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REVIEW

Disseminated intravascular coagulation: an update on pathogenesis and diagnosis

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ABSTRACT

Introduction: Activation of the hemostatic system can occur in many clinical conditions. However, a systemic and strong activation of coagulation complicating clinical settings such as sepsis, trauma or malignant disease may result in the occurrence disseminated intravascular coagulation (DIC).

Areas covered: This article reviews the clinical manifestation and relevance of DIC, the various conditions that may precipitate DIC and the pathogenetic pathways underlying the derangement of the hemostatic system, based on clinical and experimental studies. In addition, the (differential) diagnostic approach to DIC is discussed.

Expert commentary: In recent years a lot of precise insights in the pathophysiology of DIC have been uncovered, leading to a better understanding of pathways leading to the hemostatic derangement and providing points of impact for better adjunctive treatment strategies. In addition, simple diagnostic algorithms have been developed and validated to establish a diagnosis of DIC in clinical practice.

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Anticoagulants; coagulation; coagulation factors; disseminated intravascular coagulation; fibrin degradation products; fibrinolysis; platelets

1. Introduction

There is a myriad of clinical conditions, including severe infections, malignancies, or diseases associated with major tissue trauma destruction (trauma, acute pancreatitis, and systemic inflammation) that cause activation of the coagulation system. This coagulation activation is often subclinical and will not be detected by routinely performed blood tests, but it can be visualized by highly sensitive analyses for hemostatic activation, such as assays for peptides released from activated clotting factors or complexes between activated coagulation enzymes and their specific inhibitors [1]. In case the hemostatic activation is more vigorous, depletion of coagulation enzymes and platelets may become perceptible through elongation of usually performed hemostatic test (e.g. prothrombin time (PT) and activated partial thromboplastin time (aPTT)) and a reduced or dropping platelet count. An even more protuberant activation of hemostasis may present as disseminated intravascular coagulation (DIC). DIC is classically manifested by the synchronized occurrence of extensive (micro)clot formation in the vasculature and an enhanced hemorrhagic propensity. The constant clotting process and ensuing fibrin deposition hampers adequate oxygen delivery to the periphery, and may thereby be a major factor in the progress to multiple organ injury [2–4]. The hemorrhagic propensity is due to continuing activation of the clotting system, resulting in consumption and subsequent depletion of coagulation proteins and platelets, further accentuated by impaired production and greater degradation of these components and their regulators. As a result, the risk of bleeding tendency may increase, sometimes presenting as spontaneous widespread hemorrhage from various sites. There are two distinct types of DIC: one type is characterized by strong coagulation activation and suppressed fibrinolysis, resulting in fibrin deposition and secondary hemorrhagic complications, whereas the second type is based on excessive fibrinolysis, manifested by severe bleeding complications [2]. Most affected organs in patients with DIC exhibit intravascular fibrin at microscopic pathologic examination [5]. Studies in animals with experimental DIC have shown intra- and extravascular fibrin deposition in virtually all organs and moderation of the coagulopathy by specific interventions betters organ failure and other clinically relevant consequences. Clinical investigations have shown that DIC is an independent and controlling prognosticator of organ dysfunction and death [6,7].

2. Clinical settings complicated by DIC

It should be underlined that DIC is not an independent clinical disorder but is at all times a complication of another affection that leads to hemostatic activation [8]. The clinical disorders most frequently accompanying DIC are itemized in Table 1.

DIC may accompany the clinical presentation of about 30% of patients with serious septicemia [9]. The prevalence of DIC in patients with Gram negative of Gram positive microbial infections is essentially equivalent and systemic infections with other microorganisms including yeast, fungi, parasites, or viruses may also be complicated by DIC [10]. Microbial wall constituents, such as lipopolysaccharide or exotoxins (e.g. Staphylococcal α-toxin) may produce a strong immune reaction and elicit the production of cytokines and other proinflammatory intermediates.

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Table 1. Disorders that may be complicated by DIC.

