



Review Article

Diagnosis and treatment of disseminated intravascular coagulation: Guidelines of the Italian Society for Haemostasis and Thrombosis (SISET) ☆

Marcello Di Nisio ^{a,*}, Francesco Baudo ^b, Benilde Cosmi ^c, Armando D'Angelo ^d, Andrea De Gasperi ^e,
 Alessandra Malato ^f, Mario Schiavoni ^g, Alessandro Squizzato ^h
 on behalf of the Italian Society for Thrombosis and Haemostasis

^a Department of Medicine and Aging, Centre for Aging Sciences (Ce.S.I.), "University G. D'Annunzio" Foundation, Chieti, Italy

^b Department of Haematology, Niguarda Hospital, Milan, Italy

^c Unit of Angiology and Coagulation Disorders "Marino Golinelli", Policlinic S. Orsola-Malpighi, Bologna, Italy

^d Coagulation Service and Thrombosis Research Unit, San Raffaele Hospital IRCCS, Milan, Italy

^e Department of Anaesthesiology and Intensive Care II, Niguarda Hospital, Milan, Italy

^f Department of Haemostasis and Haematology, Policlinic P. Giaccone, Palermo, Italy

^g Department of Internal Medicine, Thrombosis and Haemostasis Center, Scorrano-Lecce, Italy

^h Research Center on Thromboembolic disorders and Antithrombotic Therapies, Department of Clinical Medicine, University of Insubria, Varese, Italy

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ABSTRACT

Background: The diagnosis and treatment of disseminated intravascular coagulation (DIC) remain extremely controversial.

Purpose: The Italian Society for Thrombosis and Haemostasis commissioned a project to develop clinical practice guidelines for the diagnosis and treatment of DIC.

Methods: Key questions about the diagnosis and treatment of DIC were formulated by a multidisciplinary working group consisting of experts in clinical medicine and research. After a systematic review and discussion of the literature, recommendations were formulated and graded according to the supporting evidence. In the absence of evidence, evidence of low quality, or contradictory evidence, a formal consensus method was used to issue clinical recommendations.

Results and Conclusions: In suspected DIC, we suggest the use of the diagnostic scores ISTH (grade C), JMHV (grade C) or JAAM (grade D) over stand alone tests. The cornerstone of the management of DIC remains the treatment of the underlying triggering disease. We do not suggest the use of antithrombin (grade D), dermatan sulphate (grade D), gabexate (grade D), recombinant factor VIIa (grade D), activated protein C (grade D), thrombomodulin (grade B). The use of unfractionated heparin or low-molecular-weight heparin is not suggested except for thromboembolic prophylaxis in patients a high risk who do not have active bleeding (grade D). In patients with severe sepsis/septic shock and DIC we suggest the use of human recombinant activated protein C (grade D). In patients with DIC and active bleeding we suggest the use of transfusion therapy (platelets, plasma, cryoprecipitate) (grade D).

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Contents

Introduction	178
Design and methods	179
Methods	179
Results	179
Diagnosis of DIC	179

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; DIC, Disseminated intravascular coagulation; FDP, fibrin degradation products; FFP, fresh-frozen plasma; ISTH, International Society on Thrombosis and Hemostasis; JAAM, Japanese Association for Acute Medicine; JMHV, Japanese Ministry of Health and Welfare; LMWH, low-molecular-weight heparin; PT, prothrombin time; RCT, randomized clinical trial; rFVIIa, recombinant activated factor VII; rhAPC, recombinant human activated protein C; SIGN, Scottish Intercollegiate Guideline Network; SISET, Società Italiana per lo Studio dell'Emostasi e Trombosi/Italian Society for Thrombosis and Haemostasis; UFH, unfractionated heparin.

☆ SISET: Società Italiana per lo Studio dell'Emostasi e Trombosi.

* Corresponding author: Tel./fax: +39 0871 358255.

E-mail address: mdinisio@unich.it (M. Di Nisio).

Recommendations	179
Literature review and analysis	179
ISTH score	179
Good practice points	180
JMHW and JAAM scores	180
Recommendation	180
The score of the Korean Society of Thrombosis and Haemostasis	180
Recommendation	180
Waveform analysis	180
Recommendation	180
Prognostic value of the ISTH, JMHW, JAAM scores and of the Wave-form analysis	180
Dynamic scores	180
Stand-alone laboratory tests	180
Recommendation	180
Literature review and analysis: treatment of DIC	181
Recommendations	181
Good practice point	181
Antithrombin	181
Recommendation	181
Dermatan sulphate	181
Recommendation	181
Unfractionated heparin	182
Recommendation	182
Low-molecular-weight heparin	182
Recommendation	182
Recombinant activated factor VII	182
Recommendation	182
Gabexate	182
Recommendation	182
Activated Protein C	182
Recommendation	182
Recommendation	182
Protein C concentrates	182
Recommendation	183
Plasma exchange	183
Recommendation	183
Thrombomodulin	183
Recommendation	183
Transfusion of platelets, plasma and cryoprecipitate	183
Recommendation	183
Recommendation	183
Recommendations for research	183
Conflict of interest statement	184
References	184

