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Review Article

Coagulation and sepsis

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ABSTRACT

Severe sepsis is almost invariably associated with systemic activation of coagulation. There is ample evidence that demonstrates a wide-ranging cross-talk between hemostasis and inflammation, which is probably implicated in the pathogenesis of organ dysfunction in patients with sepsis. Inflammation not only leads to initiation and propagation of coagulation activity, but coagulation also markedly influences inflammation. Molecular mechanisms that play a role in inflammation-induced effects on coagulation have been recognized in much detail. Pro-inflammatory cells and cyto- and chemokines can activate the coagulation system and downregulate crucial physiological anticoagulant mechanisms. Initiation of coagulation activation and consequent thrombin generation is caused by expression of tissue factor on activated monocytes and endothelial cells and is ineffectually offset by tissue factor pathway inhibitor. At the same time, endothelial-associated anticoagulant pathways, in particular the protein C system, is impaired by pro-inflammatory cytokines. Also, fibrin removal is severely obstructed by inactivation of the endogenous fibrinolytic system, mainly as a result of upregulation of its principal inhibitor, plasminogen activator inhibitor type 1 (PAI-1). Increased fibrin generation and impaired break down lead to deposition of (micro)vascular clots, which may contribute to tissue ischemia and ensuing organ dysfunction. The foundation of the management of coagulation in sepsis is the explicit and thorough treatment of the underlying disorder by antibiotic treatment and source control measures. Adjunctive strategies focused at the impairment of coagulation, including anticoagulants and restoration of physiological anticoagulant mechanisms, may supposedly be indicated and have been found advantageous in experimental and initial clinical trials.

Contents

1. Sepsis and coagulation

Sepsis is a very serious and potentially life-threatening complication of infection. Sepsis occurs when host-defense mediators released into the circulation to combat the infection elicit systemic inflammatory responses throughout the body [1]. When the septic response leads to organ dysfunction, the term severe sepsis is used. Sepsis is a frequently occurring medical condition with an incidence of about 2.5 per 1000 in the Western world and an almost 10% annual rise over the last two decades [2]. About 20% of patients with sepsis die within the hospital and severe sepsis leads to mortality rates of approximately 40% [3]. Management of sepsis is aimed at adequate antibiotic therapy, source control,

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and appropriate supportive care and organ function replacement, if needed.

Sepsis is almost invariably associated with coagulation abnormalities. These deviations range from delicate activation of coagulation that can only be identified by highly sensitive assays for coagulation factor activation to somewhat more severe hemostatic activation that may be noticeable by a subtle fall in platelet count and sub-clinical elongation of global clotting assays to fulminant disseminated intravascular coagulation (DIC), manifested by widespread microvascular thrombosis in small and mid-size vessels and simultaneous profuse hemorrhage from various sites [4,5]. Patients with sepsis and extensive forms of DIC may develop overt thrombo-embolic complications or clinically less apparent microvascular clot formation that may contribute to multiple organ failure [5,6]. In other cases, severe hemorrhage may be the dominant presentation [7], and frequently sepsis and DIC leads to simultaneous thrombosis and bleeding. Hemorrhage is due to consumption and subsequent depletion of coagulation factors and platelets, caused by ongoing activation of the hemostatic system [8]. In its most extreme manifestation this combination may present as the Waterhouse-Friderichsen syndrome, typically observed during fulminant meningococcal septicemia, although many other microorganisms may cause this clinical situation as well [9].

2. Frequency of clinically relevant coagulopathy in sepsis

Clinically relevant hemostatic changes may occur in 50 to 70% of septic patients, and approximately 35% of patients will meet the criteria for DIC [1,10]. The vast majority of patients with sepsis will develop thrombocytopenia (platelet count $< 150 \times 10^9$/l) [11,12]. Commonly, platelet count drops in the first four days following admission to the hospital [13]. The severity of sepsis correlates strongly with the decrease in platelet count [14]. Crucial factors that cause thrombocytopenia in sepsis are decreased platelet production, enhanced consumption, obliteration, or sequestration in the spleen. Impaired production of megakaryocytes in the bone marrow may seem incongruous with the high levels of platelet production-stimulating pro-inflammatory mediators, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, and elevated levels of thrombopoietin in patients with sepsis, which theoretically should stimulate megakaryopoiesis [15]. However, in a large number of patients with sepsis substantial hemophagocytosis occurs, consisting of active phagocytosis of platelet precursors and other hematopoietic cells by mononuclear cells, presumably caused by elevated concentrations of macrophage colony stimulating factor (M-CSF) in sepsis [16]. Platelet consumption is presumably also important in sepsis, due to platelet activation secondary to continuous formation of thrombin. Platelet activation, consumption, and destruction takes place at the endothelial surface as a result of the widespread endothelial cell-platelet interaction in sepsis, although the extent may differ between various vascular beds of different organs [17]. Prolonged global coagulation assays (such as the prothrombin time (PT) or the activated partial thromboplastin time (aPTT)) is detectable in 15–30% of septic patients [18]. Other coagulation assay changes include high fibrin degradation products (in >95% of patients with sepsis) [19,20] and low levels of physiological anticoagulants, such as antithrombin and protein C (90% of sepsis patients) [20,21].

