

Guidelines for the diagnosis and management of disseminated intravascular coagulation

Summary

The diagnosis of disseminated intravascular coagulation (DIC) should encompass both clinical and laboratory information. The International Society for Thrombosis and Haemostasis (ISTH) DIC scoring system provides objective measurement of DIC. Where DIC is present the scoring system correlates with key clinical observations and outcomes. It is important to repeat the tests to monitor the dynamically changing scenario based on laboratory results and clinical observations. The cornerstone of the treatment of DIC is treatment of the underlying condition. Transfusion of platelets or plasma (components) in patients with DIC should not primarily be based on laboratory results and should in general be reserved for patients who present with bleeding. In patients with DIC and bleeding or at high risk of bleeding (e.g. postoperative patients or patients due to undergo an invasive procedure) and a platelet count of $<50 \times 10^9/l$ transfusion of platelets should be considered. In non-bleeding patients with DIC, prophylactic platelet transfusion is not given unless it is perceived that there is a high risk of bleeding. In bleeding patients with DIC and prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), administration of fresh frozen plasma (FFP) may be useful. It should not be instituted based on laboratory tests alone but should be considered in those with active bleeding and in those requiring an invasive procedure. There is no evidence that infusion of plasma stimulates the ongoing activation of coagulation. If transfusion of FFP is not possible in patients with bleeding because of fluid overload, consider using factor concentrates such as prothrombin complex concentrate, recognising that these will only partially correct the defect because they contain only selected factors, whereas in DIC there is a global deficiency of coagulation factors. Severe hypofibrinogenaemia (<1 g/l) that persists despite FFP replacement may be treated with fibrinogen concentrate or cryoprecipitate. In cases of DIC where thrombosis predominates, such as arterial or venous thromboembolism, severe purpura fulminans associated with acral ischemia or vascular skin infarction, therapeutic doses of heparin should be considered. In these patients where there is perceived to be a co-existing high risk of bleeding there may be

benefits in using continuous infusion unfractionated heparin (UFH) due to its short half-life and reversibility. Weight adjusted doses (e.g. $10 \mu\text{g/kg/h}$) may be used without the intention of prolonging the APTT ratio to 1.5–2.5 times the control. Monitoring the APTT in these cases may be complicated and clinical observation for signs of bleeding is important. In critically ill, non-bleeding patients with DIC, prophylaxis for venous thromboembolism with prophylactic doses of heparin or low molecular weight heparin is recommended. Consider treating patients with severe sepsis and DIC with recombinant human activated protein C (continuous infusion, $24 \mu\text{g/kg/h}$ for 4 d). Patients at high risk of bleeding should not be given recombinant human activated protein C. Current manufacturers guidance advises against using this product in patients with platelet counts of $<30 \times 10^9/l$. In the event of invasive procedures, administration of recombinant human activated protein C should be discontinued shortly before the intervention (elimination half-life ≈ 20 min) and may be resumed a few hours later, dependent on the clinical situation. In the absence of further prospective evidence from randomised controlled trials confirming a beneficial effect of antithrombin concentrate on clinically relevant endpoints in patients with DIC and not receiving heparin, administration of antithrombin cannot be recommended. In general, patients with DIC should not be treated with antifibrinolytic agents. Patients with DIC that is characterised by a primary hyperfibrinolytic state and who present with severe bleeding could be treated with lysine analogues, such as tranexamic acid (e.g. 1 g every 8 h).

Keywords: blood coagulation, coagulation factors, disseminated intravascular coagulation, anticoagulation, thrombosis.

This guideline was written in response to requests for guidance on diagnosis and management of disseminated intravascular coagulation (DIC) from practising UK haematologists. The writing group was made up of a member of the British Committee for Standards in Haematology (BCSH) taskforce in haemostasis and thrombosis and two recognised experts in the field from the UK and Europe. Medline was systematically searched for English language publications up to June 2007 using the key terms: disseminated intravascular coagulation, coagulopathy, consumptive coagulopathy, natural anticoagulants, platelets, blood products, transfusion. Relevant references generated from initial papers and published guidelines/reviews were also examined. Meeting abstracts were not

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included. A draft guideline was produced by the writing group, revised and agreed by consensus. Further comment was made by the members of the haemostasis and thrombosis task force of the BCSH. The guideline was reviewed by a sounding board of approximately 40 UK haematologists, the BCSH and the Committee of the British Society for Haematology and comments were incorporated where appropriate. Criteria used to quote levels and grades of evidence are as outlined in Appendix 7 of the Procedure for Guidelines commissioned by the BCSH (<http://www.bcsghguidelines.com/process1.asp#appendix7>) (see Appendix 1).