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 can be also associated with (severe) bleeding due to the consumption of platelets and coagulation factors. Currently, no clinical sign, symptom or stand-alone laboratory test owns a sufficiently high diagnostic accuracy to establish or rule out the diagnosis of DIC. Diagnostic scores combining clinical signs and laboratory parameters have been proposed [1,2]. Ideally, the score should be easy to calculate, have prognostic value and allow prognostic and therapeutic changes. It is still a matter of debate which score or tests should be used for the diagnosis of DIC.

DIC may arise in patients with a wide spectrum of disorders including sepsis, malignancy, or pregnancy complications [1,2]. Despite several studies that have suggested a higher mortality and organ dysfunction in association with DIC [1,2], it remains unclear whether the coagulopathy in itself carries a worse outcome or it rather represents an epiphenomenon of an underlying disease with a worse prognosis.

The cornerstone of the management of DIC is the treatment of the underlying condition triggering the coagulopathy which will lead in many cases to a spontaneous resolution of the DIC. However, additional treatment aiming at the coagulation abnormalities may be required. To reduce the risk of unbalanced concomitant treatments and underlying co-morbidities, the efficacy and safety of treatments for DIC should be ideally evaluated in randomized clinical trials (RCTs) using a no-treatment or placebo control group. Due to the paucity of such evidence, a number of uncertainties remain over the management of DIC including the type, dose, and regimens of medications to use.

Therefore, the Italian Society for Thrombosis and Haemostasis (SISST) commissioned a project to develop clinical practice guidelines for the diagnosis and treatment of DIC. The recommendations were generated through a systematic search of evidence and formulated according to explicit methods for consensus development. The objective of the present guidelines was to provide recommendations to all clinicians involved in the diagnosis and treatment of DIC, with the aim of optimizing the management of DIC, and improving the quality of life and the clinical outcomes (reduction in thrombotic and bleeding events, and increased survival) with a possible reduction in healthcare costs.

Table 1
Diagnostic scores for disseminated intravascular coagulation.

	ISTH	JMHW	JAAM	KSTH
Underlying disorder known to be associated with DIC	Required	1 point	0 points	0 points
Bleeding	0 points	No hematological malignancy: 1 point Hematological malignancy: 0 point	0 points	0 points
Thrombosis related organ failure	0 points	Present: 1 point; absent: 0 point	0 points	0 points
Systemic inflammatory response syndrome criteria	0 points	0 points	0–2: 0 points ≥3: 1 point	0 points
Prolonged thrombin time	<3 sec: 0 points ≥3 sec: 1 point ≥6 sec: 2 points	Prothrombin time ratio: <1.25: 0 points 1.25–1.67: 1 point ≥1.67: 2 points	Prothrombin time ratio <1.2: 0 points ≥1.2: 1 point	>3 sec: 1 point (or aPTT >5 sec: 1 point)
Fibrinogen level (g/L)	>1: 0 points ≤1: 1 point	>1.5: 0 points 1.0–1.5: 1 point ≤1: 2 points	≥3.5: 0 points <3.5: 1 point	<1.5: 1 point
Elevated fibrin related marker (e.g. soluble fibrin monomers, d-dimer)	No increase: 0 point Moderate increase: 2 points (D-dimer: increase ≤10 fold limit of normal) Marked increase: 3 points (>10 fold limit of normal)	Fibrin degradation product (µg/mL): <10: 0 point 10–20: 1 point 20–40: 2 points ≥40: 3 points	Fibrin/fibrinogen degradation products (mg/L) <10: 0 point ≥10 and <25: 1 point ≥25: 3 points	D-dimer increase: 1 point
Platelet count (x10 ⁹ /µL)	>100: 0 point ≤100: 1 point ≤50: 2 points	Patients with hematological malignancy: 0 points Patients without hematological malignancy: >120: 0 points 80–120: 1 point 50–80: 2 points ≤50: 3 points	≥120: 0 point ≥80 and <120 or >30% decrease within 24 hrs: 1 point <80 or >50% decrease within 24 hrs: 3 points	<100: 1 point
Total	DIC ≥5 points No DIC <5 points	Patients with hematological malignancy: ≥4 points No hematological malignancy: ≥7 points	DIC ≥5 points No DIC <5 points	DIC ≥3 points No DIC <3 points

Design and methods

Methods

These guidelines were issued following a predefined methodology defined by the Siset Guidelines Program Steering Group and approved by the Siset Executive Committee. Details on the methodology are published elsewhere [3]. A systematic search of the MEDLINE, EMBASE and the Cochrane Library databases up to February 2011 was performed to identify studies reporting on the diagnosis and treatment of DIC. The grading system adopted is the one designed by the Scottish Intercollegiate Guideline Network (SIGN) [4]. The Siset Executive Committee convened a multidisciplinary working group consisting of experts in clinical medicine and research relevant to the diagnosis and treatment of DIC. The draft recommendations were reviewed by an external panel of two internationally recognized experts in the field and by the Siset Executive Committee.

