The hemostatic system is an intricate co-operative network of proteins and cells that produces then dissolves fibrin clots. Disruptions in the balance between stimulatory and inhibitory forces that drive clotting and fibrinolysis cause hemorrhagic or thrombotic disorders, the most severe of which is disseminated intravascular coagulation (DIC). DIC is a secondary complication of infections, inflammation and neoplasia. It contributes to morbidity and mortality through systemic microvascular thrombosis. Since clinical signs and imaging techniques are insensitive to thrombosis, laboratory testing is essential for DIC detection. Early diagnosis and mitigation can potentially improve survival and decrease hospitalization costs of affected animals.

PATHOPHYSIOLOGY OF DIC

Our view of physiologic hemostasis has evolved from the concept of a series of sequential cascading “waterfall” enzymatic reactions to more complex interrelated reactions that are grounded on cell surfaces, primarily provided by activated platelets. For a more in-depth appreciation of this “cell-based model” of hemostasis, the reader is referred to a recent review. DIC essentially represents this normal hemostatic process gone viral—instead of being localized to a site of vessel injury and to platelet surfaces, hemostasis becomes unrestricted, uncontrolled, and systemic in DIC. Bacterial sepsis is one of the main causes of DIC in humans and animals. As such,
animal models of sepsis have provided substantial insight into how hemostasis becomes sufficiently perturbed to manifest in DIC. There is some redundancy in the ways in which the hemostatic system responds to triggering stimuli; however, it is unlikely that "one rule fits all." The type of stimulus and the resulting interplay between the different cellular and enzymatic hemostatic components and between hemostasis and inflammation likely dictate the mechanisms by which DIC is initiated and progresses in different disorders and the interventions required to limit or halt this process. Below is a summary of current concepts on the pathophysiology of DIC.

Two central themes of DIC are that thrombin generation is excessive and uncontrolled and that thrombin generation occurs and is amplified and disseminated on cell surfaces. This indicates that the coagulation cascade must be excessively activated in DIC and that cell surfaces must be available to propagate and disseminate thrombin generation. Tissue factor (coagulation factor III, tissue thromboplastin) has been designated the main culprit in activation of coagulation in DIC. Exposure of large amounts of tissue factor in the extravascular space or intravascular expression of tissue factor on circulating cells or cell membrane–derived microparticles begins the process of DIC (Fig. 1). Tissue factor activates the coagulation cascade (in health and in DIC) by binding to and activating its circulating enzymatic partner, coagulation factor VII (FVII), in the extrinsic pathway of coagulation. When complexed with tissue factor, activated FVII efficiently activates surface-bound factor X (FX) and factor IX. Once the extrinsic pathway generates thrombin via activated FX, thrombin amplifies its own production by activating other coagulation factor enzymes (factor XI) and cofactors (factors VIII and V) of the intrinsic and common pathways. This eventually terminates in fibrin production (and thrombus formation). When tissue factor is exposed intravascularly or in large amounts, the normal spatial restriction of coagulation is lost and inhibitory mechanisms are disrupted, leading to excessive thrombin generation. Although tissue factor is important in initiation of DIC, there are other ways in which the coagulation cascade can be activated in disease states. For example, snake venom components and cancer proteases can directly activate other coagulation factors, including FX, inducing a DIC-like syndrome.

Tissue factor fuels the fire of DIC, but alone is insufficient to result in dissemination of coagulation. Rather, thrombin generation is facilitated and propagated systemically through phospholipid-containing microparticles, lack of appropriate inhibition and a feedback cycle that is initiated (at least in inflammatory causes of DIC) between coagulation and inflammation. Microparticles are small (<1 μm) vesicles that are shed from the surface membrane of many different cell types (platelets, monocytes, granulocytes, erythrocytes, and endothelial cells), particularly after activation. Membrane-derived microparticles are enriched in phosphatidylserine, a negatively charged phospholipid that is normally found on the inner leaflet of cell membranes, but is flipped to the outer membrane when cells become activated. Phosphatidylserine is the binding site for Gla-domain–containing coagulation factors and enables the assembly of the tenase (FX activating) and prothrombinase (thrombin activating) complexes on cell surfaces. The formation of coagulation factor complexes on phosphatidylserine-bearing surfaces produces high local factor concentrations, protects factors from inhibition, and amplifies their activity over 1000-fold. Due to their small size, microparticles are not restricted to an injured site and persist in the circulation, thus providing a large functional surface area on which coagulation can propagate systemically. Under physiologic conditions, activated platelets are the main source of phosphatidylserine membranes (both the intact cell and shed microparticles); however, in DIC, additional procoagulant membranes are provided by
other cell types, notably tissue factor–expressing monocytes, cancer cells, and apoptotic cells.\textsuperscript{6,14,16,17} Thus, the driving force for coagulation—tissue factor—and the membrane support—phosphatidylserine—are colocalized to a greater degree in DIC than under physiologic conditions. Studies in humans demonstrate that oxidized lipoproteins can also provide phospholipid membrane support for coagulation and may have a role in dissemination of coagulation in DIC associated with sepsis\textsuperscript{18}; however, the extent to which this occurs in domestic species is unknown.

