Sepsis-Induced Coagulopathy and Disseminated Intravascular Coagulation

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Abstract

Disseminated intravascular coagulation (DIC) has been recognized as a deadly complication in sepsis, and its early recognition followed by appropriate management of the underlying infection are the current management strategies. The activation of coagulation, inflammation, and other pathways are fundamental host responses against infection but also produce injury to the host. Recent advances have helped define the critical roles of thrombus formation in overcoming infection. In addition to activation of coagulation induced by pathogens, other important pathways including damage-associated molecular patterns, neutrophil extracellular traps, extracellular vesicles, and glycocalyx damage are involved in the pathogenesis of sepsis-induced DIC. The hallmark of DIC is thrombosis in the microvasculature; however, sepsis-induced DIC is a laboratory diagnosis based on coagulation test results and clinical setting. Although simplified criteria were recently introduced, DIC should be distinguished from other similar conditions such as thrombotic microangiopathy and heparin-induced thrombocytopenia. In DIC, treating the underlying cause is crucial, and additional adjunct therapies including antithrombin, thrombomodulin, and heparins may have potential benefit, but evidence supporting their use in terms of improvement of clinically relevant outcomes continues to be debated. In this review, we introduce recent findings regarding the pathophysiology, diagnosis, and treatment of sepsis-induced DIC. In addition, we also discuss future potential therapeutic approaches regarding this complex, life-threatening complication.

Keywords
- sepsis
- disseminated intravascular coagulation
- antithrombin
- thrombomodulin
- heparin
- coagulation

The activation of coagulation and inflammation are essential reactions for host defense during sepsis. Engelmann and Massberg[1] introduced the concept of "immunothrombosis," referring to the close interaction between coagulation and innate immunity. In sepsis, activation of the coagulation system is common and can lead to disseminated intravascular coagulation (DIC), which is associated with organ dysfunction and/or hemorrhage. Microorganisms and their components such as lipopolysaccharides, described as pathogen-associated molecular patterns, are known to induce the expression of tissue factor on monocytes and macrophages by binding to pattern-recognizing receptors on immune cells. Tissue factor has been recognized as the main initiator of coagulation in sepsis, together with the clotting factors, factor VIIa, factor Xa, thrombin, and fibrin.[2] These components are known to induce proinflammatory responses via protease-activated receptors.[3] However, recombinant tissue factor pathway inhibitor (TFPI) administration failed to produce a positive result in Phase 3 trials performed in patients with severe sepsis.[4] The failure of the TFPI trial was suggested to be due to the inability of a single

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inhibitor of coagulation activation to regulate an overactivated coagulopathy. Multiple factors influence sepsis-induced coagulopathy (SIC) and therapy requires a multimodal approach in addition to the underlying infection.[5]

Damage-Associated Molecular Patterns

Sepsis induces cellular damage and cell death, releasing various cellular components that further propagate inflammation.[6] Host-released proinflammatory substances are known as damage-associated molecular patterns (DAMPs) that play key roles in the innate immune system and tissue repair.[6] DAMPs also contribute to the pathogenesis of inflammation and thrombogenesis that can lead to microcirculatory abnormalities and organ dysfunction.[6] The aforementioned DAMPs, which include histones, chromosomal DNA, mitochondrial DNA, nucleosomes, high-mobility group box 1 protein (HMGB1), and heat shock protein, are all important initiators of coagulation and have the potential to induce DIC (►**Fig. 1**).[6]

Damage-associated molecular patterns can be highly injurious to the host, and as a result, they are released in a regulated process catalyzed by serine proteases that include DNase1 and factor VII-activating protease.[7] DNA released from cells contributes to coagulopathy by initiating hemostatic activation, platelet aggregation, and fibrinolytic inhibition that together interfere with clot stability. After neutrophil extracellular trap (NET) formation, DNA released intravascularly is both procoagulant and cytotoxic. Proteins that bind to DNA including histones and HMGB1 are also procoagulant and contribute to DIC pathogenesis.[8]

Neutrophil Extracellular Traps

Coagulation activation induced by NETs represents important host defense mechanisms that contribute to the compartmentalization and killing of bacteria but may also initiate DIC.[9] An in vitro study has shown that fibrin is colocalized with free DNA in blood clots, and increased levels of free DNA occur with deep vein thrombosis.[10] These findings suggest that NET formation plays important roles in promoting thrombogenesis. This concept is supported by the inability of a knockout mouse model of peptidyl arginine deiminase type 4, an essential enzyme for NETs formation, to form thrombi.[11] Interestingly, the disintegration of NETs by