Results

Diagnosis of DIC

Recommendations

- 1) In patients with suspected DIC, we suggest the use of either the International Society on Thrombosis and Hemostasis (ISTH) score (grade C), the score of the Japanese Ministry of Health and Welfare (JMHW) (grade C), or the score of the Japanese Association for Acute Medicine (JAAM) to make the diagnosis (grade D)

- 2) In patients with a suspected DIC, we do not suggest the use of the score of the Korean Society on Thrombosis and Haemostasis to make the diagnosis (grade D)
- 3) In patients with suspected DIC, we do not suggest the use of the Wave-form analysis to make the diagnosis (grade D)
- 4) In patients with suspected DIC, we do not suggest the use of stand-alone laboratory tests (grade D)

Literature review and analysis

For the diagnosis of DIC, 7588 studies were identified, 41 selected based on the title or abstract and 6 included in the review [5–10]. The scores of the ISTH [5], the JMHW [6], the score of the Korean Society of Thrombosis and Hemostasis [9] were evaluated in one study each; the JAAM score in two studies [7,8]. The only stand-alone laboratory tests whose accuracy was verified by a reference test were the Wave-form Analysis [5,10] and the fibrin degradation products (FDP) [6].

ISTH score

In 2001 the ISTH proposed a score for the diagnosis of DIC whose prerequisite is the presence of an underlying disorder known to be associated with DIC. A diagnosis of overt-DIC is made for score ≥5 (Table 1). The diagnostic accuracy of the ISTH score has been evaluated in 217 consecutive patients with a suspicion of DIC who were admitted to the Intensive Care Unit [5]. DIC was diagnosed or excluded by a panel of experts using clinical and laboratory data. A quantitative rapid enzyme-linked immunosorbent D-dimer assay was used as fibrin-related parameter with levels <0.4 µg/mL considered as normal,

between 0.4 and 4.0 $\mu\text{g/mL}$ as moderately increased, and $>4.0 \mu\text{g/mL}$ strongly increased. The ISTH score showed sensitivity, specificity, positive and negative predictive value of 91%, 97%, 96% and 97% respectively. Although the levels of protein C, antithrombin, thrombin-antithrombin complexes, fibrinogen, and soluble fibrin significantly differed between patients with and without DIC, none of these parameters increased the accuracy score.

Good practice points

- 1) We suggest using D-dimer as a fibrin-related marker considering as moderate an increase up to 10 times the upper limit of normal, and as strong an increase above this threshold
- 2) The ISTH score gives prothrombin time (PT) in seconds whereas in clinical practice the PT is often expressed as a ratio. Considering PT values <1.25 (15/12 sec) as normal, 0 points should be assigned for $\text{PT} < 1.25$, 1 point for PT between 1.25 and 1.50, and 2 points for PT above 1.50.

JMHW and JAAM scores

The first score proposed for the diagnosis of DIC was the one of JMHW. A diagnosis of DIC is made for score ≥ 5 in patients with and ≥ 7 in those without a hematological malignancy. Since the '80s, the JMHW score has been mainly evaluated for its prognostic value, while its diagnostic accuracy has been assessed only in a relatively small cohort of patients with acute leukemia [6]. A diagnosis of DIC was made in 36 out of 125 patients (28.8%) by two independent experts who used additional laboratory parameters and clinical information. The JMHW score had a sensitivity of 78% (95% confidence intervals [CI]: 64% to 92%), specificity of 91% (95% CI: 85% to 97%), positive predictive value 80% (95% CI: 67% to 93%), and a negative predictive value of 90% (95% CI: 84% to 96%). The corresponding estimates for the ISTH score calculated on the same population were 50% (95% CI: 34% to 66%), 99% (95% CI: 97% to 100%), 95% (95% CI: 85% to 100%) and 80% (95% CI: 72% to 88%).

In a prospective multicenter study of 273 patients with platelets $<150 \times 10^9/\text{L}$ the JAAM score was compared to the ISTH and JMHW scores [7]. The authors suggested that the JAAM score was able to diagnose a significantly higher number of patients with DIC and detect 97% of DIC cases identified by the other two scoring systems. In a recent retrospective cohort of 314 trauma patients, Sawamura and colleagues found that the JAAM score was able to diagnose all patients who developed ISTH overt-DIC at early time points [8].