The guidance may not be appropriate for all patients and individual patient circumstances may dictate an alternative approach.

Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) is a clinicopathological syndrome which complicates a range of illnesses. It is characterised by systemic activation of pathways leading to and regulating coagulation, which can result in the generation of fibrin clots that may cause organ failure with concomitant consumption of platelets and coagulation factors that may result in clinical bleeding (Fig 1). The spectrum of DIC and its management are the subject of recent reviews (Levi, 2004, 2005). The purpose of this guideline is to briefly outline the pathogenesis and associations of DIC and to review and grade the evidence that is available with regard to the diagnosis and treatment of the syndrome.

Associations and pathogenesis

DIC never occurs in isolation and recognition that a patient has a clinical disorder which may result in the development of DIC is the key to appropriate investigation and management. DIC may arise in patients with a wide spectrum of disorders including sepsis, malignancy, trauma, liver disease and vascular anomalies. It is also seen when pregnancy is complicated by placental abruption or amniotic fluid embolism and may

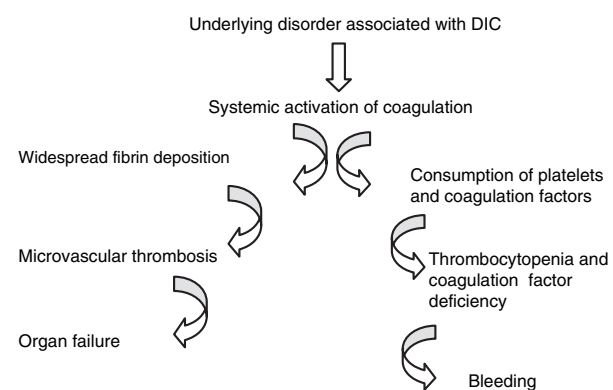


Fig 1. Processes in DIC.

Table I. Conditions associated with DIC.

Sepsis and severe infection
Trauma
Organ destruction e.g pancreatitis
Malignancy
Solid tumours
Leukaemia
Obstetric
Amniotic fluid embolism
Placental abruption
Pre-eclampsia
Vascular abnormalities
Large haemangiomas
Vascular aneurysm
Severe liver failure
Toxic and immunological insults
Snake bites
Recreational drugs
ABO transfusion incompatibility
Transplant rejection

complicate poisoning, envenomation and major transfusion reactions (Table I). All of these conditions share the ability to induce systemic activation of coagulation either by activating cytokines as part of a systemic inflammatory response or by causing the release of, or exposure to, procoagulant substances.

The pathogenesis of DIC is complex and centres on the enhanced generation of thrombin *in vivo*. The contributing components include increased tissue factor expression, sub-optimal function of natural anticoagulant systems, dysregulation of fibrinolysis and increased anionic phospholipid availability.

Diagnosis of DIC

There is no single laboratory test that can establish or rule out the diagnosis of DIC. Thus, it is of utmost importance to assess the whole clinical picture, taking into account the clinical condition of the patient, the diagnosis, and all available laboratory results. As such, a diagnosis of DIC should be made based on an appropriate clinical suspicion supported by relevant laboratory tests. Also, DIC is an extremely dynamic situation and the tests are a snapshot of this dynamic state. In addition, the underlying clinical condition can have an influence on the laboratory tests. However, a combination of tests when repeated in a patient with a clinical condition known to be associated with DIC can be used to diagnose the disorder with reasonable certainty in most cases (Bick, 1996; Levi *et al*, 1999; Toh & Dennis, 2003). This concept has been taken into consideration by the International Society of Thrombosis and Haemostasis (ISTH) (Taylor *et al*, 2001).

