Supportive management strategies for disseminated intravascular coagulation
An international consensus

Alessandro Squizzato1; Beverley J. Hunt2; Gary T. Kinasewitz3; Hideo Wada4; Hugo ten Cate5; Jecko Thachil6; Marcel Levi7; Vicente Vicente6; Armando D’Angelo5; Marcello Di Nisio7,10

1Research Center on Thromboembolic Disorders and Antithrombotic Therapies, Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy; 2Department of Haematology, Pathology and Lupus, Guy’s & St Thomas’ NHS Foundation Trust, London, UK; 3Pulmonary and Critical Care Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA; 4Department of Molecular and Laboratory Medicine, Mie University School of Medicine, Mie, Japan; 5Department of Internal Medicine and Cardiovascular Research Institute, Maastricht University Medical Center, Maastricht, The Netherlands; 6Department of Haematology, Manchester Royal Infirmary, Manchester, UK; 7Department of Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; 8Division of Hematology and Clinical Oncology, Hospital Universitario Morales Meseguer, Murcia, Spain; 9Coagulation Service and Thrombosis Research Unit, Scientific Institute San Raffaele, Milano, Italy; 10Department of Medical, Oral, and Biotechnological Sciences, Università “G. D’Annunzio” of Chieti-Pescara, Chieti, Italy

Summary
The cornerstone of the management of disseminated intravascular coagulation (DIC) is the treatment of the underlying condition triggering the coagulopathy. However, a number of uncertainties remain over the optimal supportive treatment. The aim of this study was to provide evidence and expert-based recommendations on the optimal supportive and antithrombotic treatment strategies for patients with DIC. A working group defined five relevant clinical scenarios. Published studies were systematically searched in the MEDLINE and EMBASE databases (up to May 2014). Seven internationally recognised experts were asked to independently provide clinical advice. A two-phase blinded data collection technique was used to reach consensus. Only three randomised controlled trials (RCTs) on the supportive management of DIC were identified. The RCTs (overall less than 100 patients) investigated the use of fresh frozen plasma and platelet transfusion and found no differences in survival between the intervention and control groups. The experts’ approach was heterogeneous, although there was consensus that supportive management should vary according to the underlying cause, clinical manifestations and severity of blood test abnormalities. Platelet transfusion should be given to maintain platelet count > 50×10⁹/l in case of bleeding while a lower threshold of 20 to 30×10⁹/l may be used in DIC without bleeding. Thromboprophylaxis with low-molecular-weight heparin is advised until bleeding ensues or platelet count drops below 30×10⁹/l. In conclusion, in the absence of solid evidence from RCTs, an individualised supportive management of DIC is advisable based on the type of underlying disease, presence of bleeding or thrombotic complications and laboratory tests results.

Keywords
Disseminated intravascular coagulation (DIC), prophylaxis, venous thrombosis, fresh frozen plasma, platelet transfusion

Introduction
Disseminated intravascular coagulation (DIC) is a syndrome characterised by the systemic activation of blood coagulation, which generates intravascular fibrin leading to thrombosis of small- and medium-sized vessels and eventually contributes to organ dysfunction (1). In addition, the consumption of platelets and coagulation factors may predispose patients with DIC to haemorrhagic complications. There is no gold standard for the diagnosis of DIC and no single test that confirms the diagnosis. Thus, the presence of underlying conditions known to cause DIC, clinical symptoms and signs together with laboratory assays including coagulation assays and blood count may allow clinicians to diagnose DIC. Blood tests have been combined in diagnostic scoring systems to aid diagnosis (2, 3).

DIC has been further subdivided into “non-overt DIC”, a term used when the haemostatic system is stressed but compensated, and “overt DIC” when the haemostatic system is stressed and decompensated. Non-overt DIC represents a subtle haemostatic dysfunction, while overt DIC is often associated with clinical consequences. Recently, it has been proposed to categorise DIC into four clinical types, i.e. bleeding, organ failure, massive bleeding, and...
non-symptomatic type, where each of them is the consequence of the predominance of hypercoagulability, hyperfibrinolysis or platelet and coagulation factor consumption over the other pathophysiological mechanisms (2).

