CLINICAL APPROACH TO THE BLEEDING DOG

Urs Giger, PD Dr med vet, Diplomate ACVIM & ECVIM
School of Veterinary Medicine
University of Pennsylvania, Philadelphia, PA

Hemorrhage is a common clinical presentation and complication of surgical and medical management. Various point-of-care tools and diagnostic tests have been developed and become available for clinical practice. Their clinical application and the correct interpretation of test results permit a specific diagnosis of the bleeding disorder and prompt and appropriate management including local hemostasis, and drug & transfusion therapy.

Hemostasis is the complex physiologic response to bleeding and can be divided into primary and secondary hemostasis. Vascular endothelium, platelets, and von Willebrand factor (vWF), are required for primary hemostasis or the formation of the unstable platelet plug, which is sufficient to stop capillary bleeding. Von Willebrand factor, a large plasma protein synthesized by endothelium, facilitates adhesion between platelets and subendothelium. With larger vessel injury, coagulation factors are also needed to form a stable fibrin clot known as secondary hemostasis.

The coagulation cascade plays three pivotal roles in the formation of fibrin from fibrinogen: acceleration of fibrin generation >10 million-fold, regulation of fibrin plug size appropriate for injury, and localization of fibrin clot formation to site of injury. The coagulation cascade can be divided into an extrinsic and intrinsic system, which merge into the common pathway. Coagulation factors are enzymes, cofactors, or substrates of particular reactions of the coagulation cascade. Calcium (factor IV) is required for most reactions and is the reason why chelators, e.g. citrate and EDTA, are used for blood collection and processing, where plasma or blood cells are analyzed. All coagulation factors are synthesized in the liver and circulate as inactive precursors in the plasma. They need to be activated at the site of vessel injury. Vitamin K is needed for the functional synthesis of the coagulation factor II, VII, IX, and X. The half-lives of the coagulation factors vary from hours (Factor VII) to a few days (Fibrinogen). Following a fibrin plug formation, plasminogen will be activated and plasmin, an unspecific protease will commence breaking down fibrinogen as well as fibrin which results in fibrinogen lysis and fibrin(-ogen) split product (FSP) as well as D-dimer formation.

Hemostatic disorders can be conveniently classified into vasculopathies, thrombocytopenias, thrombopathias, von Willebrand disease (vWD), and coagulopathies realizing that some disease processes cause combined hemostatic defects (e.g. disseminated intravascular coagulopathy [DIC]). Hemorrhagic presentations may suggest certain hemostatic disorders and practical tests are available to characterize the bleeding tendency. An accurate diagnosis of the cause of bleeding will influence the treatment and outcome of a patient.

Signalment & History - Although hereditary coagulopathies may occur in any breed, each coagulopathy has thus far only been reported in certain breeds. Hemophilia A and B occur in many different breeds and are X-chromosomal recessively inherited. Signs of bleeding typically occur at an early age and are often recurring, but may not be recognized until adulthood. Bleeding may be induced (trauma, surgery) or appear spontaneous. Careful history taking may reveal exposure to toxins (rodenticides, mushrooms) and drugs (warfarin, heparin). It is important to identify the specific product, as e.g. different rodenticides have quite varied potency. Any evidence of other diseases, e.g. hepatopathies and cancer, may be responsible for the hemorrhage.

Physical Examination - Careful clinical evaluation may differentiate between primary and secondary hemostatic defects. Surface bleeding is typically seen with primary hemostatic disorders. Petechia and ecchymosis are hallmark features of thrombocytopenias. However, von Willebrand disease (vWD) and thrombopathias are causing bleeding at sites of injury (trauma, dental disease, estrus, gastrointestinal) rather than petechiae or ecchymoses. Coagulopathies may be associated with single or multiple sites of bleeding characterized by cavity bleeding (hematoma), but gastrointestinal hemorrhage and bruising may also occur.

Hemostatic Tests are indicated whenever an animal is bleeding excessively, prior to surgery when an increased bleeding tendency is suspected, to monitor therapeutic interventions, and for genetic screening in certain breeds or families with a known bleeding disorder. Hemostatic abnormalities should be assessed prior to instituting therapy whenever possible or at least appropriate blood samples should be collected pretreatment. Excellent venipuncture with discard of the first few drops of blood (to avoid platelet activation and tissue factor) and extended compression over jugular, saphenous or femoral vein is required. The cuticle bleeding time crudely assesses overall hemostasis, but is not standardized and painful and is, therefore, not recommended. A minimal database includes a packed cell volume and total protein evaluation. Evaluation of a blood smear can provide a platelet estimate and identify platelet size and clumping as well as schistocytes. The results can provide some measure of the extent of blood loss and red blood cell transfusion requirement.

