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were performed, but none of them have been recognized as a standard therapy because recombinant activated protein C was withdrawn from the market owing to its insufficient efficacy in a randomized controlled trial.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 thrombo-modulin 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.

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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, 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%.

Coagulation abnormalities, particularly a prothrombotic state, frequently occur during sepsis. 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. 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. 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. Thus, therapeutics that control DIC are required for protection against the development of MODS in sepsis, while maintaining the host defense mechanisms.
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. During SIRS, production of multiple pro- and anti-inflammatory cytokines within the bloodstream are exacerbated. 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. These conditions often result in extensive cross-talk that exists between inflammation and coagulation, with a potential final outcome of MODS and eventual death.

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, and by the TF-expressing microparticles from platelets, monocytes, and macrophages. 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. 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. Animal models, this univocal sequence induces a procoagulant and antifibrinolytic state in less than 3 hours. In humans, if septic injury is controlled, this hemostatic imbalance diminishes in a few days with a final progressive fibrinolytic state. 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. 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. Moreover, a rapid depletion of AT and PC is associated with a poor prognosis.

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.

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. The activation of coagulation contributes to compartmentalization of bacteria and reduces bacterial invasion. By contrast, an early inhibition of fibrin generation 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. 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. Concerning fibrinolysis, the correlation between the secondary increase in plasminogen activator inhibitor-1 levels and organ failure is supported by numerous studies. 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. 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, 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. 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. 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. 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.

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

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. Dysregulation of the hemostatic system is well known to lead to
DIC, which results in microvascular thrombosis, hypoperfusion, and subsequent multiple organ failure and death in severe sepsis.

At the same time, a considerable number of experimental and clinical studies demonstrate that natural anticoagulants modulate intracellular signaling, cytokine secretion, cellular or lymphocyte apoptosis, and leukocyte—endothelial interactions.39 This indicates that, in addition to their role as anticoagulants, they also have important functions in modulating inflammation. Therefore, these findings promote the rationalization that the inhibition of the overactivated coagulation cascade by natural anticoagulants or antiplatelet agents could help the resolution of DIC and reduce the mortality of sepsis.

7. Treatment with endogenous anticoagulation agents

7.1. TFPI

TFPI inhibits the activity of TF Factor VII complex and Factor X on prothrombinase complex, thus suppressing the primary steps of thrombin generation.41 In addition, anti-inflammatory effects of TFPI depend on its ability to suppress the inflammatory intracellular signaling of thrombin binding to protease-activated receptor-1.

Several studies evaluating the protective effects of recombinant TFPI (rTFPI, Tifacogin) on sepsis found that rTFPI significantly decreases thrombin generation, but no conclusions have been verified from Phase 1 or 2 clinical trials.40–42 A large-scale randomized controlled trial (RCT), the optimized phase 3 tifacogin in multicenter international sepsis trial (OPTIMIST), showed an absence of any improvement in 28-day mortality in severe sepsis after rTFPI treatment.43 However, exploratory analysis revealed that rTFPI treatment improved survival in patients with severe community-acquired pneumonia not receiving concomitant heparin.42 In addition, the other placebo-controlled Community Acquired Pneumonia Tifacogin Intra Venous Administration Trial for Efficacy (CAPTIVATE) trial was discontinued earlier than planned because no beneficial trend was validated.43

7.2. AT

AT inhibits several serine proteases, including FXa, IXa, Xla, and thrombin. It is a direct 1:1 thrombin inhibitor, leading to thrombin—antithrombin complex formation and subsequent elimination. Furthermore, its activity is maximized after binding with glycosaminoglycans serving as cofactors on the endothelial surface.44

The anti-inflammatory effects of AT inhibit rolling and adhesion of leukocyte activation partly due to the release of prostacyclin45 and the suppression of P-selectin.46 In addition, after binding to heparin sulfate proteoglycan on the endothelial surface, AT harnesses the expression of proinflammatory cytokines.47,48

AT levels are diminished by consumption as a consequence of sustained thrombin generation49 and cytokine-induced down-regulation of endothelial heparin sulfate proteoglycans in sepsis.50 The early administration of high doses of recombinant AT improves the outcome in experimentally induced sepsis probably because of its combined anticoagulation and anti-inflammatory effects.51,52

