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RECOMMENDATIONS AND GUIDELINES

Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation

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1 | INTRODUCTION

The International Society of Thrombosis and Haemostasis (ISTH) in 2001 defined disseminated intravascular congestion (DIC) as "an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes that can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction."[1] Current information supports the concept that DIC in sepsis is a coagulation disorder induced by infection, but also represents an acute systemic inflammatory response that leads to endothelial dysfunction.[2,3] In sepsis, endothelial injury and subsequent tissue injury due to circulatory abnormalities cause multi-organ failure, and the ensuing DIC is a thromboinflammatory response that affects patient outcomes.[4]

The effectiveness of anticoagulant therapy for sepsis-associated DIC is controversial despite multiple randomized controlled trials (RCTs); however, these studies were performed in patients with sepsis but not consistently with concomitant DIC. Recent studies report that anticoagulant therapy may improve outcomes in septic patients with coagulopathy or DIC,[5,6] and similarly subgroup analyses of anticoagulant therapy in large-scale RCTs reported trends toward a greater risk reduction in mortality only in the subgroup with coagulopathy or DIC.[7,8] As a result, we believe identifying septic patients with coagulopathy is pivotal for targeting anticoagulant therapy.[9]

However, screening all patients with multiple coagulation tests is costly, and as a result, simple and easy-to-use diagnostic criteria have been proposed by the Scientific and Standardization Committee (SSC) on DIC of the ISTH diagnostic criteria for overt DIC.[9] Screening for overt DIC on the day of intensive care unit (ICU) admission was associated with lower mortality, and the association became stronger if the screening was repeated 2 days later, suggesting that DIC screening by itself might lead to improved outcomes.[10] However, patients with advanced coagulopathy, including many with overt DIC based on ISTH criteria, may have illness progression that is no longer amenable to benefit from anticoagulant therapy.[11] Therefore, the DIC SSC proposed a new category identifying an earlier phase of DIC, called "sepsis-induced coagulopathy" (SIC).[12] The SIC diagnostic criteria are important for clinical practice to facilitate early recognition and provide guidance for inclusion criteria for future DIC studies. In this guidance document, we describe the different characteristics of overt DIC and SIC, and outline a two-step sequential

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TABLE 1 ISTH overt DIC and SIC scoring systems

Item	Score	ISTH overt DIC Range	SIC Range
Platelet count (−10^9/L)	2	<50	< 100
	1	≧50, <100	≧100, <150
FDP/D-dimer	3	Strong increase	—
	2	Moderate increase	—
Prothrombin time (PT ratio)	2	≧6 s	(>1.4)
	1	≧3 s, <6 s	(>1.2, ≦1.4)
Fibrinogen (g/mL)	1	<100	—
SOFA score	2	—	≧2
	1	—	1
Total score for DIC or SIC		≧5	≧4

ISTH, International Society on Thrombosis and Haemostasis; DIC, disseminated intravascular coagulation; SIC, sepsis-induced coagulopathy; SOFA, sequential organ failure assessment; SOFA score is the sum of 4 items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA, renal SOFA).

approach using both systems for diagnosing sepsis-associated coagulopathy. We also update diagnostic and therapeutic strategies from the previous ISTH DIC guidance report published in 2013.[13]

2 | DIAGNOSIS OF SEPSIS-ASSOCIATED DIC AND SIC

2.1 | International Society on Thrombosis and Haemostasis overt DIC (ISTH overt DIC)

DIC reduces platelet counts and coagulation factor levels due to pathological activation of hemostasis and consumptive coagulopathy.[14] In 1983, the Japanese Ministry of Health and Welfare created the first diagnostic criteria for DIC comprising both clinical features and laboratory parameters, including platelet count, prothrombin time (PT) ratio, fibrin/fibrinogen degradation products (FDP), and fibrinogen. Subsequently, the ISTH DIC SSC recommended criteria for overt DIC[1] that emphasized laboratory markers, including adding D-dimer as another fibrin-related marker besides FDP (Table 1). The relative importance of the platelet count was decreased, while the importance of fibrin-related markers was increased. Although ISTH overt DIC criteria are widely used,[4] other DIC scoring systems are also employed. In particular, the Japanese Association for Acute Medicine (JAAM) DIC diagnostic criteria are commonly used in Japan to diagnose DIC and for initiating anticoagulant therapy.[11,15] JAAM DIC is specifically designed for the acute onset of DIC occurring in sepsis- and trauma-associated DIC, where scoring for fibrinogen is eliminated but scoring for systemic inflammatory response syndrome (SIRS) is added. Unlike ISTH criteria, platelet count changes can also influence scoring. Previous reports have compared the differences and potential benefits between these scoring systems.[11] However, because no gold standard for DIC diagnosis exists, definitive comparison of the diagnostic accuracy of different scoring systems is challenging.[16] Attempts to evaluate diagnostic accuracy by comparing the predictive value for mortality have been made.[17] However, this is problematic because DIC diagnostic criteria do not directly assess disease severity, unlike such measures as the acute physiology and chronic health evaluation (APACHE) or sequential organ failure assessment (SOFA) scoring systems.

