Bleeding disorders: causes and treatment

Daria Starybrat DVM MRCVS; Joy Fenner BVM BVS CertAVP(ECC) MRCVS; Simon Tappin MA VetMB CertSAM DipECVIM-CA MRCVS, Dick White Referrals, The Six Mile Bottom Veterinary Specialist Centre, Station Farm, Cambridgeshire, UK,
review normal haemostasis before outlining the diagnostic approach, therapies and specific causes of abnormal coagulation

Figure 1: Marked haematemesis in a dog with rodenticide toxicity.

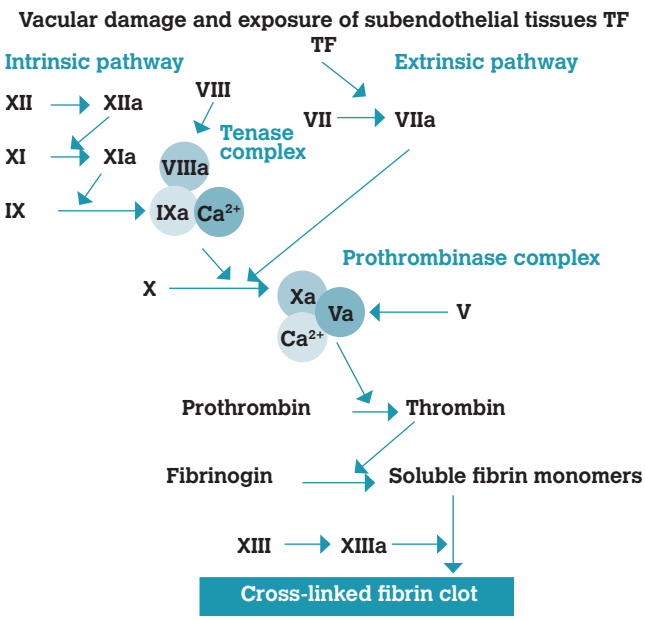

Figure 2: The classic coagulation cascade with the intrinsic and extrinsic pathways leading to the formation of fibrin.

Classically, haemostasis is divided into three different phases. Whilst this helps with understanding of the mechanics of coagulation, it is important to understand, all phases overlap. Primary haemostasis occurs first with damage to blood vessels leading to vasoconstriction and the formation of a platelet plug. This is followed by secondary haemostasis, the clotting cascade, which results in formation of fibrin. Lastly, tertiary haemostasis allows breakdown of the fibrin clot (fibrinolysis) and healing of the vessels wall.

Animals with bleeding disorders often present with spectacular and obvious blood loss (see Figure 1), although some animals are relatively stable with minimal clinical signs. All suspected coagulopathies should always be considered as potential life-threatening conditions due to the possibility of haemorrhage leading to acute deterioration. Rapid diagnosis of the exact cause of bleeding as a primary, secondary or tertiary disorder will allow appropriate treatment and improved case management.

PRIMARY HAEMOSTASIS

Primary haemostasis refers to the initial phase of haemostasis that leads to clot formation. When a blood vessel is damaged, the initial response is vasoconstriction (mediated by thromboxane A_2, serotonin and adrenaline produced by platelets and the endothelium) followed by formation of a platelet plug. This requires functioning blood vessels, adequate numbers of functioning platelets and platelet adhesion factors (including von Willebrand Factor [vWF]). Platelets adhere to subendothelial collagen via an interaction with vWF and the platelet receptor GP1b. Binding of this receptor activates the platelet changing its shape to develop multiple pseudopods, which project in numerous directions. Activation allows aggregation of platelets into a plug through vWF binding to GP11a/IIIb receptors. Activation also exposes platelet factor 3 (PF3), which provides scaffolding onto which fibrin can then be deposited following secondary haemostasis.

SECONDARY HAEMOSTASIS

Secondary haemostasis results in the formation of fibrin, classically through the traditional enzyme cascade model that divides secondary haemostasis into the intrinsic,

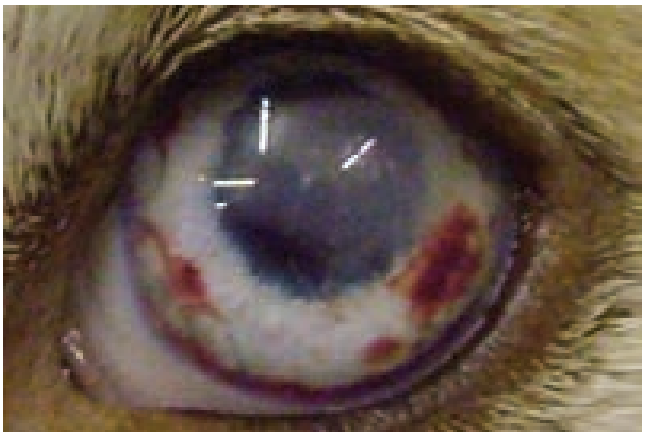

Figure 3: Petechial haemorrhage on the iris of a Siberian Husky with immune-mediated thrombocytopenia.