Despite several studies that have suggested a higher mortality and organ dysfunction in association with DIC (1), it remains unclear whether the coagulopathy in itself carries a worse outcome or whether it 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 that will lead in many cases to a spontaneous resolution of DIC (2, 3). Additional supportive treatment aiming at modifying the haemostatic abnormalities is often practiced, but remains challenging due to the frequent concomitant comorbidities and the lack of clinical trials to guide the decision on the type, dose, and regimens to use (3, 4).

The aim of this paper was to tackle specific and clinically relevant questions on the supportive haemostatic and antithrombotic management strategies of DIC not covered by published consensus guidelines and where best clinical practice remains uncertain (3, 4).

**Methods**

On behalf of the Italian Society for Thrombosis and Haemostasis (SISET), a working group (AS, MDN, and AD) devised five hypothetical clinical scenarios on supportive treatment for DIC. Supportive treatment was defined as any treatment used with the primary aim to prevent or manage clinical manifestations of DIC, i.e.

![Studies selection progress diagram]

**Figure 1: Studies selection progress.**
bleeding and thrombosis. The first clinical scenario was based on the management of patients with DIC without bleeding or thrombotic events (i.e. ‘non-overt’ or ‘non-symptomatic’ type); the second considered the treatment of patients with mild bleeding; the third the use of platelet transfusion; the fourth, the duration of pharmacological prophylaxis for venous thromboembolism (VTE); and the last the treatment of patients with a VTE and bleeding during an episode of DIC.

According to a methodology adopted in previous guidance documents (5), the working group performed the systematic review of the literature using the electronic databases MEDLINE (from 1966 to November 2015) and EMBASE (from 1980 to November 2015). An extensive search strategy, which included also CENTRAL, was adopted for the SISET guidelines on DIC diagnosis and management and used for this paper with a first update to March 2013 (detailed information on search strategies available at the following web page www.siset.org/images/PDF/LG9.pdf) (3). A further update of the search was run up to November 2015 using the following search terms: ‘disseminated intravascular coagulation’, ‘disseminated intravascular clotting’, ‘randomised controlled trial’, ‘controlled clinical trial’, ‘meta-analysis’, ‘systematic review’, and ‘Cochrane review’. The selection process is summarised in Figure 1. Two reviewers performed study selection independently, with disagreements resolved through discussion and, if necessary with the involvement of a third reviewer. Only randomised controlled trials (RCTs), systematic review and meta-analysis on supportive treatments for DIC were selected for inclusion. Finally, the evidence from identified RCTs was summarised in evidence tables (Table 1). As scant evidence was available for the five hypothetical clinical scenarios, the working group contacted a panel of seven international experts (HW, GK, HTC, BJH, VV, ML, JT) who were asked to discuss their approach and reach a “evidence-based” and a “clinical-based” consensus on the optimal supportive haemostatic and antithrombotic treatment strategies in the proposed clinical scenarios to formulate practical recommendations. The international panel involved in this work included worldwide-recognised thrombosis and haemostasis experts from different specialties (HW, Laboratory Medicine; GK, Intensive Care and Pulmonary Medicine; HTC, Internal and Vascular Medicine; BJH, Haematology; VV, Haematology; ML, Internal and Vascular Medicine; JT, Haematology) with undisputable experience in DIC.

In the first phase of the consensus process, the experts were contacted via e-mail and requested to briefly explain their approach to the five hypothetical clinical scenarios blinded to the answers of the other peers (Table 2). When different therapeutic options were indicated in the various scenarios, each panellist was invited to express his judgement on the whole bunch of therapeutic possibilities proposed by the others in the first phase (Table 3). When a therapeutic approach was endorsed by at least five experts, the working group and the panellists formulated a recommendation. In all other cases a narrative summary is proposed.

No formal method for the grading of recommendations was applied given the low quality of published evidence.