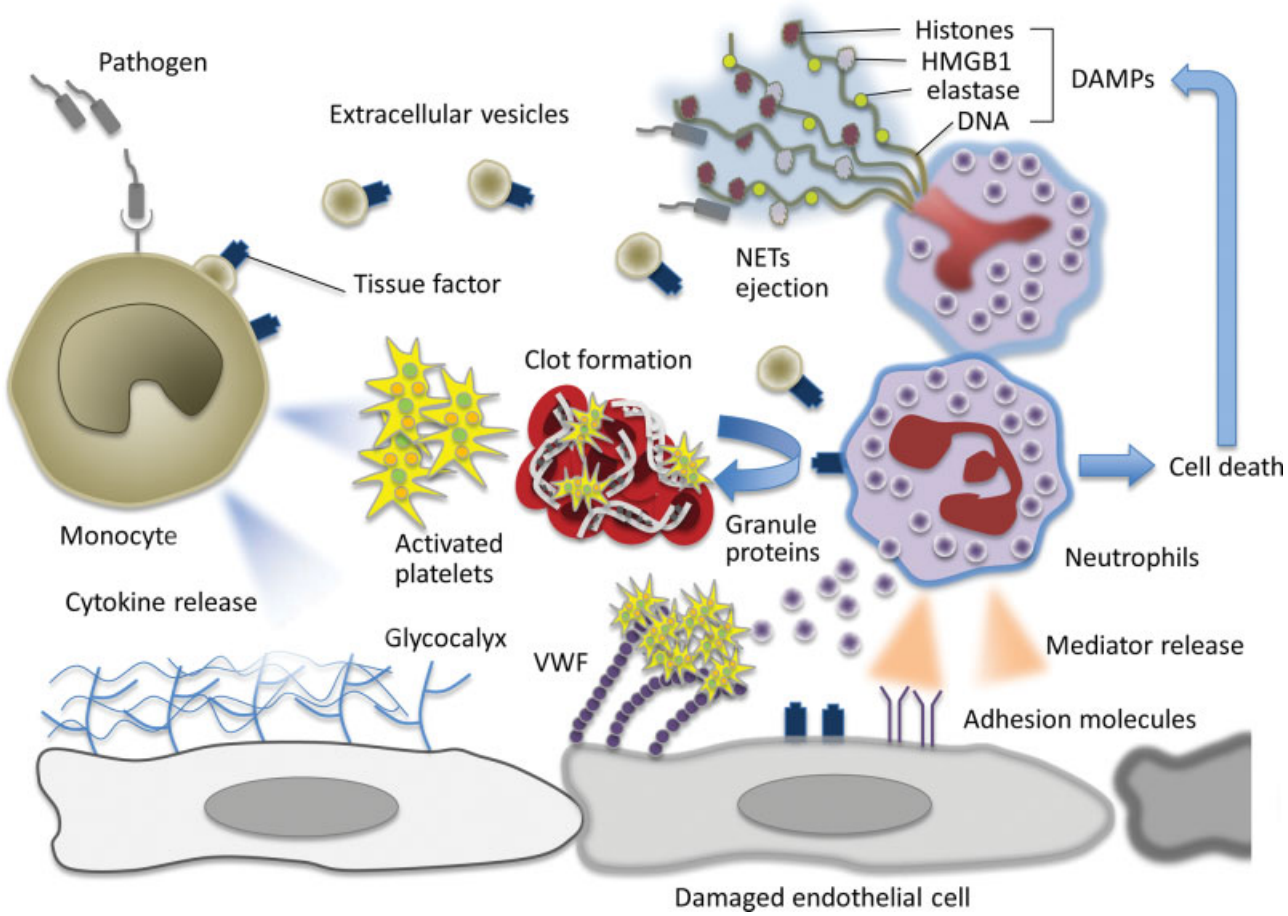

Fig. 1 Complex mechanisms for the activation of coagulation during sepsis. Pathogens and their components stimulate monocytes through specific receptors on the cell surface. Activated monocytes release cytokines, chemokines, and several chemical mediators that activate platelets, neutrophils, and endothelial cells. Monocytes and other cells release extracellular vesicles that express procoagulant tissue factor and phosphatidylserine on their surfaces. Damaged endothelial cells change their anticoagulant properties to procoagulant through the disruption of the glycocalyx and the expression of ultralarge von Willebrand factor (VWF). Neutrophils play major roles in the activation of coagulation by expressing tissue factor and releasing granule proteins and mediators. Neutrophils also activate coagulation by expelling neutrophil extracellular traps (NETs), composed of procoagulant DNA, histones, and other damage-associated molecular patterns (DAMPs).