The importance of these scoring methods is to determine which patients might benefit from a specific therapy and to evaluate treatment effect. For example, a post hoc analysis revealed that patients with ISTH overt DIC who were treated with recombinant activated protein C (APC) showed a greater relative risk reduction in mortality compared with the patients without treatment; however, benefit was not observed in patients without overt DIC.[8] This example supports the concept that overt DIC criteria are appropriate not only as a diagnostic tool, but also as identifying patient groups in whom targeted therapies may be most effective.

2.2 | Sepsis-induced coagulopathy (SIC)

One hallmark of sepsis-associated DIC is excessive suppression of fibrinolysis caused by overproduction of plasminogen activator inhibitor-1,[18,19] with potential for associated prothrombotic effects.[20,21] In contrast, such suppression is rarely seen in malignancy-associated DIC.[22] As a result, organ dysfunction often develops in sepsis-associated DIC due to reduced tissue perfusion, while systemic bleeding is a more common feature in (nonsepsis) fibrinolytic phenotype DIC.[22] Consequently, hypofibrinogenemia is not common in sepsis and elevation in fibrin-related markers is not associated with sepsis severity.[23] In contrast, platelet count declines and PT prolongation are correlated with increased mortality in sepsis.[23]

Based on these considerations, SIC criteria were developed by members of the DIC SSC of the ISTH in 2017 to categorize patients with "sepsis and coagulation disorders."[12] These criteria were also designed to be relevant for the updated Sepsis-3 criteria that defined sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection."[24] In this setting, the SOFA score is used for the diagnosis of organ dysfunction and thus, SIC

should be defined as "infection-induced organ dysfunction and coagulopathy." SIC diagnostic criteria are simple and include only three items: platelet count, PT-international normalized ratio (INR), and the SOFA score. The SOFA score was included to confirm the presence of sepsis but does not reflect the sepsis severity; therefore, the score for SOFA was limited to two points even if the SOFA score was more than two. Regarding the assessment of organ dysfunction, the use of SOFA is preferable in the emergency settings and its efficacy should be examined.

The usefulness of the SIC score has been validated.[25-28] The ISTH DIC SSC members compared SIC and ISTH overt DIC scoring systems in sepsis patients with coagulopathy.[25] It was found that almost all patients with overt DIC also met criteria for SIC, and that SIC preceded overt DIC in every case. In another study, SIC criteria appeared to identify a patient group similar to that identified using JAAM DIC criteria.[26] The result was interesting because in SIC criteria, FDP/D-dimer adopted by JAAM DIC criteria was eliminated and SIRS score was replaced with SOFA score. Another validation study[27] reported the usefulness of the SIC criteria based on a Japanese cohort of septic patients. This study found the frequency for meeting positive criteria for ISTH overt DIC was only about half of that for SIC, whereas mortality rates for both sets of criteria were relatively high and comparable. Furthermore, the beneficial effects of anticoagulant therapy were observed in patients who met criteria either for SIC or for ISTH overt DIC.[27] Accordingly, we propose a simplified "two-step" sequential scoring system for the early detection of DIC, consisting of screening first with the SIC score, and in patients who meet criteria for SIC, calculating the overt DIC score as the second step[29] (Figure 1). We believe this approach will increase the potential to identify in a timely fashion those patients who might benefit from anticoagulant therapy and we will discuss this subsequently.

3 | TREATMENT FOR DIC AND SIC

3.1 | Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH)