Results

Systematic review of the literature

Overall, 16,054 articles were identified. Studies selection progress is summarised in Figure 1. There were no published RCTs that specifically evaluated the use of cryoprecipitate transfusion or the prophylaxis or treatment of VTE in DIC patients. We identified two systematic reviews on the use of fresh frozen plasma (FFP) and platelet transfusion in patients with DIC that included only two RCTs relevant for the current study, and a recent RCT on FFP transfusion before invasive procedure in critically ill patients (6–10). The first trial randomised 33 neonates to whole blood, FFP and platelet transfusion, or no transfusion. The second RCT included a heterogeneous group of patients only some of whom had DIC. They were randomised to FFP vs pathogen-inactivated FFP and no difference in blood testing was detected. There was no difference in changes of coagulation parameters and/or survival between the intervention and control groups in both RCTs (Table 1) (8, 9). The third RCT included a heterogeneous group of

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Patients</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross, 1982</td>
<td>RCT (3–arms)</td>
<td>33 neonates</td>
<td>Additional exchange transfusion (using whole blood) or FFP and platelet infusions</td>
<td>No transfusion</td>
<td>No differences in survival nor in the rates of improvement of coagulation tests</td>
</tr>
<tr>
<td>Beck, 2000</td>
<td>RCT</td>
<td>40 patients with dilution coagulopathy, liver disease, DIC, polytrauma or connected to extracorporeal circulation</td>
<td>Reduced levels of protein S and alpha2-antiplasmin in solvent/detergent virus-inactivated plasma</td>
<td>FFP</td>
<td>No significant differences in the levels of coagulation factors</td>
</tr>
<tr>
<td>Muller, 2015</td>
<td>RCT</td>
<td>81 critically ill patients with a coagulopathy before invasive procedures (31 patients with DIC)</td>
<td>Prophylactic transfusion of FFP (12 mL/kg) before an invasive procedure</td>
<td>No transfusion</td>
<td>Incidence of bleeding did not differ between groups, with a total of one major and 13 minor bleedings. Reduction of INR to less than 1.5 in 54% of transfused patients</td>
</tr>
</tbody>
</table>

RCT, randomised controlled trial; FFP, fresh frozen plasma; DIC, disseminated intravascular coagulation; INR, international normalised ratio.
critically ill patients with a coagulopathy, including also DIC (10). They were randomised to prophylactic transfusion of FFP (12 ml/kg) before an invasive procedure or no transfusion. Incidence of bleeding did not differ between groups. Overall, the heterogeneity of the study populations, the small size of the studies, and methodological shortcomings limit the applicability of the results to clinical practice.

Table 2: Phase 1 - summary of the questions and expert opinions.

<table>
<thead>
<tr>
<th>1. How would you treat a patient with DIC, without bleeding or thrombosis, with a treatable underlying disorder such as acute promyelocytic leukaemia (a), severe sepsis (b) and during pregnancy (c)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
</tbody>
</table>

Summary: Treatment approach is different depending on the underlying disease.

2. How would you treat a patient with overt DIC, minor bleeding (e.g. bruising, epistaxis), and an untreatable underlying disorder? Refer specifically to patients with an underlying metastatic solid cancer and specify: how long would you continue your treatment (in particular, plasma and/or platelet transfusion)?

| 1 | Transfusions for a limited period of time, and until bleeding is clinically relevant. |
| 2 | Transfusions for a limited period of time. |
| 3 | In case of only minor bleeding, platelet transfusion is administered if the platelet count is < 20 × 10⁹/l. Tranexamic acid is given daily until the minor bleeding has stopped. |
| 4 | I would assess PT, aPTT, D-dimer and Plt count. In those with an overt DIC I would replace missing constituents and give low dose LMWH to switch off the thrombotic drive due to TF; in those with a primary hyperfibrinolytic state I would administer tranexamic acid. |
| 5 | Based on the severity of the disease, short time prognosis, Plt level and fibrinogen levels, supportive therapy with platelets and fibrinogen should be considered. Topical anti-fibrinolytic drug could be useful for minor bleeding. |
| 6 | Transfusions for a limited period of time, then monitoring or tranexamic acid |
| 7 | I will not treat such patients with any blood products for minor bleeding. Unless major bleeding ensues and the platelet count or fibrinogen is low, these patients will be kept under surveillance. I will, however, discuss the merits of prophylactic LMWH. |

Summary: Consensus on stopping transfusion when bleeding has ceased or reduced.
Table 2: Continued.

