

DISSEMINATED INTRAVASCULAR COAGULATION: AN UPDATE FOR THE CLINICIAN **Susan G. Hackner, BVSc.MRCVS.DACVIM.DACVECC.**

Disseminated intravascular coagulation (DIC) is a syndrome characterized by the systemic activation of coagulation, leading to widespread microvascular thrombosis which compromises organ perfusion and can contribute to organ failure. The ongoing activation of coagulation may exhaust platelet and coagulation factors, resulting in a hypocoagulable state and bleeding, particularly in patients at risk for blood loss, such as surgical patients. DIC is a complex and dynamic process; thrombosis and bleeding can occur separately or concurrently, and the diverse clinical characteristics of this disorder make diagnosis and management challenging. DIC is associated with substantial mortality in humans and in animals. Mortality rates of 50-77% are reported in dogs, and 93% in cats.

ETIOPATHOGENESIS

DIC invariably occurs as a complication of an underlying disorder. Numerous infectious and noninfectious inflammatory conditions have been associated with DIC (Table 1). Sepsis and the systemic inflammatory response syndrome (SIRS) are the most common causes in humans and dogs. In human patients, sepsis is complicated by DIC in 25-50% of cases. DIC is also relatively common with a variety of malignancies. In 208 dogs with malignancies, 12.2% of dogs with solid tumors had evidence of DIC. The incidence of DIC was highest in dogs with hemangiosarcoma (46.7%), mammary gland carcinoma (28.5%), and pulmonary adenocarcinoma (50%). While DIC was not identified in any dogs with hematopoietic neoplasia in this study, DIC has been subsequently documented in association with canine lymphoma. In a retrospective study of feline DIC, the most common underlying disorders were neoplasia (40%), pancreatitis (26%), sepsis (19%), and infectious diseases (13%). Of the cats with neoplasia, most had lymphoma or carcinoma.

Inflammation and hemostasis are intimately linked. Leukocytes release cytokines, notably tumor necrosis factor (TNF)- α , interleukin (IL)-1 and IL-6, which are the pathophysiologic initiators of DIC. Inflammatory molecular and cellular cross-talk amplifies thrombin generation, depresses natural anticoagulants, and inhibits fibrinolysis, leading to loss of localization of hemostasis and widespread microvascular thrombosis.

Cytokines damage microvascular endothelium and induce the expression of tissue factor (TF) on mononuclear, endothelial, and tumor cells, activating the TF-fVIIa pathway. Platelets are also activated by leukocyte-secreted platelet activating factor (PAF). Plasma levels of antithrombin (AT) are reduced due to consumption, degradation by neutrophil elastase, and impaired hepatic synthesis. The protein C pathway appears to be most adversely affected by inflammation. As DIC progresses, levels of activated protein C (APC) decline as a result of consumption, cytokine-mediated down-regulation of endothelial thrombomodulin (TM), oxidative injury of TM by neutrophils, impaired hepatic synthesis, and decreased concentrations of protein S. A study in humans revealed that in fatal DIC, protein C antigen was 40% at the time of death, and protein C activity was undetectable. Inflammatory cytokines also stimulate production of the major inhibitor of fibrinolysis (plasminogen activator inhibitor-1, PAI-1) such that the fibrinolytic system is largely suppressed at the time of maximal activation of coagulation. Given the anti-inflammatory functions of AT and APC, decreased activities result not only in unchecked coagulation but also in the unopposed escalation of inflammation.

