

Review Article

Disseminated Intravascular Coagulation: Present and Future Perspective

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Introduction

The haemostatic response could be considered a defensive function: it prevents or avoids blood loss from damaged vasculature (haemorrhage) and ensures adequate blood flow, maintaining the vascular tree free of obstruction (thrombosis). Procoagulant activity (inactive haemostatic proteins) is modulated or inhibited by several mechanisms. Endothelial cells play a key role in the control of these functions. The adequate equilibrium between activation and inhibition of haemostasis depends on interactions between endothelial cells, platelets, circulating blood cells, coagulation activators and inhibitors.

Disseminated intravascular coagulation (DIC) may represent loss of haemostatic equilibrium – induced by numerous clinical entities – resulting in life-threatening consequences.

This review summarises the data recently obtained concerning the aetiology, pathophysiology, clinical findings and laboratory diagnostics as regards DIC. Current and future DIC diagnostic and treatment modalities are discussed. It should be realised at the outset that disease presents differently among a continuum of events. Patients may undergo DIC anywhere in this continuum and, depending on the position in the continuum, exhibit radically different clinical and laboratory effects.

Terminology

Disseminated intravascular coagulation (DIC), is also known as consumptive coagulopathy, an inappropriate descriptor because, although some coagulation proteins (factors and inhibitors) are consumed, many factors and other plasma constituents are biodegraded by plasmin (Jandl 1991). Another descriptor, defibrination syndrome, would be more appropriately retitled 'defibrinogenation syndrome', because fibrinogen is both consumed and biodegraded. Therefore, the term disseminated intravascular coagulation is given preference – it describes the dynamic process of disseminated coagulation taking place intravascularly – expressed as both haemorrhage and thrombosis (Feldman 1981; Slappendel 1988b). DIC is obviously expressed by haemorrhagic diatheses. But, DIC is also associated with diffuse thrombosis (and is sometimes called diffuse intravascular thrombosis; DIT) leading to impairment of blood rheology, ischaemia and multiorgan failure, perhaps causing irreversible damage and, ultimately, patient mortality.

Aetiology

DIC is associated with numerous clinical conditions (Table 1). Depending on the activation rate of the haemostatic system, DIC may occur as an acute and life-threatening event or as a chronic form without severe thrombosis and haemorrhage. DIC may be initiated by a single cause or by multiple causes occurring sequentially or simultaneously. The anticipated events inducing DIC – in most conditions – are related to:

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Table 1. Conditions associated with disseminated intravascular coagulation

A. Intravascular haemolysis	G. Malignancy (Table 3)
Haemolytic transfusion reactions	H. Massive tissue injury
Haemolytic anemia	Trauma
B. Septicaemia (Table 2)	Burns
Gram negative (endotoxin)	Surgical procedures
Gram positive (bacterial coat mucopolysaccharide)	Heat stroke
C. Viraemia (Table 2)	I. Venoms and Toxins
D. Parasitic infections	Snake bite
Protozoal infection	Bee/insect sting
Metazoal infection	Aflatoxin (see J.)
E. Obstetric complications	J. Liver disease
F. Miscellaneous	K. Pancreatitis
Gastric dilatation/volvulus	
Diabetes mellitus	

1. Tissue factor (TF) or thromboplastin-like substances liberated into the circulation;
2. Damaged endothelia/monocytes converting procoagulants into active forms (activated procoagulants);
3. Blood flow interruption preventing hemodilution of activators;
4. Impaired removal of activated procoagulants by the liver.

Intravascular Haemolysis

Intravascular haemolysis is a considerable trigger for DIC. The acute haemolytic transfusion reaction represents a major DIC stimulus. The release of erythrocytic adenosine diphosphate (ADP) and/or membrane phospholipoproteins may directly stimulate platelet aggregation and coagulation (Bick 1985; Borrego et al. 1991). Even transfusion of autologous haemolysed blood was found to cause decrease in factors X, VIII, fibrinogen and to cause pulmonary arterial thrombosis in dogs (Cotter 1992).

Infectious Agents

DIC has been reported in association with many infectious agents (Table 2) including numerous Gram-negative and Gram-positive organisms (Stein and Libertin 1990; Morris 1991). Bacterial coat lipopolysaccharide (LPS) released as a result of proliferation or lysis of Gram-negative bacteria (endotoxin), has the ability to initiate DIC (Warr et al. 1990) by direct activation of endothelium, the contact system (the kinin system and factors XII and XI), complement, leucocytes and platelets (Ewert et al. 1985; Moher 1988). Gram-positive bacteria have mucopolysaccharide coats which may induce DIC by the same mechanisms noted with endotoxins. Septicaemia due to bacterial infection

Table 2. Bacteria and viruses incriminated in disseminated intravascular coagulation

Bacteria ^a	Viruses ^b
Gram-negative bacteria	Infectious canine hepatitis
<i>Escherichia coli</i>	Canine distemper
<i>Pasteurella hemolytica</i>	Canine herpes virus
<i>Pasteurella multocida</i>	Feline infectious peritonitis
<i>Salmonella</i> species	Feline panleukopenia
Gram-positive bacteria	Hog cholera
<i>Staphylococcus</i> species	African swine fever
<i>Streptococcus</i> species	Blue tongue
<i>Clostridium</i> species	Epizootic haemorrhage of deer
<i>Mycobacterium</i> species	Fowl plague
	Viral haemorrhagic disease of rabbits

^a Ellison et al. (1988), Kiper and Paulsen (1988), Isogai et al. (1989), Bowersock et al. (1990), Braun et al. (1990), Kokosharov et al. (1990), Stein and Libertin (1990), Morris (1991), Anderson et al. (1992).

^b Ward and Conway (1980), Howerth et al. (1988), Pan et al. (1988), Greene (1990), Greene and Scott (1990), Huang (1991).

is accompanied by acidosis which may provide an independent trigger for DIC (Bick 1985). However, the clinical presentation is probably the summation of several or all of these activation events.

Viruses

Viruses responsible for triggering DIC may do so by involvement in associated circulating antigen-antibody complexes which activate the endothelium and possibly the contact system. Viruses can also induce the platelet release reaction (Bick 1985; Cosgriff 1989; Studdert 1994).

