REVIEW ARTICLE

New therapeutic options for patients with sepsis and disseminated intravascular coagulation

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KEY WORDS

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ABSTRACT

The severity of sepsis increases along with the degree of coagulation disorder, and a fulminant coagulation abnormality is recognized as disseminated intravascular coagulation (DIC). The mortality in sepsis-associated DIC remains as high as 40%, which is comparable to that in septic shock. Even though intensive research is ongoing, there is currently no established therapy for this life-threatening complication. Heparins are the oldest, most popular, and least-expensive anticoagulants available; however, their usefulness for the treatment of septic DIC has never been proved. Expectations for antithrombin concentrate were once high, but high-dose antithrombin failed to demonstrate a survival benefit, and global sepsis guidelines no longer recommend its use. Recombinant activated protein C was the only recommended anticoagulant for the treatment of severe sepsis until 2011, but it was subsequently withdrawn from the world market after the failure of the latest clinical trial. Recombinant thrombomodulin is newly developed and has been utilized in Japan since 2008; however, its efficacy has not yet been proved. As shown above, progress has not been as fast as expected, but some new agents are upcoming. The efficacy of anticoagulant therapy for septic DIC has long been discussed and aggressively studied, and we have finally realized that correcting the coagulation disorder is not sufficient to conquer this deadly complication. Since many natural anticoagulants have pleiotropic functions, we need to examine these effects and apply them to the right target at the right timing.

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Introduction The cornerstone for the management of sepsis-associated disseminated intravascular coagulation (DIC) is the management of the underlying infection.[1] No one opposes this fundamental strategy, but the management of sepsis is not always easy in actual clinical situations. As a result, the mortality rate in sepsis remains high. The latest report from the Japanese Association for Acute Medicine (JAAM) revealed that a 28-day mortality rate was 21.7% for cases with severe sepsis, while it increased to 38.4% for cases with severe sepsis and DIC.[2] As a treatment for severe sepsis, physiological anticoagulants with pharmacological doses of activated protein C (APC), antithrombin, and tissue factor pathway inhibitor (TFPI) have been examined, but all of them have failed to demonstrate a survival benefit. However, the effects of these agents on sepsis-associated DIC have not yet been determined. Some subgroup analyses of subjects with sepsis-associated DIC in large-scale randomized controlled trials (RCTs) have demonstrated the effects of anticoagulants on mortality.[3,4] In addition, the physiological doses of natural anticoagulants have been reported to be efficient for the resolution of DIC.[5] Under these circumstances, the "harmonized guidance for DIC" has been released by the International Society on Thrombosis and Haemostasis.[6] In this guidance, the recommendations for each anticoagulant were graded, and unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) were recommended with low-quality evidence, while antithrombin concentrate and recombinant thrombomodulin were graded as "potentially recommended, but needs further

evidence." The present review will explain the current status of these anticoagulant therapies.

