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**TOWARDS A DEFINITION, CLINICAL AND LABORATORY
CRITERIA, AND A SCORING SYSTEM FOR
DISSEMINATED INTRAVASCULAR COAGULATION**

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**on behalf of the Scientific Subcommittee on Disseminated Intravascular Coagulation
(DIC) of the International Society on Thrombosis and Haemostasis (ISTH)**
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ABSTRACT

Disseminated intravascular coagulation (DIC) is a syndrome characterized by a systemic activation of coagulation, which may complicate a variety of disorders. Although the general concept of DIC is known to most clinicians, a uniform definition of the syndrome and straightforward diagnostic criteria have never been defined. In this manuscript, the scientific subcommittee on DIC of the International Society on Thrombosis and Hemostasis (ISTH) proposes a definition and a diagnostic scoring system for overt DIC. In addition, a template for a similar scoring system for non-overt DIC is formulated. Consensus on the definition of DIC and its diagnostic criteria may facilitate basic and clinical research in this area, which may eventually lead to progress in the clinical management of patients with DIC.

INTRODUCTION

Already in the 19th century some of the first clinical and pathological observations related to DIC were made. One of the first reports comes from Dupuy in 1834, who describes the effect of the intravenous injection of brain material in animals (1). The animals almost immediately died and at autopsy there were widespread clots in the circulation, presumably due to what we would now call tissue factor-dependent systemic activation of coagulation. A more precise description of DIC and its underlying pathogenesis had to wait until the 20th century, when more insight in the mechanism of blood coagulation was attained and better laboratory tests had become available. Ratnoff described into detail the coagulation abnormalities in a woman with abruptio placentae and severe bleeding (2) and Seegers described microangiopathic thrombosis in the microvasculature of a woman who had amniotic fluid embolization during parurition (3). Although the general picture of DIC is known to most clinicians, a precise description of the syndrome, a good working definition and a useful scoring system are not available. The SSC subcommittee on DIC has worked over the last years to come closer to achieve these goals.

Traditionally DIC is diagnosed in association with the following clinical and pathophysiologic events:

1. Initiation of a massive localized or generalized inflammatory response with release of host proteases, cytokines, and hormones from multiple inflammatory and vascular cell types leading to an extensive damage to microvascular endothelium (4).
2. This is accompanied by, (a) vasodilatation, loss of tight junctions between endothelial cells leading to capillary leak and shock, (b) escape from regulatory control, activation of coagulation pathways and excessive thrombin generation with microthrombus formation locally and at sites remote from the site of original injury, leading to ischemia and multiple organ dysfunction, and (c) subsequent consumption and exhaustion of platelets and coagulation factors leading to bleeding and hemorrhage into tissues (5, 6).

Considering these premises, the consensual definition of DIC as proposed by the SSC/ISTH subcommittee on DIC and as further explained in this manuscript, is as follows: “DIC is an acquired syndrome characterized by the 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”.

In this manuscript the subcommittee on DIC has attempted to put forward a concept of DIC and a scoring system as a first step in the ultimate aim of improving outcome in this area. It therefore has to be useful for those practicing clinical medicine as well as those involved in clinical and basic research, so that progress can be made both in the understanding of pathogenesis and therapy.

ONE CONCEPT AND SIX CONSIDERATIONS

The assumption under which the subcommittee worked is that DIC is characterized by the generation of fibrin related products (soluble fibrin monomer, fibrin degradation products, D-dimer, etc.) and that it reflects an acquired (inflammatory) or non-inflammatory disorder of the microvasculature (4). The microvasculature is defined as a transport organ composed of blood and the vascular structures in contact with blood, including mononuclear cells and endothelium (RES/microvasculature).

