Disseminated Intravascular Coagulation

A Practical Approach

Jecko Thachil, M.D., M.R.C.P., F.R.C.Path.

The Clinical Scenario

A 46-yr-old woman is admitted to the critical care unit with worsening respiratory function requiring mechanical ventilation. She presented with a week's history of shortness of breath and productive cough, confirmed microbiologically to be due to *Streptococcus pneumoniae*. Complete blood count at presentation showed mean hemoglobin concentration of 13.4 g/dl, which has dropped to 11 g/dl at critical care admission, while the platelet count dropped from 470 × 10⁹/l to 200 × 10⁹/l. Prothrombin and activated partial thromboplastin times (PT/APTT) are normal at 12.5 and 29.5 s, respectively, and within normal value range by our institutional criteria, while the fibrinogen value is 1.9 g/l. Her renal function has started deteriorating despite not being on nephrotoxic drugs. Is this patient likely to have or to develop disseminated intravascular coagulation (DIC)?

Normal hemostasis is a well-orchestrated process where adequate amounts of thrombin are generated at the site of vascular injury. Thrombin coordinates a balance between the competing procoagulant/anticoagulant and the fibrinolytic/antifibrinolytic systems, whereby the circulatory flow is maintained with no perturbation from growing thrombus.¹ These physiologic processes are altered to various degrees in patients who develop DIC, where an excess of thrombin is generated due to the inciting factors (e.g., endotoxin in sepsis) (fig. 1). This leads to the development of *intravascular coagulation*, which can *disseminate* to the different organs and cause clinical effects. The International Society of Thrombosis and Haemostasis (ISTH) DIC subcommittee defines DIC as “an acquired syndrome characterized by intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which, if sufficiently severe, can produce organ dysfunction.”²

The Hyperfibrinolytic versus Procoagulant Forms of DIC

Disseminated intravascular coagulation is often described as a thrombohemorrhagic disorder. Patients can present with thrombosis or bleeding at different times or simultaneously, which may be explained by the two different ways of thrombin generation—one where it is extremely rapid and another where it is relatively slower. An extremely rapid burst of excess thrombin production may be postulated to lead to a “hyperfibrinolytic” form of DIC (e.g., trauma-related DIC or obstetrical DIC), whereas more gradual, but still excess, amounts of thrombin may be considered to lead to a “procoagulant” form of DIC (e.g., septic DIC; please see discussion under Modulation of Hyperfibrinolytic Response). Although both procoagulant and hyperfibrinolytic processes may proceed at the same time in DIC, depending on the predominant mechanism at a particular time, the clinical presentation will either thrombosis or bleeding, respectively (fig. 1).

Clinical Presentations of DIC

Since DIC is secondary to an underlying disease, the primary disease features may represent the clinical presentation of DIC.³ What may be termed as unique to DIC are hemorrhages that occur simultaneously from distant sites and thrombosis in the microcirculation. Most professionals consider the possibility of DIC only when there is extensive and uncontrollable bleeding from multiple sites, although microvascular ischemia leading to organ (renal, pulmonary, or central nervous system) dysfunction may represent the onset of DIC.

¹This article is featured in “This Month in Anesthesiology,” page 1A. Figures 1 and 2 were enhanced by Annemarie B. Johnson, C.M.I., Medical Illustrator, Vivo Visuals, Winston-Salem, North Carolina.

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DIC in conjunction with laboratory abnormalities (platelet count, PT/APTT, serum fibrinogen, and fibrin degradation marker). It is important to point out that laboratory markers in isolation and a single set of these values are NOT helpful in DIC diagnosis. This approach is based on the ISTH concepts of overt and nonovert DIC.

Overt and Nonovert DIC

Any diagnostic process would be most useful if it can detect early changes of DIC. In “nonovert DIC,” worsening clinical condition will reverse quickly when the predisposing condition is removed or controlled. However, the “nonovert” form if uncontrolled can proceed along a continuum to “overt DIC.”