Laboratory studies used in the diagnosis and evaluation of patients with DIC need to reflect the changes in haemostatic function and keep pace with the critical nature of the condition. Screening assays for haemostatic function, such as

the prothrombin time (PT), activated partial thromboplastin time (aPTT) or platelet count, provide important evidence of the degree of coagulation factor consumption and activation. In addition, the extent of fibrin formation can be indirectly gauged through measurements of its lysis, through assays such as those that measure fibrin D-dimers. Also reviewed here are other methods, available in some specialist laboratories, which can measure specific parameters. The extent to which these add to already available information from the above tests will be discussed. An analysis of five reports of patient groups with DIC, with a total of over 900 patients described suggests that the laboratory abnormalities reported, in decreasing order of frequency, are thrombocytopenia, elevated fibrin degradation products, prolonged PT, prolonged aPTT, and a low fibrinogen (Al-Mondhiry, 1975; Siegal *et al*, 1978; Mant & King, 1979; Spero *et al*, 1980; Wilde *et al*, 1989).

Platelet count

A reduction in the platelet count or a clear downward trend at subsequent measurements is a sensitive (though not specific) sign of DIC. Thrombocytopenia is a feature in up to 98% of DIC cases with the platelet count $<50 \times 10^9/l$ in approximately 50% (Spero *et al*, 1980). A low platelet count correlates strongly with markers of thrombin generation, because thrombin-induced platelet aggregation is mainly responsible for platelet consumption (Neame *et al*, 1980; Akca *et al*, 2002). A single determination of the platelet count is not very helpful as the original platelet count may remain in the 'normal' range of $150\text{--}400 \times 10^9/l$. At the same time, a continuous drop *even within a normal range* may indicate the active generation of thrombin. In the same manner, a stable platelet count suggests that thrombin formation has stopped. It is also important to bear in mind that a low or decreasing platelet count is not very *specific* for DIC as many of the underlying conditions that are associated with DIC, such as acute leukaemia or sepsis, also may cause a low platelet count in the absence of DIC (Akca *et al*, 2002).

Fibrin degradation products and D-dimers

In addition to enhanced thrombin formation, fibrinolytic activity, which may be measured as fibrin degradation products (FDP) by specific enzyme-linked immunosorbent assay (ELISA) or by latex agglutination assays, is also increased in DIC. However, assays of FDPs do not discriminate between degradation products of cross-linked fibrin and fibrinogen degradation, which limits their specificity (Prisco *et al*, 1989; Boisclair *et al*, 1990). New assays aimed at the detection of neo-antigens on degraded cross linked fibrin have been developed; one such test detects an epitope related to plasmin-degraded cross-linked fibrin, resulting in fragment D-dimer (Shorr *et al*, 1999). However, it is important to remember that many conditions other than DIC, such as trauma, recent surgery or venous thromboembolism, are

associated with elevated FDPs including D-dimer. Also, because FDPs are metabolised by the liver and secreted by the kidneys, liver and kidney impairment can influence levels (Nakamura *et al*, 1992). Thus, FDPs including D-dimers should not be considered as stand-alone tests in DIC but as a useful indicator of the DIC process when there is an elevation in D-dimer levels with concomitant falls in the platelet count and changes in coagulation times. Tests for FDP or D-dimers may also be helpful to differentiate DIC from other conditions that are associated with a low platelet count or prolonged clotting times, such as chronic liver disease (Carr *et al*, 1989; Bick & Baker, 1992).

Studies have been performed to try to establish the cut-off levels for D-dimer measurements that define a 'moderate' or 'strong' increase because this is required in order to use the scoring system (see Section Scoring system). One approach has been to determine the interquartile range (Dempfle *et al*, 2004a), while other investigators classified the rise as moderate or strong based on a cut-off point in a Dutch intensive care cohort (Bakhtiari *et al*, 2004). As issues remain regarding the accuracy of high D-dimer estimations with current assay systems and work is ongoing for standardising reagents for this purpose, precise definitions of D-dimer cut-off levels are not meaningful at the current time. As a result, D-dimer assay results need to be interpreted based on the clinician's experience and consideration of the clinical circumstances and other available laboratory investigations.

