

D-dimer testing in the treatment and monitoring of septic patients

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Sepsis and septic shock lead to local and systemic activation of different response systems, including coagulation and fibrinolysis.

Despite numerous attempts the high mortality rate of these patients has remained stable over the last 20 years.

In this overview the pathophysiological insights and possible implications of measuring D-dimer plasma levels are given. D-dimer as a marker of fibrin generation and degradation reflects the turnover of the coagulation system.

Special regard is given to the diagnosis of disseminated intravascular coagulation (DIC) by the use of scoring systems. The supplement of a DIC score to frequently used scores like APACHE II, SAPS II or others might be an addition in the management of patients with sepsis or trauma.

Therefore suggestions for using the D-dimer levels as a monitoring tool are given.

Sepsis is one of the leading causes of death in intensive care medicine increased nearly 10 % each year during the last 2 decades. Sepsis is an overwhelming primary local infection leading from systemic inflammatory response syndrome (SIRS) to shock and multiple organ failure (MOF) with a mortality rate of 60 %.

The main pillars in the treatment are local clearance, early effective antimicrobial therapy, supporting intensive care and special forms of organ support.

Infection leads to activation of inflammatory processes inevitably involving activation of coagulation.

An overwhelming inflammatory response may lead to organ failure, and the coagulation and fibrinolysis involvement may lead to disseminated intravascular

coagulation (DIC), a pathological activation of coagulation that leads to the formation of small blood clots inside the blood vessels throughout the body.

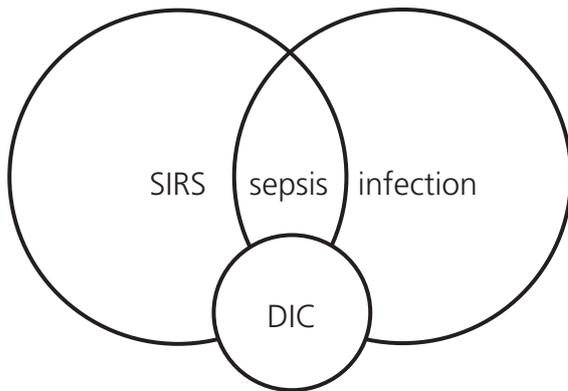


FIGURE 1

A number of interactive systemic factors appear to promote the development of organ failure and cytokine-induced coagulation, and thrombin activates immune cells.

Coagulation activation is almost always present in infections and systemic host response, as indicated by elevated plasma levels of D-dimer, prothrombin fragments and thrombin-antithrombin complexes.

During sepsis, the regulatory mechanisms of blood coagulation are severely disturbed, resulting in fibrin deposition in the microcirculation, which is thought to be the major cause of organ failure.

Multiple studies have suggested that coagulation abnormalities may develop even before the onset of clinical symptoms of severe sepsis or septic shock.

Coagulopathy, as evidenced by the consumption of coagulation factors and suppression of the fibrinolytic system, results in the microvascular fibrin deposition responsible for multiple organ failure in severe sepsis.

Physiology remarks

Formation and dissolution of fibrin are key events in hemostasis. Physiologically, coagulation is initiated by the tissue factor – factor VIIa complex – which promotes

thrombin generation subsequently converting fibrinogen to fibrin monomers. Active factor XIII links the so-called D-domains of fibrin monomers and thereby generates a solid fibrin clot.

Specific degradation of fibrin in monomeric and crosslinked form is achieved by the plasminogen system, which in turn is counterbalanced by inhibitors released by endothelial cells or platelets.

D-dimer, which is present in the degradation products, is not present in fibrinogen or the fibrin monomer. Therefore, plasma levels of D-dimer are specific for the plasmin-catalyzed degradation of the fibrin polymer.

Thereby D-dimer plasma levels specifically reflect the turnover of the coagulation system. Even in healthy subjects D-dimer plasma levels can be detected, indicating a certain level of fibrinogen-fibrin turnover under normal physiological conditions.

A blockade of the plasmatic coagulation by anticoagulants as well as a blockade of fibrinolysis using antifibrinolytics will therefore decrease D-dimer plasma levels.

Septic patient

In septic patients endothelial activation may lead to locally induced coagulation. A large variety of fibrin compounds can be detected in plasma from patients with intravascular coagulation activation.

D-dimer assays predominantly detect high-molecular-weight crosslinked fibrin complexes. Thereby D-dimer might be used as a marker of microcirculatory failure [1]. Almost all patients admitted with sepsis have elevated D-dimer levels very closely related to organ dysfunction and outcome.

In addition, changes of coagulation parameters within the first 2 days have a huge influence on the development of new or resolution of organ dysfunction and consequently on the mortality of septic patients [2].

This may indicate that early therapeutic interventions in

a newly admitted septic patient are the most important ones and that early diagnosis and treatment of coagulopathy are necessary for septic patients.

Patients with trauma

Patients admitted to hospital after trauma generally have elevated D-dimer levels, indicating ongoing coagulation and fibrinolysis. During the course of stay D-dimer levels decline, indicating that there is no longer increased coagulation and fibrinolysis.

Declining D-dimer levels also suggest that the associated DIC is resolving, whereas non-resolving or even increasing D-dimer levels are associated with posttraumatic DIC, complications, multiple organ failure and death [3].

Hypoperfusion during shock or organ failure with ongoing microthrombosis results in hyperfibrinolysis, measurable by increasing levels of D-dimer. Plasma D-dimer levels may even predict poor outcome after acute intracerebral hemorrhage.

Patients with prolonged fibrinolytic response are at risk of major bleeding due to consumption of coagulation factors [4].

