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Review Article

Coagulation abnormalities in sepsis

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ABSTRACT

Although the pathophysiology of sepsis has been elucidated with the passage of time, sepsis may be regarded as an uncontrolled inflammatory and procoagulant response to infection. The hemostatic changes in sepsis range from subclinical activation of blood coagulation to acute disseminated intravascular coagulation (DIC). DIC is characterized by widespread microvascular thrombosis, which contributes to multiple organ dysfunction/failure, and subsequent consumption of platelets and coagulation factors, eventually causing bleeding manifestations. The diagnosis of DIC can be made using routinely available laboratory tests, scoring algorithms, and thromboelastography. In this cascade of events, the inhibition of coagulation activation and platelet function is conjectured as a useful tool for attenuating inflammatory response and improving outcomes in sepsis. A number of clinical trials of anticoagulants were performed, but none of them have been recognized as a standard therapy because recombinant activated protein C was withdrawn from the market owing to its insufficient efficacy in a randomized controlled trial. However, these subgroup analyses of activated protein C, antithrombin, and thrombomodulin trials show that overt coagulation activation is strongly associated with the best therapeutic effect of the inhibitor. In addition, antiplatelet drugs, including acetylsalicylic acid, P2Y12 inhibitors, and glycoprotein IIb/IIIa antagonists, may reduce organ failure and mortality in the experimental model of sepsis without a concomitant increased bleeding risk, which should be supported by solid clinical data. For a state-of-the-art treatment of sepsis, the efficacy of anticoagulant and antiplatelet agents needs to be proved in further large-scale prospective, interventional, randomized validation trials.

1. Introduction

Sepsis, defined as infection-induced systemic inflammatory response syndrome (SIRS), is widely recognized as a clinical syndrome that carries significant morbidity and mortality. A large investigation that reviewed national data in the United States from 1979 to 2000 revealed an 8.7% annual increase in incidence of sepsis,[1] despite improvements in the medical field and intensive care setting. In Taiwan, the annual increase in incidence of sepsis was 3.9% from 1997 to 2006, and the incidence of multiple organ dysfunction syndrome (MODS) reached 27.6%, although the mortality rate in hospitals did not change too much, at about 30.8%.[2]

Coagulation abnormalities, particularly a prothrombotic state, frequently occur during sepsis.[3] In severe sepsis, the dysregulation of hemostatic system may lead to disseminated intravascular coagulation (DIC) and result in microvascular thrombosis, hypoperfusion, and ultimately MODS, and death.[4] The activation of coagulation, the downregulation of anticoagulant pathways, and the impairment of fibrinolysis play a crucial role in the pathogenesis of microvascular thrombosis in DIC associated with sepsis.[5,6] However, studies demonstrate that the physical entrapment of bacteria by fibrin induced by infection may limit the bacterial capacity to disseminate into nearby tissues and systemic circulation.[7,8] Thus, therapeutics that control DIC are required for protection against the development of MODS in sepsis, while maintaining the host defense mechanisms.

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This review will outline the coagulation changes associated with sepsis and highlight the potential use of anticoagulation and platelet agents in the treatment of sepsis.

2. Sepsis

In sepsis, an uncontrolled infection results in progressive and dysregulated inflammation, which can lead to SIRS.[9] During SIRS, production of multiple pro- and anti-inflammatory cytokines within the bloodstream are exacerbated.[10] The abnormal production of cytokines contributes to the abundant activation of coagulation factor and platelets as well as damage to vascular endothelial cells, which give rise to vascular leakage and DIC. In addition to ensuring thrombosis generation after activation of the coagulation system, advanced DIC may result in bleeding at the time that platelets and coagulation factors are exhausted.[11] These conditions often result in extensive cross-talk that exists between inflammation and coagulation, with a potential final outcome of MODS and eventual death.[5,12]

3. Coagulation cascades

3.1. Coagulation activation

During sepsis, coagulation activation is ubiquitous and induced by pathogen-associated molecular patterns, such as lipopolysaccharide (LPS) and exotoxins. The coagulation cascade, such as upregulated fibrinogen and factor V, is thought to be mediated by the expression of tissue factor (TF) on monocytes and macrophages,[13] and by the TF-expressing microparticles from platelets, monocytes, and macrophages.[14]

This procoagulant reaction is partially reversed by temporal activation of fibrinolysis attributable to increased expression of endogenous tissue plasminogen activator. And this reaction is rapidly inhibited by an increased synthesis of plasminogen activator inhibitor-1.[15] Thrombin-activatable fibrinolysis inhibitor (TAFI) is also involved in sepsis-associated hypofibrinolysis. In patients with severe sepsis complicated DIC, the levels of TAFI increase, and the enhancement of TAFI activation further accelerate the thrombogenic pathway.[16] In animal models, this univocal sequence induces a procoagulant and antifibrinolytic state in less than 3 hours.[17] In humans, if septic injury is controlled, this hemostatic imbalance diminishes in a few days with a final progressive fibrinolytic stage. However, if the insult is explosive, the hemostatic sequence loses control continuously and induces widespread thrombosis and hemorrhages, recognized as DIC.

