Mini Review

Sepsis-induced disseminated intravascular coagulation: an international estrangement of disease concept

Noritaka Ushio,[1] Takeshi Wada,[2] Yuichiro Ono,[3] and Kazuma Yamakawa[1]

[1]Department of Emergency and Critical Care Medicine, Osaka Medical and Pharmaceutical University, Takatsuki, Japan, [2]Division of Acute and Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Hokkaido University Faculty of Medicine, Sapporo, Japan, and [3]Kakogawa Acute Care Medical Center, Hyogo Prefectural Kakogawa Medical Center, Kakogawa, Japan

Disseminated intravascular coagulation (DIC) is an acquired syndrome characterized by widespread intravascular activation of coagulation, which can be caused by infectious and noninfectious insults, such as trauma, postcardiac arrest syndrome, and malignant diseases. At present, diagnosis and treatment of DIC clearly differ between Japan and Western countries; in Japan, DIC has long been considered a therapeutic target, and much evidence on DIC has been published. However, there has recently been no international consensus on whether DIC should be a therapeutic target with anticoagulant therapy. This review describes the coagulofibrinolytic system abnormalities associated with sepsis and discusses related management strategies. It also explores the reasons why DIC is perceived differently in different regions. There is a major discrepancy between diagnostic and treatment options in Japan, which are based on holistic assessments of trials, as well as the results of post hoc subgroup analyses and observational studies, and those in Western countries, which are based mainly on the results of sepsis mega trials, especially randomized controlled trials. The differences might also be due to various patient factors in each region, especially racial characteristics in thrombolytic mechanisms, and differences in interpretation of evidence for candidate drugs. Hence, Japanese researchers need to distribute their high-quality clinical research data not only to Japan but also to the rest of the world.

Key words: Anticoagulant, diagnosis, disseminated intravascular coagulation, East Asian paradox, immunothrombosis, sepsis

INTRODUCTION

DISSEMINATED INTRAVASCULAR COAGULATION (DIC) is a rare and severe condition characterized by abnormal coagulation and fibrinolysis in acute pathologies, including sepsis, trauma, postcardiac arrest syndrome, burns, acute pancreatitis, and obstetric hemorrhage, as well as malignancies, such as acute leukemia and solid cancers.[1] Disseminated intravascular coagulation is well-known among clinicians in Japan, where the concept of DIC management (i.e., appropriate diagnosis and early intervention) is firmly rooted.[2] However, there has recently been no international consensus on whether DIC is a validated therapeutic target with anticoagulant therapy.[3–5] Antithrombin and thrombomodulin are approved by the Japanese national health insurance and widely administered for DIC in Japan, but these DIC medications are not common for this purpose outside Japan.[2,6,7] This review aims to explore the reasons behind the big discrepancies in how DIC is perceived in different regions. This section focuses on coagulofibrinolytic abnormalities associated with sepsis, for which plenty of evidence has been pooled, and discusses the relevant management strategies.

FAILURE OF LARGE-SCALE TRIALS AND POSITIONING OF INTERNATIONAL GUIDELINES

AT PRESENT, DIC management guidelines differ between Japan and Western countries. A review article published in 1999 in the *New England Journal of Medicine* states that inflammation, which is emphasized in Japan, activates the clotting cascade, dysregulates coagulation control mechanisms, and suppresses fibrinolysis, thereby leading to microthrombi formation; disseminated thrombosis causes organ damage, and anticoagulation therapy has anti-

Corresponding: Kazuma Yamakawa, MD, PhD, Department of Emergency and Critical Care Medicine, Osaka Medical and Pharmaceutical University, 2-7 Daigakumachi, Takatsuki, Osaka 569-8686, Japan. E-mail: kazuma.yamakawa@ompu.ac.jp.

Received 8 Sep, 2022; accepted 5 Apr, 2023

Funding Information

No funding information provided.

inflammatory and fibrinolytic effects in addition to anticoagulant property.[8] Hence, there was similar awareness of abnormal coagulation in sepsis in European countries.[9] The interest in this pathology prompted researchers to investigate the effectiveness of antithrombin formulations (KyberSept trial) and activated protein C (PROWESS trial).[10,11]

