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Guidance for diagnosis and treatment of disseminated intravascular coagulation from harmonization of the recommendations from three guidelines

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Introduction

Disseminated intravascular coagulation (DIC) is a syndrome characterized by the systemic activation of blood coagulation, which generates intravascular fibrin, leading to thrombosis of small and medium-sized vessels, and eventually organ dysfunction [1]. DIC may occur as a complication of infections, solid cancers, hematologic malignancies, obstetric diseases, trauma, aneurysm, and liver diseases, among others, and each type of DIC presents characteristic features related to the underlying disorder. The diagnosis and treatment of DIC must therefore take into consideration these underlying etiologic features. Patients with DIC resulting from sepsis, hematologic malignancy or obstetric disease can be successfully treated for DIC, whereas DIC associated with solid cancers may not respond to standard treatments [2–5]. There were no significant differences in outcome between solid cancer patients with and without DIC [5]. Three guidelines for DIC [2–4] have been published in the literature from the British Committee for Standards in Haematology (BCSH), the Japanese Society of Thrombosis and Hemostasis (JSTH), and the Italian Society for Thrombosis and Hemostasis (SISET). Although they are broadly similar, there are variations in the recommendations (Tables 1 and 2). This communication is an attempt to harmonize the three guidelines for DIC by the active members of the subcommittee for DIC of the Scientific and Standardization Committee (SSC) of the ISTH. The quality of the evidence and the definitions for recommendations were evaluated by use of a modified GRADE system [6] (Table 3), and agreed among all active members of the ISTH/SSC subcommittee for DIC between 1 July 2011 and 10 December 2012. Drugs that are frequently used in clinical practice were considered under the category of 'Potential Recommendation' in cases of disagreement between the three guidelines or insufficient randomized controlled trial (RCT) results. It needs to be stressed that this harmonization may not be appropriate for all patients, and individual patient circumstances may dictate the selection of alternative approaches.

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Diagnosis of DIC

Recommendations:

There is no gold standard for the diagnosis of DIC, and no single test that is, by itself, capable of accurately diagnosing DIC.

Table 1 Differences between the guidelines from British Committee for Standards in Haematology (BCSH), Japanese Society of Thrombosis and Hemostasis (JSTH) and Italian Society for Thrombosis and Hemostasis (SISET) and recommendations of the ISTH/Scientific and Standardization Committee (SSC)

	BCSH	JSTH	SISET	ISTH/SSC (evidence level and definitions for R)
Scoring system for DIC	R; grade C	R	R; grade C	R (moderate quality)
Single test analysis for DIC	NR	NR	NR; grade D	NR (moderate quality)
Treatment of underlying disease	R; grade C	R; consensus	R; cornerstone	R (moderate quality)
Platelet concentration	R; grade C	R; consensus	R; grade D	R (low quality)
FFP	R; grade C	R; consensus	R; grade D	R (low quality)
Fibrinogen, cryoprecipitate	R; grade C	NM	R; grade D	R (low quality)
Prothrombin complex concentrate	NM	NM	NM	NM
FVIIa	NR	NM	NR; grade D	NR (low quality)
UFH (treatment for thrombosis)	R; grade C	R; level C	NR; grade D	R (low quality)
UFH (prophylaxis for VTE)	R; grade A	NM	R; grade D?	R (moderate quality)
LMWH (treatment for thrombosis)	R; grade C	R; level B2	R; grade D	R; preferred to UFH (low quality)
LMWH (prophylaxis for VTE)	R: grade A	NM	R; grade D?	R (high quality)
Heparin sulfate	NM	R; level C	NM	NM
Synthetic protease	NM	R; level B2	NR; grade D	NM
rhAPC	R; grade A→D	NM	R; grade D	PR
Protein C concentrate	NM	NM	NR; grade D	NM
AT	NR; grade A	R; B1	NR; grade D	PR
rhTM	NM	NM	NR; grade B	PR
Antifibrinolytic agents	R; grade C	NR; level D	NM	R (low quality)
Plasma exchange	NM	NM	NR; grade D	NM

AT, antithrombin; DIC, disseminated intravascular coagulation; FFP, fresh frozen plasma; LMWH, low molecular weight heparin; NM, not mentioned; NR, not recommended; PR, potentially recommended, needs further evidence; R, recommended; rhAPC, recombinant human activated protein C; rhTM, recombinant human thrombomodulin; UFH, unfractionated heparin; VTE, venous thromboembolism.

