Disseminated intravascular coagulation

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Objective: **To review the current knowledge on the clinical manifestation, pathogenesis, diagnosis, and management of disseminated intravascular coagulation (DIC).**

Data Source: **Selected articles from the MEDLINE database.**

Data Synthesis: **DIC may complicate a variety of disorders and can cause significant morbidity (in particular related to organ dysfunction and bleeding) and may contribute to mortality. The pathogenesis of DIC is based on tissue factor–mediated initiation of systemic coagulation activation that is insufficiently contained by physiologic anticoagulant pathways and amplified by impaired endogenous fibrinolysis. The diagnosis of DIC can be made using routinely available laboratory tests and scoring algorithms. Supportive treatment of DIC may be aimed at replacement of platelets and coagulation factors, anticoagulant treatment, and restoration of anticoagulant pathways.**

Conclusions: **Insight into the pathogenesis of DIC has resulted in better strategies for clinical management, including straightforward diagnostic criteria and potentially beneficial supportive treatment options. (Crit Care Med 2007; 35:2191–2195)**

KEY WORDS: disseminated intravascular coagulation; coagulation; fibrinolysis; tissue factor; blood coagulation factor inhibitors; multiple organ failure

A variety of disorders, including infectious or inflammatory conditions and malignant disease, will lead to activation of coagulation. 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 when sensitive molecular markers for activation of coagulation factors and pathways are used (1). However, if activation of coagulation is sufficiently strong, a decreasing platelet count and prolongation of global clotting times may become manifest. Systemic activation of coagulation in its most extreme form is known as disseminated intravascular coagulation (DIC). DIC is classically characterized as the simultaneous occurrence of widespread (micro) vascular thrombosis, thereby compromising an adequate blood supply to various organs, which may contribute to organ failure (2). Due to ongoing activation of the coagulation system and other factors, such as impaired synthesis and increased degradation of coagulation proteins and protease inhibitors, exhaustion of factors and platelets may occur, resulting in profuse bleeding from various sites.

Clinical Setting and Relevance

It is important to stress that DIC is not a disease in itself but is always secondary to an underlying disorder that causes the activation of coagulation. The underlying disorders most commonly known to be associated with DIC are listed in Table 1.

Severe sepsis may be complicated by DIC in about 35% of cases (3, 4). Classically, infection with Gram-negative microorganisms has been associated with DIC; however, the prevalence of DIC during Gram-positive infections is similar (5). Other microorganisms, such as viruses and parasites, may lead to DIC as well (6). Factors involved in the development of DIC in patients with infections may be bacterial endotoxins (e.g., from Gram-negative bacteria) or exotoxins (e.g., staphylococcal alpha toxin).

Both solid tumors and hematologic malignancies may be complicated by DIC (7, 8). There is increasing evidence that tissue factor expressed by cancer cells is important in the pathogenesis of DIC in cancer (9). Solid tumor cells can also express other procoagulant molecules, such as cancer procoagulant, a cysteine protease with factor X-activating properties. The prevalence of DIC in cancer is not precisely known and may vary between centers and be dependent on diagnostic criteria used; however, some series, in particular in patients with metastasized adenocarcinoma or lymphoproliferative disease, report a prevalence of up to 20% in consecutive cases (7).

Severe trauma is another clinical condition frequently associated with DIC (10). Systemic cytokine patterns in patients with severe trauma have been shown to be virtually identical to those of septic patients (11), hence the activation of coagulation thought to be due to a systemic inflammatory state. In addition, release of tissue material (such as tissue thromboplastin, in particular in patients with head trauma) into the circulation and endothelial damage may contribute to the systemic activation of coagulation. The precise prevalence of DIC in patients with severe trauma is not known. It may be difficult to differentiate DIC from the coagulopathy due to massive blood loss and the dilutional coagulopathy that may occur in the first hours after major trauma.

In obstetrical calamities, such as placental abruption and amniotic fluid emboli, acute and fulminant DIC may occur (12). The degree of placental separation in patients with abruptio placentae correlates with the extent of DIC, suggesting that leakage of thromboplastin-like material from the placental system is responsible for the occurrence of DIC. Indeed, amniotic fluid has been shown to be able to activate coagulation *in vitro*.