When discussing sepsis and anticoagulant therapy, it is essential to mention the "drama" that originated from the PROWESS trial. The PROWESS trial was an international phase III randomized controlled trial (RCT), which aimed to validate the effectiveness of activated protein C.[11] Importantly, this trial examined an overall sepsis cohort regardless of the presence of DIC. In the result, a 6.1% reduction in mortality was observed in the activated protein C treatment group; the finding generated enthusiasm about the potential applications of activated protein C in sepsis worldwide. In response to this trial, the Surviving Sepsis Campaign Guideline (SSCG) 2004 suggested that activated protein C can be used for sepsis patients at a high risk of death.[12] However, the 2008 revision of SSCG modified both the recommendation strength and target population: the recommendation was limited to patients expected to have an Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 25 points or more and was not indicated for patients with APACHE II scores of less than 20 points.[13] This was a major change of the recommendation in just 4 years. Moreover, regarding adverse events, an increased risk of bleeding due to the administration of activated protein C was stressed. As the evidence supporting the recommendation was based on a subgroup analysis of the PROWESS trial, the United States Food and Drug Administration and other regulatory authorities requested another trial targeted at a severely ill patient group.[14] This was the PROWESS-SHOCK trial including only septic shock patients, which did NOT show that activated protein C improved survival outcomes. Ultimately, the product was completely withdrawn from the market.[15] This series of "dramas" that unfolded in the SSCG also revealed some nonscientific aspects (such as how pharmaceutical companies had funded the guideline drafting process and lobbied members of the drafting committee), as well as scientific aspects (such as interpretation of subgroup analyses and early discontinuation of clinical trials).[16]

Unfortunately, all large RCTs examining specific anticoagulant therapy for sepsis, such as the PROWESS, KyberSept, and OPTIMIST trials, failed (Fig. 1). In 2016, when the SCARLET trial was expected to have results, the term "DIC" appeared in SSCG 2016 and briefly gained attention; this trial also failed in 2019.[17] Therefore, the current international standard, SSCG 2021, eliminated not only the pharmaceutical recommendations but also the term "DIC," which was described in the previous 2016 edition.[7] Consequently, researchers and clinicians in Western countries might not think of the coagulation abnormalities accompanying sepsis as a therapeutic target.

JAPAN'S CONTRIBUTION TO THE DEVELOPMENT OF DIAGNOSTIC CRITERIA AND MANAGEMENT OF SEPSIS-INDUED DIC

IN 1951, A pathological examination of three cases of placental abruption by Dr Schneider, an American obstetrician, confirmed the formation of fibrin thrombi in the blood vessels, and this condition was named "disseminated intravascular coagulation."[18] With this as a turning point, the concept of DIC gained wide recognition, but DIC diagnosis was unfeasible in real clinical practice because of the requirement for pathological evidence of microthrombi. Against this background, Japanese researchers with great interest in DIC developed the Japanese Ministry of Health and Welfare (JMHW) DIC diagnostic criteria based on a scoring system using general coagulation and fibrinolysis markers in the 1980s,[19] and substantial evidence on DIC has emerged based on the JMHW diagnostic criteria. The International Society on Thrombosis and Hemostasis (ISTH) overt-DIC criteria,[20] which was established with reference to the JMHW criteria, has been the global gold standard; however, the two criteria diagnose DIC, the condition might already be at a stage of irreversible decompensation, thus late from the therapeutic time window.[1] Japanese physicians complained about the low sensitivity of these diagnostic criteria, leading to the establishment of the Japanese Association for Acute Medicine (JAAM) DIC diagnostic criteria in 2008, which were specifically designed for the diagnosis of DIC related to acute diseases, including sepsis and trauma.[21] This criterion is characterized by high sensitivity for early DIC diagnosis while maintaining diagnostic specificity and has been shown to be predictive of DIC severity and outcomes.[22] Therefore, existing DIC diagnostic criteria, including the ISTH overt-DIC diagnostic criteria, have been developed based on evidence mainly originating in Japan.

As mentioned above, there has long been a high level of interest in DIC in Japan, and anticoagulants have been widely used as insurance-approved drugs for DIC.[23] A meta-analysis of RCTs on the effectiveness of anticoagulant therapy for sepsis indicated that the survival rate did not change with anticoagulant therapy in the overall sepsis cohort or the sepsis cohort with any mildly deranged coagulation parameters, but increased in the confirmed sepsis-induced DIC cohort.[24] The results of this study reiterated that the optimal population benefiting from anticoagulant therapy comprises those with sepsis-induced DIC, rather than those with overall sepsis.