The efficacy of anticoagulant therapy for sepsis-associated DIC remains controversial and thromboprophylaxis is not a common treatment in an international setting. In the former ISTH guidance, LMWH was rated higher than UFH for the treatment of thrombosis and prophylaxis for the venous thrombosis without the support of high-quality evidence.[13] Actually, UFH and LMWH are difficult to study in part because they are also commonly administered for venous thromboprophylaxis. The effect of UFH for sepsis was examined in a RCT and no survival benefit was reported.[30] However, this study was performed in patients with suspected sepsis and who did not necessarily have associated DIC. Two RCTs have compared heparin versus other anticoagulant agents in patients with septic DIC. Aikawa et al[31] performed a subanalysis of a Phase 3 study that examined the effect of recombinant soluble thrombomodulin (rsTM). In 80 sepsis cases, the mortality was 21.4% in the rsTM and 31.6% in the heparin group (95% confidence interval: −9.1% to 29.4%). Aoki et al[32] compared UFH (control group) with APC. They examined the mortality in 49 APC-treated patients and 55 UFH-treated patients, and reported significantly better survival in the APC group (20.4% versus 40%, $P < .05$). In contrast, Liu et al[33] examined the effect of low-dose heparin in 37 sepsis-associated pre-DIC patients and reported an

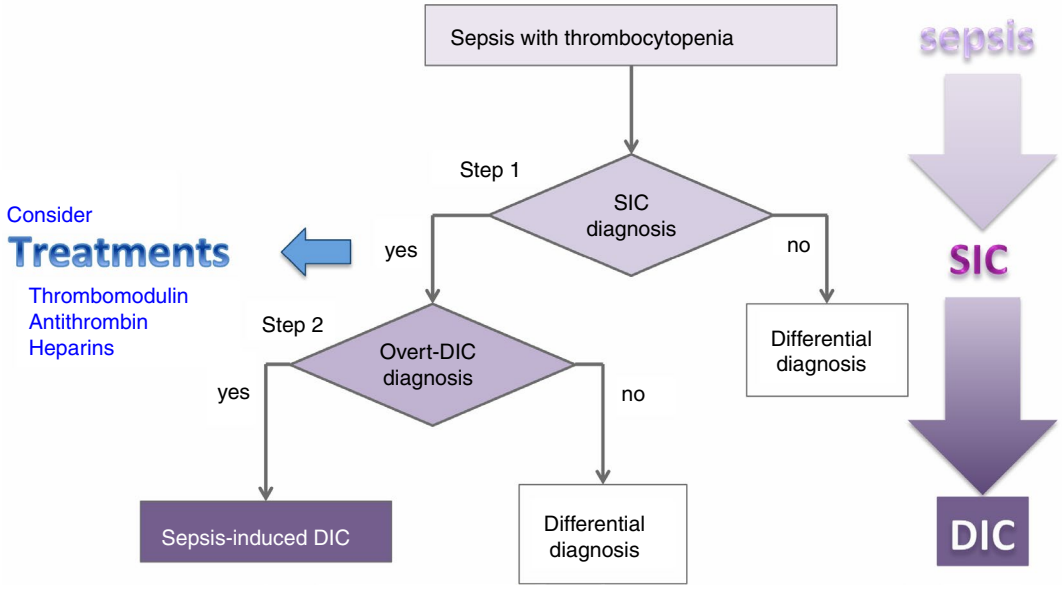

FIGURE 1 Two-step diagnosis for sepsis-associated DIC. The figure depicts an algorithm to diagnose sepsis-induced coagulopathy (SIC) and overt disseminated intravascular coagulation (DIC). Sepsis patients with thrombocytopenia (platelet count < 150 × 10^9 L^{-1}) are screened by using SIC diagnostic criteria (Step 1), and then by using overt DIC diagnostic criteria (Step 2). The rationale for this approach is that SIC and overt DIC represent a continuum wherein onset of SIC typically precedes that of overt DIC, and where early therapeutic intervention with anticoagulant therapy is most likely to be beneficial

improvement in the hypercoagulable state, multiple organ dysfunction, and period of hospitalization. However, these studies were too small to reach definitive conclusions. In summary, therapeutic doses of heparin should be considered in coagulopathic patients to avoid the progression from coagulopathy to DIC, and the use of LMWH is preferred to the use of UFH.

3.2 | Antithrombin

Antithrombin is an important physiological anticoagulant that circulates in the plasma at relatively high concentrations of approximately 2.57 μmol/L (0.125 to 0.160 mg/mL), and inhibits thrombin as well as acute inflammatory reactions.[34] However, in sepsis, antithrombin levels are decreased by increased vascular permeability (extravasation), consumed by pathologically activated coagulation, and cleaved by proteases,[34] but also decreased hepatic synthesis occurs with acute hepatic dysfunction often observed in sepsis. Thus, antithrombin supplementation for treating septic DIC is often used[6] despite its efficacy not being established in a high evidence study. KyberSept, a large-size Phase 3 trial that examined the effects of high-dose antithrombin for sepsis, did not show any benefit (but did show increased bleeding).[35] This trial did not specifically target patients with DIC; however, a subanalysis demonstrated that high-dose antithrombin could be effective for septic patients with coagulopathy (who were not also treated with heparin),[7] with a subsequent meta-analysis that included the KyberSept study showing a statistically significant survival benefit.[36] Several large observational studies have consistently demonstrated favorable effects of antithrombin supplementation in septic patients with DIC.[37] Accordingly, the Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock recommends the use of antithrombin to DIC patients with decreased antithrombin activity,[38] although this practice is not common outside of Japan.