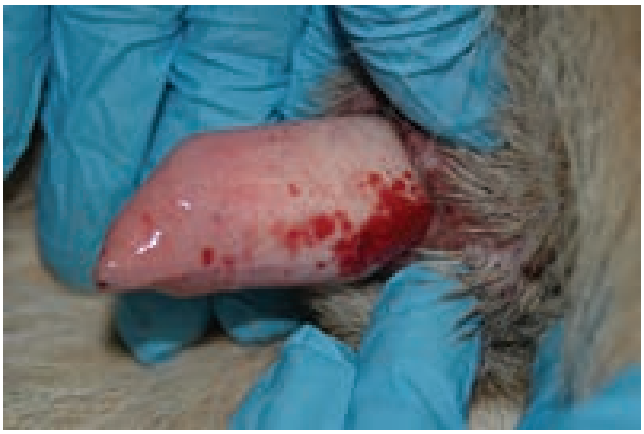

Figure 4: Petechial haemorrhage and ecchymosis on the penis of a dog with immune-mediated thrombocytopenia.

extrinsic and common pathways (MacFarlane, 1964). Tissue factor initiates the clotting cascade on the extrinsic side, which is then amplified in the intrinsic pathway. Thrombin generation activates platelets and provides the major feedback loop for further activation of the clotting cascade (see Figure 2). The majority of the clotting factors involved in the process are produced in the liver with vitamin K needed for the production of factors II, VII, IX and X as well as protein C and protein S. A more complex, and more physiologically accurate, model describes the cell-based model for coagulation, enhancing the role of interaction of coagulation proteins and cell surfaces, in particular, the surface of the platelet (Hoffman and Monroe, 2001). This then leads to three stages of initiation, amplification and propagation, ultimately leading to the formation of fibrin as per the classic common pathway. Combination of both models illustrates how the extrinsic pathway initiates a coagulation process and is then amplified by the intrinsic pathway.

TERTIARY HAEMOSTASIS

Processes leading to clot formation are balanced by reactions aiming to prevent clot formation within the vessels and breakdown of clots already created (Ganong, 2005). Plasmin (fibrynolysin), product of activation of inactive plasminogen, is an active enzyme that lyses fibrin and fibrinogen. Fibrinolysis is initiated by the same processes that activated the clotting cascade, with plasmin formation in the area local to the clot. Plasmin cleaves fibrinogen and fibrin, leading to the formation of various measurable fibrin degradation products, and cleaves cross-linked fibrin into fibrinogen degradation products (FDP) such as D-dimers.

DIAGNOSIS

Immediate and systemic diagnostic approach is crucial and the clinician should strive to answer a few key questions:

- Does the patient have a systemic bleeding disorder or does the bleeding result from local agents (eg. trauma)?
- If a presence of the bleeding defect is confirmed, is it due to defects in primary, secondary or tertiary haemostasis (or a combination of these)?
- Is the bleeding disorder likely to be inherited or acquired?

HISTORY AND PHYSICAL EXAMINATION

After initial triage and stabilisation a thorough history and clinical examination should take place. Owners can seek veterinary attention for investigation and management of evident bleeding. Equally, a patient may be presented to a veterinary practice with signs that owners rarely associate with occult bleeding (eg. pulmonary haemorrhage presenting as dyspnoea). Signalement is important as a young dog may have inherited disease, which is almost always due to a single defect in the coagulation cascade. Some present at less than six months of age, but von Willebrand's factor deficiency may not become apparent until after surgery or trauma. Adult animals are more likely to suffer from an acquired disorder. There are also some breed predispositions for example, immune-mediated thrombocytopenia in Cocker Spaniels or delayed postoperative bleeding in greyhounds. (Silverstein and Hopper, 2015). Additionally, not all defects cause bleeding, such as the deficiency of factor XII, which causes significant prolongation of coagulation times without clinical bleeding tendencies.

Establishing whether the bleeding was spontaneous or due to trauma is an important aspect of history. Spontaneous bleeding is more suggestive of thrombocytopenia, vitamin K deficiency and some inherited disorders (haemophilia). Pre-existing medical conditions (eg. hepatic or renal disease) or medications (eg. NSAIDs, beta-blockers, barbiturates) ought to be identified as these can trigger immune-mediated conditions or precipitate pre-existing coagulopathies. A history of travel abroad should be established, although with the increase of previously only continental diseases in the UK, this can't completely exclude previously foreign parasitic disorders, such as *Erhlichia*. Additionally, potential exposure to rodenticides should be taken into consideration, especially in free-roaming animals or those with a history of hunting.

