The Coagulopathy of Sepsis: Pathophysiology and Management

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Abstract

Sepsis is an infection-induced inflammatory syndrome that results in a complex network of adaptive and maladaptive alterations in homeostatic mechanisms. Severe sepsis, defined as sepsis associated with acute organ failure, is a serious disease with a mortality rate of 30–50%. The coagulation system, through complex interactions, has an important role in the final outcome of the sepsis-induced inflammatory cascade. A fine and delicate balance that normally exists between anticoagulant mechanisms and the procoagulant response is altered in sepsis. Activated protein C, an endogenous vitamin K-dependent anticoagulant, plays a major role in the down-regulation of the procoagulant arm. It also possesses anti-inflammatory properties. Endothelial damage during sepsis impairs the endothelium-dependent activation of protein C, thus shifting the balance towards thrombosis. This shift may contribute to the development of sepsis-related multi-organ failure. Evidence suggesting that activation of the coagulation system may contribute to sepsis-related morbidity and mortality has led to extensive research attempting to correct the hemostatic defects seen in septic patients. Indeed, a recent randomized controlled trial demonstrated a reduction in overall mortality in patients with severe sepsis treated with APC. In this review we discuss the pathogenesis of the coagulopathy of sepsis, as well as the new therapeutic approaches aimed at correcting the defects in the coagulation system.

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Sepsis is a series of inflammatory and hemostatic alterations that occur in response to systemic infection. Severe sepsis is defined as sepsis associated with acute organ failure. Despite advances in critical care, the rate of death from severe sepsis still ranges from 30 to 50% [1]. In the United States, approximately 750,000 cases of sepsis occur each year, 225,000 of which are fatal [2].

Normally the coagulation system comprises two major arms – the procoagulant arm responsible for the initiation of coagulation and maintenance of normal hemostasis, and the balancing anticoagulant arm that down-regulates the procoagulant arm and prevents widespread thrombosis.

Different cytokines such as interleukin-1 and 6 and tumor necrosis factor-alpha can activate the procoagulant arm, contributing to thrombosis in various vascular beds [3]. Endothelial injury and dysfunction during sepsis further reduce natural anticoagulant mechanisms [4]. These two effects shift the hemostatic balance towards coagulation, resulting in thrombin generation and fibrin deposition. The end-result may be diffuse endovascular injury and thrombosis, contributing to multiorgan dysfunction, and death.

APC = activated protein C

Activated protein C plays an important role in the down-regulation of the procoagulant arm. Endothelial injury during sepsis impairs the endothelium-dependent activation of protein C, shifting the balance towards thrombosis [5]. It follows that interventions that aim to restore the delicate balance of the coagulation system and its interactions with sepsis-induced inflammatory cascade may have beneficial effects.

Physiologic procoagulant and anticoagulant pathways

The procoagulant arm

Reviewing the coagulation pathway is beyond the scope of this article. The classical coagulation cascade is depicted in Figure 1. Certain clinical observations that cannot be accounted for by the classical coagulation pathway have led to a revision of the classic coagulation theory. With regard to the revised coagulation theory, clinical evidence shows that factor XII-deficient individuals are phenotypically normal, questioning the importance of the intrinsic pathway in mediating *in vivo* hemostasis [6]. On the other hand, congenital deficiencies of factor VIII (hemophilia A) and IX (hemophilia B) are associated with an increased risk of spontaneous deep tissue bleeding, illustrating that the extrinsic pathway alone could not account for all clinical observations [7].
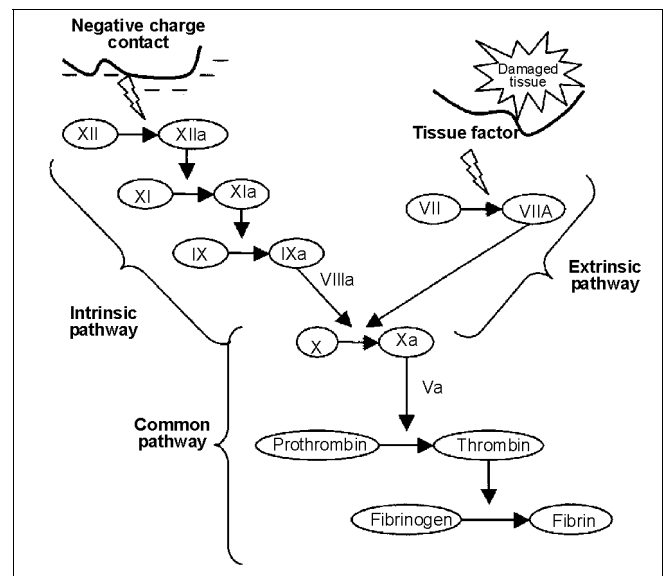

