



Cornell Feline Health Center Information Bulletin

Feline Hematology and Hemostasis Testing

Marjory Brooks, D.V.M.

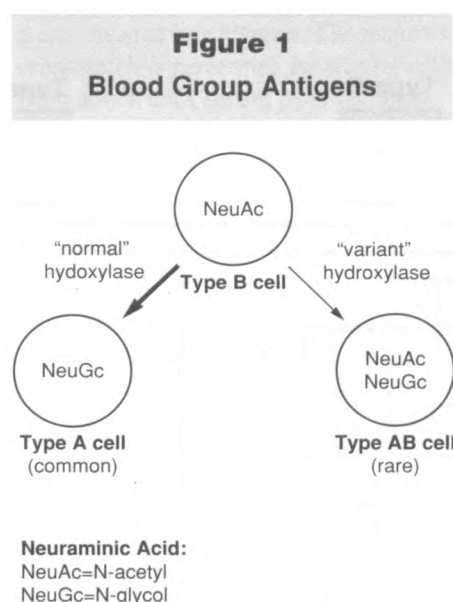
Hematology is a broad discipline encompassing disorders of both cellular and fluid-phase components of blood. This bulletin presents overviews of the feline blood group system and a diagnostic approach to feline bleeding disorders.

Feline Blood Group System

Blood groups are defined by the presence of species-specific antigens on the surface of red blood cells. Cats have a single blood group system consisting of *three blood types: type A, type B, and the very rare type AB*. All cats have one of these three types; there are no negative or type O feline cells.

The antigenic determinants on red cell membranes responsible for feline blood types have been examined in detail. The critical feature is the specific form of neuraminic acid present on membrane glycolipids. Type A cells have the N-glycolyl (NeuGc) form of neuraminic acid, and type B cells have N-acetyl-

neuraminic acid (NeuAc). A hydroxylase enzyme converts NeuAc to NeuGc, and it is hypothesized that blood-type A cats have this enzyme whereas blood-type B cats lack the enzyme. In this model, one theory for type AB is that a mutation in the hydroxylase enzyme causes less than total conversion of NeuAc to NeuGc (**figure 1**).



Inheritance of Feline Blood Types

Feline blood type is inherited as an autosomal trait, with type A dominant to type B. All type B cats are homozygotes (bb genotype), whereas type A cats are either homozygotes (AA genotype) or heterozygotes (Ab genotype).

Crosses between two type B cats are expected to produce only type B offspring. Crosses between two type A cats, however, may produce both type A and type B offspring. **Table 1** lists the expected proportion of type A and type B kittens produced from different matings of type A and type B parents.

Table 1
Predicted Offspring Blood Type

Parental Blood Type (genotype)	Offspring Blood Type (genotype)
I. type B x type B (bb) (bb)	all type B (bb)
II. type B x type A (bb) (AA) or (bb) (Ab)	all type A (Ab) 1 type A : 1 type B (Ab) (bb)
III. type A x type A (AA) (AA) or (AA) (Ab) or (Ab) (Ab)	all type A (AA) all type A (AA, Ab) 3 type A : 1 type B (AA, Ab) (bb)

Frequency of Feline Blood Types

Extensive surveys of blood type in purebred and domestic shorthair (DSH) and longhair (DLH) cats have been conducted throughout the United States. The proportion of type A and type B cats varies in different geographic locations and within certain pure breeds. Most DSH and DLH are type A; there is, however, geographic variation. The Southwest and Northwest have the highest proportion of type B individuals, with up to 5 percent of the DSH tested in California having type B.

In contrast to DSH, there is little geographic variation within pure breeds. Virtually all Siamese are type A, whereas Rex cats and British Shorthair cats have an almost even, or 1:1, ratio of type A to type B individuals. The frequencies in other breeds such as Persians, Himalayans, and Abyssinians fall somewhere between these two extremes.