Parasitic Infections

Protozoal infections such as trypanosomiasis (Olubayo and Muger 1985; Suliman and Feldman 1989), babesiosis (Krooshof et al. 1984; Blood and Radostits 1989), and sarcocystosis (Frelier and Lewis 1984; Dauschies et al. 1989) may induce DIC.

Metazoal infection associated with DIC is exemplified by heartworms in dogs (Dillon and Braund 1982). The vascular damage induced by these blood parasites and the associated embolic phenomena causes release of tissue thromboplastin, the key to triggering DIC in heartworm patients (Kociba and Hathaway 1974; Cooley et al. 1987).

Obstetric Complications

Obstetric complications commonly trigger DIC (Seegers 1971). DIC may occur in association with dystocia, eclampsia, Caesarean section, and retained

fetal placenta (Dodds 1985; Braun et al. 1990). A physiological potential hypercoagulable state has been reported to be associated with parturition (Murano and Bick 1980; Gentry et al. 1991). The proposed mechanisms that initiate DIC in obstetric complications include: (1) the release of amniotic fluid (with activity similar to thromboplastin, platelet factor 3 or phospholipoprotein into maternal circulation) (Lockwood et al. 1991; Parihar et al. 1991); (2) release of placental enzymes or tissues with thromboplastin-like activity into the maternal circulation (Bick 1985; Braun et al. 1990; Wagner et al. 1990; Suchartwatnachai et al. 1991); and (3) release of necrotic fetal tissue or enzymes (with activation of the maternal haemostasis) into the maternal circulation (Angelov 1989; Bosner et al. 1989; Braun et al. 1990).

Miscellaneous

DIC has been identified as an important complication that affects both mortality and morbidity in gastric dilatation–volvulus patients (Drazner 1982). The damaged organs release large amounts of thromboplastins into the circulations; local acidosis may occur leading to DIC (Hall 1972; Lippincott and Schulman 1989). Acidosis triggers DIC through sloughing of endothelial cells and subsequent activation of the contact system (Baker 1989).

In *diabetic* patients DIC may be initiated by injury of the vascular endothelium (Bick 1979), peripheral capillary stasis (Bick 1982, 1985), microangiopathy, and enhancement of platelet aggregation (Titova et al. 1989; Barnett 1991).

Malignancy

Malignancy is reported as the underlying disease in 39% of dogs diagnosed with DIC (Feldman et al. 1981). Haemangiosarcoma, disseminated carcinomas, haematopoietic and lymphoreticular tumours are commonly associated with DIC in small animals (Helfand 1988; Hammer et al. 1991; Hargis and Feldman 1991). DIC has been suggested as the major pathophysiological mechanism underlying microangiopathic haemolytic anaemia (MAHA) often associated with malignancy in small animals (Helfand 1988; Slappendel 1988a). The presence of large tumour burdens or tumours associated with bone marrow, spleen or liver (specifically widespread infiltration – haemangiosarcoma, lymphosarcoma or leukaemia) are conditions associated with MAHA in dogs (Madewell and Feldman 1980; Rebar et al. 1980). There are five possible mechanisms that trigger DIC in cancer patients and these are listed in Table 3. Some cancer patients develop typical DIC with secondary fibrinolysis and/or primary activation of fibrinolysis that overwhelms the fibrinolytic inhibitor response. In cancer patients, subclinical compensated DIC is more common than either compensated DIC

Table 3. Mechanisms that incite disseminated intravascular coagulation in cancer patients

1. Stimulation of the coagulation cascade
 - (a) Cancer cells induce platelet activation and aggregation (Hammer et al. 1991; Hargis and Feldman 1991; Suchartwatnachai et al. 1991).
 - (b) Cancer cells release thromboplastin and/or other procoagulant factors (PCA) that enhance coagulation (Madewell and Feldman 1980 Helfand 1988; Slappendel 1988a).
 - (c) Cancer cells stimulate macrophages and monocytes to release PCA factors (Rebar et al. 1980; Radomski et al. 1991).
 - (d) Cancer cells release a specific factor X activator, a cysteine protease known as cancer PCA factor which is released by a variety of malignant cells including breast, liver, renal and lung carcinomas, undifferentiated sarcomas, liposarcomas, melanomas (Edwards et al. 1990; Spearman et al. 1991).
 - (e) Non-enzymatic activation of factor X by the sialic moiety of mucin in mucinous adenocarcinomas (Mohanty et al. 1991).
2. Vascular damage by neoplastic growth or vascular damage of vessels within neoplastic tissues might lead to exposure of subendothelial collagen (Rebar et al. 1980).
3. Enhancement of the haemostatic system by complications of malignancy such as surgery, chemotherapy and sepsis (Rebar et al. 1980).
4. Decrease hepatic synthesis of antithrombin III (AT III), and protein C in metastatic cancer (Gordon 1984; Clouse and Comp 1986; O'Keefe and Couto 1988; Lefrere et al. 1989; Roncaglioni et al. 1989; Clauss et al. 1990; Irimura et al. 1990; Kubota et al. 1991).
5. Activation of the fibrinolytic cascade by a plasminogen activator (urokinase-like) (Clauss et al. 1990) or a tissue-type plasminogen activator released from some tumour cells (Jones et al. 1980; Giger and Gorman 1984; Badenoch et al. 1986; Camiolo and Greco 1986; Kapina et al. 1986; Duffy 1990; Reilly et al. 1991).

with thrombosis or uncompensated DIC leading to haemorrhage (Madewell and Feldman 1980; Giger and Gorman 1984). Haemorrhagic DIC has been seen with various tumours including thyroid carcinoma, haemangiosarcoma, mammary carcinoma, intrathoracic carcinoma, and adrenal tumour (Jones et al. 1980; Green 1981; O'Keefe and Couto 1988). In contrast to humans, DIC appears to be uncommon in dogs with leukaemia. It has been suggested that DIC may complicate leukaemia in cats (Kobilinsky et al. 1979; Jacobse-Geels et al. 1980).

Traumatic Shock

Traumatic shock is a well-recognised cause of DIC (Hardaway 1981; Ordog and Wasserberger 1986). Thromboplastic substances are released from traumatised tissue into the circulation, precipitating the development of DIC. In addition, the decreased flow of capillary blood induced by hypovolaemia is a contributing factor (Hardaway 1980a,b). Clinical and laboratory evidence indicate that the passage of blood through traumatised tissue causes erythrocyte lysis triggering coagulation (Hardaway and Williams 1987, 1990). The release of cellular enzymes in combination vasoactive substances already in the circulation also contribute to

the induction and perpetuation of DIC (Hardaway 1980a; Ordog and Wasserberger 1986; Hardaway and Williams 1990). As the fibrinolytic system is also activated both microthrombi and haemorrhage may be observed (Hardaway 1981).

