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Topical Review

Update on Disseminated Intravascular Coagulation: When to Consider It, When to Expect It, When to Treat It

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ABSTRACT

Disseminated intravascular coagulation (DIC) spans a continuum in which clinical signs can range from a prothrombotic to a hemorrhagic phenotype, with some patients suffering from both concurrently. DIC is always caused by an underlying condition, with most cases linked to systemic inflammation or infection. Numerous factors contribute to the development of DIC, including aberrations in endothelial function, and altered levels of endogenous procoagulant, anticoagulant, and fibrinolytic factors. Excessive thrombin generation, or failure to localize thrombin production, is the unifying theme throughout this broad condition. DIC can be described as overt or nonovert, each with varying degrees of severity. The ability to concisely define and diagnose such a broad condition has proven challenging, especially in veterinary medicine, where interspecies differences result in phenotypic variability. In most patients, DIC is recognized when a patient experiences noteworthy hematologic changes, such as a drop in circulating platelet count in concert with a 20% to 30% prolongation in the activated partial thromboplastin time. Similar to diagnosing, proven benefits of any particular therapy are difficult to identify. Despite these difficulties, therapy can be optimized with an understanding of the underlying pathology(ies). With appropriate care and a committed owner/veterinary team, patients with DIC can have a favorable outcome.

Disseminated intravascular coagulation (DIC) is described as both a consumptive coagulopathy and a thrombohemorrhagic state, and poses a unique challenge to concisely define, diagnose, and manage.[1] The difficulty stems from the varied clinical presentations that encompass DIC: some patients suffer from thrombotic tendencies, others a bleeding diathesis, whereas in others the 2 occur simultaneously. Because a single definition of DIC would be imprecise, DIC should be viewed as a broader condition (such as anemia) under which numerous causes and subtypes exist.[1] It represents a continuum that likely starts as a procoagulant (prothrombotic) phenotype, but often is not recognized until substantial consumption has occurred and patients suffer from bleeding. The underlying disease or trigger can be as diverse as DIC itself and requires recognition and therapy for definitive treatment.[1] Because DIC encompasses a broad spectrum of presentations, this article will focus on the mechanisms by which DIC may arise, serving as a template to broaden our understanding rather than an individualized approach.

Mechanisms of DIC Pathogenesis

Coagulation is inextricably intertwined with inflammation, and many causes of DIC are associated with a marked systemic inflammatory response or infection. Localized thrombosis conceivably plays an important role in the body's response to inflammation and infection by limiting systemic spread of microorganisms and promoting tissue repair.[2] Coagulation itself can induce inflammation and all prothrombotic elements have the potential to be pro-inflammatory, whereas endogenous anticoagulants are generally considered to be anti-inflammatory. Take for instance thrombin, which not only accounts for decreases in fibrinogen, platelets, and numerous factors (II, V, VIII, and XIII) during a consumptive coagulopathy,[3] but also acts to promote inflammation by inducible cytokine production through protease-activated receptors.[4,5] DIC develops as a consequence of activation in the inflammation/coagulation axis and results in a state characterized by an imbalance in procoagulant and anticoagulant factors, dysregulated fibrinolysis, or endothelial injury. The end result is a failure to retain thrombin at the site of injury, or initiation of thrombin generation at sites distant from the injury, resulting in widespread intravascular coagulation and formation of microthrombi in end organs.[6] Widespread activation of coagulation will thus contribute to the persistence of a systemic inflammatory state, and organ hypoxia from microthrombi may add fuel to this fire.

Tissue Factor Activation and Thrombin Generation

Our current understanding of coagulation suggests that virtually all coagulation in vivo is initiated by tissue factor (TF).[7-9] The TF pathway (extrinsic pathway) becomes activated with exposure of factor VIIa to TF (e.g., as a consequence of endothelial disruption, which exposes sub-endothelial TF). Once initiated, coagulation progresses through thrombin generation and subsequent formation of cross-linked fibrin (see models of coagulation section for more details). TF is also expressed on the surface of endothelial cells that have been exposed to inflammatory cytokines such as tumor necrosis factor (TNF-α), interleukin-1, or endotoxin.[10] Monocytes/macrophages express TF upon stimulation by the same inflammatory cytokines. Despite numerous possible sources of TF, identifying the source of initiating TF in any given disease has proven challenging in vivo. In addition to initiating coagulation via the extrinsic pathway, TF has also been implicated in perpetuating inflammation by activating nuclear factor κB, resulting in the production of TNF-α.[11] Many neoplastic processes may also cause intravascular coagulation by exposure of TF. In dogs, tumors of epithelial cell origin were shown to constitutively express

