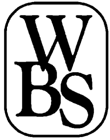

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Disseminated intravascular coagulation Current concepts of etiology, pathophysiology, diagnosis, and treatment

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Disseminated intravascular coagulation (DIC) is a complex disorder with pathophysiology that is variable and highly dependent on the triggering event, the host response, and comorbid conditions. As a result of these complicated interactions, the clinical expression and laboratory findings are varied, thereby affecting the specifics of diagnosis and therapeutic approaches. The highly complex and variable pathophysiology of DIC often results in a lack of uniformity in clinical manifestations, a lack of consensus in the specific appropriate laboratory criteria of diagnosis, and a lack of specific therapeutic modalities. Indeed, recommendations for therapy and the evaluation of the efficacy of management regimens are often difficult because the morbidity and survival are more dependent on the specific cause of DIC and because the generally used specific therapeutic approaches, which include heparin, low-molecular-weight heparin, antithrombin concentrate, protein C concentrate, and so forth, have never been subjected to objective, prospective randomized trials, except for antithrombin concentrates.

Herein is a discussion of the complex and varied pathophysiologic events in DIC to provide objective guidelines and criteria for the clinical diagnosis, the laboratory diagnosis, and the definition of severity. This knowledge, augmented by an understanding of complex and varied pathophysiology, can be used for objective evaluation of therapeutic responses and results.

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DIC is an intermediary mechanism of disease usually seen in association with well-defined clinical disorders [1–5]. The pathophysiology of DIC serves as an intermediary mechanism in many disease processes, which sometimes remain organ-specific. This catastrophic syndrome spans all areas of medicine and presents a broad clinical spectrum that is confusing to many. Disseminated intravascular coagulation was called "consumptive coagulopathy" in early literature [6,7]; this term is not a proper description because little is "consumed" in DIC—most factors and plasma constituents are plasmin-biodegraded. The terminology after this phrase was "defibrination syndrome" [8,9]; however, a more suitable term would be "defibrinogenation syndrome." The contemporary term is DIC; this term is a useful descriptive pathophysiologic term if one accepts the concept that "coagulation" is expressed as both hemorrhage and thrombosis [1–3,5]. Most physicians consider DIC to be a systemic hemorrhagic syndrome, but only because hemorrhage is evident and often impressive. Less commonly appreciated is the profound microvascular thrombosis and sometimes, large-vessel thrombosis occurring. The hemorrhage is often simple to contend with in patients with fulminant DIC, but it is the small- and large-vessel thrombosis, with impairment of blood flow, ischemia, and associated end-organ damage, that usually leads to irreversible morbidity and mortality. Throughout this article, fulminant DIC versus "low-grade" compensated DIC and the attendant differences in clinical manifestations, laboratory findings, and treatment are discussed. These descriptions are often pure and theoretical clinical spectrums of a disease continuum; however, patients may present anywhere in this continuum and may lapse from one end of the spectrum into another. A clear definition of DIC is outlined in Box 1.

Etiology

Disseminated intravascular coagulation usually is seen in association with well-defined clinical entities. Those clinical disorders and circumstances most commonly associated with DIC are summarized in Table 1.

Obstetric accidents are common events leading to DIC. Amniotic fluid embolism with DIC is the most catastrophic and common of the life-threatening obstetric accidents [1–6]. The syndrome of amniotic fluid embolism is manifested by the acute onset of respiratory failure, circulatory collapse, shock, and DIC. The first description of this syndrome was by Steiner and Lushbough in

Box 1. Definition of DIC (minimal acceptable criteria)

A systemic thrombohemorrhagic disorder seen in association with well-defined clinical situations and laboratory evidence of (1) procoagulant activation, (2) fibrinolytic activation, (3) inhibitor consumption, and (4) biochemical evidence of end-organ damage or failure.

Table 1
Accepted disease entities generally associated with DIC

Fulminant DIC	Low-grade DIC
Obstetric accidents	Cardiovascular diseases
Amniotic fluid embolism	Autoimmune diseases
Placental abruption	Renal vascular disorders
Retained fetus syndrome	Hematologic disorders
Eclampsia	Inflammatory disorders
Abortion	
Intravascular hemolysis	
Hemolytic transfusion reactions	
Minor hemolysis	
Massive transfusions	
Septicemia	
Gram negative (endotoxin)	
Gram positive (mucopolysaccharides)	
Viremias	
HIV	
Hepatitis	
Varicella	
Cytomegalovirus	
Metastatic malignancy	
Leukemia	
Acute promyelocytic (M-3)	
Acute myelomonocytic (M-4)	
Many others	
Burns	
Crush injuries and tissue necrosis	
Trauma	
Acute liver disease	
Obstructive jaundice	
Acute hepatic failure	
Prosthetic devices	
Leveen or Denver shunts	
Aortic balloon-assist devices	
Vascular disorders	

1941 [10]. In placental abruption with DIC, placental enzymes or tissues, including thromboplastin-like material, may be released into the uterine and then the systemic maternal circulation and lead to activation of the coagulation system. In the retained-fetus syndrome, the incidence of DIC approaches 50% if the woman retains a dead fetus in utero for greater than 5 weeks. The first findings are usually those of a low-grade compensated DIC, which then progresses into a fulminant thrombohemorrhagic form. In this instance, necrotic fetal tissue, including enzymes derived from necrotic fetal tissue, is released into the uterine and then the systemic maternal circulation and acts at diverse sites to activate the procoagulant and fibrinolytic systems and trigger fulminant DIC [1–6,11,12]. In eclampsia, DIC often remains low grade and organ-specific to the renal and placental microcirculation; however, in approximately 10% to 15% of women, the process becomes systemic and fulminant [13,14]. Many patients who have

had a hypertonic saline-induced abortion develop a DIC-type process, which, sometimes, becomes fulminant and at other times remains compensated until the abortion is completed [15].

Intravascular hemolysis of any etiology is a common cause of DIC. A frank hemolytic transfusion reaction is a triggering event for DIC; however, hemolysis of any etiology, even though minor, may trigger intravascular coagulation. During hemolysis, the release of red cell adenosine diphosphate (ADP) or red cell membrane phospholipoprotein activates the procoagulant system, and a combination of these factors may account for DIC associated with major or minor hemolysis [2,3,5,16–19].