3. Pathways leading to coagulation abnormalities in sepsis

In the last three decades the pathways involved in the coagulopathy of sepsis have for an important part been elucidated [4]. It is clear that various mechanisms in the coagulation system act simultaneously towards a prohemostatic state. Apparently the most important factors that mediate this derangement of the coagulation system during sepsis are cytokines. Ample evidence indicates an extensive cross-talk between inflammation and coagulation, where besides inflammation-induced coagulation activation but coagulation also markedly influences inflammatory activity (Fig. 1) [22]. Of note, systemic activation of coagulation and inflammation in sepsis may manifest with organ-specific presentations that are relevant for the specific organ failure resulting from severe sepsis [23].

The most important initiator of thrombin formation in sepsis is tissue factor. Studies of experimental or human endotoxemia or cytokinemia have demonstrated a central role of the tissue factor/factor VIIa system in the initiation of thrombin generation [24]. Abrogation of the tissue factor/factor VII(a) pathway by specific interventions aimed at tissue factor or factor VIIa activity resulted in a complete abrogation of thrombin generation in experimental settings [25,26]. Also, in severe Gram negative sepsis, ex vivo tissue factor expression on monocytes of patients was demonstrated [27]. Experimental low dose endotoxemia in healthy humans resulted in a 125-fold increase in tissue factor mRNA levels in blood monocytes [28]. An alternative source of tissue factor may be its localization on other blood cells [29], although it is not likely that these cells themselves produce tissue factor in substantial quantities [30]. Based on the assessment of transfer of tissue factor from mononuclear cells to activated platelets in an ex vivo perfusion setting, it was postulated that this 'blood borne' tissue factor is shuttled between cells through microparticles [31].

Platelets have a central role in the development of coagulation abnormalities in sepsis. Platelets can be triggered directly by pro-inflammatory mediators, such as platelet activating factor [32]. Generated thrombin will further activate platelets. Activation of platelets may also stimulate fibrin formation by alternative mechanism. The expression of P-selectin on the platelet membrane not only mediates the adherence of platelets to leukocytes and endothelial cells but also enhances the expression of tissue factor on monocytes [33]. The underlying molecular pathway relies on nuclear factor kappa-B (NFκB) expression, induced by binding of activated platelets to neutrophils and monocytes. P-selectin can be shed from the surface of platelets membrane and soluble P-selectin levels are indeed increased during systemic inflammation [33].

In normal circumstances activation of coagulation is controlled by three important physiological anticoagulant pathways: the antithrombin system, the activated protein C system and tissue factor pathway inhibitor (TFPI). In sepsis all three pathways are importantly deranged [34]. Due to a combination of impaired synthesis, ongoing consumption and proteolytic degradation (e.g. by neutrophilic elastase) levels of all three coagulation inhibitors are low. Also, significant downregulation of thrombomodulin and endothelial protein C receptor (EPCR) in inflammatory conditions will cause impaired conversion of protein C to activated protein C. In addition, at the time of the greatest activation of coagulation in sepsis, endogenous fibrinolysis is largely turned off. After the acute release of plasminogen activators (i.e. tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA)) from storage sites in vascular endothelial cells during inflammatory conditions, the increase in plasminogen activation and subsequent plasmin generation, is annihilated by a sustained increase in plasminogen activator inhibitor, type 1 (PAI-1) [35]. Of interest, studies have shown that a functional mutation in the PAI-1 gene, the 4G/5G polymorphism, not only affected the plasma levels of PAI-1, but was also linked to clinical outcome of Gram negative sepsis. Patients with the 4G/4G genotype had significantly higher PAI-1 concentrations and an increased mortality [36]. Other studies showed that the PAI-1 polymorphism increased the risk of developing septic shock from meningococcal infection [37].

4. Inflammation and the coagulopathy of sepsis

Like virtually all systemic inflammatory effects of infection, the derangement of the hemostatic system in sepsis is orchestrated by several cytokines. Most pro-inflammatory cytokines have been demonstrated to initiate coagulation activation in vitro. In sepsis high levels of cytokines can be found in the circulation of affected patients and