

Disseminated Intravascular Coagulation

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KEY WORDS

- dog
- cat
- fibrinolysis
- disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC), previously referred to as consumptive coagulopathy or defibrination syndrome, refers to a complex syndrome in which (1) excessive intravascular coagulation leads to multiple organ microthrombosis and (2) inactivation or excessive consumption of platelets and clotting factors secondary to enhanced fibrinolysis leads to paradoxical bleeding.^{1,2} DIC is not a specific disorder but rather is a common pathway in a variety of neoplastic and nonneoplastic disorders. Moreover, DIC constitutes a dynamic phenomenon in which marked changes in the patient's status and in the results of coagulation tests occur rapidly and repeatedly during the course of treatment. This syndrome is relatively common in dogs and cats.

PATHOGENESIS

Several general mechanisms (e.g., endothelial damage, platelet activation, and release of tissue “procoagulants”)^{1,2} can lead to disseminated or multifocal activation of intravascular coagulation, and hence DIC.

Endothelial damage commonly results from electrocution and heatstroke, although it may play a role in sepsis-associated DIC. Platelets can be activated by a variety of stimuli, mainly by viral infections (e.g., feline infectious peritonitis in cats)³ and endotoxemia; in addition, due to unknown reasons, platelets in dogs with cancer may be hyperaggregable.^{4,5} Release of tissue procoagulants occurs in several common clinical conditions, including trauma, pancreatitis, bacterial infections, erythema multiforme, and some neoplasms (e.g., hemangiosarcoma [HSA]).^{1,2,6,7}

The best way to understand the pathophysiology of DIC is to think about this syndrome as an extremely magnified physiologic process in which coagulation and fibrinolysis are markedly exacerbated and occur

systemically rather than locally. Although listed sequentially, most of the following events occur simultaneously and the intensity of each individual process varies with time, thus leading to an extremely dynamic process.

First, the primary (i.e., platelets and blood vessels) and secondary (i.e., clotting factors) hemostatic plugs are formed; because this is happening in multiple small vessels simultaneously, multiple thrombi are formed in the microcirculation, which if left unchecked will eventually lead to ischemic necrosis and organ failure. During this excessive intravascular coagulation, platelets are utilized or consumed in large quantities, leading to thrombocytopenia. Second, the fibrinolytic system is activated (i.e., there is circulating plasmin), resulting in clot lysis, inactivation (or lysis) of clotting factors, and impaired platelet function (due to release of fibrin degradation products [FDPs]). Third, antithrombin III (AT III) (and possibly also proteins C and S) is (are) consumed in attempts to halt intravascular coagulation, thus leading to “exhaustion” of the normal anticoagulants. Fourth, the formation of fibrin within the microcirculation leads to hemolytic anemia, as the red blood cells (RBCs) are sheared by these fibrin strands (i.e., fragmented RBCs or schistocytes).

When taking all of this into consideration, it is easy to understand why a patient with multiple organ thrombosis (due to excessive intravascular coagulation and depletion of natural anticoagulants) is bleeding spontaneously (due to thrombocytopenia, impaired platelet function, and inactivation of clotting factors) and why one of the therapeutic approaches that appears to be beneficial (see below) in patients with DIC is to paradoxically halt the bleeding by administering heparin. If sufficient AT III is available, heparin will halt intravascular coagulation, which in turn will decrease the activation of the fibrinolytic system, thus releasing the inhibitory effect on the clotting factors and platelet function.^{8,9}

In addition, impaired tissue perfusion results in secondary “enhancers” of DIC, including hypoxia; acidosis; hepatic, renal, and pulmonary dysfunction; and release of myocardial depressing factor.² Also the function of the mononuclear phagocytic system (MPS) is impaired, so that FDPs and other by-products, as well as bacteria absorbed from the intestine, cannot be cleared off circulation. These factors also need to be addressed therapeutically (see below).

A variety of disorders are commonly associated with DIC in dogs and cats (see box on left on p. 42).

