

WHAT'S NEW IN INTENSIVE CARE



# What's new in the diagnostic criteria of disseminated intravascular coagulation?

Satoshi Gando<sup>1\*</sup>, Ferhat Meziani<sup>2,3</sup> and Marcel Levi<sup>4</sup>

© 2016 Springer-Verlag Berlin Heidelberg and ESICM

## Introduction

In the early 1990s, most critical care physicians considered disseminated intravascular coagulation (DIC) to merely be the terminal phase of multiple organ dysfunctions and it was largely ignored as an epiphenomenon associated with various serious illnesses. DIC was therefore not considered to be a disease or syndrome that required precise diagnosis and treatment. During the 1990s, it was increasingly recognized that DIC might be a relevant factor in the outcome of several illnesses. The pathogenesis of DIC was gradually untangled and it was established that it was characterized by the inflammatory cytokine-initiated activation of tissue factor-dependent coagulation, insufficient control of the anticoagulation pathways, and the plasminogen activator inhibitor-1-mediated suppression of fibrinolysis, leading to organ dysfunction [1]. DIC may not only be viewed as a coagulation disorder, but also as a delayed symptom of emerging systemic vascular inflammatory disease and endothelial dysfunction [2]. With the implementation of specific diagnostic criteria, DIC has finally been recognized as an established disease entity that often warrants supportive management independently of the treatments of the underlying basic conditions [3]. In the present study, we aim to briefly introduce the recent points of view on the diagnosis of DIC.

## Diagnostic criteria

Diagnostic criteria have two major purposes: (1) to diagnose disease in order to improve patient outcomes by intervening with specific treatments; (2) to identify a homogenous group of patients with the same basic

pathophysiology and clinical characteristics, as has been established by numerous long-term experimental and clinical studies. Using a homogenous patient group, we can understand the epidemiology of the disease and compare the results of treatment interventions. To achieve these purposes, the diagnostic criteria should meet three conditions: (1) they should be readily available and easy to use; (2) they should have diagnostic accuracy; and (3) they should display prognostic value.

The International Society on Thrombosis and Haemostasis (ISTH) diagnostic criteria for overt DIC (Supplementary Table 1), which adopt routine coagulation tests that are available everywhere, were prospectively validated on the basis of the independent opinions of two hemostasis and intensive care experts, as there is no gold standard for the diagnosis of DIC. The ISTH overt DIC scoring system proved to provide sufficient accuracy in the diagnosis of DIC, while also predicting 28-day mortality in diverse ICU patient populations [4]. The ISTH confirmed, on the basis of the 5-year overview, that a score of  $\geq 5$  by this scoring system could identify overt DIC [5]. The sensitivity and specificity of the ISTH overt DIC score were 91 and 97 %, respectively. Increased scores were strongly correlated with increased mortality. The ISTH overt DIC scoring system is calculated on the basis of the platelet count, prothrombin time, fibrinogen levels, and fibrin-related markers. The ISTH overt DIC diagnostic criteria also have diagnostic and prognostic power without the inclusion of the fibrinogen [4, 5]. The ISTH showed that in addition to prothrombin time, the international normalized ratio, which is usually used for the monitoring of vitamin K antagonist, can be used to calculate the score, which will facilitate the greater dissemination of the scoring system and its worldwide standardization [6]. Recently, the ISTH announced that the DIC scoring system correlates with key clinical observations and outcomes and recommended the use of the diagnostic criteria [7].

\*Correspondence: gando@med.hokudai.ac.jp

<sup>1</sup> Division of Acute and Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Japan  
Full author information is available at the end of the article

The Japanese Association for Acute Medicine (JAAM) diagnostic criteria (Supplementary Table 2) have been prospectively validated by a comparison with the established DIC diagnostic criteria in diverse populations of ICU patients [8]. The results demonstrated that the JAAM scoring system has good diagnostic properties and that it can predict the 28-day outcome of DIC. The JAAM DIC diagnostic criteria exhibit better prognostic value in predicting multiple organ dysfunctions and 28-day and hospital mortality in patients with severe sepsis [9]. They can also predict massive transfusion and the hospital mortality of severely injured trauma patients [10].

Comparing DIC scores is not an easy task [11]. However, a prospective study of the different DIC diagnostic criteria demonstrated that the ISTH and the JAAM DIC diagnostic criteria are significantly correlated with poor outcomes and that the odds ratios for death as indicated by a ISTH score of  $\geq 5$  and JAAM score of  $\geq 4$  were 2.55 and 1.99, respectively [12]. The results indicate that both diagnostic criteria are useful for diagnosing DIC. Considering the components included in the scoring systems and the results of many studies, the two diagnostic criteria are believed to meet the three conditions that are required of diagnostic criteria.