DIC may occur subsequent to bone fracture and fracture surgery. The direct release of large amounts of lipids and tissue thromboplastin from fractured bones into the circulation initiates hypercoagulability in some patients (Buntain 1980; Raphael 1982). All surgical procedures activate the haemostatic system. This is especially true of prolonged abdominal surgical procedures (Buntain 1980; Lipowitz 1985).

Thermal injuries are relatively uncommon in domestic animals, especially large animals. Severely affected patients commonly develop DIC, with several mechanisms operative (Johnston 1985; Iashvili et al. 1986; Ono 1987). DIC in burned animals presumably results from both haemolysis and tissue necrosis and release of tissue components, cellular enzymes, and phospholipoprotein-like materials into the circulation (Bick 1982). The aetiology of DIC in the early stages after thermal injury remains unclear. However, massive thrombin generation and decrease of anticoagulant activity, mainly antithrombin III (ATIII) concentrations, have been observed (Goodwin 1989; Ueyama et al. 1991).

Heat stroke can directly provoke DIC by widespread vascular and tissue damage (Drazner 1982; Holman and Schneider 1989).

Liver Disease

Development of DIC is a common event in severe *hepatopathy* in dogs and cats (Green 1989). Impairment of hepatic synthesis of coagulation proteins or impaired hepatic clearance functions may manifest as thrombotic, fibrinolytic or haemorrhagic complications (Hersch et al. 1987; Green 1989). The enhanced plasmin generation noted in liver disease promotes activation of the kinin system causing hypotension, shock and end-organ damage, as well as biodegradation of coagulation factors by plasmin (Kaplan and Silverberg 1987). Failure of clearance of fibrin(ogen) degradation products (FDPs) by the diseased liver will allow FDPs to further impair fibrin polymerisation and platelet aggregation (Drazner 1982). Ingestion of *aflatoxin* contaminated dog food has been reported to cause DIC (Hagiwara et al. 1990). The resultant severe hepatocellular degeneration and necrosis is sufficient to initiate DIC through extensive release of tissue thromboplastin (Baker and Green 1987).

Venoms and Toxins

Snake venoms contain enzymes that may trigger haemostasis in unique ways. Venoms contain thrombin-like enzymes or substances that specifically activate

factor X (*Bothrops atrox*) or factor II (Wintrobe et al. 1981). *Echis carinatus* venom was found to rapidly induce DIC in mongrel dogs by direct activation of prothrombin (Schaeffer et al. 1986). The venom of *Pseudonaja textilis textilis* – an Australian snake – contains prothrombinase. This converts prothrombin into α -thrombin directly, resulting in fibrinogen degradation (Masci et al. 1990). Crude venoms also contain substances that act as thromboplastins and produce intravascular red cell lysis and massive vascular endothelial damage (Wintrobe et al. 1981). Hymenoptera (bees, wasps and hornets) stings in dogs result in acute DIC which can be fatal, or more chronic forms of DIC (Cowell et al. 1991). DIC is initiated by Hymenoptera venom which includes components such as phospholipase A, histamine, acetylcholine, serotonin and kinins.

Pancreatitis

Pancreatitis may trigger DIC by activation of trypsin, kallikrein (KK) and phospholipase A₂ in the pancreatic (and surrounding) tissue (Uehara et al. 1989; Williams 1989). These enzymes have thrombin-like activity or factor Xa-like activity which results in activation of the haemostatic system and DIC. The release of leucocyte elastase during pancreatitis has the capacity to degrade plasma proteins such as α 2-antiplasmin, ATIII and factor XIII. This protein degradation may cause more tissue damage and can further potentiate DIC (Axelsson et al. 1990).

Pathophysiology (Fig. 1)

Disseminated intravascular coagulation may be considered an uncontrolled burst of thrombin generation and activity. This massive activation overwhelms haemostatic inhibitors, depletes procoagulants and platelets, induces thrombosis, and as a final result tissues are severely damaged. Thrombus formation and subsequent ischaemia and necrosis may activate an enhanced fibrinolytic response which would impair platelet function and deplete coagulation factors (Schrier 1993).

The *inflammatory response* has important interactions with haemostasis, may activate haemostasis or impair its inhibition. Recent studies, have described some of these interactions.

1. Neutrophil activation and degranulation liberates lactoferrin, a prominent component of neutrophil secondary granules. Lactoferrin is an iron-binding protein and thus has a physiological role in the regulation of inflammation and other host defence mechanisms. Lactoferrin has potent heparin-neutralising activity during thrombin inhibition by serine proteinase inhibitors ATIII and heparin cofactor II. It has been observed that specific inflammatory mediators as tumour necrosis factor- α (TNF- α) increased the concentration of both platelet factor 4 (PF-4), which inhibits