1 Use of a scoring system is recommended (moderate quality).
2 The scoring system for DIC criteria is known to correlate with key clinical observations and outcomes (moderate quality).
3 It is important to repeat the tests to monitor the dynamic changes on the basis of laboratory results and clinical observations (moderate quality).

Scoring system

The underlying clinical condition can have an influence on the laboratory tests that are usually performed to diagnose DIC. To facilitate the diagnostic process, scoring systems are recommended by the three different guidelines [3–5]. Different diagnostic criteria have been established by the ISTH/SSC [1], the Japanese Ministry of Health, Labor and Welfare (JMHLW) [7], and the Japanese Association of Acute Medicine (JAAM) [8]. The ISTH overt DIC score is useful for the diagnosis of DIC resulting from infective and non-infective etiologies [9,10]. The JMHLW score predicts the outcome in DIC [11], and the JAAM score in septic patients also correlates with the ISTH and JMHLW scores and outcomes [8,10]. A prospective study in Japan reported no significant difference in the odds ratio for the prediction of DIC outcomes for these three diagnostic criteria [12]. A combination of tests repeated over time in a patient with suspected DIC can be used to diagnose the disorder with reasonable certainty in most cases [13–15]. A template for the non-overt DIC scoring system, including global tests, changes in global tests, and hemostatic molecular markers, has been proposed [1,16,17].

Laboratory tests

Screening assays (global coagulation tests), such as the prothrombin time (PT), fibrinogen, platelet count, and fibrin-related markers (FRMs), provide important evidence of the degree of coagulation factor activation and consumption. Although PT is prolonged in approximately 50–60% of cases of DIC at some point during the course of the disease [13], the abnormalities are often observed in patients with concomitant liver disease or warfarin treatment. A reduction in the platelet count or a clear downward trend in subsequent measurements is a sensitive (although not specific) sign of DIC [2]. A reduced fibrinogen level is valuable for the diagnosis of DIC, but is not observed in most DIC patients [2]. The elevated FRMs, such as fibrinogen and fibrin degradation products [18], D-dimers [19], and soluble fibrin (SF), reflect thrombin formation. SF [20] assays offer theoretical advantages in DIC, in that they give a closer reflection of thrombin action on fibrinogen. However, it is important to remember that many conditions, such as trauma, recent surgery, or venous thromboembolism (VTE), are associated with elevated FRMs.

Reductions in the levels of natural anticoagulants such as antithrombin (AT) and protein C (PC) are common in

Table 2 Recommendation levels in the three guidelines

Grade	BCSH	JSTH	SISET
		Consensus: treatment does not have HQ of Ed, but it should be carried out as common sense	
A	Requires at least one RCT as part of a body of literature of overall GQ and consistency addressing specific Rm (EdL Ia, Ib)	Treatment has HQ of Ed, and the CU is clear	EdL 1++ and DATTTP *or* EdL 1+, DATTTP, and DOCOR
B	Requires the availability of well-conducted clinical Sys but no RCT on the topic of Rm (EdL IIa, IIb, III)	B1: treatment has moderately HQ of Ed, or it has HQ of Ed but the CU is not significant. B2: treatment does not have HQ of Ed, but it has few deleterious effects and it is carried out clinically	EdL 2++, DATTTP and DOCOR *or* EEd from Sys (EdL 1++ or 1+)
C	Requires Ed obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical Sys of GQ (EdL IV)	Treatment does not have HQ of Ed or the CU is not clear	EDL 2+, DATTTP and DOCOR *or* EEd from Sys (EdL 2++)
D		Treatment has HQ of Ed, and it has deleterious effects	EdL 3 or 4; *or* EEd from Sys (EdL 2+)