- Severe infections/sepsis
  - Gram positive or Gram negative microorganisms
  - Fungi/yeast infection
  - Viral infections/viral hemorrhagic fevers
  - Parasites (e.g. malaria)
- Trauma
  - Polytrauma
  - Brain trauma
  - Large burns
- Malignant Disease
  - Adenocarcinomas (e.g. pancreas, prostate)
  - Acute promyelocytic or monocytic leukemia
  - Malignant lymphomas, acute lymphatic leukemia
- Obstetrical complications
  - Placental abruption
  - Amniotic fluid embolism
  - Retained death fetus-syndrome
- Vascular malformations
  - Large aortic aneurysms
  - Giant hemangiomas/Kasabach-Merritt syndrome
  - Other large vascular abnormalities
- Hypoxia
  - Post-resuscitation
- Heatstroke
- Severe immunologic/anaphylactic reactions

Multi-trauma is another situation recognized to be linked to DIC [2]. DIC is a component of a more widely defined syndrome of trauma-associated coagulopathy that involves dilutional coagulation derangement that happens upon major hemorrhage and the infusion of plasma replacement treatment and trauma-associated vessel wall dysfunction [11]. Systemic levels of inflammatory mediators in serious trauma patients were shown to be similar to those of severe sepsis patients [12]. In addition, release of tissue debris (such as cellular tissue factor, especially in patients with cerebral trauma) and perturbation of endothelial cells may exacerbate the systemic hemostatic activation. Severe obstetric complications including a retained death fetus, amniotic fluid embolism, or placental abruption, can be complicated by sudden and fulminant DIC [13]. The magnitude of placental separation in placental abruption has a strong correlation with the intensity of DIC, which has led to the hypothesis that systemic release of thromboplastin (tissue factor) coming from placental or amniotic sources into the maternal circulation is causing the activation of hemostasis and DIC. Malignant disease can be complicated by DIC caused by the expression of procoagulant components by tumor cells [14]. The incidence of DIC in some forms of cancer, such as metastasized adenocarcinoma or malignant lymphoma or lymphoid leukemia, can be as large as 20%. DIC in oncological patients has usually a less ferocious manifestation compared to the coagulopathy that may accompany other conditions, such as sepsis and trauma. Cancer leads to a more stealthy sustained disseminated coagulopathy that can be non-symptomatic for a long time. Eventually, thrombocytopenia and low coagulation factor levels become apparent leading to bleeding complications and this can be the first sign pointing at the existence of a cancer-induced coagulopathy. A specific type of DIC may accompany malignancies such as promyelocytic leukemia or some forms of adenocarcinoma, characterized by excessive fibrinolysis and a strong bleeding tendency [15]. DIC due to large vascular abnormalities is thought to be caused to local hemostatic activation overflowing in the systemic circulation accompanied by massive release of plasminogen activators from the disrupted endothelial cells that are present in the vascular malformations, leading to excessive endogenous fibrinolysis and fibrinogenolysis [16]. Another mechanism may occur in giant hemangiomas where massive release of large multimeric von Willebrand factor may cause enhanced platelet-vessel wall interaction leading to thrombotic microangiopathy.

Alternative clinical settings leading to DIC are given in Table 1 and are less prevalent. In most of these conditions, the severity of the accompanying systemic inflammatory response caused by the underlying condition will be an important factor in the pathogenesis of an eventual DIC.

3. Pathogenetic pathways in DIC

A combination of pathogenetic pathways comes together in the development of DIC, regardless of the underlying condition. In summary, initiation of coagulation by tissue factor exposure to circulating blood, increased platelet-vessel wall interaction, impaired regulation of coagulation due to impaired anticoagulant mechanisms and defective endogenous fibrinolysis act in concert leading to the coagulopathy defining DIC. These mechanisms are outlined in more detailed in the following paragraphs.

3.1. Triggers of coagulation activation in DIC

The systemic inflammatory response accompanying most of the underlying conditions known to be associated with DIC is a crucial factor in the pathogenesis of DIC, whereby pro-inflammatory cytokines and chemokines act as key mediators [17]. There is ample evidence that there is considerable cross talk between inflammatory activation and hemostatic activity. This interaction is bidirectional so that inflammation not only leads to coagulation activation, but activated coagulation proteases also importantly regulate inflammation [18]. In some cases, such as in severe infection or sepsis, systemic activation of inflammation and coagulation can manifest in an organ-specific fashion, which can be relevant for ensuing organ dysfunction. The dysregulation of bronchoalveolar coagulation in severe pneumonia, playing a major role in the pathogenesis of acute lung injury and adult respiratory distress syndrome (ARDS) is an example of this [19]. As mentioned here above specific clinical conditions accompanied by DIC may result in additional triggers for coagulation activation, including the release of tissue factor-rich debris in (brain) trauma, or the expression of procoagulant factors (such as tissue factor and cancer procoagulant expression on tumor cells in patients

with malignancies, or leakage of tissue factor from the placenta into the maternal circulation.