Pathophysiology of septic disseminated intravascular coagulation and the concept of anticoagulant therapy The activation of coagulation is an almost universal event during sepsis and is initiated by pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS), peptidoglycan, and other pathogen-related components. Since hemostasis is an important host defense mechanism, random suppression may not be a good treatment strategy.[7] However, full-blown DIC often leads to tissue malcirculation and subsequent death. Tissue factor (TF) expressions on innate immune cells, including monocytes and macrophages, have been thought to be the major initiator of the coagulation cascade. More recently, TF-expressing microparticles from platelets, monocytes, and endothelial cells have been shown to participate in this mechanism.[8] In addition to PAMPs, substances that originate from the host cells and induce inflammation, known as "alarmins" (including histones, nucleosomes, and high mobility group box 1 [HMGB1]), are also capable of inducing coagulation.[9] Eventually, inflammation and malcirculation result in cell apoptosis and necrosis, and alarmins released from these dead cells further propagate coagulation.[10] This vicious cycle accelerates both the inflammation and coagulation systems and progresses until the death of the host. The procoagulant reaction is further accelerated by an increased synthesis of plasminogen activator inhibitor 1 (PAI-1). Thrombin-activatable fibrinolysis inhibitor (TAFI) is also involved in hypofibrinolysis, and the levels of TAFI reportedly increase in patients with DIC as a complication.[11] If the infection can be controlled, this hemostatic imbalance diminishes spontaneously. However, if the insult is strong and sustained, the hemostatic sequence results in multiple-organ failure and death. Thus, anticoagulant treatment seems to be a rational approach. To counteract the hemostatic reaction, natural and artificial coagulation inhibitors, such as heparins, antithrombin, APC, thrombomodulin, and protease inhibitors, are the treatment of choice. Recent studies have revealed that some anticoagulants also have important functions for modulating inflammation. For example, APC ameliorated the inflammatory reactions and improved survival in the animal models of sepsis.[12] In mice with genetic deficiencies of protein C, endotoxemia was associated with a more marked increase in pro-inflammatory cytokines, compared with wild-type mice.[13] Similar anti-inflammatory effects were reported in other natural anticoagulants.[14] Following the favorable results in animal models, some large-scale RCTs were performed in the early 2000s, but only recombinant APC showed a survival benefit.[15] Thus, the question, "Is anticoagulant therapy effective for sepsis or septic DIC?", has remained unanswered. We will try to address this important question in the following section.

Anticoagulant therapy **Heparins** UFH is a sulfated polysaccharide with a heterogeneous structure and a molecular weight of 3 to 57 kDa. UFH binds to antithrombin and induces a conformational change that increases the flexibility of the reactive site loop of antithrombin, which increases the anticoagulant activity approximately 1000 times. Activated antithrombin inactivates thrombin and other coagulation factors such as factors Xa and IXa (FIGURE 1).

Even though UFH is widely used for the treatment of DIC, its efficacy has not yet been proved. Until now, only two RCTs have reported results for patients with sepsis-associated DIC, and both those trials failed to demonstrate a survival benefit.[16,17]

With respect to LMWH, dalteparin has been approved by the Japanese Ministry of Health and Welfare (JMHW) for the treatment of DIC. A multicenter cooperative double-blind trial[18] showed that dalteparin suppressed the development of organ failure (P <0.05), tended to reduce bleeding symptoms (P <0.1), and had a better safety profile than UFH (P <0.05).

A recent topic regarding the use of heparins is the suppression of the procoagulant activity of histones. Histones are DNA-binding proteins with a positive charge. Although intranuclear histones are harmless, they express strong damaging effects and propagate coagulation activities once released into the bloodstream. Heparins are highly sulfated and negatively charged; thus, they can bind to histones and diminish their toxicity. However, since high-dose heparin increases the risk of bleeding, Wildhagen et al.[19] developed nonanticoagulant heparin and reported its efficacy. At the moment, no RCT, systematic review, or meta-analysis has proven that heparins are effective for the treatment of sepsis-associated DIC. However, a recent large-scale trial, known as the XPRESS trial, showed a nonsignificant benefit of a prophylactic dose of heparin for venous thromboembolism (VTE) on a 28-day mortality in patients with severe sepsis compared with placebo (28.3% vs. 31.9%, P = 0.08).[20] Although many patients with sepsis are treated with low-dose heparin for the prevention of VTE in intensive care units, whether these patients may benefit in ways other than VTE prevention remains unclear.

