BLEEDING DISORDERS: DIAGNOSTIC APPROACH SIMPLIFIED

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Bleeding disorders are classified as disorders of primary hemostasis (platelet or vascular disorders) or disorders of secondary hemostasis (coagulation protein disorders). Differentiation is an essential step in the diagnostic workup.

Emergency Approach to the Bleeding Patient

Bleeding disorders should always be considered life threatening. Even the stable patient with a bleeding disorder can decompensate rapidly from massive bleeding or bleeding into a vital organ. Rapid diagnosis is paramount, such that rational therapy can be instituted with minimal delay.

The patient may be presented for bleeding that is evident to the owner. It may also present for symptoms related to anemia from ongoing hemorrhage, or symptoms due to acute bleeding that compromises organ function or hemodynamics. Patients in an anemic crisis are depressed or moribund, with marked pallor, tachypnea, tachycardia, and bounding pulses. If bleeding has been gradual and there has been sufficient time for compensatory fluid shifts, the patient may be weak but hemodynamically stable. If anemia is due to substantial acute blood loss, symptoms of hypoperfusion predominate. Hemorrhage into the brain, spinal cord, myocardium, or lungs can result in acute organ compromise without significant anemia or shock.

A primary survey should be performed in any emergency patient. This is the initial rapid assessment of vital organ systems to determine if a life-threatening situation exists. Hypovolemic shock, anemic crisis, and pulmonary or brain hemorrhage constitute life-threatening situations in the bleeding patient. Venous access should be established without delay and blood collected from the catheter for a minimum database, including a packed cell volume (PCV) and total protein (TP) concentration. In the bleeding animal, both PCV and TP are usually decreased. In acute hemorrhage, however, the PCV may be normal or elevated as a result of compensatory splenic contraction. A low TP value in a hypovolemic patient is a good clue to acute blood loss, regardless of the PCV. Additional blood samples should be collected before initiating therapy, to avoid treatment-induced changes in laboratory parameters. These should include a blood smear, serum, and EDTA and citrated plasma samples. A blood smear should be examined, with particular emphasis on: platelet numbers, platelet morphology, and the presence of schizocytes. Depending on the findings in the individual patient, additional testing may include: a CBC, chemistry profile, screening coagulation tests, immune testing, and/or serology.

Following sample collection, therapy should be initiated to stabilize the patient. Initial stabilization of the bleeding patient involves (1) control of hemorrhage, when possible, (2) blood transfusion, if anemia is significant, and (3) blood volume replacement, when hypoperfusion is present. In hemorrhagic shock, the most life-threatening problem is hypoperfusion. Initial therapy, therefore, should involve aggressive fluid therapy (crystalloid with or without colloid fluids) until blood is available. There is no justification for withholding fluid therapy in the anemic patient. Hypoperfusion will only exacerbate the tissue hypoxia.

Physical trauma should be avoided in any patient with a bleeding disorder. Animals should be kept quiet and unstressed. Subcutaneous injections should be avoided, where possible, and venipuncture performed only when required for platelet enumeration. Venipuncture sites should be held off with manual pressure for 5 minutes. An intravenous catheter usually can be placed safely and is used to collect all other blood samples.

The patient should be monitored closely for evidence of ongoing or recurrent hemorrhage, including evaluation of perfusion, respiratory, and neurologic status, mucus membrane color, PCV and TP, as well as blood pressure.

Physiology: a Very Basic Review

While the mechanisms involved in hemostasis are complex and inter-related, for the purpose of simplicity, the hemostatic system can divided into 3 major component parts: primary hemostasis, secondary hemostasis and fibrinolysis.

Primary hemostasis: Primary hemostasis involves interactions between the vessel wall and the blood platelets, terminating in the formation of a primary hemostatic plug. This constitutes a temporary seal over the injured vessel. At the site of vascular injury, platelets adhere to the subendothelial collagen, mediated by von Willebrand's factor (vWF) and membrane glycoproteins. Following adherence, the platelets undergo activation, and release platelet agonists. These agonists act to recruit other platelets to the site, activate them, and promote aggregation. Aggregated platelets constitute the primary hemostatic plug, and serve as a stimulus and template for secondary hemostasis. Defects in primary hemostasis can be due to platelet or vascular disorders. Platelet disorders are quantitative (thrombocytopenia) or qualitative (thrombopathia). Vasculopathies can result in excessive fragility, or abnormal interaction with platelets.

Secondary hemostasis: Secondary hemostasis involves the formation of fibrin, in and around the primary hemostatic plug. All coagulation factors are produced in the liver, with the exception of factor VIII. Vitamin K is required for the formation of factors II, VII, IX and X (as well as protein C and protein S). Classically, two relatively separate pathways for activation of the coagulation cascade were described: an intrinsic and an extrinsic pathway. More recently, however, the cell-based model of hemostasis has recognized the central role of the extrinsic coagulation pathway in initiating secondary hemostasis (via tissue factor), and the role of an intrinsic system in amplifying the response through “cross-talk” and feedback mechanisms. The intrinsic pathway is surface activated, and operates strictly with components present in the blood. It does not play a role in the initiation of secondary hemostasis *in vivo*. Defects of secondary hemostasis may be due to quantitative or qualitative coagulation factor disorders.

