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IM - REVIEW

Disseminated intravascular coagulation: a review for the internist

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Abstract Disseminated intravascular coagulation (DIC) is a syndrome characterized by systemic intravascular activation of coagulation, leading to widespread deposition of fibrin in the circulation. Recent knowledge on important pathogenetic mechanisms that may lead to DIC has resulted in novel preventive and therapeutic approaches to patients with DIC. The diagnosis of DIC can be made by sensitive laboratory tests; however, most of these tests are not readily available in a clinical setting. A reliable diagnosis can also be made on the basis of a small series of laboratory tests that can be combined in a scoring algorithm. The cornerstone of the management of DIC is the specific and vigorous treatment of the underlying disorder. Strategies aimed at the inhibition of coagulation activation may theoretically be justified and have been found beneficial in experimental and clinical studies. These strategies comprise inhibition of tissue factor-mediated activation of coagulation or restoration of physiological anticoagulant pathways.

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Introduction

In virtually all critically ill patients, some degree of coagulation activation may be detected. In many cases, this activation of coagulation will not lead to clinical complications and will not even be detected by routine laboratory tests, but can only be measured with sensitive molecular markers for activation of coagulation factors and pathways [1]. However, if activation of coagulation is sufficiently strong, the platelet count may decrease and global clotting times may become prolonged. In its most extreme form, systemic activation of coagulation is known as disseminated intravascular coagulation (DIC). DIC is characterized by the simultaneous occurrence of widespread (micro)vascular thrombosis, thereby compromising blood supply to various organs, which may contribute to organ failure [2, 3]. Because of ongoing activation of the coagulation system and other factors, such as impaired synthesis and increased degradation of coagulation proteins and protease inhibitors, consumption of clotting factors and platelets may occur, resulting in bleeding from various sites.

Relevance of DIC

Activation of coagulation in concert with inflammatory activation can result in microvascular thrombosis, which contributes to multiple organ failure in patients with severe systemic inflammation [4]. In support of this concept, post-mortem findings in patients with coagulation abnormalities

and DIC on the background of severe sepsis include diffuse bleeding, hemorraghic necrosis of tissues, microthrombi in small blood vessels and thrombi in mid-size and larger arteries and veins. Importantly, intravascular thrombi appear to be one of the drivers of organ dysfunction. Experimental bacteremia or endotoxemia causes intra- and extravascular fibrin deposition in the kidneys, lungs, liver, brain and other organs in animals. Amelioration of the hemostatic defect by various interventions in these models reduces fibrin deposition, improves organ function and, in some cases, reduces mortality. In clinical studies, DIC has shown to be an independent predictor of organ failure and mortality [5, 6]. In addition to microvascular thrombosis and organ dysfunction, coagulation abnormalities may have other harmful consequences. Critically ill patients with a platelet count of $<50 \times 10^9$/L have a four to five-fold higher risk for bleeding than those with higher platelet counts [7]. Although the overall risk of intracerebral bleeding in patients in the ICU is less than 0.5 %, up to 88 % of patients with this complication have platelet counts less than 100×10^9/L. Thrombocytopenia itself is a risk factor for adverse outcome in critically ill patients, but not solely due to bleeding. In particular, thrombocytopenia that persists more than 4 days after ICU admission, or 50 % greater decrease in platelet count during the ICU stay, is associated with a four to sixfold increase in mortality. In fact, the platelet count appears to be a stronger predictor for ICU mortality than composite scoring systems, such as the Acute Physiology and Chronic Evaluation (APACHE) II or Multiple Organ Dysfunction Score (MODS). Decreased levels of coagulation factors, as reflected by prolonged global coagulation times, also increase the risk of bleeding. Prolongation of the prothrombin time (PT) or activated partial thromboplastin time (aPTT) to over 1.5 times the control is associated with an increased risk of bleeding and mortality in critically ill patients.