For other underlying causes (Table 1), DIC is a relatively rare complication. In most conditions, the severity of the associated systemic inflammatory response in

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combination with situational circumstances, such as liver dysfunction, will determine whether severe activation of coagulation will occur.

The clinical relevance of DIC leading to severe thrombocytopenia and low levels of coagulation factors in patients with serious, sometimes untreatable, bleeding is quite obvious. However, major bleeding occurs in only a minority of patients with DIC (2). The prevalence of major bleeding (i.e., intracranial, intrathoracic, or intra-abdominal bleeding or bleeding requiring transfusion) in patients with DIC was 5–12% in recent studies in patients with severe sepsis (13, 14). Critically ill patients with a platelet count of $<50 \times 10^9$/L have a 4- to 5-fold higher risk for bleeding as compared with patients with a higher platelet count (15, 16). In 88% of patients with intracerebral bleeding in the ICU, platelet counts were $<100 \times 10^9$/L (17).

More common is the occurrence of organ failure, and there are several lines of evidence indicating that activation of coagulation (in its most extreme form manifesting as DIC) has an important pathogenetic role in the development of organ failure (18). First, many organs show fibrin deposition at pathologic examination, and the presence of intravascular thrombi seems to be clearly related to the clinical dysfunction of the organs (19). Autopsy findings in patients with overt DIC include diffuse bleeding, hemorrhagic necrosis, microthrombi in small blood vessels, and thrombi in midsize and larger arteries and veins (20, 21). Fibrin deposition in small and midsize vessels in patients with DIC in these studies was invariably associated with ischemia and necrosis and with clinical dysfunction of organs. Also, intravascular and bronchoalveolar fibrin deposition is a hallmark of acute lung injury in sepsis and other conditions (22). Second, experimental bacteremia or endotoxemia in animals causes intravascular and extravascular fibrin deposition in kidneys, lungs, liver, and brain, and amelioration of the hemostatic defect improves organ failure and, in some cases, mortality (23–28). Finally, DIC has been shown to be an independent and relatively strong predictor of organ dysfunction and mortality in patients with sepsis and severe trauma (3, 4). In patients with sepsis and DIC, mortality is almost two times higher as compared with patients who do not have DIC.

Table 1. Clinical conditions that may be associated with disseminated intravascular coagulation

Sepsis/severe infection (any microorganism)
Malignancy
Myeloproliferative/lymphoproliferative malignancies
Solid tumors
Trauma (e.g., polytrauma, neurotrauma, fat embolism)
Obstetrical calamities
Amniotic fluid embolism
Abruptio placentae
Organ destruction (e.g., severe pancreatitis)
Severe toxic or immunologic reactions
Snake bites
Recreational drugs
Transfusion reactions
Transplant rejection
Vascular abnormalities
Kasabach-Merritt syndrome
Large vascular aneurysms
Severe hepatic failure

Pathogenesis

In recent years, many mechanisms involved in the pathologic derangement of coagulation in patients with DIC have been elucidated. It is now clear that various mechanisms at different sites in the hemostatic system act simultaneously in the promotion of a procoagulant state (Fig. 1). The most important mediators that orchestrate this imbalance of the coagulation system in DIC are cytokines (2). The initiation of coagulation activation leading to thrombin generation in DIC is mediated exclusively by the tissue factor/factor VII(a) pathway. Inhibition of tissue factor or factor VIIa resulted in a complete abrogation of endotoxin- or microorganism-induced thrombin generation (29). The most important source of tissue factor is not completely clear in all situations. Tissue factor may be expressed on mononuclear cells in response to proinflammatory cytokines (mainly interleukin-6) but also on vascular endothelial cells or on cancer cells. Despite the potent initiation of coagulation by tissue factor, the activation of coagulation cannot be propagated if physiologic 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) seem to be impaired (30). 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 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 down-regulation of endothelial