The prime initiator of coagulation factor activation in DIC is tissue factor. Even mild experimental stimuli such as systemic infusion of low dose lipopolysaccharide (LPS) in healthy human subjects cause a more than 100-fold increase in tissue factor mRNA levels in circulating mononuclear cells resulting in thrombin generation and further hemostatic activation [20]. In fulminant Gram negative infection in patients and experimental bacteremia in animals tissue factor expression on circulating mononuclear cells monocytes has been demonstrated [21]. Abolition of the tissue factor pathway by various interventions, such as specific antibodies against tissue factor or its binding to factor VII(a) could completely abrogate thrombin generation in LPS-infused chimpanzees and prevented coagulopathy and death in baboons infused with live bacteria [22,23]. Likewise, in severe trauma or in malignant disease it was demonstrated that DIC was initiated by the tissue factor-factor VII pathway [14,24]. It has been hypothesized that an alternative source of tissue factor in DIC can be disrupted endothelial cells, although direct *in vivo* evidence for this idea is lacking so far [25,26]. In addition, tissue factor was detected on the surface of neutrophils [27], although it is less probably that polymorphonuclear cells are capable of producing tissue factor in relevant quantities [28]. A more tenable explanation is that tissue factor is shuttled between cells via microparticles derived from activated monocytes and possibly endothelial cells [29].

3.2. Platelet-vessel wall interaction in DIC

Platelets are crucial in the development of coagulation abnormalities in DIC [26]. Activated platelets provide a surface on which activation of coagulation factors is greatly facilitated. Direct platelet activation can occur through pro-inflammatory chemokines, such as platelet activating factor [30]. Thrombin that is generated as a result of tissue factor-initiated activation of coagulation may further activate platelets [31]. Platelet activation accelerates further fibrin formation by expression of P-selectin, which potentiates expression of tissue factor on monocytes and orchestrates adherence of platelets to leukocytes and to the vessel wall [32]. P-selectin is readily released from the activated platelet membrane and soluble P-selectin levels are accurate markers of systemic inflammation [32].

There is ample evidence that DIC is accompanied by increased platelet-vessel wall interaction, in its most extreme form presenting as thrombotic microangiopathy in a subgroup of DIC patients [33]. A pivotal factor in the occurrence of this boosted platelet-vessel wall interaction is the release of ultralarge multimeric von Willebrand factor from inflammation-induced injured endothelium. Indeed, von Willebrand factor is an acute phase factor that is importantly upregulated and released upon systemic activation of inflammatory pathways [34]. Extreme levels of von Willebrand factor antigen and von Willebrand factor propeptide (reflection enhanced release) and in particular ultralarge multimeric von Willebrand factor are present in the circulation of patients with sepsis and show a strong correlation with sepsis severity [35]. Apart from being the crucial ligand between platelets and the (sub)endothelium, ultralarge von Willebrand factor may are mediating further attraction of white blood cells to perturbed endothelial cells and potentiate complement activation, thereby stimulating adhesion of microorganisms to the vascular surface.

The level of (ultralarge) von Willebrand factor multimers in patients with DIC is inversely correlated with plasma concentrations of its endogenous cleaving protease, ADAMTS13. A series of studies have demonstrated the correlation between reduced ADAMTS13 levels and severity of sepsis [34,35]. The cause of the deficiency of ADAMTS13 is most likely consumption and depletion of this protease due to the excessive inflammation-mediated release of von Willebrand factor from the endothelium consumes. ADAMTS13 deficiency leads to inadequate cleavage and control of von Willebrand factor multimeric size [36]. Alternative explanations for the low plasma levels of ADAMTS13 are proteolytic cleavage by elastase from activated neutrophils, thrombin, or plasmin [37]. Lastly, high levels of thrombospondin-1 may results in competitive inhibition of ADAMTS13 binding to von Willebrand factor. In severe systemic inflammation, release of thrombospondin from activated platelets may cause a 100-fold increase in its plasma concentration) [38].

Clinical studies show that in about 30% of patients with sepsis and DIC ADAMTS13 levels are below 50% of normal [34,36]. Studies in children with severe and complicated sepsis also demonstrated reduced ADAMTS13 levels in the majority of cases, whereby the lowest levels strongly correlated to a more intense DIC [39,40]. Apart from sepsis, reduced levels of ADAMTS13 are frequently observed in patients with overt DIC and are clearly related to more severe kidney failure [36,41]. Lastly, a strong association between the extent of ADAMTS13 deficiency and an adverse outcome was found. Significantly reduced ADAMTS13 levels were observed at the time of intensive care admission in non-surviving patients [42]. Patients with ADAMTS13 plasma concentrations ≤ 50% had an approximate 10% higher mortality compared with patients who presented with no or only a mild deficiency of ADAMTS13 [39]. Further analysis revealed that the predictive value of ADAMTS13 deficiency for mortality was as strong as the APACHE II score or similar risk algorithms.