Pathogenesis of DIC

In recent years, the molecular mechanisms of coagulation pathways have been defined. Activation of blood coagulation requires several cofactors. For development of DIC, the surfaces of cell remnants or intact cells, inflammatory mediators and coagulation proteins are required. For example, in the coagulopathy resulting from Gram-negative sepsis, endotoxin directly binds to CD 14 on monocytes, and binds to endothelial cells after forming a complex with lipopolysaccharide binding protein (LBP) and Toll-like receptors [8]. Through these interactions, endotoxin induces signaling pathways that culminate in NFκB activation and initiates the expression of proinflammatory cytokines The most important mediators that orchestrate the disbalance of the coagulation system in DIC are the cytokines tumor necrosis factor-α, interleukin-1 and interleukin-6 [4].

The initiation of coagulation activation leading to thrombin generation in DIC is mediated exclusively by the tissue factor/factor VII(a) pathway (Fig. 1). Inhibition of tissue factor or factor VIIa results in a complete abrogation of endotoxin- or microorganism-induced thrombin generation. The most significant source of tissue factor is not completely clear in all situations. Tissue factor may be expressed not only in mononuclear cells in response to proinflammatory cytokines (mainly IL-6), but also in vascular endothelial cells or cancer cells. Despite the potent initiation of coagulation by tissue factor, the activation of coagulation cannot be propagated if physiological anticoagulant pathways function properly. However, in DIC all major natural anticoagulant pathways [i.e., antithrombin III, the protein C system, and tissue factor pathway inhibitor (TFPI)] appear to be impaired [9]. Plasma levels of antithrombin III, the most important inhibitor of thrombin, are markedly reduced during DIC, due to a combination of consumption, degradation by elastase from activated neutrophils and impaired synthesis. A significant depression of the protein C system may further compromise

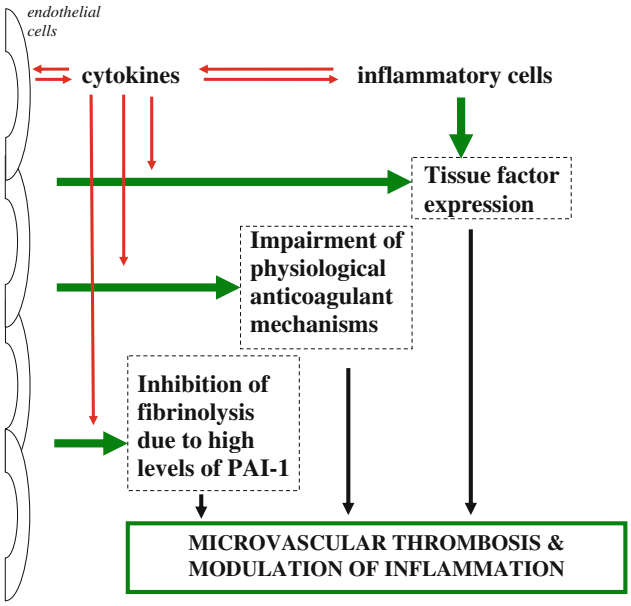

Fig. 1 Pathogenesis of disseminated intravascular coagulation pathways involved in the activation of coagulation in DIC. Both perturbed endothelial cells and activated mononuclear cells may produce proinflammatory cytokines that induce tissue factor expression, thereby initiating coagulation. In addition, downregulation of physiological anticoagulant mechanisms and inhibition of fibrinolysis promote intravascular fibrin deposition. *PAI-1* plasminogen activator inhibitor, type 1

an adequate regulation of activated coagulation. This impaired function of the protein C system is caused by a combination of impaired protein synthesis, cytokine-mediated downregulation of endothelial thrombomodulin and a fall in the concentration of the free fraction of protein S (the essential co-factor of protein C), resulting in reduced activation of protein C [10]. Lastly, there seems to be a disbalance of TFPI function in relation to the increased tissue factor-dependent activation of coagulation [11]. All these anticoagulant pathways are linked to the endothelium, and it is likely that endothelial cell perturbation and dysfunction are important for the impaired function of these anticoagulant systems. Lastly, experimental and clinical studies indicate that during DIC, the fibrinolytic system is largely suppressed at the time of maximal activation of coagulation. This inhibition of fibrinolysis is caused by a sustained rise in the plasma level of plasminogen activator inhibitor-1 (PAI-1), the principal inhibitor of the fibrinolytic system.