Animals with coagulation disorders vary widely in their presentation depending on the severity of the disease and any inciting trauma to blood vessels. In general, animals with defects in primary haemostasis present with petechial haemorrhages [which are only seen in primary disorders] and bleeding from mucosal surfaces (for example epistaxis,

- Disorders of blood wall vessels, eg. vasculitis leading to increased vascular fragility.
- Thrombocytopenia
- Bone marrow disease leading to reduced production
- Platelet destruction (primary or secondary immune-mediated thrombocytopenia)
- Platelet consumption, eg. DIC, haemorrhage, haemangiosarcoma, heartworm
- Abnormal platelet function
- Inherited disorders
- von Willebrand Disease (vWD)
- Thrombocytopathia, eg. Glanzmann's thrombasthenia
- Acquired disorders
- Renal disease
- Aspirin administration

Table 1: Common differential diagnoses for primary haemostatic disorders.

Manual evaluation of a blood smear is essential for the accurate conformation of platelet numbers. Platelets clump easily and as a consequence may not be counted correctly during automated counting. Similarly, machines that count platelets by size alone may be confused by the presence of small red cells (counting them as platelets) or macrothrombocytes (counting them as red blood cells). If clumping is a consistent problem, then citrate anticoagulant, rather than EDTA can be used. Some breed variation occurs with greyhounds having normal platelet counts in a range lower than other breeds and Cavalier King Charles Spaniels normally have circulating macrothrombocytes.

Evaluation of a blood smear is achievable with a practice microscope and in house stains. A blood smear should be prepared as soon after sampling as possible to reduce the possibility of the platelets clumping and stained once dry. This should be evaluated firstly under low power to evaluate the smear quality and overall pattern, then under oil emersion (x100) to evaluate the platelet numbers specifically. Platelets should be counted in the area just behind the feathered edge, where the red cells are just touching one another.

A manual platelet count can be evaluated as each platelet counted manually per high power field is equivalent to roughly $15x10^9$/L platelets. Several areas should be examined and the count averaged. The edges of the smear should be examined for platelet clumps and the blood tube also examined for potential clots. If platelet clumps are present, an accurate count can not be established but an overall impression of adequate platelet numbers may be achieved. Macrothrombocytes may be present and can indicate regenerative thrombopoiesis. These platelet precursors are also functional, with primary coagulation being more proportional to the volume of platelets rather than the actual number of platelets present.

Table 2: Manual evaluation of platelet counts.

gastrointestinal bleeding, haematuria). Mucous membranes (oral, ocular, rectal and the prepuce or vulva) should be carefully checked; clipping fur sometimes reveals an area of haemorrhage (see Figures 3 and 4). Clinical signs in animals with defects of secondary haemostasis are often more dramatic than the primary defects. Haemorrhages into body cavities (pleural space, peritoneal space, lungs, joints) are often seen, as well as larger ecchymotic haemorrhages in subcutaneous tissues. Re-bleeding after an initial platelet plug has failed to stabilise, may also occur.

TESTING PRIMARY HAEMOSTATIC

Primary haemostasis requires adequate numbers and

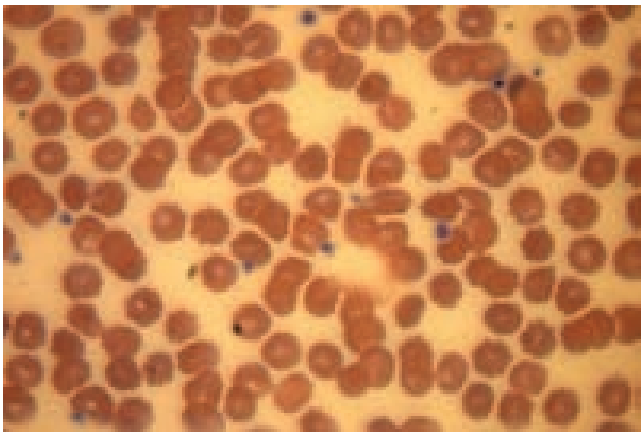

Figure 5: Normal numbers of platelets.

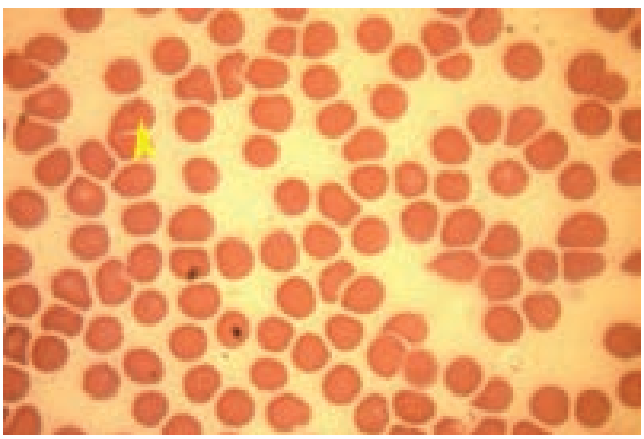

Figure 6: Severe thrombocytopenia.

adequately functioning platelets. Reduced platelet numbers or inadequate platelet function (eg. vWD) or a thrombocytopathia) will lead to signs of a primary coagulopathy (see Table 1). Platelet numbers are measured by an automated or manual platelet count and platelet function assessed most easily by measuring a buccal mucosal bleeding time. If a platelet count is low on a machine analyser, it is important to perform a blood smear and manual count to confirm platelet numbers (see Figures 5-8 and Table 2). As a rough rule of thumb, spontaneous bleeding usually occurs if the platelet count falls below $30x10^9$/l and bleeding following surgery or trauma if the platelet count is less than $50x10^9$/L.