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high levels of TF,[12] and promyelocytes have been shown to contain TF in people with acute promyelocytic leukemia.[13]

In addition to their role in clot formation, activated platelets and phospholipid microvesicles (microparticles) derived from platelets and numerous other cell types may provide the necessary phospholipid surface to disseminate TF in DIC[14] (see coagulation and inflammation section for more details).

Endothelium

In the basal state, the endothelial barrier exhibits an antithrombotic phenotype, helping to maintain normal blood flow. Widespread endothelial activation is central to the host response in sepsis, shifting the endothelial barrier from an anticoagulant to a prothrombotic phenotype. The endothelial barrier is comprised of vascular endothelial cells and a thin carbohydrate-rich luminal glycocalyx. The 2 combined are responsible for regulating vasomotor tone, maintaining fluids and larger molecules within the blood vessel lumen, preventing aberrant thrombus formation, and ultimately maintaining organ perfusion.[15] The endothelial glycocalyx is comprised of a large network of negatively charged proteoglycans, glycosaminoglycans, and glycoproteins, with heparan sulfate (HS) constituting 50% to 90% of the proteoglycans present in the glycocalyx.[15-17] Several important anticoagulant elements can bind to the glycocalyx, including antithrombin (AT), heparin cofactor II (HCFII), thrombomodulin (TM), and tissue factor pathway inhibitor (TFPI). AT is able to bind to HS, enhancing the rate of thrombin inhibition.[18] HCFII, when bound to the vessel wall, is activated by dermatan sulfate, also greatly enhancing the inactivation of thrombin.[19] Both AT and HCFII have little factor-inhibiting ability when free in plasma, with their actions greatly accelerated only when localized to the glycocalyx.[20] TFPI is believed to bind to the glycocalyx via HS and requires this proteoglycan to degrade TFPI-Xa complexes.[21,22] The glycocalyx also serves as a mechanoreceptor sensing changes in blood flow, leading to the release of nitric oxide during states of increased shear stress, not only altering vasomotor tone but also exerting anticoagulant effects.[23]

The glycocalyx acts to buffer (protect) the endothelial cells from inflammatory cytokines by preventing cytokines from binding to cell surface receptors.[24] In inflammatory disease states (e.g., sepsis), hemorrhagic shock, and states of decreased microvascular perfusion, TNF-α and hypoxia can damage the glycocalyx, resulting in loss of function or even shedding of the glycocalyx.[25-27] Markers that indicate shedding of the glycocalyx have been identified in people with sepsis, with higher concentrations of these markers in nonsurvivors.[28,29] As a key contributor to the endothelial barrier function, the glycocalyx is responsible for preventing extravasation of fluids. Edema formation is a common feature in most species with sepsis, implying that glycocalyx breakdown likely occurs across species.

Endothelial cells can become activated by inflammatory cytokines (e.g., TNF-α), thrombin, bradykinin, histamine, and vascular endothelial growth factor.[30-33] When activated or injured, endothelial cells release von Willebrand factor (vWF) from preformed stores (Weibel-Palade Bodies), in particular ultralarge multimers of vWF (UL-vWF) are released.[34] UL-vWF multimers are more active at inducing coagulation (e.g., aggregating platelets leading to a consumptive thrombocytopenia); however, these UL-vWF multimers are generally cleaved into smaller (less active) multimers by a disintegrin-like and metalloproteinase with a thrombospondin type 1 repeats, member 13 (ADAMTS13) under normal circumstances.[35] In people with endotoxemia or sepsis, a subsequent decrease in ADAMTS13 is not uncommon; however, the exact mechanism for this decrease remains unknown (e.g., consumption during cleavage of UL-vWF, protease inactivation).[36-39] More recently, decreased ADAMTS13 levels were associated with hemodynamic shock, renal failure, and failure to survive in people with septic shock, but not in patients with organ failures unrelated to sepsis.[40] Although classically associated with thrombotic thrombocytopenic purpura in people, decreased ADAMTS13 and elevated concentrations of UL-vWF may well be a contributor to the marked thrombocytopenia and coagulopathy seen in some DIC patients after endothelial activation.