3.3. Propagation of coagulation activation in DIC

Under normal circumstances hemostatic activity is controlled by natural anticoagulant pathways: antithrombin, activated protein C and tissue factor pathway inhibitor (TFPI). In DIC all these control mechanisms are dysfunctional, which enables further propagation of thrombin generation.

Antithrombin is a serine protease inhibitor with affinity for factor IIa (thrombin) and factor Xa. After binding to the reactive center, it inactivates these coagulation factors. In patients with DIC antithrombin levels are markedly reduced. The reason for this decrease is a combination of diminished synthesis due to liver impairment, augmented clearance through the formation of thrombin-antithrombin and factor Xa-antithrombin complexes, and proteolytic cleavage due to elastase released from activated polymorphonuclear cells [26]. As antithrombin activity is greatly catalyzed by the availability of heparin, impairment of glycosaminoglycan formation

(including heparin sulfates) at the vascular surface may further compromise antithrombin function.

Activated protein C is responsible for proteolytic degradation of the pivotal coagulation cofactors Va and VIIIa and is thereby another important regulator of thrombin generation. The conversion of protein C to activated protein C occurs after thrombin binds to endothelial thrombomodulin [43]. This process is importantly potentiated by binding of protein C to the endothelial protein C receptor (EPCR) [44]. In DIC, there is a significant cytokine-mediated downregulation of both thrombomodulin and EPCR, which causes reduced protein C activation. The downregulation of thrombomodulin also affects the clearance of thrombin, as thrombomodulin has a very high affinity for free thrombin. As activated protein C exerts also a series of anti-inflammatory effects, reduced formation of activated protein C may also seriously affect endogenous anti-inflammatory pathways. In observational clinical studies reduced plasma concentrations of protein C were associated with a higher risk of death [45]. Abrogation of protein C activation by various interventions increased mortality in baboons challenged with live bacteria [46,47]. In contrast, administration of activated protein C resolved the coagulopathy and improved survival in these experiments. Based on these findings, it seems that activated protein C is of pivotal relevance in the regulation of DIC.

Regulation at the level of tissue factor is governed by tissue factor pathway inhibitor (TFPI). TFPI is associated to the endothelium or bound to lipoproteins in the circulation. It is a direct inhibitor of the tissue factor-factor VIIa complex, which therefore cannot activate factor Xa, blocking downstream coagulation activation. Observational studies in patients with DIC provide conflicting results regarding plasma levels of TFPI [48]. However, TFPI deficiency in an experimental DIC model in rabbits aggravated the coagulopathy [49]. Also systemic administration of TFPI ameliorated organ dysfunction and DIC in baboons challenged with a Gram negative bacterial infection and completely blocked the activation of coagulation in LPS-infused healthy human subjects [50,51]. These findings may suggest there is a relative insufficiency of the TFPI system in regulating tissue factor-mediated activation of coagulation in DIC. Clinical studies on TFPI in DIC, however, did not show benefit [52].

Lastly, a shutdown of the endogenous fibrinolytic system in DIC prohibits adequate intravascular fibrin removal once it has been formed [53]. The underlying mechanism is a sustained increase in the most important inhibitor of plasminogen activators, that is plasminogen activator inhibitor, type 1 (PAI-1) [54].