In the diagnosis of DIC, the lack of a gold standard makes difficult, if not impossible, to determine the superiority or inferiority of the diagnostic criteria. The reported rates of agreement between the JMHW, JAAM and the ISTH scores suggest that the former may be considered as valid alternatives for the diagnosis of DIC [6,11,12]. Whether one score may perform better than the others depending on the type of DIC and underlying condition needs further investigation [8,13].

Recommendation

In patients with suspected DIC, we suggest the use of either the ISTH score (grade C), the JMHW score (grade C), or the JAAM score (grade D) to make the diagnosis.

The score of the Korean Society of Thrombosis and Haemostasis

The score of the Korean Society of Thrombosis and Haemostasis has been evaluated retrospectively in 131 patients and found to have a 85% rate of agreement with the ISTH score [9].

Recommendation

In patients with a suspected DIC, we do not suggest the use of the score of the Korean Society on Thrombosis and Hemostasis to make the diagnosis (grade D).

Waveform analysis

In the photo-optical monitoring of clot formation a normal waveform is characterized by a lag phase due to the formation of a critical fibrin clot, followed by a sharp decrease in the light transmittance that occurs with the rapid polymerization into larger fibrin fibrils. Characteristic of an abnormal biphasic waveform is the early drop in light transmittance, i.e. before the actual formation of the clot. In the prospective study of Bakhtiari and colleagues the abnormal biphasic waveform showed a sensitivity of 88% and a specificity of 97% [5]. In another study conducted among hospitalized patients who had a suspicion of DIC, the sensitivity was 59% and 48% when the diagnosis was made by the scores of the ISTH and JMWH, respectively [10]. Specificity was 95% in both cases.

Recommendation

In patients with a suspected DIC, we do not suggest the use of the Wave-form analysis to make the diagnosis (grade D).

Prognostic value of the ISTH, JMHW, JAAM scores and of the Wave-form analysis

A strong correlation between increasing ISTH score and mortality has been demonstrated by several studies [5,14,15]. For any increase of 1 point in the ISTH score there was a 1.25 higher risk of 28-day mortality [5]. In a retrospective series of 797 patients admitted to the Intensive Care Unit, a higher mortality was predicted by the ISTH score independently of the Acute Physiology and Chronic Health Evaluation (APACHE) or the Logistic Organ Dysfunction scores [14]. Similarly, the abnormal biphasic waveform, the JMHW and JAAM scores have been found to predict a worse prognosis [5,15,16], although studies have not always been concordant [17].

Dynamic scores

A major disadvantage of the diagnostic scores discussed so far is to be static assessments which may not capture the dynamically changing scenario of the coagulopathy. Thrombocytopenia, for instance, is observed in up to 98% of DIC patients although a single determination of the platelet count may still remain in the 'normal' range of $150\text{--}400 \times 10^9/\text{L}$. Dynamic scores that take into account the temporal dynamic changes of the platelets and coagulation parameters have been recently proposed [18,19]. However, these scoring systems have been assessed only in terms of prognostic value which leaves them outside the scope of the current review.

Stand-alone laboratory tests

The diagnostic accuracy of stand-alone laboratory tests has not been evaluated in comparison with a reference standard. The only exceptions are represented by the Waveform analysis discussed above and the FDP which have been compared to the scores of the ISTH and of the JMHW [6]. Yanada and colleagues found a sensitivity of 92% and a specificity and overall accuracy comparable to the scoring systems. Concerns over the generalizability of these findings arise from the fact that elevated FDPs might be found in many conditions other than DIC, such as trauma or venous thromboembolism. In addition, FDPs are metabolized by the liver and excreted by the kidneys, and therefore liver and kidney impairment can influence their levels [20].

Recommendation

In patients with a suspected DIC, we do not suggest the use of stand-alone laboratory tests (grade D).