Activation of platelets may also accelerate fibrin formation by another mechanism [12]. The expression of TF in monocytes is markedly stimulated by the presence of platelets and granulocytes in a P-selectin dependent reaction [13]. This effect may be the result of nuclear factor kappa B (NF-κB) activation induced by binding of activated platelets to neutrophils and mononuclear cells [14].

In addition to activating coagulation protein zymogens, coagulation proteases also interact with specific cell receptors and trigger signaling pathways that elicit pro-inflammatory mediators (Fig. 2) [4]. Factor Xa, thrombin and the tissue factor VIIa complex have such effects. Thrombin has a variety of non-coagulant effects. Thrombin induces the release of chemokines from fibroblasts, epithelial cells and mononuclear cells in vitro. Thrombin also induces interleukin production in endothelial cells. Cell activation by tissue factor VIIa, factor Xa and thrombin is likely mediated by protease-activated receptors.

Direct evidence of the in vivo relevance of these phenomena comes from a study showing that recombinant factor VIIa infusion in volunteers induces an increase in plasma levels of interleukins [15]. Although the concentrations of factor VIIa infused far exceed those found in patients with sepsis, it is possible that factor VIIa-induced cytokine production is of physiological importance. Thus, this information adds to the concept that several coagulation proteases induce pro-inflammatory mediators that augment procoagulant activity and amplify the consumptive process.

Underlying causes of DIC

The spectrum of clinical and laboratory presentation of DIC is affected by several parameters and may range from an acute or severe consumption coagulopathy to subacute or even chronic coagulopathies [16]. This variability in presentation may be confusing, particularly because sometimes cases of so-called DIC are not disseminated, intravascular or even related to deranged coagulation. Acute, severe DIC is characterized by diffuse multiorgan bleeding, hemorrhagic necrosis, microthrombi in small blood vessels and thrombi in medium and large blood vessels. This condition may occur in the setting of sepsis, major trauma, obstretric calamities and severe immunologic responses. In contrast to the acutely ill patient with complicated, severe DIC, other patients may have mild or protracted clinical manifestations of consumption or even subclinical disease manifest by only laboratory abnormalities [17]. The clinical picture of subacute to chronic DIC is exemplified by the chronic hypercoagulability that may accompany malignancy, in particular with mucin-producing adenocarcinomas and acute promyelocytic leukemia.

DIC is not a disease in itself, but is always secondary to an underlying disorder that causes the activation of coagulation (Table 1).

There are many syndromes that may present with a clinical and laboratory picture reminiscent of DIC. Table 2 lists the most important of these clinical entities and some cues on how to distinguish these conditions from DIC.

Infection and sepsis

Severe systemic infections or sepsis are among the most common causes of DIC. Immunocompromised patients, asplenic patients whose ability to clear bacteria (particularly pneumococci) is impaired and newborns whose anticoagulant systems are immature are particularly prone to infection-induced DIC. Infections may be superimposed on trauma or malignancies, which themselves are potential triggers of DIC. Clinically overt DIC occurs in 30–50 % of patients with Gram-negative or Gram-positive sepsis, but also in infections with non-bacterial pathogens, such as viruses, protozoa (malaria) and fungi [18]. An extreme form of DIC is represented by purpura fulminans, a severe, often lethal form of DIC in which extensive areas of the skin over the extremities and buttocks undergo hemorrhagic necrosis.

DIC in trauma and burns

Extensive exposure of damaged tissue [including tissue factor (TF)] to the blood circulation and hemorrhagic shock probably are the most immediate triggers of DIC in trauma. An alternative hypothesis is that cytokines play a pivotal role in the occurrence of DIC in trauma patients [19]. Bleeding, laboratory tests indicative of DIC and vascular microthrombi in biopsies of undamaged skin have been described in patients with extensive burns. Kinetic studies