Septicemia often is associated with DIC. An early organism that was associated with DIC was meningococcus [20]. Later, other gram-negative organisms also were associated with DIC [21–23]. The triggering mechanisms consist of the initiation of coagulation by endotoxin–bacterial coat lipopolysaccharide [24,25]. Endotoxin activates factor XII to factor XIIa, induces a platelet-release reaction, causes endothelial sloughing with later activation of XII to XIIa or XI to XIa, and releases granulocyte procoagulant materials; any of these reactions independently might trigger DIC. Endotoxin also induces release of tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and complement activation, all leading to endothelial damage and disruption and endothelial permeability and multi-end-organ damage. What is most common is a clinical summation of several or all of these activation events. Later, many gram-positive organisms also were noted to be associated with DIC, and the mechanisms have been described aptly [1–3,5,26,27]. Bacterial-coat mucopolysaccharides induce DIC by the same mechanisms noted with endotoxin; however, as with gram-negative endotoxemia, what is seen clinically is probably a summation of several or all of these activation events [1–5].

Many viremias, including human immunodeficiency virus, are associated with DIC; the most common are varicella, hepatitis, or cytomegalovirus infections [28,29]. Many other acute viremias also induce DIC [1–3,5,26,27]. The triggering mechanisms are unclear but may represent antigen-antibody–associated activation of factor XII, a platelet-release reaction, or endothelial sloughing with subsequent exposure of subendothelial collagen and basement membrane [30].

Severe viral hepatitis and acute hepatic failure of any etiology (including drug, toxin, or infectious) can lead to DIC, which can be difficult to separate from the myriad other coagulation abnormalities associated with severe hepatic dysfunction. Also, intrahepatic or extrahepatic cholestasis, especially when present for greater than 5 days, may be accompanied by DIC [1–3,5].

Disseminated intravascular coagulation is common in malignancy, and most patients with disseminated solid malignancy have at least laboratory evidence of DIC that may or may not become manifested clinically [31–36]. Many hematologic disorders also are associated with DIC. Agnogenic myeloid metaplasia has been associated with DIC, and many patients with polycythemia rubra vera have clinical and laboratory findings of an underlying compensated DIC process [2–4, 34,36]. There is an increased tendency for thrombosis or thromboembolization

in patients with paroxysmal nocturnal hemoglobinuria, representing DIC that is manifested clinically primarily as thrombosis [35,37]. Metabolic abnormalities, particularly acidosis, have been implicated as "triggers" for DIC [1–3,5].

Acidosis has been noted commonly as a triggering event with the conceptual construct that endothelial sloughing with activation of XII to XIIa, activation of XI to XIa, and platelet release provides the basis for activation of the procoagulant system. Several problems exist in characterizing the metabolic changes as causal in DIC, because almost all of the clinical circumstances that produced the acidosis are also causal in the complex pathophysiology of DIC. Recent evidence has implicated cytokine release as an important mediator of the initiation and propagation of DIC, and it is likely that the metabolic changes are secondary events to such release. Certainly, release of TNF, IL-1, IL-6, and interferon-γ have been shown to participate in the activation of the coagulation sequence with resultant local fibrin deposition [38,39]. The pathophysiologic events that result from TNF administration mimic those events seen in shock and associated DIC [38–43]. Also, acidosis, along with IL-1, IL-6, endotoxin, and TNF, inhibits endothelial and soluble thrombomodulin activity, leading to inhibition of thrombin-mediated activities, some of which are antithrombotic in nature, such as activation of the protein C and S system, thus providing more propensity for thrombus formation in DIC [44,45]. Decreased levels of thrombomodulin are associated with elevation of TNF-α, which also leads to further endothelial damage and disruption, creating a vicious loop, the endpoint of which is enhanced end-organ damage [46].

Patients with extensive burns often develop DIC, and several mechanisms exist [47,48]. Microhemolysis, with release of red cell membrane phospholipid or red cell ADP, may provide the trigger [2,3,5]. Also, necrotic burn tissue may release tissue materials or cellular enzymes into the systemic circulation and initiate DIC. Any patient with a large crush injury and attendant tissue necrosis also may develop DIC because of the release of tissue enzymes or phospholipoprotein-like materials into the systemic circulation [20,49,50]. Patients with open head wounds or those undergoing craniotomy may develop relatively local or systemic DIC from the brain phospholipid released into the surrounding area or systemic circulation; this complication is usually catastrophic and often fatal [36,51].

Selected vascular disorders and other miscellaneous disorders can be associated with DIC [1,3,5,52]. The Kasabach-Merritt syndrome is the association of giant cavernous hemangiomata and DIC [53,54]. Approximately 25% of patients with giant cavernous hemangiomata develop a low-grade "compensated" DIC that may accelerate into fulminant DIC; the transformation into a fulminant form may happen without identifiable reasons. Approximately 50% of patients with hereditary hemorrhagic telangiectasia have a low-grade DIC that occasionally becomes fulminant [1,3,5,52]. Individuals with systemic small-vessel disease such as vasospastic phenomena (including Raynaud's syndrome), severe diabetic angiopathy, or angiopathy associated with autoimmune disorders or Leriche's syndrome may develop compensated DIC, which often becomes fulminant. Collagen vascular diseases may be associated with DIC, and any patient with a

collagen vascular disorder, especially when associated with significant small-vessel involvement, may develop DIC. This DIC, usually in a compensated form, may be seen in patients with severe rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, dermatomyositis, and scleroderma [1,3,5,53]. Hemolytic-uremic syndrome, like eclampsia, shares a pathophysiology similar to DIC; however, hemolytic-uremic syndrome often remains organ-specific and localized to the renal microcirculation [2,3,5]. In approximately 10% of individuals with hemolytic-uremic syndrome, the syndrome becomes systemic [2,3,5]. Chronic inflammatory disorders, including sarcoidosis, Crohn's disease, and ulcerative colitis, can be associated with compensated or fulminant DIC [2,3,5,54–56].

Cardiovascular diseases also may be associated with low-grade DIC, and occasionally, patients with acute myocardial infarction develop a compensated or fulminant DIC process [2,3,5,57]. The mechanisms are unclear but may include shock, hypoxia, and acidosis with resultant endothelial sloughing or activation of the contact activation system through stasis. Various prosthetic devices may trigger DIC. Exposure of the blood to foreign surfaces often is linked with activation of the procoagulant system and provides a major obstacle to the use of certain prosthetic devices [58]. The hemostatic complications that accompany the insertion of prosthetic devices include activation of coagulation factors, "consumption" of coagulation factors and other plasma proteins and platelets, and the generation of microthrombi. Also, life-threatening thrombosis or thromboembolism may develop in those with prosthetic devices [1–3,5,59]. Intra-aortic balloon-assist devices may activate the coagulation system with an attendant low-grade DIC, which may become fulminant [5]. LeVeen or Denver valve shunting for peritoneovenous or pleurovenous shunting is a common palliative procedure, and generalized DIC often is seen with the use of these shunts [1,5,59,60]. The removal of ascitic fluid at the time of LeVeen or Denver valve implantation and the use of low-dose heparin may abort DIC [1–3,5]. In an acute situation, simply placing the patient with a LeVeen shunt and DIC in a sitting position usually blunts shunt function and temporarily aborts the DIC process [5].