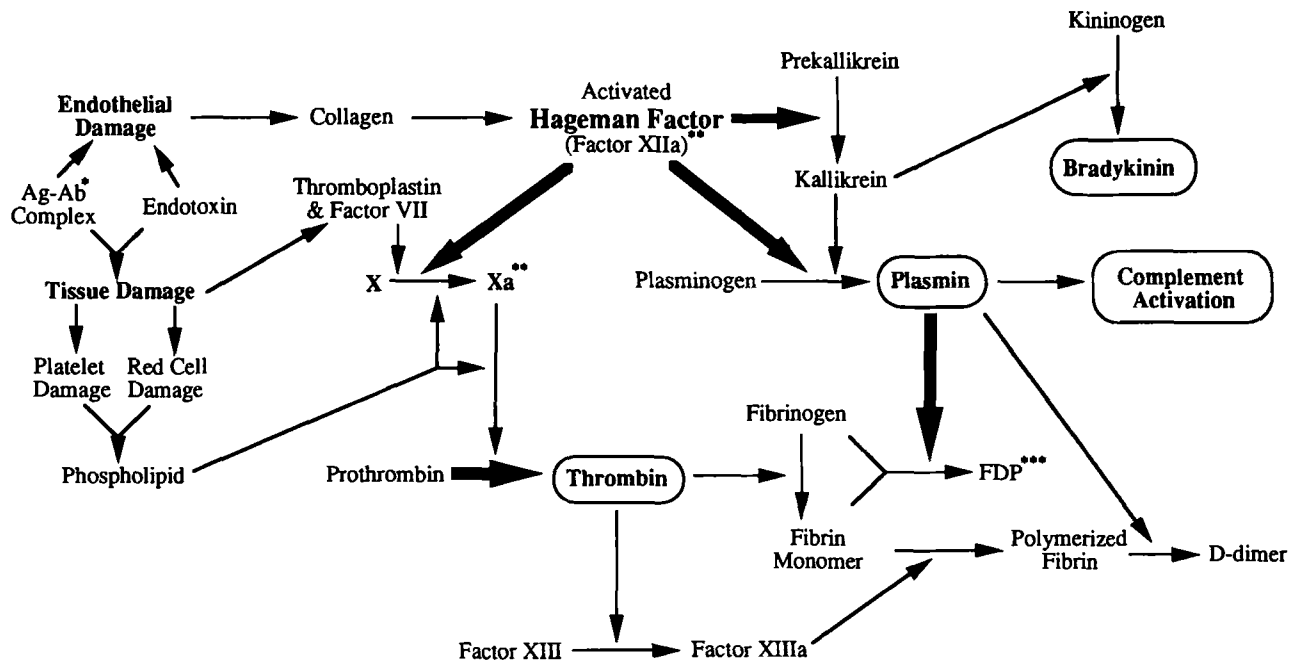


Fig. 1. Pathophysiology of disseminated intravascular coagulation (DIC). * Antigen-antibody complex; ** Activated factor; *** Fibrin(ogen) Degradation Products.

heparin, as well as plasma lactoferrin (Wu et al. 1995). Activated neutrophils adhere to endothelium and release elastase which cleaves and may inactivate thrombomodulin (TM) (Esmond 1994). Platelet aggregation may be induced by activated neutrophils, mediated by platelet activating factor-acether (PAF-acether). PAF is a phospholipid produced by vascular endothelium, platelets and monocytes (Nguyen et al. 1995).

2. The cytokines TNF- α and interleukin 1 (IL-1), may initiate the endothelial expression of adhesion molecules (one of which is E-selectin; others have yet to be identified) that bind monocytes and neutrophils. P-selectin requires thrombin activation to be mobilised from endothelial Weibel-Palade bodies. This fact may involve platelet adhesion to endothelial cells and monocytes, and could serve as a focal point to amplification reactions involved in thrombin generation (Edmond 1994).

3. Complement terminal components C5b-9, induce a procoagulant activity in platelets. Coagulation factors can adhere to negatively charged phospholipids such as phosphatidylserine, which normally, is not exposed on the surface of inactivated platelets. It is suggested that platelet activation may induce membrane vesiculation and formation of microparticles. This may be considered a critical component of prothrombin activation (Esmond 1994; Sandberg et al. 1985).

The contact system includes factors XII (FXII) and XI (FXI) and the kinins. Activation of the contact system occurs through contact with negatively charged surfaces, cerebroside sulphates, glycosaminoglycans, plasmin, hypersensitivity/anaphylactic reactions, and

lipid A component of endotoxins (Wachtfogel et al. 1993). The consequences are:

1. Coagulation factors VII and XI are activated (by FXIIa);
2. Complement fraction C1 is activated (by FXIIa);
3. Prourokinase and plasminogen are activated by FXIIa and kallikrein;
4. Neutrophils are activated by FXIIa and kallikrein;
5. Kininogens increased the activation of FXI, but inhibit cellular adhesion to endothelium (monocytes, neutrophils and platelets). In addition, bradykinin increases vascular permeability and hypotension.

Endothelial cells and monocytes may express tissue factor when these cells are exposed to endotoxins, IL-1 and TNF (Esmond 1994). The formation of factor VII-TF complexes induces factor X and factor IX activation. The inhibitory activity of tissue factor pathway inhibitor (TFPI) may possibly be overwhelmed if TF exposure is extensive. Furthermore, the experiment administration of human recombinant TFPI in animal models of endotoxin-induced shock reduced mortality. The inhibitory activity of TFPI on inflammatory response is also suggested because lower concentrations of IL-6, were found in these animals (Taylor 1994; Petersen et al. 1995).

Endothelial damage caused by circulating antigen-antibody complexes, endotoxaemia, or other forms of tissue damage can change the endothelial cell anti-coagulant phenotype. This results in a massive pro-coagulant fibrinolytic counterattack on the luminal side of the endothelial cell through the expression of TF and release of tissue plasminogen activator (tPA) (Taylor 1994). Trauma and haemolysis may also liberate TF into

the circulation (Mant and King 1979; Slappendel 1988b; Muller 1989; Nakamura et al. 1990). When one of these insults occurs, there are many potential elements for uncontrolled generation of circulating thrombin and plasmin. Circulation of these two enzymes systematically may be considered DIC. Despite the differing activation pathways by which thrombin and plasmin are generated, the resultant pathophysiology of DIC basically remains the same (Mant and King 1979; Slappendel 1988b).

Thrombin activates the *protein C pathway*. The early activation of protein C (and subsequent consumption) in sepsis has been observed in human patients. Thrombin bound to TM – an endothelial cell surface receptor – activates protein C, and results in feedback inhibition of thrombin (thrombin loses its coagulant effect). Activated protein C (APC) bound to the cofactor protein S, cleaves FVa and FVIIIa. Protein S circulates free or bound to C4b binding protein (C4bBP), an inhibitor of complement (and at the same time an inhibitor of the protein C pathway). Activated PC is inhibited by protein C inhibitor (PCI) – a heparin-dependent reaction – and α 1-antitrypsin. Protein C inhibitor also binds KK. KK may also play a regulatory role in protein C activity (Alcaraz et al. 1995). The effect of cytokines on the protein C pathway has been studied, especially related to septic shock. It has been observed that infants with protein C deficiency may develop purpura fulminans. Patients with severe septic shock present with similar cutaneous lesions which resemble this process (Walsh et al. 1991). Thereafter, C4bBP behaves as an acute phase reactant which can reduce free protein S concentrations (Esmond 1994). Endotoxins and cytokines (IL-1 and TNF) also downregulate TM expression (Edmond 1994). In conclusion, coagulation inhibition is severely impaired potentiating thrombus formation.