3. In a patient with overt DIC do you always try to achieve a platelet count >50 × 10^9/l?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>In most of the cases, no effort to reach the 50 × 10^9/l level.</td>
</tr>
<tr>
<td>2</td>
<td>Only in case of major bleeding; transfusion strategy is mainly based on clinical parameters.</td>
</tr>
<tr>
<td>3</td>
<td>50 × 10^9/l is the threshold for major bleeding problems; 20 × 10^9/l in case of minor bleeding.</td>
</tr>
<tr>
<td>4</td>
<td>Usually if the patient is bleeding: we use platelet pools (equivalent to 5 × single donations). There is no maximum limit but usually patients only require 2 or less pools a day.</td>
</tr>
<tr>
<td>5</td>
<td>It depends on the severity and on bleeding site. We have not established the maximum number of platelet units to be transfused per day and we usually try to achieve Plt levels &gt;50 × 10^9/l.</td>
</tr>
<tr>
<td>6</td>
<td>No target is &gt;20 × 10^9/l in non-bleeding ICU patients.</td>
</tr>
<tr>
<td>7</td>
<td>Only if the patient is bleeding. Otherwise, if the platelet count is less than 10–15 × 10^9/l. Maximum units per day will be two.</td>
</tr>
</tbody>
</table>

Summary  |
---|
Substantial agreement on a lower Plt target in non-bleeding patients. No formal agreement on the Plt cut-off level and on clinical parameter to be used.

4. What should be the duration of VTE prophylaxis in patients with overt DIC? In case you start pharmacological VTE prophylaxis, when do you consider stopping it (when the patient bleeds, when Plt count is low (please indicate a cut-off), when PT or aPTT are prolonged (please indicate a cut-off), or a combination of these conditions)?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bleeding patients and/or when Plt count is less than 30 × 10^9/l and/or PT is prolonged more than 5 seconds and/or aPTT ratio is more than 1.5.</td>
</tr>
<tr>
<td>2</td>
<td>Bleeding patients and/or when Plt count is less than 30 × 10^9/l and/or PT ratio is more than 1.5 and/or aPTT ratio is more than 1.5.</td>
</tr>
<tr>
<td>3</td>
<td>Bleeding patients and/or when Plt count is less than 40 × 10^9/l.</td>
</tr>
<tr>
<td>4</td>
<td>In the condition in which I use pharmacological VTE prophylaxis (DIC is driven by TF and the treatment of the underlying cause is taking a while to work, thrombotic DIC, and chronic low grade DIC), I would support the whole coagulation profile with blood component support, so the bleeding risk remains low.</td>
</tr>
<tr>
<td>5</td>
<td>Moderate/severe bleeding and/or Plt count &lt; 30 × 10^9/l and/or fibrinogen level &lt; 1 g/l.</td>
</tr>
<tr>
<td>6</td>
<td>In all critically ill patients.</td>
</tr>
<tr>
<td>7</td>
<td>I use pharmacological VTE prophylaxis in all patients with DIC who do not have active bleeding or at risk of life-threatening or limb-threatening bleeding, especially if platelet counts are &gt;20 × 10^9/l.</td>
</tr>
</tbody>
</table>

Summary  |
---|
Consensus on stopping pharmacological VTE prophylaxis in bleeding or at high-risk of bleeding patients.

