Iba *Critical Care* (2016) 20:307
DOI 10.1186/s13054-016-1464-5

Critical Care

LETTER Open Access

# Bleeding complications of anticoagulant therapy in sepsis-induced disseminated intravascular coagulation

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See related research by Yamakawa et al. http://ccforum.biomedcentral.com/articles/10.1186/s13054-016-1415-1

I thoroughly enjoyed reading the research article by Yamakawa et al. [1]. They reported the possible survival benefit of anticoagulant therapy in septic patients with coagulopathy and/or a severe condition. This result was consistent with former studies [2, 3]. However, I have some concerns regarding the increase in bleeding adverse events. Though the differences were not statistically significant, the bleeding rates tended to increase in the treated groups and the rate of bleeding requiring transfusion was between 13 and 27 %. I wonder why the incidence was so high in this study. Recombinant thrombomodulin and antithrombin were the two most popular anticoagulants in Japan and they were the dominant anticoagulants in this study. Eguchi et al. [4] reported that serious bleeding was recognized in 121 cases out of 1787 sepsis-induced disseminated intravascular coagulation (DIC) patients treated with recombinant thrombomodulin (6.8 %). We have also reported the incidence was 5.36 % in 1026 sepsis-induced DIC patients who underwent antithrombin supplementation [5]. One possible explanation for the high incidence of bleeding in Yamakawa et al.'s study was the longer observation period. Eguchi et al. and we observed the incidence of bleeding for 28 days after treatment, whereas Yamakawa et al. might have calculated it for up to 100 days (not clearly stated). Since the use of anticoagulants was usually no more than one week (thrombomodulin less than 7 days, antithrombin less than 6 days), I do not think the late phase bleeding should be included. It is reasonable to think that sustained DIC or a very severe condition lasting more than one month might contribute to an increased risk of bleeding. Since past studies revealed that inappropriate doses significantly increase the incidence, we were very careful on this point. Therefore, the recent studies performed in Japan have repeatedly demonstrated that the incidence did not increase with anticoagulant therapy [4, 5]. Thus, we would like to see the short-term bleeding incidence in Yamakawa et al.'s study. In addition, since Umemura et al. [3] reported that the incidence was substantially different depending on the agent used, information regarding which anticoagulants were responsible for the increased bleeding would also be appreciated.

## Authors' response

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We thank Professor Iba for his valuable and insightful comments regarding the bleeding complications associated with anticoagulant therapy for sepsis-induced disseminated intravascular coagulation (DIC). As Prof. Iba mentioned, the frequency of bleeding complications in our study [1] was relatively high compared with those in previous studies [3–5]. Prof. Iba considered that the higher frequency of bleeding complications might be attributable to the longer observation period but in our registry study incidences of bleeding were recorded only during 7 days after ICU admission. What then was responsible for the relatively high incidence of bleeding complications in our study? In the present study, we defined the bleeding complications as any bleeding events including the occurrence of intracranial hemorrhage, transfusion requirements related to bleeding, and bleeding requiring surgical intervention. However, most of the bleeding complications in this study were,

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indeed, transfusion requirements related to bleeding. Because transfusion therapy was applied at the discretion of the attending physician based on the treatment principles of each hospital, it is possible that different transfusion principles might lead to an unexpectedly increased incidence of transfusion requirements.

Another possible explanation for the high incidence of bleeding in our study is the combination therapy with two anticoagulant agents. Among 1247 patients in the anticoagulant group, 633 patients (50.7 %) were treated with a combination of more than two anticoagulant agents and this was associated with significantly higher risk of bleeding complications (17.2 % for combination use versus 13.0 % for single use). Also, because the risks of bleeding complications in this study were different according to the anticoagulants used (unadjusted odds ratio [OR] with 95 % confidence interval [CI] 2.65 [2.07–3.39] for antithrombin, 1.48 [1.14–1.92] for recombinant thrombomodulin, 1.98 [1.45–2.70] for serine protease inhibitors, 1.50 [0.94–2.41] for heparin), the types of anticoagulants might be responsible for the high incidence of bleeding complications in the treatment group.

Again, we thank Professor Iba for his insightful comments and providing valuable data. Bleeding complications are one of the greatest concerns associated with anticoagulant therapy. Decisions on the utilization of anticoagulant therapy depend on the balance between efficacy and safety of the therapy. We recognize that the design of the present study is not sufficient to provide definitive evidence for indications of anticoagulant therapy in sepsis. Further investigations are needed to delineate the optimal types, indications, dosages, and durations of anticoagulant therapy to gain the maximum survival benefits with minimal risk of bleeding complications.

#### Abbreviation
DIC: Disseminated intravascular coagulation

#### Author's contribution
TI wrote the manuscript.

#### Author's information
TI is a member of the ISTH/DIC subcommittee.

#### Competing interests
TI received research funds from Ono Pharmaceutical Co. Ltd, Nihon Pharmaceutical Co. Ltd, and Asahi Kasei Pharmaceutical Co. Ltd.

#### Consent for publication
TI read and approved the final manuscript.

Published online: 28 September 2016

#### References
1. Yamakawa K, Umemura Y, Hayakawa M, Kudo D, Sanui M, Takahashi H, Yoshikawa Y, Hamasaki T, Fujimi S. Benefit profile of anticoagulant therapy in sepsis: a nationwide multicentre registry in Japan. Crit Care. 2016;20:229.
2. Yoshimura J, Yamakawa K, Ogura H, Umemura Y, Takahashi H, Morikawa M, 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.
3. 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.
4. Eguchi Y, Gando S, Ishikura H, Saitoh D, Mimuro J, Takahashi H, et al. Post-marketing surveillance data of thrombomodulin alfa: sub-analysis in patients with sepsis-induced disseminated intravascular coagulation. J Intensive Care. 2014;2:30.
5. Iba T, Gando S, Saitoh D, Wada H, Di Nisio M, Thachil J. Antithrombin supplementation and risk of bleeding in patients with sepsis-associated disseminated intravascular coagulation. Thromb Res. 2016;145:46–50. doi:10.1016/j.thromres.2016.07.016.