Thrombin activates FV, FVIII:C and FXIII and cleaves fibrinopeptides A and B from fibrinogen to yield fibrin monomers. The monomers polymerise into fibrin clots. This leads to microvascular and macrovascular thrombosis and ensuing ischaemia and organ failure (Muller 1989; Jandl 1991). Thrombin also binds irreversibly to platelets promoting platelet adhesion to endothelial cells, platelet aggregation, and induces secretory release of platelet α and dense granule contents (Nomura et al. 1991; Venturini and Kaplan 1992). ADP and thromboxane A₂ (TxA₂) release will further accelerate platelet aggregation causing amplification of coagulation processes and thrombin generation. Platelets are trapped in micro- or macrothrombi. This results in the clinical manifestations of thrombocytopenia (Feldman 1981; Feldman et al. 1988; Jandl 1991).

Plasmin is generated by the enzymatic conversion of circulating plasminogen (a proenzyme, synthesised by kidneys, liver and eosinophils). Tissue PA is secreted by injured endothelium and macrophages near the injured area, and contact system activation also contributes to plasmin generation. Plasmin is capable of hydrolysing not only fibrin and fibrinogen but also other proteins such as factors V, VIII, IX, XI, insulin, ACTH, casein

and gelatin (Muller 1989; Jandl 1991). Digestion of fibrinogen by plasmin results in fibrin(ogen) degradation products (FgDP) composed of fragments X, Y, D and E (Muller 1989). FDPs in the circulation interfere with fibrin monomer polymerisation (basically by inhibiting fibrin polymerisation and blocking the receptor sites of fibrinogen on thrombin) causing further amplification of fibrinolysis, impairment of haemostasis and, resultant haemorrhage (Feldman 1981; Muller 1989; Jandl 1991). Other FDPs (fragments D and E) have high affinity for platelet membranes, inducing platelet dysfunction through granule release and platelet aggregation inhibition (Wintrobe et al. 1981). This contributes to clinical haemorrhage. Thus, systemic release of FDPs in large quantities also contributes to some of the bleeding problems encountered in patients with DIC. Plasmin is capable of activating the complement system (C1 and C3), and contributes to the activation of the contact system. Subsequent neutrophil activation, red cells lysis, platelet activation and/or lysis results (Muller 1989; Carroll et al. 1990; Nomura et al. 1991). Damage to both red cells and platelets provides more substrate in the form of procoagulant materials accentuating thrombocytopenia. Activation of the complement system and BK affects the endothelium, enhancing vascular permeability ultimately leading to hypotension and shock.

In summary, inflammation activates haemostasis through neutrophil activation (inducing platelet aggregation, inactivation of heparin-dependent serine proteases and the protein C pathway), monocyte expression of TF, complement activation (inducing platelet procoagulant activity) and cytokine release (which induces endothelial TF expression and endothelial changes more receptive to coagulation).

Activation of the contact system has several consequences: coagulation activation, activation of fibrinolysis, complement activation, neutrophil activation, and kinin activation. Kinin activation may inhibit adhesion of neutrophils, monocytes and platelets to endothelium, increasing vascular permeability.

If these activation mechanisms overwhelm haemostatic inhibitors and thrombin formation is uncontrolled, thrombus formation is potentiated and subsequent organ failure may develop.

Thrombus formation, contact system activation and endothelial leasin (liberating tPA) all activate fibrinolysis. If plasmin activation is extensive, some coagulation factors are severely depleted.

Clinical Findings

Although the classic presentation of DIC may include fever, acidosis, hypoxaemia, proteinuria, bleeding, shock and evidence of multiple organ failure (Bick 1985; Slappendel 1988b), it is essential to note that there is considerable variability in clinical findings. DIC can be

acute or chronic depending on whether the underlying illness is acute (decompensated DIC) or chronic (compensated DIC). The clinical manifestations may also differ among diseases, from patient to patient, and even chronologically in the same patient. Physical findings that accompany microthrombosis-associated DIC are associated with decreased organ perfusion. Renal thrombosis leads to severe renal dysfunction, common sequelae in horses with DIC (Carlson 1990). Gastrointestinal thrombosis results in acute colic secondary to submucosal necrosis and ulceration, a severe complicating event in equine patients with primary gastrointestinal disease. This results in spontaneous gastrointestinal haemorrhage clinically expressed as gross or occult faecal blood (Carlson 1990). In acute DIC, bleeding may occur at puncture sites, intravenous catheter sites, and surgical wounds (Bick 1982; Morris 1988; Carlson 1990). Large vessel bleeding sites are particularly prone to haematoma formation. The resulting pressure on other vital tissues may compound the clinical problem (Ampel et al. 1985). Prominent clinical manifestations in horses are the tendencies to major vessel thrombosis, especially after catheterisation, and thrombosis of smaller cutaneous blood vessels manifested by arborising subcutaneous 'cords' (Morris 1988). Melena or haematochezia are seen mostly in ruminants and dogs with DIC (Slappendel 1988b; Carlson 1990). Digital ischaemia, subsequent to microthrombosis, frequently accompanies DIC in horses and plays a key role in the development of laminitis (McClure and McClure 1982; Holland et al. 1986). Pulmonary function may also be compromised by microvascular thrombosis in DIC, causing tachypnoea and hypoxaemia. Cerebral microvascular thrombosis might lead to altered consciousness, convulsion and/or coma (Carlson 1990). Compensated DIC develops in patients with illness that produces a low-grade or intermittent procoagulant release stimulus. This allows longer time periods during which consumed or degraded coagulants, anticoagulant proteins, and platelets may be replenished. This compensated state may become unbalanced by stress, concurrent diseases, or worsening of the primary disease. Veterinary clinicians rarely see patients in the early phases of DIC. Fulminant DIC is more likely with resultant poor prognoses.

Laboratory Findings

Laboratory results vary according to the underlying cause of DIC and the evolution of the process. Many newer analytes have become available for evaluating patients with DIC; however, many of these are not, as yet, validated for veterinary use. The diagnosis of DIC cannot be achieved with a single test result and it is not possible to define which alterations are pathognomonic for DIC. But, the tests described below are helpful to diagnose DIC and to monitor therapy.

