

The Pathogenesis and Management of Disseminated Intravascular Coagulation

Hussain I. Saba, MD, PhD, and Genevieve A. Morelli, BA

Dr. Saba is the Director of the Hemophilia and Thrombosis Center in the Department of Internal Medicine at the University of South Florida College of Medicine in Tampa, where Ms. Morrelli is an Associate in Research. Dr. Saba is also the Chief, Hematology/Oncology, James A. Haley Veterans Hospital, and a member of the Malignant Hematology Program, Moffitt Cancer Center and Research Institute in Tampa, Fla.

Address correspondence to:

Hussain I. Saba, MD, PhD
Hematology/Medical Oncology #111-R
James A. Haley Veterans Hospital
13000 Bruce B. Downs Blvd.
Tampa, FL 33612;
Tel: 813-972-7582; FAX: 813-903-4862
E-mail: saba@moffitt.usf.edu

Abstract: The pathologic and progressive generation of thrombin in human blood can result in the development of disseminated intravascular coagulation (DIC), a syndrome associated with many underlying conditions and manifested as microvascular thrombosis, tissue hypoxia, and organ damage. DIC can be either acute or chronic, with acute DIC resulting from generation of a large amount of thrombin in a brief time period and chronic (compensated) DIC developing as a result of exposure of the coagulation system to small amounts of tissue factor leading to increased but nonacute levels of thrombin generation. DIC can also be considered a thrombohemorrhagic syndrome. Acute DIC at first manifests in a hypercoagulable state and leads to thrombosis, but can be followed by the development of a so-called hypocoagulable phase caused by depletion of clotting factors. This depletion can sometimes lead to bleeding. Bleeding is less common in chronic DIC, as coagulation factors and platelets are more likely to be able to be replenished in the majority of patients. Diagnosis of DIC can sometimes be difficult, depending upon the stage and presentation of the syndrome. During the thrombotic phase of DIC, many common laboratory parameters remain normal, with the important exception of an early drop in circulating platelets. DIC is easier to diagnose when the patient is bleeding, as abnormalities can normally be detected in global coagulation tests and factor assays. Therapy involves identification and treatment of the underlying condition, if possible. In the interim, measures to control bleeding can be administered, if necessary, and may include supportive care with blood products, antithrombin, heparin, and other agents.

Disseminated intravascular coagulation (DIC) is a coagulation disorder induced by systemic activation of the coagulation cascade in response to some underlying pathologic condition in the human body.^{1,2} DIC can be mild and clinically insignificant (nonovert DIC) or, at times, may lead to extreme systemic activation of the coagulation cascade (overt or acute DIC).³ This widespread microvascular thrombosis represents a hyperthrombinemic (ie, hypercoagulable) state, inducing microvascular thrombosis and tissue injury/organ damage.^{4,5} The ongoing activation of the coagulation system can cause decreased levels of

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procoagulants and platelets because of overutilization, increased degradation, and/or impaired synthesis of clotting factors, leading to bleeding. Therefore, overt DIC can be considered a two-stage phenomenon: initial activation of the coagulation cascade (ie, hypercoagulable state) that can sometimes result in bleeding (ie, hypocoagulable state or so-called consumptive coagulopathy).⁶⁻⁹

Pathogenesis of DIC

Our understanding of the pathogenesis of DIC comes from animal and human experimental models as well as from clinical experience in patients with sepsis.^{10,11} Several reactions have been considered to play important roles in the pathogenesis of DIC. These include: generation of a hyperthrombinemic state, alterations of physiologic anticoagulants, inhibition and impairment of the fibrinolytic mechanism, and activation of proinflammatory cytokines.

Generation of a Hyperthrombinemic State

It appears that the tissue factor (TF) pathway, rather than the contact factor pathway, plays the dominant role in the development of a hyperthrombinemic state in DIC, as suggested by experimental models of human endotoxemia.¹² In these models of endotoxin-induced DIC, increases in the mediator tumor necrosis factor (TNF) and release of interleukin (IL)-6 failed to show any change in the markers of activation of the contact system.¹²⁻¹⁴ In contrast, blockage of the TF/factor VIIa pathway using monoclonal antibody directed against TF completely inhibited thrombin generation and prevented the onset of DIC.^{13,14} The TF pathway can be activated by tissue injury, such as can occur in severe trauma, septicemia, or cancer. Severe trauma, inducing release of tissue phospholipids, can initiate activation of the clotting cascade. Once released, TF complexes with factor VII, which is activated by factor Xa to form the TF/VIIa complex. This complex activates factor IX and factor X, leading to the development of thrombin.¹⁵ Thrombin plays an important role in conversion of fibrinogen into fibrin.¹⁶ Thrombin can further activate factor V to Va and factor VIII to VIIIa, rapidly amplifying thrombin generation. Thrombin generation and its effects are shown in Figure 1.