If platelet count is normal (200-$500x10^9$/L) and a primary disorder is still suspected, a buccal mucosal bleeding time should be performed which assess platelet function and vWF levels, testing the formation of a platelet plug, independent of fibrin formation. Buccal mucosal bleeding time should not be performed in patients with a severe thrombocytopenia and is performed by tying the upper lip upwards reasonably with open weave bandage, to slightly impair venous return. A shallow cut in the lip is made with a standard spring-loaded device and timing started. Excess blood is blotted with paper towel or filter paper from the edge of the cut. It is important not to touch the incision or to disrupt the clot. The normal range is 1.5 to 4.5 minutes in dogs and one to 2.5 minutes in cats. This will be slightly longer (but <5 minutes)

The Dept of Agriculture Sick Leave Scheme Has Been Halved: Could You Afford To Be Sick?

TAILORED INCOME PROTECTION FOR VETS

In recent times, the Dept of Agriculture Sick Leave Scheme has been halved, down to three months full pay / three months half. If you became unwell due to accident or illness, would you be able to maintain your cost of living beyond three months?

Income Protection Cover provides a payment benefit that commences when your Dept of Agriculture Sick Leave Scheme benefit reduces and ultimately ceases. This ensures a continuance of salary so that you can maintain your standard of living and focus on your recovery.

www.omegafinancial.ie/vets

OFM Financial Ltd t/a Omega Financial Management is regulated by the Central Bank of Ireland

FIND OUT MORE / REQUEST A QUOTE:

1850 260 261
info@omegafinancial.ie

Omega Financial Management

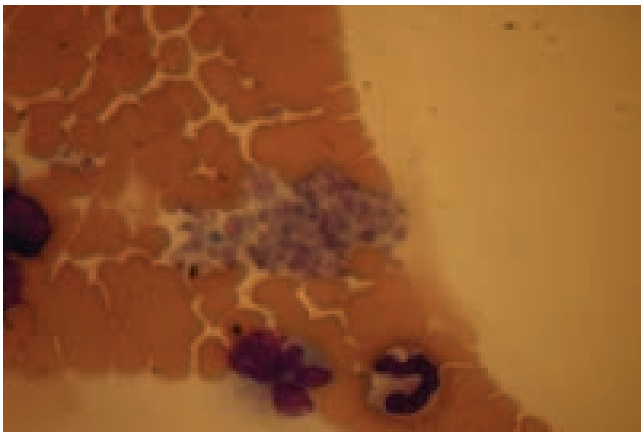

Figure 7: Platelet clump at the feathered edge.

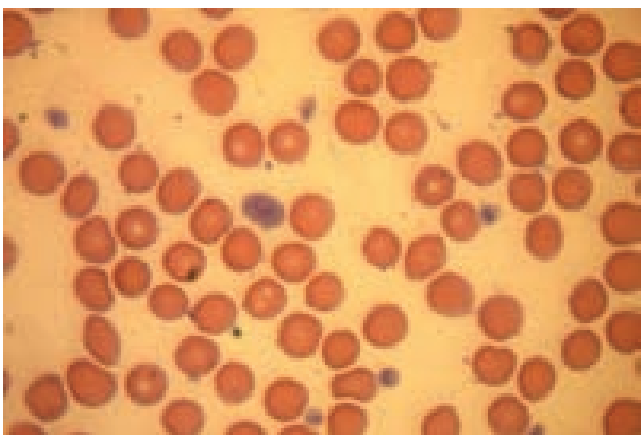

Figure 8: Macrothrombocyte (blue arrow).

in sedated or anaesthetised animals. The buccal mucosal bleeding test will detect dogs with severe vWF deficiency, but may miss those that are slightly affected.

Further assessment of platelet function is difficult as platelet function tests are not readily available. Platelet function tests assessing aggregation need to be performed immediately on fresh blood, so, at present, are more of a research tool than applicable to clinical cases.

Flow cytometry assessing the expression of GPIIb/IIIa, which is produced when platelets become activated, is also useful as a research tool. Specific measurement of vWF is available at specific laboratories and the individual is tested for the amount of vWF (by ELISA or immunoelectrophoresis) present compared to normal pooled plasma. The value is expressed as a percentage with greater than 70% being normal 50-70% being equivocal and may suggest the animal is a carrier and less than 50% confirming the animal has von Willebrand disease. Specific DNA tests are also available for some breeds with identified point mutations (for example Scottish terriers), however, they will not predict disease severity.

TESTING SECONDARY HAEMOSTASIS

Significant deficiencies in one of more coagulation factor lead to reduced fibrin production and signs of a secondary coagulopathy.