Two interesting papers on the diagnosis of DIC in sepsis patients have been published [2, 13]. In the first study [2], the authors demonstrated that endothelial-derived microparticles are relevant biomarkers of septic shock-induced DIC. Microparticles could be used to evaluate early endothelial injury, which may help clinicians to improve the early assessment of DIC in patients with septic shock. Presepsin is a truncated N-terminal fragment of CD14. A scoring system for sepsis-induced DIC has been proposed in which presepsin and protein C are used

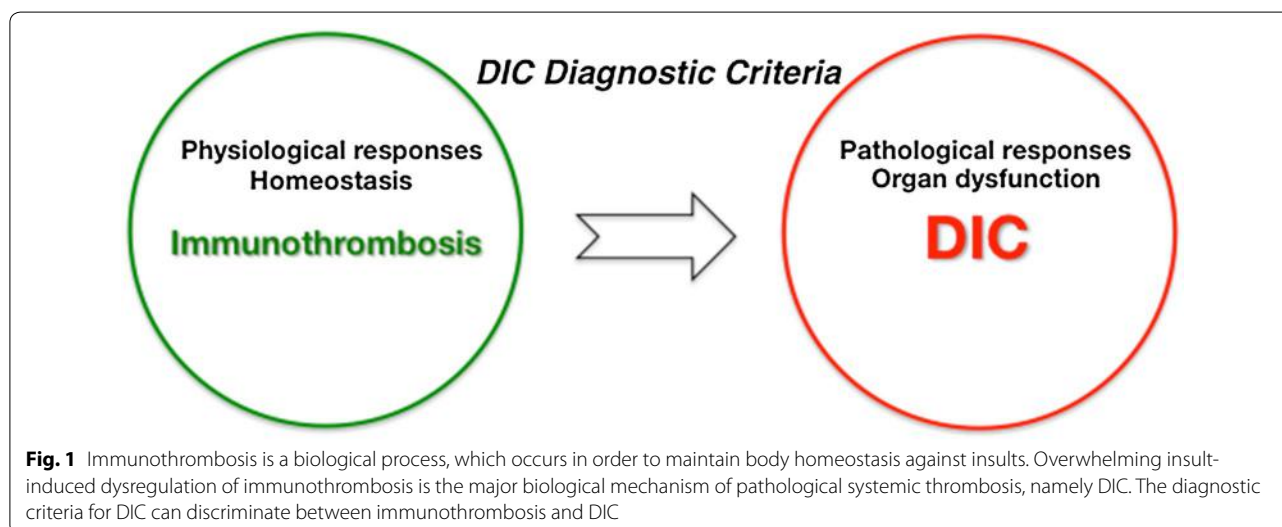
as markers of inflammation and coagulation, respectively [13]. The system is simple, easy to implement, and may be used as a point-of-care test in the ICU setting.

### Viscoelastic devices

A recent systematic review concluded that viscoelastic devices could be promising tools for the diagnosis of coagulopathies, including DIC, in sepsis [14]. The review noted that more insight into the kinetics of the coagulation alterations, as diagnosed by the viscoelastic devices, is necessary before their use can be advocated in the detection of DIC. We should keep in mind that there are still some concerns about the standardization of these assays. The data from the external quality assessment (EQA) by the UK National External Quality Scheme for Blood Coagulation indicated that regular EQA/proficiency testing is needed for these devices [15]. An international standardization study showed significant interlaboratory variance among these devices and concluded that significant work is necessary to improve their reliability and reproducibility [16]. The robustness of the viscoelastic devices that are used in the diagnosis of DIC in diverse ICU patients still needs to be comprehensively evaluated.

### How to use the diagnostic criteria

The ISTH criteria added a table of “clinical conditions that may be associated with DIC” and these conditions were mandatory to diagnose DIC before DIC scoring [3]. The JAAM scoring system presents the same table, while adding another table of “clinical conditions that should be carefully ruled out” in order to increase the specificity of the criteria [9]. These tables suggest that physicians need to be careful not to diagnose DIC solely on the basis



**Fig. 1** Immunothrombosis is a biological process, which occurs in order to maintain body homeostasis against insults. Overwhelming insult-induced dysregulation of immunothrombosis is the major biological mechanism of pathological systemic thrombosis, namely DIC. The diagnostic criteria for DIC can discriminate between immunothrombosis and DIC

of the total score. Daily repeated scoring is mandatory for both a definite diagnosis and to rule out DIC, as well as to specify the severity and the prognosis of DIC [3, 9]. The recently developed concept of immunothrombosis indicates that thrombosis at the site of insults is a physiological reaction that occurs in order to maintain homeostasis; however, this condition proceeds to DIC and gives rise to organ dysfunction once the body is overwhelmed by insults (Fig. 1) [17]. The strict discrimination between simple coagulopathy and DIC and the timing of treatment initiation are considered to be essential. We therefore believe that these points justify the use of the DIC diagnostic criteria, which enable us to appropriately use promising drugs, such as recombinant soluble thrombomodulin, for treatment of DIC [18].

#### Electronic supplementary material

The online version of this article (doi:10.1007/s00134-016-4257-z) contains supplementary material, which is available to authorized users.