Endogenous Inhibitors of Coagulation (Natural Anticoagulants)

Every prothrombotic element is balanced by an endogenous anticoagulant in the body. This is necessary for a complex system, such as the coagulation system, to respond to a wide array of insults and protect the host. In DIC, aberrations in the 3 main anticoagulant systems are associated with the progression of the coagulopathy, namely activated protein C (APC), AT, and TFPI. By virtue of their antithrombotic nature, all of these are also anti-inflammatory (see endogenous anticoagulants for more details).

Protein C is converted to APC when trace amounts of thrombin bind TM on the endothelium. During inflammatory states, cytokines decrease endothelial cell expression of TM, in turn decreasing activation of protein C.[8,41,42] Patients with sepsis also have elevated circulating levels of TM, likely because of endothelial cell dysfunction/injury, rendering TM less functional (because TM must be localized to the endothelium for normal function).[40] APC, in the presence of cofactor protein S, degrades factor Va and VIIIa, decreasing the amplification of coagulation via the intrinsic pathway, while also directly inhibiting further coagulation by binding thrombin (see endogenous anticoagulants for more details). Initial studies of the anticoagulant and anti-inflammatory effects of APC, when administered to people with severe sepsis, suggested that elements of the inflammatory state could be modulated, resulting in a decrease in relative risk of death in this severely ill patient population.[43] However, subsequent studies could not identify any beneficial effect and the patented product Xigris was pulled from the market in October of 2011.

AT primarily acts to inhibit thrombin, factor Xa, and to a lesser extent factor IXa. The rate of inhibition of thrombin is increased greater than 1000-fold in the presence of heparin and AT's endothelial localizing elements.[44] AT inactivation of thrombin can also be enhanced nearly 8-fold by binding of AT to TM, in the presence of thrombin.[45] AT is commonly decreased in inflammatory disease states because of consumption (thrombin generation), decreased production (negative acute phase protein), and degradation by elastase from neutrophils.[46-48] Both protein C and AT activity have been evaluated in dogs with naturally occurring sepsis, and both decreased in the majority of dogs during the first 2 days of hospitalization. Nonsurviving dogs with sepsis were noted to have lower protein C and AT than survivors.[49]

Tissue factor pathway inhibitor is released from the endothelium and acts to bind and inhibit the TF-VIIa complex and factor Xa, in essence preventing activation of coagulation via the extrinsic pathway[50] (see endogenous anticoagulants for more details). The exact role of TFPI in DIC or inflammatory disease states remains to be determined, but exogenous TFPI appeared to be capable of preventing mortality during systemic inflammation and infection in early experimental studies.[7] More recent clinical trials of recombinant TFPI in people have not yielded convincing results, with no benefit in overall mortality.[51,52] Baseline levels of TFPI in veterinary species and the effects of inflammatory disease remain to be determined.

Fibrinolysis

Fibrinolysis is the final protective step to prevent vascular occlusion that can lead to microvascular thrombosis and subsequent organ dysfunction. During clot formation, plasminogen is incorporated and bound to fibrin. Tissue-specific plasminogen activator (tPA) is released from the endothelium and serves to activate plasminogen to plasmin, leading to cleavage of fibrin. Cleavage of crosslinked fibrin by

plasmin produces a degradation product termed D-dimers (named from the structural characteristics of the fibrin molecule).[53-55] Plasminogen activator inhibitor-1 (PAI-1) is a key inhibitor of tPA and acts to balance fibrinolysis. In the face of inflammation, coagulation largely proceeds without a concurrent increase in fibrinolysis.[56,57] The effect of inflammation on endothelial cells appears to initially result in increased concentrations of plasminogen activators (tPA), but a more sustained rise in PAI-1 predominates.[57] Inflammatory cytokines (TNF-α and interleukin 1-β) are at least one mechanism by which PAI-1 is stimulated.[57,58]

Causes of DIC

Any disease process that increases prothrombotic factors, decreases endogenous anticoagulants, causes endothelial dysfunction, or leads to defects in fibrinolysis can trigger DIC in small animals. Typically these are conditions associated with a heightened inflammatory response (e.g., sepsis); however, many other causes have been reported (Table 1).