Soluble fibrin monomer (SF) measurements offer theoretical advantages in DIC in reflecting thrombin action on fibrinogen. As SF is only generated intravascularly, it should therefore not be influenced by extravascular fibrin formation as caused by local inflammation or trauma. Most clinical studies have shown a sensitivity of 90–100% for the diagnosis of DIC but a very low specificity (Horan & Francis, 2001). However, its incorporation into the ISTH DIC scoring system instead of D-dimer as the fibrin-related marker can improve the specificity of diagnosing DIC (Dempfle *et al*, 2004a). Nonetheless, a major problem remains that of reliable quantitation, with wide discordance reported amongst various assay systems (McCarron *et al*, 1999; Dempfle *et al*, 2001).

PT and aPTT

The PT or aPTT is prolonged in about 50–60% of cases of DIC at some point during the course of illness (Bick, 1996). This is mainly attributed to the consumption of coagulation factors but impaired synthesis, due to abnormal liver function, vitamin K deficiency or loss of the coagulation proteins, due to massive bleeding, may also play a role (Bick, 1996; Asakura *et al*, 2001). In nearly half of patients who have DIC, the PT and aPTT are normal or even shortened. The reasons for normal or shorter times are the presence of circulating activated clotting factors, such as thrombin or Xa, which can accelerate the formation of thrombin (Asakura *et al*, 2001). Thus, normal clotting times for either the PT or

aPTT do not exclude activation of the haemostatic system (Olson *et al*, 1989) and repeat monitoring is required. It should also be emphasised that the PT, not the International Normalized Ratio (INR), that is to be monitored; the latter being validated only for oral anticoagulant monitoring. The thrombin time (TT) may be performed in ill patients with suspected DIC. It does not have a place in the agreed scoring system but may be used along with a reptilase time to exclude heparin contamination of samples in patients with prolonged APTT.

Fibrinogen

Measurement of fibrinogen has been widely advocated as a useful tool for the diagnosis of DIC but in fact is not very helpful in most cases (Levi & Ten, 1999). Fibrinogen acts as an acute-phase reactant and despite ongoing consumption, plasma levels can remain well within the normal range for a long period of time. In a consecutive series of patients, the sensitivity of a low fibrinogen level for the diagnosis of DIC was only 28% and hypofibrinogenemia was detected in *very severe* cases of DIC only (Levi *et al*, 1999). Fibrinogen levels can be normal in as many as 57% of patients (Spero *et al*, 1980). Sequential measurements of fibrinogen might be more useful and provide diagnostic clues. The BCSH guidelines on fibrinogen assays suggest the use of the Clauss method in clinical situations where DIC is suspected although it should be borne in mind that the measured fibrinogen level may be influenced by interference on the assay from high FDP levels (Mackie *et al*, 2003).

Blood film

Fragmented red blood cells, although reported in patients with DIC, rarely constitute >10% of the red cells. However, in some cases of chronic DIC with elevated D-dimers but normal coagulation screening assay results, the presence of fragmented red cells can provide confirmatory evidence (Spero *et al*, 1980). The finding of fragments is neither sensitive nor specific to DIC. When they are seen in increased numbers, other potential diagnoses, such as thrombotic thrombocytopenic purpura (TTP) and other causes of thrombotic microangiopathy, should be considered.

Global haemostatic profiles

New point-of-care testing methods have been described based on thromboelastography (TEG) techniques that have linked diagnostic changes to haemostatic dysfunction (Zuckerman *et al*, 1981). Though these tests have been reported to be abnormal in septic patients, their diagnostic sensitivity/specificity for DIC is unclear (Collins *et al*, 2006). The prevailing evidence for TEG use relates more to predicting blood loss in cardiovascular surgery (Mongan & Hosking, 1992).

More recently, an atypical light transmittance profile on the aPTT has been associated with DIC (Downey *et al*, 1997; Toh

et al, 2000). Referred to as the biphasic waveform, this abnormality occurs independently of prolongation in the clotting times and, through prospective studies, has been shown to be a simple, rapid and robust indicator of DIC (Downey *et al*, 1998; Bakhtiari *et al*, 2004; Dempfle *et al*, 2004b; Matsumoto *et al*, 2006). In a 1187-patient study on all consecutive admissions into the intensive therapy unit, there was an increasing positive predictive value for DIC with increasing waveform abnormality and the latter often precede any abnormality in the more conventional parameters used for diagnosing DIC (Downey *et al*, 1998). However, its performance is limited to specific photo-optical analysers that display clot formation over time.