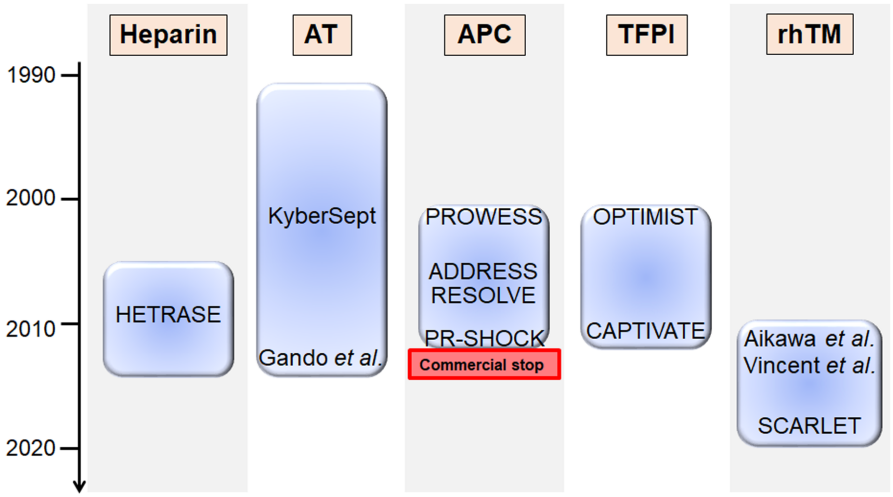

Fig. 1. History of randomized controlled trials evaluating the efficacy of anticoagulants for sepsis pathologies. All randomized controlled trials (RCTs) shown in this figure failed to demonstrate a survival benefit for each anticoagulant. Of note, most of these RCTs included patients with sepsis and severe sepsis, but not those with disseminated intravascular coagulation. ADDRESS, Administration of Drotrecogin Alfa in Early stage Severe Sepsis; APC, activated protein C; AT, antithrombin; CAPTIVATE, Community-Acquired Pneumonia Tifacogin Intra-Venous Administration Trial for Efficacy; HETRASE, Unfractioned Heparin for Treatment of Sepsis; OPTIMIST, Optimized Phase 3 Tifacogin in Multicenter International Sepsis Trial; PROWESS, Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis; PR-SHOCK, Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis and Septic Shock; RESOLVE, Researching Severe Sepsis and Organ Dysfunction in Children, A Global Perspective; rhTM, recombinant human thrombomodulin.; SCARLET, Sepsis Coagulopathy Asahi Recombinant LE Thrombomodulin; TFPI, tissue factor pathway inhibitor.

With this background, the Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020 (J-SSCG 2020) have emphasized the importance of DIC management.[2] These guidelines have suggested antithrombin replacement therapy and administration of recombinant human thrombomodulin (rhTM) as therapeutic interventions. However, it should be noted that an RCT to evaluate the efficacy of antithrombin at the standard Japanese dosage (30 IU/kg per day for 3 days) for patients diagnosed using the JAAM DIC diagnostic criteria showed an increasing recovery rate from DIC on day 3, but no improvement in the 28-day mortality.[25] Furthermore, the most recent RCT that verified the efficacy of rhTM in patients with sepsis-associated coagulopathy also failed to determine the efficacy of this drug.[17] Despite the results of these RCTs, antithrombin supplementation for sepsis-induced DIC has remained the same as before, and the proportion of patients with sepsis-induced DIC receiving rhTM has increased since its launch in 2008.[23] Although the causal relationship is unknown, the mortality rate of patients with sepsis-induced DIC decreased after rhTM was launched.[23] Importantly, some clinicians in Japan believe that anticoagulant therapy is unnecessary for coagulopathy associated with sepsis.[6]

UNDERSTANDING THE PATHOPHYSIOLOGY OF SEPSIS-INDUCED DIC

DISSEMINATED INTRAVASCULAR COAGULATION can be caused by various underlying diseases, with the single mutual denominator being "an excessive coagulation response and the presence of microthrombosis." However, the pathology widely differs depending on the triggering insults.[1,26] There are considerable variations in progression manners, collapsed physiologies, clinical symptoms, and blood test results. Moreover, sepsis-induced DIC, obstetric-induced DIC, trauma-induced DIC, and leukemia-induced DIC have distinct pathologies, clinical signs, and laboratory findings.[1,26] Therefore, it is often difficult for general clinicians to understand the pathophysiology. Disseminated intravascular coagulation was historically categorized into inhibited and increased fibrinolysis. The pathological analysis of sepsis-induced DIC has advanced over the last decade.[26,27] It is crucial to understand the process by which sepsis becomes complicated due to sepsis-induced DIC.

The concept of "immunothrombosis" has recently been acknowledged, in which the change in clotting and declotting associated with sepsis is regarded as a natural

physiological response.[28] When pathogenic microorganisms enter our body, the formation of thrombi protects us by preventing bacterial dissemination and reducing blood flow, thereby allowing immune cells to come into contact with the invaders.[29] The main substances in immunothrombosis are neutrophil extracellular traps (NETs) released from activated neutrophils and histones, which have strong coagulation inflammation-inducing potency. If NETs and histones act synergistically and vascular endothelial disorder induces impairment of anticoagulant activity, including the actions of antithrombin, tissue factor pathway inhibitor, and thrombomodulin, nonderanged immunothrombosis, which is usually a normal physiological process, will eventually become pathological, leading to sepsis-induced DIC.[30] Therefore, it would be reasonable that immunothrombosis, a normal reaction to infection at early-stage sepsis, should not be a treatment target. Sepsis-induced DIC is a terminology that reflects a dysregulated inflammatory coagulofibrinolytic response, leading to a harmful reaction.[1,31]

The main players of this dysregulated inflammatory coagulofibrinolytic response are NETs released from activated neutrophils and histones, as mentioned above (Fig. 2). It has been proven that all the elements consisting of an abnormal cascade of sepsis-induced DIC, including hypercoagulability, which is enhanced by endothelial cell injury, inflammatory response, suppressed fibrinolysis, and cytotoxicity, can be induced by NETs and histones.[32,33] From this viewpoint, there have been ideas to treat sepsis by combatting histones and NETs, which have been the subjects of basic research.[32,33]