Literature review and analysis: treatment of DIC

Recommendations

- 1) In patients with DIC secondary to severe sepsis/septic shock, obstetric complications, burn injury, or advanced liver disease we do not suggest the use of antithrombin (grade D)
- 2) In patients with hematological malignancy and DIC we do not suggest the use of dermatan sulphate (grade D)
- 3) In patients with DIC we do not suggest the use of unfractionated heparin (UFH) except for thromboembolic prophylaxis in patients a high risk who do not have active bleeding (grade D)
- 4) In patients with DIC we do not suggest the use of low-molecular-weight heparin (LMWH) except for thromboembolic prophylaxis in patients at high risk who do not have active bleeding (grade D)
- 5) In patients with DIC and solid tumors or obstetric complications we do not suggest the routine use of recombinant activated factor VII (rFVIIa) in case of bleeding (grade D)
- 6) In patients with sepsis, cancer or undergoing surgery and with DIC we do not suggest the use of gabexate (grade D)
- 7) In patients with severe sepsis/septic shock, APACHE II score >25 (EMEA: at least 2 organs compromised) and DIC we suggest the use of recombinant human activated protein C (rhAPC) (grade D)
- 8) In patient with obstetric complications and DIC we do not suggest the use of APC (grade D)
- 9) In children with sepsis/septic shock and DIC, we do not suggest the use of protein C concentrates (grade D)
- 10) In patients with sepsis and DIC we do not suggest the use of plasma exchange (grade D)
- 11) In patients with hematological cancer or infection and DIC, we do not suggest the use of thrombomodulin (grade B)
- 12) In patients with DIC and active bleeding we suggest the use of transfusion therapy (platelets, plasma, cryoprecipitate) (grade D)
- 13) In patients with chronic DIC or without active bleeding we do not suggest transfusion therapy based only on laboratory parameters (grade D)

Good practice point

Due to the lack of studies, no recommendation can be formulated in patients with DIC and underlying diseases other than those reported above. Thus, the routine use of the treatments discussed further cannot be suggested in such cases.

A total of 7445 studies related to the therapy of DIC were identified, 58 selected based on the title or abstract and 26 included [21–46]. The primary efficacy outcome was the resolution of DIC as defined by the authors. Of note, while the majority of the studies reported an effect of the intervention on the platelet count and/or one or more coagulation parameters, only 8 studies specifically used DIC as an outcome [22,24,28,30,34,36,37,43]. Where available, clinical outcomes were considered and reported to provide a full picture of the individual treatment effects. Overall, the quality of the studies was poor and most of them enrolled relatively few participants. These weaknesses together with the heterogeneous definition of DIC and the frequent lack of an adequate control group represent serious limitations to the results external validity and contributed to the final judgment about the applicability of the intervention. For some treatment modalities, indications were derived from other close medical settings and therefore should be taken with caution.

Antithrombin

The use of antithrombin for the treatment of DIC has been summarized in a review of 3 RCTs including 364 DIC patients with severe sepsis and shock who were assigned to antithrombin or placebo [21]. Short-term mortality was significantly lower with antithrombin (odds ratio [OR] 0.65;95%CI: 0.42 to 0.99), with comparable rates of bleeding (OR 1.16;95%CI: 0.42 to 3.19). In one of the RCTs included

in the review, the coagulopathy had resolved at 10 days in 71% and 33% of patients, respectively ($p < 0.05$) [22]. While encouraging, the results of this review need to be considered carefully. Potential limitations are represented by the heterogeneity of the DIC definition and of the dose and duration of treatments. Moreover, two studies were post-hoc analyses of trials whose primary inclusion criteria were not DIC.

In a RCT of 51 patients with DIC and shock, antithrombin (dose to maintain the plasma antithrombin at 100%) was compared to UFH (3000 U bolus followed by 250 U/h in continuous infusion), and the combination of antithrombin plus UFH (1000 U bolus followed by 100 U/h) [23]. The amount of blood transfused was significantly higher in patients treated with the combined treatment. A faster improvement of coagulation parameters was achieved in the groups treated with antithrombin ($p = 0.001$).

In a second RCT, patients ($n = 40$) with sepsis and platelet count $< 100 \times 10^9/L$ or with a platelet reduction $\geq 20\%$ during the 24 hours preceding the randomization, were assigned to 14 days of antithrombin (plasma antithrombin target 140%) versus no antithrombin [24]. All patients received prophylactic UFH. Antithrombin was associated with a resolution of the DIC with organ function improvement in all cases whereas no significant changes were observed in the control group.

In a third RCT, patients ($n = 39$) with DIC secondary to obstetric complications (i.e. abruptio placentae and post-partum bleeding) were randomized to antithrombin (3000 U/day) or gabexate (20–39 mg/kg/day) [25]. The overall clinical efficacy was 92% for antithrombin and 60% for gabexate ($p < 0.05$). Coagulation parameters were improved in 92% and 53% ($p < 0.01$), respectively. No adverse events were reported.

A fourth RCT has been conducted in patients ($n = 31$) with severe burn injury [26] who were randomized within the first 24 hours after injury, to standard treatment or standard treatment plus antithrombin (plasma antithrombin target $> 150\%$) for four consecutive days. According to the ISTH criteria, 9 patients had overt DIC and 19 non-overt DIC at admission. Patients treated with antithrombin showed a significant improvement in the Sequential Organ Failure Assessment score and had an absolute reduction in 28-day mortality due to organ failure of 25%, as compared to no antithrombin treated patients ($p = 0.004$). No treatment related side effects were observed.