These are usually evaluated by measuring the activated partial thromboplastin time (aPTT), which recognises

- **Inherited disorders**
- **Factor VIII deficiency (haemophilia A)**
- **Factor IX deficiency (haemophilia B)**
- **Factor X deficiency**
- **Factor XII (Hageman factor) deficiency seen in various cat breeds and rarely clinically significant**
- **Acquired disorders**
- **Vitamin K-dependent coagulopathies**
- **Rodenticide toxicity (antagonism of vitamin K)**
- **Severe intestinal disease causing lack of absorption of vitamin K (for example exocrine pancreatic insufficiency, bile duct obstruction)**
- **Severe hepatic disease leading to reduced production and a lack of activation of vitamin K-dependent factors**
- **Disseminated intravascular coagulation**

Table 3: Common differential diagnoses for secondary haemostatic disorders.

deficiencies of intrinsic and common pathway, while prothrombin time (PT) evaluates the extrinsic and common pathways (Stokol, 2005). To see an elevation in either test requires over 70% of the normal factor level to be depleted. In case of depletion of multiple clotting factors PT prolongation will be noted first due to short half-life of factor VII (four to six hours).

Prolongation of aPTT will follow when other factors get depleted but that takes approximately two days. (Stokol, 2005), When measuring PT and aPTT good blood sampling technique is required as tissue damage and release of tissue factor will invalidate the sample. The sample needs to be spun within 20 minutes of collection to separate plasma from the cells. The correct anticoagulant to blood ratio is also extremely important.

Recent advances in in-house analysers have allowed coagulation testing to become more accessible to general practitioners. Most benchtop analysers require a small amount of whole or citrated blood samples and produce results within minutes guiding further diagnostic work up and treatment. If access to a coagulation testing is not possible then the activated clotting time (ACT) or whole blood-clotting time can be measured. The ACT detects defects in intrinsic and common pathways but is less sensitive than aPTT and unlike aPTT relies on patient's platelets and calcium to support the reaction. For this reason, ACT will be prolonged in animals with severe thrombocytopenia.

To measure the whole blood clotting time 2mls of whole blood are put in a glass (this is important do not use plastic) tube and kept at 37°C. The time to beginning of clot formation is recorded. Times of three to 13 minutes are recorded in normal animals. It is important to remember that platelets are needed to active this test, so prolonged times will be present in thrombocytopenic patients

If indicated, specific factor assays can be performed to diagnose specific factor deficiencies (for example, haemophilia A and B).

Patient plasma is used to try to correct known deficiencies in test plasma. If the test comes back normal, the patient does not have that deficiency. A single-factor deficiency of <30% of normal is likely to be significant. Plasma has to be submitted to a specialised laboratory and results usually take several days to return which may necessitate the initiation of treatment prior to specific diagnosis.

TESTING TERTIARY HAEMOSTASIS

Elevation of D-dimer levels, a product specific for active coagulation and fibrinolysis, is indicative of continuous fibrinolysis due to D-dimer's short half-life (approximately five hours). Increase in its values can be noted in conditions such as disseminated intravascular coagulation (DIC), hepatic or renal disease, neoplasia or thromboembolism.

Some coagulation screening profiles include measurement of fibrinogen levels. Increase in fibrinogen levels is nonspecific as fibrinogen is one of the acute phase proteins and its production might increase in response to inflammation. Its elevation has been also noted in renal disease in cats. Decreased levels of fibrinogen carry more significant diagnostic value as they may indicate liver failure or excessive fibrinogen consumption often witnessed in DIC (see Table 4).

THERAPEUTIC APPROACH

In general, patients with signs of spontaneous bleeding, need intensive treatment. Stress and excitement should be avoided, trauma minimised and exercise limited to cage rest or short lead or harness walks. Venipuncture should be limited to peripheral veins and whenever possible small gauge needles should be used. Venipuncture site should be compressed for several minutes after blood collection and a compressive dressing applied after the pressure is released. Invasive procedures, such as cystocentesis or fine needle aspiration of parenchymal organs, are generally strongly discouraged as they might cause further blood loss.