#### Author details

<sup>1</sup> Division of Acute and Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Japan. <sup>2</sup> Service de Réanimation Médicale, Nouvel Hôpital Civil, Hôpitaux Universitaires de Strasbourg, Strasbourg, France. <sup>3</sup> EA 7293, Fédération de Médecine Translationnelle de Strasbourg (FMTS), Faculté de Médecine, Université de Strasbourg, Strasbourg, France. <sup>4</sup> Department of Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands.

#### Compliance with ethical standards

#### Conflicts of interest

The authors have no conflict of interest to declare.

Received: 1 December 2015 Accepted: 28 January 2016

Published online: 8 February 2016

#### References

- Levi M, Ten Cate H (1999) Disseminated intravascular coagulation. *N Engl J Med* 341:586–592
- Delabranche X, Boisramé-Helms J, Asfar P, Berger A, Mootien Y, Lavigne T, Grunebaum L, Lanza F, Gachet C, Freyssinet JM, Toti F, Meziani F (2013) Microparticles are new biomarkers of septic shock-induced disseminated intravascular coagulopathy. *Intensive Care Med* 39:1695–1703
- Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M (2001) Toward definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *J Thromb Haemost* 86:1327–1330
- Bakhtiari K, Meijers JCM, de Jonge E, Levi M (2004) Prospective validation of the international society of thrombosis and haemostasis scoring system for disseminated intravascular coagulation. *Crit Care Med* 32:2416–2421
- Toh CH, Hoots WK (2007) The scoring system of the Scientific Standardisation Committee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Haemostasis: a 5-year overview. *J Thromb Haemost* 7:604–606
- Kim HK, Hong KH, Toh CH (2010) Application of the international normalized ratio in the scoring system for disseminated intravascular coagulation. *J Thromb Haemost* 8:1116–1118
- Wada H, Thachil J, DiNisio M, Mathew P, Kurosawa S, Gando S, Kim HK, Nielsen JD, Dempfel CE, Levi M, Toh CH (2013) Guidance for diagnosis and treatment of disseminated intravascular coagulation from harmonization of the recommendations from three guidelines. *J Thromb Haemost* 11:761–767
- Gando S, Saitoh D, Ogura H, Mayumi T, Koseki K, Ikeda T, Ishikura H, Iba T, Ueyama M, Eguchi Y, Otomo Y, Okamoto K, Kushimoto S, Endo S, Shimazaki S (2008) 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* 36:145–150
- Gando S, Saitoh D, Ogura H, Fujishima S, Mayumi T, Araki T, Ikeda H, Kushimoto S, Miki Y, Shiraishi S, Suzuki K, Suzuki Y, Takeyama N, Takuma K, Tsuruta R, Yamaguchi Y, Yamashita N, Aikawa N (2013) A multicenter, prospective validation study of the Japanese Association for Acute Medicine disseminated intravascular coagulation scoring system in patients with severe sepsis. *Crit Care* 17:R111
- Oshiro A, Yanagida Y, Gando S, Henzan N, Takahashi I, Makise H (2014) Hemostasis during the early phase of trauma: comparison with disseminated intravascular coagulation. *Crit Care* 18:R61
- Dempfle CE (2009) Comparing DIC scores: not an easy task indeed. *Thromb Res* 124:651–652
- Takemitsu T, Wada H, Hatada T, Ohmori K, Takeda T, Sugiyama T, Yamada N, Maruyama K, Katayama N, Isaji S, Shimpo H, Kusunoki M, Nobori T (2011) Prospective evaluation of three different diagnostic criteria for disseminated intravascular coagulation. *Thromb Haemost* 105:40–44
- Ishikura H, Nishida T, Murai A, Nakamura Y, Irie Y, Tanaka J, Umemura T (2014) New diagnostic strategy for sepsis-induced disseminated intravascular coagulation: a prospective single-center observational study. *Crit Care* 18:R19
- Müller MC, Meijers JCM, Vroom MB, Juffermans NP (2014) Utility of thromboelastography and/or thromboelastometry in adults with sepsis: a systematic review. *Crit Care* 18:R30
- Kitchen DP, Kitchen S, Jennings I, Woods T, Walker I (2010) Quality assurance and quality control of thromboelastography and rotational thromboelastometry: the UK NEQAS for blood coagulation experience. *Semin Thromb Hemost* 36:757–763
- Chitlur M, Sorensen B, Rivard GE, Young G, Ingerslev J, Othman M, Nugent D, Kenet G, Escobar M, Lusher J (2011) Standardization of thromboelastography: a report from TEG-ROTEM working group. *Hemophilia* 17:532–537
- Engelmann B, Massberg S (2013) Thrombosis and intravascular effector of innate immunity. *Nat Rev Immunol* 13:34–45
- Yamakawa K, Aihara M, Yuhara H, Hamasaki T, Shimazu T (2015) Recombinant human soluble thrombomodulin in severe sepsis. A systematic review and meta-analysis. *J Thromb Haemost* 13:508–519