Fibrinolysis: The fibrinolytic system consists of plasminogen and all activators that convert it to its active form, plasmin. Plasmin is responsible for dissolution of the fibrin clot. The action of plasmin is on fibrinogen, as well as fibrin, and results in the production of various fragments, known as fibrin split products (FSPs) or fibrin degradation products (FDPs). These have anticoagulant activity, including interference with platelet function and inhibition of thrombin, and are ultimately removed from the circulation by the liver. The half-life of circulating FSPs is normally approximately 9 to 12 hours. D-dimer is a specific FSP that is released when cross-linked fibrin is lysed. Excessive fibrinolysis and the generation of increased quantities of FSPs and d-dimers may occur in conditions such as disseminated intravascular coagulation (DIC) and hepatic disease.

Diagnostic Approach

Once the patient has been stabilized, every effort should be directed toward the rapid establishment of a diagnosis. The clinician must answer 3 initial questions: (1) Is the bleeding due to local factors, or does the animal have a generalized bleeding disorder? (2) If a systemic disorder does exist, what is the nature of the hemostatic defect? (3) Is the defect congenital or acquired? These questions can usually be answered based on information gained from the history, physical examination, and screening coagulation tests. This is generally sufficient to guide further testing to determine a specific etiology, and to institute rational therapy.

History

The importance of a thorough and detailed history cannot be overemphasized. Information should be sought regarding past or present bleeding episodes that required intervention or a history of recent trauma. In some cases, bleeding may not be apparent to the owner. Lameness may result from hemarthrosis and

dyspnea from intrapulmonary hemorrhage. The owner should be questioned regarding any evidence of bleeding in other sites that would indicate a systemic bleeding disorder.

The signalment of the patient can be informative. Severe inherited disorders are generally apparent within the first 6 months of life. Milder forms, such as von Willebrand disease (vWD), may not be diagnosed until surgery, trauma, or concurrent disease precipitates bleeding. Acquired hemostatic anomalies are seen more commonly in mature animals. It can be difficult to differentiate between a mild inherited defect and a newly acquired disorder. A history of repeated bleeding episodes suggests an inherited coagulopathy. Acquired disorders can occur in any breed. Some breeds, however, appear to be more prone to certain disorders (e.g., immune-mediated thrombocytopenia in Cocker Spaniels). Inherited disorders show a much higher breed predilection.

The clinician should try to determine whether bleeding episodes occurred spontaneously or were precipitated by injury or surgery. Some inherited disorders (e.g., hemophilia) and many acquired disorders (e.g., thrombocytopenia, vitamin K deficiency) produce spontaneous bleeding, whereas milder forms of these diseases and other conditions (e.g., vWD, factor VII deficiency) more commonly require some form of trauma to make the impairment clinically apparent. The assessment of response to trauma may also enable the clinician to date the onset of the disorder. A patient that has tolerated surgery is unlikely to have a severe inherited bleeding disorder.

The history should include detailed enquiries about previous illnesses and past and present medications. Many systemic diseases can compromise hemostasis and precipitate bleeding, particularly in a patient with an already compromised hemostatic mechanism. Numerous drugs have been associated with thrombocytopenia, thrombopathias, and coagulopathies. Live virus vaccines and certain drugs can cause thrombocytopenia 3 to 10 days post administration. A travel history may elucidate exposure to infectious diseases. Specific enquiries about the environment and patient behavior may reveal exposure to toxins or trauma.

When possible, information should be sought concerning family members. Although a family history of bleeding disorders has great diagnostic significance, a negative history does not exclude the possibility of a heritable disorder.

Physical Examination

The distribution, extent and nature of current hemorrhage should be noted in an attempt to determine if the bleeding is due to local causes or a systemic bleeding disorder. This requires careful examination of all body systems including the skin, mucus membranes, eyes, and joints, as well as the urine and feces. The presence of hemorrhage in more than one site is suggestive of a bleeding disorder. The nature of the hemorrhage helps to characterize the defect (Table 1).

Defects of primary hemostasis are characterized by petechiae or ecchymosis and spontaneous bleeding from mucosal surfaces, including epistaxis, gingival bleeding, hyphema, hematuria, and melena. Platelet and vascular abnormalities cannot be distinguished by physical examination alone. Defects of secondary hemostasis usually are characterized by single or multiple hematomas and bleeding into subcutaneous tissue, body cavities, muscles, or joints. Some acquired disorders, such as disseminated intravascular coagulation (DIC), defy this classification because multiple hemostatic defects are present. vWD usually has the characteristics of a primary hemostatic defect, but in its most severe form it may mimic a secondary hemostatic disorder.

Many systemic diseases have the potential to impair hemostasis and result in bleeding, or to precipitate bleeding in an animal with already compromised hemostasis. It is important that a thorough examination be aimed at identifying such diseases. Hepatic failure can produce a variety of hemostatic defects. Thrombopathias have been associated with renal disease and neoplasia. Some forms of neoplasia can

result in immune-mediated thrombocytopenia or DIC. Examination should evaluate for evidence of other immune-mediated disease (e.g., cutaneous or mucocutaneous lesions, arthropathy, chorioretinitis).

Screening Coagulation Tests

Laboratory tests are essential to confirm and characterize the hemostatic defect (Table 2). These tests should be performed and interpreted carefully, along with the clinical findings, and with their limitations in mind. The more common screening tests are presented. Normal values are listed in Table 3.