Other markers of haemostasis

The natural anticoagulants antithrombin and protein C are often reduced in DIC and these have been shown to have prognostic significance (Conway & Rosenberg, 1988; Fourrier *et al*, 1992; Mesters *et al*, 1996; Faust *et al*, 2001). The availability of chromogenic assays rather than a reliance on ELISA techniques has meant that results can be made available more rapidly. Nonetheless, their general availability is still limited and single determinations are neither sensitive nor sufficiently specific for DIC.

In very rare cases purpura fulminans develops secondary to profound acquired deficiency of protein S. This is most commonly described following varicella infection. Although management strategies for this specific indication are not clear the association is notable.

Scoring system

The ISTH Sub-Committee of the Scientific and Standardization Committee (SSC) on DIC has recommended the use of a scoring system for overt DIC (Taylor *et al*, 2001; Toh & Hoots, 2007). Based on the Japanese Ministry of Health and Welfare score, which has demonstrated a close correlation between an increasing score and increasing mortality (Wada *et al*, 1995), the ISTH criteria proposes a 5-step diagnostic algorithm to calculate a DIC score, utilising simple laboratory tests that are available in almost all hospital laboratories (Table II). The presence of an underlying disorder known to be associated with DIC is a prerequisite for the use of the algorithm. For overt DIC, a cumulative score of five or more from prolonged PT, reduced platelets and fibrinogen, and elevated fibrin-related markers (e.g. D-dimer or FDP) was proposed. The scoring system pertains to conditions that are associated with both acute onset DIC, e.g. sepsis, and chronic DIC, e.g. vascular malformations and aneurysms.

The ISTH overt DIC score has been shown to be sensitive to DIC of infective and non-infective aetiologies (Gando *et al*, 2005; Matsumoto *et al*, 2006). Compared to blinded 'expert' assessments for DIC, Bakhtiari *et al* (2004) found the sensitivity of the ISTH overt DIC score to be 91% with a specificity of

Table II. ISTH Diagnostic Scoring System for DIC.

Scoring system for overt DIC

Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?

If yes: proceed

If no: do not use this algorithm

Order global coagulation tests (PT, platelet count, fibrinogen, fibrin related marker)

Score the test results

- Platelet count ($>100 \times 10^9/l = 0$, $<100 \times 10^9/l = 1$, $<50 \times 10^9/l = 2$)
- Elevated fibrin marker (e.g. D-dimer, fibrin degradation products) (no increase = 0, moderate increase = 2, strong increase = 3)
- Prolonged PT ($<3 s = 0$, >3 but $<6 s = 1$, $>6 s = 2$)
- Fibrinogen level ($>1 g/l = 0$, $<1 g/l = 1$)

Calculate score:

≥ 5 compatible with overt DIC: repeat score daily

< 5 suggestive for non-overt DIC: repeat next 1–2 d

97%. A strong correlation between an increasing DIC score and mortality has been demonstrated by several studies. For each DIC point, increases in the odds of mortality of 1.25–1.29 have been demonstrated (Bakhtiari *et al*, 2004). Several other studies have similarly confirmed that the presence of overt DIC by the ISTH algorithm is independently predictive of mortality (Gando *et al*, 2005; Sivula *et al*, 2005; Cauchie *et al*, 2006). These studies show that patients with sepsis and DIC, according to the scoring system, have a significantly higher mortality of 43%, as compared with 27% in patients without DIC. Indeed, scoring for DIC has added prognostic value in better predicting mortality than the use of the acute physiology and chronic health evaluation (APACHE) II scores alone (Angstwurm *et al*, 2006). For each 'DIC point' in the system, the odds ratio (OR) for mortality was 1.29, whereas in comparison, for each APACHE point the OR for mortality was 1.07.

Recommendations

The diagnosis of DIC should encompass both clinical and laboratory information (Grade C, Level IV).