Many other disorders are associated with DIC, including the allergic vasculidities (such as Henoch-Schönlein purpura) and the other allergic purpuras, such as sarcoidosis, amyloidosis, and the acquired immune deficiency syndrome [1–5]. Compensated DIC may occur in patients who have hyperlipoproteinemias [1,5]. On rare occasions, patients may develop DIC in which no apparent etiology is defined [1–3,5].

Fig. 1 illustrates the mechanisms by which a broad spectrum of unrelated pathophysiologic insults can give rise to the same common ultimate pathway, the syndrome of DIC. There are many disorders associated with endothelial damage, circulating antigen-antibody complexes, endotoxemia, tissue damage, platelet damage or release, and red cell damage [2,3,5,61]. When one of these insults happens, there are many potential activation pathways by which systemically circulating plasmin and circulating thrombin may arise; when these two enzymes are circulating systemically, DIC is the usual result [2,3,5,61]. Conversely, both

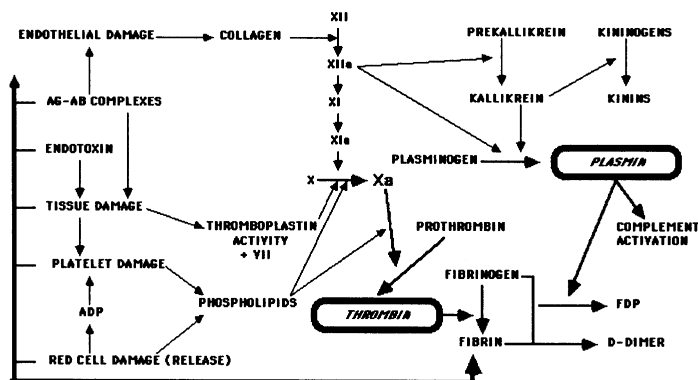

Fig. 1. Triggering mechanisms for DIC. AG-AB = antigen-antibody; ADP = adenosine diphosphate.

enzymes must be present for development of DIC. Often, the pathways leading from the first pathophysiologic insult to the generation of systemic thrombin and plasmin are different; despite the differences in initiating the activation pathway, once triggered, the resultant pathophysiology of DIC is the same [2,3,5]. Only recently has the important contribution of cytokines and vasoactive peptides in leading to end-organ damage and necrosis in DIC become appreciated [62].

Pathophysiologic events

The pathophysiology of DIC, once a triggering event is provided, is summarized in Fig. 2. After the coagulation system has been activated and both thrombin and plasmin circulate systemically, the pathophysiology of DIC is similar in all disorders.

Consequences of systemic thrombin activity

When thrombin circulates systemically, fibrinopeptides A and B are cleaved from fibrinogen, leaving behind fibrin monomer, which polymerizes into fibrin (clot), leading to microvascular and macrovascular thrombosis and interference with blood flow, peripheral ischemia, and end-organ damage [2,3,5,63,64]. As fibrin is deposited in the microcirculation, platelets become trapped and thrombocytopenia follows [2,3,5,65]. On the other side of the "circle" depicted in Fig. 2, plasmin also circulates systemically and cleaves the carboxy-terminal end of fibrinogen into fibrin(ogen)-degradation products (FDPs), creating the clinically recognized X, Y, D, and E fragments [3,5,64,66–68]. Plasmin also rapidly releases specific peptides, the B-beta 15 through 42 and related peptides, which serve as diagnostic molecular markers. Fibrin(ogen)-degradation products may combine with circulating fibrin monomer before polymerization, and the fibrin monomer becomes "solubilized." This complex of FDPs and fibrin monomer is called "soluble-fibrin monomer"; the presence of soluble-fibrin monomer forms

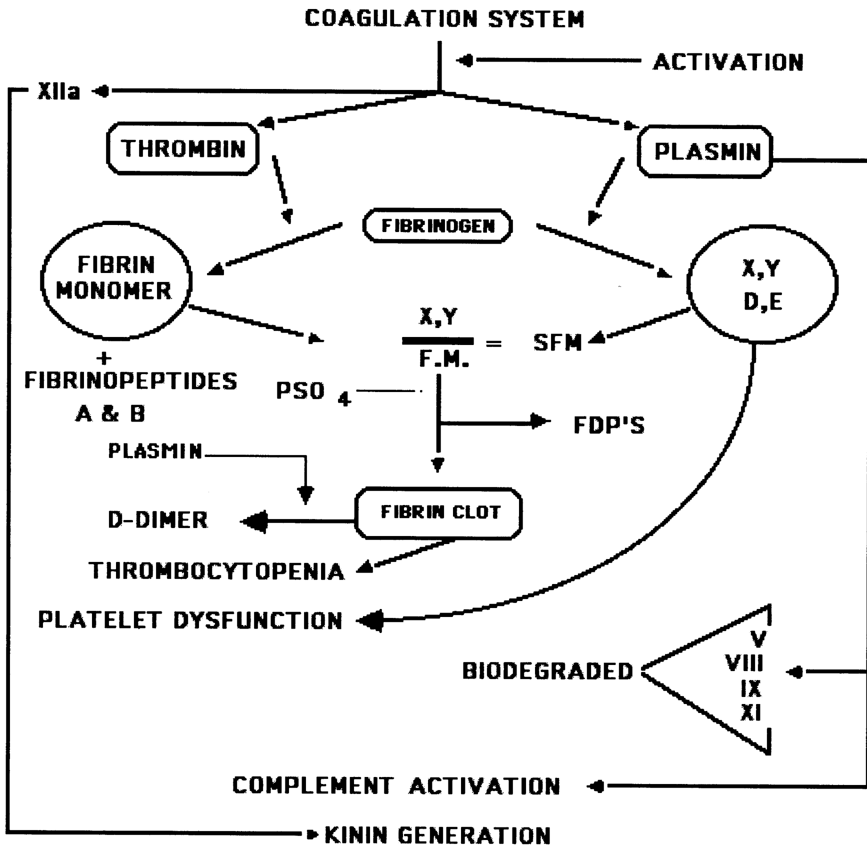

Fig. 2. The pathophysiology of DIC. SFM = soluble fibrin monomer.

the basis of the "paracoagulation" reactions, the ethanol gelation and protamine sulfate tests [69–72]. The systemically circulating FDPs interfere with fibrin monomer polymerization; this interference further impairs hemostasis and may lead to hemorrhage [2,3,5]. The subsequent fragments (D and E) have a high affinity for platelet membranes and induce a profound platelet function defect, which may contribute to clinically significant hemorrhage [2,3,5,73–75]. Fibrin(ogen)-degradation products and D-dimer, discussed later, induce synthesis and release of monocyte/macrophage-derived IL-1, IL-6 ,and plasminogen activator inhibitor-type 1. Interleukin-1 and IL-6 induce additional vascular endothelial damage and disruption, leading to more end-organ damage, and elevated plasminogen activator inhibitor-1 inhibits fibrinolysis, leading to accelerated thrombus formation [70]. Thrombin also induces monocyte release of TNF, IL-1, and IL-6, and may induce endothelial release of soluble thrombomodulin and endothelin and selectin [48,76]. The endothelin release can produce intense vasoconstriction, vasospasm, and subsequent thrombus and vascular occlusion, leading to further end-organ damage and failure [77]. The selectin E

