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Medicine on a Budget
Mini Series

Session Two: “If you prick us, do we not bleed?” - Coagulation disorders in small animals

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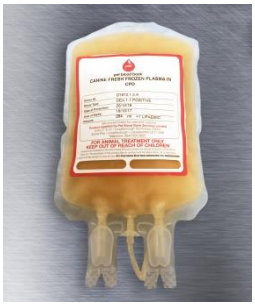

Coagulation

Laboratory haemostasis testing generally is divided into preanalytical, analytical (the test), and postanalytical (interpretation) phases. The preanalytical phase covers all aspects of preparation of the patient, collection of the sample, processing and storage, labelling, and submission. Haemostasis testing requires stringent attention to detail, particularly during the preanalytical phase, due to variation in interpretation associated with haematocrit, haemolysis, choice of anticoagulant, and fill volume (anticoagulant to whole-blood ratios). Discussions are ongoing in human medicine about the preanalytical phase (i.e., which test do I order for these clinical signs?), and interpretative haemostasis services can assist with all phases. Common preanalytical mistakes include inappropriate choice of anticoagulant (e.g., underfilling the citrate tube, or using EDTA instead of citrate), incorrect ratio of anticoagulant to blood, cooling or heating of samples, delayed laboratory transport and inappropriate centrifugation speeds. All of these factors can impact interpretation significantly and could lead to inappropriate therapeutic decisions. Strict adherence to sample collection and handling guidelines is essential for proper interpretation of the results.

History and Physical Exam

A comprehensive history of a patient with a suspected disorder of haemostasis must include previous bleeding episodes (e.g., associated with surgery), the anatomical distribution of bleeding, whether the bleeding was spontaneous or secondary to injury, and whether the bleeding was immediate or delayed. Breed, age at first episode, travel history, and current medication or toxin exposure should be recorded. Although both congenital and acquired bleeding disorders can cause bleeding anywhere, specific patterns can help to distinguish one bleeding disorder from the other. In general, acquired disorders typically first appear later in life. These patients often have no history of bleeding during previous surgeries (e.g., spay, castration) and could have comorbid conditions. Congenital bleeding disorders often manifest as bleeding episodes associated with challenge to the haemostatic system during youth.

A thorough physical examination is essential, with careful evaluation of the skin, eyes, joints, mucous membranes, urine, and faeces for evidence of bleeding. Disorders affecting the platelet and the vascular wall can include thrombocytopenia, thrombocytopathia, abnormalities of von Willebrand factor (vWF), and vasculitis. Thrombocytopenia can lead to petechiation if the platelet count is low, while thrombocytopathia, von Willebrand disease (vWD), and vasculitis more often cause mucosal surface bleeding and bruising. Coagulation factor deficiencies or disorders result in ecchymoses, haematomas, and/or muscle, joint, or body cavity bleeding. In animals at risk for thrombosis, a thorough evaluation of perfusion (e.g., careful palpation of pulses, extremity temperature, mentation, urine output) and the respiratory system are essential. Secondary evaluation of perfusion, to include ultrasound of suspected areas (e.g., distal aorta, femoral vessels, etc.), can be helpful in diagnosing peripheral thromboembolism. Evaluation of the respiratory system for pulmonary thromboembolism can reveal an oxygen deficit (tachypnea, pulse oximetry and PaO_2 below accepted range, increased alveolar-arterial gradient; with normal thoracic radiographs or mild radiographic changes incongruous with the severity of the clinical signs (e.g., minimal pleural effusion, loss of definition of the pulmonary artery, hyperlucent lung regions)

Sample Collection and Storage Methods

All specimens should be collected prior to therapeutic interventions. Elimination or minimization of preanalytical errors in collection and storage will optimize interpretability of results. Communicating with the laboratory regarding aspects that may affect the test (e.g., haemolysis, icterus, ingestion of a fatty meal) is important. Venipuncture, tube/additive selection, and storage are particularly important. Direct venipuncture into a Vacutainer is the preferred method of collection, as this approach results in less haemolysis than needle and syringe collection. Results for prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen for dogs have been demonstrated to agree clinically between the two collection methods. If using a central line for collection, flushing with heparinized saline followed by removal of at least 3 mL of blood from the catheter before specimen collection will minimize contamination with heparin, saline, or other fluids. The clearance blood may be returned to the patient but will have undergone some degree of contact activation.