Clinical Importance of Feline Blood Groups

Most cats have antibodies directed against foreign red-cell antigens. These antibodies (hemolysins or agglutinins) are naturally occurring, present whether or not the individual has been transfused. *The most clinically severe incompatibility reactions are caused by anti-A isoagglutinins in blood-type B cats.* Blood group incompatibilities are responsible for two different categories of clinical disorders:

1. Transfusion reactions. Type B cats transfused with type A cells are at risk for immediate reactions characterized by acute apnea, bradycardia, and collapse. These reactions are potentially fatal. In type B cats with high titers of anti-A antibodies, severe reactions occur after transfusion of very small volumes (<2–3 ml) of type A blood. Hemolytic reactions have also been described in

type B cats following transfusion of type A cells. Type A cats transfused with type B blood are unlikely to have a clinically severe reaction, but the transfused B cells will have shortened life span in comparison with type-compatible cells.

2. Neonatal hemolysis. Type A kittens born to type B queens are at risk for neonatal isoerythrolysis (NI), or hemolytic disease of newborns. Maternal antibodies directed against foreign red cell antigens are transmitted to kittens in colostrum, and clinical signs appear in the first few days of life. These signs include anemia, icterus, pigmenturia, necrosis of tail and ear tips, weakness, failure to nurse, and death. **Figure 2** presents a sample pedigree of a type B female bred to type B and type A males.

Figure 2

Sample Pedigree

Female type B bred to type B and type A males

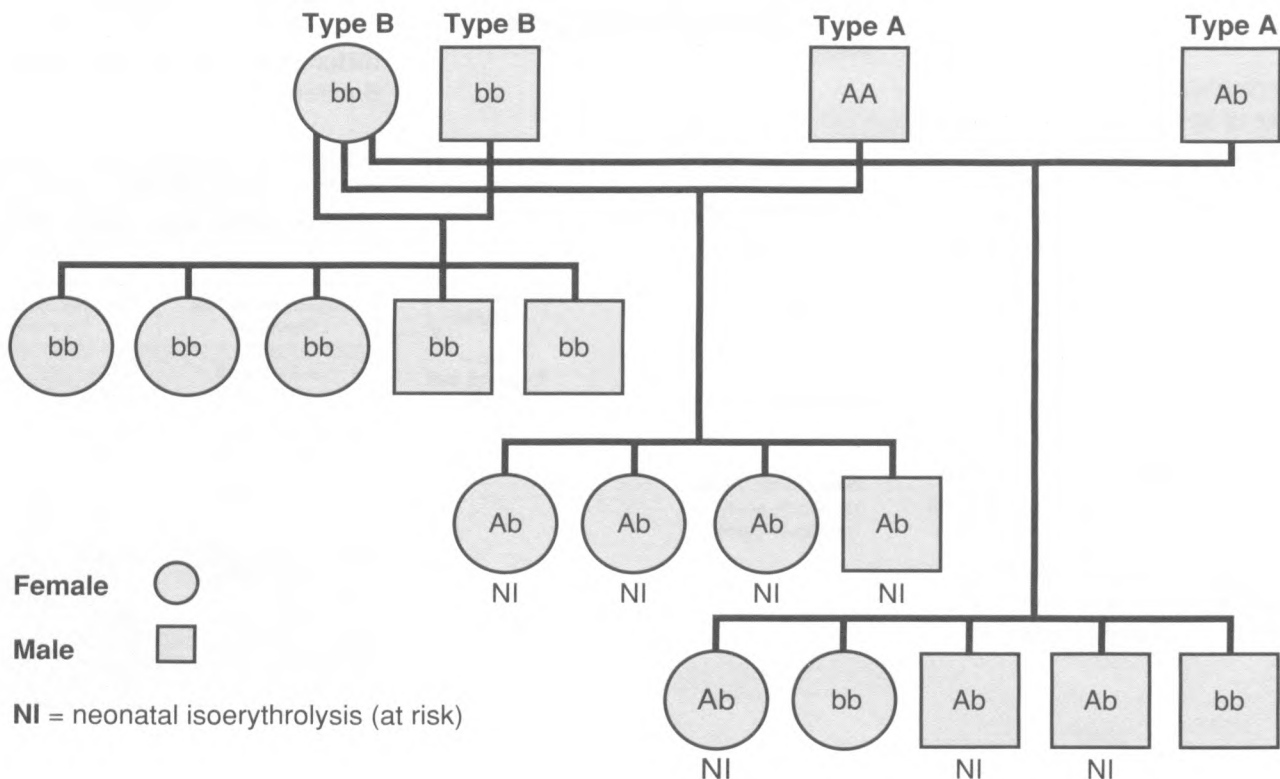
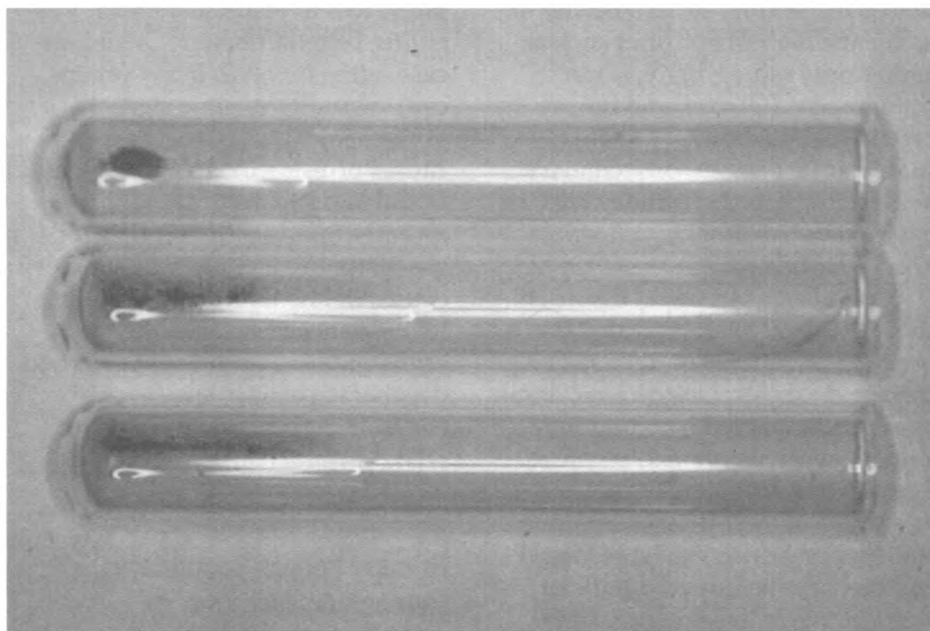