OPTIMAL THERAPEUTIC TARGETS FOR SPECIFIC ANTICOAGULANT THERAPY IN JAPAN

LATELY, IN JAPAN, it has been regarded important that target subjects for specific anticoagulants should be selected according to not only diagnostic criteria but also

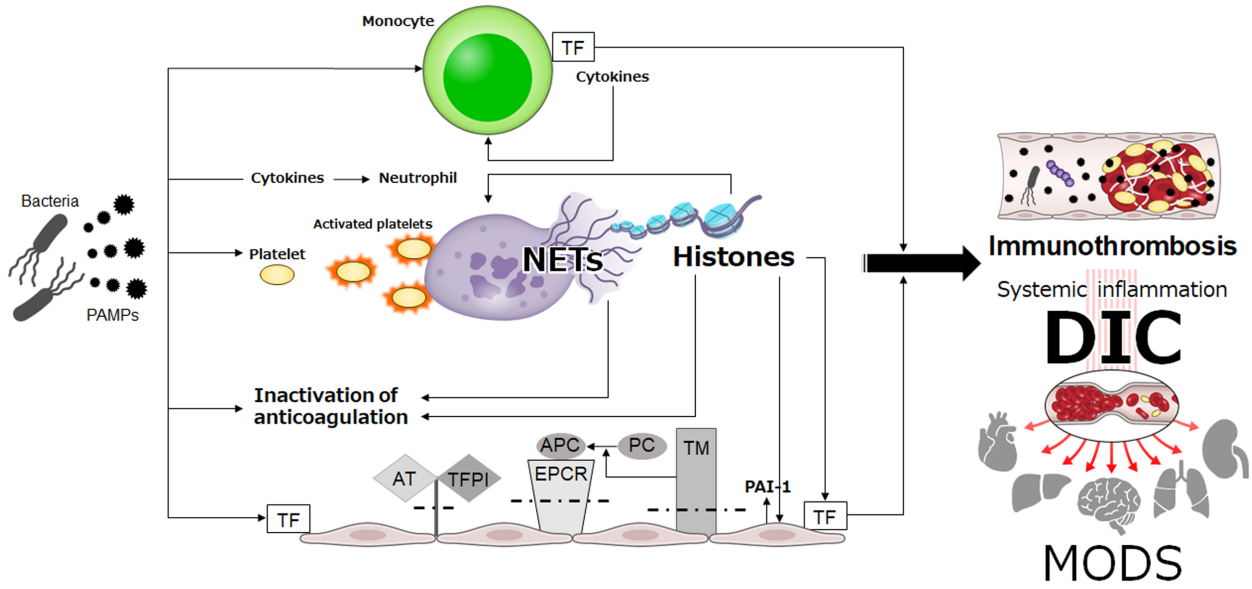

Fig. 2. Pathophysiological schema of immunothrombosis and disseminated intravascular coagulation (DIC). Cytokines released from immune cells stimulated by pathogen-associated molecular patterns (PAMPs) derived from bacteria induce tissue factor expression on the surface of monocytes and endothelial cells, causing endothelial injury, followed by inactivation of anticoagulant mechanisms, including antithrombin (AT), tissue factor pathway inhibitor (TFPI), and thrombomodulin (TM), leading to further activation of coagulation. In addition, neutrophil extracellular traps (NETs) are released from activated neutrophils through cytokines and platelets activated by PAMPs. Histones, a major component of NETs, facilitate further release of NETs. This interaction between NETs and histones promotes coagulation activation by the recruitment of platelets and impairment of anticoagulant mechanisms and antifibrinolysis through increased plasminogen activator inhibitor-1 (PAI-1) expression, contributing to the progression of physiological immunothrombosis into pathological DIC. AT and TFPI bind to heparan sulfate (gray bar) secreted by endothelial cells. Dashed lines indicate cleavage of anticoagulant proteins from endothelial cells and their dysfunctional state. APC, activated protein C; EPCR, endothelial protein C receptor; MODS, multiple organ dysfunction syndrome; PC, protein C; TF, tissue factor.

disease severity.[34] In a Japanese observational study that stratified "disease severity" by the Sequential Organ Failure Assessment (SOFA) score, anticoagulant therapy showed a beneficial effect on mortality in participants with SOFA scores of 13–17 points.[35] Another study revealed that anticoagulant therapy improved patient mortality only in severe cases with APACHE II scores of 24–29 points.[36] Hayakawa *et al*.[37] utilized antithrombin activity to group patients and examined its replenishment, and they found improved survival only in the group with antithrombin activity of 43% or less. Furthermore, recent observational studies showed that patient age could affect therapeutic effectiveness.[38]

