Disseminated Intravascular Coagulation

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ABSTRACT: Disseminated intravascular coagulation (DIC) is a serious, life-threatening condition in humans and animals. A secondary complication in a variety of disorders, it is a complex syndrome in which excessive intravascular coagulation leads to microthromboses in and consequential failure of multiple organs with concurrent paradoxical bleeding due to inactivation and excessive consumption of platelets and clotting factors. This article discusses the pathophysiology, diagnosis, and treatment of DIC in dogs and cats. Novel treatments and laboratory tests, some of which are still being experimentally evaluated, are also discussed.

Disseminated intravascular coagulation (DIC) is a serious, life-threatening complication in humans and animals, previously called consumptive coagulopathy or defibrination syndrome. In this complex syndrome, excessive intravascular coagulation leads to diffuse microthromboses and subsequent failure of multiple organs. Inactivation and excessive consumption of platelets and clotting factors cause concurrent paradoxical bleeding. DIC is not a primary disease but rather a secondary complication of several disorders (Box 1). Moreover, it constitutes a dynamic phenomenon during which the patient’s status and laboratory coagulation test results may fluctuate markedly, rapidly, and repeatedly. It is relatively common in dogs and uncommon in cats.

PATHOPHYSIOLOGY

In healthy animals, the normal mechanisms of clot formation and fibrinolysis are well balanced so that coagulation and clot formation occur only on demand. In DIC, this balance is disrupted, leading to concurrent excessive clot formation and bleeding (Figure 1). Thus, DIC may be considered as an uncontainable burst of thrombin generation and activation resulting in systemic fibrin formation, plasmin activation, suppression of the physiologic anticoagulation mechanisms, and delayed fibrin removal as a consequence of impaired fibrinolysis.

During this excessive intravascular coagulation phase, platelets and coagulation factors are consumed, resulting in thrombocytopenia, thrombocytopathy, and depletion and inactivation of coagulation factors.

DIC is an acquired syndrome that occurs as a result of a primary disorder. Three factors, commonly termed Virchow’s triad, predispose patients to thrombosis: stasis, hypercoagulability, and blood vessel wall injury. Therefore, any disease process that results in capillary stasis, loss of...
vascular integrity, or hypercoagulability (e.g., the presence of inappropriate matter in the bloodstream, tissue necrosis) can lead to disruption of the balance between hemostasis and fibrinolysis and subsequently induce DIC.\textsuperscript{5,8} Depending on the activation rate of the hemostatic system, DIC may present on the one extreme as a peracute, life-threatening clinical event and on the other as a chronic condition with no overt hemorrhage or thrombosis.\textsuperscript{5,8,10,11}

Many common systemic diseases associated with inflammation have been reported to initiate DIC in dogs and cats\textsuperscript{12–17} (Box 1). In a recent study\textsuperscript{13} that included 164 dogs with solid tumors, 12.2\% of the dogs presented with DIC, and dogs with hemangiosarcoma, mammary gland carcinoma, or pulmonary adenocarcinoma had a significantly higher incidence of DIC. In another study\textsuperscript{12} of 54 dogs with heatstroke, 50% presented with DIC.

Regardless of whether the intrinsic or extrinsic activation pathway is initiated, once triggered, DIC follows the same course. Only recently has the importance of the inflammatory mechanism in the up-regulation of procoagulant factors been recognized. This up-regulation results in increased thrombin generation, systemic fibrin formation, down-regulation of natural anticoagulants, and delayed fibrin removal as a consequence of inadequate fibrinolysis.\textsuperscript{18,19} In addition, inflammation tends to lead to an increase in fibrinogen levels, unless fibrinogen consumption is concurrent.\textsuperscript{20,21} In sepsis or inflammation, the propagation of the coagulation cascade is also promoted by a reduction in the physiologic anticoagulation activity. With extensive clot formation, antithrombin (AT) is consumed by binding in a one-to-one fashion with each clotting factor. Moreover, the presence of endotoxin or inflammatory mediators reduces the endothelial expression of glycosaminoglycans, such as heparan sulfate, that normally augment the activity of AT, leading to reduced AT\textsuperscript{1} activity and endothelial antithrombotic function\textsuperscript{22–26} (Figure 2).