Immediately following filling, tubes should be inverted 4-6 times. The preferred anticoagulant for complete blood count and platelet count is K^+EDTA, a chelating agent that binds calcium. Sodium citrate (3.2%, 1 : 9 ratio citrate to blood) is the anticoagulant of choice for most coagulation assays.

Tests of Platelets and the Vascular Wall

Platelet Count

Thrombocytopenia may be due to decreased platelet production, destruction, loss, or sequestration. Sources of error in automated counts include cells (i.e., microspherocytes, cell fragments) of similar size being counted as platelets, giant platelets being counted as other cells, and agglutination. Manual platelet estimates can be performed by evaluation of a peripheral blood smear using EDTA-anticoagulated blood or fresh samples.

Buccal Mucosal Bleeding Time (BMBT)

The BMBT should only be performed on a patient with a normal platelet count and coagulation panel.

Cuticle Bleeding Time (CBT)

The CBT test is unpredictable and unreliable, in addition to causing pain. Interpretation is affected by paw movement, which can disturb the forming haemostatic plug. Sedation or anaesthesia is often needed, especially if multiple nail cuts are required. The CBT test is not recommended in veterinary patients.

Platelet Function Testing

Options for detection of thrombocytopathia include impedance whole blood platelet aggregometry (WBA), plasma-based light transmission aggregometry, and a commercially available platelet function analyzer (PFA-100). There are also adaptations to thromboelastography/ometry (TE) for testing of thrombocytopathia. Aggregometry techniques, due to cost and requirements for trained personnel, have classically been used for research, but a rapid, automated multiple electrode aggregometry technique (Multiplate) has been developed for WBA with potential for clinical use.[15]

The PFA-100 measures time to cessation of whole blood flow (closing time) through a central aperture under high shear conditions. The membrane is coated with collagen and either epinephrine or adenosine-5'-diphosphate (ADP). The collagen/ADP cartridge has a higher sensitivity for canine platelets. Whole blood is collected in sodium citrate and held at room temperature prior to processing. The PFA-100 is easy to use and gives accurate and rapid results that are reproducible. Platelet aggregation is dependent on platelet number and function, as well as functional vWF. Results can be affected by holding time, anticoagulants, haematocrit and medications. The PFA-100 is used as a screening test to detect abnormalities of platelet function but is not specific for any particular disease. A normal PFA-100 closing time result generally rules out a severe platelet function defect or severe vWD, but milder forms of these diseases may still be present. The test had a 95.7% sensitivity and 100% specificity in dogs using the collagen/ADP cartridge in one report.

Tests of Coagulation

Prothrombin Time (PT)

The PT evaluates the tissue factor pathway (extrinsic; FVII) and the common pathway (FX, FV, prothrombin, fibrinogen. Citrated plasma is added to $CaCl_2$ and tissue factor in a lipid membrane (thromboplastin); the PT is the time until formation of the first fibrin strands. A prolonged PT (with a normal aPTT) indicates FVII deficiency. Heparin does not generally prolong the PT due to the inclusion of heparin antagonists in commercial PT reagents. Due to the short half-life of FVII, PT prolongation in vitamin K deficiency initially is due to FVII deficiency (not associated with bleeding), but the clinical bleeding occurs with development of prothrombin deficiency.

Activated Partial Thromboplastin Time (aPTT)

The aPTT evaluates the contact pathway (prekallikrein, FXII, FXI); the intrinsic pathway (VIII, IX); and the common pathway (FX, FV, prothrombin, fibrinogen). Note that the only coagulation factors that do not impact the aPTT are FVII and FXIII. Citrated plasma is incubated with a contact activator (e.g., celite, kaolin) and lipids to allow for the generation of FXIIa and FXIa, then recalcified to allow for downstream coagulation steps. The aPTT is the time from recalcification until formation of the first fibrin strands. A prolongation of the aPTT (with a normal PT) is consistent with deficiency of FXII, FXI (haemophilia C), FVIII (haemophilia A), FIX (haemophilia B), or with heparin therapy. Note that FXII deficiency (commonly seen in cats) is a clinically irrelevant incidental finding as it is not associated with clinical bleeding.