Figure 3
Tube Agglutination Reactions
 Type A cells reacting with anti-A antibodies



Blood Typing and Crossmatching

Blood typing requires specific reagents, or antisera, that react in a defined manner with red cell antigens. Feline typing is accomplished by setting up reactions combining patient cells with reagents specifically directed against either type A or type B cells.

Type A cats have a strong agglutination reaction when their cells are combined with anti-A antisera, but there is no reaction when their cells are mixed with anti-B reagent. Type B cells react only with anti-B reagent. Back-typing is performed by mixing cells of known blood type with plasma or serum from the patient. Serum from type B cats shows a strong agglutination reaction when mixed with type A cells, but no reaction with type B cells.

Crossmatching does not require special reagents, or knowledge of a cat's blood type. Cells from one cat are mixed with serum from another cat, and any agglutination or

hemolysis is noted. A crossmatch can be performed to detect incompatibilities between blood donors and recipients, prospective mates, or a queen and her kittens. *The major crossmatch is performed by mixing cells from donor with serum from recipient.*

A strong agglutination reaction in the major crossmatch is typical of antibodies in a type B cat's serum reacting to donor type A cells (**figure 3**). This reaction denotes a serious incompatibility. A simple slide agglutination crossmatch test should be performed before each transfusion when the blood type of the recipient is unknown.

Crossmatch technique: Place two drops of serum from recipient on a glass slide, add one drop of donor blood and mix gently for 10–15 seconds. After 1 minute, check for gross or macro-agglutination. Any agglutination reaction is a contraindication for proceeding with the transfusion.