DNAse1 limited the efficacy of bacterial killing and prevented thrombosis in mice.[12] An inverse correlation between DNase activity and thrombosis also suggests a pathogenic role of NETs in thrombosis.[12] Coagulation activation that occurs with NETs is important in sepsis and DIC. For example, extracellular tissue factor release by NETs favors factor VIIa–mediated thrombin formation, and the polyanionic surface of NETs also activates contact activation proteins, including factor XII (Hageman factor). Neutrophil elastase in NETs also upregulates the coagulopathic response through the proteolytic cleavage of serine protease inhibitors including α2-antiplasmin, antithrombin, and C1-esterase inhibitor. Histones can also bind via the A1 domain to von Willebrand factor to initiate GPIbα-mediated platelet adhesion. In septic DIC, varying degrees of thrombocytopenia can occur, and the magnitude of the platelet drop is reportedly associated with disease severity and mortality.[13] Thrombocytopenia in septic patients also occurs due to activated platelets adhering to neutrophils stimulated by NETs[13] and is considered to be an effect of NETs formation with DIC.

Extracellular Vesicles

Extracellular vesicles (EVs) are a generic name for submicron-sized spherical particles that are enclosed by bilayer phospholipid membranes released from most cell types into plasma or other sites.[14] Several subclasses of EVs exist based on their biogenesis and phenotypic origin, including apoptotic bodies, exosomes, and microvesicles.[15] Research on EVs began with the exploration of their procoagulant properties,[5,15] as primarily expressed through the expression of tissue factor and phosphatidylserine on their surfaces. Although platelet-derived EVs were initially reported to be the main type in SIC, endothelial cells, leukocytes, red blood cells, and other cell types contribute to proinflammatory and procoagulant reactions during sepsis.[16] Sepsis is associated with a massive release of leukocyte-derived EVs, particularly neutrophil-derived EVs that retain DNAs, histones, and other DAMPs from neutrophils, contributing to the procoagulant activity.[17] As a result, DIC is associated with neutrophil-derived EVs generation because they contain procoagulant NETs components. Delabranche et al[18] reported an increase in NETs and nucleosomes in EVs during sepsis-induced DIC. Hence, it is reasonable to think that components of NETs that contain EVs contribute to the pathogenesis of sepsis-induced DIC.[19]

Glycocalyx and Endothelial Damage

The vascular endothelial surface is covered by the glycocalyx, a gel-like layer that exhibits important properties such as antithrombogenicity and anti-inflammation.[20] The endothelial glycocalyx is composed of three structures: membrane-binding proteoglycans (such as syndecan and glycan), glycosaminoglycan (GAG) side chains conjugated with core proteoglycans, and plasma proteins (such as albumin and antithrombin). Each glycocalyx component is critical to its physiologic functions: syndecans act as mechanosensors, GAGs contribute to antithrombogenicity, and plasma proteins regulate vascular permeability. The glycocalyx is synthesized by vascular endothelial cells and covers the endothelial cell surface, and subsequently released into the circulation.[21] Similar structures penetrate the intercellular clefts and play important roles in the regulation of vascular permeability. Structures expressed in the spaces between the endothelial cell and basement membrane are also known to function as a foothold for cells. The glycocalyx on the luminal surface of endothelial cells is extremely important for the maintenance of antithrombogenicity in the vascular lumen. Under inflammatory conditions, reactive oxygen species, heparanases, and other proteases disrupt the glycocalyx to produce shedding. Once this occurs, E-selectin, intercellular adhesion molecule 1, and other adhesion molecules that are exposed on the denuded endothelium recruit platelets and neutrophils causing thrombus and fibrin formation. Microvascular dysfunction occurs due to the loss of the glycocalyx, and results in acute inflammation, increased capillary permeability, and loss of vascular responsiveness.[21] Moreover, the loss of the glycocalyx accelerates the devastating hypercoagulation that occurs during sepsis. Subsequently, the decreased blood flow and the impaired oxygen delivery result in multiorgan failure. Therefore, even if the global oxygen delivery is increased, the tissue capillary beds cannot receive an adequate oxygen supply because of endothelial injury.