Conditions associated with prolongation of both the PT and aPTT include anticoagulant rodenticide exposure (vitamin K deficiency), liver disease, disseminated intravascular coagulation (DIC), and hypo- or dysfibrinogenemia.

Activated Clotting Time (ACT)

The ACT is a simple, rapid, inexpensive test that is similar to the aPTT (evaluating all factors except FVII and FXIII) except that it uses whole blood. The tube contains a contact activator, and the platelets in the blood sample provide the lipid surface; note that the ACT therefore can be prolonged with severe thrombocytopenia even when the coagulation cascade is intact. The ACT can screen for rodenticide intoxication, hemophilia, hepatopathy-associated coagulopathies, and DIC.

Factor Levels

Concentrations of individual coagulation factors can be measured using specialized modifications of the PT or aPTT. These tests usually only are available in specialized veterinary laboratories. Factor testing is required to confirm a suspicion of FXII deficiency, or haemophilia A, B, or C, in a patient with a normal PT but prolonged aPTT. The laboratory should be contacted prior to phlebotomy to discuss appropriate sample preparation and testing.

Tests of Fibrinogen and Fibrinolysis

Fibrinogen

Fibrinogen defects can be qualitative (dysfibrinogenemia) or quantitative (hypo- or afibrinogenaemia) and either acquired (consumption, decreased hepatic synthesis, or inhibitory antibodies) or congenital. In addition to its role in coagulation, fibrinogen is a strong acute phase reactant in dogs, with increases (hyperfibrinogenaemia) occurring during inflammation and infection. The most common assay for detection of fibrinogen activity is the Clauss method, which is coagulation assay based. Low fibrinogen concentrations measured by this method can indicate either hypofibrinogenaemia or dysfibrinogenaemia. With this method, false decreases can occur due to the presence of anticoagulants, elevations in FDP (fibrin[ogen] degradation product) concentrations, hypoalbuminaemia, factor XIII deficiency, or amyloidosis.

Thrombin Time (TT)

In the TT, citrated plasma is made to clot through the addition of thrombin. The TT is the time from recalcification until formation of the first fibrin strands. The TT is an indicator of fibrinogen concentration and/or function. As with the Clauss method, TT results can be increased due to the presence of anticoagulants, elevations in FDPs, hypoalbuminaemia, factor XIII deficiency and amyloidosis. Similar to the Clauss method, other factors may falsely prolong the TT.

Fibrin[ogen] Degradation Products (FDPs)

FDPs are created when plasmin lyses fibrinogen, soluble fibrin monomers, insoluble fibrin, and/or cross-linked fibrin. The presence of excess FDPs merely indicates plasmin activity; FDPs are not specific for cross-linked fibrin degradation. FDP concentrations can be increased in a variety of disorders, such as DIC, anticoagulant rodenticide intoxication, hepatic disease, thrombosis, IMHA, neoplasia, pancreatitis, gastric dilation-volvulus, heatstroke, and others.

D-dimer

D-dimers are a form of FDP that can only be generated from cross-linked fibrin. Most available assays are immunologic, with no cross-reactivity with fibrinogen or fibrin monomer fragments.

Increased D-dimer concentrations indicate thrombin generation, fibrin formation, cross-linking by FXIIIa, and plasmin activity. Because D-dimers have a short half-life, their presence indicates recent (≈5 hours) fibrinolysis. Increased D-dimer concentrations have been reported in dogs with IMHA, liver and renal disease, heart failure, neoplasia, internal haemorrhage, and after surgery. D-dimer assays are commercially available and require a single citrate sample, but not all assays designed for human samples cross-react with animal D-dimers.

Antithrombin (AT) Assay

AT is a member of the serine protease inhibitor (serpin) family. It is an important inhibitor of multiple coagulation enzymes, the most clinically relevant of which are thrombin and FXa. The inhibitory action of AT requires the binding of sulfated proteoglycans (either endothelial cell surface–associated heparans or pharmacologically delivered heparins). Plasma levels of AT can be evaluated via a chromogenic functional assay that measures the *in vitro* ability of AT (provided by the patient sample) to inhibit bovine FXa in the presence of added heparin (both provided by the assay kit). Because many animal AT molecules inhibit bovine FXa with different potency than does human FXa, the degree of inhibition is tested against a standard of pooled normal plasma from the species being tested. The results are then reported as a percentage of normal. AT deficiency is a known risk factor for development of thrombosis. Deficiency can occur due to decreased hepatic production, consumption associated with coagulation activation, or renal or enteric loss.