**Generation of Thrombin**

The systemic generation of thrombin in animal models of DIC is mediated exclusively by the extrinsic pathway, involving tissue factor and activated factor VII (VIIa).\textsuperscript{18} Levi and colleagues\textsuperscript{27} showed that inhibition of tissue factor or factor VIIa totally suppressed the endotoxin-induced generation of thrombin, whereas interference in the intrinsic pathway of coagulation did not affect the activation of coagulation.
The conditions that lead to DIC are the same as those associated with systemic inflammatory response syndrome and are characterized by activation of cytokine production. The principal mediators are interleukins 1 and 6 and tumor necrosis factor (TNF), which are released from the monocyte–macrophage system. These cytokines stimulate macrophages to express several procoagulant moieties (mainly tissue factor) on their outer surface. The reactions involved in coagulation initiation and amplification require a membrane surface that contains negatively charged phospholipids. Normally, these negatively charged phospholipids are not expressed on cell surfaces in sufficient concentrations for initiation and propagation of the coagulation cascade to take place. To express the optimal procoagulant lipid surface, potent cell agonists, such as a combination of collagen and thrombin, are required. In addition, increased interleukin-1 levels have been shown to increase platelet reactivity and thrombogenic potential.

**Impairment of Fibrinolysis and the Role of Fibrin Degradation Products**

Studies in animal models of DIC indicate that the fibrinolytic system is largely suppressed when coagulation is maximally activated. This inhibition is caused by up-regulation and a sustained increase in the plasma level of fibrin degradation products (FDPs). The presence of FDPs indicates that fibrin degradation is occurring and that the fibrinolytic system is inhibited.

plasminogen activator inhibitor, the principal inhibitor of the fibrinolytic system, as well as depression of tissue plasminogen activator production.8,27,32 Fibrin deposition forms multiple microthrombi within small blood vessels, leading to tissue ischemia and necrosis in vital organs.7,33 Although the fibrinolytic system is largely activated through the actions of thrombin, as evidenced by increased plasma levels of plasmin–α-2-antiplasmin (PAP) complexes, fibrinogen degradation products (FDPs), and D-dimers as well as a concurrent decrease in plasminogen levels, the degree of fibrinolysis is too low to counteract the massive systemic fibrin deposition.34–38 During the acute inflammatory response and the initiation of DIC, this inadequacy is exacerbated by the increased plasma concentrations of the protease inhibitors α2-macroglobulin and α1-antitrypsin (also known as α1-proteinase inhibitor), both of which inhibit coagulation as well as fibrinolysis.39 In patients with pancreatitis, the excessive release of active trypsin into the bloodstream culminates in a marked depletion of protease inhibitors,40 leading to overt coagulation and fibrinolysis.

The systemically circulating FDPs interfere with fibrin monomer polymerization, leading to further impairment of hemostasis and potential hemorrhage. FDPs, especially fragments D and E, are strong inhibitors of platelet function and, when present in sufficient quantities, coat platelet surfaces and induce platelet dysfunction.41,42 Fibrin-related materials, including FDPs, are normally metabolized by the liver; failure of the liver to clear them from the bloodstream may therefore lead to development of DIC or to worsening of an existing condition.43 Liver failure is a common complication in DIC due to a combination of microthrombosis, anemia, bleeding, and hypoxia; conversely, patients with primary hepatic failure are prone to develop DIC due to the liver’s main role in the production of hemostatic proteins.

**Inhibition and Consumption of Natural Anticoagulants**

Excessive intravascular coagulation results in reduction and down-regulation of the natural anticoagulants AT, and through binding to the cofactor protein S. APC prevents amplification of procoagulant activity by inactivating factors Va and VIIIa and enhances fibrinolysis through inhibition of plasminogen activator inhibitor.47–49 The protein C pathway appears to be more negatively influenced by inflammation than all other natural anticoagulants. Endothelial cell thrombomodulin and protein C receptor are down-regulated by inflammatory cytokines such as TNF-α.50,51 In a canine model of DIC, APC activity decreased after injection of endotoxin.52 APC’s main function in preventing excessive coagulation during inflammation is exemplified by the fact that APC prevented organ damage in experimental models of sepsis by limiting leukocyte and cytokine elaboration and microvascular coagulation.52,53 Thus, marked impairment of APC activity during DIC promotes tissue damage, exacerbates the inflammatory and procoagulant mechanisms contributing to DIC, and further compromises the regulation of activated coagulation.52,6,47 In DIC, APC activity is decreased by a combination of impaired synthesis, a cytokine-mediated decrease in endothelial thrombomodulin expression, and a decline in levels of protein S.5,47

**CLINICAL SIGNS**

Dogs with DIC may present with a variety of clinical signs. Three phases of DIC are recognized: the peracute

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**Disseminated intravascular coagulation is characterized by excessive intravascular coagulation leading to diffuse microthromboses and multiorgan failure. Bleeding occurs concurrently due to excessive inactivation and consumption of platelets and clotting factors.**