Diagnosis

DIC is a continuum (from prothrombotic to bleeding), and the diagnosis is complicated by the difficulty in identification of an individual's position on this continuum. In addition, it is often difficult to determine whether the condition is disseminated or localized. Many conditions can mimic DIC on blood work, and yet are localized to a single organ. An example is the dog with a nonbleeding splenic mass or contained splenic hematoma. These patients commonly have evidence of consumption on blood work, yet the hematologic abnormalities stem from a splenic pathology that is causing localized consumption of platelets and coagulation factors. After splenectomy, these coagulation abnormalities quickly resolve, typically without any other intervention.

For the purpose of defining and diagnosing DIC in humans, the Scientific Subcommittee of the International Society on Thrombosis and Haemostasis on DIC divided the condition into nonovert and overt DIC.[59] Here, overt DIC ("uncompensated") represents the advanced end of the continuum in which a patient has experienced marked consumption of coagulation factors and platelets, and generally exhibits a hemorrhagic phenotype. This occurs when antithrombotic measures and other endogenous defenses are overwhelmed. Nonovert DIC ("compensated") describes the patient that is difficult to diagnose, as coagulation is activated but still harnessed by antithrombotic elements. These patients typically do not experience bleeding, but are conceivably at highest risk for thrombosis.

Traditionally, DIC in veterinary medicine has been diagnosed based on a clinical condition capable of inciting DIC and 2 or more laboratory abnormalities from the following: thrombocytopenia, prolonged activated partial thromboplastin time (aPTT)/prothrombin time (PT)/or thrombin clot time, hypofibrinogenemia, decreased AT, elevated markers of fibrinolysis (fibrin[ogen] degradation products or D-dimers), or erythrocyte fragmentation on a blood smear (schistocytes, keratocytes, acanthocytes).[60] Using greater numbers of abnormalities for diagnosis of DIC increases the specificity, whereas using lesser numbers of coagulation abnormalities increases the sensitivity for detection (although less specific). This approach is, however, aimed at markers of consumption and will not reliably identify nonovert DIC patients.

Scoring systems have also recently been proposed to increase the utility of coagulation testing for the diagnosis of DIC. In a recent study, a broad array of coagulation parameters were assayed in ill dogs admitted to 2 university hospitals. Among the values assayed were coagulation times (PT and aPTT), endogenous coagulation inhibitors (protein C and S, AT), components of the fibrinolytic system (plasminogen, α2-antiplasmin), and a marker of fibrinolytic activity (D-dimer).