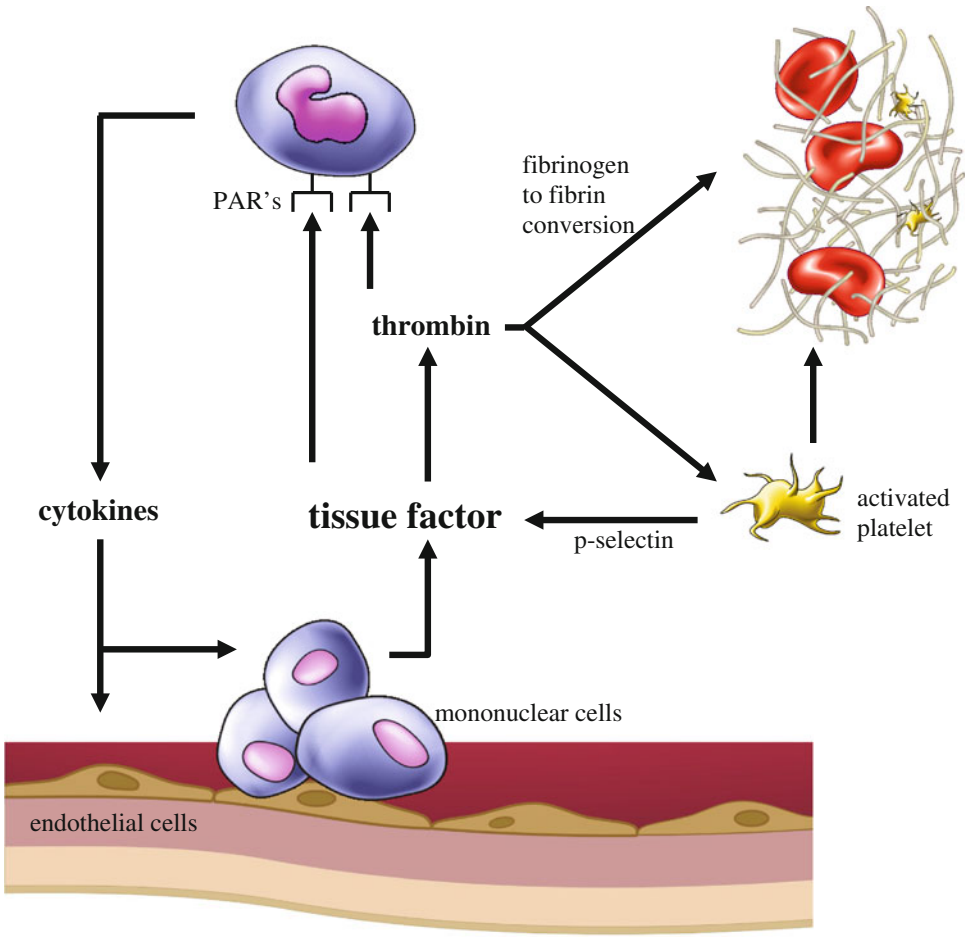

Fig. 2 Schematic representation of the link between infection/inflammation and coagulation. Activated mononuclear cells and endothelial cells induce expression of tissue factor that activates platelets and the coagulation system. Activated coagulation proteases bind to protease-activated receptors (PARs), that may induce additional pro-inflammatory stimuli by releasing cytokines that target endothelial cells and mononuclear cells

Table 1 Clinical conditions that are most frequently complicated by DIC

Sepsis/severe infection
Trauma/burn/heatstroke
Malignancy
Solid tumors
Acute leukemia
Obstetrical conditions
Amniotic fluid embolism
Abruptio placentae
HELLP (hemolysis, elevated liver enzymes, low platelet)-syndrome
Vascular abnormalities
Kasabach-Merrit syndrome
Other vascular malformations
Aortic aneurysms
Severe allergic/toxic reactions
Severe immunologic reactions (e.g., transfusion reaction)

with labeled fibrinogen and labeled platelets disclose that, in addition to systemic consumption of hemostatic factors, significant local consumption occurs in burned areas.

