Disseminated intravascular coagulation and coagulation disorders

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Purpose of review
An update on recent developments in diagnosis and treatment of disseminated intravascular coagulation.

Recent findings
Disseminated intravascular coagulation is defined as a typical disease condition with laboratory findings indicating massive coagulation activation and reduction in procoagulant capacity. Clinical syndromes associated with the condition are consumption coagulopathy, sepsis-induced purpura fulminans, and viral hemorrhagic fevers. Consumption coagulopathy is observed in patients with sepsis, aortic aneurysms, acute promyelocytic leukemia, and other disseminated malignancies. Sepsis-induced purpura fulminans is characterized by microvascular occlusion causing hemorrhagic necrosis of the skin and organ failure. Viral hemorrhagic fevers result in massively increased tissue factor production in monocytes and macrophages, inducing microvascular thrombosis and consumption of platelets and coagulation factors. Current scoring systems do not distinguish between patients with asymptomatic disseminated intravascular coagulation, consumption coagulopathy and thrombotic syndromes. Patients with sepsis may be identified by activated partial thromboplastin time waveform analysis performed as part of routine coagulation testing. Drotrecogin α (activated) reduces mortality in patients with severe sepsis with and without disseminated intravascular coagulation and has been used in patients with sepsis-induced purpura fulminans. Tifacogin does not reduce mortality in severe sepsis associated with impaired coagulation. Patients with heterozygous factor V Leiden mutation and severe sepsis showed a lower 28-day mortality than patients without this mutation, supporting the assumption that an enhanced level of coagulation activation may be beneficial in patients with severe sepsis.

Summary
Whereas antithrombin and tifacogin failed to improve clinical outcome in severe sepsis, drotrecogin α (activated) increased the chances of survival of patients with severe sepsis with and without disseminated intravascular coagulation.

Keywords
disseminated intravascular coagulation, sepsis, drotrecogin α (activated), tifacogin, acute promyelocytic leukemia, aortic aneurysm

Abbreviations
aPTT activated partial thromboplastin time
DAA drotrecogin α (activated)
DIC disseminated intravascular coagulation
FRM fibrin-related marker
ISTH International Society for Thrombosis and Hemostasis

Introduction
The diagnosis of disseminated intravascular coagulation (DIC) is based on the combination of a disease condition with laboratory findings indicating massive coagulation activation and reduction in procoagulant capacity (Table 1). Current scoring systems include elevated fibrin-related markers (FRMs), prolonged prothrombin time, low platelet count, and low fibrinogen level. Additional indicators of DIC are low levels of coagulation inhibitors such as antithrombin or protein C, and other indicators of coagulation activation, such as thrombin–antithrombin complexes and prothrombin fragment F1.2. Most investigators use D-dimer antigen or fibrin degradation product assays as FRMs, but assays for soluble fibrin may also be employed [1].

Two scoring systems have been suggested for the diagnosis of overt DIC: the system of the Japanese Ministry of Health and Welfare [2], and the system of the International Society for Thrombosis and Hemostasis (ISTH) [3]. Wada et al. [4] compared the results of the scoring systems in a group of 1284 Japanese patients with DIC and found an agreement of 67.4% for the diagnosis of overt DIC. Wada et al. [5**] identified one problem with the scores: both scoring systems use low fibrinogen levels as an indicator of DIC, although high rather than low fibrinogen levels are associated with poor clinical outcome. Despite this limitation, the diagnosis of overt DIC has a prognostic value in patients with sepsis and other clinical conditions. According to the study of Gogos et al. [6] the diagnosis of overt DIC in patients with sepsis is associated with a mortality of 62%, whereas the mortality of patients with sepsis without overt DIC is 28%.

Consumption coagulopathy is an acquired bleeding disorder observed in patients with sepsis as well as in a variety of other diagnoses, ascribed to the consumption of procoagulant factors and platelets in the course of coagulation activation. The coagulation process may be
Table 1. Definitions of procoagulant conditions observed in sepsis

<table>
<thead>
<tr>
<th>Overt DIC</th>
<th>Consumption coagulopathy</th>
<th>Purpura fulminans</th>
</tr>
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<tbody>
<tr>
<td>Clinical condition which may be associated with DIC</td>
<td>Laboratory criteria of overt DIC</td>
<td>Bacterial or viral infection which may be associated with development of purpura fulminans</td>
</tr>
<tr>
<td>High FRM</td>
<td>Bleeding</td>
<td>(meningococcal or pneumococcal infections, hemophilus, others)</td>
</tr>
<tr>
<td>Prothrombin time prolongation/ increased INR</td>
<td>Low protein C</td>
<td>High FRM</td>
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<tr>
<td>Decreased platelet count</td>
<td>Microvascular</td>
<td></td>
</tr>
<tr>
<td>Decreased fibrinogen level</td>
<td>Thrombosis (skin, organs)</td>
<td></td>
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<tr>
<td></td>
<td>Tissue necrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bleeding</td>
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DIC, disseminated intravascular coagulation; FRM, fibrin-related marker.