***Sample collection*:** Blood samples should be collected before initiation of any therapy. Hemostatic tests make high demands on sampling techniques. Improper technique or use of an incorrect container or handling results in activation of coagulation and false results. For platelet enumeration, blood anticoagulated with ETDA is required. Most of the tests for secondary hemostasis, the individual coagulation factors, and D-dimers are measured using citrated blood or plasma. Prefabricated sample containers are generally used. Citrated tubes contain sufficient volume of citrate solution such that the ratio of citrate to blood is 1:9. Should there be deviations in this ratio, false test results are obtained. This ratio, however, is valid for animals with a physiologic hematocrit. It can be adjusted via controlled underfilling for patients with a decreased hematocrit and controlled overfilling for those with an increased hematocrit. Blood collection should be performed without, or after brief (<30 seconds), venous congestion. Puncture should be quick and atraumatic, and result in a rapid, smooth flow of blood. The first few drops of blood should be discarded. Puncture of the same vein should not be repeated within 30 minutes. Collection can be performed via a Vacutainer system, or via aspiration with a syringe followed by immediate transfer into the tube. Importance should be attached to rapid and thorough mixing of the collected blood with the anticoagulant, by careful inversion and rotation.

Platelet Enumeration / Estimation: Quantitative platelet disorders are detected via a platelet count. This should be performed in all patients with a suspected bleeding disorder. Samples are collected in ETDA and analyzed either manually (by hemocytometer) or with an automated cell counter. Both techniques are reliable for canine blood. In cats, there is considerable overlap between erythrocyte and platelet volumes, resulting in erroneous results from automated counters. Feline platelets must be enumerated manually, or electronically on platelet-rich plasma.

Examination of a blood smear allows for rapid estimation of platelet numbers. This is essential in the emergency setting where automated counts may not be available, and in cats where automated counts are frequently inaccurate. Smear examination also serves to verify findings of automated counters.

Because platelet clumping can result in artifactually low counts, a decreased platelet count should always be verified via smear evaluation and, if necessary, the count repeated on a freshly drawn blood sample. On a well-distributed smear, an average of 11 to 25 platelets per high-power field is considered normal. Each platelet in such a field represents a count of approximately 15,000/μl. It is necessary to first examine the feathered edge of the smear to detect platelet clumping.

Attention should be paid to platelet morphology, as the presence of large platelets (macroplatelets or 'shift' platelets) is generally indicative of megakaryocytic hyperplasia and a regenerative response. Blood smear examination also allows for the assessment of other cell types. Specifically, the presence of schizocytes is highly suggestive of microangiopathic hemolysis that can result from DIC or vascular neoplasia.

***Bleeding Time*:** The bleeding time is the duration of hemorrhage resulting from infliction of a small standardized injury involving only microscopic vessels. The buccal mucosal bleeding time (BMBT) is the most reliable and reproducible method. Cats usually require light sedation for a BMBT. The patient is restrained in lateral recumbency and a strip of gauze is tied around the maxilla to fold up the upper lip, tightly enough to cause moderate mucosal engorgement. A two-blade, spring-loaded device (Simplate II, Organon Teknika Corporation, Jessup, MD) is used to make two 1-mm deep incisions in the mucosa of the

upper lip. The incisions should be made at a site devoid of visible vessels and inclined so that the blood flows toward the mouth. Shed blood is blotted carefully with filter paper, taking extreme care not to disturb the incisions. The BMBT is the time from incision to cessation of bleeding.

Cuticle bleeding time is the duration of bleeding after the tip of the dermis of the nail has been severed by a guillotine-type nail clipper. It is significantly less reliable and reproducible than the BMBT, and thus cannot be recommended.

The bleeding time reflects *in vivo* primary hemostasis. It is prolonged with thrombocytopenia, thrombopathia, and vascular anomalies. It is indicated in patients with a suspected primary hemostatic defect when the platelet count is adequate. The test is unnecessary in the thrombocytopenic patient.

Activated Clotting Time (ACT): The ACT is a simple, in-office screening test for the intrinsic and common pathways. Blood (2 ml) is drawn into a prewarmed (37° C) commercial tube containing diatomaceous earth, which serves as a chemical activator of factor XII. The first few drops of blood are discarded because of the possible presence of tissue factor. The sample is mixed by inversion and then placed in a 37° C heat block or water bath for 50 seconds. It is inverted every 10 seconds, observed for clot formation, and replaced. The ACT is the interval to first clot formation. The ACT is not prolonged until a single factor is decreased to below 10% of normal concentration, or multiple defects are present. It is therefore a relatively insensitive, but easily performed, test. Severe thrombocytopenia (<10,000/μl) causes mild prolongation of the ACT (10 to 20 seconds). Similarly, hypofibrinogenemia and some thrombopathias may result in ACT prolongation.

Activated Partial Thromboplastin Time (PTT:) The PTT tests the intrinsic and common pathways. Only factors VII and XIII are not evaluated. In general, at least one factor must be decreased to below 30% of normal concentration before PTT prolongation occurs. This test is more sensitive than the ACT and is not affected by primary hemostatic disorders.