Figure 1. The coagulation pathway is described classically as a cascade of proteolytic enzymatic reactions, resulting in the formation of fibrin via the limited cleavage of fibrinogen, a process mediated by the serine protease thrombin.

In view of these observations, a revised model of hemostasis was developed that emphasizes the role of different cell surfaces in the localization and control of the coagulation process, rather than a process controlled by the levels and kinetics of the different coagulation proteins. This model, described in Figure 2, views hemostasis as a process involving three overlapping phases.

- *Initiation* – takes place on tissue factor-bearing cells. Once a sufficiently strong procoagulant stimulus is generated, enough factors Xa, IXa and thrombin are formed to initiate the coagulation process.
- *Amplification* – as platelets adhere to the initiation site, they become activated and accumulate co-factors on their surfaces amplifying the procoagulant stimulus.
- *Propagation* – active proteases combine with their co-factors on the surfaces of activated platelets, and through the generation of a burst of thrombin, propagate the procoagulant process, resulting in fibrin polymerization [8].
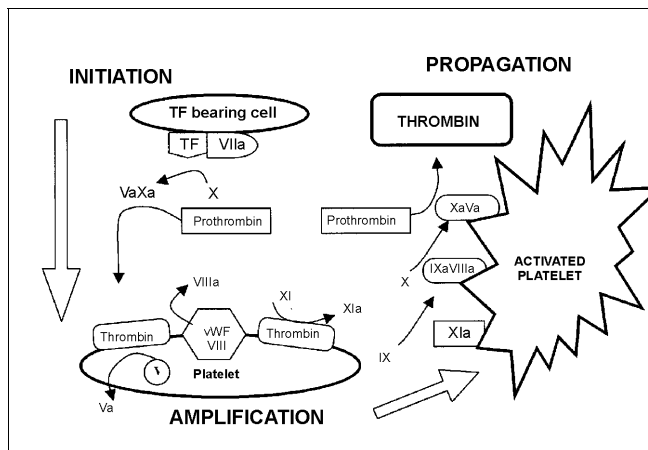
The anticoagulant arm

A series of anticoagulant mechanisms collectively serve to dampen the procoagulant response. These mechanisms are divided into those that do not involve the action of specific proteases, such as blood flow and non-activated cell surfaces, and those that do. These mechanisms are depicted in Figure 3.

The importance of these anticoagulant pathways is supported by clinical and experimental observation. Patients with congenital deficiencies in one or more of these pathways are at increased risk for thrombosis [13].

The coagulopathy of sepsis

Extensive data have been gathered over the years from post-mortem examination of patients with sepsis-related disseminated intravascular coagulation [14]. These findings include diffuse bleeding at various sites, hemorrhagic necrosis of tissue, micro-thrombi in small vessels and thrombi in middle-sized and large arteries and veins [15]. Several studies provide evidence that diffuse fibrin deposition contributes to the multiorgan failure of sepsis. The presence of these intravascular thrombi appears to be related to organ dysfunction. Animal models of sepsis show fibrin deposition in several organs. The amelioration of the hemostatic defect by various measures seems to improve organ function and in some cases reduces mortality [16]. Finally, DIC has been shown to be an independent predictor of mortality in patients with severe sepsis [17].