Homeostasis is maintained by complex vascular and reticuloendothelial factors that operate on each other to maintain a steady state. If, however, there is a significant injury, the RES cell population is activated and the vascular endothelium is perturbed. Ultimately the degree of this perturbation and the integrity of regulatory mechanisms determined whether homeostasis is re-established or acceleration towards DIC occurs. The subcommittee proposes that the RES/microvasculature system be viewed as a distinct physiologic organ, the function of which, on injury may be switched from homeostatic regulation to amplification of its own dysfunction (“inflammation gone amok”). Since this RES/microvasculature organ supplies all the other organs, failure of this organ can be a predictive indicator of morbid events leading to multiple organ failure. Further, if DIC (with the associated change in biological markers) is viewed as an indicator of dysfunction of the RES/microvascular organ, a conceptual model for both diagnosis and therapy is created. This, for example, would be analogous to oliguria and rising serum creatinine being a *de facto* indicator of renal organ failure.

In developing a practical diagnostic approach and set of criteria for the diagnosis of DIC and RES/microvascular dysfunction, the DIC subcommittee has operated with six objectives in mind:

1. To establish the importance of the presence of the underlying disorder for the development of overt DIC and to integrate diagnostic criteria for e.g. sepsis and organ failure with the criteria for the evaluation of the severity of DIC (table 1) (7, 8). Since the hemostatic system is an integral part of the larger 'microvascular organ', its dysfunction may be considered as a dysfunction of the microvasculature. Although the microvascular derangement is closely linked to other clinical markers of inflammation and organ dysfunction, we have chosen not to include criteria for organ failure to be part of the DIC score. The main reason for this, is that the DIC score itself is likely to become part of scores for organ failure.
2. To establish diagnostic criteria for the diagnosis of a stressed, but compensated hemostatic system (non-overt DIC) as well as for the diagnosis of a stressed but decompensated hemostatic system (overt DIC). To be worthwhile, any new diagnostic approach must account for evolution in procoagulant and inflammatory processes that begins with incipient or biochemical changes indicative of early DIC (which we will call "non-overt DIC" and proceeding along a continuum to the full clinical syndrome of DIC (which we will designate "overt DIC").
3. To establish clinical and laboratory criteria, which will aid in distinguishing between (a) "controlled" overt DIC, in which the endothelial regulatory network (e.g. activation of protein C by endothelial thrombomodulin) is temporarily overridden and which will reverse quickly when the predisposing condition or cause is removed or stopped (e.g. transfusion reaction, or abruptio placentae), and (b) "uncontrolled" overt DIC, in which there is both an override of the regulatory factors and degradation of the endothelial regulatory network (e.g., sepsis, trauma).
4. To establish the importance of continuing to use readily available laboratory tests (e.g. global coagulation tests) in diagnostic screening for DIC (9). An essential feature for adequately defining both overt and non-overt DIC is the use of diagnostic criteria that reflect both progression and modulation of the process. It should incorporate four key

elements: simplicity, practicality, flexibility, and reliability. It is clear that global coagulation tests primarily reflect ongoing consumption and impaired synthesis rather than directly assess activation of coagulation; however, these tests are widely available and may be done immediately. It should be realized, however, that these global markers become less reliable in chronic or recurrent inflammatory settings, in the face of problems associated with instrumentation, liver function, nutrition, and ischemia-reperfusion. In an acute setting, such as meningococcal sepsis, these global markers are more likely to accurately reflect the presence of DIC. Assessment of a low and/or decreasing platelet count more accurately reflects both consumption and thrombin generation and is helpful in establishing the presence and severity of DIC (10). Additionally, tests for the presence of fibrin (either directly or indirectly by measuring fibrin degradation products) are helpful in establishing intravascular fibrin formation (11-13). The diagnosis of DIC, therefore, should continue to be based on clinical and global tests of coagulation as well as on a screening assay (if available) for intravascular soluble fibrin formation or fibrin degradation products. Indeed, previous studies have confirmed the feasibility to use global coagulation tests to accurately assess the presence or absence of overt DIC. However, for the diagnosis of non-overt DIC these global tests may be insufficiently sensitive.