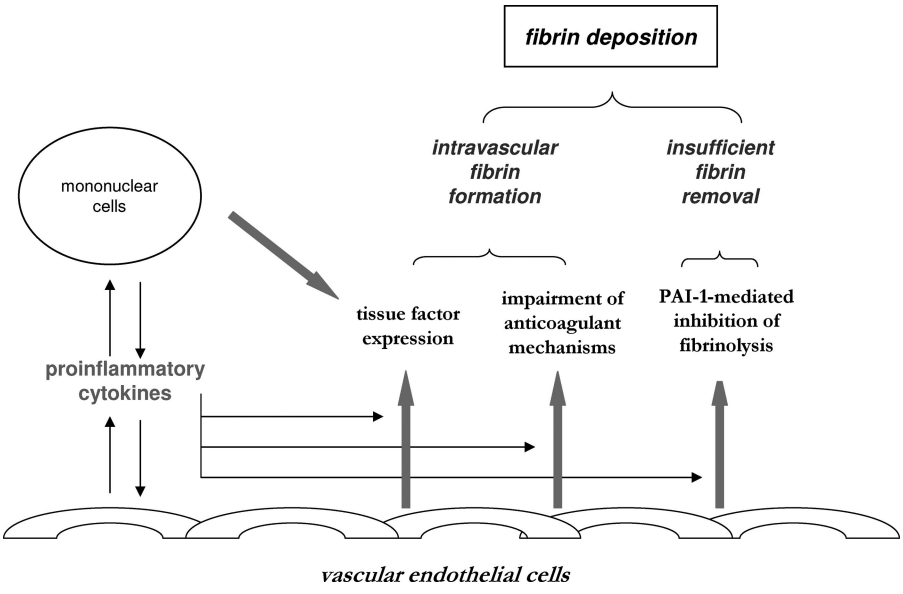

Figure 1. Schematic representation of pathogenetic pathways in disseminated intravascular coagulation. During systemic inflammatory response syndromes, both perturbed endothelial cells and activated mononuclear cells may produce proinflammatory cytokines that mediate coagulation activation. Activation of coagulation is initiated by tissue factor expression on activated mononuclear cells and endothelial cells. In addition, down-regulation of physiologic anticoagulant mechanisms and inhibition of fibrinolysis by endothelial cells will further promote intravascular fibrin deposition. *PAI-1*, plasminogen activator inhibitor, type 1.

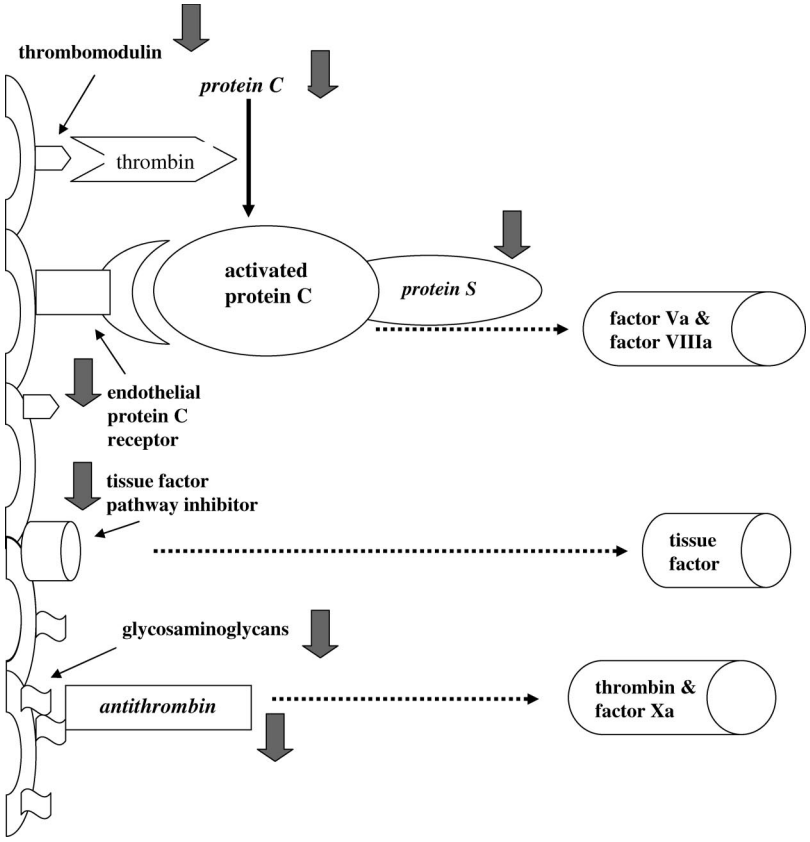

Figure 2. Schematic representation of the three important physiologic anticoagulant mechanisms and their point of impact in the coagulation system. In sepsis, these mechanisms are impaired by various mechanisms (*arrows*). The protein C system is dysfunctional due to low levels of zymogen protein C, down-regulation of thrombomodulin and the endothelial protein C receptor, and low levels of free protein S due to acute phase–induced high levels of its binding protein, C4b-binding protein. There is a relative insufficiency of the endothelial cell–associated tissue factor pathway inhibitor. The antithrombin system is defective due to low levels of antithrombin and impaired glycosaminoglycan expression on perturbed endothelial cells.