Table 1
Reported causes of DIC in dogs and cats

- **Dogs**
  - *Neoplasia*
    - Hemangiosarcoma[74-77]
    - Mammary carcinoma[74,75]
    - Splenic tumor[74]
    - Renal carcinoma[78]
    - Lymphoma[74,79]
    - Heart base tumor[74]
    - Leukemia[74]
    - Malignant histiocytosis[74]
    - Pulmonary adenocarcinoma[75]
  - *Infections*
    - Sepsis[74,80-82]
    - Babesiosis[83,84]
    - Infective valvular endocarditis[85,86]
    - Leishmaniasis[87]
    - *Pseudallescheria boydii*[88]
    - *Dirofilaria immitis*[89]
    - Angiostrongylus vasorum[74]
    - Leptospirosis[90]
    - *Anaplasma phagocytophilum*[91]
  - *Immune-mediated Disorders*
    - Immune-mediated hemolytic anemia[74,92,93]
    - Immune-mediated thrombocytopenia[74]
    - Hemophagocytic syndrome[94]
    - Erythema multiforme[95]
  - *Toxicoses*
    - D-limonene-based dip[94]
    - Zinc toxicosis[96]
    - Aflatoxicosis[97]
  - *Miscellaneous Conditions*
    - Snake envenomation[74,98]
    - Hepatopathy[74,82,99]
    - Heatstroke[82,100,101]
    - Gastric dilatation volvulus[74,102]
    - Polytrauma[74,103]
    - Pancreatitis[74,82]
    - Hemorrhagic gastroenteritis[74]
    - Liver lobe torsion[104]
    - Nephrotic syndrome[105]
- **Cats**
  - *Neoplasia*
    - Cranial mediastinal mass[106]
    - Lymphoma[62]
    - Biliary adenocarcinoma[62]
    - Hepatocellular carcinoma[62]
    - Mastocytosis of spleen and bone marrow[62]
    - Pulmonary adenocarcinoma[62]
    - Multiple myeloma[62]
    - Metastatic carcinoma[62]
    - Pancreatic adenocarcinoma[62]
    - Fibrosarcoma[62]
    - Metastatic anaplastic neoplasm[62]
  - *Infections*
    - Sepsis[62,106,107]
    - Cytauxzoonosis[108]
    - Panleukopenia virus[62,106]
    - Feline infectious peritonitis virus[62,106,109,110]
    - Cutaneous abscess/cellulitis[62]
    - Toxoplasmosis[62]
    - Yeast septicemia[62]
    - Feline leukemia virus[62]
    - Pyelonephritis[62]
  - *Immune-mediated Disorders*
    - Immune-mediated hemolytic anemia[62]
    - Vaccine reaction[62]
  - *Miscellaneous Conditions*
    - Lymphadenitis[106]
    - Nephritis[106]
    - Pancreatitis[106]
    - Diabetic ketoacidosis[106]
    - Peritonitis[62,106]
    - Hepatic lipidosis[111]
    - Cholangiohepatitis[106,112]
    - Congestive heart failure secondary to cardiomyopathy[106]
    - Renal amyloidosis[62]
    - Uroperitoneum[62]
    - Trauma[62]
    - Penetrating brain injury[113]

The "gold standard" for diagnosis of DIC was consensus among a panel of experts in the field. The final inclusion for the proposed scoring system included fibrinogen, PT, aPTT, and D-dimer. These values are plugged into a formula for prediction of the probability of DIC.[61] A scoring system will likely increase the predictability of DIC in dogs, and undoubtedly help unify the definition, but also highlights that no particular test, or even group of tests, fits all patients, and those with relatively mild coagulation perturbations may be missed. In the authors' experience, a sudden drop in circulating platelet count accompanied by a mild to moderate prolongation (20%-30%) of aPTT in a patient at risk for systemic inflammation should arouse suspicion for DIC. The reason behind the prolongation of aPTT over PT may indicate ongoing perpetuation of clots, occurring primarily via the intrinsic pathway. Although initial thrombin is generated by TF, the bulk of the factor consumption will be generated via the intrinsic pathway during amplification of coagulation.

Newer coagulation tools may help in the future to better detect patients with nonovert DIC. Some of these tests are currently available (such as quantification of thrombin-antithrombin complexes, which are circulating products of coagulation); however, they have not been assessed in veterinary patients with DIC. Viscoelastic coagulation analysis is another unique test that can give a global overview of coagulation, including fibrinolysis, and may prove useful for characterizing an early prothrombotic state. A significant drawback to viscoelastic analyzers, particularly in DIC, is the sensitivity of the technology, variables affecting results (such as anemia, thrombocytopenia, elevated fibrinogen), and differing methods and coagulation stimuli (activators) that are used. Many of these issues will soon be addressed by a standardization committee on viscoelastic coagulation testing, hopefully unifying the way in which this test is performed and allowing comparison of results between institutions. Despite these drawbacks, viscoelastic coagulation is one of the few methodologies that can document hypercoagulability, a phenomenon that can be challenging to prove with available tests.

Limitations will continue to exist for diagnosing DIC based on laboratory changes in small animals. Different species have idiosyncrasies in coagulation testing, different laboratories use varying assays and reagents, and many assays are difficult to validate. For example, cats with DIC do not seem to be at risk of substantial hemorrhage as is seen in dogs.[60,62] Although thrombocytopenia is among the more consistently seen laboratory changes in dogs with consumption, platelets are notoriously difficult to accurately assess in cats and may result in an inability to truly assess this parameter.[60]

Nonovert DIC should not be ignored simply based on a lack of laboratory abnormalities in a patient at risk for coagulopathy. D-dimers have been proposed as a test that can exclude thromboembolism or thrombus formation, and this test has previously been shown to be highly sensitive and specific for identifying thrombi in subsets of dogs.[63,64] However, no test is perfect, and some patients with life-threatening thrombotic disease will have very little or no laboratory abnormalities to suggest such a process is occurring, potentially because fibrinolysis has not yet been initiated because of the inflammatory state of the patient.