Antithrombin Antithrombin, a vitamin-K-independent glycoprotein with a molecular weight of 59 kDa, is an essential inhibitor of thrombin and other serine proteases, such as factors Xa and IXa. Antithrombin forms a 1:1 complex with thrombin (thrombin–antithrombin complex) and inactivates its enzymatic activity. Antithrombin contains a heparin-binding domain, and its anticoagulation activity is enhanced by several orders of magnitude after binding with heparin in the blood stream or glycosaminoglycans on the vascular endothelium (FIGURE 1). Acquired antithrombin deficiency is commonly

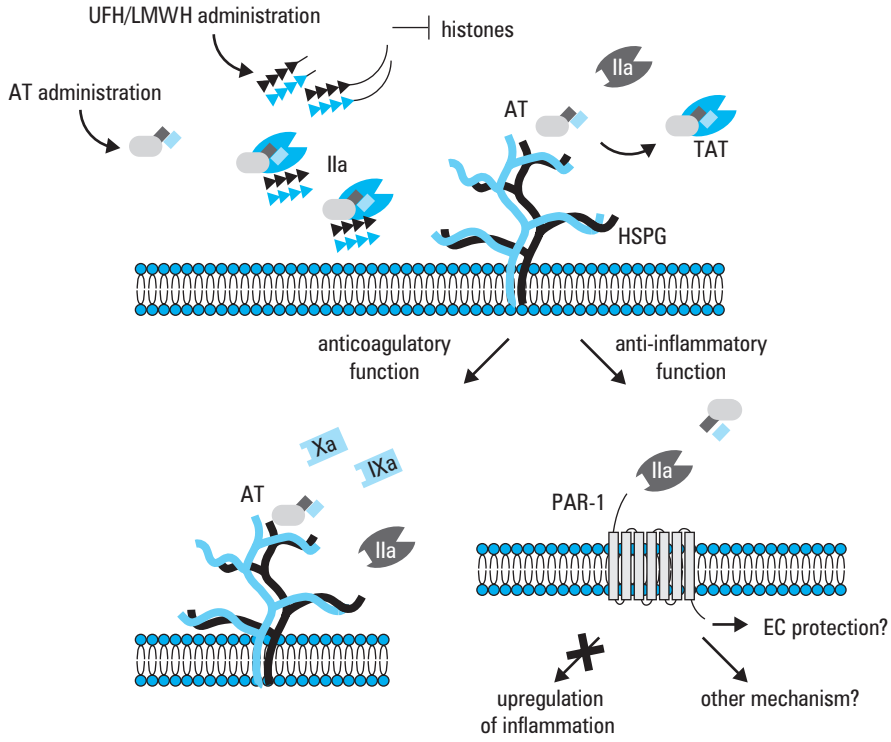

FIGURE 1 Interaction between antithrombin (AT) and the endothelium. The affinity of AT to thrombin and its enzymatic inhibition is increased by the binding of AT to cellular heparin sulfate proteoglycans or externally administered heparins at a heparin-binding site. Thrombin loses its coagulant activity after the formation of the thrombin–antithrombin complex. Other than thrombin, AT also inactivates factor Xa and IXa. As for the anti-inflammatory function, AT inhibits the cellular reaction through the inactivation of protease-activated receptor 1 by inactivating thrombin. Heparins are known to inactivate histones.

Abbreviations: IIa – thrombin, EC – endothelial cell, HSPG – heparin sulfate proteoglycans, LMWH – low-molecular-weight heparin, PAR-1 – protease-activated receptor 1, TAT – thrombin–antithrombin, UFH – unfractionated heparin

observed during severe sepsis primarily through the increased consumption or loss of antithrombin. The plasma level in acquired deficiency decreases along with the severity of sepsis; thus, it could be a good predictor of the patient outcome.[21]

Regarding the antithrombin use, there are major differences among countries. The Japanese guidelines recommend the use of antithrombin concentrates for the treatment of septic DIC,[22] while the British guidelines do not.[23] Other than the DIC guidelines, the Surviving Sepsis Campaign Guidelines,[24] a set of global guidelines for the management of severe sepsis, do not recommend the use of antithrombin. The reason for this difference is related to different interpretations of the KyberSept trial,[25] which was the only mega-scale RCT to study high-dose antithrombin; however, this trial failed to demonstrate any efficacy with regard to the survival of patients with severe sepsis, while it showed an increased risk of bleeding, especially when antithrombin was administered together with heparin. However, Kienast et al.[4] demonstrated that patient survival was increased by the treatment in a subgroup of patients with DIC as a complication (odds ratio, 0.512; 95% confidence interval, 0.291–0.899). In fact, the KyberSept trial examined the effects of high-dose antithrombin on severe sepsis but not the effects on DIC, and the dose was set to target the supranormal level. Furthermore, the concomitant use of heparin was not prohibited, and an increase in bleeding events was observed in this population.