Diagnosis of disseminated intravascular coagulation (DIC)

Within established scoring systems for organ dysfunction the presence of coagulation abnormalities or DIC only play minor roles: The most widely used APACHE II score combines surrogate markers of different organ failures with demographic data.

White-blood-cell count, body temperature, blood pressure or heart rate has no relevant influence on D-dimer levels in septic patients although all these parameters are part of the APACHE II score.

Coagulation or disseminated intravascular coagulation is not part of established scoring systems. This ignores the prognostic significance of coagulation activation processes in severely ill patients.

Multiple organ failure always involves coagulation activation, and ongoing DIC leads to purpura fulminans and bleeding due to consumption coagulopathy or microvascular thrombosis.

The combination of different organ dysfunction scoring systems with DIC scores may be a clinically applicable approach [5].

Several diagnostic criteria for disseminated intravascular coagulation (DIC) have been proposed, such as the DIC scoring system of the International Society of Thrombosis and Hemostasis (ISTH) for non-overt and overt DIC [6] or the JAAM DIC score [7, 8].

According to these diagnostic criteria, four widely available parameters should be used: prothrombin time, platelet count, fibrinogen level and a fibrin-related marker. Possible fibrin-related markers are D-dimer plasma levels, fibrin degradation products, or soluble fibrin.

Both the overt and non-overt scoring systems have been prospectively validated, and this demonstrated the overt DIC scoring system to be sufficiently accurate to diagnose DIC in intensive care unit (ICU) patients [9].

It is useful to determine D-dimer plasma levels during the course of sepsis and septic shock: Continuation or worsening of coagulopathy during the first day of severe sepsis was associated with increased development of new organ failure and 28-day mortality.

Successful interventions

Mortality from sepsis correlates with the number of failing organs and the degree of organ dysfunction. Patients without organ failure have a mortality rate of approximately 15 % compared with 70 % for those with three or more failing organs.

Consequently, prevention of new or worsening organ dysfunction is a primary goal in the treatment of patients with severe sepsis. DIC can be seen as a separate organ failure, which might be prevented. Anticoagulation leads to lowering levels of D-dimer in patients with thromboembolic diseases.

It cannot be assumed that this intervention may be simply done in patients with septic DIC: If the coagulation system is already exhausted and bleeding occurs, no further coagulation inhibition seems to be effective.

The frequency of DIC in severe sepsis ranges between 40.7 % in the KyberSept trial (antithrombin) [10] and 22.4 % in the PROWESS study (recombinant activated protein C) [11].

Patients with increasing DIC severity usually have decreasing anticoagulant activities as shown in 257 own patients.

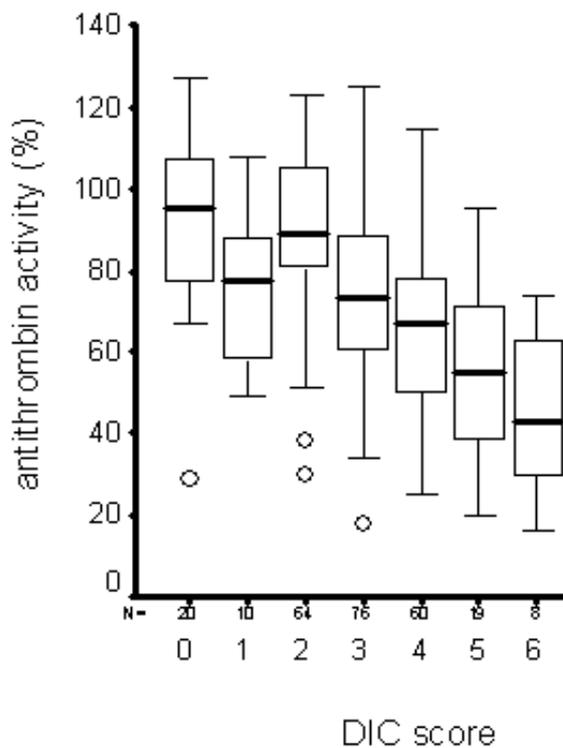


FIGURE 2: Increasing DIC score and antithrombin activity in septic patients

Various studies in patients with DIC clearly showed that a decrease in DIC severity is associated with beneficial outcome, whereas a worsening DIC to overt DIC is associated with organ failure and death.

Therefore early interventions with anticoagulants like heparin, antithrombin, activated protein C or tissue

factor pathway inhibitors might be useful for improving the mortality in patients with DIC.

The most efficient treatment might be achieved in patients at risk before the development of DIC than in the already fully overt DIC patients.

In a newly diagnosed septic patient changes during the first day of treatment had the highest impact on mortality, development and resolution of organ failure.

The activated protein C study in patients with severe sepsis [11] was the first study demonstrating a possible proof of the principle: Intervention in the coagulation pathways clearly leads to a change in D-dimer plasma level.

This was associated with a better outcome. The study was, however, not intended to study patients with severe sepsis and with DIC.

Future

Using scoring systems for both organ dysfunction and DIC may separate patients who will most likely benefit from anticoagulant therapy from those in whom the coagulation must be strengthened.

D-dimer may serve as a parameter to demonstrate high fibrinogen turnover. Especially those patients might benefit the most. This has to be demonstrated.

Combining the composite coagulopathy score with the APACHE II score improved the ability to identify patients who would progress to multiple organ failure [2].

Conclusion

Anticoagulant agents might be useful for improving the mortality in patients with DIC, especially during the early phase of DIC. The initiation of DIC treatment based on the new diagnostic DIC criteria may reduce the mortality rate of patients with DIC.

One major component in the laboratory assessment of DIC is D-dimer, which is suggested to be monitored from day 1 until resolution of septic insult.

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