

INTRODUCTION

Disseminated Intravascular Coagulation (**DIC**) is an acquired syndrome representing a hypercoagulable state potentially progressing to multiple organ failure and hemorrhagic symptoms. Despite criteria for diagnosing DIC, DIC remains difficult to definitively diagnose. Distinguishing between clinical features attributable to the underlying disease and those of DIC is also difficult in some instances. Disseminated intravascular coagulation results from overwhelming systemic activation of the coagulation, fibrinolytic and anti-thrombotic (CFA-T) systems. The mechanism of DIC is very complex and is triggered by an underlying disease process (Table 1). Recognizing these triggers is important in daily practice as early intervention in treating the primary problem can reduce or eliminate the secondary effects on the hemostatic system resulting in DIC. There are two forms of DIC, acute (acute and fulminant) and chronic (compensated). The **chronic form** is not overwhelming or life-threatening as there is an increased production of all components of the CFA-T systems to compensate for their utilization. The primary clinical features of this are petechiae, ecchymoses, and mild bleeding in areas constantly abraded such as the gingiva. The coagulopathy associated with the chronic and acute form of DIC is caused by the enzymatic action of plasmin on fibrinogen and fibrin with production of peptides known as fibrin degradation products [FDP's] or fibrin split products [FSP] and their effect on platelets and fibrin polymerization. One peptide fragment known as D-dimer is used in diagnosing DIC in humans and veterinary medicine to a lesser degree. The chronic form of DIC, unlike the acute form, may not require emergency treatment, however the underlying disease process must be identified and removed.

TABLE 1. Predisposing Factors of DIC

Endothelial Damage	Abnormal Blood Flow	Hypercoagulable State
IMHA	Endocarditis	Liver failure
Other immune-mediated disease	Polycythemia	Cushing's
Pancreatitis	Dehydration	Pancreatitis
Arteriosclerosis	Shock (<i>p. 603, Table 1</i>)	All infections
Atherosclerosis	Cardiac Disease	PLE and PLN
Heartworm	Neoplasia	Neoplasia
Vasculitis	Hyperviscosity	Thrombocytosis
Endotoxin	Gastric dilation-volvulus	Snake envenomation
All infections	Hypovolemia	Platelet hyperreactivity
Pneumonia	Hyperthermia	IMHA (red cell stroma)
Neoplasia		Brain injury
Trauma		Acidosis
		Hypoxia
		Trauma

This chapter will focus on the **identification and therapy of acute DIC**, which will be present in many of the pathological situations presented in this manual. The clinical spectrum of DIC is one of coagulation and thrombosis followed by fibrinolysis and hemorrhage. A very brief pathophysiological discussion of the mechanism of DIC is presented in order to familiarize the reader with the rationale for suggested laboratory tests and therapy.

Three 'trigger' mechanisms are involved (1) **activation of the extrinsic coagulation pathway** by tissue factor released during cell injury; (2) **contact activation of the intrinsic coagulation pathway** secondary to vascular endothelial injury and exposure of the sub-endothelium; and (3) **direct activation of coagulation factors** by various components, for example, enzymes such as trypsin and elastase in pancreatitis. Also, many of the underlying diseases or 'triggers' for DIC listed in **Table 1** are inflammatory with production of a variety of cytokines. **Cytokines** stimulate cells of the immune system which further up-regulate cytokine production and procoagulation. Injury to endothelium also occurs during inflammation. Experimental studies, based on models of gram-negative sepsis, show that DIC is characterized by strongly enhanced inflammatory activity, where activated neutrophils play a pivotal role in the pathophysiology of