1° HEMOSTASIS: PLATELET COUNT AS WELL AS FUNCTION AND VWF

Platelet counts can be estimated on a blood smear or specifically counted by a hematology instrument. Since 8-15 platelets (1 platelet equals 20,000/µl) are normally found per high power oil emersion microscopic field, an absence to low number of platelets suggests a severe thrombocytopenia. Various modern impedance and laser hematology instruments have the ability to count platelets and measure their mean size including size distribution; they have been validated, but some have difficulties in differentiating large platelets from erythrocytes. Furthermore, canine platelets can readily be activated which results in platelet aggregation, hence, platelet counts need to be confirmed by a careful review of a blood smear including the feather edge for platelet clumps. Hemorrhage is generally not observed unless the platelet count is <40,000/µl (normal 150-500,000/µl).

Detection of platelet-associated antibodies further supports an immune-mediated thrombocytopenia, but this test is rarely available. Serum titer, antigen and PCR tests
for tick-born (ehrlichiosis, babesiosis, rocky mountain) and other infectious diseases are indicated in certain countries or areas. The presence of schistocytes and thrombocytopenia suggests intravascular disseminated coagulation, where intravascular fibrin strands fragment erythrocytes. Because von Willebrand disease is such a common mild primary hemostatic defect in dogs, plasma vWF measurements by ELISA are indicated. For breeding purposes, DNA testing is available for some canine breeds. Finally, in light of normal platelet count and plasma vWF values, a prolonged buccal mucosal bleeding time (BMBT) indicates a thrombopathy. Disposable devices are available that facilitate making 1-2 standard 1mm deep mucosal incisions. The platelet function analyzer (PFA100) is a simple tool to functionally assess primary hemostasis. Electron microscopic and platelet aggregation and nucleotide studies allow further characterization of platelet dysfunctions in specialized laboratories.

2° HEMOSTASIS: COAGULATION TESTS

Whereas the whole blood clotting time test is insensitive and inaccurate, there are several standardized coagulation screening tests that are useful to define coagulopathies in clinical practice. Nearly all coagulation tests assess the function of certain parts of the coagulation system in fresh whole blood or fresh (or frozen) plasma to generate fibrin in a fibrometer; recalcified citrated plasma is used and many tests are comparing a patient sample directly with a simultaneously obtained control or pool plasma (plasma from 10 animals). Generally coagulation times, the time to clotting (fibrin formation), are much shorter in small animals than in humans; thus, every coagulation test needs to be validated for the animal species.

The intrinsic and common pathways are assessed by either the activated coagulation time (ACT) or activated partial thromboplastin time (PTT). Factor XII of the intrinsic cascade is activated by diatomaceous earth (celite) in the ACT test and by kaolin or other contact phase substrates in the PTT test. The extrinsic and common pathways can be assessed by either the prothrombin time (PT) or the protein induced by vitamin K antagonism or absence (PIVKA) test. Different tissue factors (thromboplastins) are activating factor VII, which in turn will lead to fibrin formation. It should be noted that the PIVKA test is not specific for the detection of anticoagulant rodenticide poisoning, but detects any coagulation factor deficiency of the extrinsic and common pathway and does not add information to the generally run PT test. Until recently the ACT tube test was the only point of care test available for clinical practice, whereas PTT and PT tests were performed in reference laboratories. There are now new point of care coagulation instruments (e.g. SCA2000) introduced that are capable of determining without delay on small amounts (50µl) of fresh citrated whole blood the PTT and PT, thereby making the chilling, rapid separation of citrated plasma and shipment of frozen plasma on dry ice to the laboratory for initial coagulation screening unnecessary. In fact, a reasonable and simple approach for a bleeding animal to be screened for a coagulopathy would be to measure the ACT or PTT first as either test detects all coagulopathies (except for hereditary factor VII deficiency in Beagles). If the PTT (or ACT) is prolonged, a PT test would be indicated to differentiate between an intrinsic and common pathway defect or a combined coagulopathy involving several coagulation factors.