Wiedermann et al.[26] demonstrated the potential efficacy of antithrombin for septic DIC in their systematic review. In addition, a recent small-scale RCT conducted by the JAAM/DIC Study Group demonstrated that a supplemental dose of antithrombin substitution, administered for 3 days with the aim of enabling recovery to the normal level in septic DIC patients with an initial antithrombin activity level of 50% to 80% resulted in a significant decrease in DIC scores and superior recovery rates from DIC. Moreover, the incidence of bleeding complications did not increase.[5] In addition to this study, a recent post-marketing surveillance of antithrombin concentrates has reported the effectiveness of a supplemental dose of antithrombin for the treatment of septic DIC. According to this survey, the administration of 3000 IU of antithrombin per day efficiently reduced the mortality rate, compared with the administration of 1500 IU/d.[27]

To replace plasma-derived antithrombin, recombinant agents are now under development in some countries, and a Phase 3 study for

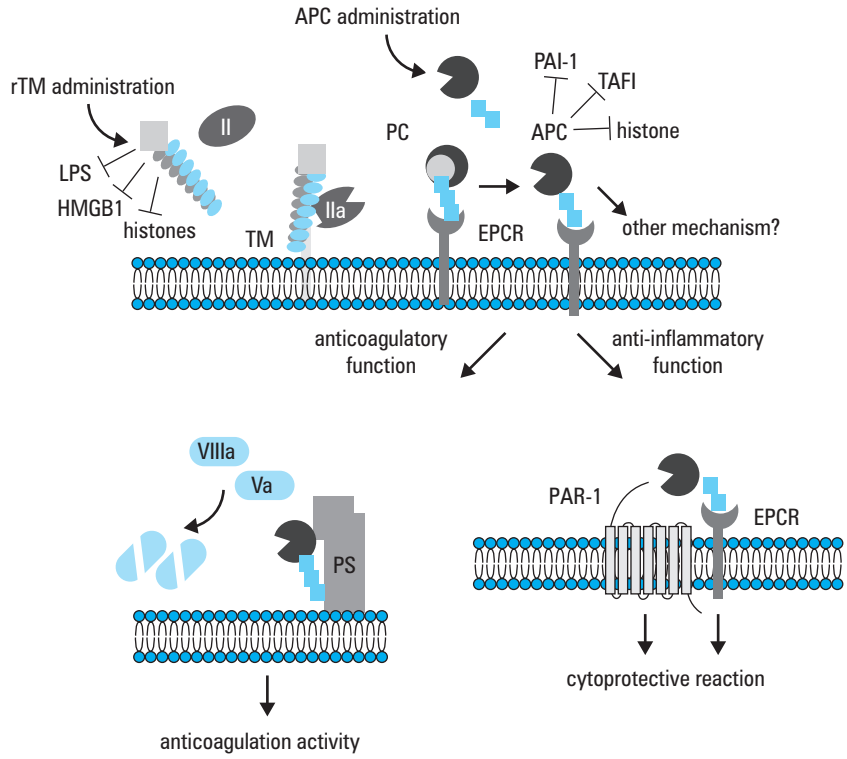

FIGURE 2 Functions of thrombomodulin–protein C (PC) system. PC is activated by the thrombin–thrombomodulin complex on the endothelial surface, and this activation is facilitated by endothelial PC receptor. Activated PC exerts its anticoagulant activities through the proteolytic inactivation of factors Va and VIIIa aided by protein S on negatively charged phospholipid membranes. Activated PC associated with endothelial PC receptor then cleaves protease--activated receptor 1 to initiate cell signaling with cytoprotective effects that may include anti-inflammatory and antiapoptotic activities, altered gene expression profiles, and barrier-protective effects.
Abbreviations: APC – activated protein C, II – prothrombin, TM – thrombomodulin, rTM – recombinant TM, LPS – lipopolysaccharide, HMGB1 – high mobility group box 1, EPCR – endothelial protein C receptor, PAI-1 – plasminogen activator inhibitor 1, TAFI – thrombin-activatable fibrinolysis inhibitor, PS – protein S, others – see FIGURE 1

KW-3357 is currently underway in Japan. This study has already completed case recruitment, and its results will be released this year. With respect to product homology, one must remember that recombinant antithrombin is not exactly the same as plasma products. Plasma-derived antithrombin consists of approximately 85% to 95% of the α-form, with the remaining 5% to 15% consisting of the β-form.[28] These 2 isoforms do not differ in their thrombin-inhibiting effects, but they do differ in their affinity for heparins. The α-form is glycosylated at 4 of its asparagine molecules, while the β-form lacks glycosylation at asparagine 135, resulting in a 3- to 10-fold greater affinity for heparin.[29] Since KW-3357 consists of 100% α-form, its anticoagulant activity is thought to be less than that of a plasma product when heparin is used concomitantly. In other words, because the anticoagulant activity is milder, the anti-inflammatory effect of the α-form can be expected.