Summary of Key Points

1. There is a single blood group system in cats: the AB system.
2. Most DSH/DLH cats are type A, but frequency of blood type varies widely in different pure breeds.
3. Type A and type B cats have naturally occurring antibodies against the alternate red cell type.
4. The most clinically severe reactions are caused by anti-A antibodies found in type B cats.
5. Type A kittens born to type B queens are at risk for neonatal hemolysis.
6. There is no "universal" feline donor blood type.
7. Transfuse type A cats with type A blood, transfuse with type B cats with type B blood.
8. Check a major crossmatch (1 drop donor blood mixed with 2 drops recipient serum) before any transfusion between cats of unknown blood type.

Diagnosis of Bleeding Disorders

Bleeding is a common chief complaint. In each case, a defect or breakdown in one component of the hemostatic mechanism predominates. The most successful approach to managing these cases is based on identifying which component of normal hemostasis is defective, and then providing specific, as well as symptomatic, treatment. Normal hemostasis includes three basic components: blood vessels, primary hemostasis (platelets and von Willebrand factor), and secondary hemostasis (coagulation cascade).

Preliminary Evaluation: Vessel Disorder versus Bleeding Diatheses

The goal of initial evaluation is to differentiate bleeding from damaged or diseased blood vessels from a systemic bleeding disorder, involving either primary or secondary

hemostasis (**figure 4**). The principal means of identifying vessel disorders is inspection, either visually or using ancillary diagnostics such as endoscopy, radiography, ultrasonography, CT scan, and biopsy. In certain cases, laboratory evaluation to rule out a primary or secondary hemostatic disorder is indicated before invasive diagnostic inspection is performed.

Clinical signs of vessel disorders show different characteristics, depending on the size of diseased or damaged vessels. Large-vessel damage is accompanied by blood-loss anemia, with history and physical examination revealing involvement of a single or well-defined anatomic site. Primary causes of large-vessel hemorrhage include traumatic or surgical injury, erosion or infiltration from neoplastic, infectious, or granulomatous lesions, and vascular anomaly or arteriovenous shunt.

Small-vessel disorders (vasculopathies) rarely cause sufficient blood loss to result in anemia. Vasculitis, or inflammatory vessel disease, often involves many organs, causing multisystemic signs. Involvement of cutaneous vessels causes bruising or ecchymoses, and ocular signs include uveitis and retinitis. Specific differentials for vasculopathy include inflammatory causes (feline infectious peritonitis, toxoplasmosis, systemic lupus erythematosus, drug eruption) and degenerative disorders (hypercortisolism [producing fragile vessels], intrinsic collagen defect).

Bleeding Diatheses: Primary versus Secondary Hemostatic Disorder

The combination of clinical signs, history, and screening tests will differentiate primary from secondary hemostatic disorders in most cases (**figure 5**).

Primary hemostasis includes interactions between the vessel wall at the site of injury, platelets, and von Willebrand factor. The endpoint of these interactions is formation of a platelet plug. A platelet plug is sufficient to control hemorrhage from capillaries and small vessels. Disorders of primary hemostasis most typically cause petechiae and mucosal bleeding, as well as bleeding from sites of surgery or trauma.

Secondary hemostasis includes the reactions of the clotting factors of the coagulation cascade. The endpoint of these reactions is formation of a fibrin clot. Clotting factors are enzymes or coenzymes that circulate in plasma in an inactive form. The coagulation cascade acts like a chain reaction, with sequential activation and amplification of the factors, culminating in the transformation of fibrinogen to fibrin. The activation reactions are localized to the site of vessel injury because they