Red Cell Fragmentation

Schistocyte or fragmentocyte formation is usually abundant in patients with low-grade DIC, but as only occasionally seen in fulminant DIC. The presence of fragmentocytes may also be seen in a variety of conditions such as MAHA, Heinz body anaemia, iron deficiency, and may even be seen as spurious finding of blood smear preparation (Slappendel 1988b).

Thrombocytopenia and/or Thrombopathia

The platelet count is typically decreased in DIC; though the percentage decrease may be quite variable. Platelet counts are often elevated as a non-specific inflammatory response. Decreased platelet numbers may, therefore, be relative. Platelet function tests including the template bleeding time and platelet aggregation are abnormal, as a late stage finding in patients with DIC. Therefore, platelet function in DIC patients may be variable (Bick 1988; Muller 1989). Increased platelet turnover and decreased survival is common with DIC patients; platelet factor 4, β thromboglobulin, and TxA₂ concentrations are markers of overall platelet reactivity and release. These concentrations are usually elevated in DIC patients (Bick 1988).

Tests of Secondary Haemostasis

The prothrombin time (PT) is anticipated to be prolonged in DIC for multiple reasons. The PT depends upon the ultimate conversion of fibrinogen into fibrin. In DIC there is usually consumption-induced hypofibrinogenaemia and increased FDPs, which interfere with fibrin monomer polymerisation. Also lysis of factors V (and numerous other factors) by plasmin could prolong the PT. However, a PT within the reference interval in DIC patients may be observed as the underlying process progresses from peracute to acute; PT changes from a shortened test – activation of factors X and prothrombin (II) – through the reference interval and, finally, becoming prolonged.

The activated partial thromboplastin time (APTT) is also anticipated to be prolonged in fulminant DIC because of plasmin-induced biodegradation of coagulation factors. However, APTT may not be prolonged in DIC patients for the same reasons mentioned above in reference to PT.

Thrombin time (TT) or Reptilase time, tests of the final common coagulation pathway, are anticipated to be prolonged in DIC. Both tests may be prolonged by circulating FDPs and subsequent interference with fibrin monomer polymerisation (Jandl 1991). Appropriate results for these tests can be observed in DIC patients when FDP accumulations are a relatively late happening.

Coagulation factor assays provide insufficient clinically useful information in patients with DIC (Feldman

1981). Fibrinogen concentration is dramatically decreased in patients with fulminant DIC (Feldman 1981). However, normal or elevated concentrations may be seen in patients with early and compensated DIC – where fibrinogen production exceeds degradation (McKay 1983). In addition, most of the underlying disease processes are actively inflammatory (Feldman 1981; Slappendel 1988b). This results in elevated concentrations of fibrinogen early in the process. Fibrinogen concentration is not reliable for diagnosis of DIC in horses, since horses rarely develop hypofibrinogenaemia (Johnstone and Crane 1986). However, return of fibrinogen concentration in other species towards the reference interval may be the best prognosticator of therapeutic success.

Thrombin Activation

Coagulation activation markers as thrombin–anti-thrombin III complexes (TAT) are widely used in human medicine to observe thrombin activation in hypercoagulable state (Asakura et al. 1991). Thrombin–ATIII complex determination has been performed in veterinary medicine (Monreal et al. 1993).

Production of fibrinopeptide A is related to thrombin activation. It is usually elevated in patients with DIC as well as in a wide variety of other micro- or macrovascular thrombotic events. The test provides an overall assessment of haemostasis activation indicating the presence of thrombin-induced fibrinogen proteolysis. Disappearance of fibrinopeptide A may aid in assessing the efficacy of therapy in DIC (Jensen and Ens 1991).

Determination of an effective test of prothrombin activation markers – F1 + 2 fragments – was not shown to be useful in rabbits (Monreal et al. 1993).

Soluble fibrin monomer (FM) – the complex of FDPs and fibrin monomer – can be detected by protamine gelation and agglutination tests. Positive results may appear in patients with a variety of diseases which might be associated with DIC but definite proof of DIC diagnosis is still lacking. Therefore, the tests for FM are valuable mainly as broad screening tests (Slappendel 1988b). Recently, an immunological assay was developed in human medicine which can directly quantify the amount of soluble fibrin monomers (SF) formed in blood. This study examined this assay system in the diagnosis of DIC and found that it was a good indicator for both fibrin formation and for DIC. It also correlated well with serum levels of FDPs (Nakagawa et al. 1994).

Fibrinolysis

Elevated FDP concentrations are late-stage findings in most patients with DIC (Feldman 1981; Slappendel 1988b). FDPs are the result of plasmin biodegradation of fibrinogen or fibrin, and thus are indicative of plasmin presence in the circulation. This may be a result of primary fibrinolysis (rare in most animal species includ-

ing human) or secondary as in DIC. FDP concentration results are variable and inconsistent in cats (O'Rourke et al. 1982). Canine patients with FDP concentrations of 10 $\mu\text{g/ml}$ or more are considered to have increased fibrinolysis; the concentration may be as high as 320 $\mu\text{g/ml}$ in overt DIC patients (Slappendel 1988b). FDPs greater than 40 $\mu\text{g/ml}$ in equine patients are only suggestive of DIC (Morris 1988). In the horse, interpreting FDP concentrations is difficult and their presence is certainly not pathognomonic for DIC.

Newer analytes for diagnosis of DIC such as quantification of B- β 15–42 fragments and distinct fibrinogen or fibrin degradation products are widely used in human medicine, and begin to be utilised in veterinary medicine (Monreal et al. 1993). Fibrinogen degradation products (FgDP) and fibrin degradation products (FbDP) by ELISA have been suggested to be reliable and sensitive assays for diagnosis of DIC (Jensen and Ens 1991; Bick and Backer 1992). As yet, however, these analytes have not been validated for routine use in veterinary medicine. The radioimmunoassay for B- β 15–42 and related peptides, when performed in conjunction with fibrinopeptide A, can aid in the differential diagnosis of DIC versus primary fibrinolysis (Bick 1988; Muller 1989). B- β 15–42 and related peptides result from cleavage of B- β peptides from the B- β chain of fibrinogen by plasmin (Fig. 2). Elevation of B- β 15–42 and related peptides without concurrent fibrinopeptide A elevation is strong evidence for primary fibrinolysis, whereas the elevation of both is evidence of DIC (Bick 1988).