Activated protein C Protein C, a 62-kDa vitamin--K-dependent plasma glycoprotein, is a precursor to a serine proteinase named APC. The activation of protein C results from the thrombin-mediated cleavage of protein C. The membrane cofactor thrombomodulin enhances this action of thrombin on protein C. APC proteolytically inactivates factors VIIIa and Va, exerting profibrinolytic properties through its ability to inhibit PAI-1 activity and the activation of TAFI.[30] Therefore, protein C is the central factor in the natural antithrombotic pathway. In addition, several cytoprotective effects of APC have been reported, including antiapoptotic activity, anti-inflammatory activity, beneficial alterations of the gene expression profiles, and endothelial barrier stabilization.[31] These activities of APC, which require the endothelial protein C receptor (EPCR) and protease-activated receptor 1 (PAR-1), have been a major focus of research. APC reportedly elicits cytoprotective signaling through the cleavage of PAR-1 and modulates endothelial function by binding to EPCR (FIGURE 2).[32]

Between 2001 and 2011, recombinant APC (drotrecogin alfa) was used as the only internationally approved anticoagulant for the treatment of severe sepsis. The initial evidence demonstrated its efficacy for the treatment of severe sepsis in the PROWESS trial,[33] which targeted patients with severe sepsis, of whom 29% had overt DIC.

Dhainaut et al.[4] performed a subgroup analysis of these patients. Interestingly, the drotrecogin-alfa-treated patients with overt DIC tended to have a greater relative risk reduction in mortality than untreated patients without DIC (29% vs. 18%, P = 0.261). Nevertheless, drotrecogin alfa was withdrawn from the world market after the failure of the most recent RCT, the PROWESS-SHOCK trial.[34] Unlike the PROWESS trial, the use of recombinant APC did not result in a significant reduction in mortality. Instead, nonserious bleeding events were more common in patients receiving drotrecogin alfa than in those receiving placebo (8.6% vs. 4.8%, P = 0.002), and the same was observed for serious bleeding events (1.2% vs. 1.0%, P = 0.81). Do these results really indicate that recombinant APC is useless? In addition to the report by Dhainaut et al.,[4] 1 meta-analysis[35] and 1 cohort study[36] reported a significant reduction in mortality after the use of drotrecogin alfa. In contrast, another meta-analysis reported the opposite result.[37] Consequently, the efficacy of drotrecogin alfa remains controversial.