Figure 4
Preliminary Evaluation

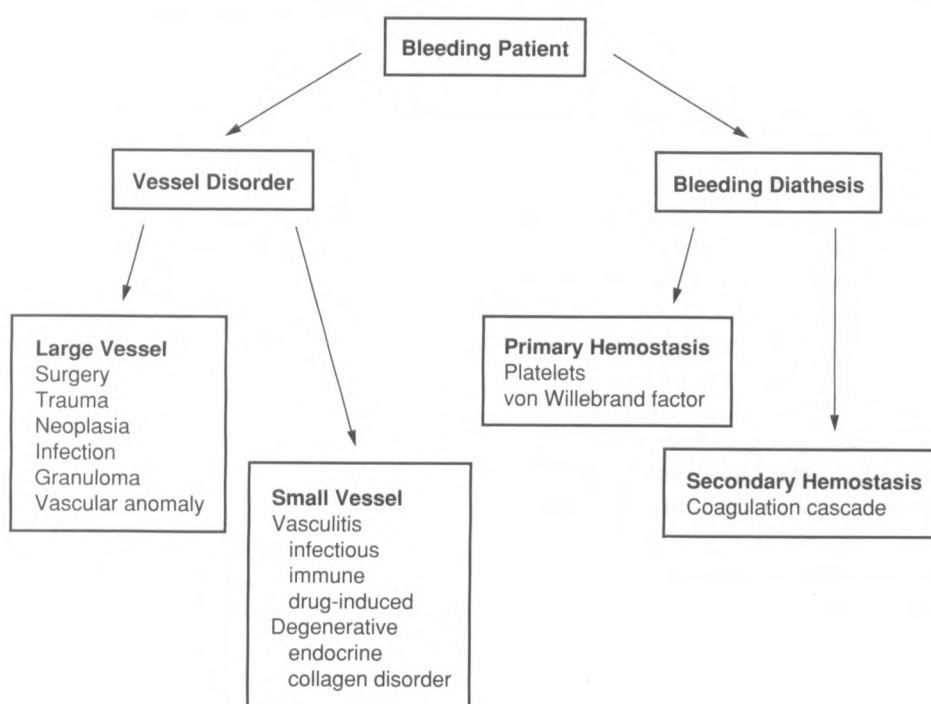
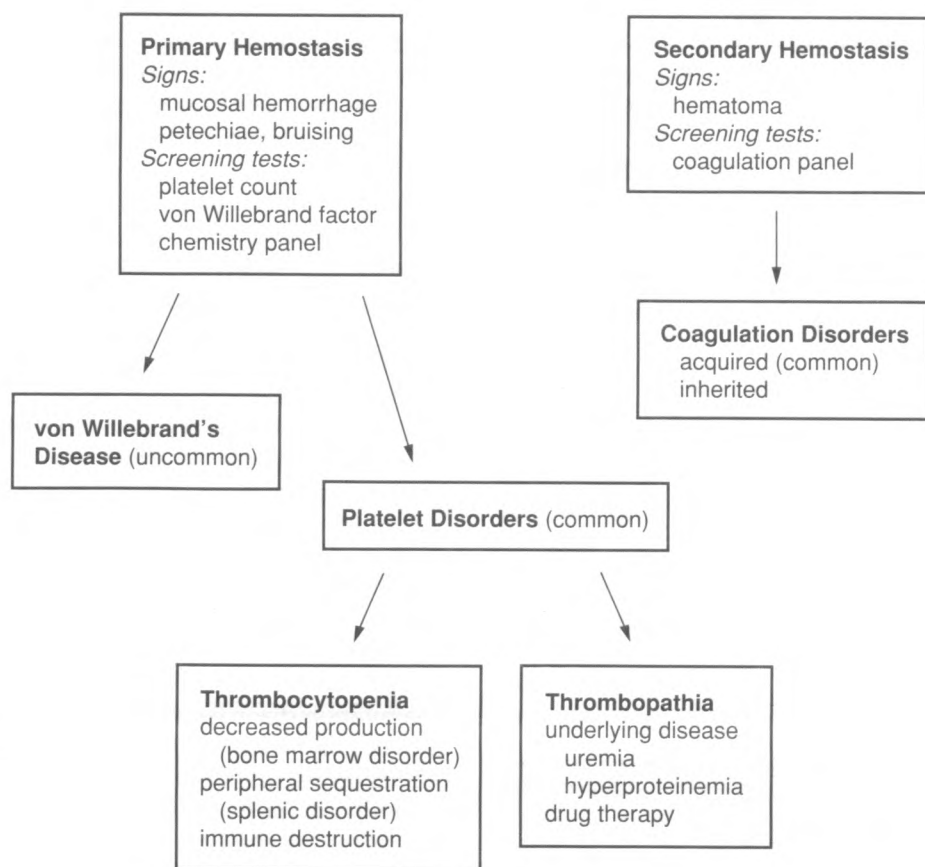


Figure 5
Primary versus Secondary Hemostatic Disorders



require tissue and platelet phospholipids. Fibrin clot formation is needed to control hemorrhage from damaged medium or large vessels. The clinical signs of coagulation disorders are hematoma formation (subcutaneous, intramuscular), hemothorax, hemoperitoneum, and bleeding from sites of surgery or trauma.