Although hereditary coagulopathies can be suspected based upon the pattern of coagulation test abnormalities, specific factor analyses are needed to confirm a diagnosis. A bleeding male animal with a prolonged PTT (or ACT) and normal PT likely has hemophilia A or B (factor VIII or IX deficiency), an X-chromosomal recessive disorder. However, factor XI deficiency is associated with the same test abnormalities and is inherited by an autosomal recessive trait (e.g. Kerry blue terriers). Finally, factor XII deficiency, particularly common in domestic short-hair cats, and prekallikrein deficiency causes marked PTT (ACT) prolongations but no excessive bleeding tendency. Rodenticide poisoned animals that are bleeding or are at risk for bleeding will have prolongations in all of the above coagulation tests, but would have a normal thrombin time (TT). The thrombin time is independent of vitamin K-dependent coagulation factors and is a functional assay for fibrinogen to form fibrin. The PIVKA test is not diagnostic, but a toxicological investigation (product identification, blood toxicology analysis) may confirm the rodenticide poisoning. Moderate thrombocytopenia may be associated with rodenticide poisoning. All liver diseases may result in varied coagulopathies due to impaired coagulation factor synthesis and vitamin K malabsorption. Similarly, disseminated intravascular coagulopathies (DIC), due to many different disorders is associated with variably prolonged coagulation times. More helpful to the diagnosis of DIC are the recognition of schistocytes, thrombocytopenia, low antithrombin III levels, and increased D-dimers and fibrin split (degradation) products.

MANAGEMENT

A high suspicion of a hemostatic dysfunction based upon signalement, history, clinical signs, and laboratory tests, as well as definitive identification of the specific hemorrhage defect is important in order to institute promptly the most effective and safe treatment. Whereas the diagnostic approach to the bleeding patient was discussed in a previous manuscript, this paper will cover the treatment modalities for hemorrhage focusing on transfusion medicine. Depending on the severity of the hemorrhage conservative prevention of further hemorrhage to intensive care and transfusion support may have to be instituted. There are several general therapeutic principles to consider:

- Provide local hemostasis with wound pressure, ligations, and topical agents.
- Rehydrate the patient in case of rapid blood and other fluid loss with electrolytes.
- Avoid plasma expanders as they can induce a bleeding tendency.
- Collect diagnostic blood samples prior to treatment as blood components and drugs can affect results.
- Transfuse packed red blood cells as needed for the correction of severe anemia.
- Administer other blood components to replenish deficient coagulation factors and rarely platelets.
- Remove triggering agents such as toxins and infectious agents with antimicrobial therapy.
- Treat underlying disease whenever possible.
- Monitor the patient’s bleeding tendency and overall well-being, prevent reexposure to toxins.
- Delay any harmful surgical interventions, and avoid exposure to drugs that impair hemostasis.
Transfusion therapy - Only blood type compatible blood should be administered. Thus, red cell, platelet and plasma recipients and blood donors should be typed with simple in practice or laboratory methods, and previously transfused animals also need to be cross-matched to assure compatibility and prevent transfusion reactions. The transfusion trigger varies widely depending on the rapidity of anemia onset and degree of the anemia as well as severity of clinical signs; there is no specific PCV at which to transfuse, but at a PCV of <15-20% oxygenation of tissues becomes drastically reduced. Volume of blood component to be administered depends on the degree of anemia and the size of the animal: Volume (ml) of whole blood = 2 x PCV rise desired (%) x body weight (kg)

The rate of transfusion depends on the hydration status, degree of anemia, and general health condition of an animal. Initial rate is slow, starting with 1-3 ml over the first 5 minutes to observe for any transfusion reactions, even with blood typed and/or crossmatched transfusions. This is followed by a rate of about 10-20 ml/kg/hr. In animals with cardiac failure, do not exceed 4 ml/kg/hr. Transfusion of a single bag should be completed within 4 hours. Monitor response to transfusion by obtaining PCV/TP readings prior to, immediately, and 6 and 24 hours post-transfusion, and consider continued blood loss and/or hemolysis.

In thrombocytopenia or thrombopathia, one unit of PC, PRP or FWB will increase the platelet count by 10,000/µL in a recipient weighing 30 kg. In animals with serious or life-threatening bleeding, the platelet count should be increased to above 40,000/µL. Platelet counts are monitored prior, 1 hour, and 24 hours after platelet transfusion.