Concurrent with thrombin generation is activation of fibrinolysis, resulting in the release of fibrin split products. However, fibrinolysis may be inhibited to some degree in DIC, particularly in later stages of sepsis and trauma. Inhibition is mediated through thrombin itself, high concentrations of which result in the production of thick strands of lysis-resistant fibrin and activation of a carboxypeptidase that inhibits fibrinolysis (thrombin-activatable thrombolysis inhibitor).\textsuperscript{1,19} The concomitant release of polyphosphates from activated platelets\textsuperscript{20} and tissue plasminogen activator inhibitors from the endothelium contributes to inhibition of fibrinolysis, particularly in sepsis.\textsuperscript{2}
Inhibition of fibrinolysis would favor the development of thrombi, which is characteristic of DIC. However, since increased concentrations of fibrin split products are a characteristic and early laboratory finding in DIC with tests for these products having high negative predictive values, fibrinolysis is always occurring in DIC to some degree.

Thrombin generation is normally balanced by inhibitors, specifically antithrombin (AT), activated protein C, and tissue factor pathway inhibitor. Inhibitory function can be defective in DIC, either as a direct consequence of this process or secondary to the underlying disease. During DIC, inhibitors (AT, activated protein C) are consumed as they complex with their activated targets and are cleared from the circulation. In inflammation-induced DIC, inflammatory cytokines can downregulate production of inhibitors or their cofactors or receptors, resulting in decreased inhibitor activity. Inhibitors or their cofactors can also be degraded by neutrophil proteases. Thus, inhibitors no longer constrain coagulation, which is excessive to begin with, resulting in the progression and dissemination of DIC.

It is now well accepted that coagulation and inflammation are intertwined. Inflammation is one of the most common instigators of DIC, with inflammatory cytokines and complement components upregulating tissue factor, downregulating inhibitors, and activating various cells inducing vesiculation and phosphatidylserine exposure. Conversely, activated coagulation factors (notably thrombin, FX, and the tissue factor–FVII complex) can potentiate the inflammatory response by binding to and activating protease-activated receptors (PARs) on platelets, leukocytes, and endothelial cells. Activated PAR induce G protein–coupled cell signaling in these cells, resulting in upregulation of adhesion molecules (eg, intracellular adhesion molecule-1) and secretion of inflammatory mediators (eg, interleukin-6 and interleukin-8). Coagulation-induced inflammation is potentiated by the loss of hemostasis inhibitors, which can elicit anti-inflammatory and cell-protective responses, particularly activated protein C. The extent to which this positive feedback loop is initiated in DIC may depend on the underlying cause of DIC and the precise balance between coagulation activating and opposing forces. The recognition of these intimate links between inflammation and coagulation has advanced the use of activated protein C concentrates for treating DIC, with the intent on capitalizing on the inflammatory versus the anticoagulant properties of this inhibitor.

This summary of the pathophysiology of DIC has focused on the coagulation cascade, cell surfaces, and inhibitors, with little emphasis being placed on platelets. Yet platelets are important in perpetuating and disseminating coagulation and their contribution cannot be underestimated. Whether platelets are activated directly by the primary disease or as a consequence of generation of activated coagulation factor proteases, activated platelets are still likely the main structural scaffold on which DIC proceeds and are a rich source of phosphatidylserine-expressing microparticles, platelet and inflammatory agonists, and coagulation factors. However, it is unlikely that platelet activation or phosphatidylserine exposure alone will result in DIC without concurrent direct activation of the coagulation cascade.