BCSH, British Committee for Standards in Haematology; CU, clinical usefulness; DATTTP, directly applicable to the target population; DOCOR, demonstrating overall consistency of results; Ed, evidence; EdL, evidence level; EEd, extrapolated evidence; GQ, good quality; HQ, high quality; JSTH, Japanese Society of Thrombosis and Hemostasis; RCT, randomized controlled trial; Rm, recommendation; SISET, Italian Society for Thrombosis and Hemostasis; Sy, study. Ed levels in BCSH are as follows. Ia: Ed obtained from meta-analyses of RCTs. Ib: Ed obtained from at least one RCT. IIa: Ed obtained from at least one well-designed controlled Sy without randomization. IIb: Ed obtained from at least one other type of well-designed quasi-experimental Sy. III: Ed obtained from well-designed non-experimental descriptive Sys, such as comparative Sys, correlation studies, and case Sys. IV: Ed obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Ed levels in JSTH are as follows. 1a: systematic review (with homogeneity) of RCTs. 1b: Individual RCT (with narrow confidence interval). Ic: all or none case series. 2a: systematic review (with homogeneity) of cohort Sys. 2b: individual cohort Sy (including low-quality RCT, e.g. < 80% follow-up). 2c: outcomes research; ecological Sys. 3a: systematic review (with homogeneity) of case–control Sys. 3b: individual case-controlled Sy. 4: case-series (and poor-quality cohort and case-controlled Sys). 5: expert opinion without explicit critical appraisal, or based on physiology, bench research, or 'first principles. Ed levels in SISET are as follows. 1++: HQ meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias. 1+: well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias. 1−: meta-analyses, systematic reviews, or RCTs with a high risk of bias. 2++: HQ systematic reviews of case-controlled or cohort Sys. HQ case-controlled or cohort Sys with a very low risk of confounding or bias, and a high probability that the relationship is causal. 2+: well-conducted case-controlled or cohort Sys with a low risk of confounding or bias, and a moderate probability that the relationship is causal. 2−: case-controlled or cohort Sys with a high risk of confounding or bias, and a significant risk that the relationship is not causal. 3: non-analytic Sys, e.g. case reports, case series. 4: expert opinion.

Table 3 Quality of evidence and definitions for recommendation in the modified GRADE system

High quality	Further research is very unlikely to change our confidence in the estimate of the effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of the effect, and may change the estimate
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of the effect, and is likely to change the estimate

DIC. Although measuring AT activity may be useful for achieving the full efficacy of heparin [21], it is not quickly and easily measured in all hospitals. A reduction in ADAMTS-13 activity and elevations of soluble thrombomodulin (TM), plasminogen activator inhibitor-1 (PAI-1) and von Willebrand factor propeptide are often observed in DIC, and these have been shown to have prognostic significance [22–24]. An atypical light transmittance profile on the activated partial thromboplastin time (APTT) as the biphasic waveform has been associated with DIC, and appears to have a positive predictive value for DIC [25,26]. Although many attractive markers have been reported for DIC, there is no single marker that is able to diagnose DIC. Therefore, these three guidelines [2–4] recommend that DIC should not be diagnosed with a single marker, but with a combination of laboratory markers.

Treatment of DIC

Treatment of the underlying disease

Recommendation:

1 The cornerstone of DIC treatment is the treatment of the underlying condition (moderate quality).

The most important treatment for DIC is the specific and vigorous treatment of the underlying disorder, such as administration of antibiotics or surgical drainage. All three guidelines [3–5] agree on this point, although there

is no high-quality evidence. The DIC will spontaneously resolve in many cases, when the underlying disorder is properly managed. However, some cases require additional supportive treatment, specifically aimed at the abnormality in the coagulation system. In an RCT of all-*trans*-retinoic acid (ATRA) as compared with conventional chemotherapy in patients with acute promyelocytic leukemia (APL), the mortality rate of APL was significantly lower in the ATRA group than in the conventional chemotherapy group (overall survival: 69% vs. 45%, respectively) [27]. ATRA exerts not only differential effects on APL progression, but also anticoagulant and anti-fibrinolytic effects [28]. Similarly, several RCTs on the treatment of sepsis have shown a parallel improvement in coagulation derangement and DIC, although data have not been always concordant [29–34].