3.4. Bidirectional interaction between coagulation and inflammation in DIC

The primary interface between inflammation and coagulation are pro- and anti-inflammatory cytokines. In DIC due to almost all different underlying conditions elevated concentrations of cytokines can be found in the blood and experimental challenges with live bacteria or LPS leads to increase cytokines levels [26]. Amongst the most important factors affecting coagulation the cytokines tumor necrosis factor alpha (TNF-a), interleukin (IL)-1, and IL-6 seem to possess crucial roles. TNF-a is one of the earliest cytokines that peaks after bacteremia or endotoxemia but a series of experiments blocking the activity of this cytokine (with monoclonal antibodies or TNF-a receptor antagonists) did not show any beneficial effect on coagulation [26,55]. In addition, randomized controlled trials in patients with sepsis and DIC evaluating TNF-blocking treatment were not capable of identifying any clinically relevant benefit [56]. Interestingly, inhibition of IL-6 by means of a specific antibody caused a complete inhibition of LPS-induced coagulopathy in non-human primates [57]. Additional proof for a central role of IL-6 in activating coagulation came from clinical studies in patients with advanced malignancies, demonstrating that administration of recombinant IL-6 caused significant hemostatic activation, although inhibition of IL-6 in clinical trials did not show an effect on the coagulopathy [58,59]. Similar experimental and clinical studies point to a role of IL-1 in coagulation activation as well. Blockage of IL-1 through systemic infusion of a IL-1 receptor antagonist partially blocked activated coagulation in septic primates and administration of IL-1 receptor blockers attenuated activation of coagulation in humans [60].

A reverse interaction between inflammation and coagulation is represented by activated coagulation components interacting with cellular receptors, thereby eliciting pro- and anti-inflammatory responses. Several coagulation proteases and protease inhibitors may bind to protease activated receptors (PARs), which then causes cleavage of an activation sequence from the PAR and subsequent self-activation of this receptor and downstream signaling [61]. PAR subtype 1, 3, and 4 are receptors of thrombin and PAR-1 and 2 are activated by factor VIIa bound to tissue factor, and factor Xa. Inhibition of PAR-1 decreases activation of coagulation and inflammation in human endotoxemia [62].

Other factors that seem to have a crucial role in the pathogenesis of DIC are extra-nuclear DNA and DNA-binding proteins (including histones and high mobility group box 1 protein [HMGB1]). Circulating extracellular and DNA binding factors are released from the nucleus of injured cells and may provide a scaffold on which formation of activated coagulation protease complexes is markedly facilitated [63]. In addition, histones are direct activators of platelets, which may further potentiate hemostatic activation [64]. Capture of neutrophils by networks of DNA and DNA binding proteins leads to the assembly of neutrophil extracellular traps (NETs) that importantly promote vascular thrombosis and inflammation [65]. NETs seem to increase the presence of mononuclear cells expressing tissue factor as well [66]. Propagation of coagulation is further boosted by the proteolytic cleavage of antithrombin and protein C due to the release of elastase by the neutrophils in NETs [67]. Lastly, NETs have been shown to cause endothelial cell injury and ensuing activation of inflammation at the vascular surface [65,68].

A bidirectional interaction between inflammation and coagulation also occurs at the level of natural anticoagulant factors. Antithrombin is a regulator of inflammation, by mechanisms such as blunting cytokine and chemokine receptor expression after direct binding to inflammatory cells [69].

In experimental models of severe systemic infection, administration of antithrombin not only attenuated the intensity of DIC, but also lowered the expression and plasma levels of proinflammatory cytokines. Similarly, activated protein C blocks LPS-induced synthesis and release of TNF-α, and several interleukins *in vitro* [70,71]. Administration of activated protein C inhibits cytokine release and mononuclear cell activation in septic rats and activated protein C inhibition aggravated the inflammatory effects in baboons challenged with live bacteria [72,73]. Transgene mice with a heterozygous protein C deficiency displayed a stronger coagulation response to LPS and simultaneously had a more severe activation of inflammatory pathways [74]. However, recombinant human activated protein C failed to mitigate inflammatory and coagulation responses to human endotoxemia [75].

4. Advances in the diagnosis of DIC

The diagnosis of DIC is based on clinical findings in combination with laboratory parameters [76]. A diagnosis of DIC can only be made if there is a primary condition known to be associated with DIC and clinical signs and symptoms are compatible with this underlying disease. In addition, purpura fulminans or hemorrhagic thrombosis of the skin and underlying tissue can be visible. Thromboembolism of larger vessels will present itself as well by symptomatology compatible with the occlusion in circulation. Widespread bleeding from mucosal tissue (such as gingiva, nose or digestive tract) and from insertion points of indwelling catheters can be another typical finding, particularly in primary hyperfibrinolytic DIC [77]. Characteristic findings in routine laboratory assays are thrombocytopenia or a rapid decrease in subsequent platelet counts, abnormal screening assays (such as PT or aPTT) and a marked elevation of products that are formed during fibrin formation and subsequent degradation (D-dimer or any other form of fibrin degradation products [76]. However, there are alternative diagnoses that can cause these changes (Table 2), and these need to be considered as they may have differential therapeutic consequences [76].