Vitamin K Deficiency

Vitamin K deficiency is one of the most commonly acquired coagulopathies in small animals and it usually is caused by ingestion of vitamin K antagonist rodenticides. Less common causes include decreased vitamin K synthesis from the intestinal microflora and decreased vitamin K absorption.

Vitamin K is an important cofactor in production and activation of the vitamin K–dependent coagulation factors II, VII, IX, and X, and the endogenous anticoagulant proteins C and S. Vitamin K in the reduced form is essential for carboxylation of the glutamic acid residues of these coagulation factors. Anticoagulant rodenticides antagonize vitamin K epoxide reductase, causing rapid depletion of the vitamin K–dependent coagulation factors. Factors II, VII, IX, and XI have relatively short half-lives (42, 6.2, 13.9, and 16.5 hours, respectively), and decreased factor levels can be detected shortly after anticoagulant rodenticide ingestion. Dogs and cats consuming rodents intoxicated with anticoagulant rodenticides are unlikely to have coagulopathies result, as the amount of rodenticide within the rodent is small.

Clinical signs of bleeding typically are observed 2-5 days after ingestion of anticoagulant rodenticide, and they include epistaxis, melena, haemoptysis, haematochezia, haematoma, ecchymoses, haematuria, and gingival bleeding. Other clinical signs include dyspnoea, coughing, lethargy, collapse, and pallor. Proteins induced by vitamin K absence/antagonism (PIVKA) levels start to increase within 12 hours of ingestion. PT will be prolonged within 36 to 72 hours, followed by prolongation of PTT and ACT. Blood and serum rodenticide concentrations peak within a few hours of ingestion; liver tissue at necropsy can be used for measuring rodenticide concentration.

A point-of-care test is available to detect anticoagulant rodenticide in blood, but it was only useful in detecting warfarin and not second-generation anticoagulant rodenticides in one dog study. A diagnosis of anticoagulant rodenticide intoxication usually is based on consistent history, clinical signs, and coagulation test results.

Following acute ingestion, emetics, adsorbents and cathartics should be given to minimize absorption. Most commercial anticoagulant rodenticides are second generation (bromadiolone, brodifacoum, and diphacinone) and have a half-life of 5-6 days; therefore, oral vitamin K_1 treatment is recommended for 2-4 weeks. It is so important to check product type and BSAVA guidelines before prescribing weeks' worth of vitamin K therapy. Prothrombin time typically normalizes 14-36 hours after starting vitamin K_1 therapy. Plasma transfusion quickly will replenish coagulation factors while awaiting the onset of effect of vitamin K_1 therapy, if clinical haemorrhage is significant. Red blood cell transfusion can be necessary in severe haemorrhage cases. Prothrombin time should be rechecked 36-48 hours after discontinuing vitamin K_1 therapy to ensure normal coagulation status and sufficient treatment duration.

Hepatic Failure

The liver is responsible for synthesizing most pro- and anticoagulant factors, and it plays a central role in haemostasis. Most patients with liver disease have a parallel decline in pro- and anticoagulant proteins, resulting in a relatively balanced haemostatic system *in vivo* in initial disease stages. *In vitro* haemostatic defects (prolonged PT/PTT) commonly are detected in patients with liver disease, but clinical bleeding is uncommon and usually is associated with fulminant or end-stage liver failure. Vitamin K deficiency can result from liver disease and it can exacerbate coagulation factor deficiency.

Given the complex and multiple effects that liver disease has on haemostasis, bleeding and/or thrombosis can be consequences. In people with liver failure, the following abnormalities favouring bleeding have been reported: thrombocytopenia, thrombocytopathia, and vessel wall interaction, decreased levels of coagulation factors II, V, VII, IX, X, XI, dysfibrinogenemia, and decreased alpha$_2$-antiplasmin. The following abnormalities favoring thrombosis have been reported: elevated levels of factor VIII and von Willebrand factor and decreased levels of proteins C and S, antithrombin, and plasminogen.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a systemic activation of coagulation, leading to intravascular fibrin deposition, thrombosis, and organ dysfunction. DIC is a consumptive coagulopathy that can result from many systemic diseases including widespread inflammation, sepsis, and neoplasia.