DISORDERS ASSOCIATED WITH DIC IN DOGS AND CATS

Dogs

Hemangiosarcoma
Sepsis
Immune
hemolytic anemia
Pancreatitis
Metastatic
malignancies
Erythema multiforme

Cats

Lymphoma (liver)
Cholangiocarcinoma
Pancreatic
adenocarcinoma
Sepsis
Hepatic lipidosis

At the Veterinary Teaching Hospital at The Ohio State University (VTH-OSU) severe DIC is most commonly associated with HSA, followed by sepsis and pancreatitis in dogs; in cats, primary or metastatic hepatic neoplasms, hepatic lipidosis as a consequence of protracted anorexia, and sepsis are causes of DIC. The pathogenesis of DIC in dogs with HSA appears to be complex and multifactorial; it was believed that the major mechanism triggering intravascular coagulation in dogs with this neoplasm was the abnormal irregular endothelial surface within the tumor (i.e., leading to exposure to subendothelial collagen and activation of coagulation).¹⁰ However, because dogs with HSA and small tumor bulk can have severe DIC whereas some dogs with widely disseminated HSA may have normal hemostasis *in vitro*, it is my belief that some canine HSAs synthesize a procoagulant.

CLINICAL FEATURES

There are several clinical presentations in dogs with DIC; the two common forms are chronic (silent or subclinical) and acute (or fulminant). In the chronic or silent form, there is no evidence of spontaneous bleeding, but laboratory evaluation of the hemostatic system reveals abnormalities compatible with this syndrome (see below). This form of DIC appears to be common in dogs with a variety of malignancies, in dogs with sepsis, and in most cats with hepatic neoplasms or sepsis. The acute or fulminant form is characterized by spontaneous bleeding; it may represent a true acute phenomenon (e.g., after acute chemotherapy-induced pancreatitis) or, more commonly, acute decompensation of a chronic silent process (e.g., dogs with HSA). Acute DIC is extremely rare in cats.

Regardless of the pathogenesis, dogs with acute DIC are often presented for evaluation of profuse spontaneous bleeding in combination with constitutional signs secondary to the anemia or to parenchy-

DIAGNOSTIC CRITERIA FOR DIC IN DOGS AND CATS

Hemolytic anemia
Schistocytes (RBC fragments)
Prolonged OSPT
Prolonged APTT
Positive FDPs
Thrombocytopenia

mal organ thrombosis (i.e., end-organ failure). The clinical signs of bleeding are suggestive of both primary (i.e., petechiae, ecchymoses, mucosal bleeding) and secondary (i.e., blood in body cavities) bleeding. In addition, clinical and laboratory evidence of organ dysfunction is present (see below). Most dogs in acute DIC have ventricular arrhythmias due to myocardial hypoxia/thrombosis.

DIAGNOSIS

Several hematologic findings help support a presumptive clinical diagnosis of DIC, including regenerative hemolytic anemia (although occasionally, given the fact that the patient is affected by a chronic disorder such as cancer, the anemia is nonregenerative or only mildly regenerative), hemoglobinemia (due to intravascular hemolysis), presence of RBC fragments or schistocytes, thrombocytopenia, neutrophilia with left shift, and, rarely, neutropenia. Most of these features are evident after evaluating a spun hematocrit and a blood smear.^{11,12}

Serum biochemical abnormalities in dogs and cats with DIC may include hyperbilirubinemia (secondary to hemolysis and/or hepatic necrosis), azotemia and hyperphosphatemia (if severe renal microembolization has occurred), increased liver enzyme activity (due to hypoxia or hepatic microembolization), decreased total CO₂ content (due to metabolic acidosis), and, if the bleeding is severe enough, panhypoproteinemia.¹²

A urinalysis usually reveals hemoglobinuria and bilirubinuria, with occasional proteinuria and cylindruria. In this regard, urine samples in patients with acute DIC should not be obtained by cystocentesis, since severe intravesical or intramural bleeding may occur.¹²

Hemostatic abnormalities in dogs and cats with DIC include several of the following (see box on right above): thrombocytopenia, prolongation of the one-stage prothrombin time (OSPT) and/or activated partial thromboplastin time (APTT) of over 25% of the concurrent control, positive FDP test, and decreased