Proving the presence of a thrombus ante mortem can be challenging, particularly when the clinician has no reliable blood tests to increase or decrease suspicion. Dramatic physical examination changes, such as asymmetric edema or a change in pulses or temperature of extremities, should raise concern for thrombotic complications in an at-risk patient. Pulmonary thromboembolism (PTE) (hypoxemia without marked radiographic changes) and portal vein thrombosis (profuse diarrhea, vomiting, and abdominal discomfort) are also common locations for critically ill patients to develop clots. Sometimes, PTE may be suspected based on the presence of pulmonary hypertension detected using echocardiography in the form of tricuspid regurgitant flow (see diseases associated with thrombosis).

Similar to laboratory testing, the ideal imaging modality for identifying thrombi does not exist in veterinary medicine. Testing is often dictated by location, for instance an experienced ultrasonographer can often identify a portal vein thrombus, whereas computed tomography angiography is likely the best available modality for identifying PTE.[65-67] The key is determining when to pursue these diagnostics with little guiding information. In this situation, there is no substitute for experience on the part of the clinician. Although early diagnosis of thrombotic issues is important to allow the best intervention, early recognition of risks and prevention should be the goal.

Treatment

An essential first line of therapy for DIC is the recognition and, ideally, therapy to address the underlying trigger. In the case of sepsis, this would include appropriate antimicrobials and surgery (if indicated to address the source of infection). The inciting cause of the DIC can be as endangering as the coagulopathy that ensues. Treatment should also include supportive care as indicated for each particular patient (e.g., intravenous fluids to maintain euvolemia). Oxygen delivery to tissues must be maintained in patients at risk for or suffering from DIC (Fig. 1). This will prevent tissue hypoxia and the inflammation associated with reperfusion of ischemic tissues.

Commonly used medications for antithrombotic effects in veterinary medicine include aspirin and clopidogrel to decrease platelet function, unfractionated or low-molecular-weight heparins for inhibition of secondary hemostasis, and less commonly warfarin for inhibition of secondary hemostasis (see antithrombotic therapy for details and dosages). The use of these drugs is typically guided by knowledge of the underlying disease process (e.g., a platelet-mediated clotting disorder or predominance for arterial thromboembolism will likely benefit from platelet function inhibitors). The efficacy of aspirin in cats has come into question based on recent platelet studies, and should thus probably be used when other options are not available.[68] Antiplatelet medications are not commonly used in patients with thrombocytopenias and have the added disadvantage of requiring oral administration, which is not always tolerated in critically ill patients. Although platelets are implicated in the pathogenesis of DIC, the use of antiplatelet medications in this condition have not been studied, and inhibition of platelet function in a patient with low platelet count may be more likely to result in hemorrhage.

For these reasons, the primary anticoagulant drug used for therapy of the procoagulant phase of DIC is heparin. The correct target or guide for heparin therapy is not known for small animals (see antithrombotic therapy). Other studies on the ability of viscoelastic coagulation testing (e.g., thrombelastography) to monitor anticoagulation with heparins are promising, but definite targets have not yet been defined.[69] Warfarin is generally reserved for specific cases, because it requires experience with its use to effectively treat dogs without causing excessive bleeding and is also administered orally.

Therapy for Overt DIC

Dogs are most commonly diagnosed with DIC when they are in a state of overt DIC and have evidence of a consumptive coagulopathy. Blood products are indicated when these patients exhibit spontaneous bleeding. Fresh frozen plasma is generally used for replacement of consumed coagulation factors. Dogs and cats need a dose of at least 6 to 10 mL/kg (up to 20 mL/kg) for correction of bleeding from factor deficiency. Cryoprecipitate may also be used when a deficiency in fibrinogen is the primary disturbance, because cryoprecipitate contains primarily factor VIII, vWF, factor XIII, and fibrinogen. Fresh frozen plasma also contains these elements but is delivered in a larger volume. The aPTT and PT should always be reassessed after transfusion for bleeding or prolonged aPTT/PT, because many patients may require additional therapy. Packed red blood cells (pRBC) are given to