In patients with major blood loss, such as occurring in trauma, it may be hard to differentiate DIC from the coagulopathy due to excessive loss of platelets and coagulation factors and the dilutional changes in coagulation that can occur after infusion of large volumes of colloids or crystalloids that may be necessary in the initial management.

Severe infection and sepsis per se can cause a low platelet count and the gravity of sepsis correlates with the extent of thrombocytopenia. The principal causes of sepsis-associated thrombocytopenia are reduced platelet production, enhanced consumption of platelets, or platelet sequestration in the vasculature of the spleen. In addition, a peculiar feature of sepsis is the occurrence of hemophagocytosis, which is characterized by active phagocytosis of platelet precursor cells and other bone marrow cells by monocytes and macrophages [78].

Quantitation of individual coagulation factors in DIC has only limited significance. Some coagulation factors (including factor VIII and fibrinogen) display a significant acute phase response, and are typically not decreased or may even show increased levels, except in extreme cases of hyperfibrinolytic DIC [77]. Sequential measurements, however, can show that despite levels in the normal range significant consumption can occur. Nevertheless, the measurement of fibrinogen, which is often suggested in the laboratory diagnosis of DIC, is usually not very helpful, except in extreme cases of hyperfibrinolytic DIC. Other dynamic fluctuations in coagulation proteins and platelets may sometimes add useful information. A significant downward trend in the platelet count, an increasing prolongation of global coagulation assays, or sustained surge in fibrin degradation products, even when still in the normal range, can point to an early stage of DIC [7].

Interestingly, screening for DIC seems important to improve overall survival of critically ill patients [79]. A single laboratory assay that can reliably confirm or reject a diagnosis of DIC is not available. However, a combination of tests will usually enable to do this in a relatively accurate fashion. The International Society on Thrombosis and Hemostasis (ISTH)

Table 2. Differential diagnosis of low platelet count and/or prolonged coagulation assays in patients with an underlying disease known to be associated with DIC.

Thrombocytopenia*	Prolonged prothrombin time (PT) and/or activated partial thromboplastin time (aPTT)
Bone marrow insufficiency – Usually all three cell lines (erythrocytes, white blood cells and platelets decreased)	Isolated coagulation factor deficiencies – Inherited disorders (hemophilia) – Acquired deficiency due to inhibiting antibody
Thrombotic microangiopathy – May also occur in combination with DIC – Coombs-negative hemolysis with schistocytes in blood film – Deficiency of ADAMTS13	Vitamin K deficiency – Reduced factors II, VII, IX and X – Correction after oral or intravenous administration of Vitamin K
Immune thrombocytopenia – Autoimmune disorder or drug-induced – Antiplatelet antibodies may be detectable	Liver failure – Global coagulation factor deficiency except factor VIII – In case of cirrhosis also low platelet count due to splenomegaly
Heparin-induced thrombocytopenia – Usually 7–10 days after starting heparin – Associated with venous and arterial thrombosis – More common with therapeutic dose unfractionated heparin	Use of anticoagulants – Unfractionated heparin prolongs aPTT – Vitamin K antagonists prolong PT and aPTT – Direct oral anti-Xa agents (rivaroxaban, apixaban) prolong PT – Direct oral anti-thrombin agents (dabigatran) may prolong aPTT
Massive hemorrhage –Loss and dilution of platelets In combination with loss/dilution of clotting factors (prolonged PT/aPTT)	Massive hemorrhage – Loss and dilution of coagulation factors – In combination with low platelet count

*): Always check the blood film to exclude *in vitro* platelet clumping as cause of thrombo-cytopenia. If that is the case, repeat full blood count in citrated sample.

Table 3. Scoring system for the diagnosis of DIC.

(1) Presence of an underlying disorder known to be associated with DIC *If no: do not proceed with this algorithm*	
(2) Score global coagulation test results	
• platelet count *(> 100 = 0; < 100 = 1; < 50 = 2)*	
• level of fibrin markers (e.g. D-dimer, fibrin degradation products) *(no increase: 0; moderate increase: 2; strong increase: 3)#*	
• prolonged prothrombin time *(< 3 sec. = 0; > 3 sec. but < 6 sec. = 1; > 6 sec. = 2)*	
• fibrinogen level *(> 1.0 g/L = 0; < 1.0 g/L = 1)*	
(3) Calculate score	
(4) If ≥ 5: compatible with DIC; If < 5: no DIC, repeat next 1–2 days	