A patient-side coagulometer (SCA 2000, Synbiotics, San Diego, CA) is an attractive alternative to conventional laboratory PTT determination in the emergency setting. Although the methodology enables

testing of either nonanticoagulated blood or citrated whole blood, the latter is preferable with respect to sensitivity and specificity. Using citrated whole blood, reported sensitivity is 100%, with a specificity of approximately 83%. As such, it is an excellent screening test for defects of the intrinsic and common pathways. False-positive results, however, do occur. A prolonged PTT on the SCA should be validated via conventional laboratory testing. In the author's experience, marked prolongations are usually clinically significant; mild prolongations should be interpreted with caution.

***Prothrombin Time (PT)*:** The PT tests the extrinsic and the common pathways. As such, it is the principal test of the extrinsic pathway. Because of the short half-life of factor VII, this test is very sensitive to vitamin K deficiency or antagonism. It is less sensitive to heparin than is the PTT.

The patient-side coagulometer is also a relatively accurate method for PT testing. Using citrated whole blood, reported sensitivity and specificity are 85.7% and 95.5%, respectively. That is, some defects of the extrinsic system will not be detected, and false-positive results occur. Abnormal results that do not correlate with clinical findings should be verified via conventional laboratory testing.

***Fibrin Split Products (FSPs) / Fibrin Degradation Products (FDPs)*:** FSPs are the end-products of fibrinolysis, and are generated when fibrinogen, soluble fibrin, or cross-linked fibrin is lysed. Commercial latex agglutination kits (Thrombo-Wellcotest, Wellcome Reagents, Beckenham, England) constitute a rapid, semi-quantitative method for FSP determination. The test utilizes latex particles coated with anti-human FSP antibodies, which also cross-react with the FSPs of other species. However, these will also detect

fibrinogen. Special tubes are used which contain thrombin, to clot the sample and remove the fibrinogen from solution, as well as an inhibitor of fibrinolysis to prevent further fibrin breakdown.

Elevated concentrations commonly occur in DIC but are not universally present, nor specific, for the syndrome. Increased concentrations may also occur in hepatic disease, due to enhanced fibrinolysis and reduced clearance. False elevations may occur in patients on heparin therapy or those with dysfibrinogenemia.

D-dimers: d-Dimers are unique FSPs that are formed when cross-linked fibrin is lysed by plasmin. In contrast to FSPs which indicate only the activation of plasmin, d-dimers indicate the activation of thrombin and plasmin and are specific for active coagulation and fibrinolysis. The half-life of d-dimers is short (approximately 5 hours). As such, they are useful only for detection of recent or ongoing fibrinolysis. The traditional laboratory assay of d-dimers is the enzyme-linked immunosorbent assay (ELISA). An in-office latex bead agglutination test (Accuclot d-dimer, Sigma) and a canine-specific point-of-care test (AGEN canine d-dimer test, Sigma) have been shown to compare favorably.

The d-dimer is a sensitive test for DIC and likely is superior to traditional FSP assays for this purpose. However, d-dimer concentrations are not always elevated in patients with DIC, and elevated d-dimer levels are certainly not specific for DIC. Elevated concentrations have been demonstrated in dogs with thromboembolism, neoplasia, hepatic disease, renal failure, cardiac failure, internal hemorrhage, and following surgical procedures. It should be considered an ancillary diagnostic test, with the diagnosis of DIC relying on the appropriate constellation of clinical findings and abnormal results of hemostatic testing.

Disorders of Primary Hemostasis

Causes of disorders of primary hemostasis are listed in Figure 1. An algorithm outlining the approach to primary hemostatic disorders is presented in Figure 2.

Thrombocytopenia

Thrombocytopenia is the most common primary hemostatic defect. It can result from decreased platelet production, platelet destruction, consumption, or sequestration. Spontaneous bleeding generally does not occur until platelet counts fall below 30,000/μl to 50,000/μl, unless a concomitant bleeding disorder exists. The bleeding patient with a mild or moderate thrombocytopenia either has a combined defect, or the thrombocytopenia is merely a consequence of acute hemorrhage. Disorders of consumption or sequestration generally result in a mild or moderate degree of thrombocytopenia. Exceptions occur in some cases of splenic torsion and DIC, in which thrombocytopenia can be marked. (When DIC results in severe thrombocytopenia, it is almost invariably accompanied by other abnormal hemostatic test results.)

The secondary hemostatic mechanisms should be evaluated in all thrombocytopenic animals to investigate DIC or other combined defects. If these are normal, a bone marrow aspirate or biopsy is indicated to evaluate platelet production. Three to five megakaryocytes per smear are generally considered normal. Megakaryocytic hypoplasia may result from numerous conditions. In the absence of a compatible drug history, or evidence of myelophthisis on bone marrow examination, further testing should be directed toward the investigation of neoplastic, infectious or immune-mediated etiologies. The possibility of an estrogen-secreting tumor should be considered, and pursued if indicated. Chronic rickettsial disease (e.g., *Ehrlichia canis*) frequently produces other clinical signs (e.g., anemia, leukopenia, arthropathy, glomerulonephropathy), and is best diagnosed by serology. Serologic testing for FeLV and FIV is imperative in the cat. Immune-mediated megakaryocytic hypoplasia can present a diagnostic dilemma. The platelet factor 3 (PF3) test is insensitive, and megakaryocytes may be present in insufficient numbers to detect antiplatelet antibodies. In these situations, and after exclusion of other differentials, response to immunosuppressive therapy is an appropriate diagnostic tool.