A five-step diagnostic score of more than 5 is compatible with overt DIC, whereas a score of less than 5 may be indicative (but is not affirmative) for nonovert DIC. The diagnostic accuracy of the ISTH score has been validated by several studies and correlated well with the mortality of patients with sepsis. Recently, the Japanese Association for Acute Medicine (JAAM) DIC study group brought forward a new DIC diagnostic criteria. When JAAM DIC patients met the criteria of the ISTH overt DIC, the risk of multiorgan dysfunction syndrome and mortality was found to be higher, suggesting its usefulness in septic patients with compensated DIC. In summary, JAAM criteria are the most sensitive for septic DIC and the ISTH criteria are the most specific for septic DIC. A description of the three diagnostic criteria is given in table 1.

Some Practice Pointers

Thrombocytopenia is the commonest laboratory diagnostic feature of DIC (93% of cases). In many cases of DIC, the thrombocytopenia may not be severe. It is crucial to note a downward trend in the platelet count even if the recent count remains in the normal range. A drop in platelet count may be accompanied by platelet dysfunction, which can contribute to the bleeding and can be overlooked in nonsevere cases (50 $\times$ 10^9/l). Thrombocytopenia may also be related to platelet aggregation or increased adhesion to the vascular endothelium consistent with the finding that ADAMTS-13, the Von Willebrand cleaving protease enzyme, is typically reduced in patients with DIC. Although not confirmed in prospective randomized trials, a low ADAMTS-13 level in DIC has been linked to organ dysfunction, especially renal impairment.

In relation to the coagulation screen, PT/APTT may be normal in up to 50% of cases of DIC, while severe hypofibrinogenemia is very rare in DIC (3%). Since APTT is shortened by factor VIII increase, which can occur in many underlying conditions that lead to DIC, its prolongation may lag behind clinical manifestations. There is currently a lot of controversy over the choice of fibrin degradation marker and whether it should be D-dimer or soluble fibrin monomer. Although D-dimer is commonly used, there are multiple assays and methodologies available, with attempts at harmonization of the test having
been unsuccessful. In addition, increased value needs not always reflect DIC, with sepsis, renal and liver impairment known to increase their values.

Repeated measurements of the above-mentioned laboratory markers (under general principles) are likely to provide meaningful results rather than one set in monitoring a patient with DIC. Several other laboratory markers for DIC were used in the past mostly in the research setting, while some newer markers have been suggested to have potential for mainstream use in the evaluation of DIC and are discussed in a recent review (table 2).

There is considerable interest in the use of point-of-care tests in the critically ill population. DIC, being a condition, with contributions from the various pathways of coagulation including procoagulant and fibrinolytic systems and also the platelets, it would be logical to think that a global assay that incorporates all these parameters would help in its diagnosis. A systematic review of thromboelastometric (TEM) techniques (Haemoscope Corporation, USA) and ROTEM (Tem GmbH, Germany) looked at 18 studies in patients with sepsis in their ability to detect coagulopathy. The results were very heterogeneous with both hyper- and hypocoagulability being noted in different studies. In five of these studies, impaired fibrinolysis in sepsis was the only abnormality. Thus, although TEM looks promising in patients with septic DIC, validation is required with future studies where clearer definition of hyper- and hypocoagulability and appropriate cutoff points are used for analysis.

Many of the clinical features and laboratory markers of DIC can mimic several other conditions. Some similarities and differences for the different conditions that can present like DIC in the critical care unit are given in table 3.