DIC, particularly by contributing to inflammation and vascular injury. All procoagulant stimuli ultimately result in **thrombin generation** mediated by the extrinsic (tissue factor/factor VIIa dependent pathway) system. Thrombin converts fibrinogen to fibrin monomers; factor XIIIa activated by thrombin, ‘firms’ the fibrin monomers into a stable clot. Widespread microvascular thrombosis occurs when the fibrin clots gain access to the systemic circulation. As there is reduced perfusion in these areas, ischemia (causing multiple organ dysfunction [MOD]), cell death and ultimately organ failure (multiple organ failure [MOF]) can occur. Thrombin can also act as a potent agonist for platelet activation. Platelet activation also occurs as a direct effect of endotoxins or cytokines. **Thrombocytopenia** due to consumption, and thrombopathia due to coating of the platelets by FRA contributes to hemorrhage. Antithrombin is a major inhibitor of thrombin and factors XIIa, XIa, Xa, IXa, plasmin kallikrein and plasmin, thereby inhibiting the intrinsic and common pathways. **Consumption of antithrombin** during DIC promotes potential thrombosis. Thrombomodulin-Protein C-Protein S is an endothelial-based inhibitor system, which binds thrombin, preventing amplification of procoagulant activity. During DIC, this system is consumed resulting in unopposed coagulation. Activated Protein-C is used to treat selective critically ill human patients with DIC due to overwhelming inflammation. Inhibitors of fibrinolysis are α 2-antiplasmin, plasminogen activator inhibitor, α 2-macroglobulin, α 1 antitrypsin and C1-inhibitor, which may also contribute to DIC by inactivating plasmin. Activation of complement also occurs as plasmin activates C1 resulting in red cell and platelet lysis. Peptides produced through complement activation increase vascular permeability resulting in decreased perfusion and edema, with subsequent reduction in oxygen delivery to tissues. The contact system is also activated by complement with production of kinins. These vasoactive peptides result in hypotension, ischemia and shock. If perfusion status is not improved, the reduced blood flow results in acidosis and hypoxia, both triggers for DIC.

As you can see, DIC is a spectrum from initiation of coagulation through to multiple organ failure and hemorrhage. The key to managing this disease is (1) **know it exists** based on the presenting illness or injury, even though there may be no visible, or on occasion, laboratory evidence, (2) **treat and prevent further microthrombi** and progression of the disease through improving perfusion and oxygen delivery to the tissues; (3) **treat and prevent further hemorrhage** if this is present; and (3) **treat the underlying disease or remove the inciting focus as soon as possible**.

DIAGNOSIS

History/Signalment

- The diagnosis of DIC is commonly made on physical examination and in association with an underlying disease predisposing to DIC. Laboratory tests support the diagnosis.
- As DIC is not a primary disease, the history will vary according to the presenting illness. Questions to the owner will depend on presenting signs and the generated list of differential diagnoses.
- DIC is more common in dogs and rare in cats.

Clinical Signs/Physical Examination

- Patients with chronic DIC may have no, or minimal (petechia, ecchymoses or minimal gingival hemorrhage) clinical signs which may be noted on routine physical examination. However, an underlying problem may be identified.
- As inflammation is a ‘trigger’ for acute DIC and DIC involves a spectrum of events, clinical signs may initially only be referable to an underlying problem and the initial stages of DIC are only detected on laboratory evaluation (e.g., thrombocytopenia, prolonged ACT, neutrophilia).
- With more serious illness, **acute DIC** may be suspected if petechia and ecchymoses are present in a patient that has an underlying illness predisposing to DIC (Table 1).
- As DIC progresses, signs referable to multi-organ dysfunction due to microvascular thrombosis/injury may be recognized:
 - Hematoma at venipuncture sites
 - Dyspnea with lung involvement
 - Oliguria/anuria or hematuria as renal failure approaches
 - Hemoptysis, hematochezia and melena with gastrointestinal involvement
- As **fulminant DIC** approaches, the patient is depressed/moribund due to shock with massive bruising and hemorrhage.
- Clinical signs associated with **DIC may be due to DIC itself in addition to those of the underlying disease**, or may be similar to the underlying disease itself. For example, hematuria in dogs with leptospirosis may be due to DIC or injury to the kidney by the spirochete. However, these dogs have DIC based on the pathophysiology of the disease.