Defects of Primary Hemostasis

Platelet disorders are classified as either quantitative defects (thrombocytopenia) or qualitative defects (thrombopathia). In almost all cases, platelet disorders are acquired rather than inherited.

Thrombocytopenia is screened for by examination of a stained blood film under oil immersion.

Fewer than 5 to 10 platelets per field is indicative of thrombocytopenia and should be confirmed by platelet count. Thrombocytopenia is not a specific diagnosis, and further evaluation to determine etiology is indicated. Thrombocytopenia results from one of three processes:

1. decreased production (bone marrow disorder)
2. peripheral sequestration (splenic disease, disseminated intravascular coagulation [DIC])
3. increased destruction (immune-mediated, DIC)

Production deficiencies are common in cats, and result from either infiltrative or aplastic disorders. Splenomegaly secondary to neoplastic, infectious, or hepatic disease

may cause sequestration and loss of platelets from the vasculature. Immune-mediated platelet destruction is an uncommon cause of thrombocytopenia in cats. Diagnostic workup to characterize thrombocytopenia in cats may include complete blood count (CBC), chemistry panel, bone marrow aspiration cytology, retrovirus serology, abdominal ultrasound, and hepatic-splenic aspiration cytology.

Thrombopathia occurs in association with underlying metabolic disorders. The most common disorders include uremia and hyperproteinemia, and in these cases platelet dysfunction may complicate management and diagnosis of the primary disease process.

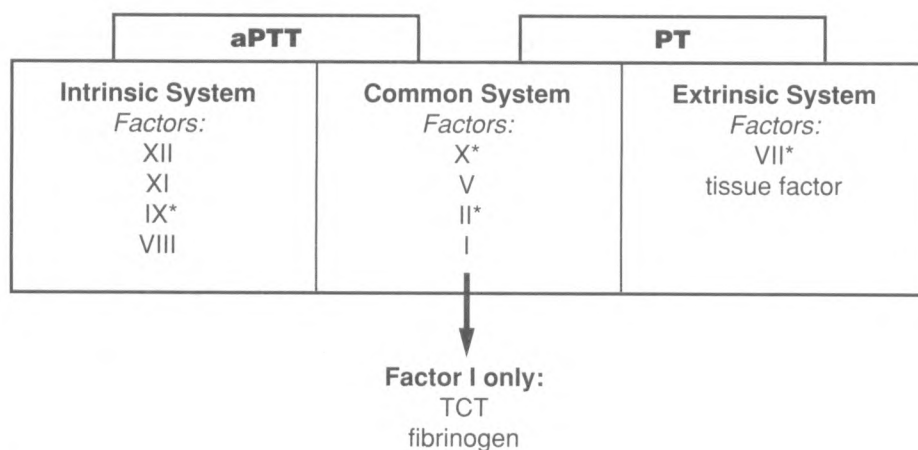
von Willebrand's disease (vWD) is uncommon in cats, but has been identified in purebred (Himalayan) as well as DSH/DLH cats. Affected cats had severe reduction in plasma von Willebrand factor (vWF) concentration, and severe clinical signs of spontaneous epistaxis, bleeding from gingiva at sites of tooth eruption, and excessive hemorrhage and bruising at sites of surgery.

Platelet count and coagulation assays are normal in vWD-affected cats. Assays used routinely to measure canine (or human) vWF must be adapted or modified to measure feline vWF, and each laboratory must validate its assay and develop a normal feline range.

Defects of Secondary Hemostasis (Coagulation Disorders)

Coagulation disorders are caused by either acquired or inherited deficiency of one or more clotting factors. Clotting factors are synthesized in the liver, and a subset of these factors, the prothrombin group, requires vitamin K for activation after synthesis. Factors are consumed during the process of clot formation, and loss of localized clot formation, as in DIC, results in depletion of factors.