(ELAM-1) released binds to granulocytes, lymphocytes, and monocytes/macrophages, inducing further cytokine release and release of platelet-activating factor. Platelet-activating factor induces further thrombocytopenia [76–78]. Additionally, FDP may induce monocyte release of monocyte-derived IL-1 and tissue factor [79], both of which enhance thrombosis [75]. The binding of granulocytes to endothelium also induces release of granulocyte cathepsins and elastases, which can produce end-organ damage and further cytokine release [80–82].

Plasmin, unlike thrombin, is a global proteolytic enzyme and has equal affinity for fibrinogen and fibrin [2,3,5]. Plasmin also effectively biodegrades factors V, VIII:C, IX, XI, and other plasma proteins, including growth hormone, adenocorticotrophic hormone (ACTH), insulin, and many more [2,3,5,9,64,83]. As plasmin degrades cross-linked fibrin, specific FDPs appear in the circulation; one of these is D-dimer. Plasmin free in the circulation may activate the complement sequence [2,3,5,64,84]. Complement also is activated by TNF, by way of thrombin-mediated release of TNF from the monocyte/macrophage system [48,85]. Red cell lysis releases red cell ADP and red cell membrane phospholipids, supplying more procoagulant material. Complement-induced platelet lysis prompts further thrombocytopenia and provides more platelet procoagulant material. Of added clinical importance, activation of the complement system increases vascular permeability, leading to hypotension and shock [2,3,5,59]. Elevated levels of plasminogen activator inhibitor type-1 in DIC may blunt some of these activities and clearly lead to hypoactivity of overall fibrinolysis and fibrinogenolysis, thus enhancing fibrin precipitation [86].

Activation of the kinin system is also an important pathophysiologic event with serious clinical consequences in DIC. With generation of factor XIIa in DIC, there is subsequent conversion of prekallikrein to kallikrein and later conversion of high-molecular-weight kininogen into circulating kinins [87–89]. This conversion also leads to increased vascular permeability, hypotension, and shock [5].

As thrombin circulates systemically, the consequences are mainly thrombosis with deposition of fibrin monomer and polymerized (cross-linked) fibrin in the microcirculation, and occasionally, large vessels. Many of these consequences of thrombin are mediated by the procoagulant system and consequences of other thrombin-activated systems and by thrombin-induced release of cytokines. Many of these adverse actions in DIC also are mediated by subsequent endothelial damage or disruption, release of endothelial-derived products and cytokines, and endothelial interactions with granulocytes, lymphocytes, and monocyte/macrophage cells. Concomitantly, plasmin also circulates systemically and is primarily responsible for the hemorrhage seen in DIC because of the creation of FDPs and the interference of FDP with fibrin monomer polymerization and platelet function. Plasmin-induced lysis of many aforementioned clotting factors also leads to hemorrhage. By appreciating this circular concept of pathophysiology, it is understandable why most patients with DIC experience both hemorrhage and thrombosis. Clinicians are repeatedly misguided by appreciating only the hemorrhage evolving in patients with DIC, because this physical finding is the most obvious one. Of greater importance, however, is the substantial micro-

Box 2. Laboratory criteria based on DIC pathophysiology

An understanding of the pathophysiology of DIC and the usual laboratory manifestations allows for clear development of criteria to meet the laboratory diagnosis of DIC. The criteria are as follows:

1. Evidence of procoagulant activation
2. Evidence of fibrinolytic activation
3. Evidence of inhibitor consumption
4. Evidence of end-organ damage or failure

To meet these criteria, generally available laboratory tests must be used.

vascular and large-vessel thromboses that occur, because they can lead to irreversible end-organ damage. It is important to recognize that most patients with DIC not only have hemorrhage but also have significant and often diffuse thrombosis [1,2,3,5,90,91]. Understanding and appreciating the extraordinarily complex pathophysiology of DIC provides the dictum that DIC always is accompanied by (1) procoagulant system activation, (2) fibrinolytic system activation, (3) inhibitor consumption, (4) cytokine release, (5) cellular activation, and resultant (6) end-organ damage (Box 2).

Clinical findings

The systemic signs and symptoms of DIC are variable, but the specific signs, which include petechiae and purpura (found in most patients), hemorrhagic bullae, acral cyanosis, and sometimes, frank gangrene, immediately should forewarn one to the probable diagnosis of DIC [1,2,3,5,54,60,92]. Other symptoms include fever, hypotension, acidosis, proteinuria, and hypoxia; wound bleeding, especially oozing from a surgical or traumatic wound, is common in patients who have undergone surgery or experienced trauma [1–3,5]. Oozing from venipuncture sites or intra-arterial lines is another common finding [1–3,5]. Large subcutaneous hematomas and deep tissue bleeding also are seen often [5]. The average patient with DIC usually bleeds from at least three unrelated sites, and any combination may be seen [1–3,5]. A remarkable volume of microvascular and large-vessel thrombosis may occur that is not clinically obvious, unless and until the clinician looks for it [1–3,5]. Those organ systems having a high chance of microvascular thrombosis associated with dysfunction include cardiac, pulmonary, renal, hepatic, and CNS [1–3, 5,93]. Thrombotic thrombocytopenic purpura commonly is associated with CNS dysfunction; however, it should be realized that this condition is observed just as commonly in DIC [2,3,5].

Box 3. Minimal clinical findings required for a diagnosis of DIC

Understanding the usual clinical manifestations of DIC allows for minimal criteria required for the clinical component of a diagnosis of DIC:

1. Clinical evidence of hemorrhage, thrombosis, or both should be present
2. The symptoms should be occurring in the appropriate clinical setting as defined in the text

Patients with low-grade DIC, which also is termed "compensated DIC," present with subacute bleeding and diffuse thromboses instead of acute fulminant life-threatening hemorrhage [1–3,5,94]. In this instance, there is usually an increased turnover and decreased survival of many components of the hemostasis system, including the platelets, fibrinogen, and factors V and VIII:C; because of this event, most global coagulation laboratory tests are near normal or normal [1–3,5,94]. Patients with low-grade DIC, however, uniformly have elevated FDPs, leading to impairment of fibrin monomer polymerization and a clinically significant platelet function defect resulting from the coating of platelet membranes by FDP. Molecular markers of hemostatic activation are typically abnormal in low-grade DIC. The minimal clinical findings required for a diagnosis of fulminant or low-grade DIC are summarized in Box 3.