All of the above observational studies indicate that target patients with sepsis-induced DIC should be selected not merely based on whether they meet the diagnostic criteria but also by some "third criterion" (Fig. 3). Similarly, a subanalysis of large-scale RCTs (PROWESS and KyberSept trials) in the 2000s showed a benefit in patients with DIC or high severity.[13,39,40] In the same concept, these series of observational studies in Japan over the past decade suggest the importance of patient selection. These studies led to a major divergence between Japan and Western countries. Researchers in Japan consider that the therapy can be effective and needs to be incorporated into the management of sepsis patients with DIC. In recent years, many studies have reported the clustering of patients with sepsis by unsupervised learning.[41] In addition, Kudo *et al*.[42] indicated that thrombomodulin was effective in only one specific group of patients by machine learning. These findings suggest the potential use of machine learning to aid patient selection in the future. However, all the contents of this chapter were extracted from observational studies or post hoc studies. Therefore, multicenter prospective trials are required in the future.

HOW WOULD DIC BE PERCEIVED IN JAPAN AND WESTERN COUNTRIES?

THIS SECTION WILL discuss the differences in the levels of interest in the theme of this review – sepsis-induced DIC – between Japan and Western countries. First of all, is there an awareness of sepsis-induced hematological dysfunction/failure in Western countries? The answer is "Yes." It is not a major topic in the literature, but online textbooks and learning materials for trainees and specialists in North America, Europe, and Australia have never forgotten to discuss DIC.[43–45] The related content does not vary greatly among these materials: it generally starts with the causes and pathophysiology of DIC and mentions differential diagnoses and treatments. Interestingly, articles on sepsis-induced DIC written by Japanese researchers are frequently quoted, and the JAAM diagnostic criteria for DIC are suggested as one of the useful diagnostic criteria. Some of these materials appraise the Japanese criteria as having high sensitivity but low specificity, which has also been a debated topic in Japan. Thus, the contributions of Japanese scientists in this area have been recognized internationally.

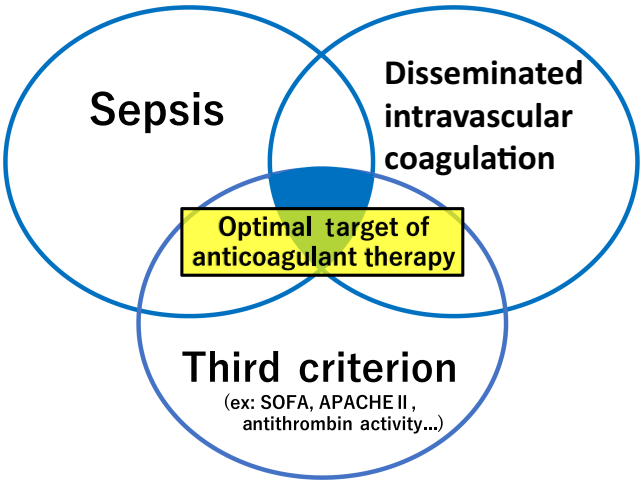

Fig. 3. Conceptual diagram for optimizing anticoagulant therapy targets in sepsis patients. The optimal target for anticoagulation therapy might be patients who meet all the three components of sepsis, disseminated intravascular coagulation, and the third criterion, given the results of observational studies. The third criterion might be severity of the disease, such as the Sequential Organ Failure Assessment (SOFA) score or Acute Physiology and Chronic Health Evaluation II (APACHE II) score, or antithrombin activity. Thus, the third criterion has not yet been determined, but may be clarified in the future.

The next question is "What kind of pictures does DIC bring to us?" One physician could envision the macroscopic clinical images, such as purpura fulminans associated with meningococcal sepsis or intracerebral hemorrhage associated with a prolonged clotting time, while another physician might think of the microscopic level of coagulation cascades and intravascular inflammatory signal transduction. Notably, the classic purpura fulminans associated with infection-driven coagulopathy, a visible form of organ failure, which has recently been renamed symmetrical peripheral gangrene, has been addressed in the aforementioned textbooks published in various Western countries.[43–45] In contrast, articles discussing this organ dysfunction written by Japanese authors tend to dedicate space to immunothrombosis and microcirculation more than macroclinical pictures.[1,21,29,30]

What is making this difference? A racial difference in thrombosis–hemostasis characteristics might affect Western and Japanese views. Asians are reported to have less venous thromboembolism compared to Europeans.[46] In addition, a theory called "East Asian paradox" has lately been discussed, mostly in the cardiovascular field.[47] This theory suggests that the ideal dosage range for antithrombotic therapies, in which a thromboprophylaxis effect is achieved with fewer hemorrhagic complications, should be individually set for East Asians, given their high risk of bleeding (Fig. 4).[47–50]

The ethnic characteristics of East Asians, including Japanese, who have a tendency towards less blood clotting and more bleeding, can lead to unique clinical pictures and different responses to anticoagulant therapy. This differences have led to the interests of clinicians between Western countries and East Asia.