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Figure 2. Contact activation (intrinsic) and tissue factor (extrinsic) coagulation pathways and fibrinolytic pathways. Conversion or activation of factors is indicated by blue arrows, inhibition actions by red arrows, actions of thrombin by gray arrows, and lytic actions by yellow arrows. HMWK = high molecular weight kininogen, PF = platelet factor, PK = prekallikrein, Serpin = serine protease inhibitor, TFPI = tissue factor pathway inhibitor.
The clinical signs of disseminated intravascular coagulation include profuse primary or secondary spontaneous bleeding in concert with hemostatic disorders. The constitutional signs are secondary to anemia or to multiorgan dysfunction due to parenchymal organ thromboses.
in 24% and 5% of the cats, respectively. These data may be biased because the patients in these studies may have been included based on their having abnormalities that met the criteria for diagnosis of DIC.

Hematology and coagulation measures relevant to DIC have been studied in cats with experimentally induced FIP. In one study, DIC was induced in kittens by the inoculation of FIP virus. Thrombocytopenia, hyperfibrinogenemia, and increased FDPs were present in all cats after the onset of clinical disease. Plasma activities of factors VIIa, VIIIa, IXa, Xa, XIa, and XIIa were depressed, and PT and aPTT were prolonged. In another study, AT activity was assessed in cats inoculated intraperitoneally with FIP virus. Although coagulation screening test results indicated that all cats had DIC, AT activity 4 days after inoculation was within or above the reference range in all but one cat. These studies prove that DIC can be induced by experimental inoculation with FIP; however, the results also suggest that low-grade DIC may be present in some cats with naturally acquired FIP. In another retrospective study that evaluated clotting times and AT activity in cats with naturally acquired diseases, DIC was diagnosed in 10 of 85 cats; all 10 cats had low AT activity. Because there is no gold standard test for the diagnosis of DIC in cats, it is possible that many feline DIC cases are missed and that the prevalence of feline DIC is higher than reported.

**Plasma D-dimer and Fibrin Degradation Product Concentrations**

D-dimers are products of cross-linked fibrin degradation. Factor XIIIa catalyzes the γ-chain cross-linkage of adjacent terminal domains (D-domains) of fibrin monomers. The D-dimer epitope is exposed when fibrin is lysed by plasmin. Thus, the presence of D-dimers is evidence of the combined actions of thrombin, factor XIIIa, and plasmin and is specific for the combined presence of coagulation and fibrinolysis (physiologic or pathologic). In contrast, an increase in FDPs is not specific evidence of active coagulation because FDPs include both fibrin and fibrinogen degradation products and thus may be increased exclusively by plasmin activity on fibrinogen. Increased FDPs do, however, prove that active fibrinolysis is present. D-dimers may be increased in dogs with non-DIC conditions associated with coagulation and fibrinolysis, including orthopedic surgery, neoplasia, and internal hemorrhage; thus, an increase in D-dimers alone cannot be regarded as confirmation of DIC.

### Table 1. Laboratory Screening Tests for DIC*

<table>
<thead>
<tr>
<th>Parameter/Test</th>
<th>Early Hypercoagulable Phase</th>
<th>Clinical Manifestation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>=↓</td>
<td>↓</td>
</tr>
<tr>
<td>Schistocytosis</td>
<td>None</td>
<td>↑</td>
</tr>
<tr>
<td>PT</td>
<td>=↓</td>
<td>↑</td>
</tr>
<tr>
<td>aPTT</td>
<td>=↓</td>
<td>↑</td>
</tr>
<tr>
<td>Activated clotting time</td>
<td>=↓</td>
<td>↑</td>
</tr>
<tr>
<td>AT activity</td>
<td>=↓</td>
<td>↓</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>↓→↑↑^a</td>
<td>↓</td>
</tr>
<tr>
<td>FDP</td>
<td>=↓</td>
<td>↑</td>
</tr>
<tr>
<td>D-dimer</td>
<td>=↓</td>
<td>↑</td>
</tr>
<tr>
<td>Total protein C</td>
<td>=↓</td>
<td>↓</td>
</tr>
<tr>
<td>TAT</td>
<td>↑</td>
<td>↓→↑^a</td>
</tr>
<tr>
<td>PAP</td>
<td>↑</td>
<td>=↓</td>
</tr>
</tbody>
</table>

*Laboratory results should always be interpreted with caution and in light of the history and clinical signs because an abnormal result from any single test is not specific for the diagnosis of DIC. These tests are not very sensitive markers of DIC, and they may yield normal results in the early hypercoagulable stage of DIC. A positive diagnosis of DIC should rely on at least three abnormal laboratory test results along with compatible clinical signs of DIC. Serial monitoring of laboratory test results to assess the trends in patients suspected of having DIC is useful.