Diagnosis of Disseminated Intravascular Coagulation

Diagnostic Criteria

In 1991, DIC was defined by the Scientific Subcommittee (SSC) on DIC of the International Society on Thrombosis and Haemostasis (ISTH) as "an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction."[22] Although the cause may differ, the systemic activation of coagulation is a common feature of DIC; thus, a diagnosis is possible using diagnostic criteria obtained from a combination of coagulation tests, and the ISTH DIC-SSC has released a set of overt DIC diagnostic criteria.[22] However, these diagnostic criteria are not widely used because of their complexity.[23] Recent progress in DIC research has shown that the characteristics of DIC differ according to the underlying disease. For example, transient excess fibrinolysis is seen in trauma-induced DIC and is viewed as a counter-response to massive thrombotic events.[24] In sepsis, coagulation activation occurs with inhibition of fibrinolysis. The clarification of these differences in pathogenesis has enabled the establishment of simple but additional diagnostic criteria for sepsis-induced DIC as follows.

The Japanese Association for Acute Medicine (JAAM) released the JAAM-DIC diagnostic criteria for acute DIC by eliminating fibrinogen as a criterion,[25] and the clinical utility of the JAAM-DIC has been repeatedly reported.[26] Recently, active members of the ISTH DIC-SSC recently proposed a simpler version for the diagnosis of SIC that is composed of only three items: sepsis-3 definitions (infection with organ dysfunction), platelet count, and the prothrombin time ratio[27] (►**Table 1**). The usefulness of these SIC diagnostic criteria has been validated, and Iba et al[28] reported that it provides an

Table 1 ISTH overt DIC and sepsis-induced coagulopathy scoring systems

	Points	ISTH overt DIC	SIC
Platelet count ($\times 10^9$/L)	2	< 50	< 100
	1	$\geqq 50, < 100$	$\geqq 100, < 150$
FDP or D-dimer	3	Strong increase	–
	2	Moderate increase	–
	1	–	–
Prothrombin time or INR (elevation)	2	$\geqq 6$ s	> 1.4
	1	$\geqq 3, < 6$ s	$> 1.2, \leqq 1.4$
Fibrinogen (g/mL)	1	< 100	–
Total SOFA score	$\geqq 2$	–	2
	1	–	1

Abbreviations: DIC, disseminated intravascular coagulation; FDP, fibrin degradation products; INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis; SIC, sepsis-induced coagulopathy; SOFA, sequential organ failure assessment.
Note: ISTH overt DIC diagnosis: total score is 5 or more; SIC diagnosis: total SIC score is 4 or more with sum of SOFA score and coagulation criteria exceeding 2. Total SOFA score is the sum of four items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA, and renal SOFA).

earlier diagnosis and includes most cases of ISTH overt DIC. An additional analysis of septic patients from Japan evaluated associations between in-hospital mortality and anticoagulant therapy according to the SIC or ISTH overt DIC sets of criteria. They reported the rate for ISTH overt DIC was about half of that for SIC, while the mortality rates for the two sets of criteria were comparable.[29] Beneficial effects of anticoagulant therapy were observed in patients with coagulopathy as defined using both sets of criteria, suggesting that some patients who do not meet the criteria for overt DIC may benefit from anticoagulant therapy. Thus, the SIC diagnostic criteria for SIC may be valuable for detecting sepsis patients who are candidates for anticoagulant therapy.

Differential Diagnoses

The early diagnosis of sepsis-induced DIC is important for management and may potentially improve outcomes.[30] While the use of a simplified diagnostic criteria is desirable, there is also the possibility of misdiagnosing diseases that mimic DIC and delay appropriate management. Important examples include heparin-induced thrombocytopenia (HIT), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), hemophagocytic syndrome, antiphospholipid syndrome, and other conditions associated with thrombocytopenia and organ dysfunction as shown in ►**Table 2**. HIT is a prothrombotic disease that requires the immediate termination of heparin and treatment with nonheparin anticoagulants. Similarly, thrombotic microangiopathy, which includes both HUS and TTP, is a broad pathophysiologic process that requires urgent management. A high mortality rate has been reported for both diseases unless adequate treatment using either C5 inhibitor or plasma exchange is performed at an appropriate time. Recently, ISTH DIC-SSC published guidance information important for the differential diagnosis of these diseases.[31]

