

LETTER TO THE EDITOR

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# Nevertheless, the importance of coagulation abnormalities should be emphasized in international sepsis guidelines

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## Abstract

It is generally accepted that a coagulation/fibrinolysis disorder is involved in the pathogenesis of sepsis, and the association of disseminated intravascular coagulation (DIC) and poor outcomes have been reported. Based on these findings, recently released “Japanese Surviving Sepsis Campaign guidelines 2020” recommend the diagnosis of DIC and the application of anticoagulants for sepsis-associated DIC. Meanwhile, the updated “International Guidelines for the Management of Sepsis and Septic Shock 2021” did not mention coagulation abnormalities or DIC. Because management strategies continue to evolve to provide improved outcomes in sepsis, the role of adjunctive anticoagulant treatment should be included in subsequent international guidelines.

**Keywords:** Sepsis, Coagulopathy, Disseminated intravascular coagulation, Endothelial cell, Anticoagulation

## Dear Editor,

We realized that there are some discrepancies between the recently updated “Japanese Surviving Sepsis Campaign guidelines 2020” and “Surviving Sepsis Campaign International Guidelines for the Management of Sepsis and Septic Shock 2021” [1, 2]. In the Japanese guidelines, the early detection of disseminated intravascular coagulation (DIC) is emphasized and the use of certain anticoagulants for sepsis-associated DIC was weakly recommended. Meanwhile, the chapter on “anticoagulation” is eliminated from the recent version of International guidelines.

It is widely accepted that an extensive connection and cross-talk between inflammation and coagulation occurs in sepsis. Indeed, the mortality of sepsis worsens considerably when a patient develops coagulation abnormalities, in its most extreme form DIC. Although

mechanistically different, COVID-19 taught us that coagulopathy and subsequent pulmonary and multiorgan microthrombosis are important in the pathogenesis of organ failure and death in thromboinflammatory diseases [3] as well as the occurrence of venous thromboembolism. As a reminder, coagulopathy that occurs in acute infectious processes represents acute inflammation, dysregulated immune reactions, platelet activation, and endothelial dysfunction [4]. For these reasons, anticoagulation is important for preventing thromboembolism but also microthrombosis in COVID-19 but also in sepsis-induced coagulopathy. Apart from that, antithrombotic prophylaxis is crucial to prevent thromboembolic complications in critically ill patients.

The early detection of coagulopathy is critical and Umemura et al. [5] reported the screening of DIC improved the outcome in patients with sepsis. Although no consistently reliable method is available to evaluate the coagulopathy in sepsis, the International Society on Thrombosis and Haemostasis introduced a scoring system for sepsis-induced coagulopathy (SIC), and emphasized the importance of early detection of a

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coagulation derangement [6]. SIC consists of a simple algorithm (platelet count, prothrombin time [international normalization ratio], and Sequential Organ Failure Assessment [SOFA] score) and has been validated to detect the coagulopathy in sepsis.

Although there is no proven effective treatment for coagulopathy and DIC in sepsis, Japanese Surviving Sepsis Campaign guidelines 2020 weekly recommend the use of antithrombin and recombinant thrombomodulin for DIC. Since some of the authors have a conflict of interest with the related pharmaceuticals, it may not be appropriate to discuss the effects of anti-coagulation in this letter. However, it is necessary to explain that although a recent randomized controlled trial examining the effect of recombinant thrombomodulin in severe sepsis (SCARLET trial) failed to show a beneficial effect on survival in an intention-to-treat population, it showed a survival benefit in patients with more severe coagulopathy [7]. Levi et al. [8] also demonstrated that patients treated with recombinant human soluble thrombomodulin having higher baseline prothrombin fragment  $_{1,2}$  or thrombin–antithrombin complex had lower mortality compared with patients receiving placebo in post hoc analysis. Furthermore, other anticoagulant interventions such as supplementation of antithrombin and restoration of glycocalyx have shown promising results in patients with severe sepsis and coagulopathy [9, 10].

We hope that in the subsequent version of the international guidelines, consideration of the role of coagulation and appropriate anticoagulant adjunctive treatment in severe sepsis will be included to underline the importance of detecting and managing coagulopathy in these critically ill patients.

#### Abbreviations

DIC: Disseminated intravascular coagulation; SIC: Sepsis-induced coagulopathy; SOFA: Sequential Organ Failure Assessment.

#### Acknowledgements

None.

#### Authors' contributions

TI and JHL wrote the draft. ON and ML reviewed and edited. All authors read and approved the final manuscript.

#### Authors' information

TI and ON are the committee members of Japanese Surviving Sepsis Campaign Guidelines 2020. LJH is a chairman of the International Society on Thrombosis and Haemostasis/Critical Care SSC.

#### Funding

None.

#### Availability of data and materials

Not applicable.

## Declarations

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

Not applicable.

#### Competing interests

IT has received research grants and scholarships from Japan Blood Products Organization, JIMRO, and Asahi Kasei Pharmaceuticals. NO received scholarships from Fuso Pharmaceutical Industries, Asahi Kasei Pharmaceuticals, Baxter Ltd., Maruishi Pharmaceutical, Teijin Pharmaceutical, Ono Pharmaceutical, Torii Pharmaceutical, Shionogi Co., Ltd. LJH serves on the Steering Committees for Instrumentation Laboratories, Octapharma, and Merck. LM 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.

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Received: 25 November 2021 Accepted: 10 January 2022

Published online: 21 January 2022

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