^aDepends on the underlying disease.

=Within normal limits; ↑ increased or prolonged; ↓ decreased or shortened.

**TAT** = thrombin–antithrombin complex

Several D-dimer assays have been evaluated in the diagnosis of DIC in veterinary medicine. Preliminary validation trials in canine patients have shown sensitivities and specificities ranging from 76% to 100% and 77% to 97%, respectively, with sensitivity largely dependent on the methodology and cutoff points used. The reference interval for canine D-dimers was established at 0.02 to 0.28 µg/mL and 0.08 to 0.39 µg/mL in two studies of healthy dogs. One study evaluated the use of latex-agglutination and immunoturbidimetric D-dimer assays and serum and plasma FDP assays in 20 dogs with DIC, using the high cutoff point of 0.39 µg/mL. The sensitivity of the latex-agglutination D-dimer assay was superior to that of immunoturbidimetry.
(100% and 65%, respectively); both assays had equal specificity (97%). Compared with the serum and plasma FDP assays, the latex-agglutination assay had similar sensitivity (85% to 100%) and specificity (90% to 100%).61 Another study64 evaluated a canine-specific D-dimer point-of-care test kit in healthy controls and dogs with DIC, thromboembolic disease, and hemorrhage. In this study, all healthy dogs had negative test results, while all dogs with DIC had positive results.64

Results from recent studies support the use of D-dimer assays in the diagnosis of DIC, combined with evaluation of the history, a complete physical examination, and other traditional laboratory coagulation tests.61,67–69 Although human D-dimer assays have been validated as reliable and accurate in dogs,61 further research is needed to determine their true sensitivity and specificity in different phases of canine DIC as well as in feline DIC. Some authors have recommended that FDPs and D-dimers be assessed in combination to improve the diagnosis of DIC in dogs.66 In one study,70 reference intervals for D-dimers were established in healthy cats as 0.09 to 0.32 µg/mL; however, in another study,71 the same immunoturbidimetric test (STA-Liatest D-DI, Diagnostica Stago, Parsippany, NJ) was found to be not useful for the diagnosis of feline DIC.

**Plasma Fibrinogen Concentration**

The plasma fibrinogen concentration can be high, normal, or low in DIC and therefore is an insensitive marker for DIC.20 A poor sensitivity of 0.8% was reported in dogs with DIC.69 Hyperfibrinogenemia may be present in a variety of conditions other than DIC, including pregnancy and inflammation. Hypofibrinogenemia is considered specific for DIC in human patients72; however, Wada and colleagues associated a poor prognosis with hyperfibrinogenemia in human leukemia and lymphoma patients with DIC.20 They suggested that the combination of hyperfibrinogenemia and decreased fibrinolysis was among the factors leading to the increased prevalence of multigorgan failure observed in these patients, resulting in a higher death rate.20 Because DIC is secondary to other diseases, opposing trends may coexist. Inflammation induces an increase in plasma fibrinogen, while consumption through coagulation and degradation by plasmin lead to a decrease.

**Schistocytosis**

The presence of schistocytes in blood smears has been studied in dogs with DIC. In one study,73 schistocytosis was recorded in 71% of the dogs; however, in a larger study of 252 dogs,73 this abnormality was present in only 10%. Schistocytosis was observed in 61% of 101 cats with DIC in one retrospective study.46 Schistocytes form in non-DIC conditions as well and thus should not be considered specific to DIC.57

**Other Tests**

Other tests that are used in human medicine for the diagnosis and monitoring of DIC have recently been evaluated in veterinary medicine. Their use in canine and feline DIC is expected to grow.

**Protein C Assay**

APC down-regulates thrombin activity by irreversibly inhibiting factors Va and VIIIa.31,55 In DIC, the generation of APC is drastically reduced by a decrease in the thrombomodulin expression on endothelial cells, whereas the production of procoagulant proteases is increased.74 Measurement of total protein C levels has been used in septic human patients to detect hypercoagulable states.2 Combining measurement of protein C with routine tests was recently shown to improve recognition of portosystemic shunts, hepatic failure, and severe hepatobiliary disease in dogs.75 Decreased protein C levels signified a grave prognosis when coupled with hyperbilirubinemia and low AT activity in hepatic failure.