This scoring algorithm has been established by the Scientific Standardization Committee of the International Society of Thrombosis and Haemostasis [81].
#: strong increase > 5 × upper limit of normal; moderate increase is > upper limit of normal but < 5× upper limit of normal.

has proposed and validated a simple scoring algorithm [80,81]. Based on routinely available laboratory parameters, that is platelet count, prothrombin time, D-dimer or another fibrin degradation product test, and a fibrinogen level the score can be calculated (Table 3). A number of studies have reported positive and negative predictive values of this scoring system of about 95% against a gold standard of DIC based on comprehensive clinical information in combination with sophisticated laboratory tests [6]. Similar algorithms have been proposed and comprehensively evaluated in other studies. Interestingly, the DIC score has a strong predictive value for mortality: a diagnosis of overt DIC roughly doubles the risk of mortality in several studies [6,82].

Many clinicians prefer point of care tests in the management of acute and critically ill patients [83]. One of the bedside tests available is thrombelastography (TEG), which is an assay that provides a global view on the function of hemostasis in a patient. Briefly, a small aliquot of blood is rotated in a cuvette and clot formation and clot strength, and subsequent clot lysis is assessed by mechanical or optical methods. Rotational thrombelastometry (ROTEM) is a variant of this global assay, whereby the cuvette is stationary but a rotational pin is placed in the blood sample and clot formation and degradation is measured by changes in flexibility of the pin. The thrombelastographic pattern that is compatible with DIC showed a good correlation with relevant organ dysfunction and survival, although it is not clear whether it affords a benefit over more conventional coagulation tests and scoring algorithms except for its ability to detect hyperfibrinolysis [84]. In a meta-analysis of randomized controlled studies and observational cohort surveys in patients with sepsis, TEG could properly assess significant coagulation changes [85]. The extent of the observed derangement in thromboelastographic (in particular related to the velocity of clot formation and clot strength) correlated with an increased risk of death. Although TEG has not been systematically assessed in other conditions underlying DIC, it may be that this assay (or other global bed side tests) can be helpful in evaluating the extent of coagulation abnormalities in critically ill patients in general [86,87].

5. Conclusion

DIC is a condition that encompasses concurrent (microvascular) thrombosis and widespread bleeding complications. The prothrombotic tendency in DIC arises from a systemic coagulation activation whereas continuing use of platelets and clotting factors are responsible for a consumption coagulopathy that enhances the risk of hemorrhage, the latter in particular in hyperfibrinolytic types of DIC. DIC does not occur by itself but is always associated with another condition, such as severe infection, malignant disease, severe (poly)trauma, or obstetric complications. In recent years a much better understanding of underlying pathways leading to the coagulopathy of DIC have been identified, including tissue factor-dependent initiation of coagulation, enhanced platelet-vessel wall interaction, loss of natural anticoagulant function, and the bidirectional interplay between inflammation and coagulation. In practice, a reliable diagnosis of DIC can be established with simple scoring algorithms that utilize readily available laboratory tests, which are likely to be routinely available in virtually all hospitals. The differential diagnosis of DIC comprises alternative explanations for thrombocytopenia in critically ill patients (including thrombotic microangiopathies, immune-thrombocytopenia, and heparin-induced thrombocytopenia), dilutional coagulopathies, and acquired inhibitors against coagulation factors.

6. Expert commentary

The past 25 year years have resulted in a much better insight in the pathways underlying DIC and the clinical consequences of this coagulopathy [2]. Nevertheless, the clinical management of patients with DIC can still be very difficult. Although it is generally accepted that DIC will subside when the underlying disease is properly treated, the optimal adjunctive treatment aimed at the derangement of coagulation is a matter of debate. Not surprisingly, in a patient who presents with thrombotic complications and bleeding at the same time it is not always obvious which is the optimal treatment choice. Theoretically, blocking the activation of coagulation with an anticoagulant intervention may be appropriate. Indeed, heparin is able to block experimental DIC and there is some evidence that heparin can effectively control DIC coming from clinical studies [88–90]. However, there is general consensus that a more effective (and safe) anticoagulant approach might be useful in DIC.