Alteration in Physiologic Anticoagulants

Normally, thrombin levels are regulated by the natural anticoagulants antithrombin, protein C, and TF pathway inhibitor (TFPI). Antithrombin and protein C have been shown to be markedly decreased in DIC.¹⁷ Antithrombin levels can be lowered as a result of consumption by the elaborated thrombin. In addition, interaction with elastase released from the neutrophils in septicemia^{6,18-20} and anoxic liver impairment⁶ can cause decreased levels

of antithrombin. Levels of protein C, another important inhibitor, can also fall due to capillary leakage, decreased synthesis from liver injury, and/or reductions in thrombomodulin expression on the vascular surface (downregulation).^{6,21} This occurs because of a release of TNF- α and other pro-inflammatory cytokines.^{22,23}

Impaired Fibrinolysis in Onset of DIC

An experimental model of DIC in sepsis has shown increased fibrinolytic activity due to release of tissue plasminogen activator (TPA) from endothelial cells.¹⁴ This hyperfibrinolysis is followed by rapid release of plasminogen activator inhibitor 1 (PAI-1), which suppresses fibrinolysis, thus playing an important role in the pathogenesis of DIC. A functional mutation of the *PAI-1* gene (4G/5G polymorphism) has also been demonstrated in DIC. This mutation induces increased plasma levels of PAI-1.²⁴⁻²⁶

Activation and Liberation of Inflammatory Cytokines in Pathogenesis of DIC

It is thought that activation of the clotting system concomitantly leads to activation of inflammatory cascades, which, in turn, induce endothelial cell synthesis of pro-inflammatory cytokines. These cytokines and other inflammatory mediators can lead to coagulation. The inflammatory cytokine thrombin and other serine proteases interact with protease-activated receptors on the cell surfaces, thereby inducing further inflammatory and clotting responses. Activated protein C (APC) has been considered to be a mediator of anti-inflammatory responses. This mediation occurs by its inhibition of endotoxin-induced production of TNF, IL-1 β , IL-6, and IL-8.^{27,28} Therefore, depletion of protein C can induce and enhance a pro-inflammatory state, which can lead to activation of coagulation reactions.

Although the majority of DIC patients are diagnosed and treated during the thrombotic phase, some cases of bleeding (hypocoagulability) in both chronic and acute DIC have been reported. Excessive bleeding in patients with DIC has been reported after routine dental extractions,^{29,30} hip replacement,³¹ aortic aneurysm,³² leukemic states, and other disorders.³³ Although the majority of elderly patients with DIC have the chronic form, severe acute bleeding can occur in this population.³⁴

DIC, therefore, can be considered to be a two-phase thrombohemorrhagic phenomenon, with thrombosis sometimes leading to bleeding.^{8,9} Clinical conditions underlying DIC can initiate hypercoagulability by activation of the clotting cascade along with depletion of natural anticoagulants, elaboration of pro-inflammatory cytokines, and abnormalities of the fibrinolytic pathway. This hypercoagulable state, if it continues to progress, can

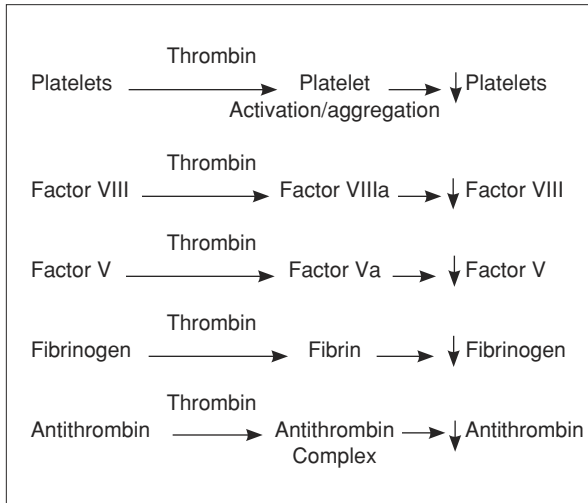


Figure 1. Effects of thrombin on coagulation.

lead to depletion of clotting factors and platelets through utilization, and can sometimes lead to a bleeding diathesis (consumptive coagulopathy).^{17,35,36}

Diagnosis of DIC

Although various laboratory assays and medical algorithms have been used to diagnose DIC (Table 1), there is no single laboratory test currently available for accurate and precise diagnosis.^{3,6} Diagnosis is further complicated because many of the available assays for diagnostic characteristics of DIC are nonspecific, limiting their use as diagnostic tools. Therefore, consideration of clinical setting is highly important, along with help from laboratory diagnostic parameters.