Treatment for Disseminated Intravascular Coagulation

Antithrombin

Antithrombin is one of the most important physiological anticoagulants that is thought to suppress acute inflammatory reactions in sepsis. However, antithrombin is rapidly consumed by thrombin, cleaved by neutrophil elastase and the bacterial enzyme thermolysin, resulting in its inactivation. Thus, the supplementation of antithrombin for the treatment of septic DIC is included in recommendations.[32] Unfortunately, the efficacy of antithrombin supplementation was not confirmed in a large-scale randomized controlled trial (RCT) known as

Table 2 Major differential diagnoses of the sepsis-induced DIC

	Causes	Clinical symptoms and laboratory findings
HIT	Presence of antiplatelet factor 4-heparin antibodies	Thrombocytopenia, bleeding tendency, thrombosis
TTP	Decrease of ADAMTS-13 activity	Thrombocytopenia, thrombosis, fever, neurological manifestation, organ dysfunction
aHUS	Dysregulation of alternative complement pathway	Hemolytic anemia, thrombocytopenia, renal dysfunction, thrombosis
STEC-HUS	STEC infection	Bloody diarrhea, hemolysis, thrombocytopenia, renal dysfunction
HPS	Epstein–Barr virus infection, malignant lymphoma, cancer, etc.	Persistent high fever, thrombocytopenia, splenomegaly, hemophagocytosis in bone marrow
APS	Presence of antiphospholipid antibodies	Multiorgan dysfunction due to arterial thrombosis, venous thrombosis
SFTS	SFTS virus infection	High fever, leukopenia, thrombocytopenia, bleeding tendency

Abbreviations: ADAMTS-13, a disintegrin-like and metalloproteinase with thrombospondin type 1 motif, member 13; aHUS, atypical HUS; APS, antiphospholipid syndrome; HIT, heparin-induced thrombocytopenia; HPS, hemophagocytic syndrome; HUS, hemolytic uremic syndrome; SFTS, severe fever with thrombocytopenia syndrome; STEC, Shiga toxin-producing *Escherichia coli*; TTP, thrombotic thrombocytopenic purpura.

KyberSept. This trial examined the effects of high-dose antithrombin for sepsis itself and did not target DIC specifically.[33] However, a subanalysis demonstrated that antithrombin supplementation could be effective in patients with sepsis and coagulopathy.[34] Other than the earlier trial, some large-scale clinical studies have consistently demonstrated favorable effects of antithrombin supplementation in septic patients with DIC.[26]

Antithrombin's anticoagulant activity is known to increase dramatically when it binds to heparan sulfate on the endothelial glycocalyx.[35] One of the unique features of antithrombin is its ability to attenuate glycocalyx injury.[36] The mechanism is presumed to involve binding to heparan sulfate on endothelial cells.[37] This phenomenon also can explain why the favorable effects of antithrombin were canceled by the concomitant use of heparin. A recent topic is the recombinant nonfucosylated antithrombin. This new agent was developed in Japan, and its applications continue to be explored.[38]

Thrombomodulin

Thrombomodulin is an endothelial anticoagulant cofactor that promotes the thrombin-mediated activation of protein C. Since the expression of thrombomodulin is down-regulated during sepsis, supplementation with recombinant soluble thrombomodulin was proposed as a therapeutic modality, and recombinant thrombomodulin was developed. Subsequently, the efficacy of recombinant thrombomodulin in SIC was examined in a randomized Phase 2b study, and a nonsignificant reduction in mortality difference of 3.8% was shown.[38] Following this study, a multinational Phase 3 study was conducted, and the preliminary results have been reported (http://www.asahi-kasei.co.jp/asahi/en/news/2018/press.html). According to the article, a nonsignificant mortality reduction of 2.6% was recognized in 800 septic patients with coagulopathy. In addition, improvements were observed in D-dimer, thrombin–antithrombin complex, and prothrombin fragment F1 + 2 levels and the platelet count. The unique feature of thrombomodulin is its lectin-like domain, which is thought to suppress inflammatory responses through the inactivation of DAMPs such as histones and HMGB1. This activity consequently leads to the suppression of leukocyte adhesion to endothelial cells, the interference of complement activation, and the inactivation of inflammatory reactions.[6]