Table 2. Algorithm for the diagnosis of disseminated intravascular coagulation (DIC) (38)

Score global coagulation test results
1. Platelet count (>100 × 10^9/L = 0, <100 × 10^9/L = 1, <50 × 10^9/L = 2)
2. Elevated fibrin-related marker (e.g., fibrin degradation products or D-dimer) (no increase, 0; moderate increase, 2; strong increase, 3)[a]
3. Prolonged prothrombin time (<3 secs = 0, >3 but <6 secs = 1, >6 secs = 2)
4. Fibrinogen level (>1.0 g/L = 0, <1.0 g/L = 1)
Calculate score
If ≥5: compatible with overt DIC
If <5: no overt DIC; repeat next 1–2 days

[a]In most prospective validation studies, D-dimer assays were used and a value above the upper limit of normal (0.4 μg/L) was considered moderately elevated, whereas a value >10 times the upper limit of normal (4.0 μg/L) was considered as a strong increase.

thrombomodulin, and a decrease in the concentration of the free fraction of protein S (the essential cofactor of protein C), resulting in reduced activation of protein C (31). In addition, there seems to be an imbalance of tissue factor pathway inhibitor function in relation to the increased tissue factor–dependent activation of coagulation (32). Interestingly, all these anticoagulant pathways are linked to the endothelium (Fig. 2), and it is likely that endothelial cell perturbation and dysfunction is important for the impaired function of these anticoagulant systems. Lastly, and importantly, experimental and clinical studies indicate that during DIC, the fibrinolytic system is largely suppressed at the time of maximal activation of coagulation (33). 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.

Diagnosis

No single laboratory test available today is sufficiently accurate to allow a definite diagnosis of DIC. Tests for the detection of soluble fibrin or fibrin degradation products play an important role in the diagnosis of DIC and have a sensitivity of 90–100% but generally a low specificity (34). In addition, there is quite some discordance among various assays (35, 36). Measurement of fibrinogen is often advocated as a useful tool for the diagnosis of DIC but in fact is not very helpful. Fibrinogen acts as an acute-phase reactant and, despite ongoing consumption, plasma levels can remain well within the normal range for a long time. In a consecutive series of patients, the sensitivity of a low fibrinogen level for the diagnosis of DIC was only 28%, and hypofibrinogenemia was detected in a very small number of severe cases of DIC only (37). Sequential measurements of fibrinogen might be more useful. In clinical practice, a diagnosis of DIC can often be made by a combination of platelet count, measurement of global clotting times (activated partial thromboplastin time and prothrombin time), measurement of one or two clotting factors and inhibitors (such as antithrombin), and a test for fibrin degradation products. A scoring system, utilizing such simple laboratory tests, has been developed by the subcommittee on DIC of the International Society of Thrombosis and Haemostasis (Table 2) (38), and it has been prospectively validated in various studies, indicating a sensitivity and specificity around 95% (3, 39). Other studies show that serial coagulation tests may also be helpful in establishing the diagnosis of DIC. A progressive reduction in the platelet count or prolongation of coagulation times may be a sensitive (although not specific) sign of DIC (14, 40).

Management

Key to the treatment of DIC is the specific and vigorous treatment of the underlying disorder. However, additional supportive treatment, specifically aimed at the coagulation abnormalities, may be required.