Role of plasma, fresh frozen plasma (FFP), coagulation factors, and platelets

Recommendations:

1 The transfusion of platelets is recommended in DIC patients with active bleeding and a platelet count of $< 50 \times 10^9$ L^{-1} or in those with a high risk of bleeding and a platelet count of $< 20 \times 10^9$ L^{-1} (low quality).

2 The administration of FFP may be useful in patients with active bleeding with either prolonged PT/APTT (> 1.5 times normal) or decreased fibrinogen (< 1.5 g dL^{-1}). It should be considered in DIC patients requiring an invasive procedure with similar laboratory abnormalities (low quality).

3 The administration of fibrinogen concentrate or cryoprecipitate may be recommended in actively bleeding patients with persisting severe hypofibrinogenemia (< 1.5 g L^{-1}) despite FFP replacement (low quality).

4 Prothrombin complex concentrate (PCC) may be considered in actively bleeding patients if FFP transfusion is not possible.

Low levels of platelets and coagulation factors may increase the risk of bleeding. However, blood component therapy should not be instituted on the basis of laboratory results alone, but reserved for those with active bleeding, requiring an invasive procedure, and who are otherwise at high risk for bleeding complications. The three guidelines [3–5] recommended the administration of platelet concentrate and FFP in patients with active bleeding or at high risk of bleeding.

The threshold for transfusing platelets depends on the clinical state of the patient. In general, platelet transfusions are administered to patients who are actively bleeding and who have a platelet count of $<50 \times 10^9$ L^{-1}. A much lower threshold of 10–20 $\times 10^9$ L^{-1} is adopted in non-bleeding patients, on the basis of RCTs in patients with thrombocytopenia following chemotherapy. Platelets may be administered at higher levels than this in patients perceived to be at high risk of bleeding on the basis of other clinical and laboratory features [35].

It may be necessary to use large volumes of plasma to correct the coagulation defects shown by prolonged APTT or PT, or a decreased fibrinogen level. Initial doses of 15 mL kg^{-1} of FFP are suggested, although there is evidence that a dose of 30 mL kg^{-1} produces more complete correction of coagulation factor levels. In this regard, the consequences of volume overload may have to be considered. Smaller volumes of PCC may be useful in this setting, although these products lack certain essential coagulation factors, such as factor V. Specific deficiencies in fibrinogen can be corrected by administration of purified fibrinogen concentrates or cryoprecipitate. The response to component therapy should be monitored both clinically and by repeating platelet counts and coagulation tests following administration of these components. The efficacy and safety of recombinant FVIIa in DIC with life-threatening bleeding are unknown, and it should be used with caution, or as part of a clinical trial.

Anticoagulants

Recommendations:

1 Therapeutic doses of heparin should be considered in cases of DIC where thrombosis predominates (low quality). The use of low molecular weight heparin (LMWH) is preferred to the use of unfractionated heparin (UFH) in these cases (low quality).

2 Prophylaxis for VTE with prophylactic doses of UFH or LMWH is recommended in critically ill, non-bleeding patients with DIC (moderate and high quality, respectively), but there is no direct evidence of the effects of anticoagulants on DIC.

There are several differences in the recommendations for heparin among the three guidelines (Table 1) [3–5]. Anticoagulant treatment may be a rational approach based on the notion that DIC is characterized by extensive activation of coagulation. Although experimental studies have shown that heparin can at least partly inhibit the activation of coagulation in DIC [36], there are no RCTs demonstrating that the use of heparin in patients with DIC results in an improvement in clinically relevant outcomes. A small RCT showed that LMWH was better than UFH in the treatment of DIC (low quality)[37]. Patients with DIC are at high risk of VTE, and VTE prophylaxis with UFH, LMWH and/or mechanical methods has become the standard of care in patients with DIC (moderate and high quality, respectively) [38,39]. A recent large trial in patients with severe sepsis showed a non-significant benefit of low-dose heparin on the 28-day mortality, and underscored the importance of not stopping heparin in patients with DIC and abnormal coagulation parameters [21]. Although it is not easy to quickly measure the AT activity level in all hospitals in order to decide whether to administer urgent heparin

treatment, measuring this might be useful for achieving the full efficacy of heparin.