Normal or increased numbers of megakaryocytes in thrombocytopenic patients are indicative of increased platelet destruction, consumption or sequestration. Some of the more common causes of platelet consumption and sequestration include: DIC, sepsis, vasculitis and splenic torsion. These can usually be excluded on the basis of clinical findings. Immune-mediated thrombocytopenia (ITP) is a common cause of thrombocytopenia in the dog. As previously discussed, definitive diagnosis can be unrewarding, so nonimmune causes should be excluded. Rickettsial disease (Ehrlichiosis, Rocky Mountain spotted fever) may induce a nonimmune thrombocytopenia with megakaryocytic hyperplasia. These are diagnosed serologically. Negative titers, however, do not exclude tick-borne disease, and should be repeated in 10 to 14 days. ITP may be idiopathic or may occur together with other autoimmune processes, such as IMHA or SLE. In addition, it may develop secondary to drug administration (most notably, sulphonamides), live-virus vaccination, neoplasia (especially lymphoid) and infection. Suspicion of ITP, therefore, should prompt a thorough search for underlying causes or systemic immune-mediated disease. Together with a complete blood count, chemistries, and urinalysis, the following diagnostic tests are indicated: radiology or ultrasound, a direct Coombs' test, and antinuclear antibody test (ANA). In addition, serology for tick-borne diseases and occult dirofilariasis should be considered in the dog, and viral serology in the cat.

Thrombopathia

Vascular disorders are a relatively uncommon cause of bleeding. In the patient with a primary hemostatic disorder and normal platelet numbers, a platelet function defect is likely. A prolonged BMBT in a patient with adequate platelet numbers confirms thrombopathia. The drug history should be carefully appraised, because numerous drugs can cause or contribute to thrombopathia. Diseases known to precipitate platelet dysfunction should be excluded. If no obvious cause of acquired thrombopathia can be found, a hereditary disorder is suspected.

Von Willebrand's disease (vWD) is the most common canine hereditary bleeding disorder. Von Willebrand's factor (vWf) is produced and stored in canine endothelial cells and plays a central role in platelet adhesion. In plasma, vWF forms a complex with coagulation factor VIII and appears to stabilize the functional half-life of this factor. High-molecular-weight vWf multimers are most effective in platelet adhesion. Deficiency of vWf, or preferential loss of high-molecular-weight forms, results in impaired adhesion.

There are three types of vWD. Type I is most common. It is associated with a partial, quantitative deficiency of vWF, with normal multimer distribution. Type I vWD has been described in numerous dog breeds, including the Doberman, Rottweiler, and German Shepherd. Isolated cases have been reported in cats. Clinical severity is variable and correlates with reduction in vWF concentration. Severely affected dogs (<20% vWF) can bleed spontaneously. Mildly affected dogs undergo bleeding only if subjected to surgery or trauma, or if the condition is exacerbated by another bleeding tendency. Type II vWD is characterized by low vWF concentration and a disproportionate loss of high-molecular-weight multimers. It has been described in German Shorthaired Pointers and Wirehaired Pointers. Type III vWD is a severe quantitative deficiency of vWF. Familial forms have been reported in Chesapeake Bay Retrievers, Shetland Sheepdogs, and Scottish Terriers. Sporadic cases have been reported in other breeds. Types II and III vWD cause a severe bleeding tendency, typically with episodes of hemorrhage occurring within the first year of life.

Diagnosis is generally achieved via ELISA testing, with results reported as a percentage of the laboratory's standard plasma. Values less than 50% are considered vWf deficient. Differentiation between types I and II vWD requires determination of multimer distribution via immunoelectrophoresis. Animals with systemic stress or critical illness may have abnormal vWf. Therefore, decreased vWF titers in such patients should not be over-interpreted.

Diagnosis of other thrombopathies requires specific platelet function testing, performed by specialized laboratories.

Disorders of Secondary Hemostasis
Causes of disorders of secondary hemostasis are listed in Figure 3. An algorithm outlining the approach to secondary hemostatic disorders is presented in Figure 4.

Hereditary coagulopathies are quantitative disorders of specific coagulation factors, usually noted in purebred dogs. Acquired disorders include vitamin K deficiency or antagonism, hepatic disease, DIC, and the presence of anticoagulants (e.g., heparin). These acquired conditions tend to affect multiple factors in both the intrinsic and extrinsic pathways. Factor VII has the shortest half-life (4 to 6 hours), so prolongation of the PT may precede PTT prolongation in early vitamin K deficiency or early acute hepatic failure. Conversely, the PTT alone may be prolonged with chronic hepatic disease, DIC, heparin therapy, or with dilution (e.g., colloid therapy or massive crystalloid fluid administration).

Anticoagulant Rodenticide Toxicity
The most common cause of vitamin K deficiency in dogs is the ingestion of anticoagulant rodenticides. Synthesis of vitamin K–dependent factors (II, VII, IX, and X) occurs in the liver. Vitamin K is an essential cofactor for carboxylation of these proteins, rendering them functional. Anticoagulant rodenticides interfere with recycling of vitamin K, resulting in rapid depletion.