Morphologic findings in disseminated intravascular coagulation

Morphologic findings in DIC consist of characteristic peripheral smear findings and hemorrhage or thrombosis in any organ [1–3,5,95,96]. Early morphologic findings are platelet-rich microthrombi [5,95,96]. These microthrombi usually are seen in association with intense vasoconstriction resulting from compounds released from platelets, including biogenic amines, adenine nucleotides, thromboxanes, and kinins [2,3,5,97]. These platelet microthrombi are replaced later by fibrin-rich microthrombi [95,96]. Another early finding is fibrin monomer deposition, occurring primarily in the reticuloendothelial system [2,3,5,97,98]. The precipitation of fibrin monomer may cause end-organ damage because of primary parenchymal damage and microvascular occlusion. This may impair reticuloendothelial clearance of FDPs, activated clotting factors, and circulating soluble-fibrin monomer. Later findings are the typical fibrin-rich hyaline microthrombi believed to replace earlier deposited platelet-rich microthrombi [94,98]. Patients with DIC may develop pulmonary hyaline membranes that account, in part, for significant pulmonary dysfunction and hypoxemia [2,3,5]. Schistocytes are seen in approximately 50% of individuals with fulminant DIC [2,3,5,98–102]. Most patients with fulminant DIC present with a mild

reticulocytosis and a mild leukocytosis, usually associated with a mild to moderate shift to immature forms. Thrombocytopenia is usually present and often obvious by examination of the peripheral blood smear [2,3,5,103]. Large platelets usually are seen on the peripheral smear, representing an increased population of young platelets resulting from increased platelet turnover and decreased platelet survival because of platelet entrapment in microthrombi [1–3,5,60,104–106].

The platelet-rich microthrombi are replaced later by hyaline (fibrin) microthrombi [73]. Hyaline microthrombi cause three types of end-organ damage: (1) globular hyaline microthrombi, which may be seen on PAS-stained peripheral blood smears and are polymerized complexes of fibrinogen, fibrin, their degradation products, and many intermediates [2,3,5]; (2) intravascular hyaline microthrombi, which typically are seen by pathologists at postmortem examination in patients with DIC—these intravascular hyaline microthrombi are homogeneous, compact, intravascular hyaline structures oriented parallel to the blood flow that occasionally contain platelets or white cell fragments, are seen easily by way of PAS staining, trichrome staining, tryptophan staining, fluorescein-labeled antifibrinogen antiserum staining, and by electron microscopy [107,108]; and (3) pulmonary hyaline membranes, which are also a form of hyaline microthrombus and are highly polymerized complexes of fibrinogen, fibrin, their degradation products, and all types of intermediates [109,110]. They usually are seen to cover the alveolar epithelium, with a preference for areas denuded of epithelial cells. The interalveolar capillaries beneath these hyaline membranes typically exhibit abnormal vascular permeability with the circulation of endothelial cells, plasma protein precipitation between endothelial borders, and the formation of interstitial edema. Many patients with DIC develop pulmonary hyaline membranes, leading to overt respiratory failure, abnormal arterial blood gases, or abnormal pulmonary function tests (especially altered diffusion capacity) [5,60].

Disseminated intravascular coagulation is a process associated with hemorrhage and thrombosis, although thrombosis is less clinically evident and less commonly appreciated by the clinician until late in the course of DIC or until autopsy. Hemorrhage often can be treated successfully in patients with DIC, whereas thrombosis in the microcirculation and macrocirculation often leads to end-organ damage with irreversible ischemic changes that lead to morbidity and death. The parameters that accelerate or precipitate microthrombi and macrothrombi in patients with DIC are: vasomotor reactions, including elevated catecholamines, acidosis, progressive vasoconstriction [105,111–113]; use of exogenous glucocorticoids or endogenous ACTH; therefore, careful thought must accompany the use of steroids in these patients; although often steroid use is desirable and warranted [2,3,5,114], and impairment of reticuloendothelial clearance may occur, resulting from fibrin monomer precipitation or the use of steroids, FDPs, circulating soluble-fibrin monomer, or activated coagulation factors [1,2,3,5,60,115]. These mechanisms and the interplay among them lead to accelerated fibrin monomer precipitation in the circulation, resulting in severe

end-organ damage that may be irreversible and often is associated with significant morbidity and mortality [2,3,5].

Laboratory diagnosis

Because of the complex pathophysiology depicted previously, many laboratory findings of DIC may be quite variable, complex, and difficult to interpret unless the pathophysiology is understood clearly and appropriate tests are performed. Fortunately, many newer modalities have become available to the routine clinical laboratory for easily assessing patients with DIC [2,3,5,60, 116–118].

Global coagulation tests in disseminated intravascular coagulation

The prothrombin time should be abnormal in DIC for multiple reasons, but often it is normal and therefore is an unreliable test in this setting [2,3,5,60]. The prothrombin time is prolonged in approximately 50% to 75% of patients with DIC and in up to 50% of patients, it is normal or short. The reasons for normal or short times are the presence of circulating activated clotting factors, such as thrombin or factor Xa, which may accelerate the formation of fibrin; and early degradation products that may be rapidly clottable by thrombin and quickly "gel" the test system, giving a normal or fast prothrombin time [2,3,5].

The activated partial thromboplastin time (aPTT) also should be prolonged in fulminant DIC for a variety of reasons, but it is more unreliable than the prothrombin time. There is plasmin-induced biodegradation of factors V, VIII:C, IX, and XI, which should prolong the aPTT. The aPTT, like the prothrombin time, is prolonged by fibrinogen levels less than 100 mg%. Also, the aPTT may be prolonged because of FDP inhibition of fibrin monomer polymerization; however, the activated PTT is prolonged in only 50% to 60% of patients with DIC, and a normal PTT certainly cannot be used to rule out the diagnosis. The reasons for a fast or normal PTT in 40% to 50% of patients are the same as for the prothrombin time [2,3,5,60]. Like the prothrombin time, the activated PTT is of minimal usefulness in DIC [5,60].

A prolonged thrombin or reptilase time is expected in DIC. Both tests should be prolonged by the presence of circulating FDPs and interference with fibrin monomer polymerization and from the hypofibrinogenemia commonly present [2,3,5,60,119], but for reasons already mentioned, these test results may sometimes be normal or fast. A "bonus test" of the thrombin or reptilase time is to observe the resultant clot for presence or absence of clot lysis [2,3,5]. This simple, nonquantitative tool may provide significant clinical information; if the clot is not dissolving in 10 minutes, clinically significant fibrinolysis is unlikely to be present. If the clot begins to lyse within this period, however, a clinically significant amount of plasmin is probably present [2,3,5].