The presence of soluble fibrin monomers is of diagnostic importance in DIC as it indicates that activation of the clotting cascade has occurred and that thrombin thus generated has acted upon fibrinogen, thereby releasing soluble fibrin monomers. Unfortunately, the detection of soluble fibrin monomers has been shown to be extremely sensitive, but not very specific.³⁷ Furthermore, reliable tests to quantify soluble fibrin monomers are not currently available. Fibrin degradation products (FDP) or fibrin split products (FSP) are released during lysis of the blood clot (ie, secondary fibrinolysis). Assays for the presence of FDP or FSP have been in widespread use for diagnosis of DIC; however, high FDP or FSP levels are not specific for DIC. D-dimer levels detect the antigen on degraded crosslinked fibrin; therefore an assay of this byproduct is considered to be more specific than one for FSP. A recent study, however, found that differences in assays for D-dimer appeared to depend upon the type of antibody

and sample used in the testing procedure.³⁸ Increased D-dimer levels also occur in disorders other than DIC.^{39,40} Yu and colleagues⁴¹ found that a combination of both D-dimer and FDP could have high sensitivity and specificity as the efficacy of this testing combination was reported to be 95%. The prothrombin fragment F1+2 is released during conversion of prothrombin to thrombin. Although somewhat difficult to measure, values are markedly high in DIC patients but, again, specificity is a problem.⁴²

In view of these diagnostic problems, several algorithms have been generated in order to accurately assess DIC. Bick⁴³ developed and presented an algorithm for diagnosis of DIC based on coagulation parameters including fibrinogen, F1+2, D-dimer, FDP, antithrombin, alpha-2-antiplasmin, fibrinogen, platelet count, blood chemistries, hematocrit, total white blood cell count, and physical findings. Unfortunately, most of the sophisticated assays involved are not normally available for routine lab testing, limiting the potential usefulness of the Bick algorithm.

Yu and colleagues⁴¹ presented a diagnostic DIC algorithm that includes clinical setting, thrombohemorrhagic events, prothrombin time, activated partial thromboplastin time (aPTT), platelet count, fibrinogen, D-dimer and antithrombin levels.

The Scientific Subcommittee on DIC of the International Society on Thrombosis and Haemostasis (ISTH) has devised a scoring system for the diagnosis of DIC using the parameters outlined in Table 2.⁴⁴ The risk of DIC according to the underlying disorder should first be assessed. If risk is identified, global laboratory tests are ordered and results are assigned values as outlined in Table 2. The ISTH DIC score is the total of the scores obtained for each of the four groups of global laboratory tests used, with a minimum score of 0 and a maximum of 8. In this system, a score below 5 is suggestive of but not definitive for DIC. Tests and scoring should be repeated daily until results normalize. Validation of this study has been investigated by Bakhtiari and coworkers⁴⁶ but further studies are needed for validation and utilization of this system. In a recent study by Sivula and coauthors⁴⁷ of intensive care unit patients with suspected DIC, the diagnostic value of plasma antithrombin levels outweighed that of plasma fibrinogen levels.

Taylor and colleagues⁴⁵ have also reported an algorithm for diagnosing nonovert DIC in patients with a negative overt ISTH DIC score. Functionality of this algorithm is again limited by assay availability, but it is considered to be workable and to have acceptable prognostic value.⁴⁸

In 1983, the Japanese Ministry of Health and Welfare established DIC diagnostic criteria in order to determine which patients should be monitored more closely.⁴⁹ In 2005, Gando and coauthors⁵⁰ developed and published

Table 1. Abnormalities of Laboratory Assays in DIC

<ul style="list-style-type: none"> • Prolongation of prothrombin time • Prolongation of activated partial thromboplastin time • Decrease in platelet count • Peripheral smear examination: schistocytes • Decrease in fibrinogen • Decrease in factor V • Decrease in factor VIII • Increase in fibrin split products (FSP) • Increase in D-dimer • Increase in prothrombin fragment 1+2 • Increase in soluble fibrin monomer • Increase in plasmin • Increase in fibrinopeptide A • Increase in fibrinopeptide B • Increase in thrombin-antithrombin complex
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Table 2. International Society on Thrombosis and Haemostasis Scoring System for Diagnosis of DIC