HOW WOULD DIC CASES BE DEALT WITH IN WESTERN COUNTRIES?

WHAT IS A treatment option when sepsis-induced DIC is diagnosed? The learning materials in North America, Europe, and Australia mentioned above emphasize treating the underlying disease with general management of DIC. Interestingly, although medications such as antithrombin and rhTM recommended in the Japanese sepsis guidelines have been somewhat recognized, their clinical efficacy is currently deemed as lacking sufficient evidence in the descriptions.[17,24]

Moreover, not just antithrombin and thrombomodulin formulations but also tissue factor pathway inhibitors, which are not approved in Japan, have been critically appraised and then judged as lacking scientific evidence for clinical use.[43–45] Importantly, no high-quality clinical trials have examined both sepsis-induced DIC and its

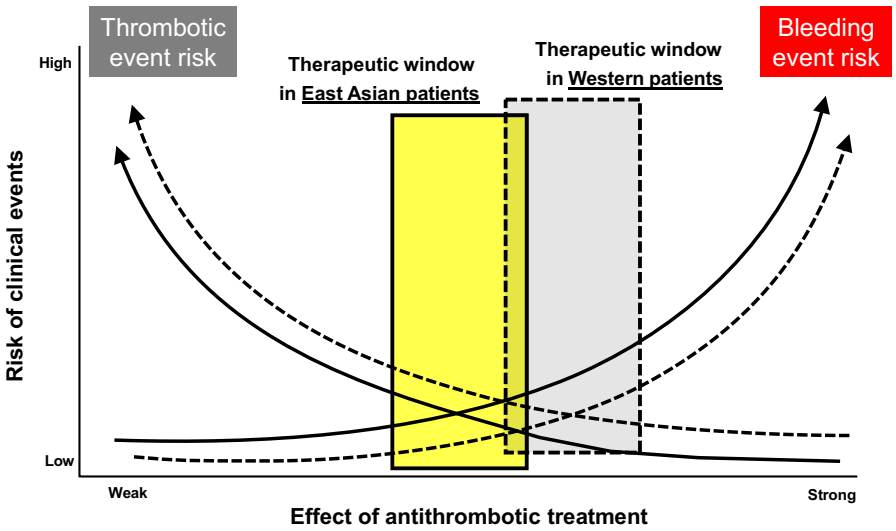

Fig. 4. Overview of the East Asian paradox. The optimal therapeutic range of antithrombotic treatment should make both hemorrhagic and ischemic risks as low as possible, therefore intersections of event risk lines represent optimal strength of the treatment. Also, when both an East Asian patient and a Western patient are given an equally strong antithrombotic agent, the East Asian patient would have higher bleeding and lower thrombotic risks. Therefore, the optimal antithrombotic strength for East Asian patients should be weaker than that for Western patients. Right arrowed solid line (→), East Asian bleeding event risk; left arrowed solid line (←), East Asian thrombotic event risk; right arrowed dotted line (⇢), Western bleeding event risk; left arrowed dotted line (⇠), Western thrombotic event risk; solid outline yellow box, optimal antithrombotic effect zone for East Asian patient; dashed outline gray box, optimal antithrombotic effect zone for Western patient.

pharmaceutical treatment options suggested in the Japanese sepsis guidelines. To emphasize, there is a major discrepancy between options overseas, which are based mainly on results of sepsis trials, especially RCTs, and those in Japan, which are based on holistic assessments with RCTs as well as the results of subgroup analyses and observational studies.

Another difference in daily practice between Japan and other regions, especially Western countries, is the frequency of heparin administration. In intensive care units overseas, deep vein thrombosis prophylactic doses of unfractionated heparin (UFH) or low molecular weight heparin (LMWH) are highly recommended for almost all admissions unless there are contraindications, such as the presence of active hemorrhage. Lauzier *et al*. reported that these anticoagulants were used in more than 80% of admitted patients, and UFH was preferred to LMWH.[51] This is not called anticoagulant therapy but is considered deep vein thrombosis prophylaxis. It is unclear whether such small doses of classic nonspecific anticoagulant, heparin, would be effective in preventing and treating sepsis-induced DIC.

SUMMARY

IN SUMMARY, THE difference in attitudes toward pharmacological DIC therapy between Japan and Western countries could be due to various patient factors, especially racial differences in thrombosis–hemostasis mechanisms, and the attitudes toward evidence on the candidate medications. To bridge the gap between Japan and Western countries in such a chaotic field of DIC, we Japanese researchers need to distribute high-quality research data to the world from Japan.

ACKNOWLEDGMENTS

WE WOULD LIKE to thank Editage for English language editing and Mr. Tsuda (Davinci Medical Illustration Office) for his medical illustration service.

DISCLOSURE

APPROVAL OF THE research protocol: N/A.

Informed consent: N/A.

Registry and registration no. of the study/trial: N/A.

Animal studies: N/A.