Coagulation factor assays provide little, if any, meaningful information in patients with DIC [2,5,60]. In most patients with fulminant DIC, systemically circulating activated clotting factors, especially factors Xa, IXa, and thrombin, are present [2,5,60]. Coagulation factor assays done by the standard aPTT- or prothrombin time–derived laboratory techniques using deficient substrates will give uninterpretable results in patients with DIC. The reasons are obvious; for example, if a factor VIII:C assay is attempted in the presence of circulating factor Xa in a patient with DIC, a high level of factor VIII:C is recorded because factor Xa "bypasses" the requirement for factor VIII:C in the test system [2,5,60,120] and a rapid conversion of fibrinogen to fibrin occurs; a rapid time will be recorded on the typical "standard curve," and this result will be interpreted as a high factor VIII:C level when there may be no factor VIII:C present.

Fibrin(ogen)-degradation products are elevated in 85% to 100% of patients with DIC [2,3,60,73,121,122]. These degradation products are only "diagnostic" of plasmin biodegradation of fibrinogen or fibrin and are therefore only indicative of the presence of plasmin [2,3,5,73]. The protamine sulfate or ethanol gelation tests for circulating soluble-fibrin monomer are usually positive [2,5,69,123,124]. Like the FDP titer, however, these products are not diagnostic because both elevated FDPs and circulating soluble-fibrin monomer may be seen in other clinical situations, including women using oral contraceptives, patients with pulmonary emboli, some patients with myocardial infarction, patients with certain renal diseases, and patients with arterial or venous thrombotic or thromboembolic events [2,3,5,125]. Sometimes, the protamine sulfate test or ethanol gelation test may be negative. The protamine sulfate test as described by Kidder et al [126] is the most sensitive and clinically applicable test for detecting circulating soluble fibrin. A quantitative assay for fibrin monomer, the FM-test (KABI, Stockholm, Sweden) has been shown to be a sensitive marker in the management of chronic DIC in patients with cancer [61].

A newer test for DIC is the D-dimer assay. D-dimer is a neo-antigen formed when thrombin initiates the transition of fibrinogen to fibrin and activates factor XIII to cross-link the fibrin formed; this neo-antigen is formed as a result of plasmin digestion of cross-linked fibrin [127,128]. The D-dimer test is therefore specific for fibrin-degradation products, whereas the formation of FDPs, the X, Y, D, and E fragments discussed previously, may be either fibrinogen- or fibrin-derived after plasmin digestion. Monoclonal antibodies have been harvested against the D-dimer neo-antigen DD-3B6/22 that are specific for cross-linked fibrin derivatives containing the D-dimer configuration [129,130]. After the harvesting of monoclonal antibodies, a latex agglutination assay was developed for the clinical laboratory. Of the common tests used in assessing patients with DIC, the D-dimer assay seems to be the most reliable test for the probability of being abnormal in patients with confirmed DIC. Using the battery of DIC tests in the appropriate clinical setting, the reliability of tests used (in descending order of reliability) are the prothrombin fragment 1 + 2, D-dimer assay (abnormal in 93%), the antithrombin level (abnormal in 89%), the fibrinopeptide A level (abnormal in 88%), and the FDP titer, which is usually abnormal in 75% of patients [131,132]. Lane et al [133]

studied the D-dimer fragment in nine patients with DIC and found the levels to be elevated in eight of the nine. Elms et al [134] performed D-dimer assays in patients with DIC and found elevated D-dimer levels in all patients with DIC. Many newer, commercially available D-dimer assays do not use the DD-3B6/22 monoclonal antibody and recently have been found to be inadequate because they are not specific for fibrin-degradation products [135–137].

Sometimes, FDP titers and paracoagulation reactions may be negative in DIC. The available FDP determinations use latex particles that are "antifibrinogen," and because they are antifibrinogen, thrombin clot tubes are supplied to clot out fibrinogen, so latex particles will not react with fibrinogen and erroneously measure fibrinogen instead of its degradation products [5,60,73]. Fibrinogen and its degradation products have common antigenic determinants, however [138]. When these thrombin clot tubes are used, not only is fibrinogen removed from the system but also fragment X and fragment Y. Commonly available FDP methodologies measure fragments D and E, and in some cases of DIC, there may be minimal secondary fibrinolytic response and minimal plasmin circulating, so there may be degradation only to the X fragment stage or some intermediate between fibrin(ogen) and fragment X. In this instance, there will be nothing for the test to measure because fragment X and its intermediates will be removed from the test system by the thrombin clot tubes used. Alternatively, in instances of acute DIC in which there is a massive secondary fibrinolytic activation and overwhelming amounts of plasmin circulating, degradation past the D and E stage may happen. Fragments D and E are the last degradation products retaining antigenic determinants capable of being detected by the available commercial FDP titer kits. Another problem is that of overwhelming release of granulocyte proteases, collagenases, and elastases, which also may degrade all available D and E fragments and again, render false-negative FDP titers in patients with acute DIC [2,3,5]. The presence of a negative FDP titer does not rule out a diagnosis of DIC. Despite these difficulties, FDP titers are elevated in most patients with DIC; however, with the general availability of the D-dimer assay, there is only limited use for the FDP titer and the protamine sulfate test in patients with DIC.

Molecular markers for the diagnosis of disseminated intravascular coagulation

The conversion of prothrombin to thrombin is a key event in the normal coagulation of blood; this activation results in the release of an inactive prothrombin fragment 1.2 (F1 + 2) from the amino terminus of the prothrombin molecule, thus generating an intermediate species, prethrombin 2. The prethrombin 2 can be scissioned internally to yield thrombin; once produced, this serine protease can either proteolyze fibrinogen with the liberation of fibrinopeptide A or combine with its major antagonist, antithrombin, to form a stable, inactive enzyme-inhibitor complex, the thrombin-antithrombin (TAT) complex [139]. Approved ELISA assays are now generally available to quantitate the levels of prothrombin fragment 1 + 2 and TAT within the circulation to provide evidence of excessive factor Xa and thrombin generation [140]. The prothrombin fragment

1 + 2 assay is an easily performed, reliable molecular marker for factor Xa generation [51,141–146], whereas the fibrinopeptide A assay is an easily performed, reliable marker for thrombin generation. Unfortunately, some commercially available prothrombin fragment assays do not provide reliable results in patients with DIC; so laboratories prefer the Behringwerke assay [51]. These activation sequences are depicted in Fig. 3. Another new assay that is highly sensitive to early procoagulant activation is the assay of thrombin precursor protein performed by way of ELISA; this assay detects circulating soluble-fibrin polymer and needs further assessment in patients with DIC but preliminarily seems useful [147,148].