localized such as in vascular malformations or aneurysms, or nonlocalized as in sepsis or disseminated malignant disease. Purpura fulminans is found in the context of meningococcal [7], pneumococcal [8], and other bacterial or viral infections [9–11]. Fibrin deposits can be detected in the microvasculature of the skin and various organs [12]. Patients with consumption coagulopathy and purpura fulminans comprise a subgroup of patients with overt DIC. The current version of the ISTH DIC score does not differentiate between patients with asymptomatic DIC and patients with consumption coagulopathy or purpura fulminans. The Japanese Ministry of Health and Welfare DIC score includes bleeding as one parameter, but evidence of microvascular thrombosis or tissue necrosis is not considered.

Treatment with anticoagulant drugs has been proposed for various conditions associated with DIC, especially severe sepsis. Three anticoagulant drugs have been tested in large multicenter, randomized, placebo-controlled phase III trials: plasma-derived antithrombin, recombinant activated protein C (drotrecogin α (activated) or DAA), and recombinant tissue pathway factor inhibitor (tifacogin). The results for antithrombin and DAA were published in 2001, the results of the tifacogin trial in 2003. For DAA, subgroup analyses published in 2003 have revealed interesting information concerning patients with factor V Leiden mutation and patients with DIC. Protein C replacement has been proposed for treatment of patients with sepsis-induced purpura fulminans, but in view of the impaired protein C activation in sepsis, treatment with activated protein C might be more effective. Massive release of tissue factor has been shown to cause DIC in primate models of viral hemorrhagic fevers. This may be the basis for development of therapeutic strategies in these diseases. Finally, it has been shown that patients with DIC frequently display an abnormality of the optical tracing of the clotting process during measurement of activated partial thromboplastin time (aPTT). According to recent results this clotting waveform abnormality is related to the presence of sepsis rather than to DIC.

**Tifacogin**

Tifacogin is a recombinant tissue factor pathway inhibitor and was developed as a potential treatment for sepsis. A phase II trial of the drug in 210 patients with severe sepsis showed a 20% reduction in 28-day all-cause mortality. The effect was most prominent in patients with an International normalized ratio (INR) in prothrombin time (PT) greater than 1.2 [13]. The elevated INR may be interpreted as a sign of disseminated intravascular coagulation activation, leading to reduced levels of factor VII and possibly factors II, V, X, and fibrinogen. Based on these data, a phase III trial, the OPTIMIST trial (Optimized phase 3 Tifacogin in multicenter international sepsis trial), was performed, including 1754 patients with severe sepsis and an INR of at least 1.2 [14**]. Patients were randomly assigned to an intravenous infusion of 0.025 mg/kg per hour of tifacogin or placebo for 96 h. The overall mortality at 28 days was 34.2% for the tifacogin-treated group and 33.9% for the placebo group (P = 0.88). Interestingly, the mortality was 29.1% for the tifacogin-treated group and 38.9% for the placebo group at the first interim analysis after inclusion of 722 patients (P = 0.006), but this effect was not sustained during the further course of the study. Despite the effect on coagulation activation (reduced levels of thrombin–antithrombin complexes and other markers of coagulation activation in plasma from patients treated with tifacogin), treatment with tifacogin did not result in increased survival in patients with severe sepsis. It is possible that tifacogin is effective in subgroups of patients with DIC not identified by current classifications, such as patients with sepsis-induced purpura fulminans or viral hemorrhagic fevers, but further clinical studies are needed.

In the group of patients treated with tifacogin, mortality was similar whether patients received concomitant low-dose heparin or not (34.6% versus 34.0%). In the placebo group, patients who received low-dose heparin had a much lower mortality (29.8% versus 42.7%). A similar finding was made in the KYBERSEPT study (Kybernin in sepsis trial) of plasma-derived antithrombin concentrate in severe sepsis. Patients receiving placebo and low-dose heparin had the lowest mortality (36.6% versus 43.6% for patients without heparin) [15]. In patients treated with high-dose antithrombin concentrate, mortality was 37.6% for patients not treated with heparin, and 39.4% for patients treated with heparin. In both the KYBERSEPT and the OPTIMIST study patients were
not randomized to receive heparin. In the OPTIMIST study, patients who received prophylactic heparin were found to be less severely ill than the corresponding patients who did not receive heparin. Without appropriate randomized studies of heparin in patients with severe sepsis and other conditions associated with DIC, it cannot be decided if patients should or should not receive heparin. Earlier studies have shown a high rate of venous thromboembolism in intensive care patients [16–18]. This may contribute to the adverse outcome of patients receiving neither heparin nor other anticoagulant drugs.