Anti-FXa agents such as Fondaparinux are recommended for the prophylaxis of deep vein thrombosis after orthopedic surgery, but there is little evidence in critically ill patients. Danaparoid sodium has been used in Japan, but no RCTs have shown a reduction in the mortality rate or an improvement in the resolution rate in DIC. Synthetic protease inhibitors such as Gabexate mesilate and Nafamostat have been used and evaluated in Japan [9,40,41], but there are no RCTs showing a reduction in the mortality rate or an improvement in the resolution rate in DIC.

Anticoagulant factor concentrates

Recommendations:

1 Further prospective evidence from RCTs confirming a benefit is required.

2 The administration of AT, recombinant human TM (rhTM) or activated protein C (APC) may be considered in DIC patients.

The use of agents that are capable of restoring the dysfunctional anticoagulant pathways in patients with DIC has been extensively studied. The three guidelines [3–5] give different recommendations for the use of anticoagulant factor concentrates (Table 1). A large-scale multicenter RCT performed to directly assess the effect of AT concentrate on mortality in patients with severe sepsis showed no significant reduction in those treated with AT concentrate (high quality) [28]. Interestingly, the subgroup of patients who had DIC and who did not receive heparin showed a remarkable survival benefit (moderate quality) [42], but this finding requires prospective validation. The clinical efficacy of recombinant human APC (rhAPC) in severe sepsis was demonstrated in a large RCT [29], but a prospective trial in septic patients with relatively low disease severity did not show any benefit of rhAPC [30]. The withdrawal of rhAPC from sepsis treatment was proposed after an RCT for sepsis shock failed to show any benefit [31]. Plasma-derived APC improved the outcome in a small RCT [43] in Japan, but it was not approved for DIC treatment. There are no useful RCTs on the use of PC concentrate for treating sepsis or DIC. An RCT comparison of rhTM with UFH [33] showed that rhTM significantly increased the resolution rate in DIC, but did not significantly decrease the mortality rate. In another RCT on severe sepsis, rhTM reduced the mortality and significantly reduced organ failure as compared with placebo [44]. Another RCT in severe sepsis showed that a recombinant human tissue factor pathway inhibitor showed no significant benefit [34].

Antifibrinolytic treatment

Recommendations:

1 Patients with DIC should generally not be treated with antifibrinolytic agents (low quality).

2 DIC patients who present with severe bleeding, characterized by a marked hyperfibrinolytic state such as leukemia (low quality) or trauma (moderate quality), could be treated with antifibrinolytic agents.

Antifibrinolytic agents are effective in bleeding patients, but the use of these agents in patients with bleeding resulting from DIC is generally not recommended [45]. An exception may be made in cases where hyperfibrinolysis dominates the clinical picture, as seen in the coagulopathy associated with acute promyelocytic leukemia (AML-M3) and in some cases of malignancy (e.g. prostate carcinoma). The three guidelines show some differences in the recommendations here (Table 1).

A study in AML-M3 has shown a beneficial effect of antifibrinolytic agents in this situation (low quality) [46], but cases complicated with severe thrombosis owing to the combined use of ATRA and tranexamic acid have been documented [47]. A recent RCT (moderate quality) [48] showed that tranexamic acid significantly reduced the mortality of patients with trauma. In these cases, antifibrinolytics should be administered in the early part of management, before the levels of PAI-1 and other endogenous antifibrinolytics are elevated.

Addendum

H. Wada was chairman and explained the JSTH guidelines. J. Thachil was co-chairman and explained the BCSH guidelines. M. Di Nisio explained the SISET guidelines and differences among three guidelines. P. Mathew examined the difference among three guidelines. S. Kurosawa was co-chairman and examined the differences among three guidelines. S. Gando was co-chairman and explained the JSTH guidelines. H.K. Kim was co-chairman and examined the diagnosis. J.D Nielsen was co-chairman and examined the treatments. C-E. Dempfle was co-chairman and examined the diagnosis. M. Levi explained the BCSH guidelines and examined the treatments. C.H Toh explained the BCSH guidelines and GRADE system. All members discussed to harmonize the three guidelines.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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