Coagulation initiation in sepsis

In experimental models, thrombin generation is detectable a few hours after infusion of microorganisms or endotoxin [18,19]. The extrinsic arm of the coagulation system, TF and factor VIIa seem to play a pivotal role in the initiating process. Monoclonal antibodies directed against TF or factor VIIa prevented thrombin generation, DIC and mortality in baboons infused with *Escherichia coli* and in
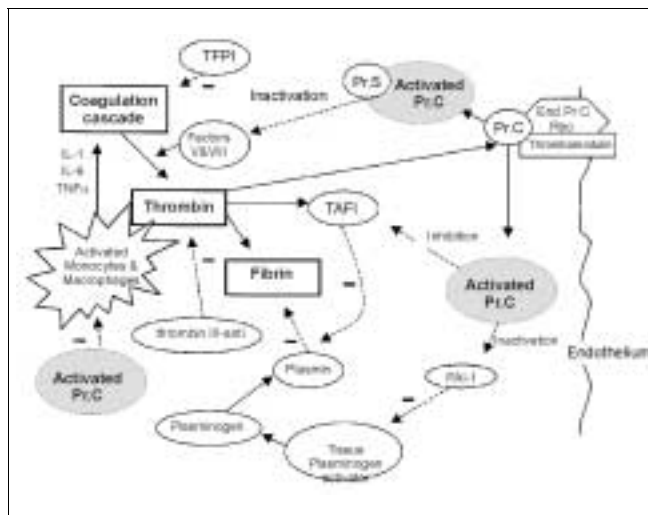
DIC = disseminated intravascular coagulation
TF = tissue factor

Figure 2. The revised cell-based model of coagulation. Coagulation occurs on different cell surfaces in three overlaping phases. *Initiation* – extravascular tissue cells bearing TF are exposed to plasma. Factor VII is activated. The TF-VIIa complex activates factors IX and X. Factor Xa can activate factor V. The complex XaVa can produce small amounts of thrombin. *Amplification* – platelets bind to the extracelular matrix and are partialy activated. Thrombin, generated in the initiation phase, binds to platelets enhancing both their binding to matrix and activation. It also activates factors V, VIII and XI . *Propagation* – on the surface of activated platelets the complex "tenase" is formed (IXa-VIIIa), which activates factor X and in conjunction with Va forms "prothrombinase," turning large quantities of prothrombin into thrombin, and a fibrin clot is formed [8,9].

Figure 3. Anticoagulant mechanisms down-regulating the procoagulant response. Tissue plasminogen activator (tPA) activates plasminogen into plasmin, which lyses fibrin. Plasminogen activator inhibitor 1 (PAI-1) inhibits the activation of plasminogen and fibrinolysis. Antithrombin III-heparan sulfate mechanism inhibits the serine proteases of the clotting cascade other than protein C, including thrombin [10]. Thrombin binds to its endothelial receptor, thrombomodulin, and activates protein C to activated protein C (APC) > 1,000-fold more than thrombin alone. In large vessels, the endothelial protein C receptor (EPCR) can bind protein C and further augment its activation by the thrombin-thrombomodulin complex [5]. APC inhibits thrombin generation through inactivation of factors Va and VIIIa [11]. APC also inhibits thrombin activatable fibrinolysis inhibitor (TAFI). Tissue factor pathway inhibitor (TFPI) is a lipoprotein-associated plasma protein that inhibits tissue factor-mediated initiation of coagulation by forming a quaternary structure with TF, factor VIIa and factor Xa [12]. Activated protein C also inhibits cytokine release and is anti-inflamatory [3].

endotoxin-challenged chimpanzees [20]. In humans with severe sepsis and DIC, mononuclear cells expressing enhanced levels of TF have been demonstrated [21]. TF has been detected on micro-vesicles derived from monocytes and platelets in patients with DIC due to meningococcal septicemia [22].

Sepsis, endothelial cell dysfunction and coagulation

Endothelial cells play an active role in coagulation modulation. Their outer membrane normally expresses various membrane-associated components with anticoagulant properties such as cell surface heparin-like molecules. These molecules accelerate inactivation of coagulation proteases by antithrombin III and, by binding the tissue factor pathway inhibitor, represent a TFPI reserve [23]. The thrombin-binding protein thrombomodulin is responsible for thrombin activity inhibition, and the thrombin-thrombomodulin complex is a potent protein C activator. During sepsis, TF procoagulant activity increases with a transcriptional up-regulation of its expression on monocytes and endothelial cells. In contrast, endothelial membrane anticoagulant components decrease with internalization of thrombomodulin and concomitant release of inactive thrombomodulin into the bloodstream [24]. High plasma levels of thrombomodulin have been observed in patients with septic shock and are associated with the development of multi-organ failure [25]. Circulating plasma thrombomodulin is therefore a marker for endothelial damage in sepsis.