DIC in obstetric calamities

Placental abruption is a leading cause of perinatal death [20]. The severe hemostatic failure accompanying abruptio placentae is the result of acute DIC emanating from the introduction of large amounts of TF into the blood circulation from the damaged placenta and uterus. Amniotic fluid has been shown to be able to activate coagulation in vitro, and the degree of placental separation correlates with the extent of DIC, suggesting that leakage of thromboplastin-like material from the placental system is responsible for the occurrence of DIC. Abruptio placentae occurs in 0.2–0.4 % of pregnancies, but only 10 % of these cases are associated with DIC.

DIC in malignancy

Patients with solid tumors are vulnerable to risk factors and additional triggers of DIC that can aggravate thromboembolism and bleeding [21]. Solid tumor cells can express different procoagulant molecules including tissue factor and cancer procoagulant (CP), a cysteine protease with factor X activating properties. Numerous reports on DIC

Table 2 Differential diagnosis of suspected DIC

Differential diagnosis	Additional diagnostic clues
DIC	Prolonged aPTT and PT, increased fibrin split products, low levels of physiological anticoagulant factors (antithrombin, protein C)
Massive blood loss	Major bleeding, low hemoglobin, prolonged aPTT and PT,
Thrombotic microangiopathy	Schistocytes in blood smear, Coombs-negative hemolysis, fever, neurologic symptoms, renal insufficiency, coagulation times usually normal, ADAMTS13 levels decreased; PT and aPTT normal
Heparin-induced thrombocytopenia	Use of heparin, venous or arterial thrombosis, positive HIT test (usually ELISA for heparin–platelet factor IV antibodies), rebound platelets after cessation of heparin; coagulation times usually normal, PT normal (aPTT may be prolonged due to heparin)
Vitamin K deficiency	PT prolonged, aPTT normal or slightly prolonged, normal platelet count
Liver insufficiency	PT and aPTT prolonged, (moderately) low platelets, liver test abnormalities, hypersplenism, jaundice

and fibrinolysis complicating the course of acute leukemias have been published. In 161 consecutive patients presenting with acute myeloid leukemia, DIC was diagnosed in 52 (32 %). In acute lymphoblastic leukemia, DIC was diagnosed in 15–20 % [22]. Some reports indicate that the incidence of DIC in acute leukemia patients might further increase during remission induction with chemotherapy. In patients with acute promyelocytic leukemia (APL), DIC is present in more than 90% of patients at the time of diagnosis or after initiation of remission induction.

DIC with vascular disorders

Rarely, vascular anomalies can trigger DIC. With some large aortic aneurysms, localized consumption of platelets and fibrinogen can produce coagulation abnormalities and bleeding [23]. In a series of patients with aortic aneurysms, 40 % had elevated levels of fibrin(ogen) degradation products, but only 4 % had laboratory evidence of DIC or bleeding [23]. Kasabach and Merritt were the first to describe bleeding in association with giant cavernous hemangiomas, benign tumors found in newborns or children, which can evolve into convoluted masses of abnormal vascular channels that sequester and consume platelets and fibrinogen.

DIC with toxic reactions or snake bites

The venom of certain snakes, particularly vipers and rattlesnakes, can produce a coagulopathy similar to that of DIC [24]. Interestingly, victims of snake bites rarely have excessive bleeding or thromboembolism despite the abnormal coagulation tests and DIC-like picture.

Diagnosis of DIC

A practical list of common laboratory abnormalities in DIC is given in Table 3. Thrombocytopenia or a rapidly declining platelet count is an important diagnostic hallmark of DIC. However, the specificity and sensitivity of thrombocytopenia for the diagnosis of DIC are limited [7]. A platelet count of $<100 \times 10^9$/L is seen in 50–60 % of DIC patients, whereas 10–15 % of patients have a platelet count $<50 \times 10^9$/L. In surgical or trauma patients with DIC, over 80 % of patients have platelet counts less than 100×10^9/L. On the other hand, in consecutive critically ill patients with thromboctypenia, only 35 % had DIC [7].