Heparin and Heparinoids

As noted in the previous section, the usefulness of anticoagulant therapy for sepsis-induced DIC remains controversial. Research on the use of heparin and heparinoids is particularly difficult because they are commonly administered for venous thromboembolic prophylaxis regardless of the presence of DIC. Jaimes et al[39] examined the effects of unfractionated heparin in a RCT and reported no survival benefit; however, this study was performed in patients suspected of having sepsis and not in the septic DIC patients. There have been three RCTs examining the effects of heparin in patients with septic DIC. Aikawa et al[40] used unfractionated heparin in 234 patients as a control for recombinant thrombomodulin, while Aoki et al[41] used unfractionated heparin as a control for activated protein C concentrate; no benefit of heparins compared with each of the therapeutic agents studied was reported in these two trials. In contrast, Liu et al[42] examined the effect of low-dose heparin in 37 sepsis-associated pre-DIC patients and reported an improvement in the hypercoagulable state, multiple organ dysfunction, and period of hospitalization compared with saline control. However, this study was too small to reach a definite conclusion. Regarding heparin use, the risk of HIT must be kept in mind, and caution is required when judging the benefit–risk balance (►**Table 3**).

Other Anticoagulants

Recombinant activated protein C was the first anticoagulant approved for the treatment of sepsis after its success in a large-scale RCT named PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis).[43] PROWESS was performed for patients with severe sepsis and resulted in a significant reduction in 28-day mortality. Dhainaut et al[44] subsequently performed a subgroup analysis of subjects with overt DIC and demonstrated an even more profound favorable effect on mortality (relative risk, 0.71; 95% confidence interval, 0.55–0.91). Nevertheless, recombinant activated protein C was withdrawn when subsequent trials showed less positive outcomes, generated some concern about potential bleeding complications, and finally, after the failure of a RCT performed in septic patients with shock.[45] According to the report, unlike the results of PROWESS, the use of recombinant activated protein C was not associated with reduced mortality but was associated with an increased risk of bleeding.

Table 3 Therapeutic agents for sepsis-induced disseminated intravascular coagulation

Agent	Mechanism of action	Clinical evidence	Reference
Antithrombin	Inhibits thrombin and other coagulation factors. Protection of endothelium	Although a large-scale RCT (KyberSept) did not show any efficacy, a meta-analysis showed a beneficial effect in survival	31,32
Thrombomodulin	Suppresses coagulation through activation of protein C. Suppresses inflammation by neutralizing DAMPs	Although not statistically significant, there are two RCTs that showed a trend toward a favorable effect in survival	36
Heparin and heparinoids	Suppress coagulation through activation of antithrombin	No sufficient supportive data except for usefulness in venous thrombosis	38–40

Abbreviations: DAMPs, damage-associated molecular patterns; RCT, randomized controlled trial.

Regarding the use of recombinant TFPI, two RCTs targeting sepsis and one RCT targeting pneumonia have been performed.[5,46] First, a Phase 2 study reported a trend toward a reduction in 28-day all-cause mortality in the treatment group. A higher baseline prothrombin time was associated with a more pronounced beneficial effect. However, a subsequent Phase 3 trial failed to demonstrate such an effect. Following these two trials, a third RCT was performed in the patients with community-acquired pneumonia. Again, no survival benefit was recognized in the treatment group despite an improvement in the coagulation parameters. Unfortunately, research on recombinant TFPI has been discontinued.

Conclusion

Disseminated intravascular coagulation is a life-threatening complication characterized by the systemic activation of coagulation in various diseases, and in particular, sepsis. Biomarker measurements of coagulation and fibrinolytic activation have further defined that DIC pathophysiology differs considerably depending on the underlying conditions. Among them, sepsis-induced DIC is characterized by the suppression of fibrinolysis typical of DIC and can easily progress to multiple organ dysfunction and failure. Thus, the early detection of DIC is extremely important. For this purpose, several sets of criteria have been proposed, each with their advantages and disadvantages. At present, we suggest a sequential diagnosis using SIC and overt DIC diagnostic criteria for every sepsis patient. This strategy enables the early initiation of treatment without missing any therapeutic opportunities. While it is unfortunate that there is still no established treatment, appropriate diagnosis remains important for judging the severity of each patient's condition.

Conflicts of Interest

Dr. Levi reports being a member of a scientific advisory board of Asahi Kasei Pharma America, outside the submitted work; Dr. Levy reports other from Boehringer, CSL Behring, Instrumentation Labs, Octapharma, outside the submitted work.