THE DIC CONTINUUM

In 2001, a Scientific Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) on DIC produced a series of recommendations aimed at standardizing diagnostic criteria for DIC to improve clinical outcomes. This subcommittee defined DIC as “an acquired syndrome characterized by intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe,
can produce organ dysfunction.” The subcommittee advanced the concept that DIC is an evolving process that can be separated into different stages: nonovert DIC, “controlled” overt DIC, and “uncontrolled” overt DIC (Fig. 2). In nonovert DIC, coagulation has been activated (usually through tissue factor exposure); however, thrombin generation is constrained by inhibitors and there is minimal incitement of inflammation. The subcommittee also refers to this stage as “a stressed but
compensated” hemostatic system, and this stage likely encompasses what has been previously referred to as “low-grade or chronic DIC.” Although not clearly stated, it is likely that microvascular thrombosis is occurring to some extent in this nonovert stage of DIC. This stage of DIC is difficult to diagnose because it is characterized primarily by thrombin generation, which cannot be reliably detected by routine coagulation screening assays, such as the prothrombin time (PT) and activated partial thromboplastin time (APTT). Overt DIC reflects an activated and uncompensated hemostatic system, where inhibitors are overwhelmed, thrombin generation proceeds unopposed, the inflammation-hemostasis feedback loop is operative, and thrombosis is causing organ dysfunction. The subcommittee defines “controlled” overt DIC as a temporary condition, which can be ceased by intervention (e.g., ruptured placenta), whereas “uncontrolled” overt DIC cannot be reversed by sole removal of the underlying cause. As thrombosis proceeds in overt DIC, platelets and coagulation factors are consumed, cleared, or cleaved, resulting in abnormalities in screening hemostasis assays, which are designed to pick up deficiencies in these cells and proteins. With time, these deficiencies may dominate the clinical syndrome, resulting in hemorrhage, which is more clinically discernable than thrombosis. This is the most severe manifestation of DIC and has been referred to as “fulminant” or “end-stage” DIC. Since this is the most clinically apparent and readily diagnosed stage of DIC, the moniker “death is coming” was coined for this hemostatic disorder. Although there is some evidence that nonovert DIC can progress to overt DIC in some patients, this progression is not inevitable and likely depends on many factors, including the nature of the underlying disease, inherent differences in susceptibility to DIC, and disease- or DIC-related variables that influence activation or containment of coagulation.

LABORATORY TESTING OF DIC IN DOGS AND CATS

The Past

In veterinary medicine, DIC has been traditionally diagnosed on a combination of clinical and laboratory criteria (Box 1). To diagnose DIC, animals must fulfill both clinical criteria (a primary disease and clinical symptoms) and have two or more abnormal laboratory tests, reflecting abnormalities in all pathways of hemostasis. The rationale for using a combination of test results for DIC diagnosis is sound, because none of these tests alone are specific for DIC. Although detection of fibrin thrombi in the microvasculature on histopathologic examination is considered the “gold standard” for diagnosis of DIC, it is a poor standard because fibrin thrombi can lyse rapidly after death; thus, DIC is essentially an antemortem clinical and laboratory diagnosis. Nevertheless, this traditional method for diagnosing DIC has major shortcomings. Hemorrhage manifests late in the course of DIC and may not be evident at all in cats with this syndrome. Unfortunately, thrombosis is far more difficult to recognize in affected patients and yet is the more important abnormality, being the major factor responsible for the high morbidity and mortality associated with DIC. Thus, clinical signs of hemorrhage or thrombosis cannot be relied upon to facilitate the diagnosis of DIC and these symptoms are not included in currently recommended DIC scoring systems in human medicine. Since we rely heavily on clinical assessment (which depends on the index of suspicion harbored by the attending clinician), this means that the presence of DIC is likely frequently missed in animals, removing a potential opportunity for altering patient outcome. There is no standardization regarding the tests (type, number, or cut-offs) used to diagnose DIC, which makes it difficult to compare across published studies. Coagulation screening assays (PT, APTT, thrombin clot time, and fibrinogen concentration) are optimized for detection of factor deficiencies and are thus geared toward detection of the most
advanced stages of DIC. These tests are insensitive to an activated but contained hemostatic system (nonovert DIC) or earlier stages of overt DIC where coagulation activation dominates over consumption.\textsuperscript{21,39,40} Furthermore, test sensitivity to DIC differs between species and criteria used in dogs are not necessarily applicable to cats. DIC is an infrequent diagnosis in cats, likely because cats rarely demonstrate clinical signs of excessive hemorrhage and routine hemostatic assays are insensitive to DIC in this species. Reduced AT activity and high fibrin(ogen) degradation product (FDP) or D-dimer concentrations are two of the more sensitive tests for diagnosis of DIC in dogs,\textsuperscript{32,33,41} but low AT activity is uncommon and FDP or D-dimer concentrations are not as reliably increased in cats with DIC (personal observations, 2011).\textsuperscript{35,38} It is difficult to diagnose overt DIC in the face of a normal platelet count in dogs, yet cats with DIC may not be thrombocytopenic.\textsuperscript{38} As indicated earlier, none of the laboratory tests are specific for DIC (even when used in combination) and some of the tests are so nonspecific (such as red blood cell fragments in cats), that they are not useful for DIC diagnosis.