Laboratory Test	Result	Score
Platelet count (cells/ μ L)	>100,000	0
	50,000–100,000	1
	<50,000	2
Increase in fibrinogen and fibrin-related markers (eg, soluble fibrin monomers, fibrin degradation products)	None	0
	Moderately increased	2
	Strongly increased	3
Prolonged prothrombin time (seconds prolonged over upper limit of reference range)	<3	0
	3–5.9	1
	\geq 6	2
Fibrinogen	> 1 g/dL	0
	\leq 1 g/dL	1

new Japanese DIC criteria for use in critically ill patients based upon problems discovered with the old system. This new system involves the evaluation and scoring of parameters including systemic inflammatory response syndrome, platelet count, FDP, PT ratio, and fibrinogen. This system was reported to be highly sensitive but of low specificity.

The diagnosis of DIC while the subject is in the thrombotic (hypercoagulable) phase can be difficult, as most of the global tests for DIC in this phase may still be normal. However, diagnosis becomes easier if the patient slips into the hypocoagulable state and has bleeding. These patients may have overt clinical evidence of bleeding and abnormalities in the global laboratory tests, such as decreased

levels of platelets, fibrinogen, and some coagulation factors, due to consumption.^{10,51–53} A recent study by Song and colleagues⁵⁴ found that factor XIII levels correlated to DIC score, and that levels in patients with overt DIC were significantly lower than those in patients with nonovert DIC, suggesting that assessment of factor XIII crosslinking activity might be useful in the diagnosis of DIC.

It should be pointed out, however, that although sensitivity and specificity of diagnostic tools remain uncertain and a more accurate scoring system is necessary, it is often possible to diagnose DIC in clinical practice. This can be done by assessing the clinical condition of the patient and by examining a combination of parameters, including platelet count, global clotting tests such as PT and PTT, measurements of clotting factors and inhibitors (eg, antithrombin), and tests for FDP.

Platelets are extremely sensitive to thrombin and slight increases can activate platelets and stimulate aggregation. As a result of thrombin stimulation, circulating platelets are lost due to adhesion and aggregation, and their levels begin to fall early in DIC.^{15,55} Therefore, a progressive decline in platelets on subsequent measurement, although not specific, can be a very sensitive sign of the onset of DIC in the presence of other clinical parameters and conditions favoring DIC. The prolongation of global clotting assays (eg, PT, PTT) in the presence of bleeding can indicate consumption and depletion of clotting factors. This finding may be substantiated by measuring one or more clotting factors.

Management and Treatment

The cardinal rule in the treatment of DIC is to identify and treat the underlying cause.^{6,56} It has been reported that 85% of patients with severe DIC in one study died due to their underlying disease and not DIC.⁵⁷ Some of the underlying conditions associated with DIC are listed in Table 3.^{7,17,30,58–61}

In many situations, when physicians treat the underlying condition that preceded the DIC state, the syndrome gets better. For example, Gram-negative sepsis responsible for the induction of DIC can be managed by appropriate antibiotics. DIC caused by dead fetus syndrome can be managed by surgical intervention to remove the dead fetus. In patients with acute promyelocytic leukemia presenting with features of DIC, treatment with all-*trans*-retinoic acid and chemotherapy improves the DIC condition.⁶² In some circumstances, however, intervention with supportive care measures may be required to control the fulminant DIC before precise treatment of the underlying condition can be instituted or proves to be effective.

The optimal DIC treatment regimen has not yet been determined. In light of this fact, it is reasonable to

assume that treatment should be based upon the clinical presentation of the patient (ie, bleeding versus thrombosis versus those with no evidence of either).⁵³

Management of Thrombotic DIC Patients

The management of DIC patients with thrombosis could prevent possible depletion of platelets and clotting factors and could save the patients from DIC-mediated bleeding complications.