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**Table 1. Diagnostic Criteria to Diagnose DIC**

<table>
<thead>
<tr>
<th></th>
<th>ISTH Criteria</th>
<th>JMWH Criteria</th>
<th>JAAM Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical condition predisposing to DIC</td>
<td>Essential</td>
<td>1 point</td>
<td>Essential</td>
</tr>
<tr>
<td>The presence of clinical symptoms</td>
<td>Not used</td>
<td>Bleeding—1 point</td>
<td>SIRS score ≥ 3—1 point</td>
</tr>
<tr>
<td>Platelet count (in ×10^9/l)</td>
<td>50–100—1 point</td>
<td>80–120—1 point</td>
<td>80–120 or &gt; 30% reduction—1 point</td>
</tr>
<tr>
<td></td>
<td>&lt; 50—2 points</td>
<td>&lt; 80 or &gt; 50% reduction—2 points</td>
<td></td>
</tr>
<tr>
<td>Fibrin-related marker</td>
<td>Moderate increase—2 points</td>
<td>FDP (μg/ml)</td>
<td>FDP (μg/ml)</td>
</tr>
<tr>
<td></td>
<td>Marked increase—3 points</td>
<td>10–20—1 point</td>
<td>10–25—1 point</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20–40—2 points</td>
<td>&gt; 25—3 points</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 40—3 points</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>&lt; 1—1 point</td>
<td>1–1.5—1 point</td>
<td>Not used</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 1—2 points</td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td>Prolongation</td>
<td>1.25–1.67—1 point</td>
<td>≥ 1.2—1 point</td>
</tr>
<tr>
<td></td>
<td>3–6 s—1 point</td>
<td>≥ 7 points</td>
<td>≥ 4 points</td>
</tr>
<tr>
<td>DIC diagnosis</td>
<td>≥ 5 points</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DIC = disseminated intravascular coagulation; FDP = fibrin degradation product; ISTH = International Society of Thrombosis and Haemostasis; JAAM = Japanese Association for Acute Medicine; JMWH = Japanese Ministry of Health and Welfare; PT = prothrombin time; SIRS = systemic inflammatory response syndrome.

**Table 2. Specialized Laboratory Tests in Disseminated Intravascular Coagulation**

- Excess thrombin generation
  - *Increased thrombin–antithrombin complexes*
  - *Increased fibrinopeptides*
  - *Increased prothrombin fragments 1 and 2*
- Decreased protein C and protein S and antithrombin
- Increased fibrinolysis
  - *Increase in plasmin*
  - *Decreased plasminogen levels*
  - *Decrease in α2-antiplasmin*
  - *Increase in plasmin–α2-antiplasmin complexes*
  - *High levels of plasminogen activator inhibitors*
- Newer markers (signifying thrombosis–inflammation cross-link)
  - Increased soluble thrombomodulin
  - Increased amount of histones and extracellular deoxyribonucleic acid
  - Increased high-mobility group box protein-1
  - Neutrophil activation in the form of neutrophil extracellular traps
  - Decreased ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13)
  - Complement markers (C3, membrane attack complex, and mannose-binding lectin)
  - Presepsin (soluble cluster of differentiation 14 subtype)

Excess thrombin generation

Most of the therapeutic measures for DIC are surprisingly NOT based on high levels of evidence. Prompt recognition is most important as stressed by the ISTH in the recent harmonized guidance. The basic principles for treating DIC are as follows:

**Management**

Tests in italics are not performed commonly in research laboratories anymore.

ADAMTS-13 is a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13.
Management of the Underlying Condition That Predisposes to DIC

Disseminated intravascular coagulation is always secondary to an underlying process. For this reason, appropriate management of the primary condition is paramount in limiting the excess thrombin generation (e.g., the correct antibiotics in sepsis and damage control resuscitation for trauma patients).\(^5,11\) Inadequate treatment of the DIC-initiating process can lead to several other complicated pathophysiologic consequences. This is exemplified in septic DIC, wherein activation of complement, neurohumoral mechanisms and heightened inflammatory responses lead to shock and tissue damage, which can further worsen DIC.

Anticoagulant Therapy

Thrombin in DIC, in addition to its coagulation effects, is also a potent proinflammatory protein and platelet agonist. Thrombocytopenia and excess thrombin have disadvantageous effects on the vascular endothelium to make it leakier leading to vasogenic edema.\(^4\) As such, neutralization of thrombin effects is crucial in stemming the DIC process.