Finally, antithrombin has been evaluated in patients ($n = 25$) with hepatic coma, DIC and a high risk of organ dysfunction who were randomized to antithrombin (3000 U bolus followed by 1000 IU/6 hrs to reach antithrombin levels > 0.80 U/mL) versus no antithrombin [27]. DIC was defined as the presence of spontaneous bleeding and platelets $< 50 \times 10^9/L$. There was no significant effect on mortality or laboratory parameters.

Recommendation

In patients with DIC secondary to severe sepsis/septic shock, obstetric complications, burn injury, or advanced liver disease we do not suggest the use of antithrombin (grade D).

Dermatan sulphate

Dermatan sulphate has been evaluated in a RCT patients ($n = 10$) with acute leukemia and DIC defined as FDPs > 500 ng/mL, PT $< 70\%$ and/or fibrinogen < 150 mg/dL [28]. Patients were assigned to a continuous infusion of dermatan sulphate (0.3 mg/kg/h, $n = 5$) or UFH (8.5 U/kg/h, $n = 5$) for a median of 15 days. There were no thrombotic events. Changes of coagulation parameters were similar between the study groups.

Recommendation

In patients with hematological malignancy and DIC we do not suggest the use of dermatan sulphate (grade D).

Unfractionated heparin

The study comparing UFH and antithrombin has been discussed previously [23]. In a second RCT, patients with DIC diagnosed by the JMW score were randomized to 5 days of LMWH (dalteparin, 75 antiXa UI/kg/day) or UFH (240U/kg/day) [29]. Survival rates were respectively 90.2% and 76.6%. Dalteparin was associated with significantly lower bleeding on day 1 (15.6% versus 6.8%). A greater improvement of the score of the JMW after the second day was reported in patients treated with UFH.

In a third RCT, patients with DIC diagnosed by a modified version of the JMW score were randomized to no anticoagulants (n = 11), gabexate (0.9–2.0 mg/kg/h, n = 10) for 4–16 days, or UFH (5–15 U/kg/h, n = 10) for 6–25 days [30]. Mortality was 91% in the no anticoagulant group (5 deaths due to DIC), 50% with gabexate (no death due to DIC), and 60% with UFH (2 cases of death due to DIC). No data were reported concerning coagulation parameters.

In a randomized prospective double-blind trial, plasma-derived human APC was evaluated against UFH for the treatment of DIC [31]. One hundred thirty-two patients with DIC were enrolled of whom 63 received APC (2.5 µg/kg/h) and 69 UFH (8 U/kg/h) by intravenous infusion for 6 days. Aggravation of bleeding was seen after treatment in 8 patients receiving UFH, but in none of those treated with APC. Improvement in bleeding was significantly better with APC (p < 0.01). The 28-day mortality was 20.4% in the APC group and 40% in the UFH group (p < 0.05). Fibrinogen, protein C, and antithrombin were significantly increased in the APC group, whereas only protein C was significantly increased in the UFH group. In the non leukemic group of patients, platelet counts increased significantly (p < 0.05) only in APC-treated patients. Of note, there was no significant difference in the rate of complete recovery from DIC between the 2 groups. No severe adverse events were reported in either group.

Although not intended for DIC, the HETRASE study showed no beneficial effect of UFH (500 IU/h for 7 days) in patients with sepsis, irrespective of D-dimer levels [32].

Recommendation

In patients with DIC we do not suggest the use of UFH except for thromboembolic prophylaxis in patients at high risk who do not have active bleeding (grade D).

Low-molecular-weight heparin

The use of LMWH has been evaluated in 2 studies [29,33], one of them discussed above [29]. In a RCT, patients (n = 56) with DIC diagnosed with the JMW score were assigned to two doses of LMWH (Fragmin, 75 U/kg/day, group I and 150 U/kg/day, group II) for 5 days in continuous infusion [33]. Mortality was 11% in group I and 10% in group II with no deaths related to DIC. Bleeding occurred in 3.7% and 10.3%, respectively. The score JMW was reduced in 63% and 59%, and it worsened in 7% and 3%.

Recommendation

In patients with DIC we do not suggest the use of LMWH except for thromboembolic prophylaxis in patients at high risk who do not have active bleeding (grade D).

Recombinant activated factor VII

rFVIIa has been evaluated in 18 patients with DIC, cancer and active bleeding not controlled by standard measures (e.g. transfusion of platelets and fresh frozen plasma) [34]. DIC was diagnosed if bleeding was accompanied by at least 3 of the following: fibrinogen < 200 mg/dL, D-dimer > 0.5 µg/mL, platelets < 150 × 10⁹/L, PT and/or aPTT prolongation, and/or antithrombin < 80%. The median number of rFVIIa doses (90 µg/kg) was 5 (range 3–10). Bleeding stopped in

15/18 patients who had a resolution of the DIC while 3 patients were not responsive. There were no thromboembolic complications.