**Fibrinopeptide A Assay**

When thrombin is generated during coagulation, fibrinopeptides A and B (FPA and FPB) are cleaved from fibrinogen, leaving behind fibrin monomers that later polymerize into fibrin through the action of factor XIIIa.58 An FPA assay can, therefore, serve as a reliable marker of actual thrombin generation and “real-time” activity. FPA and FPB levels may be increased due to conditions other than DIC, including other micro- and macrovascular thrombotic events and advanced age,78 or by other enzymes that cleave FPA.76 In humans, FPA levels are increased in patients with DIC, deep vein thrombosis, pulmonary thromboembolism, myocardial or cerebral infarction, advanced neoplasia, or diabetes mellitus.76 Measurement of FPA is complicated by its very short half-life (4 min in humans) and the potential for false-positive results from improper sampling and handling techniques. In humans, an ELISA or radioimmunoassay is used; these assays might be species specific. Their application in veterinary species has not been validated. Among several other abnormalities of
hemostasis, increased FPA levels were found in dogs undergoing experimental whole-body hyperthermia.77

**Plasmin-α₂-Antiplasmin Complex Assay**

α₂-Antiplasmin, also known as α₂-plasmin inhibitor, is one of the main inhibitors of fibrinolysis. Direct measurement of plasmin concentration is difficult because α₂-antiplasmin rapidly complexes with plasmin. PAP complex levels can be measured by either ELISA or radioimmunoassay. PAP concentration is a good indicator of the activity of the fibrinolytic system (e.g., plasmin) and the degree of depletion of its main inhibitor (α₂-antiplasmin).78 During the onset of DIC, PAP levels are markedly increased; with remission, they are expected to decrease.19,58 This test has not been validated in veterinary species; however, injection of tissue plasminogen activator has led to increased PAP concentrations in dogs.79

**Thrombin-Antithrombin Complex Assay**

In a manner similar to the formation of PAP, thrombin creates a stable complex with its inhibitor, AT (thrombin–antithrombin [TAT]). Because the half-life of thrombin is so short, thrombin concentration cannot be measured directly. TAT levels can be used to monitor ongoing activation of thrombin in patients predisposed to hypercoagulable states, such as sepsis. TAT levels determined by human-specific ELISA43 have been validated and used in experimental canine models.80 Recently, an antibody sandwich ELISA TAT test (Enzygnost TAT micro, Dade Behring Marburg, GmbH, Marburg, Germany) has been used in healthy cats and in cats with asymptomatic hypertrophic cardiomyopathy. A reference range for cats has been established at 2.0 to 20.0 µg/L.70

**Thromboelastography**

Thromboelastography (TEG) characterizes the coagulation function by recording a tracing that represents blood clot creation and breakdown. The tracing is a sum of the interactions between coagulation factors, platelets, fibrin, fibrinolysis, and time. Different TEG patterns have been identified in a variety of hemostatic disorders, including coagulation factor deficiencies, thrombocytopenia, increased fibrolysis, and hypercoagulability.82 TEG has been used in septic human patients to identify the hypercoagulable state that precedes the clinically recognizable phase of DIC.83 In veterinary medicine, TEG has been evaluated in a number of studies in dogs and cats with parvoviral enteritis as well as in healthy dogs.84-86 A 2005 study concluded that TEG monitoring of veterinary patients may be promising and that its use warrants further study.87 In a 2007 study that evaluated the efficacy of low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) in healthy cats, reference intervals were established for all TEG parameters.88

**Transmittance Waveform Charts**

Transmittance waveform charts profile light transmittance changes of standard coagulation assays, such as PT and aPTT.89 Analysis and characterization of these data provide qualitative and quantitative information that cannot be obtained from clotting times alone. In human medicine, a biphasic aPTT waveform has been found to have high specificity and sensitivity for DIC.90,91 Furthermore, the degree of the waveform abnormality has been found to correlate with the severity of the hemostatic dysfunction, assisting in monitoring and allowing a prediction of the progression from nonovert to overt DIC.89 This technique may improve the diagnosis of DIC, allowing targeted therapeutic intervention early in the progression of the syndrome.90

**TREATMENT**

Treatment should be instituted immediately when a diagnosis of DIC is established or a high index of suspicion exists.92 Removing or eliminating the precipitating cause constitutes the cornerstone and the main therapeutic goal for patients with DIC. The wide variety of underlying disorders makes the therapeutic approach to DIC particularly difficult.93 Precipitating causes that can be treated and possibly eliminated include primary hemangiosarcoma and other tumors (surgical excision), lymphoma (chemotherapy), sepsis and bacterial infections (appropriate antimicrobial treatment), snakebites (specific antivenom), heatstroke (early appropriate cooling), and immune-mediated hemolytic anemia.
However, the cause can rarely be eliminated within a short time.

The treatment aims for DIC in dogs and cats include the following:

- Impeding and possibly stopping intravascular coagulation and hemorrhage
- Maintaining good parenchymal organ perfusion
- Preventing secondary complications

Replacement therapy is the mainstay for the treatment of DIC. A dual approach of blood component therapy and heparin administration is used to halt intravascular coagulation.