Conflict of interest: K.Y. received grants from Asahi Kasei Pharma and Nihon Pharmaceutical. T.W. received honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Asahi Kasei Pharma. The other authors have no conflict of interest for this article.

DATA AVAILABILITY STATEMENT

NOT APPLICABLE.

REFERENCES

1 Gando S, Levi M, Toh CH. Disseminated intravascular coagulation. Nat. Rev. Dis. Primers. 2016; 2: 16037.
2 Egi M, Ogura H, Yatabe T *et al*. The Japanese Clinical Practice Guidelines for management of sepsis and septic shock 2020 (J-SSCG 2020). Acute Med. Surg. 2021; 8: e659.
3 Wada H, Matsumoto T, Yamashita Y. Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. J. Intensive Care 2014; 2: 15.
4 Toh CH, Dennis M. Disseminated intravascular coagulation: old disease, new hope. BMJ 2003; 327: 974–7.
5 Iba T, Asakura H. Comparison between British and Japanese guidelines for the diagnosis and treatment of disseminated intravascular coagulation. Br. J. Haematol. 2010; 149: 461–2.
6 Yamakawa K, Hasegawa D, Yasuda H *et al*. Galápagosization of sepsis management in Japan: a nationwide survey of current practices. Acute Med. Surg. 2020; 7: e561.
7 Evans L, Rhodes A, Alhazzani W *et al*. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021; 47: 1181–247.
8 Levi M, Ten Cate H. Disseminated intravascular coagulation. N. Engl. J. Med. 1999; 341: 586–92.
9 Levi M, Ten Cate H, van der Poll T *et al*. Pathogenesis of disseminated intravascular coagulation in sepsis. JAMA 1993; 270: 975–9.
10 Warren BL, Eid A, Singer P *et al*. Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. JAMA 2001; 286: 1869–78.
11 Bernard GR, Vincent JL, Laterre PF *et al*. Efficacy and safety of recombinant human activated protein C for severe sepsis. N. Engl. J. Med. 2001; 344: 699–709.
12 Dellinger RP, Carlet JM, Masur H *et al*. Surviving sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit. Care Med. 2004; 32: 858–73.
13 Dellinger RP, Levy MM, Carlet JM *et al*. Surviving sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit. Care Med. 2008; 36: 296–327.
14 Eichacker PQ, Natanson C, Danner RL. Surviving sepsis — Practice guidelines, marketing Campaigns, and Eli Lilly. N. Engl. J. Med. 2006; 355: 1640–2.