Clinical signs of a secondary hemostatic disorder generally occur 2 to 3 days post-ingestion. Prolongation of the PT occurs first but, by the time hemorrhage is evident, the PT, PTT, and ACT are usually all prolonged. FSP, d-dimer, and fibrinogen concentrations are generally normal. The platelet count is usually normal, but it may be decreased by consumption during bleeding. Toxicologic testing is not usually helpful in the emergency situation, but it may serve to confirm an uncertain diagnosis.

Hepatic Disease
Severe hepatocellular damage or biliary obstruction results in variable factor deficiencies or abnormalities in vitamin K metabolism, or both. Both quantitative and qualitative platelet disorders may occur. PT and PTT can be prolonged. FSP and d-dimer concentrations may be elevated. Excessive fibrinolysis can result from the reduced clearance of plasminogen activators and reduced synthesis of fibrinolytic inhibitors. Differentiation from DIC is sometimes impossible based on coagulation testing alone, and depends on clinical findings, serum chemistry results, and liver function testing. Bleeding tendencies must be corrected before pursuing hepatic biopsy or other invasive procedures. Transfusion of fresh frozen plasma can temporarily offset factor deficiencies. Stored whole blood and packed red blood cells should be avoided due to the increased ammonia concentrations. Vitamin K_1 may be beneficial in some patients; efficacy should be ascertained by repeat coagulation testing at least 12 hours after initiating therapy.

Disseminated Intravascular Coagulation (DIC)
Disseminated intravascular coagulation (DIC) refers to the intravascular activation of hemostasis with resultant microcirculatory thrombosis. Ultimately, exaggerated consumption of platelets and coagulation factors may result in defective hemostasis and a bleeding tendency. Fibrinolysis of microthrombi generates FSPs, further exacerbating the disorder.

DIC occurs secondary to a wide variety of underlying disease processes. These include: sepsis, the systemic inflammatory response syndrome (SIRS), severe infections (viral, bacterial, and protozoal), neoplasia, shock, heat stroke, hemolysis, pancreatitis, severe hepatic disease, trauma, and tissue necrosis. The pathophysiology and manifestations of DIC have been extensively reviewed elsewhere.

The diagnosis of acute, fulminant DIC usually is made easily, but diagnosing chronic or subclinical DIC may prove more difficult. There is always an underlying disease causing DIC that should be identified rapidly, if possible. Laboratory findings are extremely variable. Thrombocytopenia is almost invariably present, but relative changes may be undetected unless a recent count is available for comparison. The PT, and more often the PTT, may be prolonged, but both may be normal if compensatory factor production is adequate.

Significant elevations of FSP or d-dimer levels are highly suggestive of DIC, but are nonspecific. Schizocytes on blood smear examination are significant, but they are not always present and may occur with other conditions. Diagnosis of DIC, therefore, requires careful consideration of both the clinical and the laboratory findings, with no single finding being pathognomonic. Any suspicion of DIC should prompt a thorough search for an underlying cause, as successful management depends on its correction.

Inherited Coagulopathies

The clinical severity of the various inherited coagulopathies depends on the magnitude of the factor deficiency and the exposure of the animal to trauma that may precipitate bleeding. Most develop bleeding within the first year of life. Mildly affected animals may not bleed until later in life, particularly if they do not undergo surgery or trauma. Similarly, factor VII deficiency tends to produce milder disease, with later onset bleeding.

Inherited coagulopathies should be suspected in younger animals, in breeds associated with factor deficiencies, if there is a history of recurrent bleeding, and if acquired causes are ruled out or deemed unlikely. A deficiency of factor VII prolongs only the PT, whereas factor VIII and IX deficiencies (hemophilia A and B) cause prolongation of the PTT. Both parameters are prolonged with deficiencies of factors I, II, and X. Diagnosis requires specific factor assays performed by specialized laboratories.

Table 1. Clinical features helpful in differentiating between primary and secondary hemostatic abnormalities.

Disorders of Primary Hemostasis	**Disorders of Secondary Hemostasis**
Petechiae common.	Petechiation rare.
Hematomas rare.	Hematomas common.
Bleeding often involves mucus membranes.	Bleeding into muscles and joints common.
Bleeding usually at multiple sites.	Bleeding frequently localized.
Prolonged bleeding from cuts.	Bleeding may be delayed at onset, or stop and start again (rebleed).

Table 2. Screening tests for the evaluation of hemostasis.

	Screening Test	Component/Factors Evaluated
Primary Hemostasis:	platelet enumeration platelet estimation *	platelet numbers
	bleeding time (BT) *	platelet numbers and function, vascular integrity
Secondary Hemostasis:	activated clotting time (ACT) *	intrinsic and common pathways: factors XII, XI, IX, VIII, X, V, II, and fibrinogen
	partial thromboplastin time (PTT)	as with ACT, but more sensitive
	prothrombin time (PT)	extrinsic and common pathways: factors III, VII, X, V, II and fibrinogen
Fibrinolysis:	fibrin split products (FSP's) * d-dimers	products of fibrinolysis

* In-office tests

Table 3. Normal values for screening coagulation tests.

Test	Dog	Cat
Platelet count (X 10^3/µl)	150-500	200-600
Buccal mucosal bleeding time (minutes)	1.7-4.2	1.4-2.4
Cuticle bleeding time (minutes)	2.0-8.0	2.0-8.0
Activated clotting time (seconds)	60-110	50-75
Prothrombin time (seconds) - laboratory * - SCA	 7-10 < 20	 9-12 < 20
Partial thromboplastin time (seconds) - laboratory * - SCA	 9-12 < 120	 15-21 < 120
Fibrin split products (µg/ml)	< 10	< 10
D-dimers (ng/ml)	< 250	< 250

* Normal values are laboratory and technique dependent.