Tissue factor is a primary mediator of DIC. Normally, tissue factor is not exposed to the circulating blood. However, in states of inflammation and other diseases, proinflammatory cytokines and endotoxins induce tissue factor expression and release. High concentrations of tissue factor can be found on circulating monocytes, endothelial cells, neoplastic cells, microparticles, and other sources. Once in circulation, tissue factor forms a complex with activated factor VII, a potent stimulus for thrombin formation. Excess circulating thrombin cleaves fibrinogen, leaving behind multiple fibrin clots that can lead to microvascular and macrovascular thrombosis.

Coagulation inhibitors are consumed in the process, further promoting coagulation. As clots form, platelets become entrapped and thrombocytopenia is identified. Simultaneously, excess circulating thrombin results in the conversion of plasminogen to plasmin, leading to fibrinolysis. Fibrinolysis results in excess amounts of fibrinogen degradation products (FDPs), which have anticoagulant properties, possibly contributing to haemorrhage. Excess plasmin also activates the complement and kinin systems, leading to clinical signs such as shock, hypotension, and increased vascular permeability.

During the initial (nonovert, or compensated) stages of DIC, patients are in a hypercoagulable phase. However, procoagulant factors progressively become consumed, leading to a hypocoagulable (overt, or uncompensated) phase. Prolonged coagulation times accompanied by clinical signs of bleeding may be apparent in the hypocoagulable phase. Patients in acute, fulminant DIC present with bleeding; however, in more chronic forms, patients might show signs only related to the underlying disorder.

The diagnosis of DIC can be challenging due to the condition's dynamic nature and considerable variation in coagulation profiles of affected patients. Any animal having experienced prolonged hypotension, systemic inflammatory response syndrome, disturbed blood flow to a major organ, or major tissue trauma is at high risk of developing DIC. A combination of clinical and laboratory findings is used for identifying DIC. Typical laboratory findings include prolongation of coagulation times, thrombocytopenia, elevation of fibrinolysis markers (D-dimers and FDPs), hypofibrinogenaemia, decreased antithrombin, and signs of red blood cell fragmentation on the blood smear. Viscoelastic testing can be used for distinguishing between the various stages of DIC in dogs. In one study, the majority of patients suspected to be in DIC were found to have hypercoagulable tracings. In this study, mortality was associated with high D-dimer concentrations, low antithrombin concentrations, and hypocoagulable TEG tracings compared to survivors. Earlier diagnosis of DIC could lead to more prompt intervention, potentially improving survival times. However, viscoelastic test results can be confounded by anaemia, thrombocytopenia, and hyperfibrinogenaemia, potentially complicating efforts to understand the *in vivo* coagulation status of a patient with DIC.

Treatment of DIC should start by first treating the underlying condition (e.g., antimicrobials for septic patients). Intravenous fluids and oxygen therapy will promote perfusion and tissue oxygenation. Therapeutic recommendations to address consequences of DIC are controversial. Heparin therapy commonly is used in the hypercoagulable phase of DIC, despite few reports documenting its true benefit. Heparin is an indirect anticoagulant, exerting most of its effect through potentiation of antithrombin activity, which can be diminished in states of DIC. Heparin does not eliminate existing thrombi but could prevent the formation of new thrombi. Use of heparin in veterinary DIC patients has been reported, but optimal dosing regimens are not known. Increased morbidity has been reported in people with DIC who receive heparin while actively bleeding; heparin therapy should be avoided in veterinary patients with DIC and evidence of bleeding. Prophylactic plasma transfusion does not show a consistent benefit in humans with DIC, and plasma transfusions usually are recommended only in patients with clinical signs of bleeding. Similarly, fresh frozen plasma or cryoprecipitate therapy is recommended in veterinary patients with DIC and signs of bleeding secondary to factor deficiency.

