venule endothelial surfaces

TABLE 65-1

Morphological Alterations in Leukocytes

ALTERATION	CELL TYPE AFFECTED	KEY MORPHOLOGICAL FEATURE(S)	INTERPRETATION	CAUSES	REFERENCES
Hypersegmentation	Neutrophils	≥5 nuclear lobes	Increased vascular transit time	Increased endogenous (protracted stress, hyperadrenocorticism) or exogenous corticosteroid administration	Schultze (2000)
Hyposegmentation	Neutrophils	Round, bean- or horseshoe-shaped nuclei	Cellular immaturity or failure of the nucleus to segment (congenital or acquired)	Left shift: release of immature neutrophils or Pelger-Huët anomaly	Kociba (2000), Schultze (2000)
Toxic change	Neutrophils	Cytoplasmic abnormalities: Döhle bodies (basophilic, pale, angular, peripherally located inclusions), vacuolation, basophilia, toxic granulation, and/or giant neutrophils	Accelerated production of neutrophils and decreased neutrophil maturation time in the marrow Affected cells lack some functions (guarded prognosis) Can be a sensitive diagnostic aid for inflammation, systemic disease, or drug toxicity, as they may precede changes in neutrophil number and appearance of immature forms	Severe inflammation from localized or systemic infection, endotoxemia, sterile inflammation, or drug toxicity	Aroch et al. (2005)
EDTA artifact	Neutrophils	Cytoplasmic vacuolization, membrane irregularity, and pyknosis	Artifact (must be differentiated from toxic change)	Prolonged exposure to EDTA (delayed blood smear preparation)	Gossett and Carakostas (1984)
Reactive lymphocytes	Lymphocytes	Increased cell size, deeply basophilic cytoplasm, perinuclear clear zone, aggregated chromatin, and indistinct nucleoli	Antigenic stimulation	Many causes; occurs secondary to inflammation, infection, or recent immunization	Kociba (2000)
Large granular lymphocytes	Lymphocytes	Variable numbers of azurophilic to eosinophilic cytoplasmic granules Dogs: small granules clustered near the nucleus Cats: larger, evenly dispersed granules	Neoplasia or inflammation	Neoplasia or inflammation	Weider et al. (1991)

EDTA, Ethylenediamine tetraacetic acid.

TABLE 65-1

Morphological Alterations in Leukocytes—*cont'd*

ALTERATION	CELL TYPE AFFECTED	KEY MORPHOLOGICAL FEATURE(S)	INTERPRETATION	CAUSES	REFERENCES
Lymphocytes in Sézary syndrome	Lymphocytes	Large circulating neoplastic lymphocytes with intensely cleaved nuclei with prominent nucleoli	Neoplasia	Neoplasia	Foster et al. (1997)
Plasma cells	Lymphocytes	Characterized by basophilic cytoplasm, eccentrically placed nucleus with condensed chromatin, and prominent perinuclear Golgi zone	Rarely found in circulation	Antigenic stimulation from infection, inflammation, hypersensitivity reactions, systemic disease	Schultze (2000)
Degranulation or vacuolation of eosinophils (dogs)	Eosinophils	Complete or partial clearing of eosinophilic staining of granules	Artifact	Unknown, but not indicative of injury or abnormal function	Schultze (2000)

TABLE 65-2

Leukocyte Cytoplasmic Inclusions

INCLUSION	CELL(S) AFFECTED	KEY MORPHOLOGIC FEATURES	REFERENCES
Bacteria	Neutrophils, monocytes, eosinophils (rarely)	Dogs, cats: positively or negatively staining rods or cocci	Tvedten et al. (1990)
Hepatozoon spp. gametocytes	Neutrophils or monocytes	Dogs: oval, unstained to pale blue basophilic inclusions (5-10 μm)	Barton et al. (1985), Panciera et al. (2000)
Canine distemper virus	Leukocytes (particularly lymphocytes), red blood cells	Dogs: round to irregularly shaped, homogeneous, blue-gray to magenta, intracytoplasmic inclusions	McLaughlin et al. (1985)
Histoplasma capsulatum	Neutrophils, monocytes, eosinophils (rarely)	Dogs, cats: round to oval, uniform, basophilic yeast (2-4 μm) with dark central area and clear halo	Clinkenbeard et al. (1988a, 1988b)
Ehrlichia spp. morulae	*E. ewingii, E. equi,* or human granulocytotropic *Ehrlichia* spp.: neutrophils and eosinophils *E. canis:* monocytes, lymphocytes	Dogs: magenta to basophilic inclusion (2-6 μm) resembling a mulberry	Cowell et al. (1988), Rikihisa (2000)
Leishmania spp. amastigotes	Neutrophils	Dogs: 1-2 small, round to oval organisms with oval nucleus, basophilic ventral kinetoplast, and light blue cytoplasm	Schultze (2000)
Hemosiderin	Neutrophils and monocytes	Dogs: brown crystals (1-4 μm) that stain positively with Prussian blue stain; reported with immune-mediated hemolytic anemia	Gaunt and Baker (1986)

and, therefore, are not sampled during blood collection procedures.

Bone Marrow Neutrophil Production and Kinetics

I. Neutrophil production and maturation occurs in the bone marrow, with precursors progressing through stages, such as myeloblast, progranulocyte, myelocyte, metamyelocyte, band neutrophil, and mature segmented neutrophil.
II. Neutrophil precursors are divided into two pools based on their mitotic capabilities.
   A. The proliferation-mitotic pool is composed of myeloblasts, progranulocytes, and myelocytes.
   B. The storage-maturation pool (no cell division) is composed of metamyelocytes, band, and segmented neutrophils.
III. The marrow transit time (myeloblast to released segmented neutrophils) is 3.5 to 6 days.

ALTERATIONS IN WHITE BLOOD CELL NUMBERS AND MORPHOLOGY

Neutrophilia

See Box 65-1.