**The Present**

To overcome the inherent limitations of traditional criteria, the diagnostic emphasis in humans has shifted toward the application of scoring systems for diagnosis of nonovert and overt DIC and new tools for detection of thrombin activation or hypercoagulability.\textsuperscript{21,40} Although several assays for thrombin activation (eg, thrombin–AT complexes, fibrinopeptides, prothrombin fragments) and microparticle detection
have been evaluated in human patients,\textsuperscript{21,40,42} little information exists on these assays in veterinary medicine and none have been tested in animals with DIC. Rather, there is enormous interest in viscoelastographic-based coagulation testing for the detection of hypercoagulability (including that due to DIC) in animals. Thus, this section will focus on scoring systems and viscoelastographic testing.

In order to standardize DIC diagnosis for clinical use and outcome assessment, the DIC Scientific Subcommittee of the ISTH proposed a scoring system for nonovert and overt DIC.\textsuperscript{29} The scheme was deliberately based on widely available standard diagnostic assays in human medicine, such as the PT and platelet count, without the need for specialized tests, such as AT or protein C activity, fibrinopeptides, or thrombin–AT complexes. For overt DIC, the scoring system can only be applied to patients that have a predisposing disorder and no points are given for the underlying disease. Since overt DIC was defined as an excessively activated and uncontrolled hemostatic system that is characterized by widespread and ongoing thrombosis, results of routine assays that detect platelet and coagulation factor depletion and release of fibrinolytic products should be abnormal in this stage of DIC. Therefore, the overt DIC score was based on a moderate thrombocytopenia, a prolonged PT, low fibrinogen, increased fibrinolytic products (FDP, D-dimer), or soluble fibrin monomer (which is produced from the action of thrombin on fibrinogen). In essence, the overt DIC score represents a standardized format for traditional DIC testing (without a requirement for relevant clinical signs). In contrast, laboratory detection of nonovert DIC is far more difficult because this stage is characterized by an activated but contained hemostatic system (i.e., thrombin generation) and most of the routine screening assays of coagulation are insensitive to thrombin generation.\textsuperscript{39} Thus, for the nonovert score, points were given for the underlying disease (i.e., the patient is at risk of DIC) and trends in data from routine assays (PT, platelet count, fibrinolytic products, or soluble fibrin monomer) were included in order to detect a progressively activated hemostatic system with deteriorating inhibitory control. Specialized tests that reflect thrombin activation (thrombin–AT complexes, low activity of inhibitors) could be done and were included in the scheme but were not necessary for attaining a score consistent with nonovert DIC. The recommended testing interval for evaluating dynamic trends was 24 to 48 hours. Weaknesses in the ISTH scoring system were a relatively low platelet cut-off (\textless 100 \times 10^6/L) and no defined test or cut-offs for fibrinolytic products or soluble fibrin monomer (which could be used interchangeably with FDP or D-dimer). Other scoring systems for overt DIC have been used for several years in Japan.\textsuperscript{21} Prospective validation of the ISTH scoring system, particularly that for overt DIC, has been accomplished and the scheme has been subjected to a 5-year review.\textsuperscript{21} The performed studies support the continued use of the ISTH scoring system for overt DIC because patients classified with overt DIC have higher mortality rates and incidence of organ dysfunction than those not in overt DIC in most studies. Clinical treatment trials also show that the overt DIC score is useful in evaluating beneficial responses to therapy with regard to standardized patient outcomes.\textsuperscript{28,43} The studies also illustrated that the overt DIC score is largely dependent on the PT and platelet count, that fibrinogen could be eliminated from the scoring scheme, and that fibrinolytic products or soluble fibrin monomer do not contribute substantially to the score due to their high sensitivity. There is still uncertainty over which test and test cut-off for fibrin generation or lysis should be used for ISTH scoring and there is a substantial lack of concordance between the ISTH and Japanese schemes (the Japanese scoring systems, particularly that from the Japanese Association for Acute Medicine, appear to perform better overall, perhaps due to regional differences in disease demographics or because they ascribe points for the primary disorder). Less
validation of nonovert DIC has been done; however, one study demonstrated that patients in nonovert DIC have higher mortality rates than patients without DIC and some progress to overt DIC. The latter study also showed that serial monitoring of screening assays (PT, platelet count, fibrinolytic products, or soluble fibrin monomer) were useful for the diagnosis of nonovert DIC, with inhibitor assays for AT and activated protein C activity not contributing substantially to the score.