**Drotrecogin α (activated)**

In contrast to antithrombin and tifacogin, treatment with recombinant human activated protein C (DAA) reduced mortality in patients with severe sepsis [19]. The reason may be the combination of profibrinolytic and anti-inflammatory effects of DAA in addition to the anticoagulant effect.

Overt DIC, according to the laboratory criteria of the DIC subcommittee of the ISTH [3], was present in 22% of patients with severe sepsis included in the PROWESS (Protein C worldwide evaluation in severe sepsis) study [20*]. The 28-day mortality was 30.5% in patients with overt DIC treated with DAA and 43.0% in patients with overt DIC given placebo. A small number of patients with heterozygous factor V Leiden mutation had been included in the study, although earlier deep venous thrombosis or known APC (activated protein C) resistance were exclusion criteria. Interestingly the mortality of patients with heterozygous factor V Leiden mutation was considerably lower (12.1% in patients treated with DAA, 15.6% in patients given placebo) than mortality of patients without the factor V Leiden mutation (24.1% in patients treated with DAA, 31.0% in patients given placebo) [21**]. The higher level of coagulation activation in patients with heterozygous factor V Leiden mutation appears to be beneficial in sepsis, supporting the assumption that ‘latent coagulation’ or nonovert DIC is part of the defense system against sepsis. Fibrin binds active thrombin, thereby modulating in-vivo thrombin activity [22**]. Fibrin is necessary for effective activation of plasminogen by tissue plasminogen activator [23]. Thrombin modulates various cellular reactions by activation of protease-activated receptors and activates protein C. Activated protein C activates protease-activated receptor-1 [24**] and modulates inflammatory processes [25*]. Inhibition of coagulation by treatment with coagulation inhibitors such as heparin, hirudin or antithrombin impairs protein C activation [26*]. Therefore, a certain level of coagulation activation may be beneficial in patients with sepsis or other assaults to the vascular system. There are no published data on sepsis-related mortality of patients with homozygous factor V Leiden mutation, patients with combination defects such as factor V Leiden mutation plus hereditary protein C or protein S deficiency, or patients with heterozygous factor V Leiden mutation and earlier venous thromboembolism. The effect of another common thrombophilia marker, the prothrombin gene G20210A mutation [27], which is also associated with increased in-vivo thrombin formation [28], also needs to be determined.

**Sepsis-induced purpura fulminans**

Infectious purpura fulminans is a syndrome of microvascular thrombosis with hemorrhagic infarction of the skin, extremity loss and multiple organ failure [29]. It mainly occurs in patients with *Neisseria meningitides, Streptococcus pneumoniae*, or *Haemophilus influenzae* infection, although additional hereditary or acquired factors such as elevated levels of plasminogen activator inhibitor-1 may be necessary to initiate the syndrome [30,31]. Sepsis-related purpura fulminans has been observed in patients double heterozygous for factor V Leiden mutation and protein S deficiency [32], and prothrombin G20210A mutation and protein S deficiency [33]. Typically, patients with sepsis-induced purpura fulminans have very low plasma levels of protein C. Protein C replacement with protein C concentrate has therefore been recommended for treatment of such patients. Only a dose of 150 IU/kg body weight or more given every 6 h resulted in significantly increased levels of activated protein C in patients with purpura fulminans, whereas lower doses failed to cause an increase in activated protein C levels [34**]. A dose of 600 IU/kg body weight per day increased plasma protein C levels to 2–3 IU/ml and activated protein C levels to three- to fourfold of baseline [34**]. No effect of protein C concentrate infusion on mortality was found in the phase II dose-finding study [34**]. Plasma exchange may be an alternative source of protein C and other plasma components deficient in purpura fulminans [35].

Protein C activation is impaired in patients with severe sepsis [36,37]. Endothelial thrombomodulin and protein C receptor are reduced, and plasma levels of soluble thrombomodulin shed from the endothelium are increased in patients with sepsis [37]. Lignell *et al.* [38] found a prolonged half-life of protein C in a patient with meningococcal septic shock, indicating low utilization of the proenzyme. It therefore seems logical to use activated protein C in patients with sepsis-induced purpura fulminans. The median level of activated protein C in patients with severe sepsis treated with DAA is 44.9 ng/ml, in contrast to levels lower than 1 ng/ml typically found in patients with severe sepsis not treated with DAA [39*]. Case reports have been published on the use of DAA in meningococcal sepsis [40,41].
Hemorrhagic fevers