5. How would you treat an acute DVT and/or PE in patients with overt DIC and concomitant bleeding? Do you consider an inferior vena cava (IVC) filter?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>With antithrombin and low-dose LMWH; vena cava filter is definitely an option.</td>
</tr>
<tr>
<td>2</td>
<td>Vena cava filter is definitely the first option.</td>
</tr>
<tr>
<td>3</td>
<td>With therapeutic dose of LMWH, using concomitantly Plt transfusion to maintain a Plt level &gt;50 × 10^9/l and FFP to maintain aPTT ratio &lt;1.5 × normal. Hereby, the fibrinogen level should be &gt;1.5 g/l. In our institution, the insertion of a vena cava filter is a rarity.</td>
</tr>
<tr>
<td>4</td>
<td>Consider a temporary IV filter if this was liable to be an ongoing DIC; in a short term DIC, I would start full dose LMWH once cause of DIC has been treated. Concomitantly, I support the coagulation profile with blood products and platelet transfusion as necessary.</td>
</tr>
<tr>
<td>5</td>
<td>Antithrombotic therapy with LMWH should be started if minor bleeding. Vena cava filter should only be used in case of severe bleeding.</td>
</tr>
<tr>
<td>6</td>
<td>With the insertion of a retrievable inferior vena cava filter.</td>
</tr>
<tr>
<td>7</td>
<td>I treat acute VTE with LMWH. The threshold for platelet count here is 20 × 10^9/l or more. I will also try and identify a cause in these cases and try and remove it (examples – central line or sepsis). An IV filter is only inserted in the case of PE, if there is concomitant DVT below the level of the renal vein or if there is a free floating thrombus in a massive DVT and I cannot anticoagulate the patient due to low platelet count.</td>
</tr>
</tbody>
</table>

Summary  |
---|
Consensus on the use of an inferior vena cava filter. Agreement on transfusion strategies to ameliorate coagulopathy and thrombocytopenia to permit use of LMWH as soon as possible and to reduce bleeding risk.

PT, prothrombin time; aPTT, activated partial thromboplastin time; FFP, fresh frozen plasma; ICU, intensive care unit; DVT, deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; Plt, platelet; LMWH, low-molecular-weight heparin; TF, tissue factor; PPH, post partum haemorrhage.
Clinical scenarios

Practical management questions submitted to the expert panel in the first phase of the consensus process and all the responses are given in Table 2. Questions submitted to the expert panel in the second phase of the consensus process and all the responses are given in Table 3. Final recommendations on different clinical situations are reported in Table 4.

Consensus process was summarised as follow.

1. Treatment of patient with DIC, without bleeding or thrombosis (i.e. non-overt / non-symptomatic type), with a treatable underlying disorder

   – Phase 1

The supportive treatment varied according to the underlying condition and within each condition the individual approach was highly heterogeneous.

The responses on the supportive treatment for DIC secondary to acute promyelocytic leukaemia (APML) were the most disparate and included replacement with platelet transfusion, FFP, cryoprecipitate, or fibrinogen, based on the platelet count or coagulation test results, or the use of tranexamic acid.

In septic patients with DIC, the majority recommended a conservative approach of monitoring and/or the use of low-molecular-weight heparin (LMWH) for VTE thromboprophylaxis, apart from one expert who would give antithrombin concentrate.

In pregnancy, the approach ranged from monitoring of DIC to LMWH thromboprophylaxis, gabexate or FFP.

   – Phase 2

The following treatment options were proposed by at least five panellists: prophylactic platelet transfusion in APML; prophylactic dose of LMWH in severe sepsis and in pregnancy, in particular during the post-partum period. In severe sepsis and in pregnancy, prophylactic platelet transfusion was not suggested unless the platelet level was below 20 × 10⁹/l.
Table 4: Final recommendations.

1. Patient with DIC, without bleeding or thrombosis (i.e. non-overt / non-symptomatic type), with a treatable underlying disorder

**Recommendation** In a patient with overt DIC, without bleeding or thrombosis, and with a treatable underlying disorder, there was consensus that physicians should provide an individualised supportive strategy according to the underlying condition triggering the coagulopathy. In DIC patients with acute promyelocytic leukaemia, we suggest prophylactic platelet transfusion to maintain a platelet level at least above $20 \times 10^9/l$; in severe sepsis, we suggest prophylactic dose of LMWH and prophylactic platelet transfusion to maintain a platelet level at least above $20 \times 10^9/l$; in DIC secondary to pregnancy complications, we suggest prophylactic dose of LMWH, in particular during the post-partum period, and prophylactic platelet transfusion to maintain a platelet level at least above $20 \times 10^9/l$.

2. Patient with overt DIC, minor bleeding, and an untreatable underlying disorder

**Recommendation** Haemostatic transfusion support with blood products should be given for a limited period of time to a patient with DIC, minor bleeding and an underlying untreatable disorder. In particular, we suggest to continue with platelet transfusion till bleeding cease and to maintain a platelet level at least above $20 \times 10^9/l$.