There has been one preliminary study on application of a modified ISTH scoring system for diagnosis of nonovert DIC in dogs. In this study, the authors used total hospitalization days and 28-day mortality rates as outcome measures in 24 dogs with diseases associated with DIC. They combined selected nonovert and overt DIC criteria (points were given for underlying disease, a prolonged PT, thrombocytopenia, high D-dimer, and low AT activity) for diagnosing DIC and compared it to traditional assessment (three or more abnormal tests including thrombocytopenia and prolonged coagulation times) on daily blood samples, selecting the highest values for comparison. They found that more dogs were diagnosed in DIC with traditional criteria but mortality rates were higher in the dogs that were classified in DIC by modified ISTH criteria. Total days of hospitalization were no different between groups. This study suggests that ISTH criteria are potentially applicable to dogs. However, the tests and cutoffs selected for the canine ISTH scoring scheme may not have been optimized for the dog, resulting in the reduced sensitivity of the scheme compared to traditional assessment (which has since been corroborated by subsequent studies by these authors in larger numbers of dogs). For example, the APTT is more sensitive than the PT as an indicator of DIC in dogs.

The same authors have recently published a diagnostic scoring algorithm for DIC based on multiple logistic regression analysis of hemostatic assays. To develop the model, dogs admitted to a single academic veterinary hospital were tested daily for various hemostatic test results (PT, APTT, D-dimer, platelet count, fibrinogen, AT, and protein C) and results were scored per ISTH overt DIC criteria. Using data from the day of the highest ISTH DIC score, a diagnosis of DIC was made by a simple majority opinion of three experts based on traditional DIC criteria (abnormal test results reflecting coagulation factor and platelet consumption, inhibitor depletion, and fibrinolytic activity). The final model was based on results from the PT, APTT, fibrinogen, and dichotomized D-dimer (>0.5 mg/L for a latex agglutination-based card assay) from 63 dogs (37% of which had DIC per expert opinion). A logistic value of \( P > .40 \) was designated as the optimal diagnostic cut-off for the model. The model was tested on a different population of dogs from another academic institution, with the assays presumably being performed at the first institution. Dogs with \( P \) values greater than the cut-off had a higher relative risk of death (the latter was not defined). This same study also revealed that the sensitivity of ISTH overt criteria for diagnosis of DIC in dogs was lower than expert opinion. This proposed model may be a promising way to standardize diagnosis of DIC in later stages of overt disease (although is no better than expert opinion), but the model still awaits verification from additional independent studies, particularly using different methods and reagents since these assay variables may markedly influence usefulness of the model. For instance, the latex agglutination D-dimer assay used in the model is not commercially available in the United States and a previous study has shown a lack of concordance between diagnostic assays for this marker.