A specific type of DIC is observed in viral hemorrhagic fevers. Wills et al. [42] performed a prospective study in 167 Vietnamese children with dengue hemorrhagic fever and found low levels of fibrinogen, protein C, protein S, and antithrombin. Levels of plasminogen activator inhibitor-1 correlated with bleeding severity, indicating a link between microvascular occlusion and clinical symptoms, similar to bacterial sepsis-induced purpura fulminans. Geisbert et al. [43] published results of primate studies of Ebola hemorrhagic fever showing that tissue factor expression and release from Ebola virus-infected monocytes and macrophages is the key factor for the initiation of DIC and intravascular fibrin deposition. In parallel to coagulation activation, plasma levels of activated protein C drop, indicating dysfunctional protein C activation despite elevated levels of thrombin. Hemorrhage in Ebola virus infection is not caused by virus-induced cytolysis of endothelial cells or other mechanisms related to an infection of endothelial cells [44]. Treatment with DAA may also be helpful in patients with Ebola and other hemorrhagic fevers, but no clinical trials or case reports have been published to date. Drugs directly affecting tissue factor-induced coagulation activation such as tifacogin could also be effective.

Abnormal activated partial thromboplastin time waveform analysis

Downey et al. [45,46] described an abnormality of the optical transmission waveform obtained during measurement of the aPTT on a specific photometric hemostasis autoanalyzer, the MDA-180. This abnormality is related to calcium-dependent formation of complexes between very low density lipoprotein and C-reactive protein [47,48], and has been shown to be predictive for DIC [45,46]. The majority of patients with DIC in these studies were intensive care patients diagnosed with sepsis. Toh et al. [49] examined 1187 consecutive patients admitted to an intensive care unit and found an abnormal aPTT waveform in 29.1%. The mortality of patients with abnormal aPTT waveform was 44%, compared with 26% in patients without the aPTT waveform abnormality. Most patients with the aPTT waveform abnormality suffered from sepsis. The results of Toh et al. were confirmed by an investigation of Fernandes and Giles [50] showing a 3-month mortality of 42.6% in patients with an abnormal aPTT waveform. Overt DIC according to the criteria of the ISTH was present in only 10% of patients with abnormal aPTT waveform, but sepsis was diagnosed in 54%. Although most patients with abnormal aPTT waveform have clinical conditions that may be associated with DIC, the abnormal aPTT waveform appears to be an indicator of sepsis rather than coagulation activation. The abnormal aPTT waveform is an indicator for high mortality in intensive care unit patients.

Conclusion

For clinical use as well as clinical studies, the clinical manifestations of DIC need to be considered. Asymptomatic patients without bleeding or microvascular thrombosis fulfilling the laboratory criteria of overt DIC should be distinguished from symptomatic patients with acute hemorrhage or patients with microvascular thrombosis. A certain level of coagulation activation is required for effective activation of plasminogen, the protein C system, and various cellular responses, and may be beneficial in patients with sepsis, as shown by the fact that patients with APC resistance caused by heterozygous factor V Leiden mutation display a considerably lower mortality in severe sepsis. Only DAA has shown an effect on overall mortality of patients with severe sepsis and this effect is present in patients with and without DIC. The aPTT waveform analysis may be helpful in clinical routine for the early identification of patients with sepsis, which may benefit from treatment with DAA.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest
•• of outstanding interest


Original publication of the OPTIMIST Phase III trial of tissue factor in severe sepsis showing no effect on 28-day mortality.


Evaluation of the PROWESS study data concerning DIC and other parameters.


Evaluation of the PROWESS study data showing a survival advantage of patients with heterogeneous factor V Leiden mutation in severe sepsis.


Very informative paper on ‘antithrombin I’, the inhibition of thrombin by adsorption to fibrin.


Important paper for explaining the antiinflammatory activity of activated protein C, showing direct activation of protease-activated receptor 1.


Paper on the antiinflammatory mechanisms induced by treatment with DAA.


Evaluation of the PROWESS study data showing a survival advantage of patients with heterogeneous factor V Leiden mutation in severe sepsis.


Very informative paper on ‘antithrombin I’, the inhibition of thrombin by adsorption to fibrin.


Good clinical characterization the clinical picture of dengue hemorrhagic fever.


Very important animal study on Ebola hemorrhagic fever giving data on the mechanism of coagulation activation and DIC in this rare but frequently lethal disease.


Study showing that the pathomechanism of Ebola hemorrhagic fever is probably not related to endothelial dysfunction or ‘endothelitis’.


Toh CH, Samis J, Downey C, et al. Biphasic transmittance waveform in the aPTT coagulation assay is due to the formation of a Ca(++)-dependent complex of C-reactive protein with very-low-density lipoprotein and is a novel marker of impending disseminated intravascular coagulation. Blood 2002; 100:2522–2529.

Elucidation of the aPTT waveform slope-1 phenomenon in intensive care unit patients.


Clinical data on the predictive value of aPTT waveform analysis, showing that the waveform abnormality is in most cases related to sepsis.