The antithrombin determination is a key test for the diagnosis and monitoring of therapy in DIC [2,3,5,60,149,150]. During activation of DIC, there is

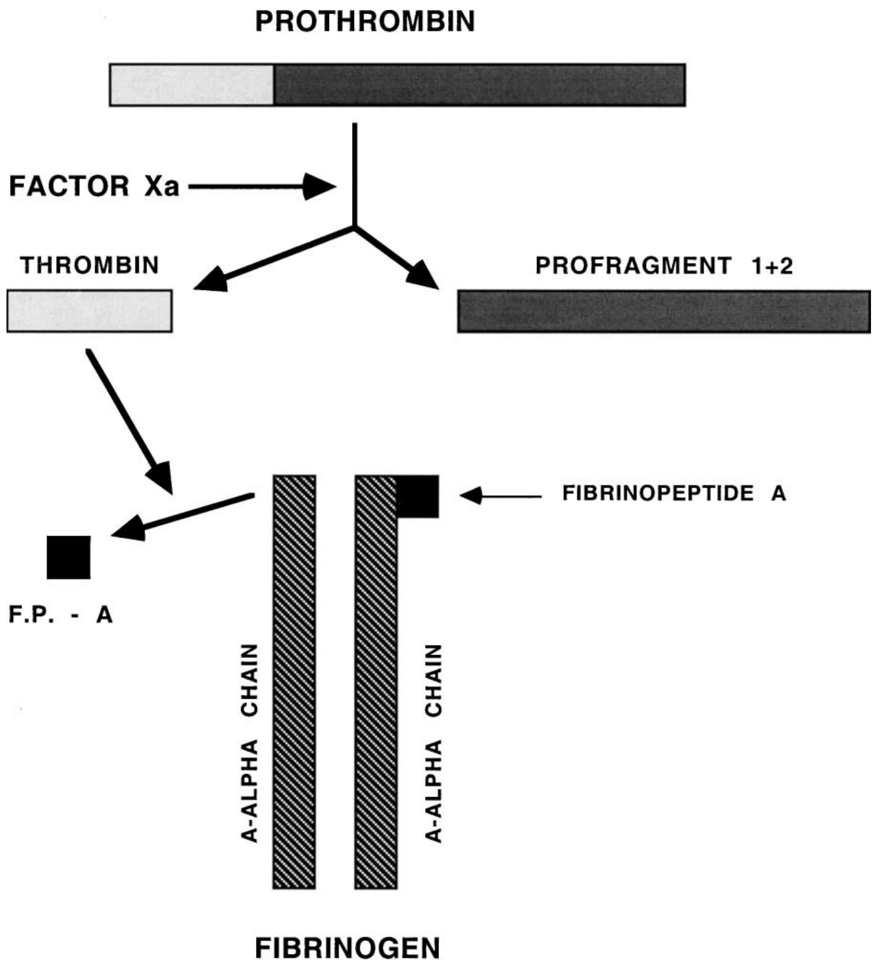

Fig. 3. Formation of prothrombin fragment 1 + 2 and fibrinopeptide A.

irreversible complexing of thrombin and circulating activated clotting factors with antithrombin, leading to considerable decreases of functional antithrombin. Several studies have compared the clinical applicability of various antithrombin methodologies, and based on these studies, synthetic substrate assays are clearly the method of choice [151,152]. Immunologic assays for antithrombin ignore biologic function and may be low or normal in DIC; therefore, they should not be used [2,3,5,73]. There has been at least one exception to the generalization that functional antithrombin levels decrease in DIC. Patients with acute promyelocytic leukemia (APL-M-3) develop a severe coagulopathy usually attributed to DIC; however, it has been reported that even though TAT complexes were significantly higher in cases of M-3 and other cases of DIC compared with normal subjects, the functional level of antithrombin remained normal in some patients with APL. It is unclear at this time why some patients with APL retain a normal antithrombin level, but this finding does support the possibility that the coagulopathy in a subset of patients with APL (subtype M-3m) is not caused by DIC but by primary fibrinolysis [153]. Fibrinopeptide A usually is elevated in patients with DIC and provides a general assessment of hemostasis activation, much like platelet factor 4 and beta-thromboglobulin levels provide a general assessment for platelets. The presence of fibrinopeptide A is "diagnostic" of the presence of thrombin acting on fibrinogen. Fibrinopeptide A determinations may be of help in assessing the efficacy of therapy in DIC [2,3,5,60,73,154,155]. The fibrinopeptide A level may be elevated in a wide variety of other microvascular or macrovascular thrombotic events and increases generally as a function of age [156]. A newer modality, available by radioimmunoassay, is that of B-beta 15 through 42 and related peptide determinations [2,3,5,157,158]. Plasmin rapidly cleaves B-beta peptides 1 through 118, 1 through 42, and 15 through 42 (after thrombin has cleaved fibrinopeptide B or amino acid sequence 1–14) from the B-beta chain of fibrinogen. When performed in conjunction with fibrinopeptide A levels, the findings of elevated B-beta 15 through 42 and related peptides may add to the differential diagnosis of DIC versus primary lysis [5]. The elevation of B-beta 15 through 42 and related peptides without fibrinopeptide A elevation is strong evidence for primary fibrinolysis, whereas the elevation of both fibrinopeptide A and B-beta 15 through 42–related peptides is strong evidence of DIC. The B-beta 15 through 42 assays are not recommended routinely because they are difficult to perform and have a long turnaround time.

The prothrombin fragment 1 + 2, thrombin precursor protein, and fibrinopeptide A elevation provide direct evidence of procoagulant activation; decreased antithrombin levels provide indirect evidence of both procoagulant activation and inhibitor consumption; and elevated TAT complex is direct evidence of procoagulant activation and inhibitor consumption.

Fibrinolytic system assays are now readily available in the clinical laboratory and provide useful information in DIC. Typically, plasminogen is decreased and circulating plasmin is present [2,3,5]. Intensity of the secondary fibrinolytic response is of clinical consequence for predicting potential microvascular thrombosis and resultant irreversible end-organ damage in patients with DIC.