Figure 1. Causes of disorders of primary hemostasis

QUANTITATIVE PLATELET DISORDERS (THROMBOCYTOPENIA)

ACQUIRED

Decreased production:

- Drug-induced (estrogen, chloramphenicol, cytotoxics)
- Immune-mediated megakaryocytic hypoplasia
- Viral (FeLV)
- Chronic rickettsial disease
- Estrogen-secreting neoplasm
- Myelophthisis (myeloproliferative disease)
- Myelofibrosis
- Cyclic thrombocytopenia (*E. platys*)
- Radiation
- Idiopathic bone marrow aplasia

Increased destruction:

- Immune-mediated (IMTP):
  - Primary - idiopathic
  - Evan's syndrome
  - systemic lupus erythematosus
  - Secondary - drugs
  - live virus vaccination
  - tick-borne disease
  - neoplasia
  - bacterial infection
- Nonimmune:
  - Drug-induced
  - Ehrlichiosis
  - Rocky Mountain Spoted fever
  - Dirofilariasis

Consumption / Sequestration:

- Disseminated intravascular coagulation
- Microangiopathies
- Sepsis
- Vasculitis
- Splenic torsion, hypersplenism
- Hepatic disease
- Heparin-induced
- Profound, acute hemorrhage
- Hemolytic uraemic syndrome

QUALITATIVE PLATELET DISORDERS (THROMBOPATHIA)

INHERITED

Von Willebrand's disease (numerous breeds)

Canine thrombopathia (Basset hounds)

Canine thromboasthenic thrombopathia (Otterhounds)

ACQUIRED

Drug-induced (eg. NSAIDs, synthetic colloid solutions, antibiotics, heparin)

Uremia

Hepatic disease

Pancreatitis

Myeloproliferative disorders

Dysproteinemia (eg. myeloma)