The overall prognosis for DIC is poor and it varies depending on the underlying disorder. Early diagnosis and intervention could lead to improved prognosis.

Acquired Anticoagulants

Spontaneous development of coagulation inhibitors rarely is reported in veterinary patients. Coagulation inhibitors are antibodies (usually IgG) that bind to and inhibit activity of coagulation factor, or cause increased coagulation factor clearance. Acquired anticoagulants can develop secondary to immune-mediated disease, drug reaction, lymphoproliferative disease and other neoplasia, DIC, and following multiple blood transfusions. Antiphospholipid protein antibody (i.e., lupus anticoagulant) inhibits interaction between coagulation proteins and cell membranes, causing prolongation of coagulation times such as PTT. Paradoxically, presence of antiphospholipid protein antibodies is associated clinically with thrombosis. Antiphospholipid protein antibodies are reported rarely in veterinary medicine. Development of factor VIII or IX inhibitory antibodies is a reported consequence of multiple transfusions of humans and dogs with haemophilia.

Clinical signs related to acquired anticoagulants can be absent or can include signs of haemorrhage. Because other aspects of haemostasis might be disrupted, hypercoagulability and thrombosis can be observed concurrently. Coagulation times (PT, PTT) are abnormal depending on which factor(s) is/are affected. A plasma mixing test can be used for supporting a diagnosis of acquired anticoagulant. In this test, various dilutions of patient and control plasma are incubated. If an inhibitor is present, coagulation factor activity in the control plasma will be inhibited and the coagulation test remains abnormal. Confirmatory testing with specific assays can be performed.

General Treatment of Acquired Hypocoagulability

Therapy to address the underlying disorder for hypocoagulability is recommended when possible. Vitamin K_1 therapy is recommended in anticoagulant rodenticide intoxication cases and in liver dysfunction causing coagulopathy. An initial dose of 2.5-5 mg/kg SC or PO, followed 6-12 hours later with maintenance therapy (0.8-1.7 mg/kg PO q 8 h) can be given. Vitamin K_1 should never be given intravenously as it has been associated with anaphylaxis. Vitamin K_3 therapy is not recommended due to slower onset of action and possible Heinz body formation.

Plasma transfusions can temporarily replenish coagulation factors. Plasma usually is administered at an initial dosage of 10-20 mL/kg. Fresh frozen plasma contains all coagulation factors and plasma proteins, including the labile coagulation factors (V and VIII). Cryoprecipitate primarily contains factors VIII and XIII, von Willebrand factor, fibrinogen, and fibronectin, at approximately 50-80% of the levels as fresh frozen plasma but in a smaller volume. Cryosupernatant, or cryo-poor plasma, has sufficient quantities of most coagulation factors except for those contained in cryoprecipitate. In comparison, stored plasma contains significantly lower concentrations of factors V and VIII but contains adequate levels of vitamin K-dependent factors and other plasma proteins. Either fresh frozen or stored plasma is suitable for replacement of vitamin K-dependent factors, as well as for treatment of other factor deficiencies. Fresh frozen plasma is recommended in patients showing signs of hemorrhage secondary to liver disease or DIC.

Hereditary Factor Deficiencies

Single or combined factor deficiencies produce variable clinical signs ranging from asymptomatic states to severe bleeding tendencies. Depending on the deficient factor(s), prolongation of PT and/or PTT is observed. Measurement of individual coagulation factor activity is required for definitive diagnosis. Genetic testing also is available for some inherited coagulation disorders.

Hemophilia A and B

Haemophilia A is a deficiency of factor VIII, and haemophilia B is a deficiency of factor IX. Haemophilia A is more common than haemophilia B, and both forms have been documented in dogs and cats. Haemophilia A and B are autosomal, X-linked, recessive traits, primarily affecting males while females are carriers. Various genetic mutations are responsible for haemophilia A or B. In some cases, haemophilia within a pedigree can be traced to the original index animal, whereas other cases are suspected to arise from *de novo* mutations.

Lack of factor VIII or IX inhibits formation of the tenase complex, hindering downstream thrombin generation and blood clot formation. Accordingly, haemorrhage is the principal clinical sign associated with haemophilia A or B, and this haemorrhage typically can manifest as prolonged bleeding after trauma or surgery, subcutaneous or intramuscular haematomas, mucosal bleeding, or lameness due to haemarthrosis.