AT III concentration/activity; hypofibrinogenemia may also be present but is uncommon (i.e., less than 40% of the patients). In addition to the presence of FDPs, enhanced fibrinolysis can also be documented in these patients by demonstrating decreased plasminogen activity or enhanced clot lysis test. At the VTH-OSU a diagnosis of DIC is made if the patient exhibits four or more of the above hemostatic abnormalities and schistocytosis.^{11,12}

TREATMENT

Once a diagnosis of DIC has been established (or even if there is a high degree of suspicion that DIC is present), treatment should be instituted without delay. Unfortunately, there are no controlled clinical trials in veterinary medicine evaluating the effects of different treatment modalities in dogs or cats with DIC. Therefore the following discussion reflects my beliefs in the management of dogs with DIC (see box at right).¹² Because acute symptomatic DIC is so rare in cats, I have limited experience in treating such patients.

It is unquestionable that removing or eliminating the precipitating cause constitutes the main therapeutic option in dogs and cats with DIC. However, this is rarely possible. Situations in which the precipitating causes can be eliminated include surgical excision of a primary HSA, chemotherapy for metastatic HSA or hepatic lymphoma, and appropriate antimicrobial treatment for patients with sepsis. In most other situations (e.g., pancreatitis, metastatic adenocarcinoma) the cause can rarely be eliminated in a short period. Therefore the treatment of dogs and cats with DIC is aimed at:

- Halting intravascular coagulation
- Maintaining good parenchymal organ perfusion
- Preventing secondary complications

It should be remembered that if blood and blood products were available in an unlimited supply (such as occurs in most hospitals for humans), dogs and cats with DIC would not die as a result of hypovolemia but rather would die as a result of pulmonary or other parenchymal organ (e.g., kidney, liver, heart) dysfunction. In our clinic, "DIC lungs" (i.e., intrapulmonary hemorrhages with alveolar septal microthrombi) appear to be a common cause of death in dogs with DIC.¹²

Halting Intravascular Coagulation

In our clinic we halt intravascular coagulation by a dual approach: administering heparin and blood or blood products. As mentioned, heparin is a cofactor

TREATMENT OF DOGS AND CATS WITH DIC

1. Eliminate the precipitating cause
2. Halt intravascular coagulation
 - Heparin**
 - Mini-dose: 5–10 IU/kg SQ tid
 - Low-dose: 100–200 IU/kg SQ tid
 - Intermediate-dose: 300–500 IU/kg SQ or IV tid
 - High-dose: 750–1000 IU/kg SQ or IV tid
 - Aspirin**
 - Dogs: 5–10 mg/kg PO bid
 - Cats: 5–10 mg/kg every third day
 - Blood or blood products (provide AT III)**
3. Maintain parenchymal organ perfusion
 - Aggressive fluid therapy
4. Prevent secondary complications
 - Oxygen
 - Acid-base status
 - Antiarrhythmics
 - Antibiotics

for AT III and therefore is not effective in preventing activation of coagulation unless sufficient AT III activity is present in the plasma. Because AT III activity in patients with DIC is usually low (due to consumption and possibly inactivation), sufficient exogenous quantities of this anticoagulant should be provided. The most cost-effective way of achieving this is through administration of whole fresh blood, fresh frozen plasma, or cryoprecipitate. The old adage that administering blood or blood products to a dog with DIC is analogous to adding "logs to a fire" has not been true in my experience. Therefore blood or blood products should never be withheld based solely on this premise.¹²

Heparin has been used historically to treat DIC in humans and dogs.^{8,9,12} However, there is still controversy as to whether it is beneficial in this syndrome. In our clinic the survival rate of dogs with DIC has increased markedly since we began routinely using heparin and blood products. Although this result can also be attributed to improvement in patient care, it is my belief that heparin is beneficial in such patients and indeed may be responsible for the increased survival rate.¹² My experience in treating cats with DIC with heparin is limited, but the results appear to be similar to those in dogs.