An observational nationwide study demonstrates that AT administration may be associated with reduced 28-day mortality in patients with severe pneumonia and sepsis-associated DIC.52 In patients with severe sepsis, a maintenance dose of 1500 IU/d of AT has been reported to induce a decrease in mortality accompanied by a considerably shorter stay in the intensive care unit (ICU), and a lower incidence of new organ failure.53 Moderate doses (30 IU/kg/d) of AT improve DIC scores, thereby increasing the recovery rate from DIC without any risk of bleeding in DIC patients with sepsis.52

Unfortunately, high-dose (7500 IU/d) AT therapy had no effect on 28-day all-cause mortality in adult patients with severe sepsis and septic shock in KyberSept trial.54 However, in the Phase 3 KyberSept trial, it was shown that high-dose AT treatment without concomitant heparin may result in a significant mortality reduction in septic patients with DIC.55

Recently, results from a Phase 4 study in patients with septic DIC indicated that higher initial AT activity, AT supplement dose of 3000 IU/d, and younger age were significant factors for improved survival without an increased risk of bleeding.56,57

7.3. APC

PC, a vitamin K-dependent protein, is converted to its activated form (APC) by proteolysis on the thrombin—TM complex. APC inactivates factors Va and Viliia, which effectively limits further thrombin generation. As with thrombin, most of the profibrinolytic actions of APC are mediated through binding of endothelial protein C receptor and inhibition of protease-activated receptor-1.58

In addition to its anticoagulant and profibrinolytic activity, APC has important anti-inflammatory effects: downregulation of proinflammatory cytokines and TF in activated leukocytes, antioxidiant properties, antiapoptotic activity, and endothelial barrier stabilization.59–62 Moreover, APC exerts additional cytoprotective functions through the degradation of histones released in fibrin networks.53

Based on these observations, recombinant APC (rAPC; Drotrecogin alfa) was produced, and the efficacy of this agent was tested in a single large-scale RCT with benefits shown in only one subgroup analysis in 2001.54 Drotrecogin alfa was then heavily promoted in the Surviving Sepsis Campaign guidelines,55 and was initially acclaimed as the most promising therapy in the treatment of sepsis. However, concerns exist regarding its cost-effectiveness and inconsistent results observed in more recent studies.66 Moreover, the production and distribution of rAPC was discontinued in 2011 inasmuch as the Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis and Septic Shock (PROWESS-SHOCK) trial revealed that the 28-day mortality did not have a significant improvement after rAPC treatment in patients with septic shock.57 Nevertheless, its subgroup analysis reveals that the relative risk of death is lower in patients with markedly reduced protein C activity at the time of entry into the study.

However, more than a few investigators may feel dissatisfied with the withdrawal of rAPC on the basis of the results of a single RCT. Casserly et al68 found that the inhospital mortality rate was significantly lower in the rAPC treatment group than in the placebo group after analyzing the Surviving Sepsis Campaign’s database containing 15,022 registered cases. The demonstrated efficacy of rAPC is statistically significant in cases complicated by multiple organ failure, but not in those with only single organ dysfunction. The meta-analysis reported by Kalil and LaRosa69 revealed an 18% reduction of the inhospital mortality following rAPC treatment, although the incidence of severe bleeding rose to 5.6%. The authors concluded that rAPC elevated the risk of bleeding, but nonetheless improved the outcome of severe sepsis.

7.4. TM

TM binds to thrombin and then converts PC to APC, providing a critical negative feedback regulation of thrombin generation.70 Independent of anticoagulation activity, its anti-inflammatory effect is considered through interference with complement activation, neutralization of LPS, and suppression of leukocyte—endothelial interaction.71,72
When compared with heparin therapy, a Phase 3 study reveals that recombinant TM (ART-123) therapy has a more significant improvement in DIC recovery and alleviation of bleeding symptoms in DIC patients with hematologic malignancy or infection. In addition, Phase 2B studies validated the hypothesis that TM downregulated the mediators/markers of thrombin generation in sepsis-associated DIC without increasing the risk of severe hemorrhage. Their subgroup analyses reveal that the survival benefit is greater in patients combined with respiratory or cardiac dysfunction and coagulopathy. According to these results, a Phase 3 study is currently being conducted in the United States among patients suffering from severe sepsis with coagulopathy.