Plasminogen and α -antiplasmin concentrations may be reduced in DIC. But enhanced fibrinolysis may be assessed by plasmin– α_2 -antiplasmin complex (PIC) quantification in human medicine. It has been observed

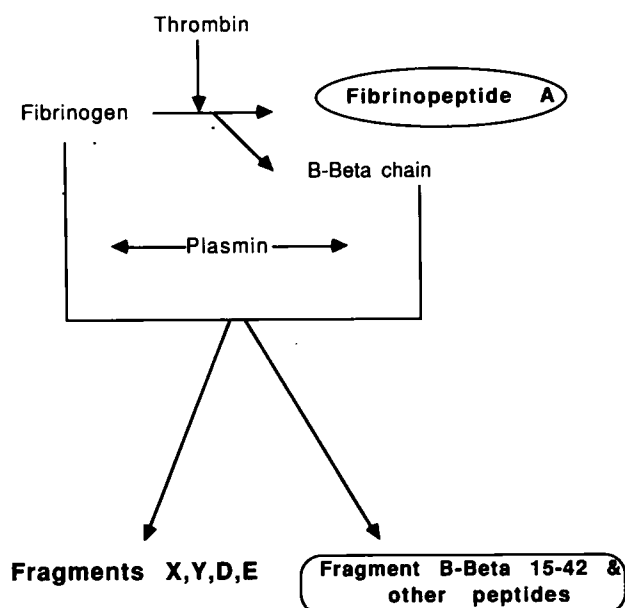


Fig. 2. Formation of fragment B-beta 15–42 from fibrin(ogen).

that the highest concentrations of PIC corresponded to DIC induced by acute promyelocytic leukaemia (APL), the concentrations being relatively lower than in DIC induced by sepsis.

Plasminogen activator inhibitors (PAI) are determined in human medicine. A significant elevation in active PAI was observed in DIC due to acute leukaemia, chronic myeloid leukaemia and sepsis, but not in APL, non-Hodgkin lymphoma, and cancer. Active PAI was higher in patients with multiple organ failure (MOF) than in those without MOF whereas PIC was lower in patients with this complication. Thus, the balance of coagulation and fibrinolysis varied according to the underlying cause of DIC; APL having more activation of fibrinolysis, whereas sepsis had greater activation of coagulation. It is suggested that the inhibition of secondary fibrinolytic activation plays an important role in the progression of MOF (Asakura et al. 1994).

Coagulation Inhibitors

Functional ATIII concentration in patients with DIC is commonly decreased (Tanaka et al. 1986). ATIII is a regulator of several procoagulation proteases including thrombin, factors IXa, Xa, XIa, XIIa and plasma KK (Green 1988; High 1988). Although a diagnosis of DIC can not be made from ATIII concentrations, monitoring ATIII activity is important in the management of DIC especially prior to heparin therapy and is helpful in prognosing clinical recovery (Gerhards 1987; Green 1988). Antithrombin III activity was not a useful coindicator of DIC in cats infected with feline infectious peritonitis (Boudreaux et al. 1989). This might be due to increased hepatic synthesis of ATIII and decreased catabolism secondary to diffuse vasculitis (ATIII may be rendered non-functional and thus unable to inhibit activated serine proteases) (Boudreaux et al. 1989).

Determinations of protein C pathway activation and contact system activation such as APC:PCI complex, KK:PCI complex, and APC- α 1-antitrypsin complex, have been accomplished in human medicine in relation to septic shock and early coagulation activation (Alcaraz et al. 1995). In acute malaria, reduction in plasma AT III concentrations, protein C, factor XII and prekallikrein (PK) activities were observed (Clemens et al. 1994).

Fibronectin

Fibronectin is one of the endothelial adhesion glycoproteins which has been recently used as a molecular marker for endothelial injury (Toschi et al. 1991; Saleh et al. 1992). The concentration of fibronectin was found to be decreased in canine patients with DIC (Feldman et al. 1985).

Thromboelastography

Thromboelastography (TEG), is a less commonly available technique used to assess haemostatic function. Analysis of TEG yields qualitative information about platelet function, thromboplastin, and their interaction with the intrinsic coagulation cascade to form a stable clot. Additional information is obtained about fibrinogen and factor XIII concentrations as well as the fibrinolytic system. TEG is more sensitive and accurate than the traditional universal coagulation tests (PT, APTT) in revealing haemostatic disorders (Bigeleisen and Kang 1991). The test has also been used in diagnosis of DIC in dogs (Johnson et al. 1983).

It is not possible, as yet, to establish minimal criteria for an early diagnosis of DIC, although such criteria may clearly improve therapy and the outcome of some patients. But DIC diagnosis is frequently based on a constellation of laboratory findings, such as thrombocytopenia, hypofibrinogenaemia and high concentrations of FDPs (Mora et al. 1995), red blood cell fragmentation, thrombocytopenia, prolonged coagulation tests and increased FDPs concentrations (Chuamsumrit et al. 1993). It is also suggested that the compensated form of activation of intravascular coagulation may be diagnosed by a decrease in ATIII, an increase in TAT, the appearance of FM and D-dimers (FbDP). Prolonged bleeding time, PT, PTT and hypofibrinogenaemia are found in severe DIC (Schneider 1994).

Rational Therapy

The treatment of DIC remains controversial. There is a global perception that therapy is often futile and that most patients die. Difficulties with therapeutics in DIC are extant because of the diverse aetiologies and clinical manifestations. Simply stated, therapy should be highly individualised.

The therapy of acute DIC should be sequential and have a logical strategy (Table 4). The most important therapeutic modality is removal of the inciting cause. If the removal of the inciting cause is not possible (exemplified by widespread metastatic disease) a specific approach may be indicated (Ruehl et al. 1982). Supportive therapy must be aggressively instituted concomitant with therapy for treatment or mitigation of the underlying event.