Anatomic damage to the endothelium has been assessed in several studies [4,26]. Pro-inflammatory cytokines, including TNFα, IL-1 and IL-6, increase permeability of endothelial cells [27]. Endothelial physical disruption could also allow inflammatory fluid and cells to shift from the blood into the interstitial space. In a model of endotoxemic rats, researchers observed endothelial cell detachment associated with an increase in cell replication [4]. In a different study in which *E. coli* lipopolysaccharide was given to rats and rabbits, endothelial cellular injury was apparent as early as 15 minutes after LPS injection, as evidenced by nuclear vacuolization, cytoplasmic swelling protrusion and fragmentation, and various degrees of endothelial detachment from its underlying layer [28].

Dysfunction of endothelial protein C activation in sepsis

Protein C is a vitamin K-dependent glycoprotein that circulates in the plasma as an inactive zymogen. Once activated, protein C requires binding of protein S as a co-factor for its anticoagulant functions.

Thrombin binds to its endothelial receptor, thrombomodulin, and activates protein C to activated protein C >1,000-fold more than thrombin alone. In large vessels, the endothelial protein C receptor can bind protein C and further augment its activation by the thrombin-thrombomodulin complex [5]. APC inhibits thrombin generation through inactivation of factor Va and VIIIa. *In vitro* studies indicate that APC also inhibits pro-inflammatory cytokine

production and limits neutrophil and monocyte adhesion to injured endothelium [3]. A recent study assessed the expression of thrombomodulin and EPCR in dermal microvasculature of children with severe meningococcemia and purpuric or petechial lesions. A marked reduction in the expression of thrombomodulin and EPCR on the endothelium of both thrombosed and non-thrombosed dermal vessels was found in children with early meningococcal disease. The plasma levels of APC were low or undetectable in children with meningococcal sepsis. Levels of APC failed to rise after administration of inactivated protein C. Plasma thrombomo-dulin levels were elevated, while thrombomodulin endothelial surface concentration was reduced, leading to the conclusion that thrombomodulin seems to be shed by the endothelium in sepsis [29]. The levels of plasma thrombomodulin in this study also correlated with the severity of the disease. Previous studies have shown that meningococci adhering to vascular endothelium act to up-regulate expression of intercellular adhesion molecules, leading to attachment of neutrophils [30]. Endothelial glycosaminoglycans are cleaved from the endothelial surface by activated neutrophils [30,31]. Thrombomodulin is bound to cell surface by glycosami-noglycans (chondroitin sulfate) and disruption of these molecules can lead to shedding and dysfunction of this protein [32].

Therapeutic strategies

The evidence that systemic activation of the coagulation system may contribute to sepsis-related morbidity and mortality led to the development of therapeutic modalities aiming at the correction of these coagulation abnormalities.

Animal studies have shown that heparin can, at least partly, inhibit the activation of coagulation in sepsis and other causes of DIC [33]. However a beneficial effect of heparin on the clinical outcome in patients with DIC has never been demonstrated in controlled clinical trials [34].

TFPI is the physiologic inhibitor of the TF pathway. Studies evaluating the ability of recombinant TFPI to block endotoxin-induced thrombin generation have shown promising results [35]. A novel approach involves a trial of rNAPc2, an anticoagulant protein derived from bloodsucking (hematophagous) hookworms. It is a potent specific inhibitor of the complex TF + factor VIIa + factor Xa. At present it is being investigated in phase II/III clinical studies [35].

Antithrombin III is one of the most important physiologic inhibitors of coagulation. Antithrombin III levels decrease pre-cipitously in the early phases of severe sepsis, and rapid depletion of antithrombin III in septic shock is associated with an unfavorable prognosis [36]. Six controlled clinical trials have been published evaluating the use of antithrombin III concentrates in patients with DIC [37]. All trials have shown some beneficial effect, such as improvement in laboratory parameters, reduced duration of DIC and even an improvement in organ function. Some antithrombin III trials have even shown a modest reduction in mortality, but this effect never reached statistical significance. A recent meta-analysis assessing the effect of antithrombin III therapy suggested a statistically significant mortality reduction (from 47 to 32%) [37].