VASCULAR DISORDERS

INHERITED

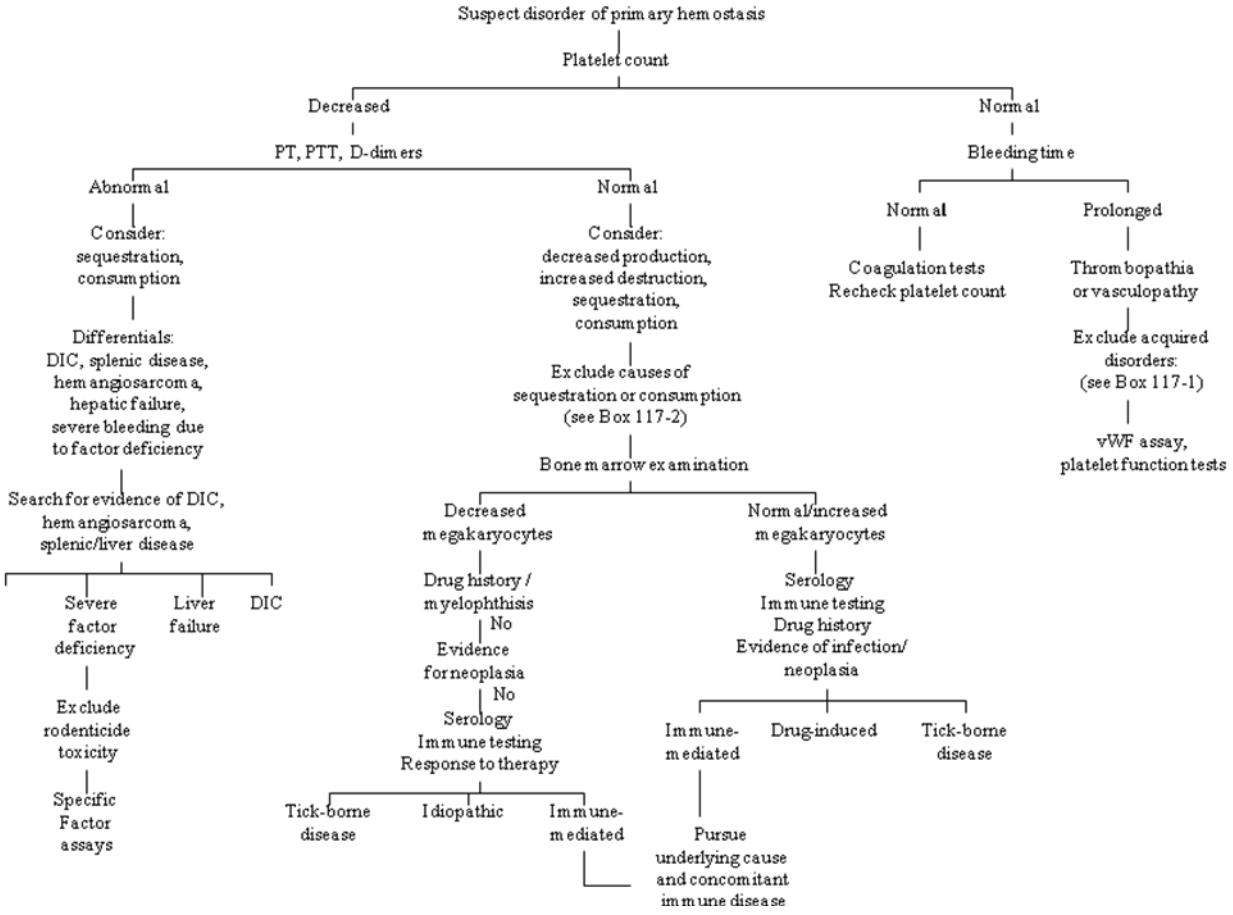
Ehrlers-Danlos syndrome

ACQUIRED

Vasculitis

Hyperadrenocorticism

Figure 2. Approach to the diagnosis of disorders of primary hemostasis



DIC = disseminated intravascular coagulation
ATIII = antithrombin III
vWf = von Willebrand's factor

Figure 3. Causes of disorders of secondary hemostasis

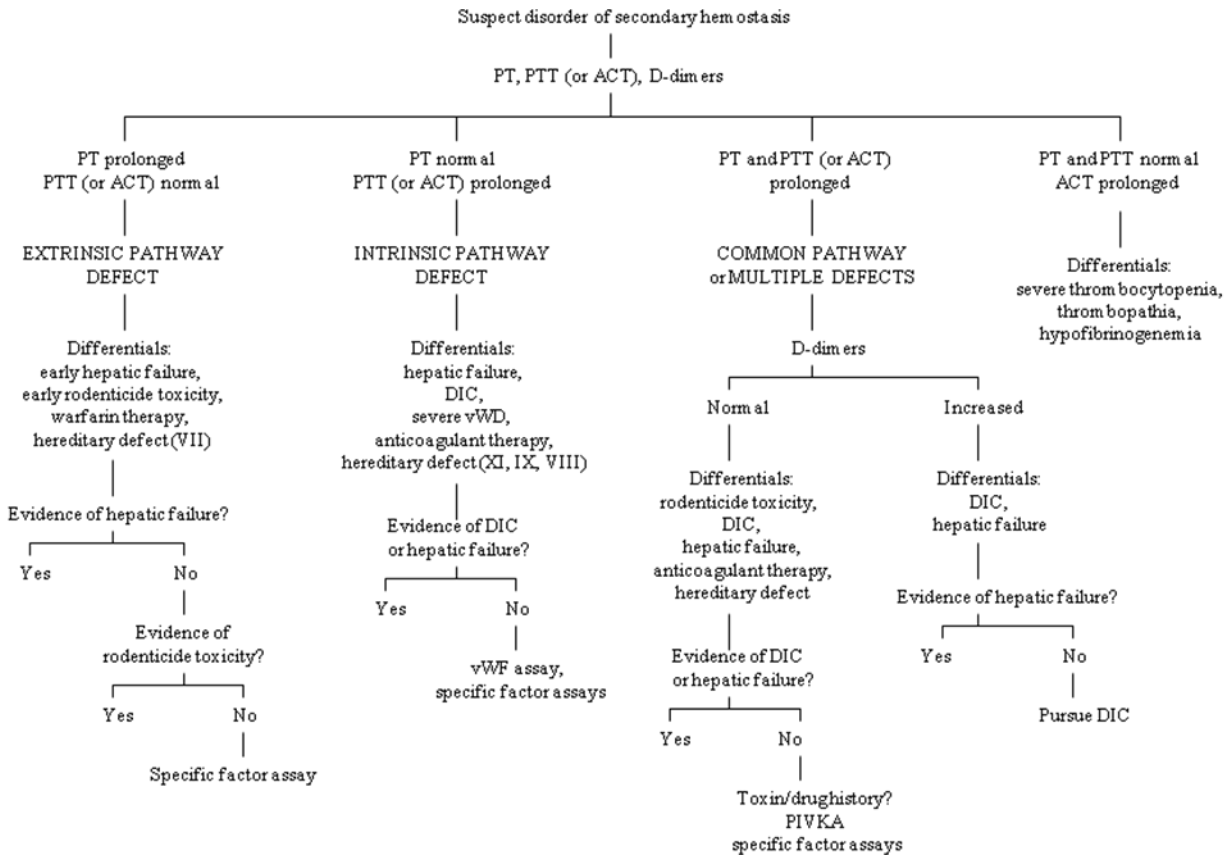
INHERITED

Factor I: Hypo/dysfibrinogenemia (St. Bernards, Borzois)
II: Hypoprothrombinemia (Boxers)
VII: Hypoproconvertinemia (Beagles, malamutes)
VIII: Hemophilia A (numerous dog breeds, mongrels, cats)
IX: Hemophilia B (numerous dog breeds, British shorthair cats)
X: Stuart Prower trait (Cocker spaniels)
XI: Plasma thromboplastin antecedent deficiency (Springer spaniels, Great Pyrenees)
XII: Hageman factor deficiency (numerous dog breeds, cats)

ACQUIRED

- Vitamin K deficiency/antagonism
- Hepatic disease
- DIC
- Circulating anticoagulants (eg. heparin)

Figure 4. Approach to the diagnosis of disorders of secondary hemostasis.



DIC = disseminated intravascular coagulation
vWf = von Willebrand's factor
vWD = von Willebrand's disease
PIVKA = test for Proteins Induced by Vitamin K Absence/Antagonism