DIAGNOSIS

Clinical Presentation

Owing to the dynamic and progressive nature of DIC, clinical signs vary considerably and range from no signs (nonovert or peracute DIC), to signs of organ failure associated with microvascular thrombosis, and culminating in overt signs of bleeding (overt or acute DIC). Bleeding occurs in a minority of patients with DIC; organ dysfunction is more common. In a canine study, the majority of dogs with DIC were

hypercoagulable as determined by thromboelastography (TEG); only 22% were hypocoagulable. In a feline DIC study, only 15% of cats had evidence of bleeding. Clinical signs of organ dysfunction vary with the organ/s involved and the extent of perfusion compromise. Common ischemic manifestations are renal failure, respiratory insufficiency, hepatic failure, and gastrointestinal compromise. Bleeding tendencies reflect disorders of primary and/or secondary hemostasis and may manifest as prolonged bleeding from venipuncture sites, petechiae/ecchymoses, epistaxis, hematoma formation, and/or gastrointestinal, urinary, or intracavitary hemorrhage. A chronic, compensated form of DIC is described, occurring weeks to months after the onset of disease. Low-grade or intermittent procoagulant release is compensated by the increased production of platelets, coagulation factors and anticoagulants. The major challenge for the clinician is to diagnose DIC in the early, hypercoagulable and nonovert stage.

Laboratory testing

DIC should be considered in any patient with a disease processes that may be associated (Table 1). Testing should be performed early and repeatedly.

Individually, most hemostatic tests are relatively sensitive, but not specific, for overt DIC. An exception is D-dimers in cats; these assays do not appear to be sensitive in this species, but one study suggested that they may be useful in detecting organ pathology and predicting impending hemostatic abnormalities. Given the lack of test specificity, tests are best evaluated together, and in the light of the clinical findings. There is neither a gold-standard nor consensus for the diagnosis of DIC in animals. Most veterinary publications have based diagnosis on the presence of an underlying condition that could trigger DIC, together with 3 or more of the following anomalies: thrombocytopenia, PT and/or aPTT prolongation, elevated FSPs or D-dimers, hypofibrinogenemia, reduced AT activity, and/or red blood cell fragmentation. The International Society on Thrombosis and Hemostasis (ISTH) recommends a diagnostic scoring algorithm for human patients. If the patient has underlying disease known to be associated with DIC, then routine hemostatic tests are performed. Test results are assigned a score of 0 to 3 based on the extent of abnormality, and cumulative scores of 5 or greater are considered compatible with overt DIC. Given the dynamic nature of DIC, recommendations are to repeat the algorithm daily in at-risk patients. A prospective evaluation of this scoring system in ICU patients revealed high sensitivity and specificity, and a strong correlation between an increasing DIC score and mortality. A similar scoring system has been developed and evaluated in dogs with DIC-associated conditions. This model, which establishes a score based on PT, aPTT, fibrinogen and D-dimers, was shown to have a good sensitivity and specificity, with positive and negative predictive values of approx. 80%.

The diagnosis of DIC by routine laboratory testing is largely restricted to identification of the overt coagulopathic stage of the disease. TEG evaluates global hemostatic status, and allows identification of the more common hypercoagulable phase. A study in dogs demonstrated that TEG differentiated hypercoagulable and hypocoagulable patients, and that 28-day mortality was significantly higher in dogs that were hypocoagulable. This suggests potential utility of TEG as a prognostic indicator and an aid to guide individualized therapy.

MANAGEMENT

Outcome is improved by early and aggressive therapy. There is general consensus that early intervention in patients with DIC increases the chances of survival. The cornerstone of DIC management is specific and vigorous treatment of the underlying condition. Specific therapy may involve surgical or medical management of neoplasia, or immunosuppressive therapy for immune-mediated disease. When a septic process is suspected, removal and/or drainage of infected, torsed, ischemic, or necrotic tissue is performed as soon as possible, and samples submitted for cytology, histopathology, culture and sensitivity. Pending results, antimicrobial therapy should be initiated as early as possible.