Use of Heparin It would be incorrect to assume that anticoagulants are the optimal therapy for DIC patients with thrombotic symptoms. Heparin is a strong antithrombotic agent and can be expected to block the thrombin activity and, therefore, inhibit further coagulation. The actual benefit of using heparin in DIC patients, however, is controversial.^{7,10,63} Heparin has, in some cases, been used successfully in chronic DIC, which occurs in conjunction with disorders normally associated with recurrent thrombosis such as solid tumors and dead fetus syndrome. If heparin is used, it is usually administered at low doses (eg, 500–750 U/hr without a bolus dose).⁶⁴ There have been reports of positive results with administration of low molecular weight heparin.⁶⁵ Heparin, nevertheless, should be used with caution, because of its potential to induce bleeding. The PTT should be closely monitored during heparin therapy, as should the clinical symptoms. If the patient starts bleeding, heparin should immediately be stopped and other supportive care measures instituted (eg, fresh-frozen plasma [FFP] and/or platelets).

Antithrombin Concentrates in DIC The use of antithrombin concentrates would seem a logical approach in the treatment of DIC in order to effectively block thrombin, the so-called culprit enzyme behind thrombosis. However, doubt has been raised regarding the efficacy of antithrombin in the treatment of DIC. Some human trials have suggested its benefit,⁶ but a large multicenter randomized trial did not show significant reduction of mortality in patients with sepsis who were treated with antithrombin concentrate.⁶⁶ Kienast and colleagues,⁶⁷ however, recently reported that high-dose antithrombin without concomitant heparin led to a significant reduction in the deaths of septic DIC patients. This observation requires further validation.

Management of Bleeding in DIC

DIC patients with low levels of platelets and coagulation factors who have clinical symptoms of bleeding should be given supportive care.⁶⁸ Possible supportive care includes the infusion of FFP, cryoprecipitate, and platelets (if required; Table 4). It is recommended that

Table 3. Underlying Conditions Associated with DIC

- Sepsis
- Cancer/solid tumor malignancies/hematologic malignancies: Myeloproliferative disorders, lymphoproliferative disorders, acute leukemia
- Severe burns/trauma
- Dead fetus syndrome
- Drug reactions
- Inflammatory diseases
- Liver disease
- Trauma-related injuries
- Obstetric complications (eg, eclampsia, HELLP [hemolysis, elevated liver enzymes, low platelets])
- Paroxysmal nocturnal hemoglobinuria
- Prosthetic devices
- Snake bite
- Transplant rejection
- Transfusion reactions
- Vascular abnormalities (eg, Kasabach-Merritt syndrome)

clinicians be judicious in the use of FFP in DIC patients; because these are sick individuals, aggressive infusion of FFP could precipitate congestive heart failure. Therefore, the pulmonary status of patients receiving FFP should be carefully monitored.

Protein C in DIC APC inactivates factors Va and VIIIa and, as a result, decreases thrombin formation. APC also interacts with PAI, stimulating fibrinolysis. Protein C is lowered in DIC, and supplementation of this natural anticoagulant has been considered beneficial.⁶⁹ A phase III trial of APC concentrate in patients with sepsis was prematurely stopped due to its efficacy in reducing mortality. Mortality from all causes at 28 days was 24.7% in the APC group versus 30.8% in the control group (19.4% relative risk reduction).⁷⁰ Recombinant human APC was subsequently approved by the US Food and Drug Administration and the European Community for the treatment of patients with severe sepsis. A 2002 study comparing the efficacy of APC to that of heparin in 132 DIC patients found that low-dose APC appeared to be more effective than heparin in treating bleeding associated with DIC, but there was little difference in DIC-related organ dysfunction.⁷¹

Tissue Factor Pathway Inhibitor TF acts on both factors VII and IX to initiate factor activation and coagulation. TFPI has the ability to complex with TF and factors VIIa and Xa. As a result, TFPI can inhibit generation of thrombin from prothrombin, and may be useful in the

Table 4. Possible Replacement Therapy for Symptomatic DIC Patients

Replacement Therapy	Suggested Dosage	Clinical Indicators for Use
Fresh-frozen plasma	15–20 ml/kg	Symptomatic bleeding with fibrinogen <100 mg/dL
Fibrinogen concentrates	2–3 g	Symptomatic bleeding with fibrinogen <100 mg/dL
Cryoprecipitate	1 U/10 kg	Symptomatic bleeding with fibrinogen <80–100 mg/dL
Platelet concentrates	1–2 U/10 kg	Platelet count <20,000 OR Platelet count <50,000 with bleeding

treatment of thrombosis associated with DIC.⁷² A phase II randomized study of recombinant TFPI (rTFPI; tifacogin [Chiron]) versus placebo showed a trend toward reduction in thrombin-antithrombin complexes and IL-6 levels.⁷³ A phase III randomized trial of the efficacy of rTFPI versus placebo in sepsis patients found that rTFPI was linked with increased bleeding risk. Mortality reduction was seen to be related to international normalized ratio (INR), with lower mortality rates in patients with low INR and no difference observed in patients with higher INR.⁷⁴