3. Platelet count in patient with overt DIC

**Recommendation** A platelet count $>50 \times 10^9/l$ is suggested in all DIC patients with an active major bleeding. In non-bleeding patients, the trigger for platelet transfusion is between $20$ and $30 \times 10^9/l$.

4. Duration of VTE prophylaxis in patient with overt DIC

**Recommendation** Pharmacological VTE prophylaxis should be stopped in case of bleeding or when platelet count is less than $30 \times 10^9/l$ and/or PT ratio is more than $1.5$ and/or aPTT ratio is more than $1.5$ and/or fibrinogen level $<1$ g/l.

5. Acute DVT and/or PE in patient with overt DIC and concomitant bleeding

**Recommendation** We suggest the use of a retrievable IVC filter in DIC patients with acute VTE and concomitant bleeding. When bleeding has ceased, risks and benefits of starting anticoagulation should be assessed daily through the close monitoring of the patient’s clinical status, laboratory tests and treatment of the underlying condition.

Final recommendation

In a patient with overt DIC, without bleeding or thrombosis, and with a treatable underlying disorder, there was consensus that physicians should provide an individualised supportive strategy according to the underlying condition triggering the coagulopathy. In DIC patients with APML, we suggest prophylactic platelet transfusion to maintain a platelet level at least above $20 \times 10^9/l$; in severe sepsis, we suggest prophylactic dose of LMWH and prophylactic platelet transfusion to maintain a platelet level at least above $20 \times 10^9/l$; in DIC secondary to pregnancy complications, we suggest prophylactic dose of LMWH, in particular during the post-partum period, and prophylactic platelet transfusion to maintain a platelet level at least above $20 \times 10^9/l$.

2. Treatment of patient with overt DIC, minor bleeding (e.g. bruising, epistaxis), and an untreatable underlying disorder

– Phase 1

Six of seven experts would give transfusion with blood products for a limited period of time whereas one of the panellists would not treat minor bleeding with any blood products. The use of topical antifibrinolytic drugs was mentioned to manage local bleeding and tranexamic acid in those with a hyperfibrinolytic state.

– Phase 2

Platelet transfusion was proposed by at least five panellists.

Final recommendation

Haemostatic transfusion support with blood products should be given for a limited period of time to a patient with DIC, minor bleeding and an underlying untreatable disorder. We suggest to continue with platelet transfusion till bleeding ceases and to maintain a platelet level at least above $20 \times 10^9/l$.

3. Target platelet count in patients with overt DIC

There was a substantial agreement among the panellists to target a platelet count $>50 \times 10^9/l$ in case of major bleeding while a lower threshold may be considered for non-bleeding DIC patients.

Final recommendation

A platelet count target $>50 \times 10^9/l$ is suggested in all DIC patients with an active major bleeding. In non-bleeding patients, the trigger for platelet transfusion is between $20$ and $30 \times 10^9/l$.

4. Duration of VTE prophylaxis in patients with overt DIC

There was consensus on stopping pharmacological VTE prophylaxis in bleeding patients or in patients judged at high-risk of bleeding based on the results of blood tests.
Final recommendation

Pharmacological VTE prophylaxis should be stopped in case of bleeding or when platelet count is less than $30 \times 10^9/l$ and/or prothrombin time (PT) ratio is higher than 1.5 and/or activated partial thromboplastin time (aPTT) ratio is higher than 1.5 and/or fibrinogen level is $< 1g/l$.

5. Treatment of acute deep vein thrombosis and/or pulmonary embolism in patients with overt DIC and concomitant bleeding

There was consensus for using an inferior vena cava (IVC) filter among four of the experts while three others would consider IVC filter in qualified circumstances. Three panellists suggested transfusion strategies to ameliorate coagulopathy and thrombocytopenia in order to permit use of heparin as soon as possible and to reduce bleeding risk.

Final recommendation

We suggest the use of a retrievable IVC filter in DIC patients with acute VTE and concomitant bleeding. When bleeding has ceased, risks and benefits of starting anticoagulation should be assessed daily through the close monitoring of the patient's clinical status, laboratory tests and treatment of the underlying condition.