The ISTH DIC scoring system provides objective measurement of DIC. Where DIC is present, the scoring system correlates with key clinical observations and outcomes (Grade C, Level IV).

It is important to repeat the tests to monitor the dynamically changing scenario based on laboratory results and clinical observations (Grade B, Level III).

Treatment of DIC*General*

Key to the treatment of DIC is the specific and vigorous treatment of the underlying disorder. In many cases the DIC

will spontaneously resolve when the underlying disorder is properly managed. Examples are the administration of antibiotics and/or surgical drainage in patients with DIC due to severe infection and sepsis. However, in some cases additional supportive treatment, specifically aimed at the coagulation abnormalities, may be required.

Recommendation

The cornerstone of the treatment of DIC is treatment of the underlying condition (Grade C, Level IV).

Plasma and platelets

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 is indicated in patients with active bleeding, in those requiring an invasive procedure and those who are otherwise at risk for bleeding complications. The threshold for transfusing platelets depends on the clinical state of the patient. In general, platelet transfusion is administered to patients who bleed and who have a platelet count of $<50 \times 10^9/l$. In non-bleeding patients, a much lower threshold of $10\text{--}20 \times 10^9/l$ is adopted based on randomised controlled trials in patients with thrombocytopenia following chemotherapy, although in patients perceived to be at high risk of bleeding based on other clinical and laboratory features, platelets may be administered at higher levels than this (Levi & Opal, 2006). The suggested initial dose of platelets is one adult UK dose ($>240 \times 10^9$).

It may be necessary to use large volumes of plasma to correct the coagulation defect. Initial doses of 15 ml/kg of fresh frozen plasma (FFP) are suggested although there is evidence that a dose of 30 ml/kg produces more complete correction of coagulation factor levels. Coagulation factor concentrates, such as prothrombin complex concentrate, come in small volumes, but lack essential factors, such as factor V. Moreover, in older literature caution is advocated with the use of prothrombin complex concentrates in DIC, since it may worsen the coagulopathy due to traces of activated factors in the concentrate. It is, however, not clear whether this is still relevant for the concentrates that are currently in use. Specific deficiencies in fibrinogen can be corrected by administration of purified fibrinogen concentrates or cryoprecipitate. A dose of 3 g would be expected to raise plasma fibrinogen by around 1 g/l. This can be given as approximately four units of FFP, two cryoprecipitate pools (10 donor units) or as 3 g of a fibrinogen concentrate. The response to component therapy should be monitored both clinically and by repeating platelet counts and coagulation tests following administration.

There are some reports of the successful use of recombinant factor VIIa in patients with DIC and life-threatening bleeding. However, the efficacy and safety of this treatment in DIC is unknown and it should be used with caution.

Recommendations

Transfusion of platelets or plasma (components) in patients with DIC should not primarily be based on laboratory results and should in general be reserved for patients that present with bleeding (Grade C, Level IV).

In patients with DIC and bleeding or at high risk of bleeding (e.g. postoperative patients or patients due to undergo an invasive procedure) and a platelet count of $<50 \times 10^9/l$, transfusion of platelets should be considered (Grade C, Level IV).

In non-bleeding patients with DIC, prophylactic platelet transfusion is not given unless it is perceived that there is a high risk of bleeding (Grade C, Level IV).

In bleeding patients with DIC and prolonged PT and aPTT administration of FFP may be useful. It should not however be instituted based on laboratory tests alone but should be considered in those with active bleeding and in those requiring an invasive procedure. There is no evidence that infusion of plasma stimulates the ongoing activation of coagulation (Grade C, Level IV).

If transfusion of FFP is not possible in patients with bleeding because of fluid overload, consider using factor concentrates such as prothrombin complex concentrate, recognising that these will only partially correct the defect because they contain only selected factors, whereas in DIC there is a global deficiency of coagulation factors (Grade C, Level IV).

Severe hypofibrinogenaemia (<1 g/l) that persists despite FFP replacement may be treated with fibrinogen concentrate or cryoprecipitate (Grade C, Level IV).