- Abnormalities in **heart rate** (increased or profoundly decreased) and **rhythm** (frequently tachycardia or ventricular arrhythmias), **respiratory rate** and **effort** (increased and may be dyspneic if pulmonary thromboemboli, or ARDS are present), **systemic blood pressure** (frequently hypotensive), **pulse pressure** (weak), **mucous membrane colour** (variable), **mentation** (usually depressed) are all dependent on the underlying disease, advanced nature of the problem and severity of DIC.
- **Abdominal palpation** may reveal a mass (i.e., hemangiosarcoma of liver or spleen); free fluid may be due to hemorrhage or peritonitis.
- **Auscultation of the thorax** may reveal reduced lung and heart sounds due to pleural fluid (blood, pus, or effusion secondary to a neoplastic process).
- **If in hospital** bleeding from catheter sites or previous venipuncture sites, surgical incisions etc.

Laboratory Evaluation/Diagnostic Imaging

Stat. All must be performed to obtain basic information on an emergent basis. This information and the physical findings are used to formulate an immediate treatment and further diagnostic plan.

- **PCV, TS** (both are usually below normal values).
- **Blood smear** (mature and immature neutrophil count and platelet count).
- **Stick BUN, urea or creatinine** may be increased.
- **Blood glucose** is usually low.
- **ACT** is always performed in our institution. We suggest incubation of the blood sample tight into the axilla, beneath the white coat, if no heating block at 37°C is available. Hand held is not advised. Consistency in testing is important when trending. **Commonly the ACT is increased (>120 secs in dogs and >90 secs in cats) and platelet count decreased below normal range (<100 x 10⁹/L).** These two point-of-care tests are very useful when DIC is suspected (*see Suggested Reading 1*). Usually animals are presented beyond a very early stage of illness where the procoagulant phase of DIC may have been missed. However, should the animal be presented early in the spectrum of illness, the ACT may be shortened to <70 secs in the dog and <60 secs in the cat. The platelet count may be in the low normal range at this time.
- The **PT/PTT** may be increased, however these tests are unreliable as a diagnostic test for DIC, unless severe, in this author's experience as they may remain within normal range.
- **Serum electrolytes** are required to identify abnormalities and aid in fluid selection.
- **Venous blood gases** will determine acid-base status (*p. 407*). Acidosis worsens DIC.
- **ECG** as ventricular (*p. 179*) or supraventricular (*p. 170*) arrhythmias may be noted.
- **Systemic blood pressure** must be measured as it is frequently low.
- Where physical examination indicates, perform **radiographic or ultrasonographic examination** of the thorax and/or abdomen.
- **Aspirates** of abdominal (*p. 28*) or pleural fluid (*p. 574*) should be evaluated. Caution: Use as small a needle as possible to avoid hemorrhage.
- **Buccal mucosal bleeding times are not recommended** as bleeding may be difficult to stop.

Extended Data Base

- **CBC** must be performed to identify leukocytosis, leukopenia, left shift (*p. 588 for criteria of sepsis*), anemia and thrombocytopenia. The presence of **schizocytes** (red cell fragmentation) may support a diagnosis of DIC, however, these are not consistently present in DIC and may occur with other conditions such as hemolytic uremic syndrome.
- **Complete biochemical profile** to assess organ function. Pancreatic enzymes may be increased and be a cause of DIC. Liver disease/failure (*p. 37*) may also be a cause of DIC.
- **Diagnostic imaging** to focus on identifying underlying pathology.

As many of the following tests are not performed in-house, and some only performed weekly in laboratories, do not wait for results prior to diagnosing the patient with DIC.

- **PT/PTT** may suggest DIC if prolonged due to reduced clotting factors as described above. However, due to the various actions of thrombin, normal or shortened times may be reported. Values will be reported together with controls by the laboratory.
- **FDP's/FSP's** may be significantly increased (>40) in DIC, but are not consistently so as adequate levels detectable by the test may not be present resulting in a false negative test. (*see Suggested Reading 3*). Also, FDP's are not specific for DIC and may be increased following surgery, in patients with hematomas, and patients with liver or renal failure.