Although recombinant APC is no longer available, plasma-derived APC is still used. A randomized double-blind trial comparing the efficacy of plasma-derived APC (CTC-111) to UFH was performed in Japan,[38] and a 28-day mortality rate was significantly lower in the group receiving plasma-derived CTC-111 (20.4% vs. 40%, P <0.05). However, the JMHW has permitted plasma-derived APC to be used only in cases with congenital protein C deficiency and thrombosis or purpura fulminans. Since plasma-derived APC consists of different glycoforms from recombinant APC, its effects should be evaluated separately in future trials. Drotrecogin alfa consists of the α-form, while about 30% of plasma protein C consists of the β-form, which is smaller than the predominant α-form: the β-form consists of 3 N-linked oligosaccharide chains, whereas the α-form consists of 4. This difference is responsible for the reduced anticoagulant activity of drotrecogin alfa.[39]

Thrombomodulin Thrombomodulin is an endothelial anticoagulant cofactor that promotes the thrombin-mediated activation of protein C (FIGURE 2). Since the expression of thrombomodulin is downregulated during septic DIC, resulting in the dissemination of procoagulant and proinflammatory molecules, supplementation with thrombomodulin may have therapeutic value. Recombinant thrombomodulin (ART-123) was developed and approved in Japan in 2008. An RCT was performed involving 234 DIC patients with hematological malignancy or infection.[40] UFH was used as a control in this study. The DIC resolution rates were 66.1% and 49.9% in the ART-123 and UFH groups, respectively (P <0.05). In addition, the incidence of bleeding-related adverse events was 43.1% in the ART-123 group and 56.5% in the control group. However, since the number of subjects with sepsis-associated DIC was only 99, and a stratified analysis showed no significant difference, further study in patients with septic DIC was needed. Subsequently, a multinational Phase 2 trial was performed.[41] Of the 741 patients who were randomized, 371 received ART-123 and 370 received a placebo. The 28-day mortality rate was 17.8% in the recombinant-thrombomodulin group and 21.6% in the control group (P = 0.273). Although this difference did not reach significance, the low prevalence of bleeding events in the treatment group is notable. The prevalence of serious bleeding was 5.1% in the ART-123 group and 4.6% in the placebo group. Since the incidence of serious bleeding was as much as 2-fold higher for other anticoagulants,[42] this result was quite attractive. Currently, a Phase 3 study is being conducted in subjects with severe sepsis and coagulopathy.

With respect to the mechanism of action, a lectin-like domain of thrombomodulin reportedly binds to inflammatory mediators such as LPS, HMGB1,[43] and histones,[44] and neutralizes their functions. Extracellular histones cause massive thromboembolism associated with consumptive coagulopathy, which is clinically diagnosed as DIC. Recombinant thrombomodulin is expected to bind to histones, neutralize them, and ultimately contribute to the improvement of DIC and the reduction of mortality.

Other anticoagulants Since the 1980s, synthetic protease inhibitors such as gabexate mesilate (GM) and nafamostat mesilate (NM) have been approved by the JMHW for the treatment of DIC. Reportedly, the bleeding risks are relatively low for these agents, and they have often been used in patients with a bleeding tendency. However, the evidence levels supporting the use of these drugs are not sufficiently high. Though 4 randomized clinical trials evaluating the use of GM[45-47] and NM[48] in the treatment of DIC have been performed, all of the studies were small-scale, some were nonblinded and nonplacebo controlled, and no significant differences were observed in the outcome or improvement of DIC. Thus, the efficacy of these agents has not yet been confirmed.