Viscoelastographic testing is a source of tremendous interest in veterinary medicine, yielding a plethora of recent publications, particularly with respect to the use of these assays for diagnosing hypercoagulability in animals, such as nonovert DIC. Viscoelastograph-based testing is referred to as a “global” hemostatic assay because
it is performed in whole blood, thus assessing all soluble factors and cellular constituents involved in hemostasis, with the exception of the endothelium and tissue-derived proteins. Interestingly, these assays are used to dictate or assess response to transfusion therapy in humans undergoing surgery and are not generally used for diagnosis of specific hemostatic disorders.10,48 There have been several recent substantive reviews on the use of viscoelastographic coagulation testing in veterinary medicine49,50; hence, only a few points will be emphasized here. Important factors that influence coagulation results from these analyzers are the type and concentration of the activator (if one is used), the timing of analysis, and hematocrit.49–53 Tissue factor and kaolin are two commonly used activators, with tissue factor activation being analogous to a whole blood PT and kaolin activation with a whole blood APTT. In support of this, tissue factor–activated thromboelastographic (TEG, performed with the TEG 5000 analyzer from Haemoscope Corporation) results display no abnormalities (similar to the PT) in blood from dogs with hemophilia A (M. Brooks, personal communication, 2011). There is a trend toward hypercoagulable tracings with storage of blood and lower hematocrits (which may be an artifact of the technique, since it is unlikely all anemic dogs are truly hypercoagulable).49,50 Thus, studies using different viscoelastic techniques, activators, and time of analysis cannot be directly compared and hematocrit is clearly a confounding variable that must be taken into consideration. Furthermore, there is no consensus on the definition of hypercoagulability, with some authors using the G or global clot strength54,55 and others using one or more abnormal TEG results, including mathematical formulae that combines most of the major tests, the coagulation index, or total thrombin generation (area under the TEG curve).56–60

Only one viscoelastographic study has been performed in dogs with DIC.55 In this study, tissue factor–activated TEG was performed 30 minutes after blood was collected from 50 dogs admitted to the intensive care unit of two university hospitals. Similar to that done previously by these authors,45 the diagnosis of DIC was based on expert opinion. Overall coagulation state (hyper-, normo-, and hypocoagulability) from the TEG was defined on global clot strength or G, a direct mathematical derivation of the maximum amplitude (MA) of clot formation, using data from the highest ISTH overt DIC score. Outcome was based on 28-day mortality rates. The authors found that hypercoagulability was the most common coagulation state in dogs with DIC but that hypocoagulable dogs had a higher risk of mortality than dogs with normal or hypercoagulable status. The influence of hematocrit on test results was not evaluated. This study and others by the same and other authors52,54,59 also illustrated the dependence of the G (or MA) on the platelet count and fibrinogen concentration, with blood from dogs with platelet counts less than $30 \times 10^6$/L being hypocoagulable and high fibrinogen being associated with hypercoagulability. These data suggest that TEG results defined by G (or MA) may provide no information on overall coagulation status in severely thrombocytopenic dogs or dogs with hyperfibrinogenemia. Indeed, hyperfibrinogenemia may be an independent risk factor for thrombosis61 and measuring fibrinogen in dogs may yield similar information on hypercoagulability than in vogue viscoelastographic techniques.

The Future

It is likely that we will continue to use traditional criteria to diagnose DIC in animals, with DIC remaining a rare diagnosis in cats. Time and additional studies will tell whether viscoelastographic coagulation testing will live up to the hoped for promise for detecting earlier nonovert or thrombotic phases of overt DIC. However, a recent study suggests TEG is not a good screening tool for detection of early hemostatic
abnormalities in experimental endotoxemia in dogs.\textsuperscript{22} It is also unlikely that a single sensitive and specific diagnostic assay for DIC will be discovered in the next few years, although new prognostic tests may become available.\textsuperscript{21,62} The search for molecular markers of thrombin activation will no doubt continue and potentially become more targeted as our understanding of the complex hemostatic system evolves. In the interim, we will continue to rely upon clinical acumen and a battery of affordable and readily available imaging and laboratory assays to diagnose DIC and detect thrombosis. Although costly, daily or alternate-day testing to monitor for trends in hemostatic test results (such as a normal but declining platelet count, progressively increasing D-dimer concentrations, or decreasing AT activity) may prove the best means to identify dogs in early or thrombotic phases of DIC.\textsuperscript{21,40} To effectively evaluate risk factors and new diagnostic tests and treatment strategies, it is imperative that we reach consensus and standardize, to the best of our ability, the definition of DIC, the best tests and test cut offs used to diagnose DIC, and outcome assessment for clinical trials or research studies in dogs and cats. The multiple logistic regression model proposed by Winberg and colleagues\textsuperscript{45} may be a good starting point to reach this consensus, once it has been independently verified and applied across clot detection methods and reagents.

REFERENCES