Heparin has been used historically as a treatment for DIC with various outcomes. The risk of bleeding has prompted some recommendations to limit its use in highly prothrombotic forms of DIC such as amniotic fluid embolism or acral/dermal ischemia.\(^7\) However, the authors’ practice based on the DIC pathophysiology of excess thrombin generation is to

### Table 3. Differential Diagnosis of DIC in Critical Care Unit

<table>
<thead>
<tr>
<th>Condition</th>
<th>Similarities with DIC</th>
<th>Differences from DIC</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver disease</td>
<td>Low platelet count</td>
<td>High factor VIII is noted in liver impairment</td>
<td>Repeated measurements with continuous worsening suggest DIC. Liver disease is a prothrombotic condition. Anticoagulation should be considered in nonbleeding patients in both DIC and liver disease.</td>
</tr>
<tr>
<td>Thrombotic microangiopathy</td>
<td>Low platelet count</td>
<td>Normal clotting screen</td>
<td>Florid red cell fragmentation is not common in patients with DIC, who may show occasional schistocytes. Extremely low platelet count with normal clotting screen unusual in DIC. Plasma exchange should be initiated as soon as possible.</td>
</tr>
<tr>
<td>Thrombotic storm</td>
<td>Low platelet count</td>
<td>Extremely rapid onset compared to DIC</td>
<td>Multiple thrombotic events affecting diverse vascular beds occurring over a brief period of time occurs in thrombotic storm. Large vessel thrombus not initial presentation of DIC.</td>
</tr>
<tr>
<td>Vasculitis including catastrophic antiphospholipid syndrome</td>
<td>Low platelet count</td>
<td>Normal clotting screen</td>
<td>May have a history of rheumatologic problems although occasionally may be the first presentation in critical care.</td>
</tr>
<tr>
<td>HIT</td>
<td>Low platelet count</td>
<td>Normal clotting screen</td>
<td>A very severe thrombocytopenia ((&lt; 20 \times 10^9/l)) is uncommon with HIT and would suggest DIC in conjunction or as the only diagnosis. HIT screen may be positive in DIC but a strongly positive antibody screen in a patient with high clinical probability (4T score) suggests HIT.</td>
</tr>
<tr>
<td>Hemophagocytic syndrome</td>
<td>Low platelet count</td>
<td>Very high ferritin</td>
<td>Patients usually have organomegaly.</td>
</tr>
</tbody>
</table>

ADAMTS-13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; DIC = disseminated intravascular coagulation; HIT = heparin-induced thrombocytopenia; TTP = thrombotic thrombocytopenic purpura.
consider heparin in all cases if there are no signs of active bleeding. The only study in this respect comes from the Japanese Ministry of Health and Welfare that used the low-molecular-weight heparin (LMWH), dalteparin, in a multicenter trial.\textsuperscript{15} This double-blind trial compared dalteparin with unfractionated heparin and showed significantly reduced organ failure and bleeding symptoms and a higher safety rate.\textsuperscript{15} The choice of heparin is often another debated issue in this regard. In those with high bleeding risk and dialysis-dependent renal failure, unfractionated heparin is preferred, and in all other cases, LMWH is preferred. Even if unfractionated heparin (UFH) or LMWH is used, we monitor their antithrombotic capacity with drug-specific anti-Xa levels. This is especially important in the case of UFH, since conventional APTT may already be prolonged due to DIC itself or underlying disorders. In addition, there is sufficient evidence in the current literature to use anti-Xa instead of APTT for monitoring UFH.\textsuperscript{16} Although recommendations cannot be given for the therapeutic range for LMWH, the standard manufacturer recommendations are followed, which are usually helpful in excluding very high or extremely low levels in the patients, who are at risk of bleeding or thrombosis. Anti-Xa monitoring of LMWH is done after three doses have been given and a steady state is reached.