Sodium heparin can be used at a wide range of doses.¹² Traditionally, there are four dose ranges for this anticoagulant (see box on p. 43). At the VTH-OSU we routinely use mini-dose heparin in combination with the blood or blood products. The rationale is that this dose of heparin (1) does not prolong the activated coagulation time (ACT) or APTT in normal dogs and, apparently, cats (a minimum of 150 to 250 IU of heparin/kg tid is needed to prolong the APTT in normal dogs) and (2) appears to be biologically active in these patients (as evidenced by our ability to reverse some of the clinical signs and hemostatic abnormalities in dogs with overt DIC). That mini-dose heparin does not prolong ACT or APTT is extremely beneficial in the management of patients with DIC. For example, if a dog with DIC is receiving low- or intermediate-dose heparin, it is impossible to determine based on hemostatic monitoring whether the prolongation of the APTT (or ACT) is due to overheparinization or to exacerbation of the DIC. As laboratory heparin determinations become widely available, this point may become moot. Until then, my clinical impression is that prolongation of the ACT or APTT in a patient with DIC receiving mini-dose heparin indicates deterioration of the intravascular coagulation, and therefore a treatment change is necessary. The first dose of heparin is usually added to the blood or plasma and allowed to sit at room temperature for approximately 30 minutes. This may allow for a better heparin-AT III interaction in vitro, so that the heparin-AT III complex is already formed and active when the blood or plasma is administered.

If evidence of severe microthrombosis (e.g., marked azotemia with isosthenuric urine, increased liver enzyme activity) is present, intermediate- or high-dose heparin can be used; the target is to prolong the ACT to 2 to 2.5 times the baseline (or 2 to 2.5 times normal if the baseline was already prolonged). If overheparinization occurs, protamine sulfate can be administered by slow intravenous infusion at a dose of 1 mg for each 100 IU of the last dose of heparin; administer 50% of the calculated dose 1 hour after the heparin and 25% 2 hours after the heparin. The remainder of the dose can be administered if clinically indicated. Protamine sulfate should be administered with caution because it can be associated with acute anaphylaxis in dogs. Once improvement in the clinical and laboratory parameters has been achieved, the heparin dose should be tapered off gradually (over 3 to 4 days); this may prevent a rebound hypercoagulable state. The main disadvantage of using intermediate- or high-dose heparin therapy is that the patients need close hemostatic monitoring because severe bleeding in-

duced by heparin is relatively common.¹²

Aspirin can also be used to prevent platelet activation and thus halt intravascular coagulation. Doses of 5 to 10 mg/kg PO (bid in the dog and every third day in the cat) have been recommended; doses as low as 0.5 mg/kg inhibit in vitro platelet aggregation in dogs. In my experience aspirin is rarely of clinical benefit, but if used the patient should be closely monitored for severe gastrointestinal bleeding; this nonsteroidal antiinflammatory drug can cause gastroduodenal ulceration, which could be catastrophic in a dog with a severe coagulopathy such as DIC.

Maintaining Good Parenchymal Organ Perfusion

Good parenchymal organ perfusion is best maintained by using aggressive fluid therapy with crystalloids or plasma expanders such as dextran (see box on p. 43).¹² The purpose of this is to "dilute out" the clotting and fibrinolytic factors in circulation, to flush out microthrombi from the microcirculation and maintain adequate blood flow, and to maintain patency of the precapillary arterioles so that blood will not be shunted to areas where oxygen exchange is not efficient. However, care should be exerted not to overhydrate a patient with compromised renal, cardiac, or pulmonary functions. In addition, dextrans can by themselves induce prolongation of the APTT and OSPT in dogs and cats.

Preventing Secondary Complications

As discussed, a number of complications occur in dogs with DIC. Attention should be directed to maintaining oxygenation (i.e., by oxygen mask, cage, or nasopharyngeal catheter), correcting acidosis (by using appropriate crystalloid solutions such as sodium bicarbonate or lactated Ringer's solution), correcting cardiac arrhythmias (by using antiarrhythmics, magnesium chloride, etc.), and preventing secondary bacterial infections (i.e., the ischemic gastrointestinal mucosa no longer functions as an effective barrier for microorganisms, bacteria are absorbed and cannot be cleared by the hepatic MPS, and sepsis occurs).

The prognosis for dogs and cats with DIC is still grave. However, if the inciting cause can be controlled, most dogs will recover with appropriate treatment.

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