Discussion

On the basis of the scarce available evidence and of the experience-based answers provided by the seven international experts, we have tried to address clinically relevant questions and provide practical recommendations for physicians dealing with DIC patients. Overall, most answers were consistent and provided useful suggestions for the supportive treatment of DIC patients.

All seven experts agreed that the management response to DIC should be dynamic, with constant clinical and laboratory monitoring. While treatment of the underlying condition remains the cornerstone of the management of DIC, supportive strategies with blood products and pharmaceutical agents are available and should be tailored to each DIC patient. Individualised treatment should consider: whether the underlying condition is treatable or not; presence and severity of bleeding; presence and severity of thrombosis; need for invasive procedure and/or surgery; results of blood tests, in particular platelet count, PT, aPTT, and fibrinogen levels. In view of the possibly changing risk-to-benefit ratio of using supportive treatment in these patients, it would therefore be advisable to reassess treatment choices at least twice daily.

Expert opinion varied regarding the management of DIC patients with a treatable underlying disorder, without clinical bleeding or thrombotic events, i.e. non-overt or non-symptomatic DIC type. They agreed that treatment approach should vary depending on the underlying disease, i.e. APML, sepsis, or pregnancy complication. Suggested treatments were antithrombin, gabexate (a protease inhibitor), tranexamic acid (an antifibrinolytic agent), therapeutic LMWH, and transfusions. Nowadays, no solid evidence supports any of the proposed options. Antithrombin concentrate was shown to improve coagulation parameters without increasing survival (3, 11–13). Similar findings are also available for gabexate (3). The expert panel agreed that VTE prophylaxis should be recommended in women at puerperium or in patients with severe sepsis, and prophylactic platelet transfusion should be administered to maintain a platelet level at least above $20 \times 10^9/l$.

There was full agreement among the experts on the indication to transfuse FFP and platelets as first options in patients with clinically relevant bleeding. Transfusion strategy (i.e. units per day, length) should be mainly based on the severity of bleeding, fluid overload risk, prognosis of the underlying condition, and blood test results. There was consensus on maintaining a platelet count $> 50 \times 10^9/l$ in patients with an active major bleeding. In those patients with minor or without bleeding, there was agreement that the trigger platelet count for platelet transfusion should be set at a lower level, perhaps a platelet count target $> 20 \times 10^9/l$. In DIC patients with minor bleeding (e.g. bruising, epistaxis) and an untreatable underlying disorder (e.g. underlying metastatic solid cancer), there was consensus on stopping FFP and/or platelet transfusion when bleeding has ceased or, at least, decreased. Moreover, there was substantial agreement in stopping pharmacological VTE prophylaxis in case of bleeding or high-risk of bleeding, such as patients with a platelet count $< 30 \times 10^9/l$, and/or PT ratio $> 1.5$ fold, and/or aPTT ratio $> 1.5$ fold, and/or fibrinogen level $< 1 g/l$. In patients with symptomatic acute VTE and concomitant bleeding, most experts agreed on the indication to insert a retrievable IVC filter starting anticoagulation as soon as possible when bleeding had ceased.

There are some limitations of the current work to acknowledge. There was heterogeneity among the responses of the experts. This variation may reflect the different backgrounds of the experts, the availability and licensing of certain drugs such as fibrinogen concentrates and gabexate in different countries, and the current lack of understanding and clinical trials in those areas. As scarce evidence was available, strength of our recommendations is weak per definition.

Conclusion

In conclusion, individualised treatments are advisable for patients with DIC. Both physicians involved in the management of the conditions underlying DIC (e.g. gynaecologist, surgeon) and experts in the management of DIC should reassess, at least daily, the patient's clinical status and bleeding/thrombotic risk profile, monitor the blood count and, coagulation tests, and modify the treatment accordingly.

Acknowledgements
Thanks to Erik Beckers and Yvonne Henskens (Maastricht University Medical Center, Maastricht) for their valuable suggestions. Thanks to Sydney Preston for help in editing.
Conflicts of interest
None declared.

References