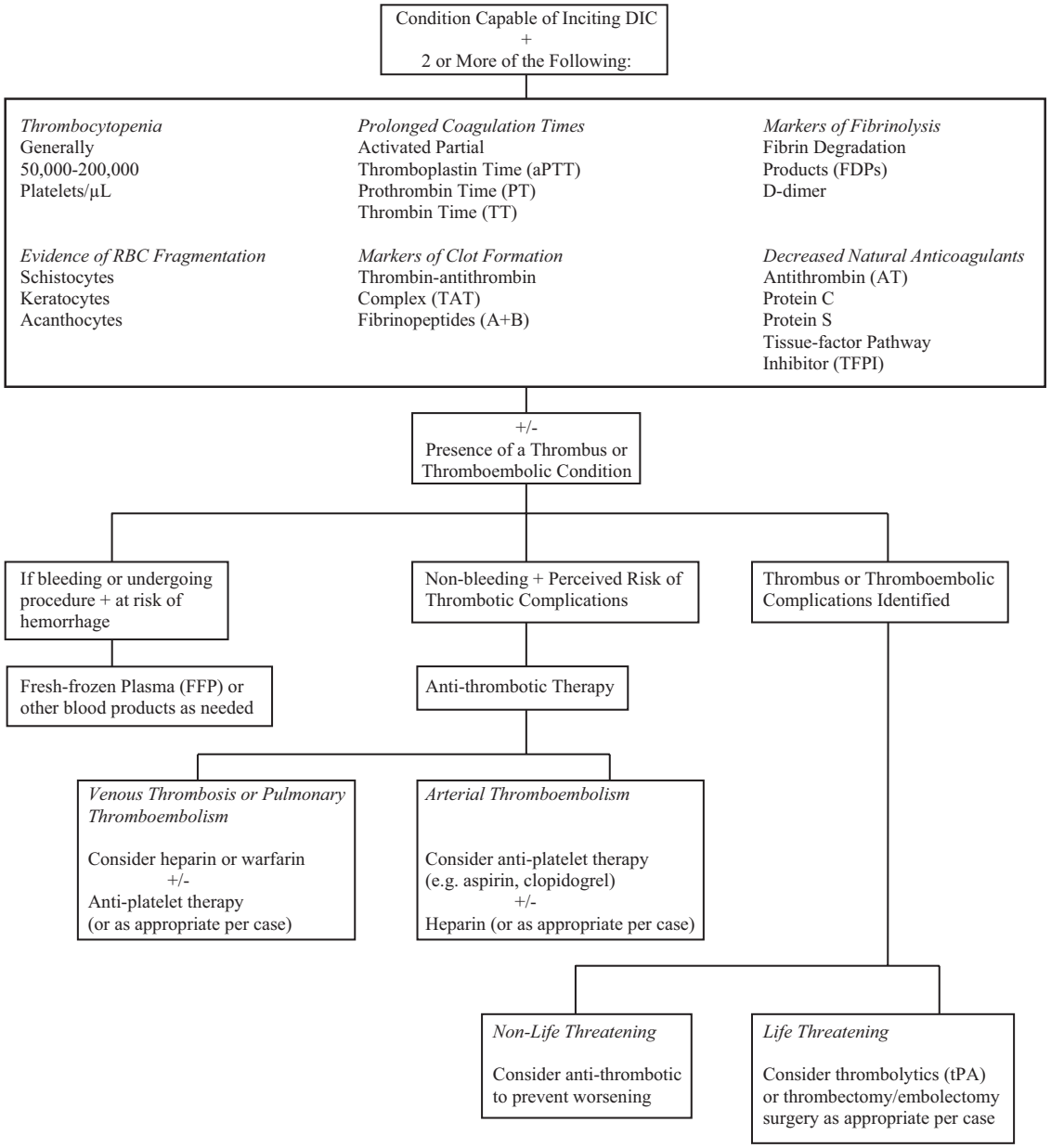

Fig. 1. Treatment algorithm for patients at risk for DIC.