In coagulopathies and von Willebrand’s disease, FFP at 6-10 ml/kg is an initial dose to stop bleeding or avoid excessive bleeding during surgery. In some cases, larger volumes and repeated administration of FFP may be needed to control bleeding. Cryoprecipitate at a dose of 1 CRYO unit/10 kg or 2-4 ml/kg body weight twice daily is ideal to treat hemophilia A and von Willebrand’s disease. Plasma support should be provided for an additional 1-3 days after the bleeding has been controlled to allow for healing and prevent rebleeding. Beside the above listed general principles and described transfusion support in controlling hemorrhagic diatheses, there are several specific therapeutic interventions for particular bleeding disorders.

Immune-mediated thrombocytopenia - Platelets in the form of platelet rich plasma, platelet concentrate, or fresh whole blood, are only transfused when the patient has severe uncontrolled or life-threatening bleeding. In fact, transfused platelets given to IMT patients have a very short survival of a few minutes to hours and thus do not generally increase the blood platelet count despite providing transiently improved hemostasis. Beside treating the underlying disease, such as ehrlichiosis, babesiosis, and drug allergy, immunosuppressive agents are used to impair the macrophage system and production of platelet antibodies. Glucocorticoids are the first choice either in the form of prednisone at 1-2 mg/kg or dexamethasone at 0.2-0.3 mg/kg BID; the initial dose is slowly tapered after the recognition of a response by no more than one third the dose every 2 weeks. Vincristine at 0.02 mg/kg strictly IV once may accelerate the platelet count recovery by impairing the macrophage system, stimulating platelet release from the megakaryocytes and platelet production. Other immunosuppressive agents such as cyclosporine, azathioprine, and intravenous immunoglobulin may also be considered, but their efficacy and safety have not been documented. Finally, splenectomy is highly effective in corticosteroid refractory IMT in human patients, but has not been adequately evaluated in dogs.

Von Willebrand disease (vWD) - Cryoprecipitate, a product rich in vWF, is the blood component of choice. The dose is approximately 2-4 ml/kg or about 3-4 units of cryoprecipitate per Doberman pinscher. The cryoprecipitate or FFP transfusion may have to be repeated every 8-12 hours depending on the control of hemorrhage. In cases of mild hemorrhage or in order to prevent excessive bleeding during minor surgeries, desmopressin at a dose of 1 µg/kg once subcutaneously may provide adequate hemostasis for a few hours. Desmopressin may improve vascular integrity as the observe increase in plasma vWF following desmopressin injection is very minimal. The effect of cryoprecipitate, FFP, and desmopressin can be monitored with the buccal mucosal bleeding time one hour after the injection.

Vitamin K antagonism (rodenticide poisoning) & deficiency - Only if the rodenticide has just been ingested should emesis be induced. When critically bleeding, vitamin K-dependent coagulation factors can be replaced with fresh frozen plasma at 10 ml/kg q 8-12 hours or with 20 ml/kg fresh whole blood, if also anemic. Vitamin K1 at an initial dose of 3-5 mg/kg po or sc at several spots is followed by 0.5-4 mg/kg po once daily depending on PT or PTT/ACT response. The dose and duration of treatment depends on the type and amount of the ingested rodenticide. In cases of malabsorption or biliary obstruction low parenteral doses of vitamin K are effective.

Disseminated intravascular coagulation (DIC) - Without being able to remove the trigger and treat the underlying disease (infection, cancer, IMHA, heat stroke), any therapeutic intervention seems futile. Administration of electrolyte fluids to maintain tissue perfusion and attempts to correct acidosis and hyper-/hypothermia are considered important supportive measures. However, the approaches to stop intravascular coagulation and supplement coagulation factors are highly controversial. No controlled studies in human patients and animals have documented their benefit. Heparin at a dose of 50-250 IU/kg either every 4 hours or by constant infusion have been recommended; the goal has been a 1-2 fold prolongation of the PTT time above normal, but direct serum drug concentration measurements may also be helpful. Low molecular weight heparin has also been used, but cannot be monitored by the routine PTT. Other anti-thrombotic agents are also being investigated. Despite the assessment of various therapeutic strategies none have been documented to be effective in clinical practice in small animals with DIC.

References available from the author upon request.