A significant number of hemorrhagic adverse events are observed in the randomized trials testing the above anticoagulants. The frequency of bleeding events in the treatment group is more than 1.7 times higher in the PROWESS APC trial and in the KyberSept AT trial. It is not surprising as anticoagulants efficiently suppress thrombin generation. But at the same time, we have learned that this adverse event often counteracts the beneficial effects of anticoagulants.

More importantly, many randomized trials of TFPI, AT, or APC were designed to include septic patients without any criteria of coagulation activation and regardless of its time sequence. In more severely ill patients, as well as mortality associated with septic shock. Furthermore, patients who are treated with low-dose ASA during their ICU stay have a significantly lower mortality at the time of the development of SIRS and sepsis. However, some studies show that the use of ASA therapy prior to the diagnosis of severe sepsis or septic shock is not associated with decreased hospital mortality.

8.2. P2Y12 inhibitors

Activation of P2Y12 receptors, a chemoreceptor for adenosine diphosphate (ADP), is essential for ADP-mediated complete activation of glycoprotein (GP) IIb/IIIa and la/IIIa, and further stabilizes platelet aggregates. The thienopyridines, including clopidogrel, prasugrel, and ticagrelor, bind to P2Y12 receptors and thereby inhibit platelet activation and aggregation stimulated by ADP. P2Y12 receptors may also be expressed in other cells of the immune system, indicating that thienopyridines could directly influence the immune system rather than only through platelets.

Recent evidence shows that a reduction in LPS-mediated thrombocytopenia, fibrin deposition in the lungs, and inflammatory mediator upregulation occurs in mice pretreated with clopidogrel. Moreover, in mice with polymicrobial sepsis, pretreatment with clopidogrel can attenuate sepsis-associated decrease in the clot formation rate of TEG as a consequence of an effect of clopidogrel on the number of circulating platelets; however, an effect on fibrinogen level remains to be tested.

This finding comes in line with recent data indicating that pretreatment with ticagrelor appears to reduce pulmonary neutrophil recruitment and lung injury in mice with abdominal sepsis. In addition, strong in vivo blockade of P2Y12 with pretreated prasugrel inhibits a broad spectrum of platelet aggregation pathways in human with endotoxemia.

Clinical studies also suggest that P2Y12 inhibitors may be associated with better outcomes in patients with pneumonia and critical illness. Prior treatment with antiplatelet agents, including clopidogrel, is associated with a favorable length of stay and fewer ICU admissions, even though community-acquired pneumonia appears to be more common among patients taking clopidogrel. Later clinical studies also report an association of antiplatelet drug therapy including clopidogrel with favorable outcome in critical illness. However, these results are mainly driven by the large number of patients receiving ASA.

Moreover, in the PLATelet inhibition and patient Outcomes (PLATO) study of patients with acute coronary syndromes, ticagrelor reduced the mortality risk following pulmonary adverse events and sepsis compared to clopidogrel, but the mechanisms for this mortality reduction remain uncertain.

8.3. GP IIb/IIIa antagonists

The platelet GP IIb/IIIa receptor has been identified as the pivotal mediator of platelet aggregation. GP IIb/IIIa antagonists block fibrinogen binding to the GP IIb/IIIa receptor on activated platelets and exert a strong antiplatelet effect by inhibiting the final common step of platelet aggregation.
9. Conclusion

Considerable evidence of activation of coagulation and down-regulation of anticoagulation and fibrinolysis are the predominant features of the proinflammatory condition in sepsis, and contribute to the outcome of the disease. Indeed, in the early stages of sepsis, excessive coagulation develops and stimulates microthrombus formation within small vessels, thereby serving as a factor responsible for the disturbed circulation through organs. Therefore, it would be useful to suppress the interaction of excessive coagulation and inflammation to maintain circulation in the treatment of sepsis.

A number of clinical trials of anticoagulants were performed, but none of them have been recognized as a standard therapy. However, a subgroup analysis of these trials shows that overt coagulation activation is strongly associated with the best therapeutically effective of the inhibitor. In addition, antiplatelet drugs may reduce organ failure and mortality in critically ill patients, whereas uncertain conclusions are extrapolated in the absence of interventional and prospective randomized trials. Therefore, even if the efficacy of anticoagulant and antiplatelet agents is acceptable, there remain many unanswered questions such as when to initiate therapy, and the tendency to underestimate the importance of bleeding. We have to address each of these questions, and the effectiveness needs to be proved in future large-scale prospective validation trials.

References

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