3.3 | Thrombomodulin

Thrombomodulin is an endothelial anticoagulant cofactor that promotes thrombin-mediated activation of protein C. Because expression of thrombomodulin is down-regulated during sepsis, therapeutic use of rsTM was developed in Japan. Subsequently, the efficacy of rsTM in sepsis-induced coagulopathy was examined in a randomized Phase 2b study, and a nonsignificant mortality difference of 3.8% was shown.[39] Following this study, a multinational Phase 3 study was conducted, and the results have been reported.[40] A nonsignificant mortality reduction of 2.6% was recognized in 800 septic patients with coagulopathy. In addition, improvements were observed in levels of D-dimer, thrombin-antithrombin complex, and prothrombin fragment F_{1+2} levels, and platelet counts. Yamakawa et al[41] performed a meta-analysis including the latest Phase 3 study and reported an approximate 13% reduction in mortality with rsTM; however, the difference was not statistically significant (relative risk, 0.87; 95% confidence interval, 0.74 to 1.03; $P = .10$; $I^2 = 0\%$). Serious bleeding complications did not increase with the treatment. Pending definitive evidence from prospective RCTs, rsTM may become a potential treatment for sepsis-associated DIC.

4 | SYMMETRICAL PERIPHERAL GANGRENE

One potential devastating consequence of sepsis and DIC is acral (distal extremity) limb loss due to microvascular thrombosis, known as "symmetrical peripheral gangrene" (SPG).[42] Studies evaluating diagnosis and treatment of sepsis generally focus on the end point of mortality, and so the impact of anticoagulant strategies (UFH, LMWH, antithrombin, rsTM, APC) on treating or preventing SPG remains uncertain. In recent years, the prodromal role of acute hepatic dysfunction ("shock liver") in predisposing to SPG has been noted, as a consequence of impaired hepatic synthesis of the crucial natural anticoagulants, antithrombin and protein C.[42,43] In theory, timely administration of heparin and antithrombin might reduce risk of microthrombosis and associated SPG in at-risk patients, although rsTM might not be effective if protein C levels are severely reduced because of hepatic dysfunction. As most patients with sepsis-associated SPG die, a potential paradoxical consequence of improving mortality rates in sepsis might be a greater proportion of survivors who manifest SPG.

5 | SUMMARY

DIC is a life-threatening complication frequently encountered in septic patients characterized by the systemic activation of coagulation. Sepsis-associated DIC is characterized by suppression of fibrinolysis induced by endothelial dysfunction, which can quickly progress to multi-organ failure and death. Thus, early detection of DIC is important. The ISTH DIC SSC and Perioperative and Critical Care SSC cooperatively suggest a two-step diagnostic approach, assessing first for SIC and if SIC criteria are met, assessing for overt DIC. This strategy will facilitate early recognition of DIC and potentially hasten intervention. As for treatment approaches, we recognize the considerable differences among countries. For those countries in which specific anticoagulant therapies such as antithrombin and rsTM are licensed, this approach is used, although an effect on mortality still remains to be demonstrated. However, because sepsis is the most frequent and serious trigger of DIC, we should continue the effort to develop novel therapies, and if monotherapy is ineffective, multimodal therapy should be examined. We believe that simplified and consistent diagnostic criteria will further enhance study of management of the sepsis-associated SIC/DIC continuum.

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CONFLICT OF INTERESTS

J.H.L. serves on the Steering Committees for Boehringer-Ingelheim, CSL Behring, Instrumentation Laboratories, Octapharma, and Leading Biosciences. T.E.W. reports having received consulting fees from Aspen Global and Octapharma; research support and consulting fees from W.L. Gore and Instrumentation Laboratory; royalties from Informa (Taylor & Francis); and consulting fees related to medical-legal testimony. T. vdP. has participated in advisory board of Asahi Kasei Pharmaceuticals America. M.L. has received grants and has participated in advisory boards of NovoNordisk, Eli Lilly, Asahi Kasei Pharmaceuticals America, and Johnson & Johnson. The other authors state that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

T. Iba and J. H. Levy wrote the initial draft. T. E. Warkentin, J. Thachil, T. van der Poll, and M. Levi reviewed and revised the manuscript.

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