15 Ranieri VM, Thompson BT, Barie PS *et al*. Drotrecogin alfa (activated) in adults with septic shock. N. Engl. J. Med. 2012; 366: 2055–64.
16 Izawa J, Uchino S, Sanui M. What should we learn from the failure of an activated protein C? J Jpn Soc. Intens.Care Med. 2012; 19: 586–94.
17 Vincent JL, Francois B, Zabolotskikh I *et al*. Effect of a recombinant human soluble thrombomodulin on mortality in patients with sepsis-associated coagulopathy: the SCARLET randomized clinical trial. JAMA 2019; 321: 1993–2002.
18 Schneider CL. Fibrin embolism (disseminated intravascular coagulation) with defibrination as one of the end results during placenta abruptio. Surg. Gynecol. Obstet. 1951; 92: 27–34.
19 Kobayashi N, Maekawa T, Takada M *et al*. Criteria for diagnosis of DIC based on the analysis of clinical and laboratory findings in 345 DIC patients collected by the Research Committee on DIC in Japan. Bibl. Haematol. 1983; 49: 265–75.
20 Taylor FB Jr, Toh CH, Hoots WK *et al*. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb. Haemost. 2001; 86: 1327–30.
21 Gando S, Saitoh D, Ogura H *et al*. Natural history of disseminated intravascular coagulation diagnosed based on the newly established diagnostic criteria for critically ill patients: results of a multicenter, prospective survey. Crit. Care Med. 2008; 36: 145–50.
22 Gando S, Saitoh D, Ogura H *et al*. A multicenter, prospective validation study of the Japanese Association for Acute Medicine disseminated intravascular coagulation scoring system in patients with severe sepsis. Crit. Care 2013; 17: R111.
23 Yamakawa K, Ohbe H, Taniguchi K, Matsui H, Fushimi K, Yasunaga H. Time trends of the outcomes and treatment options for disseminated intravascular coagulation: a nationwide observational study in Japan. JMA J. 2020; 3: 313–20.
24 Umemura Y, Yamakawa K, Ogura H, Yuhara H, Fujimi S. Efficacy and safety of anticoagulant therapy in three specific populations with sepsis: a meta-analysis of randomized controlled trials. J. Thromb. Haemost. 2016; 14: 518–30.
25 Gando S, Saitoh D, Ishikura H *et al*. A randomized, controlled, multicenter trial of the effects of antithrombin on disseminated intravascular coagulation in patients with sepsis. Crit. Care 2013; 17: R297.
26 Asakura H. Classifying types of disseminated intravascular coagulation: clinical and animal models. J. Intensive Care 2014; 2: 20.
27 Iba T, Connors JM, Nagaoka I, Levy JH. Recent advances in the research and management of sepsis-associated DIC. Int. J. Hematol. 2021; 113: 24–33.
28 Engelmann B, Massberg S. Thrombosis as an intravas-cular effector of innate immunity. Nat. Rev. Immunol. 2013; 13: 34–45.
29 Ito T. PAMPs and DAMPs as triggers for DIC. J. Intensive Care 2014; 2: 67.
30 Iba T, Levy JH. Inflammation and thrombosis: roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis. J. Thromb. Haemost. 2018; 16: 231–41.
31 Wada T, Yamakawa K, Kabata D *et al*. Age-related differences in the survival benefit of the administration of antithrombin, recombinant human thrombomodulin, or their combination in sepsis. Sci. Rep. 2022; 12: 9304.
32 Alhamdi Y, Toh CH. Recent advances in pathophysiology of disseminated intravascular coagulation: the role of circulating histones and neutrophil extracellular traps. F1000Res 2017; 6: 2143.
33 Xu J, Zhang X, Pelayo R *et al*. Extracellular histones are major mediators of death in sepsis. Nat. Med. 2009; 15: 1318–21.
34 Umemura Y, Yamakawa K. Optimal patient selection for anticoagulant therapy in sepsis: an evidence-based proposal from Japan. J. Thromb. Haemost. 2018; 16: 462–4.
35 Yamakawa K, Umemura Y, Hayakawa M *et al*. Benefit profile of anticoagulant therapy in sepsis: a nationwide multicentre registry in Japan. Crit. Care 2016; 20: 229.
36 Yoshimura J, Yamakawa K, Ogura H *et al*. Benefit profile of recombinant human soluble thrombomodulin in sepsis-induced disseminated intravascular coagulation: a multicenter propensity score analysis. Crit. Care 2015; 19: 78.
37 Hayakawa M, Yamakawa K, Kudo D, Ono K. Optimal antithrombin activity threshold for initiating antithrombin supplementation in patients with sepsis-induced disseminated intravascular coagulation: A multicenter retrospective observational study. Clin. Appl. Thromb. Hemost. 2018; 24: 874–83.
38 Takahashi K, Umemura Y, Yamakawa K *et al*. Age is associated with the efficacy of anticoagulant therapies against sepsis-induced disseminated intravascular coagulation. Clin. Appl. Thromb. Hemost. 2021; 27: 10760296211033030.
39 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: 1924–33.
40 Kienast J, Juers M, Wiedermann CJ *et al*. 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: 90–7.
41 Seymour CW, Kennedy JN, Wang S *et al*. Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. JAMA 2019; 321: 2003–17.
42 Kudo D, Goto T, Uchimido R *et al*. Coagulation phenotypes in sepsis and effects of recombinant human thrombomodulin: an analysis of three multicentre observational studies. Crit. Care 2021; 25: 114.

43 Disseminated Intravascular Coagulation (DIC). Internet Book of Critical Care (IBCC). [cited 11 July 2022]. Available from: https://emcrit.org/ibcc/dic/#top.
44 Disseminated Intravascular Coagulation (DIC). ESICM academy. [cited 11 July 2022]. Available from: https://www.esicm.org/wp-content/uploads/2020/04/Disseminated-Intravascular-Coagulation-_.pdf.
45 Disseminated intravascular coagulation (DIC). Deranged physiology. [cited 11 July 2022]. Available from: https://derangedphysiology.com/main/required-reading/haematology-and-oncology/Chapter%20201/disseminated-intravascular-coagulation-dic.
46 Liao S, Woulfe T, Hyder S, Merriman E, Simpson D, Chunilal S. Incidence of venous thromboembolism in different ethnic groups: a regional direct comparison study. J. Thromb. Haemost. 2014; 12: 214–9.
47 Kim HK, Tantry US, Smith SC Jr *et al*. The East Asian paradox: an updated position statement on the challenges to the current antithrombotic strategy in patients with cardiovascular disease. Thromb. Haemost. 2021; 121: 422–32.
48 Huo Y, Jeong YH, Gong Y *et al*. 2018 update of expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. Sci. Bull. 2019; 64: 166–79.
49 Jeong YH. "East Asian paradox": challenge for the current antiplatelet strategy of "one-guideline-fits-all races" in acute coronary syndrome. Curr. Cardiol. Rep. 2014; 16: 485.
50 Shen AY, Yao JF, Brar SS *et al*. Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. J. Am. Coll. Cardiol. 2007; 50: 309–15.
51 Lauzier F, Muscedere J, Deland E *et al*. Thromboprophylaxis patterns and determinants in critically ill patients: a multicenter audit. Crit. Care 2014; 18: R82.