augment oxygen-carrying capacity, whereas crystalloid fluids (e.g., lactated Ringer's solution) are given to replace lost volume, and artificial colloids (e.g., hetastarch or tetrastarch) may be used to maintain colloid oncotic pressure. pRBCs are generally dosed at 5 to 10 mL/kg, and an increase in hematocrit of approximately 1% can be anticipated for each milliliter per kilogram of pRBCs infused. If whole blood is used, dosing can be based on the donor hematocrit, or may be estimated as 2 to 3 mL/kg to result in a 1% increase in packed cell volume (PCV). Because of continued blood loss, ongoing underlying pathology, and possible splenic sequestration of red blood cells, it is inevitably difficult to predict a specific rise in PCV. The clinician should always assess clinical signs of perfusion (heart rate, urine output, etc.) as well as other laboratory diagnostics (lactate, PCV, etc.) to judge the need for additional transfusions.

Blood products may also be needed for patients with significantly prolonged coagulation times that are scheduled to undergo an invasive diagnostic or therapeutic procedure, even in the absence of overt hemorrhage. If invasive procedures are not planned, blood products are not necessarily indicated, and frequent reassessment of coagulation times, platelet count, and close patient monitoring is recommended. The reason that transfusions are not routinely recommended for correction of laboratory abnormalities in the absence of bleeding is because of the risk of transfusion reactions, which can range from mild to life-threatening. Transfusion of pRBCs has been

shown to cause a profound inflammatory response in dogs[70] and humans.[71]

Although thrombocytopenia is a common feature of DIC in dogs, platelet transfusions are rarely needed. There is no platelet count that predicts bleeding; however, most animals will not bleed solely from thrombocytopenia, when they have 50,000 or more platelets/μL. If a marked thrombocytopenia is contributing to ongoing hemorrhage, transfusion with platelet concentrates may be warranted. An alternative to the administration of platelet concentrates is fresh whole blood or platelet-rich plasma. Although these products will only result in a small increase in platelet count, they may provide enough active platelets to stop hemorrhage. Dimethyl sulfoxide–stabilized frozen platelet concentrate is also available, although the use of this product has not been studied extensively in dogs and likely has significantly lower coagulant activity than fresh platelets.[72]

Intervention with antithrombotic medications is difficult once the patient has developed a consumptive coagulopathy, because these patients are generally hypocoagulable and may be hemorrhaging. An experimental study using thromboplastin-induced DIC in (normal) anesthetized dogs showed that high plasma concentrations of low-molecular-weight heparin were required to halt the consumptive coagulopathy.[73] In the face of a preexisting bleeding tendency, further inhibition of coagulation usually proves challenging, and anticoagulant medications are generally not recommended in these cases.

Therapy for Nonovert DIC

Nonovert DIC intuitively would be the time to intervene with therapies for thromboprophylaxis; however, no well-designed studies are available in veterinary medicine to guide the time or type of intervention. Given the difficulty in documenting risk of thrombosis based on laboratory results, thromboprophylaxis are generally instituted when the risks of thrombotic complications are perceived to outweigh any risk of the medications. In the presence of documented thrombus formation or thromboembolic disease, aggressive anticoagulation should be initiated to prevent further thrombotic complications (see antithrombotic therapy section for more details and dosages). Surgery or thrombolytic therapy (recombinant human tPA, delivered locally or systemically) may also be needed to clear any existing thrombi in parallel with anticoagulants. Prompt recognition and commencement of therapy provide the best chance for a successful outcome in these critical patients.

Conclusion

Many colloquialisms exist for DIC, including “death is coming” or “dead in cage.” Certainly DIC, and the underlying trigger, pose serious jeopardy to the health of the patient, and coagulopathy can add to morbidity, hospital stays, and expense. However, many patients with all spectrums of DIC can be supported if given appropriate supportive care. It is essential to remember that DIC is a system-wide coagulopathy and treatment must be targeted to the whole patient. In addition to elimination of the underlying cause, maintaining perfusion and oxygen delivery (fluid support, maintenance of colloid oncotic pressure, oxygen supplementation), appropriate antimicrobial treatment, and aggressive supportive care (e.g., nutritional supplementation) are all essential elements in the arsenal to combat DIC. Emphasis should be placed on recognizing patients likely to develop DIC, prompt intervention when appropriate, and supportive care during the critical illness.

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