3.2. Anticoagulation pathways

Under physiological conditions, the surface of endothelial cells expresses various components of the anticoagulant pathways, which are rapidly and significantly decreased in the sepsis-induced DIC process.[18] This explains why decreased antithrombin (AT), protein C (PC), or tissue factor pathway inhibitor (TFPI) activities are observed in sepsis even if their coagulation appears moderately activated.[19,20] Moreover, a rapid depletion of AT and PC is associated with a poor prognosis.[21,22]

In addition, a rise in soluble plasma thrombomodulin (TM) and endothelial PC receptor was consistently observed, suggesting that damage of endothelial activation by inflammatory mediators does occur *in vivo*.[5,22]

3.3. Network microbial trapping

Following bacterial invasion, extracellular chromatin threads are formed as a fibrin network contributing to the host defense against microbial dissemination. They also enhance platelet adhesion and aggregation, impair TM-dependent PC activation, and thus activate the coagulation process.[23] The activation of coagulation contributes to compartmentalization of bacteria and reduces bacterial invasion.[7,8,24] By contrast, an early inhibition of fibrin formation by recombinant AT or activated protein C (APC) did not modify inflammation, increased pulmonary edema, and exacerbated lung pathologic changes in the rat model of *Pseudomonas aeruginosa*-induced lung injury.[25,26] Therefore, the potential risk induced by coagulation inhibition at the early stage of sepsis should be kept in mind.

4. Organ failure

Contrasting with the determinism of coagulation activation as a host defense mechanism, excessive deregulation of hemostasis is associated with subsequent organ failure and death. Overall, a high DIC score is strongly associated with mortality and, in some studies, stronger than general severity scores.[6] Concerning fibrinolysis, the correlation between the secondary increase in plasminogen activator inhibitor-1 levels and organ failure is supported by numerous studies.[5] Similarly, sequential studies of the natural coagulation inhibitors AT and PC were equally consistent with a correlation between severely decreased plasma levels and death or organ failure.[21,22] Continuous or worsening of decreases in AT and PC activities within the 1st day of severe sepsis was associated with increased development of new organ failure and 28-day mortality,[21,27] suggesting that prolonged and disproportionate coagulation and antifibrinolysis are at least partly contribute to organ failure and death.

5. Diagnosis

The current diagnostic criteria for sepsis include such general variables as hypo- or hyperthermia, tachycardia, tachypnea, hypotension, hyperglycemia, edema, and an altered mental status.[28] In addition, abnormal white blood cell count and elevated plasma levels of C-reactive protein and procalcitonin, can assist in diagnosis.

The original diagnostic criteria for DIC was established by the Japanese Ministry of Health and Welfare in 1983, followed by the overt-DIC diagnostic criteria proposed by the International Society on Thrombosis and Haemostasis in 2001.[29] Then, the Japanese Association for Acute Medicine introduced a new set of criteria, including SIRS score, platelet counts, prothrombin time, and fibrin/fibrinogen degradation products, to help initiate treatment at the appropriate time.[30] Treatment with AT or APC may not improve the outcomes of patients with sepsis at the early stage, although they may improve the outcomes in those with DIC. Thus, new diagnostic criteria for determining the appropriate time to start anticoagulant treatment are required.[31]

Thromboelastography (TEG) might give a reliable assessment of hemostatic status in sepsis.[32,33] Furthermore, TEG variables have been reported to moderately correlate with the severity of organ dysfunction[34] and predict survival in patients with severe sepsis.[35,36] Our previous studies also reported that TEG could be a potential tool to assess the extent of liver injury in endotoxemia[32] and to evaluate the efficacy of pharmacological intervention.[37]

6. Potential treatment in sepsis

The current strategy for handling sepsis-associated DIC primarily focuses on the treatment of infection and use of supplemental clotting factors or platelets depending on the necessity.[38] Dysregulation of the hemostatic system is well known to lead to