In addition to heparin, the other anticoagulant concentrates trialled until recently include antithrombin, activated protein C, and soluble thrombomodulin.

Antithrombin is one of the natural anticoagulants depleted early on in DIC and is an independent predictor of 28-day mortality in DIC (reviewed recently).\textsuperscript{17} Although early studies showed good outcome for patients with DIC, post hoc analysis of the phase III, KyberSept trial, did not show any survival advantage for antithrombin concentrates over placebo. Some emerging results have however suggested that an appropriate dose in patients selected based on the degree of decrease in antithrombin activity may show a benefit for this anticoagulant.\textsuperscript{18}

In a similar manner, activated protein C was considered a landmark in the management of patients with severe sepsis and DIC after results from the randomized controlled trial, the Protein C Worldwide Evaluation in Severe Sepsis (PROWESS). But reports from later studies were disappointing including the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) trial demonstrating no significant difference in mortality; the pediatric study, Researching Severe Sepsis and Organ Dysfunction in Children: A Global Perspective (RESOLVE) noting an increased incidence of intracranial bleeding; and Extended Evaluation of Human Recombinant Activated Protein C (ENHANCE) open-label study noting an increased incidence of serious bleeding.\textsuperscript{19} A call for reexamination of the drug led to industry-sponsored placebo-controlled PROWESS--SHOCK trial, which showed disappointing results, wherein the 28-day all-cause mortality was not better (26.4% in the treatment arm vs. 24.2% in the placebo arm).\textsuperscript{20} Due to the lack of survival benefit for patients with severe sepsis and septic shock, the U.S. Federal Drug Administration Agency have advised physicians in October 2011 that activated protein C treatment should not be started in new patients and treatment should be stopped in patients being treated with activated protein C.\textsuperscript{21}

Soluble thrombomodulin is currently the best-studied agent (mostly in Japan) in the management of DIC. Its attraction lies in the fact that it needs to bind to thrombin for its function and also that it has antiinflammatory effects such as suppression of inflammatory mediators and complement activation and inhibition of leukocyte--endothelial interaction.\textsuperscript{22} Effectiveness of thrombomodulin was shown in DIC related to hematological malignancy and infection in a multicenter, double-blind, randomized trial, ART-123.\textsuperscript{23} The results demonstrated a DIC resolution rate of 66.1% in the thrombomodulin group and 49.9% in the unfractionated heparin group and 28-day mortality of 28.0 versus 34.6% in favor of thrombomodulin.\textsuperscript{23} The thrombomodulin arm also had a lower incidence of hemorrhagic adverse events. We would currently consider the use of antithrombin or thrombomodulin as part of clinical trials.

Although direct thrombin inhibitors are logical choice for anticoagulants in DIC, they have not been studied particularly in this scenario. The author would consider their use in DIC if there is a history of heparin-induced thrombocytopenia that contraindicates the use of heparin. The shorter duration of action of bivalirudin and safety profile of argatroban in renal impaired patients are certainly attractive if a cheaper alternative such as heparin cannot be used.

**Modulation of Hyperfibrinolytic Response**

In patients with severe trauma, the extensive thrombin generated may be considered as a trigger response to rescue the host from excessive blood loss. Simultaneous excess plasmin generation is an attempt to ensure that the clots are limited and not compromising the circulation. However, the hyperfibrinolytic response will affect the strength of the clot since plasmin degrades the fibrin in the microcirculation and coagulation factors in the plasma and also inhibits fibrin polymerization, leading to hemorrhage. This early hyperfibrinolytic response is best inhibited by the administration of an antifibrinolytic agent such as tranexamic acid, which assists in the formation of a well cross-linked clot. The tremendous success of the pivotal Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial is an enough evidence for this inhibition of hyperfibrinolytic response.\textsuperscript{24} Once the acute process is passed, further thrombin generation is NOT counterbalanced by a brisk fibrinolytic response, and the balance is tipped toward thrombosis. For this reason, and due to the lack of evidence for benefits against thrombotic risk, it is preferable not to repeat the dose of antifibrinolitics. The use of TEM in this setting may provide some useful information in tailoring antifibrinolytic usage, but prospective trials are necessary for DIC in trauma before giving recommendations. In DIC related to sepsis, the balance is shifted more in favor of thrombin in comparison to plasmin, there is limited fibrinolysis, and the predominant pathophysiologic mechanism is that of...
procoagulant process. Needless to say, antifibrinolytic therapy is dangerous here, and the focus should be on limiting the various effects of excess thrombin generation. In addition to thrombogenic potential in hypercoagulable patients, there have been reports of seizures with this drug, especially in the cardiac surgery setting, possibly due to neuronal excitation by inhibiting γ-aminobutyric acid or glycine receptors.25