Shock, a severe and life-threatening complication of bleeding disorders, should be recognised and promptly addressed with appropriate fluid therapy to improve perfusion as failure to do so may exacerbate bleeding further. Rapid correction of the underlying disorder with simultaneous attempts to limit any local bleeding is required in these patients. Clinicians should monitor the patient for ongoing and new sources of blood loss and associated complications, such as pulmonary haemorrhage. Acidemia, hypothermia and haemodilution may also worsen the coagulopathy and clinician should take these factors into consideration when designing treatment plan (Silverstein and Hopper, 2015). Use of specific medications and blood-product transfusions depends on the aetiology of the disorder. Severe bleeding resulting from thrombocytopaenia or thrombocytopathia poses a therapeutic challenge. Platelet rich plasma (PRP) and platelet concentrates (PC) offer product with high concentration of platelets but due to the difficulty in acquiring those and short shelf-life their use is often limited to institutions that produce them. Cryopreserved platelets (platelet concentrates stored in DMSO solutions) offer longer storage time but their availability is limited outside the US. As a result, fresh whole blood (FWB) remains the product most commonly used for treatment of thrombocytopaenia. The average concentration of platelets in a unit of canine FWB is around $70x10^9$/l. Fresh whole blood administered at the dose of 10ml/kg is expected to raise the platelet count by $10x10^9$/l (Hux and Martin, 2012). Administration of such dose to a bleeding patient may not be sufficient to stop active bleeding so continuous monitoring is advisable. Anaemic thrombocytopaenic patient might benefit from the FWB transfusion but in non-anaemic patients with thrombocytopaenia the transfusion might lead to volume overload and polycythaemia, this is especially important to consider if the patient has underlying heart disease.

Severe bleeding caused by disorders of secondary haemostasis can be addressed by transfusion of plasma products (see Table 5). In veterinary medicine fresh frozen plasma (FFP) is the most commonly used plasma product as it contains all clotting factors including vWF. The total dose of 10-30ml/kg (in some instances higher dose might be necessary) is required to control haemorrhage resulting from disorders of secondary haemostasis (Mathews, 2006). Vitamin K deficiency should be treated with vitamin K^1 administration and should be injected subcutaneously with a small gauge needle (intravenous administration is discouraged due to high risk of anaphylaxis). Bioavailability of vitamin K^1 is better when administered orally, therefore, the patient should be switched to tablets at the earliest opportunity.

Plasma product	Indications
Canine fresh frozen plasma	Any coagulation factor deficiencies
Canine frozen plasma (stored plasma)	Vitamin K-dependant factors (II, VII, IX, X)
Canine cryo-precipitate	vWD, factor I and factor VIII deficiencies
Canine cryo-supernatant (crypoor plasma)	Vitamin K-dependant factors (II, VII, IX, X)

Table 5: Indications for use of plasma products.

SPECIFIC DISORDERS OF PRIMARY HAEMOSTASIS

THROMBOCYTOPATHIA

Problems with platelet function are rare but occur when

Disorder	Platelets	BMBT	PT	aPTT	ACT	Fibrinogen	D-dimer
Thrombocytopenia	↓	↑	N	N	N	N	N
Thrombocytopathia	N	↑	N	N	N	N	N
vWD	N	↑	N	N/↑	N/↑	N	N
Haemophilias	N	N	N	↑	↑	N	N
Rodenticide toxicity	N/↓	N/↑	↑	↑	↑	N/↓	N/↑
Hepatic failure	N/↓	N/↑	N/↑	↑	↑	N/↓	N
DIC	↓	↑	↑	↑	↑	N/↓	↑

Table 4: Laboratory changes expected in common bleeding disorders. BMBT – buccal mucosal bleeding time, PT – prothrombin time, aPTT – activated partial thromboplastin time, ACT – activated coagulation test, vWD – von Willebrand disease, N – normal, ↓-reduced or shortened, ↑ high or prolonged.

1. **Prevent further bleeding. No jugular sampling – samples are taken form the distal limbs so bleeding can be controlled with pressure bandages as needed. Control local bleeding – pressure/surgery/packs/phenylephrine.**
2. **Place large bore IV catheter. Collect minimum database from catheter if possible.**
3. **Volume resuscitate, as appropriate. Consider whole blood to increase platelet numbers. 10ml/kg whole blood will raise the platelet count by approximately $10x10^9$/l. Transfuse as needed to replace blood loss (packed red cells/oxyglobin).**
4. **Give steroids to reduce platelet destruction. Dexamethasone iv 0.5mg/kg SID then switched to prednisolone (1mg/kg/BID p/o) as appropriate. Steroids are normally tapered once platelet numbers have returned to normal, and reduced over approximately four to six months (25% reduction each month, moving to EOD treatment at about ½ way through treatment – second-line immunosuppressive drugs may help reduce the steroid dose more quickly).**
5. **Consider antibiotics if tick borne disease (eg. Anaplasmosis) is possible. Submit blood for PCR and/or cover with doxycycline (10mg/kg/SID p/o).**
6. **Consider a second line immunosuppressive. Azathioprine (2mg/kg/SID moving to every other day treatment once after 10-14 days – cheap but care with handling and long term myelosuppression) and cyclosporine (5mg/kg/SID – possibly more potent compared to azathioprine but more expensive) are good choices, these will help reduce the steroid dose and hence, side effects in the longer term. Both are reported to take between seven to 10 days for full immunosuppressive action, thus, there will be a delay in onset of their immunosuppressive action.**
7. **Consider vincristine (0.5mg/m^2 or 0.02mg/kg) through a cleanly placed IV catheter. Vincristine leads to the shattering of megakaryocytes and increased platelet numbers. It is not known if these platelets are functional but postulated that vincristine may then accumulate in macrophages, inhibiting their action. A recent paper reported that vincristine at admission reduced hospitalisation stays of ITP patients by 24 hours. Care should be taken as the patient should now be considered cytotoxic.**
8. **Consider gastroprotection. Reduces blood loss as a result of ITP, also reduces risk of steroid associated GI haemorrhage. Sucralfate (0.5-1g/QID p/o) and cimetidine (5-10mg/kg/TID SLOW IV) or Ranitidine (2mg/kg/BID SLOW IV).**
9. **Consider an IV human IgG infusion (0.5mg/kg over four hours). Human IgG is expensive but will act quickly to reduce platelet destruction. Transfusion reactions are possible; largely because of the small percentage of human albumin contained in the product (premedication with chlorphenamine [4-8mg im as a one-off] is suggested). Polyclonal human antibodies block macrophage Fc receptors reducing platelet destruction. They also dilute out antiplatelet antibodies and have long-term feedback reducing antibody production.**
10. **Consider splenectomy for chronic ongoing cases.**