5. In considering molecular markers, it should be emphasized that (a) these tests have great value in looking at both endothelial injury and hemostatic activation, (b) these tests constitute important means for diagnosing non-overt DIC, and (c) serial measurement of these parameters are important to quantitatively assess the progression and extent of microvascular injury and the progression from non-overt to overt DIC. Examples include prothrombin activation fragment F1+2 or thrombin-antithrombin (TAT) complexes as markers of thrombin generation, or thrombomodulin and elastase as markers of endothelial and/or neutrophil perturbation, respectively (14-16). However, since these markers can only be measured in specialized laboratories and can generally not be available on a daily basis in routine care, they will not form part of the scoring system.
6. To realize that the design of a system to score the presence and severity of DIC may be of importance for clinical practice as well as clinical trials on the effect of interventions

directed at pathways or components of the coagulation system to improve DIC and/or the underlying disorder (e.g. sepsis). However, the ultimate aim of the treatment is not directed at the amelioration of the DIC itself. Rather, the improvement of organ function or mortality should be regarded as more relevant outcome parameter. Nevertheless, a DIC score may be of relevance if it can be validated as a suitable intermediate outcome parameter. Prospective validation of the proposed criteria for DIC is mandatory, to determine more precisely the value of these criteria.

CRITERIA FOR OVERT DIC

Following these objectives the committee proposes a 5-step diagnostic algorithm to calculate a DIC score, as summarized in table 2. This score is partly based on a modification of the criteria for DIC, as established by the Japanese Ministry of Health and Welfare, and addresses the above-formulated premises (17). In line with the previous comments, the presence of an underlying disorder known to be associated with DIC (table 1) is a *conditio sine qua non* for the use of the algorithm (step 1). We decided not to include the clinical assessment of organ failure and bleeding as a part of the score, since the DIC score itself may form part of scores for organ failure. The results of routine laboratory tests contribute to the DIC score. Presumably, all laboratory tests required for the score will be available in most hospitals on a daily basis. Dependent of the type of test used, cut-off values for a “severely” or “moderately” elevated result of the test for soluble fibrin monomers or fibrin degradation products have to be established. Tentatively, and awaiting further prospective validation, a score equal or more than 5 is compatible with DIC, whereas a score of less than 5 may be indicative (but is *not* affirmative) for non-overt DIC (see further). It is the recommendation of the subcommittee that scoring proceeds daily in order to characterize the severity and the course of the overt DIC.

CRITERIA FOR NON-OVERT DIC

To define and score the presence and severity of non-overt DIC using a “standard” scoring system is much more complicated. Nevertheless, it is of importance to delineate the criteria

for the presence of hemostatic dysfunction when it is not yet at the stage of frank decompensation. This is relevant in two broad respects:

(a) *forewarning of impending DIC*: The uniform conclusion from all failed trials of sepsis therapy at the phase III stage is the late and sub-optimal timing of therapeutic intervention. Definition of the non-overt stage of DIC would provide a valid focus for these trials and this is absolutely essential in view of the need to improve the clinical outcome in this area. In the non-trial setting, it would provide clinicians with a set of criteria for following patients at risk of developing overt DIC.

(b) *prediction of the clinical outcome*: This applies to conditions where development of overt DIC may be a possible but not natural consequence of the presence of non-overt DIC. In this situation hemostatic function still may contribute to the outcome. The scoring system should direct guidance to the clinician in this respect, and should be useful for following the development of the non-overt DIC and contributing parameters over time.

As mentioned before, the global coagulation parameters will be of limited value in the assessment of non-overt DIC. These tests are in general insufficiently sensitive whereas simultaneously subtle changes may be too non-specific. On the other hand, more sensitive tests for this diagnosis will not be widely available. Hence, it is difficult to accomplish a scoring system that is universally applicable. The subcommittee proposes a framework for a scoring system for non-overt DIC that can be specified and refined according to local potential and/or using essential tests in the context of a clinical trial (table 3). This format will also enable one to incorporate any future advancement in either technology or pathophysiological understanding. Similar to the definition of overt DIC, the presence of an underlying disease that is known to be associated with DIC is required. If this is the case, major and specific criteria are to be considered in a scoring system. Major criteria will consist of the platelet count, prothrombin time and a test for a fibrin-related marker (such as soluble fibrin monomers or fibrin degradation products). In the proposed scoring system for non-overt DIC more emphasis on the trend over time of these results is given, thereby increasing the sensitivity of the parameters. Therefore, the subcommittee recommends that measurements proceed daily.