TFPI = tissue factor pathway inhibitor
TNFα = tumor necrosis factor-alpha
IL = interleukin
LPS = lipopolysaccharide

EPCR = endothelial protein C receptor

In a recently completed large-scale, multicentered, randomized controlled trial assessing mortality, high dose antithrombin III therapy had no effect on 28 day all-cause mortality in adult patients with severe sepsis and septic shock when administered within 6 hours after the onset of sepsis. High dose antithrombin III was associated with an increased risk of hemorrhage when administered with heparin [38].

Reduced levels of protein C are found in the majority of patients with sepsis and are associated with an increased risk of death [14,36]. It was postulated that administration of APC, with its anti-inflammatory and anticoagulant properties, could improve the coagulopathy and outcome of severe sepsis. Indeed, administration of APC was protective in a baboon model of lethal *E. coli* sepsis [39].

A randomized, double-blind, placebo-controlled, multicenter trial, conducted by the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group, assessed the efficacy and safety of recombinant human APC therapy for severe sepsis [40]. In this study 1,690 patients with severe sepsis (mean APACHE II score = 25) received the study drug or placebo (continuous i.v. drip) for 96 hours and were followed for 28 days. The primary efficacy endpoint was death from any cause, up to 28 days after initiation of therapy. A significant reduction in all-cause mortality was found, 24.7% (210 of 850) in patients treated with APC vs. 30.8% (259 of 840) in the placebo group, reflecting an absolute risk reduction of 6.1%. Of note is the fact that the greatest survival benefit was observed in the sickest patients, i.e., APACHE II score greater than 25. Plasma protein C activity (assessed in 1,574 patients) was reduced in 87.6% (placebo and study groups combined), with a median activity of 50% (normal range is 81–173%). Median pretreatment levels of plasma IL-6 (inflammation marker) and D-dimer (hypercoagulability marker) were significantly elevated. After protein C infusion, plasma D-dimer levels were significantly lower in patients in the study group than in patients in the placebo group on days 1 through 7. The decrease in serum IL-6 levels was significantly greater in patients treated with APC on day 1 of infusion and days 4 through 7. The safety of the treatment was also assessed. While the incidence of serious adverse events remained the same in the two groups, and was around 12%, there was a higher incidence of serious bleeding events in the study group, 3.5% vs. 2% (*P* = 0.06). This difference was observed during the infusion period only. Bleeding was observed mainly in those with a predisposition to bleeding, such as gastrointestinal ulceration, an elevated partial thromboplastin time, thrombocytopenia, and traumatic damage to highly vascular organs or traumatic damage of a blood vessel. Blood transfusion requirements were the same in both groups, as was the incidence of thrombotic events. It was concluded that treatment with recombinant human APC-replete anticoagulant mechanisms improved sepsis-induced coagulopathy and survival. Anti-inflammatory mechanisms may also play a role in this effect, as suggested by the reduction in IL-6 levels [40].

Summary

Sepsis-induced coagulopathy plays an important role in the pathophysiology of sepsis, leading to diffuse fibrin deposition and thrombosis of the microvasculature and contributing to multiorgan failure and death. New therapeutic approaches are currently being developed, aiming at the correction of the coagulopathy. Thus far, only activated protein C has proven beneficial. Despite the convincing results of the PROWESS trial, it should be remembered that in complex situations such as sepsis or septic shock, multiple cellular activation processes are involved and many humoral cascades are triggered, so that merely blocking a single component may be insufficient to arrest the inflammatory process. As this new drug is being introduced, additonal experience will be gathered to better define the exact role of this promising modality in the management of severe sepsis.

Addendum

In the interval between the submission of this paper and its appearance now in *IMAJ*, several studies and special articles addressing the issue of APC in sepsis were published. Long-term follow-up, cost-effectiveness analysis as well as pro-con debates intensified the discussion as to whom exactly and when we should offer this expensive yet potentially lifesaving therapy. It is our view that the final and precise role of APC in the management of severe sepsis has not yet been settled. However, this drug should be considered early in every patient with sepsis-induced organ failure in whom no contraindications are present and prognosis is reasonable.

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