Fluid Therapy

Fluid therapy is indicated to correct hypovolaemia, for prevention or alleviation of vascular stasis, and for dilution of thrombin, FDPs and activators of fibrinolysis (Ruehl et al. 1982). The use of electrolytes and/or volume expanders such as plasma protein fractions, albumin, dextran 70, hydroxyethyl starch and hypertonic saline solution combined with colloids (Ruehl et

Table 4. Sequential therapy in fulminant disseminated intravascular coagulation

1. Remove inciting cause
Use of antimicrobial or antineoplastic therapy
Control shock
Volume replacement
Glucocorticoids, antimicrobials (endotoxaemia)
2. Inhibit haemostasis
Application of heparin or
Other anticoagulant drugs (hirudin, gabexate)
Antiplatelet agents
3. Specific blood component therapy
Platelet concentrates – not currently applicable in veterinary medicine
Packed red cells (washed)
Antithrombin concentrates
or frozen plasma
Cryoprecipitate
4. Inhibit fibrinolysis (? ^a)
Epsilon-aminocaproic acid
Tranexamic acid

^aIt is questionable if inhibition of fibrinolysis in a patient with disseminated intravascular coagulation is indicated. It may, in fact, be problematic and contraindicated.

al. 1982; Concannon et al. 1992; Zoran et al. 1992) depend upon the primary disease, blood pH and electrolyte and hydration status of the patient.

Coagulation Inhibitors

Heparin is the most common anticoagulant used in correction of DIC. However, it has a limited effect depending on the availability of functional patient ATIII. The anticoagulant effect of heparin is due to its ability to form complexes with plasma ATIII, potentiating the action of the complex to neutralise thrombin, factors Xa, XIa, XIIa, XIa, as well as plasmin, KK, complement and trypsin (Rosenberg 1975; Green 1988). Administration of high-dose heparin may increase the risk of haemorrhage in patients with acute DIC. Heparin therapy can be successful in compensated DIC when functional ATIII concentrations are available (Ruehl et al. 1982). Transfusion of fresh plasma would provide ATIII and other serine protease inhibitors and subsequent administration of low doses of heparin may sustain appropriate haemostasis (Wisecarver and Haire 1989; Welch et al. 1992). Heparin may be added to the container of fresh frozen plasma and incubated, to ensure a continuous ATIII infusion and avoiding ATIII depletion (Feldman 1990). Low-molecular-weight heparins (LMWH) are obtained from standard heparin. They have greater inhibitory effects on factor Xa than on thrombin, less interaction with platelets, and may have potentially new therapeutic applications (Samama and Babinet 1991). Their mode of action on the haemostatic system is based in their anti-factor Xa and IIa

ATIII-dependent activity. Preliminary studies indicated that LMWH are effective in treatment of DIC and have less risk of haemorrhage (Oguma et al. 1990). Recently, it has been observed that administration of LMWH to horses may avoid some undesirable effects related to standard heparin administration, such as erythrocyte agglutination (Monreal et al. 1995).

Newer agents with potential therapeutic benefits for fulminant and compensated DIC are recombinant hirudin and gabexate mesilate (Hauptmann and Bruggener 1988; Umeki et al. 1988). These drugs are capable of inhibiting thrombin or factor Xa in the absence of ATIII. Experimental studies proved that hirudin (Nowak and Markwardt 1991) and gabexate mesilate (Suzuki et al. 1988) inhibit different triggering mechanisms for DIC induced by endotoxins. Further studies in the use of these products in veterinary medicine might affect morbidity and mortality from endotoxin-induced DIC. An orally active new specific inhibitor of factor Xa, DX-9065a, has been studied against two kinds of experimental DIC in rats (Yamazaki et al. 1994).

Antiplatelet Aggregant Therapy

This has been used in patients with compensated DIC (Ruehl et al. 1982; Morris 1988; Slappendel 1988b). Acetylsalicylic acid inhibits platelet aggregation and blocks TxA₂ release (Yao et al. 1991). However, platelet inhibitors should not be used in patients with severe thrombocytopenia (Ruehl et al. 1982).

Blood Product Therapy

This is indicated if haemorrhage occurs. This form of therapy necessitates the ability to continually assess the patient's haemostatic system. The severity of blood loss, thrombocytopenia, hypofibrinogenaemia, and coagulopathy, indicates the selection of blood products. Packed red cells, platelet concentrates, platelet rich plasma, fresh frozen plasma, cryoprecipitate, or fresh whole blood may be considered (Mora et al. 1955). In patients that appear to be clinically stable, administration of fresh or stored frozen plasma or cryoprecipitate may be indicated. It has been proposed that administration of blood products to a patient with ongoing DIC and microvascular thrombosis carries the risk of plasmin biodegradation of the administered coagulation factors (Bick et al. 1976; Bick 1988). Experimental administration of recombinant human activated protein C has also been studied in tissue thromboplastin-induced disseminated intravascular coagulation (DIC) in rabbits (Katsura et al. 1994). The use of ATIII concentrates in human medicine is not thoroughly discussed in relation to the clinical improvement observed (Lechner and Kyrle 1995) '... the doses [of ATIII] applied in adult intensive care patients with septicaemia does not appear to improve outcome in terms of mortality' (van Beek et al. 1994).

Fibrinolytic Inhibitors

Fibrinolytic inhibitors are rarely indicated, unless secondary fibrinolysis continues to biodegrade plasma proteins. If this occurs, antifibrinolytic (ϵ -aminocaproic acid) therapy may be considered. It is, however, important to note that this therapy is contraindicated for patients with ongoing DIC, as these patients are dependent on fibrinolysis to clear microthrombi. Also antifibrinolytic therapy should never be applied unless increased fibrinolytic activity and subsequent haemorrhage have been documented. Tranexamic acid has recently been used as a potent antifibrinolytic agent (Takada et al. 1990).

For effective therapy of DIC and to avoid complicating the existing condition, therapy should be monitored. Return of fibrinogen concentration, ATIII concentration, platelet numbers, and PT and APTT towards reference intervals are among the most consistent signals of therapeutic success. It should be noted that this statement is in direct opposition to the myth of prolonging the universal tests of coagulation (PT and APTT) towards some predetermined time.

Finally, preventive measures to reduce morbidity and mortality from endotoxaemia-induced DIC in horses have been studied. Studies involved feeding horses a diet enriched with Ω -3 fatty acids. These fatty acids alter the cell-membrane phospholipid composition. Results indicated that mononuclear phagocytes from horses on this diet have reduced ability to produce inflammatory mediators including eicosanoids and TNF, in response to endotoxins in vitro (Henry et al. 1991; Morris et al. 1991).

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