References

1 Engelmann B, Massberg S. Thrombosis as an intravascular effector of innate immunity. Nat Rev Immunol 2013;13(01):34–45
2 Østerud B, Bjørklid E. The tissue factor pathway in disseminated intravascular coagulation. Semin Thromb Hemost 2001;27(06): 605–617
3 Nieman MT. Protease-activated receptors in hemostasis. Blood 2016;128(02):169–177
4 Abraham E, Reinhart K, Opal S, et al; OPTIMIST Trial Study Group. Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. JAMA 2003;290(02):238–247
5 Zhang Y, Meng H, Ma R, et al. Circulating microparticles, blood cells, and endothelium induce procoagulant activity in sepsis through phosphatidylserine exposure. Shock 2016;45(03): 299–307
6 Liaw PC, Ito T, Iba T, Thachil J, Zeerleder S. DAMP and DIC: the role of extracellular DNA and DNA-binding proteins in the pathogenesis of DIC. Blood Rev 2016;30(04):257–261
7 Zeerleder S, Zwart B, te Velthuis H, et al. Nucleosome-releasing factor: a new role for factor VII-activating protease (FSAP). FASEB J 2008;22(12):4077–4084
8 Iba T, Ito T, Maruyama I, et al. Potential diagnostic markers for disseminated intravascular coagulation of sepsis. Blood Rev 2016; 30(02):149–155
9 Massberg S, Grahl L, von Bruehl ML, et al. Reciprocal coupling of coagulation and innate immunity via neutrophil serine proteases. Nat Med 2010;16(08):887–896
10 Fuchs TA, Brill A, Wagner DD. Neutrophil extracellular trap (NET) impact on deep vein thrombosis. Arterioscler Thromb Vasc Biol 2012;32(08):1777–1783
11 Martinod K, Demers M, Fuchs TA, et al. Neutrophil histone modification by peptidylarginine deiminase 4 is critical for deep vein thrombosis in mice. Proc Natl Acad Sci U S A 2013; 110(21):8674–8679
12 Jiménez-Alcázar M, Napirei M, Panda R, et al. Impaired DNase1-mediated degradation of neutrophil extracellular traps is associated with acute thrombotic microangiopathies. J Thromb Haemost 2015;13(05):732–742
13 Mavrommatis AC, Theodoridis T, Orfanidou A, Roussos C, Christopoulou-Kokkinou V, Zakynthinos S. Coagulation system and platelets are fully activated in uncomplicated sepsis. Crit Care Med 2000;28(02):451–457
14 Iba T, Ogura H. Role of extracellular vesicles in the development of sepsis-induced coagulopathy. J Intensive Care 2018;6(01):68
15 Nieuwland R, Berckmans RJ, McGregor S, et al. Cellular origin and procoagulant properties of microparticles in meningococcal sepsis. Blood 2000;95(03):930–935
16 Horstman LL, Ahn YS. Platelet microparticles: a wide-angle perspective. Crit Rev Oncol Hematol 1999;30(02):111–142
17 Walenta KL, Link A, Friedrich EB, Böhm M. Circulating microparticles in septic shock. Am J Respir Crit Care Med 2009;180(01): 100, author reply 100–101
18 Delabranche X, Stiel L, Severac F, et al. Evidence of NETosis in septic shock-induced disseminated intravascular coagulation. Shock 2017;47(03):313–317
19 Oehmcke S, Westman J, Malmström J, et al. A novel role for procoagulant microvesicles in the early host defense against streptococcus pyogenes. PLoS Pathog 2013;9(08):e1003529
20 Iba T, Levy JH. Derangement of the endothelial glycocalyx in sepsis. J Thromb Haemost 2019;17(02):283–294
21 Becker BF, Chappell D, Bruegger D, Annecke T, Jacob M. Therapeutic strategies targeting the endothelial glycocalyx: acute deficits, but great potential. Cardiovasc Res 2010;87(02):300–310
22 Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M; Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001;86(05):1327–1330
23 Di Nisio M, Thachil J, Squizzato A. Management of disseminated intravascular coagulation: a survey of the International Society on Thrombosis and Haemostasis. Thromb Res 2015;136(02):239–242
24 Shakur H, Roberts I, Bautista R, et al; CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet 2010;376(9734):23–32
25 Gando S, Iba T, Eguchi Y, et al; Japanese Association for Acute Medicine Disseminated Intravascular Coagulation (JAAM DIC) Study Group. A multicenter, prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill patients: comparing current criteria. Crit Care Med 2006;34(03):625–631

26 Yamakawa K, Umemura Y, Hayakawa M, et al; Japan Septic Disseminated Intravascular Coagulation (J-Septic DIC) study group. Benefit profile of anticoagulant therapy in sepsis: a nationwide multicentre registry in Japan. Crit Care 2016;20(01):229