Table 6: Management of immune-mediated thrombocytopenia (IMT).

circulating platelets can't become activated in the presence of normal platelet numbers and vWF levels. These patients will show signs of primary coagulation diseases as a result and have prolonged BMBT results. Acquired thrombocytopathia occurs with drug administration (the classic example of this is with aspirin) or in association with other diseases, such as liver failure, chronic renal disease or neoplasia.

Several inherited thrombocytopathias are reported, the best described is Glanzmann's thrombasthenia caused by an absence of GP IIb/IIIa. This leads to decreased platelet aggregation and clot retraction and is described in Otterhounds and Great Pyrenees. Signal transduction problems are reported in Basset Hounds, Spitz and Landseers secondary to abnormal adhesion. Storage pool abnormalities are reported in Grey Collies with cyclical neutropenia due to defective ADP and 5HT release.

VON WILLEBRAND DISEASE

vWD is caused by a deficiency of, or reduced levels of vWf, and has been reported in many breeds of dogs, in particular, Dobermanns, Irish Wolfhounds, and German Shepherd dogs. Severe deficiency of vWF results in impaired primary haemostasis and associated clinical signs, however, these may not be evident in less affected animals until there is an episode that leads to bleeding (eg. surgery or trauma). Drugs impairing platelet function or underlying disease, such as hypothyroidism, can worsen signs associated with vWD. Buccal mucosal bleeding test is a useful screening test for vWD but is not specific or particularly sensitive. The diagnosis should be confirmed by genetic testing or measurement of vWF antigen.

Treatment is palliative aiming to minimise haemorrhage. If bleeding is present then transfusion is needed to increase

Factor	Breeds
Factor I	Bernese, St Bernard, Borzoi, Lhasa Apso, Vizsla, Bichon Frise, Collie, DSH
Factor II	Boxer, English Cocker Spaniel, Otter Hound
Factor VII	Beagle, Boxer, Malamute, Alaskan Klee Kai, Bulldog, Miniature Schnauzer, Scottish Deerhound, DSH
Factor VIII	German Shepherd, Golden Retrievers, DSH
Factor X	American Cocker Spaniel, Jack Russell terrier, DSH
Factor XI	English Springer Spaniel, Kerry Blue terrier, Great Pyrenees, DSH
Factor XII	Miniature Poodle, Standard Poodle, German Shorthair Pointer, Shar Pei, DSH, DLH, Siamese, Himalayan cats

Table 7: Examples of breeds with reported inherited factor deficiencies – domestic shorthair (DSH), Domestic longhair (DLH).

vWF levels. Cryoprecipitate (contains high concentrations of vWf and FVIII) is the ideal blood product for treatment of vWD, although availability is limited. If cryoprecipitate is unavailable then FFP or FWB are possible alternatives; however FWB should be avoided where possible to prevent sensitisation to donor antigens in dogs that may well need further treatment with blood products in the future. Desmopressin is a synthetic analogue of antidiuretic hormone and causes release of vWF from endothelial cells. This is useful in dogs with type 1 vWD such as Dobermanns that have endothelial stores and can be given pre-surgery to reduce the risk of bleeding.

IMMUNE-MEDIATED THROMBOCYTOPENIA

IMT is usually associated with a severe thrombocytopenia, which has been confirmed on a blood smear. It is a diagnosis of exclusion so other potential causes such as limited platelet production or consumptive disorders, must be excluded. However, most other causes of thrombocytopenia (for example, DIC, infections or haemorrhage) cause mild-moderate rather than severe thrombocytopenia. IMT secondary to underlying diseases or drug treatment, can result in severe thrombocytopenia so a through history and imaging to exclude a secondary trigger are essential. Treatment relies on a combination of immunosuppression and supportive care (see Table 6).

SPECIFIC DISORDERS OF SECONDARY COAGULATION

Many inherited defects of specific coagulation factors have been reported in veterinary medicine. Examples of breeds with reported inherited factor deficiencies (see Table 7).