- **Fibrinogen** concentrations are frequently low but, depending on the stage of illness, may be high as fibrinogen is an acute phase protein and increased in inflammation. It is also increased in dehydration. Concurrent inflammation and dehydration makes interpretation difficult. Values will be reported together with controls by the laboratory.
- **D-Dimer** evaluation is commonly used in human medicine as part of the evaluation for DIC. D-dimer is a protein formed as a result of plasmin degradation of cross-linked fibrin, therefore an elevated D-dimer concentration is a specific marker for clot lysis distinguishing this from primary fibrinolysis. This test has a very high negative predictive value for DIC indicating that a negative test means that DIC is **not** occurring (confidence level of 99.5%). An ELISA-based assay has recently become available and may be of benefit in the future for veterinary patients. Also, D-Dimers are not specific for DIC and may be increased with other diseases involving thrombosis (i.e., PTE).
- **Antithrombin** values are decreased (relative to normal) and are considered an accurate marker in most animals with an illness predisposing to DIC.

MANAGEMENT

As previously mentioned, the underlying disorder must be treated; when identified, refer to appropriate chapter. Refer to Sepsis and Septic Shock *p. 588* for detailed guidelines on therapy. The following is directed towards general management of DIC.

- Oxygen** therapy by flow-by where indicated to improve potential hypoxia.
- IV catheter placement into a peripheral vein.** Do not attempt jugular catheterization as the bleeding will be difficult to control.
- Fluid therapy** is an essential part of managing or preventing DIC. As hypoxia, blood stasis, and acidosis contribute to DIC, these must be avoided by using appropriate fluid therapy. Fluid therapy also removes activated clotting factors and fibrinolytic factors from the microcirculation improving perfusion of all organs preventing organ dysfunction or failure. Optimizing perfusion of the gastrointestinal tract and the kidney is essential. Assuming all patients will have an underlying inflammatory condition there is a definite ‘art and science’ to fluid administration, therefore refer to *Sepsis/Septic Shock p. 588 and Fluid Therapy p. 347* for guidelines.
 - Balanced electrolyte solution (Plasma-Lyte® A or 148, Normalsol® R, lactated Ringer’s, or in the rare alkalemic patient, 0.9% sodium chloride). The rate to be administered will depend on severity of condition.
 - Some of these patients have capillary leak, therefore the volume of crystalloids must be carefully administered noting respiratory rate and effort and subtle signs of edema. (see *Monitoring in Sepsis/Septic Shock p. 591, Fluid Therapy p. 347*).
 - If a reduced volume of crystalloid solution is required due to capillary leak, fresh frozen plasma, synthetic colloids or 25% Human Serum Albumin is required.
- Fresh frozen plasma (FFP).** This author administers FFP to patients with acute DIC, but does not incubate with heparin. Antithrombin in the FFP will be available to combine with heparan sulfate on the endothelium. Anti-proteases, α -macroglobulins, coagulation factors and other potential factors (e.g., protein C) present in FFP may confer a benefit.
- Synthetic colloids** (pentastarch, hetastarch or Dextran-70) may be required to increase colloidal osmotic pressure and retain fluid within the intravascular space. This author cautiously administers these products for resuscitation in patients with capillary leak associated with pancreatitis, as the smaller molecules appear to leak into the pulmonary interstitial space (personal observation). Capillary leak associated with sepsis *may* not be as great an issue in this regard; the author considers the individual patient prior to administration of these products.
- 25% Human Serum Albumin (HSA)** is considered by the author in hypoalbuminemia (≤ 15 g/L [1.5 g/dL]) and capillary leak situations. (see *Hypoalbuminemia p. 431, Sepsis/Septic Shock p. 588, Acute Pancreatitis p. 45*).
- Whole fresh blood** is recommended for active hemorrhage as this will supply clotting factors and platelets. See *Transfusion Therapy p. 667* for further component therapy.