TFPI is an endogenous serine protease inhibitor, which is synthesized and secreted by endothelial cells and which inhibits factor Xa directly and the factor VIIa/tissue factor catalytic complex in a Xa-dependent fashion. TFPI is released after cellular stimulation with thrombin or heparin. To date, 2 large-scale RCTs evaluating the effects of recombinant TFPI have been performed, with the first one being performed in patients with severe sepsis[49] and the other in patients with community-acquired pneumonia.[50] Both of these studies failed to reveal any effect on the mortality outcome. A recent study revealed distinct functions for TFPIα and TFPIβ. TFPIα predominantly limits clot growth and alters bleeding in patients with hemophilia, suggesting that its primary physiological role is the modulation of clot formation. In contrast, TFPIβ is an effective inhibitor

of TF-mediated cellular migration and may act to dampen the adverse effects of TF expressed during inflammation.[51] Since the recombinant agent consists of TFPIα, it failed to demonstrate a beneficial effect and instead increased the incidence of adverse bleeding events.

Danaparoid sodium, another agent approved for DIC by the JMHW, is a heparinoid that suppresses thrombin activity through the activation of antithrombin. Danaparoid has a strong anti-factor Xa activity but a lower antithrombin activity compared with UFH, which may explain some of the differences in anti-inflammatory effects. However, in a multicenter double-blind trial, no significant difference in the efficacy or safety was observed between danaparoid and UFH.[52]

Conclusions More than a decade has passed since the recombinant APC was launched. We have learned that the unconditional application of anticoagulant therapy for severe sepsis does not lead to a favorable outcome, but rather increases the bleeding risk and may help spread the pathogen. At the same time, we have also learned that if we can find an appropriate target, proper timing, and matched dose, we might be able to control not only the coagulation abnormality but also the overinflamed reaction during sepsis. We really believe that "the dawn is near."

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ARTYKUŁ ORYGINALNY

Nowe opcje terapeutyczne dla chorych z sepsą i rozsianym krzepnięciem wewnątrznaczyniowym

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SŁOWA KLUCZOWE

antykoagulanty, hemostaza, rozsiane krzepnięcie wewnątrznaczyniowe, sepsa, zapalenie

STRESZCZENIE

Ciężkość sepsy rośnie wraz ze stopniem nasilenia zaburzeń krzepnięcia; piorunującą koagulopatię określa się jako zespół rozsianego krzepnięcia wewnątrznaczyniowego (*disseminated intravascular coagulation* – DIC). Śmiertelność w DIC związanym z sepsą utrzymuje się na poziomie 40%, porównywalnym ze wstrząsem septycznym. Mimo trwających intensywnych badań nadal nie ma ustalonego sposobu leczenia tego zagrażającego życiu powikłania. Najstarszym, najpopularniejszym i najtańszym z dostępnych antykoagulantów są heparyny, jednak ich przydatność w septycznym DIC nie została udowodniona. Wiele się spodziewano po koncentracie antytrombiny, ale nie udało się wykazać poprawy przeżywalności po stosowaniu antytrombiny w dużych dawkach, i międzynarodowe wytyczne leczenia sepsy nie zalecają już jej stosowania. Do 2011 r. rekombinowane aktywowane białko C było jedynym lekiem zalecanym w ciężkiej sepsie, ale po niepowodzeniu niedawnego badania klinicznego zostało wycofane ze światowego rynku. Najnowszym lekiem jest rekombinowana trombomodulina stosowana w Japonii od 2008 r., jednak jej skuteczność nie została jeszcze udowodniona. Jak widać, postęp nie jest tak szybki jak oczekiwano, ale na horyzoncie pojawiają się kolejne leki. Skuteczność leczenia przeciwkrzepliwego w septycznym DIC jest od dawna dyskutowana i intensywnie badana, i w końcu zdaliśmy sobie sprawę, że korekcja zaburzeń krzepnięcia nie wystarczy do pokonania tego śmiertelnego powikłania. Wiele naturalnych antykoagulantów wykazuje działania plejotropowe dlatego też musimy je zbadać i zastosować we właściwym celu we właściwym czasie.

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