A lot of attention has been given to replacement of deficient natural anticoagulant factors in DIC. In view of the central role of the activated protein C system in controlling the coagulopathy and because of its anti-inflammatory properties (at least *in vitro*), administration of recombinant human activated protein C was exhaustively studied, mostly in patients with sepsis. Eventually, the clinical results of these studies were disappointing, although subgroups of patients with the most severe coagulopathy consistently showed a benefit of this intervention on secondary outcome measures. A more recent intervention that is also aimed at the activated protein C pathway consists of the administration of recombinant human thrombomodulin. Initial phase II/III studies in patients with sepsis and DIC showed a beneficial effect of this intervention, including a significant reduction in mortality and ongoing randomized controlled trials are focused on confirming these findings. Thrombomodulin has distinctive properties targeting both coagulation and inflammation, most of which are different from activated protein C. In addition, thrombomodulin has a very high affinity for thrombin and may act as a scavenger for free circulating thrombin. Another new option that is worth exploring is recombinant ADAMTS13, in particular in DIC patients with low levels of this protease and that may therefore exhibit excessive platelet thrombi in the microvasculature.

7. Five-year view

In any case, it seems more tailored therapy for DIC is required. Individual fine-tuning of adjunctive treatment can be tailored dependent on which organ is most affected by DIC [91,92]. For instance, if ARDS or lung injury is the most conspicuous manifestation of DIC, management should target restoration of natural coagulation-regulatory systems, such as thrombomodulin or antithrombin. In DIC that primarily manifests with skin necrosis or even purpura fulminans, hypothetically reconstitution of the activated protein C pathway might be indicated. Or in case of acute kidney insufficiency restoring the levels of ADAMTS13 may be a useful strategy targeting enhanced platelet–vessel wall interaction.

A better supportive treatment of DIC might also be achieved by earlier identification of patients at risk and stratification of these risks. The diagnostic scoring systems for DIC are helpful for diagnosing overt DIC; however, the detection of DIC at a premature stage is more difficult. Sensitive laboratory markers are helpful to achieve this, but need to be available on a routine basis or – even better – as point of care tests. As the ongoing coagulation process in DIC mostly occurs at the surface of perturbed endothelial cells or activated blood cells, assays that would readily display endothelial cell perturbation or coagulation factor complex assembly at the surface of platelets or inflammatory cells would be even more helpful to detect patients at an early stage or at high risk for overt DIC and would simplify the identification of patients that would need adjunctive management aimed at the coagulopathy.

In addition, genetic differences between individuals may be pivotal in their susceptibility for developing DIC and the intensity of the coagulation derangement [93]. For example, genetic variants were demonstrated to influence fibrin formation and degradation in DIC. Transgene mice with a heterozygous protein C deficiency had a more intense DIC and related activation of inflammation [74]. In addition, the presence of activated protein C resistance due to a factor V Leiden mutation affected the development and severity of DIC in septic patients [94]. In addition, the 4G/5G polymorphism in *PAI-1*, affecting plasma concentrations of this fibrinolytic inhibitor, has been associated to relevant outcomes in children with DIC due to meningococcal sepsis [95]. A better understanding into the effects of genetic variation affecting the coagulative response in diseases that may be complicated by DIC will be useful for predicting which patients are likely to develop DIC and targeting selective treatment options to these individual patients.

Key issues

- Disseminated intravascular coagulation (DIC) is a condition causing systemic intravascular activation of coagulation, leading to widespread deposition of fibrin in the (micro) circulation.
- Increased fibrin formation and impaired removal results in vascular obstruction, which may cause tissue ischemia and ensuing organ damage.
- Ongoing and insufficiently compensated consumption of coagulation proteins and platelets may result in low concentrations of clotting factors and thrombocytopenia and predispose to major hemorrhagic complications.
- Activation of the coagulation system is initiated by expression of tissue factor on activated inflammatory cells and vascular endothelial cells. Hemostatic activation is propagated by lack of functioning of natural anticoagulant pathways, such as the activated protein C pathway and antithrombin. In addition, fibrin removal is impaired due to inactivation of endogenous fibrinolysis, mainly by high levels of its main regulator, plasminogen activator inhibitor type 1 (PAI-1).
- Various changes in routinely available coagulation parameters are present in patients with DIC, including thrombocytopenia, abnormal global clotting times, low

concentrations of coagulation inhibitors, and high levels of fibrin degradation products.

- There is not a single assay, however, that can correctly diagnose or discard the presence of DIC. However, a combination of readily available tests applied in a scoring algorithm is capable of establishing this diagnosis and can be used in identifying patients with DIC that may require specific adjunctive treatment options aimed at the coagulation system.
- A better insight into the pathogenetic pathways that lead to DIC has yielded novel supportive therapeutic options for DIC that are currently further explored in preclinical studies and further evaluated in clinical trials.

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