Figure 6
Coagulation Screening Tests



Tests:

aPTT = activated partial thromboplastin time

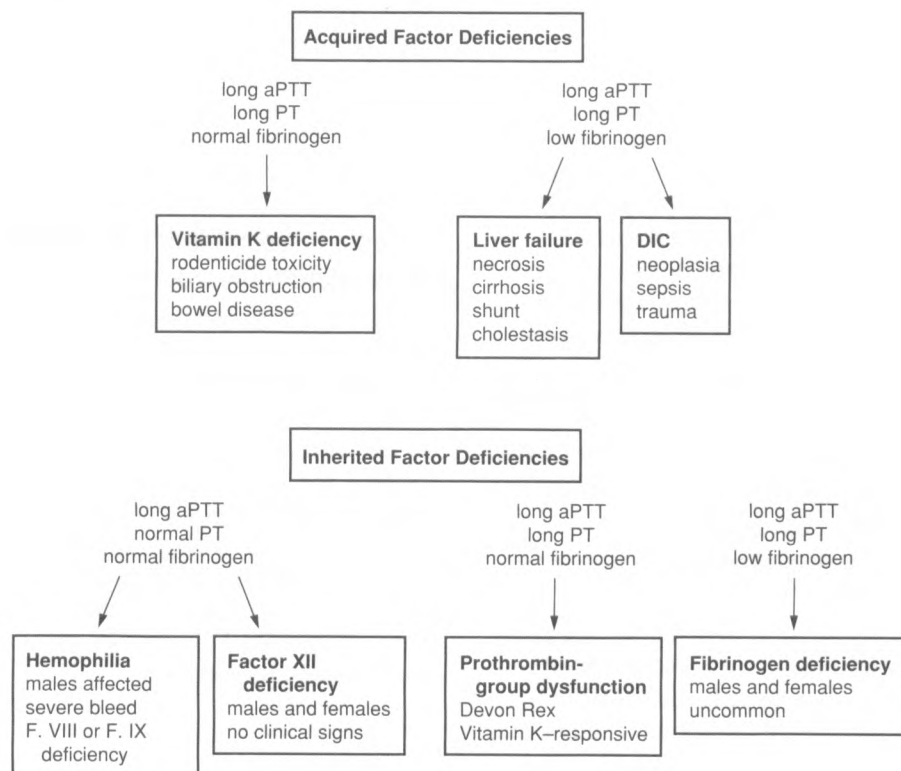
PT = prothrombin time

TCT = thrombin clotting time

Factors:

* = prothrombin group (II, VII, IX, X)

Figure 7
Differentiation of Coagulation Disorders



Coagulation screening tests identify abnormalities in pathways, or systems, within the coagulation cascade (**figure 6**). These tests are based on *in vitro* formation of a fibrin clot. Factor deficiency or dysfunction causes prolongation of the time for clot formation, and these tests are very sensitive to artifacts introduced during sample collection or processing.

Each testing laboratory should validate its assay technique, develop normal ranges for cats using that technique, and report a value for feline control with each patient tested. Routine screening tests of the coagulation cascade (coagulation panel or profile) consist of activated partial thromboplastin time (aPTT); prothrombin time (PT); and fibrinogen or thrombin time (TCT).

A severe factor deficiency is ruled out if clotting times are normal in all three screening tests. Prolongation of clotting time in one or more screening tests is indicative of a coagulation disorder, and the pattern of abnormalities depends on which individual or group of factors is involved. Individual clotting factor assays are then performed if a more specific diagnosis is needed.

Acquired factor deficiencies

Acquired factor deficiencies (**figure 7**) are common and occur primarily as a result of liver failure (production defect), vitamin K deficiency (activation defect), or DIC (defect in clot localization with secondary factor depletion and systemic lysis).

Liver disease must cause hepatic synthetic failure before clinically significant reduction in clotting factor production occurs. The diseases most commonly accompanied by coagulopathy include acute hepatic necrosis, cirrhosis, portosystemic shunts, and cholestatic liver disease.

