Commentary

Coagulation in sepsis: all bugs bite equally

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Published online: 10 February 2004 *Critical Care* 2004, **8:**99-100 (DOI 10.1186/cc2816)
This article is online at http://ccforum.com/content/8/2/99

Abstract

Sepsis almost invariably leads to hemostatic abnormalities, ranging from insignificant laboratory changes to severe disseminated intravascular coagulation. There is compelling evidence from clinical and experimental studies that disseminated intravascular coagulation is involved in the pathogenesis of microvascular dysfunction and contributes to organ failure. Data from the PROWESS phase III clinical trial of recombinant activated protein C in patients with severe sepsis confirm this notion and demonstrate that the vast majority of patients with severe sepsis have increased markers for systemic coagulation activation, decreased physiological anticoagulant proteins and depressed fibrinolysis. There is no correlation between the type of microorganism that has caused the infection and the presence or severity of the coagulation disorder.

Keywords anticoagulants, coagulation, fibrinolysis, inflammation, sepsis

In the present issue of *Critical Care*, Kinasewitz and colleagues report on the measurement of various markers of coagulation activation in patients with severe sepsis that were included in the PROWESS trial, the pivotal phase III clinical trial of recombinant activated protein C [1]. Kinasewitz and colleagues underscore the notion that severe infection or sepsis is almost invariably associated with activation of coagulation. This coagulation activation spans a wide spectrum, from a subtle prohemostatic response only detectable with sensitive molecular markers of coagulation activation, to full-blown disseminated intravascular coagulation (DIC). DIC is characterized by simultaneous widespread microvascular thrombosis and profuse bleeding from various sites [2].

How relevant is coagulation for the pathogenesis of sepsis?

There are several lines of evidence supporting an important pathogenetic role of DIC in the development of sepsis-associated organ failure [3]. Histological studies of tissues from septic patients may show diffuse bleeding at various sites, hemorraghic necrosis of tissue, microthrombi in small blood vessels and thrombi in mid-size and larger arteries and veins.

Most experimental animal studies of DIC show fibrin deposition in various organs. For example, experimental bacteremia or endotoxemia causes intravascular and extravascular fibrin deposition in the kidneys, the lungs, the liver, the brain and various other organs. Amelioration of the hemostatic defect by various interventions in these experimental models appears to improve organ failure and, in most cases, to reduce mortality. Finally, clinical studies support the notion of coagulation as an important denominator of clinical outcome.

DIC has been shown to be a strong and independent predictor of mortality in patients with sepsis and severe trauma. Clinical studies aimed at intervening in the coagulation cascade in patients with severe sepsis have recently been completed. In particular, the administration of recombinant human activated protein C has been demonstrated to be effective in reducing 28-day mortality [4].

DIC = disseminated intravascular coagulation.

The fact that other interventions such as antithrombin concentrate or recombinant tissue factor pathway inhibitor were less successful [5,6], however, may suggest that the beneficial effect of recombinant activated protein C may also rely on factors beyond coagulation. In fact, a marked interplay between coagulation and inflammatory activation at the level of the protein C system exists, and activated protein C has been shown to affect inflammation *in vitro* and in several *in vivo* models [7]. On the contrary, the optimal clinical effect of activated protein C was calibrated using a coagulation parameter (i.e. D-dimer), and patients with overt DIC (according to newly developed international criteria) have a relatively larger benefit of activated protein C treatment [8,9]. Taken together, coagulation (in conjunction with inflammation) may well be at the basis of the pathogenesis of severe sepsis.

Coagulation and inflammation biomarkers in patients with severe sepsis

Kinasewitz and colleagues, in the present issue of *Critical Care*, show plasma levels of several biomarkers of coagulation activation, anticoagulant pathways, fibrinolysis, inflammation and endothelial cell injury in patients with severe sepsis [1]. They indeed show that virtually all patients had activated coagulation, as reflected by increased levels of D-dimer and the thrombin–antithrombin complexes. In addition, the vast majority of these patients had coagulation activation that was detectable with less sensitive and more routinely available coagulation assays, such as the prothrombin time, and by measurement of antithrombin and protein C. Also, a depression of fibrinolytic activity was noted in about 50% of patients. The changes in coagulation parameters were strongly related to inflammatory activity and to markers of endothelial cell injury. The data confirm previous studies that nonsurviving patients have a more marked activation of inflammation and coagulation, and a more severely depressed anticoagulant defense.

Causative microorganism and coagulation activation

Most textbooks state that severe activation of coagulation or DIC is most commonly associated with infection with Gram-negative bacteria. However, systematic surveys show that Gram-positive bacteria may cause fulminant coagulation activation as often as do Gram-negative bacteria [10]. Other microorganisms, including viruses and parasites (such as malaria), may also cause DIC, which can dominate the clinical picture or at least play a significant role in the pathogenesis of the severe infection [11,12]. The report by Kinasewitz and colleagues also indicates that activation of coagulation in patients with severe sepsis occurs regardless of the causative microorganism. The only exception in the article by Kinasewitz and colleagues may be represented by the patients with a fungal infection. However, when corrected for disease severity, it is probable that this group would be comparable with patients with bacterial infections.

It is known that specific microorganisms may have a specific impact on the coagulation system. Viruses, such as cytomegalovirus, may cause microangiopathic thrombosis and vasculitis on top of their ability to cause activation of coagulation [3]. Gram-positive bacteria, such as certain strains of Streptococcus pyogenes, may cause a marked activation of the contact system [13]. A significant difference in the ability to induce inflammatory and coagulation activation between endotoxin preparations of various microorganisms was also noted [14]. Nevertheless, in a mixed group of patients with severe sepsis, as was admitted to the PROWESS study, in which more than 20 different causative microorganisms were isolated, no major differences in biomarkers reflecting activation of coagulation and of inflammation between groups of microorganisms were observed. This result seems to support the hypothesis that the intensity of the inflammatory or coagulation response is dependent on other factors, such as host-dependent circumstances or the site of the infection, rather than on the causative microorganism [15].

In conclusion, activation of coagulation, impairment of physiological anticoagulant pathways and depression of fibrinolysis, along with inflammatory activation, are seen in the vast majority of patients with severe sepsis. The severity of the inflammatory coagulative response does not seem to have a relationship with the causative microorganism. This once again underscores the notion that the host response rather than the underlying infection is responsible for the clinical manifestation of severe sepsis.

Competing interests

None declared.

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