Table 3 Routine laboratory value abnormalities in DIC

Test	Abnormality	Causes other than DIC contributing to test result
Platelet count	Decreased	Sepsis, impaired production, major blood loss, hypersplenism
Prothrombin time	Prolonged	Vitamin K deficiency, liver failure, major blood loss
APTT	Prolonged	Liver failure, heparin treatment, major blood loss
Fibrin degradation products	Elevated	Surgery, trauma, infection, hematoma
Protease inhibitors*	Decreased	Liver failure, capillary leakage

* e.g., protein C, AT and protein S

Consumption of coagulation factors leads to low levels of coagulation factors in patients with DIC. In addition, impaired synthesis, for example due to impaired liver function or a vitamin K deficiency, and loss of coagulation proteins, due to massive bleeding, may play a role in DIC as well. The low level of coagulation factors is reflected by prolonged coagulation screening tests, such as the PT or the aPTT. A prolonged PT or aPTT occurs in 14–28 % of intensive care patients, but is present in more than 95 % of patients with DIC.

Plasma levels of factor VIII are paradoxically increased in most patients with DIC, probably due to massive release of von Willebrand factor from the endothelium in combination with acute-phase behavior of factor VIII. Recent

studies have pointed to a relative insufficiency of the von Willebrand cleaving protease ADAMTS-13, thereby causing high concentrations of ultralarge von Willebrand multimers in plasma, which may facilitate platelet–vessel wall interaction and the subsequent development of thrombotic microangiopathy, which may contribute to organ dysfunction [12].

The measurement of fibrinogen has been widely advocated as a useful tool for the diagnosis of DIC, but in fact is not very helpful to diagnose DIC in most cases. Fibrinogen acts as an acute-phase reactant and, despite ongoing consumption, plasma levels can remain well within the normal range for a long period of time. In a consecutive series of patients, the sensitivity of a low fibrinogen level for the diagnosis of DIC is only 28 %, and hypofibrinogenemia is detected in very severe cases of DIC only [25].

Plasma levels of fibrin split products (such as D-dimer) are frequently used for the diagnosis of DIC [25]. Fibrin split products are detectable in 42 % of a consecutive series of intensive care patients, in 80 % of trauma patients and in 99 % of patients with sepsis and DIC. Most of the available assays for fibrin degradation products (FDP's) poorly discriminate between degradation products of cross-linked fibrin and fibrinogen degradation, which may cause spuriously high results. The specificity of high levels of fibrin degradation products is limited and many other conditions, such as trauma, recent surgery, inflammation or venous thrombo-embolism, are associated with elevated FDPs or D-dimer.

Plasma levels of physiological coagulation inhibitors, such as protein C or antithrombin, may be useful indicators of ongoing coagulation activation [25]. Low levels of these coagulation inhibitors are found in 40–60 % of critically ill patients and in 90 % of DIC patients.

Thrombelastography (TEG) is a method that was developed decades ago and provides an overall picture of ex vivo coagulation. Modern techniques, such as rotational thrombelastography (ROTEM), enable bedside performance of this test which has become popular recently in acute care settings [26]. The theoretical advantage of TEG over conventional coagulation assays is that it provides an idea of platelet function as well as fibrinolytic activity. There are no systematic studies on the diagnostic accuracy of TEG for the diagnosis of DIC; however, the test may be useful for assessing the global status of the coagulation system in critically ill patients. A method that has proven sensitive and specific for hypercoagulability in critically ill patients is the aPTT biphasic waveform analysis [27, 28] When this signal is detected in the plasma of individuals suspected of hypercoagulability, it confers a greater than 90 % sensitivity and specificity for subsequent development of DIC and fatal outcome [27]. However, the equipment to measure the aPTT waveform is expensive and practically not very useful for other purposes; hence, it is scarcely available.

Scoring systems for DIC

For the diagnosis of overt DIC, a simple scoring system has been developed (Table 4) [29]. The score can be calculated based on routinely available laboratory tests, i.e., platelet count, prothrombin time (or INR) [30], a fibrin-related marker (usually D-dimer) and fibrinogen. Tentatively, a score of 5 or more is compatible with DIC. Prospective studies show that the sensitivity of the DIC score is 93 % and the specificity is 98 %. Studies in series of patients with specific underlying disorders causing DIC (e.g., cancer patients or patients with obstetric complications) show similar results. The severity of DIC according to this scoring system is related to the mortality in patients with sepsis [6].