Supportive Care
The term consumption coagulopathy has been classically used for DIC, suggesting the need for blood component replacement in its management. However, at least in relation to the coagulation factors, their reduction is not usually to less than hemostatic levels except with profuse bleeding. On the contrary, an element of platelet dysfunction exists in DIC, contributing to bleeding despite a “good” platelet count.

Thresholds for transfusing blood components are recommended by the harmonized guidance.10,11 In bleeding patients or those who need procedural interventions, if platelets are less than 50 × 10^9/l then one to two platelet concentrates should be transfused; if the PT/APTT ratio is greater than 1.5 times normal values, then 15 to 30 ml/kg of fresh frozen plasma (FFP) should be considered to replace coagulation factors if volume overload is not a concern; if fibrinogen is less than 1.5 to 2.0 g/l, then either 5 to 10 units cryoprecipitate or 2 g fibrinogen concentrate should be used.10,11 The order of blood product administration in a patient with significant bleeding is fibrinogen replacement before FFP since fibrinogen is a critical coagulation factor in the hemostatic process and low levels can also contribute to prolongation of the PT/APTT.

Prothrombin complex concentrates may be considered an alternative to FFP because they have the advantages of smaller volumes, no thawing required, and viral safety. However, these agents in comparison to FFP have much reduced levels of the anticoagulant proteins, protein C, protein S, and antithrombin.26 This “shortage,” which is not preferable in DIC patients, where the levels of endogenous anticoagulants can be markedly reduced, may also translate as thrombotic potential, a feature already demonstrated in animal studies.27 For this reason, prothrombin complex concentrates should only be used in patients with DIC if monitoring of the anticoagulant proteins can be undertaken rapidly in the laboratory.

Clinical and Laboratory Surveillance
Since DIC is a dynamic process, it is important to monitor the patient for clinical improvement or worsening and to identify the early development of complications, including organ failure. In relation to laboratory tests, these may not always represent DIC, but can have contributions from the underlying disease process. For example, thrombocytopenia in a critically ill patient can be due to several factors, including DIC. Treating the underlying disease is a critical management strategy since DIC is the sequelae of different disease processes, and not a primary condition.

An algorithm that discusses an approach to a patient with DIC based on their clinical presentation with or without bleeding is given in figure 2.

Conclusions
Disseminated intravascular coagulation is a syndrome where different unrelated conditions lead to thrombotic or hemorrhagic clinical manifestations. The ISTH diagnostic criteria have paved the way for well-designed studies and helped physicians in day-to-day management of patients. Arrival of newer anticoagulant treatments has alleviated the DIC mortality to an extent. But a lot of work still needs to be done in the understanding of pathophysiology, identification of newer laboratory markers, and non-anticoagulant treatment modalities for DIC. This requires collaborative efforts among basic scientists, intensivists, hematologists, and many other specialists.
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Competing Interests
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Correspondence
Address correspondence to Dr. Thachil: Department of Haematology, Central Manchester University Hospitals NHS Foundation Trust, Oxford Road, Manchester M13 9WL, United Kingdom. jecko.thachil@cmft.nhs.uk. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY’s articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

References

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