- H. Heparin.** It is not known whether heparin administration is of benefit as no veterinary clinical trials have evaluated this. This author administers heparin to patients where hemorrhage is not apparent, the ACT or PT/PTT are not higher than 1.5 – 2x high normal value, the platelet count is low normal or higher, and there is an associated illness predisposing to thrombosis (e.g., pancreatitis, IMHA, hyperadrenocorticism, and others listed in Table 1). This author does not routinely administer heparin during sepsis. FFP should be transfused prior to heparin therapy. If ACT is >1.5 – 2x normal prior to FFP, repeat ACT after FFP transfusion; if reduced heparin may be instituted. Absolute guidelines for heparin dosages are not available, however suggested therapeutic dosages are:
1. **Heparin 75 – 100 U/kg IV** followed by 10 – 15 U/kg/h, OR
 2. **75 – 100 U/kg SC q8h** for both dogs and cats
 3. **Alternative dosages recommended are:**
 - a. 200 – 250 U/kg (dog), 75 U/kg (cat) SC q8h
 - b. Dosages **up to 500 U/kg SC q8h**
 - c. **300 U/kg IV initially followed by 12 – 15 U/kg/h** as a CRI
 4. All dosages are suggested to achieve an ACT or PT/PTT 1.5 – 2x upper end of normal.
 5. ACT or PT/PTT should be monitored prior to each SC dose, or twice daily where the CRI is employed. This author does not routinely administer heparin during sepsis.
- I. Vitamin K** 1 mg/kg SC q24h therapy may be beneficial as this may be deficient in critically ill patients, and may be a source of coagulopathy and hemorrhage. Also, patients with DIC can also become vitamin K depleted due to increased consumption.
- J. REMOVAL OF THE UNDERLYING PROBLEM**
1. Where a surgically correctable problem exists this should be performed as soon as possible. Waiting until the patient is ‘stable’ may be too late as it is the underlying disease that is causing the problem. Stability in this instance is administering the above fluids to improve perfusion and adequate systemic blood pressure, administering blood products to prevent hemorrhage and ongoing microvascular thrombosis, administering anti-arrhythmic therapy to reduce the rate (not necessarily to eliminate the rhythm) of a malignant arrhythmia.
 2. Where a surgical problem exists that predisposes to DIC in a stable patient (i.e., splenic hemangiosarcoma, diaphragmatic hernia with organ entrapment), surgery should still be performed as soon as possible before DIC becomes fulminant. This often occurs even with appropriate medical support because the underlying problem is fueling the process.
 3. Where a medical problem exists, early definitive therapy is also essential
- K. Analgesia is essential.** Opioids are the analgesics of choice.
1. **Butorphanol 0.2 – 0.4 mg/kg q2h** can be tried initially for mild to moderate pain and continued as a CRI of 0.1 mg/kg/h or to effect. Stop the CRI for 30 – 60 minutes if the patient appears overdosed and reinstitute at one-half the previous dose. If butorphanol is not adequate, then
 2. **Hydromorphone 0.025 – 0.1 mg/kg q3–4h**, or to effect. This dose may be given as a CRI over a 3 – 4h period. You may have to increase the dose of hydromorphone if butorphanol has already been administered due to its antagonistic effect.
 3. **Morphine or methadone 0.2 – 0.4 mg/kg very slowly IV**, followed by CRI (*see Morphine Infusion Chart p. 251*) is also effective.
 4. **Fentanyl 4 – 6 µg/kg bolus IV, followed by 4 – 6 µg/kg/h CRI** (*see Fentanyl Infusion Chart p. 237*).
- Remember, pain activates the sympathetic nervous system, which causes vasoconstriction and therefore poor splanchnic perfusion (especially pancreas and this, in itself, can cause pancreatitis).

SUGGESTED READINGS

1. Bateman SW, Mathews KA, Abrams-Ogg ACG, Lumsden JH, Johnstone IB, Hillows TK. Diagnosis of Disseminated Intravascular Coagulation in Dogs admitted to an intensive care unit. *J Am Vet Assoc* 1999;215:805-810.
2. Bateman SW, Mathews KA, Abrams-Ogg ACG. Disseminated Intravascular Coagulation in Dogs: Review of the literature. *J Vet Emerg Crit Care*. 1998;8(1):29-44.
3. Levi M. Sepsis and the Coagulation System. *Advances in Sepsis*. 2000;1(1):16-21.