If there is impaired activation of the fibrinolytic system, morbidity and mortality resulting from end-organ damage may be even greater than expected. Fibrinolytic system activation can be assessed by measuring plasminogen and plasmin levels by commonly available synthetic substrate techniques [159–161]. The euglobulin lysis time provides little or no clinically useful information for assessing the fibrinolytic system in clinical disorders, including DIC [2,3,5,162,163]. Direct measurement of plasmin in plasma can be difficult because it is inactivated rapidly by complexing with fast-acting alpha-2-antiplasmin, also termed alpha-2-plasmin inhibitor and slow-acting alpha-2-macroglobulin [50,97,164]. If these two fibrinolytic system inhibitors are elevated markedly, there may be an ineffective fibrinolytic response with resultant enhanced fibrin monomer precipitation, fibrin deposition, and vascular thrombosis. The plasmin-alpha-2-plasmin inhibitor complex is measured by crossed immunoelectrophoresis, ELISA, and radioimmunoassays [97,165,166]. Alpha-2 macroglobulin-plasmin complexes also can be measured by ELISA. The presence of these complexes is therefore a direct indicator of in vivo plasmin generation. The plasmin-alpha-2-plasmin inhibitor complex has been shown to be markedly elevated in DIC at the time of presentation and changes in parallel with the course of DIC, with levels decreasing in clinical remission [167]. The plasmin-alpha-2-plasmin inhibitor complex is useful in DIC because elevation suggests fibrinolytic system activation (plasmin) and inhibitor (alpha-2-plasmin inhibitor) consumption. Recently, assays for tissue (endothelial) plasminogen activator and tissue plasminogen activator inhibitor have become available; their potential role in DIC is unclear at present. Elevated plasmin and decreased plasminogen provide direct evidence of fibrinolytic activation, decreased alpha-2-plasmin inhibitor provides indirect evidence of fibrinolytic activation and inhibitor consumption, and elevated plasmin-alpha-2-plasmin inhibitor complex provides direct evidence of both fibrinolytic activation and inhibitor consumption.

The platelet count typically is decreased in DIC; however, the range may be variable, from as low as 20 to 30 $\times$ 10^9/L to greater than 100 $\times$ 10^9/L. Most tests of platelet function, including the template bleeding time, platelet aggregation, and platelet lumi-aggregation, yield abnormal results in patients with DIC. This result is caused by FDP coating of platelet membranes or partial release of platelet procoagulant materials. There is no reason to perform tests of platelet function. Increased platelet turnover and decreased platelet survival are usual in patients with DIC; platelet factor 4 levels and beta-thromboglobulin levels are markers of general platelet reactivity and release and usually are elevated in patients with DIC. It has been suggested that testing of either of these levels may be worthwhile in DIC and for monitoring efficacy of therapy for the intravascular clotting process [168,169]. Platelet factor 4 and beta-thromboglobulin levels are elevated in most patients with DIC; however, neither of these modalities is diagnostic of DIC, and levels may be elevated in pulmonary emboli, acute myocardial infarction, deep venous thrombosis, and in disorders associated with microvascular disease, such as diabetes and autoimmunity. If they are elevated in DIC, however, and then decrease after therapy, this finding suggests that therapy

Table 2
Molecular markers useful for the differential diagnosis of DIC, primary lysis, and thrombotic thrombocytopenic purpura (TTP)

Marker	DIC	Primary lysis	TTP
Fibrinopeptide A	Elevated	Normal	Normal
Fibrinopeptide B	Elevated	Normal	Normal
B-Beta 15–42 peptide	Elevated	Normal	Normal
B-Beta 1–42 peptide	Elevated	Elevated	Normal
B-Beta 1–118 peptide	Elevated	Elevated	Normal
Platelet factor 4	Elevated	Normal	Elevated
Beta-thromboglobulin	Elevated	Normal	Elevated
D-dimer	Elevated	Normal	Normal/elevated
Fibronectin	Decreased	Normal	Normal
Plasminogen activator	Normal/elevated	Elevated	Decreased
Thromboxanes	Elevated	Normal	Elevated
6-KETP-PGF-1-alpha	Normal	Normal	Decreased
Profragment 1 + 2	Elevated	Normal	Normal
Thrombin precursor protein	Elevated	Normal	Unknown

has been successful in either blunting or stopping the intravascular clotting process [2,3,5]. Elevation of either platelet factor 4 or beta-thromboglobulin provides indirect evidence of procoagulant activation.

Tests useful for aiding in a diagnosis of DIC are provided in the following list [1–3,5,170–173]:

Reliability of laboratory tests in DIC (descending order of reliability)

Profragment 1 + 2
D-dimer
Antithrombin-III
Fibrinopeptide A
Platelet factor 4
FDP
Platelet count
Protamine test
Thrombin time
Fibrinogen
Prothrombin time
Activated PTT
Reptilase time

The differential diagnosis of DIC versus primary fibrinolysis versus thrombotic thrombocytopenic purpura by molecular marker profiling is shown in Table 2 [5,60,170–173]. Most molecular markers discussed are sensitive to hemostasis activation, and careful phlebotomies are necessary.

The laboratory diagnosis of DIC requires documentation of procoagulant system activation (group I tests), fibrinolytic system activation (group II tests),

Box 4. Laboratory diagnostic criteria[a]

Those tests currently suitable for evidence of procoagulant activation (group I tests) are

1. Elevated prothrombin fragment 1 + 2
2. Elevated fibrinopeptide A
3. Elevated fibrinopeptide B
4. Elevated TAT complex
5. Elevated D-dimer[b]

Those tests currently suitable as evidence for fibrinolytic activation (group II tests) are

1. Elevated D-dimer
2. Elevated FDP
3. Elevated plasmin
4. Elevated plasmin-antiplasmin complex

Those tests currently suitable as evidence for inhibitor consumption (group III tests) are

1. Decreased antithrombin-III
2. Decreased alpha-2-antiplasmin
3. Decreased heparin cofactor II
4. Decreased protein C or S
5. Elevated TAT complex
6. Elevated plasmin-antiplasmin complex

Those tests currently suitable as evidence for end-organ damage or failure (group IV tests) are

1. Elevated LDH
2. Elevated creatinine
3. Decreased pH
4. Decreased pAO_2

[a] Only one abnormality each is needed in group I, II, and III, and at least two abnormalities are needed in group IV tests to satisfy criteria for a laboratory diagnosis of DIC.

[b] The D-dimer is only reliable for this purpose if using the correct assay and monoclonal antibody, as discussed in the text.

inhibitor consumption (group III tests), and end-organ damage (group IV tests). The manner in which the above-discussed tests are used to provide documentation of these four requirements is summarized in Box 4.

Summary

The pathophysiologic mechanisms and clinical and laboratory manifestations of DIC are complex, partly because of inter-relationships within the hemostasis system. Only by clearly understanding these extraordinarily complex pathophysiologic inter-relationships can the clinician and laboratory scientist appreciate the divergent and wide spectrum of often-confusing clinical and laboratory findings in patients with DIC. Many therapeutic decisions to be made are controversial and lack validation. Nevertheless, newer antithrombotic agents and agents that can block, blunt, or modify cytokine activity and the activity of vasoactive substances seem to be of value. The complexity and variable degree of clinical expression suggest that therapy should be individualized depending on the nature of DIC, the patient's age, etiology of DIC, site and severity of hemorrhage or thrombosis, and hemodynamics and other appropriate clinical parameters.

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