Aggressive support is required to minimize the impact of DIC. Adequate perfusion must be restored and maintained via appropriate fluid therapy, to alleviate vascular stasis, hypoxia and acidosis that promote coagulation activation. In addition, management should aim to support those organs that are susceptible

to microvascular thrombosis and ischemia, most notably the kidneys, lungs, and gastrointestinal tract. Renal function should be closely monitored via urine output, specific gravity, and serum creatinine concentration. Oliguria or renal insufficiency should prompt early adjustment of fluid therapy and, possibly, diuretic or dopamine administration. Oxygen supplementation is indicated for hypoxemia resulting from pulmonary compromise. Mechanical ventilation is sometime necessary, when oxygen supplementation fails to correct hypoxemia, or with significant hypoventilation. Early enteral nutrition supports gastrointestinal mucosal integrity. Antacid and/or antibiotic therapy may be indicated if compromised mucosal integrity is suspected.

Low levels of platelets and coagulation factors increase the risk of bleeding. Transfusion, however, is not recommended on the basis of laboratory results alone, and is only indicated in patients with active bleeding or those undergoing an invasive procedure. It has been suggested in the veterinary literature that the administration of FFP may be of benefit in DIC by supplying AT to bolster the sagging anticoagulant pathways. Evidence, however, does not support this. It has been shown that, for a beneficial effect of AT supplementation, AT must be administered in sufficient amounts to result in activity of 1.5-2.0 times normal. Even massive doses of FFP did not increase AT concentrations in humans with acute pancreatitis. Similarly, increased AT levels were not documented following moderate doses of FFP in critically ill canine patients.

Heparin has been a traditional mainstay of DIC therapy, based largely on the rationale that improved anticoagulation would balance the profound procoagulant activity of DIC. Heparin therapy has never, however, been subjected to randomized clinical trials of significant magnitude to determine if there is indeed a therapeutic benefit in human or animal patients with DIC. Much of the literature that supports the use of heparin is relatively old. The past decade has produced sufficient evidence to cast reasonable doubt regarding the role of heparin in DIC therapy. The anti-inflammatory effects of AT binding to endothelial heparan sulfates is abrogated by the administration of exogenous heparin.^{157,289} In a clinical trial designed to evaluate the use of AT concentrate in septic human patients, mortality was higher in patients that also received heparin. The debate over the rightful place of heparin in DIC therapy continues to be vigorous and will likely not be resolved until large randomized and controlled studies are performed in septic and nonseptic DIC patients. When the currently available evidence is considered, however, it suggests that heparin should not be used for patients with DIC in whom inflammatory conditions concurrently exist. Moreover, heparin can be detrimental in bleeding or hypocoagulable patients. There remains overwhelming evidence that heparins have excellent prophylactic efficacy in patients at high risk for macrovascular thromboembolism, and their use in these patients should not be questioned.

Although the pathophysiologic concept of restoring the natural anticoagulant pathways by supplementation of AT, TFPI, or APC is intriguing, and early trials in humans promising, only APC has been demonstrated to impart a survival benefit. The administration of recombinant APC to septic patients significantly reduced mortality and attenuated DIC and inflammation. These agents have yet to be evaluated in animals.

Table 1. Conditions associated with disseminated intravascular coagulation.

Infectious, inflammatory

Bacterial

- Bacterial sepsis
- Severe, localized infection

Viral

- Infectious canine hepatitis
- Canine distemper
- Canine parvovirus
- Feline infectious peritonitis
- Feline panleukopenia

Protozoal

- Severe systemic protozoal disease
- Fungal
 - Fulminating systemic fungal disease
 - Candida sepsis
- Noninfectious, inflammatory**
- Neoplasia
 - Solid tumors
 - Myeloproliferative/lymphoproliferative malignancies
- Tissue trauma, ischemia
 - Severe shock
 - Heat stroke
 - Pancreatitis
 - Massive crushing injury
 - Severe burns
 - Envenomation (snake, insect)
 - Gastric dilatation-volvulus
 - Severe gastroenteritis
 - Heartworm disease
- Immune-mediated
 - Immune-mediated hemolytic anemia
 - Hemolytic transfusion reaction

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