Anticoagulants

Based on the notion that DIC is characterised by extensive activation of coagulation, anticoagulant treatment may be a rationale approach. Experimental studies have shown that heparin can at least partly inhibit the activation of coagulation in DIC (Pernerstorfer *et al*, 1999). There are no clinical randomised controlled trials demonstrating that the use of heparin in patients with DIC results in an improvement in clinically relevant outcomes. Small uncontrolled studies have shown that (low molecular weight) heparin is capable of improving laboratory abnormalities associated with DIC (Corrigan & Jordan, 1970; Audibert *et al*, 1987; Feinstein, 1988). Patients with DIC are at high risk of venous thromboembolic (VTE) events due to one or more risk factors, including advanced age, recent surgery, immobilisation, in-dwelling vascular catheters and previous VTE history (Cook *et al*, 2005). Indeed, VTE prophylaxis using unfractionated heparin (UFH), low molecular weight heparin (LMWH), and/or mechanical methods has become standard care in patients with DIC (Samama *et al*, 1999; Patel *et al*, 2005). A recent large trial in patients with severe sepsis showed a non significant benefit of low dose heparin on 28-day mortality

and underscored the importance of not stopping heparin in patients with DIC and abnormal coagulation parameters (Levi *et al*, 2007).

Theoretically, the most logical anticoagulant agent to use in DIC is directed against tissue factor activity. Phase II trials of recombinant tissue factor pathway inhibitor (TFPI) in patients with sepsis showed promising results but a phase III trial did not show an overall survival benefit in patients who were treated with TFPI (Abraham *et al*, 2001, 2003).

Recommendations

In cases of DIC where thrombosis predominates, such as arterial or venous thromboembolism, severe purpura fulminans associated with acral ischemia or vascular skin infarction therapeutic doses of heparin should be considered.

In these patients where there is perceived to be a co-existing high risk of bleeding there may be benefits in using continuous infusion UFH due to its short half-life and reversibility. Weight adjusted doses (e.g. $10 \mu/kg/h$) may be used without the intention of prolonging the aPTT ratio to 1.5–2.5 times the control. Monitoring the aPTT in these cases may be complicated and clinical observation for signs of bleeding is important (Grade C, Level IV).

In critically ill, non-bleeding patients with DIC, prophylaxis for venous thromboembolism with prophylactic doses of heparin or low molecular weight heparin is recommended (Grade A, Level IB).

Anticoagulant factor concentrates

The use of agents that are capable of restoring the dysfunctional anticoagulant pathways in patients with DIC has been extensively studied. Antithrombin concentrate has been available since the 1980s and most trials with this compound show some beneficial effect in terms of improvement of laboratory parameters, however, none of the trials demonstrated a significant reduction in mortality. A large-scale multicentre randomised controlled trial to directly assess the effect of antithrombin concentrate on mortality in septic patients also showed no significant reduction in those treated with antithrombin concentrate (Warren *et al*, 2001). Interestingly, the subgroup of patients that had DIC and that did not receive heparin showed a remarkable survival benefit, but this finding requires prospective validation (Kienast *et al*, 2006).

Based on the rationale that depression of the protein C pathway may significantly contribute to the pathophysiology of DIC, it has been suggested that supplementation of activated protein C might potentially be of benefit. Indeed, activated protein C was shown to be effective in reducing mortality and organ failure in experimental sepsis models (Taylor *et al*, 1987). The clinical efficacy of activated protein C in severe sepsis was demonstrated in a large randomised controlled trial (Bernard *et al*, 2001). Mortality was 24.7% in the activated protein C group as compared with 30.8% in the