Neutropenia

Definition

I. Neutropenia is characterized by a neutrophil count below the lower limit of the reference range (<2900/μL in dogs and <2500/μL in cats) (Mahaffey, 2003).
II. It is common in dogs and cats and is often accompanied by leukopenia.
III. Neutropenia accompanied by anemia and thrombocytopenia indicates pancytopenia and is suggestive of bone marrow injury or effacement.

Causes and Pathophysiology

I. General mechanisms of neutropenia consist of decreased bone marrow production and tissue utilization exceeding marrow production and release (Box 65-2).
II. Neutropenia can be secondary to increased margination, sequestration, hemophagocytic syndrome, and immune-mediated damage to circulating neutrophils or granulocytic precursors in the bone marrow.
III. Neutropenia can be a negative prognostic indicator associated with increased mortality; the more severe the neutropenia, the greater the risk of infection (Aroch et al., 2005).
IV. Neutropenia resulting from tissue utilization in excess of marrow production can occur with severe, localized bacterial infections involving body cavities, the uterus, the respiratory or gastrointestinal (GI) tracts, or during generalized septicemia.
V. Neutropenia can be associated with neutrophil toxicity.
VI. Marrow suppression resulting in decreased leukocyte production may arise with the following:

Box 65-1

Causes of Neutrophilia*

Causes	Species Affected
Inflammation	
Infectious agents	
Bacteria: numerous species	Dog, cat
Fungi: numerous species	Dog, cat
Rickettsia: Rocky Mountain spotted fever	Dog
Viruses: canine distemper, feline rhinotracheitis, feline calicivirus	Dog, cat
Parasites: numerous species	Dog, cat
Protozoa: *Hepatozoon americanum*	Dog
Tissue necrosis	
Thrombosis/infarction	Dog, cat
Metabolic injury: uremia	Dog, cat
Physical injury: surgery, trauma, burns, frostbite	Dog, cat
Neoplasia	Dog, cat
Immune-mediated diseases	
Immune-mediated hemolytic anemia	Dog, cat
Polyserositis	Dog, cat
Polymyositis	Dog, cat
Rheumatoid arthritis	Dog, cat
Systemic necrotizing vasculitis	Dog (beagle)
Lupus erythematosus	Dog, cat
Physiologic leukocytosis: epinephrine release resulting from excitement, fear, exercise	Dog, cat
Corticosteroid-induced leukocytosis: increased endogenous or exogenous steroids, ACTH administration	Dog, cat
Neoplasia	
Leukemia: several types	Dog, cat
Paraneoplastic syndrome: benign and malignant tumors	Dog, cat
Genetic disorders: CD11b/CD18 leukocyte adhesion deficiency	Dog (Irish setter)
Drug administration: recombinant human or canine colony-stimulating factor	Dog, cat
Drug toxicity: early estrogen toxicosis	Dog
Miscellaneous	
Hemolysis	Dog, cat
Hemorrhage	Dog, cat
Toxemia/toxicity	
Blue-green algae toxicity	Dog
Botulism	Dog, cat
Endotoxemia	Dog, cat
Uremia	Dog, cat

ACTH, Adrenocorticotropic hormone.
*Absolute neutrophil counts >12,000/μL in dogs and >12,500/μL in cats (Mahaffey EA: Quality control, test validity, and reference values. p. 331. In Latimer KS, Mahaffey, Prasse KW (eds): Duncan and Prasse's Veterinary Laboratory Medicine: Clinical Pathology. 4th Ed. Iowa State University Press, Ames, 2003).

Box 65-2

Causes of Neutropenia*

Causes	Species Affected
Tissue utilization in excess of bone marrow release	
Infectious agents	
Acute endotoxemia, septicemia	Dog, cat
Bacteria: numerous species	Dog, cat
Rickettsia: *Ehrlichia canis*	Dog
Viruses: canine parvovirus, canine distemper virus, infectious canine hepatitis, FeLV, FIV	Dog, cat
Parasites: *Babesia canis*	Dog
Decreased bone marrow production	
Drug toxicity	
Estrogen toxicosis: iatrogenic, prolonged estrus, or Sertoli cell tumor–induced hyperestrogenism	Dog
Griseofulvin	Cat
Chloramphenicol	Cat
Idiosyncratic drug reactions	
Cephalosporins	Dog, cat
Noxzema skin creme	Dog, cat
Phenylbutazone	Dog
Trimethoprim-sulfadiazine	Dog
Phenobarbital	Dog
Thiacetarsamide	Dog
Methimazole	Cat
Myelodysplasia and myeloproliferative diseases	Dog, cat
Lymphoproliferative disease	Dog, cat
Myelophthisis	
Neoplasia: metastatic carcinoma	Dog
Granulomatous inflammation: disseminated *Histoplasma capsulatum*	Dog, cat
Myelofibrosis and osteopetrosis	Dog
Bone marrow necrosis	Dog, cat
Radiation	Dog, cat
Shifts from the circulating to marginated neutrophil pool	
Endotoxemia	Dog, cat
Anaphylaxis	Dog, cat
Congenital disorders	
Cyclic hematopoiesis	Dog (gray-coated collie)
Inherited vitamin B_{12} malabsorption	Dog (giant schnauzer)
Destruction/sequestration of neutrophils	
Immune-mediated neutropenia	Dog
Hemophagocytic syndrome	Dog

FeLV, Feline leukemia virus; *FIV,* feline immunodeficiency virus.
*Absolute neutrophil counts <2900/μL in dogs and <2500/μL in cats (Mahaffey EA: Quality control, test validity, and reference values. p. 331. In Latimer KS, Mahaffey, Prasse KW (eds): Duncan and Prasse's Veterinary Laboratory Medicine: Clinical Pathology. 4th Ed. Iowa State University Press, Ames, 2003)

A. Total body ionizing radiation
B. Myelosuppression with chemotherapeutic agents (see Chapter 72)
   1. Examples include cyclophosphamide, daunomycin, dimethyl myleran, doxorubicin, 6-thioguanine, azathioprine, cisplatin, carboplatin, chlorambucil, melphalan, methotrexate, mitoxantrone, and combination therapy with vincristine and L-asparaginase.
   2. The marrow neutrophil proliferation-mitotic pool is most sensitive to chemotherapeutics.
      a. Differentiated cells in the maturation-storage pool are unaffected, so release of mature neutrophils continues for 5 to 10 days.
      b. A neutropenic nadir often occurs during these 5 to 10 days as a result of decreased marrow production and the short (6-hour) lifespan of the circulating neutrophil.
   3. Chemotherapy-induced thrombocytopenia occurs in 1 to 2 weeks (circulating lifespan of platelets is 10 days).
   4. Anemia is uncommon.
C. Estrogen toxicosis in dogs
   1. Sources of estrogen exposure include the following:
      a. Diethylstilbestrol or estradiol cyclopentylpropionate therapy used for mismating, urinary incontinence, or infertility in females may be a cause.
      b. With exogenous estrogen therapy for perianal gland tumors in males, pancytopenia can occur with the neutropenia.
      c. Excessive endogenous estrogen with interstitial and Sertoli cell tumors (males) and granulosa cell tumors (females) can also be associated with pancytopenia.
   2. Sequential hematological abnormalities in canine estrogen toxicosis consist of the following:
      a. Immediate leukocytosis followed by rapid leukopenia
      b. Thrombocytosis followed by rapid thrombocytopenia
      c. Slow development of anemia and pancytopenia within 1 month
D. Prolonged (14 to 21 days) chloramphenicol therapy in cats: leukopenia and neutrophils with Döhle bodies
E. Idiosyncratic drug reactions with either neutropenia or pancytopenia
   1. Antibiotics: cephalosporins, trimethoprim-sulfadiazine
   2. Thiacetarsamide
   3. Griseofulvin
   4. Phenobarbital
   5. Phenylbutazone
   6. Albendazole
   7. Captopril
   8. Medicated skin cream *(Noxzema)*
   9. Methimazole
   10. Trimeprazine tartrate

F. Infectious causes of neutropenia or pancytopenia (see Chapters 112 and 115)
   1. Parvovirus infection of dogs and cats (feline panleukopenia)
   2. Feline leukemia virus (FeLV)
   3. Feline immunodeficiency virus (FIV)
   4. Canine ehrlichiosis

VII. Neutropenia or pancytopenia from significantly decreased hematopoiesis can result from the following:
   A. Reduction or complete effacement of the marrow space with bone marrow necrosis (rare) or myelophthisic disease
   B. Causes of myelophthisic disease in dogs and cats
      1. Myelofibrosis (see Chapter 66)
      2. Osteopetrosis: rare
      3. Myeloproliferative diseases or myelodysplasia (see Chapter 66)
      4. Multicentric lymphoma (lymphosarcoma [LSA]) (see Chapter 69)
      5. Disseminated granulomatous disease (e.g., systemic mycoses)
      6. Metastatic neoplasia

VIII. Neutrophils shift rapidly from the circulating to marginated pool, especially during episodes of anaphylaxis or endotoxemia in dogs (pseudoneutropenia).

IX. Hemophagocytic syndrome is a rare event.
   A. Hematology findings consist of cytopenias involving two or more of the hematologic cell lines and circulating fragments of erythrocytes.
   B. Bone marrow aspirate reveals increased numbers of macrophages containing phagocytized hematopoietic precursors, and predominantly erythroid precursors, with fewer neutrophils and platelets.

X. Uncommon causes of neutropenia include the following:
   A. Immune-mediated neutropenia can be idiopathic, drug-related, or associated with other immune-mediated diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus).
      1. Presumptive diagnosis can be made with clinical response to immunosuppressive doses of corticosteroids and with termination of therapy in cases of drug-related neutropenia.
      2. Definitive diagnosis requires demonstration of antineutrophil antibodies, which is difficult owing to fragility of the neutrophils and potential release of intracellular enzymes.
   B. Canine cyclic hematopoiesis, a genetic disorder specific for gray-coated collies, is characterized by continuous, abnormal 2- to 4-day cycles of neutropenia.
      1. Affected dogs exhibit recurrent infections by 8 weeks of age.
      2. Death usually occurs by approximately 3 years of age from septicemia or systemic amyloidosis.
   C. Inherited vitamin B_{12} (cobalamin) malabsorption in giant schnauzers results in failure to express the necessary receptor for normal intestinal cobalamin absorption.
      1. Cobalamin deficiency induces maturation abnormalities in hematopoietic precursors.
      2. Characteristic findings consist of neutropenia, neutrophil hypersegmentation, nonregenerative anemia, nucleated red blood cells (nRBCs) with nuclear:cystoplasmic asynchrony, thrombocytosis, and rare giant platelets.

Diagnosis

I. Perform routine CBCs to identify and monitor neutropenia and concurrent hematological abnormalities.

II. Question clients regarding the administration of chemotherapeutics, estrogen, or other hematotoxic compounds.

III. Serological and other tests are used for diagnosis of canine and feline viral and ehrlichial diseases (see Chapters 112 and 115).

IV. Bone marrow evaluation is a useful procedure in cases of neutropenia when the aforementioned causes of neutropenia or pancytopenia have been eliminated, and may reveal the following:
   A. Myeloproliferative disease: blast cells in circulation and in bone marrow samples; cytochemical stains required for definitive diagnosis (see Chapter 66).
   B. Myelofibrosis: obliteration of marrow spaces by increased fibrous connective tissue
   C. Myelodysplasia: peripheral cytopenias to pancytopenia, abnormal cellular morphology and/or maturation, and hypercellular bone marrow with or without blast cells
   D. Identification of bone marrow abnormalities in inherited vitamin B_{12} deficiency: decreased cellularity, hypersegmented neutrophils, giant neutrophil precursors, and erythroid dysplasia

V. Measure serum cobalamin concentrations in giant schnauzers with suspected inherited cobalamin malabsorption.

Treatment

I. Consider discontinuing or delaying chemotherapy in animals with neutrophil counts of <1000/μL, and starting prophylactic broad-spectrum antibiotics, because they are predisposed to sepsis (Kociba, 2000).

II. Lithium carbonate (11 mg/kg PO BID for 6 weeks) may reverse marrow hypoplasia and pancytopenia secondary to estrogen toxicosis in dogs (Hall, 1992).

III. Lithium carbonate at 21 to 26 mg/kg/day PO may partially alleviate neutropenia of canine cyclic hematopoiesis, but can have toxic effects at this latter dose (Campbell, 1985).

IV. Recombinant human granulocyte colony-stimulating factor (G-CSF, 2.5 to 10 μg/kg/day SC for 3 to 5 days) can be used for short-term management of neutropenia in dogs and cats, but neutralizing antibodies develop in cats and dogs within 14 and 21 days, respectively; therefore, long-term use is not recommended (Ogilvie, 2000; Phillips et al., 2005).

V. Parenteral administration of 1 mg cobalamin once monthly has resulted in temporary remission; no improvement occurs with oral therapy (Fyfe, 2000).

VI. Bone marrow transplantation and lentivirus-mediated G-CSF therapy have been used experimentally to treat or lessen the severity of canine cyclic hematopoiesis (Lothrop et al., 1988; Yanay et al., 2003).

Monitoring of Animal

I. Prognosis for recovery from neutropenia is dependent on the cause and reversibility of bone marrow damage.
II. Neutrophil counts usually rebound when chemotherapeutic agents are discontinued.
III. Recovery following estrogen toxicosis is possible but variable.
   A. Recovery may occur within 3 months.
   B. Pancytopenia may be permanent in some cases.
IV. Neutropenia associated with idiosyncratic drug reactions may resolve within 1 to 2 weeks after therapy is discontinued.
V. Neutropenia induced by infectious diseases carries a fair (FeLV) to good (ehrlichiosis) prognosis.
VI. Neutropenia associated with bone marrow necrosis and myelophthisic disease has a guarded prognosis, but recovery is possible with successful treatment of certain underlying causes, such as lymphoma.

Lymphocytosis

See Box 65-3.

Lymphopenia

See Box 65-4.

Monocytosis

See Box 65-5.

Box 65-3

Causes of Lymphocytosis*

Causes	Species Affected
Physiological leukocytosis: epinephrine response	Dog, cat
Chronic antigenic stimulation	
Infectious agents	
Bacteria: brucellosis	Dog
Mycoses: various species	Dog, cat
Rickettsia: *Ehrlichia canis,* Rocky Mountain spotted fever	Dog
Viruses: feline leukemia virus	Cat
Vaccine-induced (acute response)	Dog, cat
Hypoadrenocorticism	Dog
Lymphoid neoplasia	
Acute or chronic lymphocytic leukemia	Dog, cat
Lymphoma	Cat
Thymoma	Cat

*Absolute lymphocyte counts >2900/μL in dogs and >7000/μL in cats (Mahaffey EA: Quality control, test validity, and reference values. p. 331. In Latimer KS, Mahaffey, Prasse KW (eds): Duncan and Prasse's Veterinary Laboratory Medicine: Clinical Pathology. 4th Ed. Iowa State University Press, Ames, 2003).

Eosinophilia

See Box 65-6.

Circulating Mast Cells

Definition

Mast cells are rarely seen in peripheral blood smears, but can occur with certain conditions.

Causes

I. Inflammatory conditions (dogs): allergic dermatitis, trauma, regenerative anemia, parvovirus infection, or non–mast cell neoplasia.

Box 65-4

Causes of Lymphopenia*

Causes	Species Affected
Corticosteroid-induced	
Increased endogenous corticosteroid levels	
Acute severe stress: inflammation, infection, trauma	Dog, cat
Hyperadrenocorticism	Dog
Exogenous corticosteroid or ACTH administration	Dog, cat
Septicemia or endotoxemia	Dog, cat
Acute viral infections	
FeLV, panleukopenia, FIV	Cat
Canine parvovirus, coronavirus, distemper, infectious hepatitis	Dog
Loss of lymph fluid	
Chylothorax (see Chapter 19)	Dog, cat
Chyloperitoneum	Dog, cat
Lymphangiectasia	Dog, cat
Gastrointestinal disease	
Protein-losing enteropathy	Dog
Ulcerative or granulomatous enteritis	Dog, cat
Neoplasia	
Gastrointestinal lymphoma	Dog, cat
Enteric tumors	Dog, cat
Lymph node effacement	
Granulomatous inflammation: numerous etiologies	Dog, cat
Multicentric lymphoma	Dog, cat
Hereditary disorders	
Severe combined immunodeficiency	Dog†
Treatment-induced	
Immunosuppressive drugs	Dog, cat
Chemotherapeutic drugs	Dog, cat
Radiation	Dog, cat

ACTH, Adrenocorticotropic hormone; *FeLV,* Feline leukemia virus; *FIV,* Feline immunodeficiency virus.
*Absolute lymphocyte counts <400/μL in dogs and <1500/μL in cats (Mahaffey EA: Quality control, test validity, and reference values. p. 331. In Latimer KS, Mahaffey, Prasse KW (eds): Duncan and Prasse's Veterinary Laboratory Medicine: Clinical Pathology. 4th Ed. Iowa State University Press, Ames, 2003).
†Basset hound, Parson (Jack) Russell terrier, Cardigan Welsh corgi.

Box 65-5

Causes of Monocytosis*

Causes	Species Affected
Acute or chronic inflammation	
Protozoal, fungal, or parasitic diseases: numerous species	Dog, cat
Bacterial diseases, particularly intracellular organisms such as *Mycobacterium* spp. or *Brucella* spp.	Dog, cat
Viral diseases: feline infectious peritonitis, FeLV	Cat
Foreign-body reaction	Dog, cat
Tissue necrosis	Dog, cat
Immune-mediated diseases: hemolytic anemia, arthritis	Dog
Pyogranulomatous inflammation	Dog, cat
Neoplasia-associated inflammation	Dog, cat
Hemolysis	Dog, cat
Corticosteroid-induced leukocytosis	Cat
Rebound from neutropenia (may be first indicator of recovery)	
Recovery from neutropenia with inflammation, infection, systemic disease	Dog, cat
Congenital cyclic hematopoiesis of gray-coated collies	Dog
Recovery from feline panleukopenia or canine parvovirus	Dog, cat
Neoplasia	
Monocytic leukemia	Dog, cat
Myelomonocytic leukemia	Dog, cat
Malignant histiocytosis	Dog

FeLV, Feline leukemia virus.
*Absolute monocyte counts >1400/μL in dogs and >850/μL in cats (Mahaffey EA: Quality control, test validity, and reference values. p. 331. In Latimer KS, Mahaffey, Prasse KW (eds): Duncan and Prasse's Veterinary Laboratory Medicine: Clinical Pathology. 4th Ed. Iowa State University Press, Ames, 2003).

II. Canine or feline metastatic mast cell neoplasia
III. Mast cell leukemia
  A. Myeloproliferative disease
  B. Atypical mast cells in circulation and in aspirate or biopsy samples from bone marrow, liver, and spleen

Diagnosis

I. Occasional mast cells are seen in peripheral blood smears.
II. Differentiation of mast cell leukemia from other conditions requires examination of cellular morphological characteristics, cytochemical staining, and histological examination of tissues.

Treatment

I. When mast cells are seen in peripheral blood smears, the underlying disease should be identified and treated.
II. See Chapter 70 for further discussion of treatment of mastocytosis.

Box 65-6

Causes of Eosinophilia*

Causes	Species Affected
Parasitic disease	
Heartworm disease	Dog, cat
Nematodes: numerous species	Dog, cat
Trematodes: various species	Dog, cat
Ectoparasites	Dog, cat
Protozoa: *Babesia canis, Hepatozoon americanum, H. canis, Pneumocystis carinii*	Dog, cat
Mycoses: *Cryptococcus neoformans, Aspergillus fumigatus, Pythium* spp., *Blastomyces dermatitidis*	Dog, cat
Immediate or delayed hypersensitivity reactions	
Oral granuloma	Dog
Gastrointestinal eosinophilic granuloma	Dog
Ulcerative gastroenteritis	Dog, cat
Pulmonary granuloma	Dog
Pulmonary infiltrates with eosinophilia	Dog
Asthma	Cat
Panosteitis	Dog
Pyometra	Dog
Atopy	Cat
Feline eosinophilic granuloma complex	Cat
Food hypersensitivity	Cat
Eosinophilic keratitis	Cat
Canine eosinophilic granuloma	Dog
Neoplasia	
Eosinophilic leukemia	Cat
Myeloid leukemia	Dog
Lymphoma	Cat
Lymphomatoid granulomatosis	Dog
Paraneoplastic conditions	
Carcinomas: select types	Dog, cat
Sarcomas: select types	Dog, cat
Mast cell neoplasia	Dog, cat
Endocrine conditions	
Hypoadrenocorticism	Dog
Hyperthyroidism	Cat
Estrus	Dog
Tetracycline administration	Dog
Idiopathic hypereosinophilic syndrome	Dog (rottweiler), cat

*Absolute eosinophil counts >1300/μL in dogs and >750/μL in cats (Mahaffey EA: Quality control, test validity, and reference values. p. 331. In Latimer KS, Mahaffey, Prasse KW (eds): Duncan and Prasse's Veterinary Laboratory Medicine: Clinical Pathology. 4th Ed. Iowa State University Press, Ames, 2003).

Inflammatory Leukocytosis

Definition

I. Neutrophil supply released from the bone marrow exceeds the migration of neutrophils into sites of inflammation.
II. The end result is an increase in circulating mature and immature neutrophils.

Causes and Pathophysiology

I. Tissue demand for neutrophils exceeds the reserve of mature neutrophils in the bone marrow.
   A. Release of immature cells (left shift) in the following order: band cells, then metamyelocytes, then myelocytes
   B. Regenerative left shift
      1. It occurs with acute inflammation.
      2. It is characterized by increased numbers of WBCs (leukocytosis) that are predominantly mature neutrophils, with increased immature neutrophil precursors.
   C. Degenerative left shift
      1. The WBC count is normal to decreased with excessive numbers of immature relative to mature neutrophils.
      2. It is often seen with septicemia or endotoxemia.
      3. Prognosis is poor, because tissue demand is greater than neutrophil production in the bone marrow.
II. Neutrophilic responses vary with inflammation.
   A. Peracute inflammation
      1. Transient neutropenia develops within 1 to 3 hours.
      2. It is often in response to endotoxemia or severe infections, particularly those involving the peritoneum, lungs, or thorax.
   B. Acute inflammation
      1. Bone marrow responds within 4 to 6 hours to increased tissue demands, causing an accelerated release of neutrophils (mature and immature).
      2. The resulting inflammatory leukogram is characterized by leukocytosis, neutrophilia, and a regenerative left shift (generally >450 immature neutrophilic precursors/μL in dogs or >500 to 1000/μL in cats) (Schultze, 2000; Cowell and Decker, 2000).
   C. Chronic, prolonged (days to weeks) inflammation
      1. Characterized by leukocytosis with mature neutrophilia
      2. Results from expanded marrow production that exceeds tissue demand

Corticosteroid-Induced Leukocytosis (Stress Leukogram)

Definition and Causes

I. It is characterized by leukocytosis with mature neutrophilia, lymphopenia, and eosinopenia.
II. Concurrent monocytosis is common in the dog and infrequent in the cat.
III. It accompanies increased endogenous corticosteroid concentrations (severe stress or hyperadrenocorticism) or exogenous glucocorticoid or ACTH administration.

Diagnosis

I. A CBC demonstrates the characteristic leukogram.
   A. WBC counts from 15,000 to 25,000/μL (Schultze, 2000)
   B. Neutrophilia in the absence of a left shift
   C. Lymphocyte count <1000/μL (Latimer and Prasse, 2003)
II. Stress leukogram can also occur concurrently with an inflammatory leukogram (see Inflammatory Leukocytosis).

Extreme Neutrophilic Leukocytosis (Leukemoid Response)

Definition

I. Pronounced leukocytosis from dramatic neutrophilia (up to 100,000/μL in dogs or 75,000/μL in cats), with a significant but orderly left shift (Kociba, 2000).
II. Occasionally accompanied by eosinophilia or lymphocytosis

Causes and Pathophysiology

I. It results from inflammation or nonhematopoietic neoplasia.
II. It mimics granulocytic leukemia in cellular magnitude and composition.
III. Several causes exist.
   A. Inflammation
      1. Localized infections: pyometra, peritonitis, pyothorax, pancreatitis
      2. Hepatazoonosis
      3. Hemolysis secondary to immune-mediated hemolytic anemia
         a. Dogs: *Babesia canis*
         b. Cats: *Mycoplasma haemofelis, Mycoplasma haemominutum*
   B. Paraneoplastic conditions
      1. Production of hematopoietic-stimulating cytokines
      2. See Chapter 73
   C. Other causes
      1. Early estrogen toxicity
      2. Recombinant canine or human granulocyte-colony stimulating factor therapy
      3. Leukocyte adhesion protein deficiency in Irish setters

Diagnosis and Differential Diagnosis

I. Differentiate from chronic myelogenous leukemia (CML).
II. Both conditions have neutrophilic leukocytosis with a left shift, nonregenerative anemia, and increased myeloid: erythroid ratio, with orderly granulocytic maturation in the bone marrow.
III. Suspect CML with a disorderly left shift, neutrophil dysplasia, thrombocytopenia, decreased marrow megakaryocytes, and granulopoietic precursors in extramedullary sites (liver, spleen, and lymph nodes).
IV. Neutrophil toxicity, indicative of inflammatory conditions, drug toxicity, or systemic disease, is not typically a feature of CML.

Physiologic Leukocytosis

Definition

I. Transient leukocytosis from epinephrine release with excitement, fear, or exercise that is characterized by mature neutrophilia and lymphocytosis

II. Common in puppies and kittens
III. Uncommon in adult dogs
IV. Rapid neutrophilia
  A. Neutrophil count up to 39,000/μL in cats (Latimer and Prasse, 2003) that generally diminishes within 20 minutes
  B. Neutrophilia often accompanied by lymphocytosis (absolute lymphocyte counts usually <20, 000/μL) in young cats (Cowell and Decker, 2000)

Causes and Pathophysiology

I. Neutrophilia
  A. It results from cellular shifts from the marginated to circulating pool.
  B. It is of greater magnitude in cats (larger marginated pool).
II. Lymphocytosis: decreased migration into lymphoid tissue or increased mobilization from the thoracic duct
III. Monocyte and eosinophil numbers: unchanged or slightly increased

CONGENITAL DISORDERS OF WBCS

Morphologic and Functional Disorders

See Table 65-3.

Lysosomal Storage Diseases

Definition and Causes

I. Autosomal recessive genetic disorders characterized by multiple organ failure (Table 65-4)
II. Intracellular accumulation of incompletely degraded substrates from deficiency of the lysosomal enzyme required for their metabolism

Diagnosis

I. Examination of peripheral blood smears may reveal vacuolation or abnormal granules within leukocytes.
II. Radiography helps characterize bony malformations in animals with clinically evident skeletal abnormalities.
III. Identification of deficient lysosomal enzyme activity in plasma, leukocytes, or cultured skin fibroblasts can be attempted.
IV. The structures of lysosomal enzymes are highly conserved; therefore, techniques developed for detection of enzymatic deficiencies in humans can be used in dogs and cats.
V. Polymerase chain reaction (PCR)-based genomic screening can be used to identify some cases.
  A. Examples include dogs with fucosidosis, mucopolysaccharidosis (MPS) I, and MPS VII, and cats with MPS VI.
  B. Novel genetic mutations can occur with these diseases that may not be detected by the established testing procedures; therefore, a negative result does not eliminate a storage disease (Skelly and Franklin, 2002).
VI. Excessive urinary glycosaminoglycan excretion in animals with MPS can be detected by a urine spot test.

Treatment and Monitoring

I. Storage diseases are generally untreatable and progressive.
II. Bone marrow transplantation has resulted in clinical improvement in dogs with MPS I and cats with MPS VI.

NEOPLASIA

Myeloproliferative Disorders

See Chapter 66.

Acute Lymphoblastic Leukemia

Definition

I. Acute lymphoblastic leukemia (ALL) is characterized by progressive lymphoblastic infiltration of lymphoid organs and bone marrow.
II. Unlike lymphoma, the bone marrow is the primary tumor site.

Clinical Signs

I. Affected animals present with nonspecific signs of anorexia, lethargy, weight loss, vomiting, diarrhea, lameness, altered mentation, and intermittent fever.
II. Physical examination findings consist of pallor, hepatosplenomegaly, lymphadenopathy, and petechia.

Diagnosis

I. Lymphocytosis with circulating lymphoblasts
II. Anemia, thrombocytopenia, variable WBC counts, or pancytopenia
III. Possible absence (aleukemia) or only small numbers (subleukemia) of circulating lymphoblasts
IV. Possible bone marrow aspiration and/or biopsy findings
  A. Homogeneous population of large immature lymphocytes
  B. Replacement of normal nucleated cell population with 40% to 50% lymphoblasts
V. Possible clinical chemistry abnormalities
  A. Increased alanine and aspartate transferases (ALT, AST) and alkaline phosphatase (ALP) activities indicative of potential liver involvement
  B. Increased blood urea nitrogen concentration indicative of azotemia (prerenal or renal) or GI hemorrhage
  C. Hypercalcemia uncommon

Differential Diagnosis

I. ALL is difficult to differentiate from multicentric lymphoma with bone marrow or blood involvement (stage V disease).
II. Unlike advanced lymphoma, ALL often occurs without lymphadenopathy, is poorly responsive to chemotherapy, and has a more rapid and progressive disease course.
III. Differentiation from acute myeloproliferative diseases (see Chapter 66) requires cytochemical and immunohistochemical staining of bone marrow preparations.
IV. Lymphocytosis with mature, well-differentiated lymphocytes distinguishes chronic lymphocytic leukemia (CLL) from ALL (see below).

TABLE 65-3

Morphological and Functional Disorders of Canine and Feline Leukocytes

DISORDER	INHERITANCE	CAUSE	SPECIES	APPEARANCE/CLINICAL SIGNS	DIAGNOSIS	TREATMENT	REFERENCES
Cyclic hematopoiesis	Autosomal recessive	Stem cell abnormality	Gray-coated collie, collie-mix dogs	Continuous abnormal hematological cycles Decreased neutrophil number and function: recurrent bacterial infections, defective platelet aggregation, systemic amyloidosis	Serial CBCs every 3-6 weeks: cyclic neutropenia and anemia Clinical signs: hair coat color dilution	Broad-spectrum antibiotics for sepsis Lithium carbonate 21-26 mg/kg/day PO (potential side effects) rhG-CSF 5 µg/kg SC BID (watch for neutralizing antibodies) Bone marrow transplantation is curative	Campbell (1985), Lothrop et al. (1988), Niemeyer and Lothrop (2000)
Inherited vitamin B_{12} (cobalamin) malabsorption	Autosomal recessive	Failure to express intestinal intrinsic factor cobalamin complex receptor (cubilin)	Inbred giant schnauzer	Nuclear chromatin maturation abnormalities, neutropenia, nonregenerative anemia	Decreased serum cobalamin concentration Classic hematological abnormalities	Parenteral administration of megadose cobalamin (1 mg IM) monthly No improvement with oral cobalamin	Fyfe (2000)
Birman cat neutrophil granulation anomaly	Autosomal recessive	Fine azurophilic granules similar to progranulocyte granules	Birman cat	Prominent neutrophil granulation	Serial CBCs Differentiate from MPS VI, MPS VII, and toxic change	None; neutrophils function normally	Hirsch and Cunningham (1984)
Canine leukocyte adhesion deficiency	Autosomal recessive	Deficient expression of CD18 (subunit of B_2 integrins)	Irish setter	Recurrent infections, marked neutrophilia, chronic anemia Bone marrow myeloid hyperplasia	Flow cytometry for neutrophil CD18 expression	Antibiotics alleviate signs but not infection Affected animals usually die	Andreason and Roth (2000)
Pelger-Huët anomaly	Uncertain inheritance Acquired secondary to sepsis, drugs, MPD, viral infections	Failure of the mature nucleus to form true filaments	Cats, dogs	Peanut-shaped nuclei in granulocytes, monocytes, or megakaryocytes	Serial CBCs	None; neutrophils function normally	
Chédiak-Higashi syndrome	Autosomal recessive	Failure of granule fusion	Persian cats	Yellow-green eyes Smoke-blue hair color Hypopigmentation of eyes, skin, hair	CBC: neutropenia, abnormal granules Prolonged bleeding times Abnormal platelet aggregation	Temporary improvement with rhG-CSF Bone marrow transplant	Meyers (2000)

CBC, Complete blood count; *rhG-CSF,* recombinant human granulocyte-colony stimulating factor; *IM,* intramuscularly; *MPS,* mucopolysaccharidosis; *MPD,* myeloproliferative disease.

TABLE 65-4

Lysosomal Storage Diseases of Dogs and Cats

DISEASE	ENZYME DEFICIENCY	BREEDS AFFECTED	WHITE BLOOD CELL ABNORMALITIES	CLINICAL SIGNS
Mannosidosis	α-D-Mannosidase	English springer spaniel DSH, Persian cat	Lymphocyte, neutrophil, eosinophil, monocyte cytoplasmic vacuolization	Neurological and skeletal abnormalities Retarded growth Facial dysmorphism (flattened features)
Fucosidosis	α-L-fucosidase	English springer spaniel	Lymphocyte vacuolization	Behavioral changes Ataxia Hearing and vision loss
MPS I	α-L-iduronidase	Plott hound DSH cats	Basophilic to metachromatic (pink-purple) neutrophil cytoplasmic granules Lymphocyte granulation or vacuolization	Skeletal abnormalities Facial dysmorphism Dwarfism Corneal opacities Neurologic abnormalities
MPS VI	Arylsulfatase B	Siamese and DSH cats Miniature pinscher	See MPS I	See MPS I
MPS VII	β-Glucuronidase	Dogs, cats	See MPS I	See MPS I
GM_1 gangliosidosis	β-D-Galactosidase	Siamese, DSH cats Beagle, English springer spaniel, Portuguese water dog, mixed breed dog	Lymphocyte vacuolization	Ataxia Visual deficits
GM_2 gangliosidosis	β-D-Hexosaminidase	Korat and DSH cats Japanese spaniel	Neutrophil granulation Lymphocyte and/or eosinophil vacuolization	Corneal clouding Muscle wasting Cerebral and/or cerebellar dysfunction

DSH, Domestic short hair; *MPS,* mucopolysaccharidosis.