Vitamin K deficiency prevents activation of the prothrombin group of clotting factors. Common causes of vitamin K deficiency include anticoagulant rodenticide toxicity, biliary obstruction, and infiltrative bowel disease.

Disseminated intravascular coagulation is triggered by widespread damage to vascular tissues, platelet aggregation, or intravascular release of tissue phospholipids. Clinical disorders most commonly associated with DIC include sepsis, neoplasia (especially lymphosarcoma, mammary carcinoma, and mast cell disease), and severe trauma.

Inherited factor deficiencies

Inherited factor deficiencies (figure 7) are caused by mutations in genes coding for specific coagulation proteins. New, spontaneous mutations can arise in any purebred or DSH/DLH cat. Once a mutation occurs, the defect is most often propagated within a breed or line when asymptomatic carriers are bred.

1. Intrinsic system defects (long aPTT screening test).

a) Hemophilia is the most common severe inherited factor deficiency in cats. The inheritance pattern is X-linked recessive. Hemophilic males inherit an abnormal gene from their dam, and express the bleeding tendency. Female carriers have one normal and one abnormal gene and are asymptomatic. There are two forms of hemophilia: hemophilia A = Factor VIII deficiency, and hemophilia B = Factor IX deficiency.

b) Factor XII deficiency is common in DSH/DLH and Siamese cats. This defect is not associated with a bleeding tendency. Prolongation of clot formation is an *in vitro*, not an *in vivo* phenomenon. The inheritance pattern is autosomal recessive.

2. Intrinsic and extrinsic system defects (long aPTT and long PT screening tests). Prothrombin group deficiency is a rare coagulopathy found in Devon Rex cats. The underlying defect causes abnormal vitamin K recycling and reduced activity of all the vitamin K-dependent factors. Administration of vitamin K corrects the bleeding tendency.

3. Dysfibrinogenemia (long aPTT, long PT, long TCT, low fibrinogen). This is a rare defect in DSH caused by either deficiency or dysfunction of fibrinogen. Both males and females are affected. Spontaneous bleeding episodes are uncommon, but prolonged bleeding occurs after surgery or trauma.

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The Comparative Hematology Section, formerly affiliated with the New York State Department of Health, has recently joined Cornell University's Diagnostic Laboratory. This association brings a new menu of tests and services, readily accessible through the Diagnostic Laboratory, to assist practitioners in the diagnosis and management of feline hematologic disorders.

Summary of Key Points

1. Initial evaluation of the patient should attempt to differentiate bleeding due to damaged or diseased vessels from a systemic bleeding diathesis.
2. Preliminary screening tests should include platelet count and coagulation panel (aPTT, PT, and TCT or fibrinogen).
3. Petechiae and mucosal bleeding are suggestive of platelet disorders.
4. Thrombocytopenia in cats is more commonly caused by bone marrow aplasia or infiltration, or splenic sequestration. Primary immune-mediated platelet destruction is uncommon.
5. Coagulation factor deficiencies cause prolongation in one or more of the coagulation screening tests. Specific factor analysis may be needed for definitive diagnosis.
6. Acquired factor deficiencies are common, and are associated with multiple factor deficiencies and prolongation of more than one screening test.
7. Prolongation of aPTT and PT, with normal TCT and fibrinogen, is suggestive of vitamin K deficiency.
8. Coagulopathy due to liver failure or DIC is accompanied by prolongation of aPTT, PT, and TCT, and low fibrinogen.
9. Hemophilia is the most common severe inherited coagulation disorder. Hemophilia A and B are intrinsic system defects causing long aPTT. Males express the bleeding tendency, females are asymptomatic carriers.



About the Cornell Feline Health Center

The ultimate purpose of the Cornell Feline Health Center is to improve the health of cats by developing methods to prevent or cure feline diseases and by providing continuing education to veterinarians and cat owners. The Cornell Feline Health Center is a nonprofit organization supported primarily by private contributions.

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Cornell Feline Health Center
Cornell University
College of Veterinary Medicine
Ithaca, NY 14853-6401