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 laboratory results alone and is only indicated in patients with active bleeding and in those requiring an invasive procedure or otherwise at risk for bleeding complications. The threshold for transfusing platelets depends on the clinical situation of the patient. Based on expert opinion, platelet concentrate is, in general, transfused to patients who bleed and who have a platelet count of $<50 \times 10^9$/L. In nonbleeding patients, a much lower threshold for platelet transfusion is used (usually $<10–20 \times 10^9$/L), which is based on randomized controlled trials in patients with thrombocytopenia after chemotherapy (41, 42). It may be necessary to use large volumes of plasma to correct the coagulation defect. Coagulation factor concentrates, such as prothrombin complex concentrate, will overcome this obstacle, but these compounds lack essential factors, such as factor V. Moreover, in older literature, caution is advocated with the use of prothrombin complex concentrates in DIC because it may worsen the coagulopathy due to small traces of activated factors in the concentrate. It is, however, not clear whether this is still relevant for the concentrates that are currently in use. Specific deficiencies in coagulation factors, such as fibrinogen, can be corrected by administration of purified coagulation factor concentrates.

Based on the notion that DIC is characterized by extensive activation of coagulation, anticoagulant treatment may be a rationale approach. Experimental studies have shown that heparin can at least partly inhibit the activation of coagulation in DIC (43). A recent large trial in patients with severe sepsis supports a slight (not significant) benefit of low-dose heparin on 28-day mortality and underscored the importance of not stopping heparin in patients with DIC and abnormal coagulation variables (M. Levi, unpublished observations). Theoretically, the most logical anticoagulant agent to use in DIC is directed against tissue factor activity. Phase II trials of recombinant tissue factor pathway inhibitor in patients with sepsis showed promising results, but a phase III trial did not show an overall survival benefit in patients who were treated with tissue factor pathway inhibitor (44, 45).

The use of agents that are capable of restoring the dysfunctional anticoagulant pathways in patients with DIC has been studied relatively intensively. Antithrombin concentrate has been available since the 1980s, and most trials with this compound showed some beneficial effect in terms of improvement of laboratory variables; however, none of the trials demonstrated a significant reduction of mortality. A large-scale, multicenter, randomized, controlled trial to directly address this issue also showed no significant reduction in mortality of septic patients who were treated with antithrombin concentrate (46). Interestingly, the subgroup of patients who had DIC and who did not receive heparin showed a survival benefit, but this finding needs prospective validation (47). Based on the notion that depression of the protein C system may significantly contribute to the pathophysiology of DIC, supplementation of activated protein C might potentially be of benefit. Indeed, in experimental sepsis studies, activated protein C was shown to be effective in reducing mortality and organ failure (26). The clinical efficacy of activated protein C in severe sepsis was demonstrated in a large, randomized, controlled trial (48). Mortality was 24.7% in the activated protein C group as compared with 30.8% in the placebo group (relative risk reduction, 19.4%; 95% confidence interval, 6.6–30.5). A *post hoc* analysis showed that patients with DIC had the highest benefit of activated protein C treatment (4). Later studies confirmed the ability of activated protein C to normalize coagulation activation during severe sepsis (49). Of note, activated protein C seems to be relatively more effective in higher disease severity groups, and a prospective trial in septic patients with relatively low disease severity did not show any benefit of activated protein C (50).

In general, the use of prohemostatic agents in patients with DIC is not recommended because this may theoretically worsen the coagulopathy. There are some reports of the successful use of prohemostatic agents, in particular recombinant factor VIIa, in patients with DIC and life-threatening bleeding, but the efficacy and safety of this treatment in DIC is unknown (51). Interestingly, the administration of factor VIIa seemed not to result in an aggravation of the DIC in these patients (52).

Conclusion

DIC is a syndrome characterized by systemic intravascular activation of coagulation, leading to widespread (micro) vascular deposition of fibrin, thereby contributing to multiple organ dysfunction. The ongoing activation of coagulation may result in exhaustion of platelets and coagulation factors, which may cause bleeding. DIC is invariably seen as a complication of a variety of disorders, most commonly, severe infection or inflammation, cancer, or trauma. A diagnosis of DIC can be made by a combination of routinely available laboratory tests for which diagnostic algorithms have become available. Recent knowledge on important pathogenetic mechanisms that may lead to DIC has resulted in novel supportive therapeutic approaches to patients with DIC. Strategies aimed at the inhibition of coagulation activation may theoretically be justified and are being evaluated in clinical studies. These strategies comprise anticoagulant agents or agents that may restore physiologic anticoagulant pathways.

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