HAEMOPHILIA

Haemophilia A (deficiency of Factor VIII) and haemophilia B (deficiency of Factor IX) are the most common inherited coagulation defects in dogs. A is roughly four times more commonly reported than B. It is sex linked and usually seen in young males, who present with haematoma formation, lameness secondary to heamarthrosis or prolonged bleeding after the loss of deciduous teeth or minor surgery. Carrier females are often normal but produce roughly half the normal amount of factor. Bleeding can be a problem if there has been excessive blood loss for example after surgery or trauma. Common breeds for A include German Shepherd dogs and Golden Retrievers and for B German wire-haired pointers, but a wide range of breeds for both reported.

Diagnosis is usually made in the presence of clinical signs, an increased APTT and ACT, but normal PT and confirmed by factor analysis. Treatment is symptomatic and includes transfusion or FFP, cryoprecipitate or whole blood, however, repeated transfusion will become more challenging over time. Human recombinant factors can be used and experimentally gene therapy has been used to correct the disorder.

HAGEMAN FACTOR DEFICIENCY

This is the most common factor deficiency in cats and leads to dramatic increase in aPTT with a normal PT.
Whilst factor XII is needed in vitro, it is not required in vivo for coagulation to be activated, thus, it does not lead to bleeding disorders. It can be confirmed by measuring factor XII levels. It can also be associated with other factor deficiencies. As well as cats, it has also been reported in dogs, including Standard Poodles and German Shorthaired Pointers.

RODENTICIDE TOXICITY

Activated vitamin K is required for the activation of clotting factors II, VII, IX and X. Vitamin K is converted to its active form, which is inhibited by anticoagulant rodenticides. First-generation rodenticides (warfarin, dicoumarin, diphacinone, chlorphacinone) are generally less potent than second-generation drugs.
Repeated exposure or a large single dose is usually required for clinical signs to become apparent, with bleeding usually occuring several days post-ingestion. Half-lives are varied so treatment may be required for between seven days (warfarin) to four weeks (diphacinone). Second-generation drugs are now more common, including brodifacoum, bromadiolone and difenacoum, and are highly potent. Secondary poisoning from ingestion of rodents is also possible.
Diagnosis is usually suspected through coagulation tests and can be confirmed by mass spectrometry if samples are submitted early in the disease course. Factor VIIa has the shortest half-life of the vitamin K-dependent factors (around six hours), which causes the prothrombin time (PT) to increase before the activated partial thromboplastin time (aPTT).
However, in most cases, at diagnosis the PT, aPTT and activated clotting time will all be prolonged.
If presented within three hours of ingestion, emesis should be considered alongside absorbents such as activated charcoal. If significant absorption has already taken place then treatment with vitamin K_1 is required with subcutaneous therapy given for 24-48 hours before moving to oral medication.
Treatment is continued for seven to 28 days depending on the toxin present. Once the course of medication is completed, the PT is rechecked 48 hours after vitamin K withdrawal and if elevated treatment continued for a further 14 days. Transfusions are often required as functional clotting factors may not be generated for one to two days even with vitamin K treatment. The vitamin K-dependent clotting factors are relatively stable and either fresh or stored whole blood can be used. Plasma products (FFP or frozen plasma) may be used if available in non-anaemic patients.

TERTIARY COAGULATION DISORDERS

POSTOPERATIVE BLEEDING IN GREYHOUNDS

Racing greyhounds are reported to have much increased risk of postoperative bleeding compared with other breeds. Those dogs will typically have completely unremarkable results of pre-surgical haemostatic screening. Recent studies suggest that use of epsilon-aminocaproic acid (EACA) will significantly reduce prevalence of postoperative bleeding in racing greyhounds.
Protocol described in those publications advises initial dose of 15-40mg/kg administered IV immediately after surgery (1ml diluted in 15ml of 0.9% NaCl over 30 min), followed by oral doses of EACA (total dose of 500-1,000mg every eight hours, for five days). It might worth considering use of the EACA in racing greyhounds scheduled to undergo a surgical procedure (Marín et al, 2012).

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

DIC is a complicating feature of many diseases processes and generally is not a good prognostic signs. It might be described the activation of both of clot formation and breakdown leading to thrombotic and bleeding tendencies, which lead to complications of the underlying disease process through multi organ dysfunction and failure.
Diagnosis is difficult, with reduced platelet numbers, increased coagulation times and D-dimers usually documented. Thromboelastography has been used as a more global assessment of coagulation and has helped in the diagnosis of DIC. Treatment is difficult and controversial, so, therapy is usually reserved for patients with active bleeding.

CONCLUSION

In summary, initial approach to the coagulopathic patient should be to rapidly identify and manage cardiovascular shock, prevent further haemorrhage and then from clinical exam and history identify the likelihood of a primary or secondary haemostatic disorder.
From this, appropriate testing and follow-up therapy can then be selected. Coagulopathies can be a diagnostic and therapeutic challenge but, by following these principles successful management can be achieved.

REFERENCES

Available on request