27 Iba T, Nisio MD, Levy JH, Kitamura N, Thachil J. New criteria for sepsis-induced coagulopathy (SIC) following the revised sepsis definition: a retrospective analysis of a nationwide survey. BMJ Open 2017;7(09):e017046

28 Iba T, Arakawa M, Di Nisio M, et al. Newly proposed sepsis-induced coagulopathy precedes International Society on Thrombosis and Haemostasis overt-disseminated intravascular coagulation and predicts high mortality. J Intensive Care Med 2018. doi: 10.1177/0885066618773679. [Epub ahead of print]

29 Yamakawa K, Yoshimura J, Ito T, Hayakawa M, Hamasaki T, Fujimi S. External validation of the two newly proposed criteria for assessing coagulopathy in sepsis. Thromb Haemost 2019;119 (02):203–212

30 Umemura Y, Yamakawa K. Optimal patient selection for anticoagulant therapy in sepsis: an evidence-based proposal from Japan. J Thromb Haemost 2018;16(03):462–464

31 Iba T, Levy JH, Wada H, Thachil J, Warkentin T, Levi M. Differential diagnoses for sepsis-induced disseminated intravascular coagulation: communication from the SSC of the ISTH. J Thromb Haemost 2019;17(02):415–419

32 Nishida O, Ogura H, Egi M, et al. The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2016 (J-SSCG 2016). Acute Med Surg 2018;5(01):3–89

33 Warren BL, Eid A, Singer P, et al; KyberSept Trial Study Group. Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. JAMA 2001;286(15):1869–1878

34 Kienast J, Juers M, Wiedermann CJ, et al; KyberSept investigators. Treatment effects of high-dose antithrombin without concomitant heparin in patients with severe sepsis with or without disseminated intravascular coagulation. J Thromb Haemost 2006;4(01):90–97

35 Sobczak AIS, Pitt SJ, Stewart AJ. Glycosaminoglycan neutralization in coagulation control. Arterioscler Thromb Vasc Biol 2018;38 (06):1258–1270

36 Becker BF, Jacob M, Leipert S, Salmon AH, Chappell D. Degradation of the endothelial glycocalyx in clinical settings: searching for the sheddases. Br J Clin Pharmacol 2015;80(03):389–402

37 Endo S, Shimazaki R; Antithrombin Gamma Study Group. An open-label, randomized, phase 3 study of the efficacy and safety of antithrombin gamma in patients with sepsis-induced disseminated intravascular coagulation syndrome. J Intensive Care 2018; 6:75

38 Vincent JL, Ramesh MK, Ernest D, et al. A randomized, double-blind, placebo-controlled, Phase 2b study to evaluate the safety and efficacy of recombinant human soluble thrombomodulin, ART-123, in patients with sepsis and suspected disseminated intravascular coagulation. Crit Care Med 2013;41(09): 2069–2079

39 Jaimes F, De La Rosa G, Morales C, et al. Unfractioned heparin for treatment of sepsis: a randomized clinical trial (The HETRASE Study). Crit Care Med 2009;37(04):1185–1196

40 Aikawa N, Shimazaki S, Yamamoto Y, et al. Thrombomodulin alfa in the treatment of infectious patients complicated by disseminated intravascular coagulation: subanalysis from the phase 3 trial. Shock 2011;35(04):349–354

41 Aoki N, Matsuda T, Saito H, et al; CTC-111-IM Clinical Research Group. A comparative double-blind randomized trial of activated protein C and unfractionated heparin in the treatment of disseminated intravascular coagulation. Int J Hematol 2002;75(05): 540–547

42 Liu XL, Wang XZ, Liu XX, et al. Low-dose heparin as treatment for early disseminated intravascular coagulation during sepsis: a prospective clinical study. Exp Ther Med 2014;7(03):604–608

43 Bernard GR, Vincent JL, Laterre PF, et al; Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344(10):699–709

44 Dhainaut JF, Yan SB, Joyce DE, et al. Treatment effects of drotrecogin alfa (activated) in patients with severe sepsis with or without overt disseminated intravascular coagulation. J Thromb Haemost 2004;2(11):1924–1933

45 Ranieri VM, Thompson BT, Barie PS, et al; PROWESS-SHOCK Study Group. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med 2012;366(22):2055–2064

46 Wunderink RG, Laterre PF, Francois B, et al; CAPTIVATE Trial Group. Recombinant tissue factor pathway inhibitor in severe community-acquired pneumonia: a randomized trial. Am J Respir Crit Care Med 2011;183(11):1561–1568