**Blood Component Therapy**

Fresh plasma (FP) or fresh frozen plasma (FFP) is administered to replace the consumed coagulation factors. At least 30 to 50 mL/kg/day is administered, initially at a rate of 10 mL/kg/hr and then at a rate of 2 mL/kg/hr. Alternatively, fresh whole blood can be administered as a source of coagulation factors and inhibitors and platelets. FP/FFP administration is aimed at halting the consumption of platelets, coagulation factors, and inhibitors (e.g., AT, α2-macroglobulin) by arresting the ongoing hemorrhagic and coagulation processes.

**Heparin Administration**

Heparin may be administered during the peracute hypercoagulable phase, when PT and aPTT are shortened, and if AT activity is at least 80%. It can also be administered after FP/FFP administration, but only when laboratory coagulation test results are normal.

The veterinary literature lacks prospective placebo-controlled studies on the use of heparin in DIC. Clinical reports and retrospective studies do not clearly indicate whether heparin use is beneficial. The effects of heparin may vary depending on the underlying cause and stage of DIC. Various uncontrolled studies have shown positive effects, no effect, or negative effects of heparin treatment; therefore, its use in patients with DIC is still under debate.

Heparin enhances thrombin and factor Xa inactivation through activation of AT inhibitory actions and, therefore, is ineffective when AT plasma activity is insufficient. Because AT activity in DIC is usually low (as a result of consumption and, possibly, inactivation), it is advisable to provide the patient with sufficient quantities of AT, most efficiently through blood component replacement. In a single study of dogs with different coagulopathies, FFP therapy (10 to 15 mL/kg q12h) did not result in increased plasma AT activity.

Heparin also inhibits coagulation by inducing the release of glycosaminoglycan-bound TFPI in the microvasculature into the circulation. When coagulation is triggered by bacterial lipopolysaccharides in patients with sepsis, enhancement of TFPI activity represents an upstream anticoagulant action that is even more specific than that of AT.

To the best of our knowledge, there are no controlled prospective studies determining the appropriate heparin dose for DIC in veterinary patients or even substantiating its use in these cases. Extrapolation from the human literature is difficult because human patients at risk for DIC are generally also at high risk for deep vein thrombosis. Consequently, they are usually treated with aggressive heparin prophylaxis for deep vein thrombosis. This is generally not an issue in canine and feline patients. Controlled studies are difficult to conduct because DIC is not a primary disease, and manifestation and prognosis vary widely in accordance with the underlying disease. Several authors have, however, proposed that patients with DIC be given sodium heparin at 50 to 100 IU/kg SC q8h. This dose should be adjusted based on monitoring of aPTT and AT activity, with the aim of prolonging the aPTT by up to 30% above the upper reference interval in a hypercoagulable state. Such a value may also be achieved through replacement and supportive therapy alone and should be maintained through laboratory monitoring and heparin administration as needed.

**Low-Molecular-Weight Heparin Versus Unfractionated Heparin**

LMWH, which is composed of heparin fractions with molecular weights of 4000 to 8000 daltons, was found to be more advantageous than UFH in dampening activated coagulation in humans. In human patients with endotoxemia, it has been shown to significantly reduce mortality. In a double-blinded, controlled study in human DIC patients, LMWH was more beneficial than UFH in decreasing bleeding complications.

UFH binds to AT, resulting in a conformation change of AT that leads to greatly enhanced inhibition of many coagulation factors (e.g., thrombin, Xa, XIa, XIIa, IXa). Because of its smaller molecular size, LMWH, unlike UFH, cannot simultaneously bind to AT and thrombin;
therefore, LMWH inhibits thrombin to a lesser extent. However, compared with UFH, LMWH has greater affinity for, and enhanced inhibition of, factor Xa. LMWH also has a lesser tendency to bind to macrophages, plasma proteins, and platelets, accounting for its limited hepatic clearance, prolonged half-life, and better bioavailability. In humans, LMWH has been found to have a two- to fourfold longer half-life than UFH, with greater bioavailability and more predictable anticoagulant effects. In addition, compared with UFH, the likelihood of developing heparin-induced thrombocytopenia is reduced when LMWH is used.