Specific criteria will be established by the results of more specialized coagulation tests, such as the determination of antithrombin or protein C. Also results of tests for activation peptides or complexes between activated coagulation proteases and protease inhibitors (such as thrombin-antithrombin (TAT) complexes) may be included in these criteria. According to local availability of tests and/or criteria that are defined in the framework of a clinical trial a selection of tests can be made and a score can be calculated. Also here, prospective validation of a given score is needed.

CONCLUSION

The present manuscript represents an attempt of the SSC/ISTH subcommittee on DIC to more precisely define clinical and laboratory parameters of DIC. From a consensual concept of DIC and several predefined objectives, a relatively simple and easily applicable scoring system for overt DIC has been formulated. For non-overt DIC the requirements for a similar scoring system are proposed, of which the ultimate definition and specification will be dictated by the local availability of tests or the needs of a given clinical trial. Prospective validation of these test systems (overt and non-overt DIC) is required to establish their applicability and predictive value in patients with DIC.

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table 1

Clinical conditions that may be associated with overt DIC

sepsis/severe infection (any micro-organism)

trauma (e.g. polytrauma, neurotrauma, fat embolism)

organ destruction (e.g. severe pancreatitis)

malignancy

- solid tumors
- myeloproliferative/lymphoproliferative malignancies

obstetrical calamities

- amniotic fluid embolism
- abruptio placentae

vascular abnormalities

- Kasabach-Merrit Syndrome
- large vascular aneurysms

severe hepatic failure

severe toxic or immunologic reactions

- snake bites
- recreational drugs
- transfusion reactions
- transplant rejection

table 2: Diagnostic algorithm for the diagnosis of overt DIC

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

If yes: proceed; If no: do not use this algorithm;

2. Order global coagulation tests (platelet count, prothrombin time (PT), fibrinogen, soluble fibrin monomers or fibrin degradation products)

3. Score global coagulation test results

~~EE~~ platelet count ($>100 = 0$; $<100 = 1$; $<50 = 2$)

~~EE~~ elevated fibrin-related marker (e.g. soluble fibrin monomers/fibrin degradation products)
(no increase: 0; moderate increase: 2; strong increase: 3)

~~EE~~ prolonged prothrombin time
($< 3 \text{ sec.} = 0$; $> 3 \text{ sec. but } < 6 \text{ sec.} = 1$; $> 6 \text{ sec.} = 2$)

~~EE~~ fibrinogen level
($> 1.0 \text{ gram/l} = 0$; $< 1.0 \text{ gram/l} = 1$)

4. Calculate score

5. If ≥ 5 : compatible with overt DIC; repeat scoring daily

If < 5 : suggestive (not affirmative) for non-overt DIC; repeat next 1-2 days;

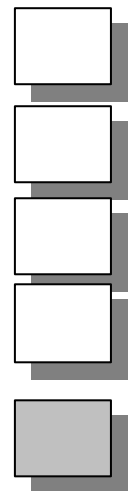


table 3: Template for scoring system for non-overt DIC

1. Risk assessment: Does the patient have a underlying disorder known to be associated with DIC?

yes = 2, no=0

score

2. Major criteria

platelet count	>100x10 ⁹ /l = 0 ()	<100x10 ⁹ /l = 1 ()
PT Prolongation	< 3 sec ()	> 3 sec ()
soluble fibrin or FDP's	normal ()	raised ()

+	rising = -1 ()	stable = 0 ()	falling = 1 ()
+	falling = -1 ()	stable = 0 ()	rising = 1 ()
+	falling = -1 ()	stable = 0 ()	rising = 1 ()

3. Specific criteria

antithrombin	normal = -1 ()	low = 1 ()
protein C	normal = -1 ()	low = 1 ()
TAT-complexes	normal = -1 ()	high = 1 ()
.....	normal = -1 ()	abnormal = 1 ()

4. Calculate score

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