Alternative scoring systems for DIC have shown similar accuracy, but are sometimes influenced by local definitions (for example, the traditionally high incidence of patients with hematological malignancies in Japanese series of DIC) or less commonly used laboratory tests [31–34].

A more dynamic approach might be useful to further increase the accuracy of composite systems with laboratory parameters for the diagnosis of DIC. This "trend" in scoring allows longitudinal assessment of the patient's coagulopathy, and, when therapy has been instituted, inference on whether the therapy has improved the course of the disease [35]. In a prospective study in 840 patients, continuation of coagulopathy during the first calendar day correlates with development of new organ failure and 28-day mortality in patients with severe sepsis [36]. Coagulopathy risk points (based on sustained abnormalities in prothrombin time and platelet count) are related to a progression from single to multiple organ failure, time to resolution of organ failure and 28-day mortality ($p < 0.001$). Adding the scoring system to APACHE II improves the ability to predict which patients may progress from single to multiple organ failure (Table 5).

Management of DIC

Adequate management of patients with DIC depends on vigorous treatment of the underlying disorder to alleviate or remove the inciting injurious cause [37]. In addition, intensive support of vital functions and supportive treatment aimed at the coagulopathy may be helpful.

Platelet and plasma transfusion

Low levels of platelets and coagulation factors may increase the risk of bleeding. However, plasma or platelet substitution therapy should not be instituted on the basis of

Table 4 Diagnostic algorithm for the diagnosis of overt DIC

1	Presence of an underlying disorder known to be associated with DIC (Table 130-2) (no = 0, yes = 2)	
2	Score of 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 s = 0; >3 s but <6 s = 1; >6 s = 2)	
	Fibrinogen level (> 1.0 g/L = 0; <1.0 g/L = 1)	
3	Calculated score	
4	If ≥5: compatible with overt DIC; repeat scoring daily If <5: suggestive (not affirmative) for non-overt DIC; repeat next 1–2 days	

* According to the Scientific Standardization Committee of the International Society of Thrombosis and Haemostasis [29]

Strong increase >5 × upper limit of normal; moderate increase is >upper limit of normal, but <5 × upper limit of normal

laboratory results alone; it is indicated only in patients with active bleeding and in those requiring an invasive procedure or who are at risk for bleeding complications [38]. The presumed efficacy of treatment with plasma, fibrinogen concentrate, cryoprecipitate or platelets is not based on randomized controlled trials, but appears to be rational therapy in bleeding patients or in patients at risk of bleeding who have a significant depletion of these hemostatic factors. Replacement therapy for thrombocytopenia should consist of 5–10 U platelet concentrate to raise the platelet count to 20–30 × 10^9/L, and in patients who are actively bleeding or need an invasive procedure to 50 × 10^9/L.

Anticoagulant treatment

Heparin therapy in patients with DIC remains controversial. Experimental studies have shown that heparin can at least partly inhibit the activation of coagulation in DIC. However, a beneficial effect of heparin on clinically important outcome events in patients with DIC has not definitively been demonstrated in controlled clinical trials. Also, the safety of heparin treatment is debatable in DIC patients who are prone to bleeding. A large trial in patients with severe sepsis shows a slight, but non-significant benefit of low-dose heparin on 28-day mortality in patients with severe sepsis, who were also treated with activated protein C and had no major safety concerns [39]. There is general consensus that administration of heparin is beneficial in some categories of DIC, such as metastatic carcinomas, purpura fulminans and aortic aneurysm (prior to resection). Heparin is also indicated for treating thromboembolic complications in large vessels and before surgery in patients with chronic DIC. Apart from all these considerations, current guidelines dictate the universal use of prophylactic doses of heparin or low molecular weight heparin to prevent venous thromboembolic events in critically ill patients [38].