Haemophilia A or B is suspected in patients with a bleeding diathesis and prolonged PTT or ACT, with a concurrently normal PT. Measurement of coagulation factor activity (FVIII:C or FIX:C) is required for a definitive diagnosis. Normal factor activity levels are 50-150%. Haemophilia is considered mild when the corresponding factor level is ≈6-20%; moderate and marked haemophilia can be defined when factor levels are ≈2-5% and <2%, respectively. Severity of factor deficiency correlates with clinical signs in affected people, although additional variables such as function of other haemostatic proteins, the patient's physical condition, and concurrent illness play a role. Occurrence of spontaneous bleeding episodes was not significantly different between dogs with mild, moderate, and severe haemophilia A in one study.

Depending on the severity of haemorrhage episodes, transfusion can be used for replacing deficient factors and alleviating short-term bleeding. While injection of desmopressin temporarily increases circulating factor VIII concentrations in people, the same does not appear to be true in dogs. Prophylactic transfusion might be warranted in patients with haemophilia prior to performing invasive procedures.

The prognosis for dogs and cats with haemophilia appears variable. Severely affected animals likely die at birth. Prognosis did not correlate with degree of factor deficiency in dogs with haemophilia A in one study. Following transfusion, the patient can develop inhibitors to the deficient factor (i.e., factor VIII or IX inhibitors), leading to higher transfusion requirements on subsequent transfusions. Post-transfusion purpura was reported in a dog with haemophilia A and was successfully treated with corticosteroids. Pedigree analysis and factor activity levels should be analyzed in breeding groups that have given rise to individuals affected by haemophilia.

Factor levels often are low-normal in carrier females and can overlap with those of unaffected females, making it difficult to determine carrier status based on factor analysis alone. Lack of clinical signs in carrier or mildly affected animals can lead to propagation of the condition through a pedigree.

Other Inherited Coagulation Factor Deficiencies

Hereditary fibrinogen (factor I) disorders include complete or partial lack of fibrinogen (afibrinogenaemia and hypofibrinogenaemia, respectively) and qualitative defects in fibrinogen (dysfibrinogenemia). Disorders of fibrinogen appear to be uncommon in dogs but have been reported. Depending on the severity of the disorder, haemorrhage might occur spontaneously or after trauma or surgery. Paradoxically, affected patients also can have thrombosis. Fibrinogen defects can be suspected when PT, PTT, ACT, and TCT are prolonged; quantitative fibrinogen disorders will have a concurrently decreased fibrinogen concentration. Patients with dysfibrinogenaemia typically have normal to low fibrinogen concentrations and low functional fibrinogen activity. Due to the uncommon nature of hereditary fibrinogen disorders, more common causes of low fibrinogen concentrations such as DIC or liver disease should be ruled out first.

Other inherited factor deficiencies resulting in haemorrhage have been described, including factor II deficiency in dogs; factor VII deficiency in dogs; factor X deficiency in dogs and cats; factor XI deficiency in dogs and cats; and factor XIII deficiency in a dog.

Feline factor XII deficiency (Hageman trait) is the most common defect of the intrinsic (contact) pathway factors. Cats with factor XII deficiency demonstrate prolonged PTT, but haemorrhage or other clinical signs do not result from this deficiency as *in vivo* clot formation is primarily dependent on factor VII and tissue factor activation. Concurrent haemophilia A or B has been reported in cats with factor XII deficiency, and it can give rise to clinical signs of haemorrhage.

Treatment of Inherited Coagulopathies

Single or combined factor deficiencies can be treated using a plasma product transfusion to temporarily replenish the deficient factor(s) during episodes of haemorrhage. Plasma dosages are similar to those outlined above for acquired coagulopathies. Fresh frozen plasma can be used for most factor deficiencies, including haemophilia A. Stored plasma lacks factors V and VIII but can be used to treat other factor deficiencies. Cryoprecipitate is suitable for transfusing smaller plasma volumes rich in factors I, VIII, and XIII; cryosupernatant is lacking in those factors but can be used for treating other deficiencies. Factor XII deficiency does not require treatment as it does not result in clinical signs.