The use of rFVIIa in patients with post-partum bleeding has been summarized in a review of 11 studies that included 39 patients, 18 (59%) with DIC [35]. Bleeding was controlled in 29/39, reduced in 9/39 with no response in one case.

Recommendation

In patients with DIC and solid tumors or obstetric complications we do not suggest the routine use of rFVIIa in case of bleeding (grade D).

Gabexate

Gabexate has been evaluated in 2 studies previously discussed [25,30]. In another RCT, patients (n = 40) from the Intensive Care Unit with a JMW score between 6 and 8 were randomized to 7 days of gabexate (2 mg/kg/h) or placebo (saline 2 mg/kg/h) [36]. The use of platelets and antithrombin concentrates was permitted. There was no difference in DIC score reduction nor in the 1-month mortality between the study groups.

Recommendation

In patients with sepsis, cancer or undergoing surgery and with DIC we do not suggest the use of gabexate (grade D).

Activated Protein C

The use of rhAPC for the treatment of DIC has been assessed post-hoc in the “for the Recombinant human Activated Protein C Worldwide Evaluation In Severe Sepsis” study [37,38]. Patients with severe sepsis were randomized to rhAPC (DrotAA, 24 µg/kg/h for 96 hrs) or placebo. A total of 454/1568 (29%) had a diagnosis of DIC (score ISTH > 5). The 28-day mortality was 43% in patients with DIC versus 27.1% in those without DIC. In the group receiving rhAPC these estimates were 30.5% and 22.1%, respectively. rhAPC was associated with a 12.5% and 5% absolute risk reduction of the 28-day mortality in patients with and without DIC (p = 0.26). In the group with DIC, thrombotic events occurred in 0.4% patients treated with rhAPC versus 2.3% in the placebo (RR 0.19; 95%CI: 0.02 to 1.61). Compared to baseline, a significant lower number of patients treated with rhAPC had a diagnosis of DIC at 6 and 14 days (p = 0.037 and 0.047).

Recommendation

In patients with severe sepsis/septic shock, APACHE II score > 25 (EMEA: at least 2 organs compromised) and DIC we suggest the use of rhAPC (grade D).

A plasma-derived activated protein C (5000–10000 IU intravenous for 2 days) has been assessed in a cohort of 16 patients with DIC (diagnostic criteria for DIC not specified) secondary to abruptio placentae [39]. All laboratory parameters were significantly modified and the DIC resolved at 24 hours although there were no changes in the platelet count. No adverse events were reported.

Recommendation

In patient with obstetric complications and DIC we do not suggest the use of activated protein C (grade D).

Protein C concentrates

The use of protein C concentrates has been evaluated in case series of children with sepsis (overall 24 patients) and found associated with an improvement or normalization of coagulation parameters, protein C levels and clinical signs [40–42]. In a double-blind RCT, children (n = 40) with sepsis/septic shock were assigned to placebo or protein C concentrates (200 UI/kg, 400 UI/kg, or 600 UI/kg) for a maximum of 7 days [43]. Protein C concentrates were associated with a

significant increase in protein C levels and improvement of coagulation parameters. Twenty-three patients had DIC diagnosed by platelet $\leq 150 \times 10^9/L$, fibrinogen ≤ 2 g/L, factor V $\leq 60\%$ and an increase of FDP. No data were reported separately for the subgroup with DIC.

Recommendation

In children with sepsis/septic shock and DIC, we do not suggest the use of protein C concentrates (grade D).

Plasma exchange

The use of plasma exchange has been evaluated in a cohort of 8 children with sepsis and DIC defined by fibrinogen <150 mg/dL and aPTT >50 sec [44]. Eighty-eight percent of these patients survived. There were no bleeding or thrombotic complications during treatment.

Recommendation

In patients with sepsis and DIC we do not suggest the use of plasma exchange (grade D).

Thrombomodulin

In a multicenter, double blind RCT, patients ($n = 234$) with DIC (JMHW score) and hematological cancer or infection were assigned to 6 days of human soluble thrombomodulin (ART-123, 0.06 mg/kg for 30 min, qd) or heparin sodium (8 U/kg/h for 24 h) [45]. The a priori defined primary efficacy endpoint was DIC resolution rate at 7 days after the start of the infusion. DIC resolved in 66.1% versus 49.9% (absolute difference 16.2%; 95% CI: 3.3% to 29.1%). The mortality rate was not significantly lower with thrombomodulin either in patients with hematological malignancy (absolute difference -0.8% ; 95% CI: -14.2% to 12.5%) or those with infections (absolute difference -6.6% ; 95% CI: -24.6% to 11.3%). The incidence of bleeding-related adverse events up to 7 days was reduced with thrombomodulin (43.1% vs. 56.5%, respectively; $p = 0.049$). There were 2/116 serious bleeding-related adverse events during the infusion of thrombomodulin compared to 3/115 in the heparin group.