Recombinant human soluble thrombomodulin binds to thrombin to form a complex that inactivates thrombin's coagulant activity and activates protein C and, thus, is a potential drug for the treatment of patients with DIC. In a phase III randomized double-blind clinical trial in patients with DIC, administration of the soluble thrombomodulin

Table 5 Fundamentals of DIC treatment

Modality	Details	Expectations/rationale
Treating the underlying disorder	Dependent on the primary diagnosis	Inhibit or block the complicating pathologic mechanism of DIC in parallel with the response (if any) of the disorder
Antithrombotic agents	Prophylactic heparin to prevent venous thromboembolic complications	Risk of thromboembolism is greatly increased in critically ill patients, trauma patients or patients with cancer
	(Low dose) therapeutic heparin in case of confirmed thromboembolism or if clinical picture is dominated by (micro) vascular thrombosis and associated organ failure	Prevent fibrin formation; tip the balance within the microcirculation toward anticoagulant mechanisms and physiologic fibrinolysis; allow reperfusion of the skin, kidneys and brain
Transfusion	Infuse platelets, plasma and fibrinogen (cryoprecipitate) if patient presents with bleeding or is at high risk of bleeding	Bleeding should diminish and stop during an interval of hours
		Platelet count, clotting times and fibrinogen should normalize significantly
Anticoagulant factor concentrates	Recombinant human-activated protein C does not decrease mortality, but may be effective in ameliorating DIC and sepsis (24 ug/kg/h for 4 days); is currently not available	Restore anticoagulation in microvascular environment and be beneficial on inflammatory activity
	Antithrombin concentrate does not decrease mortality, but may be effective in ameliorating DIC (5,000–7,500 U/24 h)	
Fibrinolytic inhibitors	Tranexamic acid (e.g., 500–1,000 mg q8–12 h or ε-aminocaproic acid 1,000–2,000 mg q8–12 h	In particular, useful when (hyper) fibrinolysis dominates the picture
		Bleeding ceases, but there is risk of keeping vascular channels occluded with thrombus

has a significantly better effect on bleeding manifestations and coagulation parameters than heparin. Currently ongoing trials with soluble thrombomodulin focus on DIC, organ failure and mortality rate.

Physiological anticoagulant factor concentrates

Restoration of the levels of physiological anticoagulants in DIC may be a rational approach [9]. In several small clinical trials, the use of very high doses of AT concentrate shows a modest reduction in mortality, however, without being statistically significant. A large-scale, multicenter, randomized controlled trial also shows no significant reduction in mortality of patients with sepsis, and an overall meta-analysis of clinical trial results shows no reduction in mortality, but a 1.5-fold (95 % confidence interval 1.3–1.8) increased risk of bleeding with the use of AT concentrate [40, 41]. Interestingly, post hoc subgroup analyses of the randomized trial indicate some benefit in patients who do not receive concomitant heparin who had DIC, but this is a retrospective subgroup observation that needs prospective validation.

A randomized controlled phase III trial of recombinant human-activated protein C (APC) in patients with severe sepsis was prematurely stopped because of its efficacy in reducing mortality in these patients [42]. Patients who have DIC according to international criteria benefit more from therapy with APC than patients who do not have overt DIC [6]. However, a meta-analysis of the published literature concludes that the basis for treatment with APC, even in patients with a high disease severity, is not strong. A recently completed placebo-controlled trial in patients with severe sepsis and septic shock was prematurely stopped due to the lack of any significant benefit of APC [43]. Subsequently, the manufacturer of APC has decided to withdraw the product from the market, which has resulted in a revision of current guidelines for the treatment of DIC [44]. There have been some smaller studies on the efficacy of zymogen protein C (not activated) in patients with DIC; however, the results of these studies are equivocal and this intervention needs further evaluation [45].

Fibrinolytic inhibitors

Most guidelines recommend against the use of anti-fibrinolytic agents, such as ε-aminocaproic acid or tranexamic acid in patients with DIC. This is because these drugs block already suppressed endogenous fibrinolysis and may further compromise tissue perfusion. However, in patients with DIC accompanied by primary fibrino(geno)lysis, as in some cases of acute promyelocytic leukemia, giant cavernous hemangioma, heat stroke and metastatic carcinoma of the prostate, the use of fibrinolytic inhibitors can be undertaken if the patient has profuse bleeding that does not respond to replacement therapy.

Conflict of interest None.

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