V. Eliminate other causes of pancytopenia via bone marrow examination.

Treatment and Monitoring

I. Treat ALL using established protocol treatments for canine or feline lymphoma (Fan, 2003; Couto, 2001)
   A. Use of vincristine and L-asparaginase therapy together may result in neutropenia.
   B. Prognosis is poor, as treatment-induced remission is short and survival is generally less than a few months.
II. Initiate broad-spectrum antibiotic therapy in animals with fever or neutropenia (<1000/μL).
III. For animals with anemia and/or thrombocytopenia, consider fresh whole blood, packed RBCs, platelet-rich plasma, or platelet concentrate transfusions (see Chapter 71).

Chronic Lymphocytic Leukemia

Definition and Causes

I. Chronic lymphocytic leukemia (CLL) is characterized by lymphocytic leukocytosis, with a predominance of small lymphocytes.
II. There is no reported association between CLL and FeLV infection in cats.
III. Most cases of CLL in dogs are of T-cell origin.
IV. CLL is rare in cats.

Clinical Signs

I. Possibly asymptomatic
II. Nonspecific signs: lethargy, anorexia, weight loss, vomiting, diarrhea, polyuria/polydipsia, lameness
III. Physical examination: hepatosplenomegaly, peripheral lymphadenopathy, pallor

Diagnosis

I. CBC findings
   A. Persistent marked lymphocytosis
   B. Lymphocyte counts: >1,000,000/μL in dogs and up to 250,000/μL in cats (Workman and Vernau, 2003)
   C. Concurrent hematological findings: nonregenerative, normocytic, normochromic anemia, thrombocytopenia, neutropenia, or pancytopenia from myelophthisis
   D. Findings in cats: not well characterized
II. Bone marrow aspirate and/or biopsy samples: >30% small mature lymphocytes

III. Serum biochemistry results
   A. They can indicate multiple organ involvement.
   B. Serum and urine electrophoresis is indicated in dogs with hyperglobulinemia, as a monoclonal gammopathy occurs in up to 30% of dogs with hyperglobulinemia.
IV. Immunophenotyping procedures (Burnett et al., 2003)
   A. It uses PCR amplification of cellular DNA from peripheral blood.
   B. It identifies neoplastic populations of circulating small lymphocytes based on unique rearrangements of the T cell receptor γ (T-cell lymphoma) or immunoglobulin (B-cell lymphoma) sequences.
   C. It helps to differentiate CLL from other nonneoplastic causes of persistent lymphocytosis, which can be difficult.

Differential Diagnosis

I. Other causes of persistent lymphocytosis
   A. Transient leukocytosis (epinephrine response)
   B. Immune-mediated or other chronic, systemic diseases
   C. Chronic ehrlichiosis, Rocky Mountain spotted fever and babesiosis infections (dogs), and toxoplasmosis (cats)
II. Large granular lymphocyte (LGL) leukemia
   A. LGL leukemia in cats is uncommon, may accompany lymphoma, and involves the alimentary tract or mesenteric lymph nodes.
   B. In dogs, LGL leukemia presents as either ALL or CLL.
III. Acute lymphoblastic leukemia
IV. Multicentric lymphoma

Treatment and Monitoring

I. Treatment for CLL is not often required, especially in the absence of bone marrow involvement and hematological abnormalities (anemia or other cytopenias), or evidence for multiorgan involvement (lymphadenopathy, splenomegaly, enzyme abnormalities).
II. Chemotherapy is not recommended until the development of clinical signs, cytopenias, or marked lymphocytosis (generally defined as 60,000 to 100,000/μL).
III. A combination protocol of oral chlorambucil and prednisone is effective dogs and cats (Workman and Vernau, 2003).
   A. Treatment in dogs involves the following:
      1. Chlorambucil: 0.2 mg/kg or 6 mg/m^2 PO SID for 7 to 14 days, then 0.1 mg/kg or 3 mg/m^2 PO SID, then long-term maintenance at 2.0 mg/m^2 QOD
      2. Prednisone: 30 mg/m^2 PO SID for 7 days, followed by 20 mg/m^2 for 7 days and 10 mg/m^2 QOD
   B. Treatment in cats involves the following:
      1. Chlorambucil: 0.2 mg/kg or 2 mg/cat QOD
      2. Prednisone: 1 mg/kg SID
   C. Dosages are modified based on clinical response.
   D. Monitor CBCs weekly for the first month and monthly thereafter.
   E. Prognosis is variable and depends on the extent of disease and response to therapy.

Sézary Syndrome in Dogs

Definition and Cause

I. Lymphoproliferative disease in dogs (uncommon) and cats (rare)
II. Characterized by cutaneous lymphoma and a circulating population of large neoplastic T lymphocytes with intensely cleaved or indented nuclei and prominent nucleoli

Clinical Signs

I. Ulcerative dermatitis, pruritus, anorexia, alopecia, and peripheral lymphadenopathy
II. Hematologic abnormalities
   A. Lymphocytic leukocytosis with abnormal lymphocyte morphology
   B. Possible monocytosis, neutrophilia, and nonregenerative, normocytic, normochromic anemia

Diagnosis

Dermal-epidermal infiltration by neoplastic lymphocytes in skin biopsy samples combined with the presence of circulating neoplastic lymphocytes.

Treatment and Monitoring

I. Chemotherapeutic protocols for canine lymphoma can be tried.
II. Prognosis is poor.

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