Studies in dogs and cats have shown that LMWH is well tolerated by both species. A study evaluating the pharmacokinetics and pharmacodynamics of UFH in healthy dogs showed that maximal antifactor Xa (aXa) activity after subcutaneous administration of 200 IU/kg of UFH was 0.56 aXa IU/mL and that this peak was reached within approximately 2 hours. In another study in dogs, subcutaneous administration of the same dose of LMWH resulted in a peak activity of 0.9 aXa IU/mL within 3 hours. A third study conducted in dogs with experimentally induced DIC showed that high doses of LMWH are required to interrupt the consumption reaction. A loading dose of 20 aXa IU/kg IV of LMWH followed by a continuous rate infusion (CRI) of 16.7 aXa IU/kg/hr of LMWH was found to be too low to halt the consumption reaction; however, a double loading dose of 40 aXa IU/kg IV of LMWH followed by a CRI of 33.3 aXa IU/kg/hr of LMWH was able to halt intravascular coagulation. This second dose resulted in a maximal aXa activity of 0.63 to 0.9 aXa IU/mL.

**Monitoring Heparin Therapy**

LMWH therapy cannot be adequately monitored with conventional coagulation tests such as PT and aPTT. Instead, aXa activity in patients receiving LMWH should be monitored with assays such as the Heptest assay or chromogenic aXa assays. The Heptest assay measures the ability of heparin to catalyze the inactivation of exogenous bovine factor Xa by AT in the presence of naturally occurring plasma antagonists. Chromogenic aXa assays, in which the plasma sample reacts with bovine factor Xa and AT in the presence of chromogen, are considered by many to be the gold standard tests for clinical monitoring of UFH or LMWH therapy. However, Kovacs et al showed that clinically significant differences exist between commercial chromogenic aXa assays. A recent study of healthy cats compared the pharmacokinetics and the effects of LMWH and UFH on several laboratory tests evaluating hemostasis. There were no significant differences between UFH and two brands of LMWH (dalteparin and enoxaparin) in aXa activity at 4 hours after injection. However, all UFH-treated cats were above the therapeutic target aXa activity and showed hypocoagulability by TEG at 4 hours after treatment, while no dalteparin-treated cats and only two of five enoxaparin-treated cats achieved the therapeutic target aXa activity. The authors of the study concluded that based on the pharmacokinetics demonstrated in this study, cats have rapid absorption and elimination kinetics with LMWH therapy and thus require higher LMWH doses and more frequent administration to achieve a therapeutic target aXa activity of 0.5 to 1.0 U/mL.

In our hospital, heparin use in patients with DIC is limited to patients in the early hypercoagulable phase of DIC with an aPTT prolongation of not more than 30% of the upper reference interval and adequate (≥80%) plasma AT levels. Heparin is given along with FP transfusion. Although studies comparing the use of UFH with that of LMWH in dogs and cats with DIC have yet to be published, we currently recommend LMWH because of its above-mentioned advantages over UFH. However, aXa activity monitoring may not be readily available compared with aPTT testing.

**Recently Described Treatment Modalities in Human Patients**

Novel treatments have recently been proposed in human medicine. Some are under experimental evalua-
tion, while others are in use. The future will tell which, if any, will find their way into veterinary medicine.

**Antithrombin Therapy**

AT is considered to be the primary inhibitor of circulating thrombin, and AT levels are considerably reduced in DIC.112 The administration of high doses of AT (100 IU/kg/day) to achieve supraphysiologic concentrations has been shown to reduce sepsis-related mortality in animal models.113 By comparison, the estimated AT level found in FFP (based on extrapolations from humans and our laboratory experience) is approximately 1 IU/mL. Recent studies113,114 have shown that AT has antiinflammatory properties that may further justify its use in the treatment of DIC. Several studies in human patients have shown that AT administration improved several coagulation parameters and organ functions.53,115 However, in a phase III clinical trial in patients with severe sepsis, no survival advantage was found when a combination of high-dose AT and heparin was administered.116 Patients who received AT therapy alone showed a tendency toward increased survival.116 Future studies will indicate if high-dose AT treatment is indeed beneficial.

**Activated Protein C and Thrombomodulin**

Infusion of APC and thrombomodulin has been shown to prevent DIC and mortality in animal models of sepsis.53,115 Several trials in human patients have evaluated the usefulness of APC in sepsis-induced DIC.115,117,118 In one trial, a combination of human recombinant APC and thrombomodulin demonstrated benefits in patients with DIC.115 In another human trial, transfusion of concentrated APC limited leukocyte activation, cytokine elaboration, and microvascular coagulation and prevented organ damage.47 In a phase III clinical trial, patients with severe sepsis showed improved survival when treated with recombinant human APC.218 These results led to the acceptance of APC treatment in certain human patients with severe sepsis. However, treatment with APC also caused an increased bleeding tendency. Although APC is available, it is very expensive and has the potential to cause antigenic reactions because it is a recombinant human protein.