Antifibrinolytic Agents Antifibrinolytic agents, such as tranexamic acid and epsilon aminocaproic acid, are rarely required for the treatment of DIC.^{75,76} Exceptions can be seen in conditions linked to high levels of fibrinolysis with bleeding (eg, some cases of prostate cancers, acute promyelocytic leukemias). If necessary, they may be given to control severe bleeding or in conditions associated with strong fibrinolysis, but they should be given in combination with heparin after all other treatment modalities have been attempted.^{10,77} Use of these agents should be cautious because they can easily lead to deaths from disseminated coagulation and thrombosis.

Other Potential Therapeutic Modalities in DIC

Thrombomodulin

Wada and colleagues⁷⁸ have recently reported results of a pharmacologic study of plasma thrombomodulin in DIC patients. In this study, 0.3–30 U/mL of thrombomodulin was found to significantly inhibit thrombin generation and stimulated APC production. The results of this study

suggest that thrombomodulin deserves further investigation in DIC.

Activated Factor VII in DIC

Sallah and coworkers⁷⁹ reported the results of administration of recombinant factor VIIa in DIC patients with bleeding states associated with advanced cancer. In this study, 15 of the 18 patients stopped bleeding and had improvement of their coagulation parameters. Successful administration of recombinant factor VIIa has also been reported in a patient with postsurgical abdominal bleeding and DIC secondary to sepsis.⁸⁰ Although the administration of factor VIIa is not advocated for DIC,⁸¹ these reports suggest that further studies may be warranted.

Gabexate Mesylate

Gabexate mesylate is a synthetic inhibitor of serine proteases such as thrombin, and it has anticoagulant activity in the absence of antithrombin. One early study on its use in 15 DIC patients versus 8 patients treated with heparin found that gabexate mesylate was more effective than heparin in patients with low antithrombin levels.⁸² A later study reported similar results.⁸³ Systemic investigation of this drug in DIC has not been done.

Hirudin

A pilot study using recombinant hirudin in DIC patients suggested that this strong thrombin inhibitor may be useful in the treatment of DIC patients, but no organized investigation of its use has been done in the United States.⁸⁴

Summary and Future Perspectives

DIC is a progressive coagulation disorder induced by the pathologic generation of thrombin in circulation. The etiology and causation of DIC can be varied, and the syndrome of DIC includes both thrombosis (hypercoagulation) and bleeding (hypocoagulation).

Management for DIC is complex and dependent upon clinical presentation and underlying condition. One of the priorities of DIC treatment is to identify and correct the underlying condition inducing the DIC state. Heparin may be necessary in very active and acute DIC progressing toward consumption coagulopathy and bleeding. Heparin use in this condition, however, should be very cautious and involve low doses. Coagulation parameters and thrombocytopenia ought to be closely monitored and discontinued if bleeding occurs or there is no improvement. Supportive care measures with FFP, platelets, and cryoprecipitate should be the mainstay of treatment. The concept of “adding fuel to the fire,” even in the thrombotic phase of DIC, has not withstood the test of time

and should not prevent the use of these supportive care measures in progressive and acute DIC. If bleeding resulting from consumption ensues in these patients, support is the main treatment and should be used aggressively. In some situations of DIC with consumption coagulopathy and bleeding, the use of other modalities of treatment may be considered, including TPA-1, antithrombin, factor VIIa infusions, and antifibrinolytic agents.

Conclusion

DIC is a coagulation disorder induced by the development of a pathologic level of thrombin in human blood. This hyperthrombinemic state occurs mainly by the activation of the TF pathway and can lead to microvascular thrombosis, anoxic injury, and, ultimately, organ failure. The activation of the clotting cascade can be, in some cases, very exuberant and lead to thrombocytopenia and consumption of clotting factors—so-called “consumption coagulopathy”—leading to bleeding states.

An increased understanding of the pathogenetic mechanisms of DIC has led to the development of several different diagnosis and management strategies utilizing the patient's clinical background and simple global coagulation laboratory tests. The best treatment of DIC remains the treatment of the underlying condition; however, several strategies counteracting thrombin generation and interfering with the clotting system (eg, use of antithrombin, APC, and TPA-1) have been shown to be of benefit in experimental and clinical studies and await further confirmation trials for their efficacy.

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