Recommendation

In patients with hematological cancer or infection and DIC, we do not suggest the use of thrombomodulin (grade B).

Transfusion of platelets, plasma and cryoprecipitate

The use of platelets or plasma in patients with DIC has been assessed in a systematic review of 3 RCTs which found similar changes in coagulation parameters and/or survival between the intervention and control groups [46]. The heterogeneity and small size of the studies included as well as the methodological shortcomings limit the applicability of these conclusions. In the absence of strong evidence, the transfusion of platelets or plasma (components) to patients with DIC should not primarily be based on laboratory results, but rather meant for patients who present with bleeding.

In patients with DIC and active bleeding or at high risk of bleeding (e.g. postoperative patients or patients due to undergo an invasive procedure), we suggest the administration of fresh-frozen plasma (FFP) (10–15 mL/kg) while monitoring carefully the clinical evolution to assess the efficacy of the intervention and the need for dose adjustments. In case of fluid overload concerns, factor concentrates such as prothrombin complex concentrate might be considered as an alternative. Severe hypo-fibrinogenemia (<1 g/l) that persists despite FFP replacement may be treated with fibrinogen concentrate or cryoprecipitate. In patients with active bleeding or at high risk of bleeding who have a platelet count $<50 \times 10^9/L$ transfusion of platelets should be considered.

Recommendation

In patients with DIC and active bleeding we suggest the use of transfusion therapy (platelets, plasma, cryoprecipitate) (grade D).

Recommendation

In patients with chronic DIC or without active bleeding we do not suggest transfusion therapy based only on laboratory parameters (grade D).

Recommendations for research

In general, although the diagnosis and treatment of DIC represent important clinical problems with several pharmacoeconomic implications, the evidence in the literature remains scarce with few studies of relatively low methodological quality. In agreement with the recently published guidelines of the British Society of Haematology [47], the ISTH score emerged as the best diagnostic tool for DIC. However, other scores not considered in that guideline such as the JMHW and JAAM scores, look promising and seem to perform as well as the ISTH score. It remains unclear whether the accuracy of the ISTH, JMHW or JAAM scores is similar for DIC due to different underlying diseases. In fact, the absence of a “gold” standard for the diagnosis of DIC complicates the judgment over the diagnostic accuracy of the scoring systems. Their relevance in clinical practice could be, therefore, more related to how efficiently the score identifies patients with adverse prognosis who may benefit from specific additional diagnostic and/or therapeutic procedures. In this regard a comparison of the usefulness of the ISTH, JMHW, and JAAM against the recently proposed dynamic scores seems warranted.

As underlined in the recent guidelines of the British Society, there appears to be a role for rhAPC in the treatment of DIC associated with severe sepsis. However, the evidence in support remains limited and, given the observed higher risk of major bleeding with the administration of rhAPC, additional studies evaluating safety issues as well as the costs are needed before stronger recommendations can be made. Interestingly, in the Japanese guidelines for the treatment of DIC, rhAPC was not even mentioned since it was not approved in Japan [48]. At variance with the current guidelines and those of the British Society of Haematology [47], the Expert consensus for the treatment of DIC in Japan recommends antithrombin supplementation when DIC is associated with organ failure [48]. These discrepancies could arise from a different interpretation of efficacy, which was judged by the correction of coagulation abnormalities in Japan as opposed to the improvement in clinical outcomes [49,50]. In the present guideline, we used the resolution of DIC as the primary outcome and, nonetheless reach divergent conclusions from the Japanese group. While the effects of antithrombin in terms of clinical outcomes and coagulation parameters were encouraging, the evidence was judged still too limited with several methodological issues noted above, to recommend the use of antithrombin in clinical practice. Thrombomodulin, not considered in the British guidelines, has been recommended with some restrictions by the Japanese Expert group. However, the evidence in support of thrombomodulin in DIC comes from a single RCT with an active control group. These data, while promising, need confirmation in further studies before endorsing the use of thrombomodulin.

Among the suggestions useful for the application of these guidelines, the Working Group considered that the following points should be emphasized:

- 1) In the suspicion of DIC, the ISTH score and the JMHW and JAAM scores could be used as the reference diagnostic tools while waiting for a more thorough evaluation of the dynamic scores.
- 2) The cornerstone of the management of DIC remains the treatment of the underlying triggering disease. This will be often accompanied by a parallel improvement of the coagulopathy

- 3) With the few exceptions discussed above, the use of the various treatment modalities targeting DIC appears not supported by the literature and should be carefully evaluated by the treating physician for the individual patient.

Conflict of interest statement

DAA reports honoraria from Kedrion and Baxter. DGA reports being consultant for Baxter, Grifols and Novo Nordisk. MDN, FB, BC, AM, MS, and AS declare that they have no conflicts of interest.

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