Thrombomodulin therapy may be beneficial in DIC as a sole treatment with no APC transfusion.119 Thrombomodulin had a beneficial effect on coagulation in humans and animals and appeared to reduce pulmonary vascular injury and leukocyte accumulation.94,120 These effects were not dependent on thrombomodulin’s thrombin-binding properties but were probably mediated through an increase in APC.94,119

**Interleukin-10 and Anti-Tumor Necrosis Factor Antibodies**

Tissue inflammation has been proposed as an important mechanism in DIC associated with sepsis or major trauma. Administration of recombinant interleukin-10, an antiinflammatory cytokine, has been shown to completely nullify the endotoxin-induced effects on coagulation.121 Similarly, the use of monoclonal anti-TNF antibodies has shown a significant benefit in septic patients.35 In this respect, the antiinflammatory effects of APC, including the modulation of TNF-α, interleukin-6, and interleukin-8 levels, may also be beneficial to patients with DIC.47

**PROGNOSIS**

The prognosis of patients with DIC is guarded to poor, depending on the underlying disease, phase and severity of DIC, and patient’s age and status. Early diagnosis and treatment are important factors in the outcome.19 In humans, high plasma fibrinogen levels are associated with organ failure and low fibrinogen levels with an increased risk for bleeding, both indicating a poor prognosis.20 Several clinical studies in humans with sepsis have demonstrated that low levels of AT and protein C are also associated with a poor outcome.122-124 In animal studies, restoration of AT levels has been associated with improved outcome in terms of diminished occurrence of organ failure and a reduction in mortality.125,126 Total clotting time and AT activity were found to be highly reliable indicators for prognosis, and if both are out of the reference range 48 hours after initiation of therapy, a poor prognosis can be established.54

**CONCLUSION**

DIC is a dynamic, secondary, acquired syndrome associated with variable primary triggers and clinical presen-
tations, and its diagnosis is complex. Because there is no uniformly accepted gold standard test, the diagnosis of DIC should be based on the history and clinical signs as well as the results of several serial diagnostic laboratory tests. Feline DIC is much less commonly diagnosed than canine DIC and thus has not been as extensively studied; differences in the clinical signs and diagnostic parameters are apparent and should be recognized when diagnosing DIC in cats. Novel, specific laboratory tests and newer therapeutic modalities that are available or are being scrutinized in human medicine will gradually reach veterinary practice. With time, these new tools are expected to improve the understanding of the pathophysiology, diagnosis, and treatment of DIC in dogs and cats.

REFERENCES


60. Wada H, Gabazza EC, Asakura H, et al. Comparison of diagnostic criteria
59. Bakhshi S, Arya LS. Diagnosis and treatment of disseminated intravascular


**CE TEST**

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1. **D-dimer is a product of**
   a. platelets.
   b. fibrinogen.
   c. cross-linked fibrin degradation.
   d. fibrin monomers.

2. In DIC, fibrinogen concentrations can be
   a. higher than normal.
   b. lower than normal.
   c. normal.
   d. any of the above

3. Increased D-dimer levels occur in patients
   a. with DIC.
   b. with thromboembolism.
   c. after orthopedic surgery.
   d. all of the above

4. **Which statement regarding DIC is incorrect?**
   a. Clinical signs are different in cats and dogs.
   b. Chronic DIC may be silent.
   c. Clinical signs of DIC always include spontaneous bleeding.
   d. DIC is not a primary disease.
5. Which statement regarding DIC in cats is true?
   a. DIC is a rare complication in cats.
   b. Hypofibrinogenemia is common.
   c. Bleeding is common.
   d. Cats present with clinical signs similar to those in dogs.

6. Bleeding in DIC is due to
   a. depletion of coagulation factors.
   b. excess FDPs.
   c. uncontrolled coagulation.
   d. all of the above

7. In DIC, formation of microthrombi is due to
   a. fibrin deposition.
   b. increased AT activity.
   c. protein C activation.
   d. a and b

8. In canine DIC, AT activity
   a. is mostly decreased.
   b. is mostly increased.
   c. is mostly associated with protein C.
   d. can be decreased, increased, or unchanged.

9. Heparin treatment in patients with DIC is
   a. recommended to stop coagulation in all phases of DIC.
   b. contraindicated due to increased risk of bleeding.
   c. useful only in the presence of sufficient AT.
   d. useful only in the presence of sufficient thrombin.

10. Chronic DIC is common in patients with
    a. heatstroke and gastric dilatation–volvulus.
    b. immune-mediated hemolytic anemia and snakebite.
    c. malignancy and chronic disorders.
    d. anticoagulant intoxication and hemolytic transfusion reaction.