placebo group (relative risk reduction 19.4%, 95% confidence interval, 6.6–30.5). A *post hoc* analysis showed that patients with DIC had the highest benefit of activated protein C treatment (Dhainaut *et al*, 2004). Later studies confirmed the ability of activated protein C to normalise coagulation activation during severe sepsis (De Pont *et al*, 2005). Administration of recombinant human activated protein C increases the risk of major bleeding from approximately 2.0% to 3.5% and the risk of intracerebral haemorrhage from 0.1% to 0.3%, respectively in septic patients (Bernard *et al*, 2003, 2004; Abraham *et al*, 2005). In all studies with recombinant human activated protein C, patients with severe thrombocytopenia ($<30 \times 10^9$ or 80×10^9) were excluded. In view of the relatively short elimination half-life, the drug can be rapidly discontinued shortly before invasive procedures. Activated protein C therapy causes prolongation of coagulation times especially the aPTT and this should be borne in mind during treatment. Of note, activated protein C appears to be relatively more effective in higher disease severity groups and a prospective trial in septic patients with relatively low disease severity did not show any benefit of activated protein C (Abraham *et al*, 2005). There are some case series of patients with severe meningococcal sepsis and DIC that showed a beneficial effect of plasma-derived protein C concentrate. However, in the absence of properly controlled randomised studies, the efficacy of this treatment remains unknown. There are no comparative studies between recombinant human activated protein C and plasma-derived protein C concentrate.

Recommendations

Consider treating patients with severe sepsis and DIC with recombinant human activated protein C (continuous infusion, 24 µg/kg/h for 4 d) (*Grade A, Level Ib*).

Patients at high risk of bleeding should not be given recombinant human activated protein C. Current manufacturers guidance advises against using this product in patients with platelet counts of $<30 \times 10^9/l$. In the event of invasive procedures, administration of recombinant human activated protein C should be discontinued shortly before the intervention (elimination half-life ≈ 20 min) and may be resumed a few hours later, dependent on the clinical situation (*Grade C, Level IV*).

In the absence of further prospective evidence from randomised controlled trials confirming a beneficial effect of antithrombin concentrate on clinically relevant endpoints in patients with DIC and not receiving heparin, administration of antithrombin cannot be recommended (*Grade A, Level Ib*).

Antifibrinolytic treatment

Antifibrinolytic agents are effective in bleeding patients but the use of these agents in patients with bleeding due to DIC is

generally not recommended (Mannucci & Levi, 2007). In fact, since fibrin deposition is an important feature of DIC, inhibition of the fibrinolytic system seems inappropriate. An exception may be made in rare cases where primary or secondary hyperfibrinolysis dominates the clinical picture. This is the case in the coagulopathy associated with acute promyelocytic leukemia (AML-M3) and in some cases of DIC secondary to malignancies (e.g. prostate carcinoma). Uncontrolled observations and one randomised controlled clinical trial have shown a beneficial effect of antifibrinolytic agents in this situation (Avvisati *et al*, 1989). More recent studies have failed to show a reduction in bleeding for patients with acute promyelocytic leukaemia treated with tranexamic acid (de la Serna *et al*, 2008). The standard of care for patients with acute promyelocytic leukaemia is with the differentiating agent all *trans*-retinoic acid (ATRA), which may itself increase thrombosis risk. Cases of severe thrombosis complicating the combined use of ATRA and tranexamic acid have been documented (Brown *et al*, 2000). Because of this there is very rarely a role for tranexamic acid in management of acute promyelocytic leukaemia.

Recommendations

In general, patients with DIC should not be treated with antifibrinolytic agents (*Grade C, Level IV*).

Patients with DIC that is characterized by a primary hyperfibrinolytic state and who present with severe bleeding could be treated with lysine analogues, such as tranexamic acid (e.g. 1 g every 8 h) (*Grade C, Level IV*).

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Disclaimer

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M. Levi has been principal investigator in clinical trials of recombinant human activated protein C, chairman of the Data and Safety Monitoring Board of the current TFPI trial (CAPTIVATE, Novartis), and a member of the steering

committee of ongoing trials with recombinant thrombomodulin (ART-123, Artisan, US).

C. H. Toh has three issued patents related to the aPTT wave form.

J. Thachil has no conflict of interest to declare.

H. G. Watson has no conflict of interest to declare.

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Appendix 1

Classification of evidence levels

- Ia Evidence obtained from meta-analysis of randomised controlled trials.
- Ib Evidence obtained from at least one randomised controlled trial.
- IIa Evidence obtained from at least one well-designed controlled study without randomization.
- IIb Evidence obtained from at least one other type of well-designed quasi-experimental study*.
- III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
- IV Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Classification of grades of recommendations

- A Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing specific recommendation. (Evidence levels Ia, Ib).
- B Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation. (Evidence levels IIa, IIb, III).
- C Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV).