

## Disseminated Intravascular Coagulation

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### ABSTRACT

*Disseminated Intravascular Coagulation (DIC) is an acquired pathological syndrome, featured by a hypercoagulable state, bleeding symptoms, and multiple organ failure. Based by these very distinct features, DIC is classified into four types namely Bleeding type, Organ failure type, Massive bleeding type, and Asymptomatic type. Diagnosing DIC is a challenge to the health practitioner, considering that DIC is a multifactorial syndrome, which always is a complication of some underlying diseases. To diagnose DIC, it is necessary to do a comprehensive evaluation of clinical symptoms and laboratory results. The necessary laboratory results include platelets count, fibrin degradation products (FDPs), fibrinogen, and PT-aPTT.*

**Key words:** *bleeding, disseminated intravascular coagulation (DIC), organ failure*

### ABSTRAK

Koagulasi Intravaskular Diseminata (KID) adalah sindroma patologikal yang didapat, ditandai dengan gejala hiperkoagulasi, perdarahan, dan gagal organ multipel. Berdasarkan 3 gejala yang sangat berbeda ini, KID diklasifikasikan menjadi empat yaitu *Bleeding type, Organ failure type, Massive Bleeding type, dan Asymptomatic type*. Penegakan diagnosa KID merupakan sebuah tantangan bagi praktisi kesehatan, mengingat KID merupakan sindroma multifactorial yang selalu merupakan sebuah komplikasi dari penyakit yang mendasari. Untuk mendiagnosa KID, perlu untuk melakukan penilaian komprehensif antara data klinis dan hasil laboratorium. Hasil laboratorium yang digunakan juga harus mencakupi beberapa seperti hitung trombosit, *fibrin degradation products (FDPs)*, fibrinogen, dan waktu PT-aPTT.

**Kata kunci:** *gagal organ, koagulasi intravaskular diseminata, perdarahan*

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### Introduction

Disseminated intravascular coagulation (DIC) is an acquired pathological syndrome, featured by activation of the coagulation pathway which triggers systemic hypercoagulable states. These hypercoagulable states leads to fibrin deposition that interferes with blood flow to the organs, causing organ failure. At the same time, increased consumption of platelets and coagulation factors result in clinical bleeding. DIC itself is not a disease but it is always a complication of an underlying disease.<sup>1</sup>

The pathophysiology basics of DIC is the activation of systemic coagulation system that is triggered by the systemic inflammation process. The cause may be constituted by various conditions such as sepsis, obstetric complication, malignancy, and others. This inflammatory process leads to increased pro-coagulant in hemostatic system.

When the body cannot compensate the balance between pro-coagulant and anti-coagulant, it leads to DIC. Based on its distinct features, DIC is classified into Bleeding type, Organ failure type, Massive bleeding type, and Non-symptomatic type.<sup>1</sup>

Comprehensive evaluation is needed in diagnosing DIC, as it has dynamic situation and multifactorial causes. The evaluation must be done comprehensively, between clinical symptoms and laboratory results. Some of the laboratory results that can be considered are platelet counts, FDPs, fibrinogen, and PT-aPTT. The diagnosis then can be calculated through ISTH criteria. The focus of DIC management is to treat the underlying disease. In some cases, administration of supportive treatment can be considered, such as blood transfusions, anticoagulation, anticoagulant factor concentrates and anti-fibrinolytic.

The basis of the DIC is the activation of the systemic coagulation cascade that is triggered by systemic inflammation process. In fact, many clinical conditions can lead to activation of systemic coagulation<sup>3</sup>. Table 1 summarizes some of the clinical conditions.

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Table 1. Clinical conditions associated with DIC.<sup>3</sup>

Condition	Causes
<b>Sepsis/severe infections</b>	Gram-positive bacteria, Gram-negative bacteria, spirochetes, rickettsiae, protozoa, fungi, viruses
<b>Trauma</b>	Polytrauma, neurotrauma, fat embolism, burns
<b>Malignancy</b>	Solid tumors, myeloproliferative/lymphoproliferative malignancies
<b>Obstetric complication</b>	Amniotic fluid embolism, abruptio placentae, placenta previa, retained dead fetus syndrome
<b>Vascular disease</b>	Large vascular aneurysms, Kasabach-Merritt syndrome
<b>Organ destruction</b>	Severe pancreatitis, severe hepatic failure
<b>Toxin reaction</b>	Snake bites, recreational drugs
<b>Immunologic reaction</b>	Hemolytic transfusion reaction, transplant rejection

Sepsis and severe infections are the most frequent clinical conditions associated with DIC. Components of the microorganisms' cell membranes (lipopolysaccharide or endotoxin), or staphylococcal exotoxin (alpha hemolysin), which induces a general inflammatory response by producing pro-inflammatory mediators, such as cytokines<sup>3</sup> These inflammatory mediators can then activate the coagulation cascade via the intrinsic pathway, which leads to DIC<sup>1</sup> There is no difference in the incidence among patients with gram negative bacteria sepsis with DIC and gram positive bacteria sepsis with DIC<sup>3</sup> Severe trauma and burns often associated with DIC, as well as cancer. Clinical state of DIC on cancer can be divided into hyper-fibrinolysis, hyper-coagulable state, and subclinical state. In Acute Pro-myelitic Leukemia (AML-M3), a blood cancer that is most often associated with DIC, is more likely induce a hyper-fibrinolysis state<sup>4</sup> Some of the complications of obstetric, such as placental abruption or amniotic fluid embolism, is associated with DIC at prevalence rates as high as 60-80%<sup>1</sup> DIC can also occurs in some vascular diseases, such as hemangioma, severe aortic aneurysm, and intoxication or severe immunological reaction in snakebite, drug reaction, hemolytic transfusion reaction, or transplant rejection<sup>3</sup>

### Pathophysiology

Clinical abnormalities on patients with DIC are the result of imbalance between pro-coagulant (e.g *Tissue Factor (TF)*, *Plasminogen Activator Inhibitor-1 (PAI-1)*, *Platelet Activator Factor (PAF)*, *P-selectin*), and anti-coagulant (Protein C, *Endothelial Protein C Receptor (EPCR)*, *Tissue Factor Pathway Inhibitor (TFPI)*, *Antithrombin-III (AT-III)*, *tissue-Plasmin Activator (t-PA)*) in hemostatic system<sup>4,6</sup> Normally, thrombin production is strictly regulated by the natural anticoagulant mechanism (AT-III and Protein C), as well as fibrinolytic mechanism that improve the vascular patency after the formation of hemostatic plug. TFPI decreases coagulation through bind complex into TF/Factor VIIa/Factor Xa. Haemostatis system is vulnerable to disturbance. When the function of endothelial cells is disrupted and the body is unable to compensate the elevated pro-coagulant, regulation of haemostatis system will be disrupted, causing a DIC<sup>6</sup>

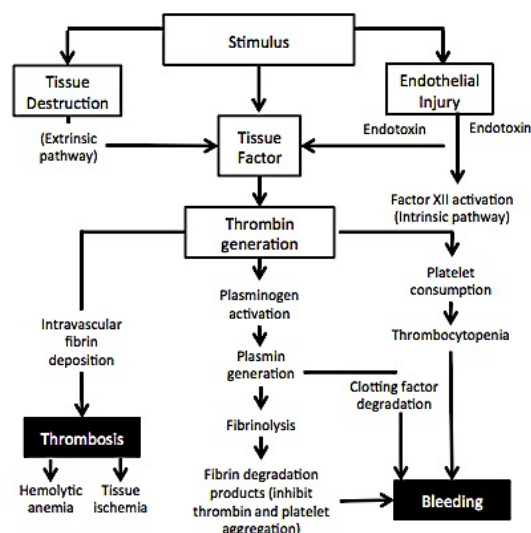


Figure 1. The pathophysiology of DIC<sup>7</sup>

The pathogenesis of DIC (Figure 1) is a complex process and centered on elevated intrinsic thrombin production. It is influenced by increased expression of TF, suboptimal functioning of the natural coagulation system, fibrinolysis and increased upregulated phospholipids<sup>5</sup> Disturbance in the endothelium causes the exposure of smooth muscle cells and fibroblast, which will lead to increase TF activity. This can occur in obstetric complication (placental abruption) or severe trauma.

TF is a trans membrane protein co-factors that are constitutively expressed by certain cells, such as fibroblasts. TF will then bind with factor VII to become complex TF/factor VII-a, which then initiate the activation of factor IX and X. TF can also induces activation of ROS that will disrupt the endothelial function. Activities of TF are high in the brain, lungs, and the placenta. Its activation is induced by endothelial cell and monocytes, as a response to cytokines, interleukin-1 (IL-1) and tumor necrosis factor (TNF), or endotoxin<sup>6</sup> Cytokines, along with its pro-inflammatory function, attracts the neutrophils and monocytes. Neutrophils produce neutrophil elastase, which has several effects: 1) inhibit the thrombomodulin activities, which will decrease the activation of activated protein C, 2) decrease the fibrinolytic protease activity, and 3) cause a direct injury to the endothelial cells. The cytokines can also activate PAI-1 that will disrupt the fibrinolytic process. A combination of these complex processes will result in increased formation of thrombin through activation of P-selectin and PAF<sup>1</sup> Same with every physiological hemostatic process, coagulation cascade will induce the activation of t-PA, triggering a fibrinolysis process which will produce FDPs. These FDPs have a negative feedback to the platelet activation, making the body into a bleeding state. Moreover, increased consumption of platelets and coagulation factors are contributed to the bleeding symptoms<sup>6</sup>

**Types**

In accordance with its pathogenesis, DIC can occur due to the result of the two vectors, namely hyper-coagulation and hyper-fibrinolytic state<sup>4</sup> (Figure 2)

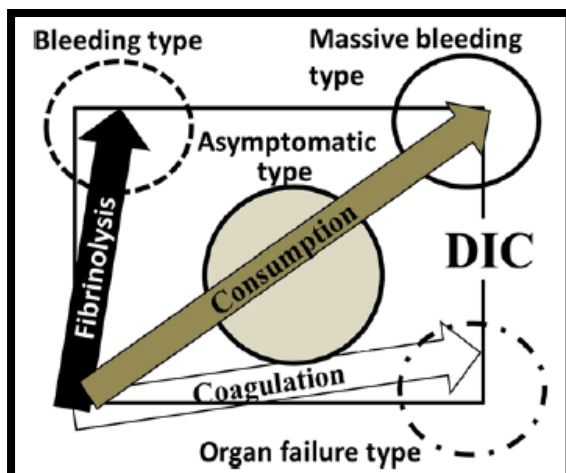


Figure 2. Bleeding, Organ failure, Massive Bleeding, and Non-symptomatic type of DIC.<sup>4</sup>

In the state of hyper-fibrinolytic dominant, bleeding is the main symptom; this type is known as a bleeding type (BL) or hyper-fibrinolysis predominance type of DIC. This type is often found in patients with leukemia such as APL, complications of pregnancy, or aortic aneurysm. In other circumstances, when a hypercoagulable state vector is more dominant, organ failure is the main symptom; type known as organ failure (OF) or hyper-coagulation predominance hypo-fibrinolysis type or type of DIC. This type is often found in patients with severe infection or sepsis<sup>6</sup> Increased cytokines and lipopolysaccharide resulted in increased activation of PAI-1 in intravascular, which will lead to hypofibrinolysis<sup>4,6</sup> If both vectors occur simultaneously, massive hemorrhage can occur, and may lead to death if transfusion is not given immediately; this type is referred to as massive bleeding (MB) or consumptive type of DIC.

This type is observed in patients with massive bleeding after surgical procedures or obstetric complications. Finally, when the both vectors are weak, there will be no clinical symptoms, although some abnormalities appear in laboratory results; This type is referred to as non-symptomatic DIC (NS) or pre-DIC. This classification is done to facilitate the diagnosis and management of the four types. It is important to remember that the state of DIC may shift and change. Observation needs to be done daily<sup>5,6</sup> We should also know that DIC with solid tumors cannot be classified into these four types, hence it should be observed separately<sup>6</sup>

**Clinical Symptoms**

Two distinct features that can happen simultaneously makes clinical symptoms of DIC varies, based on its underlying diseases. If the clinical state is more likely to hyper-coagulation or hypo-fibrinolytic state, then the ischemic symptoms (OF) will be dominant.

Conversely, if the clinical state is more likely to hypo-coagulation or hypo-fibrinolytic state, then the bleeding symptoms (BL) will be dominant<sup>4,7</sup> (Table 2)

Table 2. Ischemic and bleeding presentations of DIC based by organs.<sup>8</sup>

Organ	Bleeding	Ischemic
Skin	Petechie, ecchymosis, oozing	Purpura. Fulminan Gangrene Acral cyanosis
CNS	Intracranial bleeding	Delirium/Coma Infarcts
Renal	Hematuria	Oliguria/Azotemia Cortical necrosis
Cardiovascular		Myocardial dysfunction
Pulmonary	Hemorrhagic lung	Dyspnea/Hypoxia Infarct
GI/Endocrine	Massive hemorrhage	Ulcers, infarcts, renal infarcts

### Diagnosis

The syndrome of DIC is a multifactorial and always a complication of an underlying disease. Thus, it is important to assess the whole clinical picture, evaluation between the clinical condition of the patient and the laboratory results. It is also important to remember that the state of DIC is an extremely dynamic situation, hence a daily evaluation and observation should be done. The diagnosis cannot be made with one laboratory test as each of them has low specificity to DIC. Some of the laboratory results that can be considered are platelet counts, FDPs, fibrinogen, and PT-aPTT<sup>5</sup>

### Platelet Count

Moderate-to-severe thrombocytopenia (platelet count  $<100 \times 10^9/l$ ) is observed in most DIC patients, while severe thrombocytopenia (platelet count  $<50 \times 10^9/l$ ) is seen in 10-15% of DIC. These low platelet counts result is associated with increased risk of bleeding complications. Patients with severe thrombocytopenia have a five times higher risk of bleeding than patients with a normal platelet count<sup>9</sup> Keep in mind that a stable platelet count is a sign of no thrombin production. Low platelet count is sensitive markers for DIC, but not specific. Several conditions can lead to thrombocytopenia without DIC, such as acute leukemia, or sepsis<sup>5,9</sup>

### FDPs and D-dimer

Increased fibrinolysis activity caused by elevated thrombin production, will lead to an increase in FDPs. However, it is necessary to remember that many conditions can cause an increase in FDPs and D-dimer, which are trauma, surgical history, venous thromboembolism. Because these fragments are metabolized in the liver and excreted by kidneys, disturbance to both organs will lead to increased FDPs and D-dimer levels<sup>5,9</sup>

### Fibrinogen

Fibrinogen acts as an acute-phase reactant. Apart from the consumption of fibrin, plasma levels could remain at normal levels for a long time. Low fibrinogen levels only has a sensitivity 28% for diagnosing DIC. Hypofibrinogenemia is only detected in the case of heavy DIC. Its level may be normal in 57% of the DIC patient<sup>9</sup>

### PT and aPTT

Prolonged PT and aPTT is seen only in 50-60% of patients with DIC. It can also occurs in liver function disorders, vitamin K deficiency, and bleeding. Increased circulation of active complex coagulation factors can cause a shorten PT and aPTT<sup>5,9</sup> To facilitate the diagnosis of DIC, the Sub-Committee of the International Society on Thrombosis and hemostasis (ISTH) for DIC, together with the Scientific and Standardization Committee (SSC) to recommend the use of DIC scoring system for overt or acute.

#### 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:**

$\geq 5$  compatible with overt DIC: repeat score daily

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

Figure 3. Diagnostic scoring system ISTH for overt DIC.<sup>10</sup>

Overt DIC is a condition in which the endothelial cells and its components lose the ability to compensate, and is unable to restore hemostatic. Criteria ISTH introduces a 5-step diagnostic algorithm (Table 3) to calculate the scoring KID. The diagnosis of overt DIC is made when a cumulative score of 5 or more, in prolonged PT, thrombocytopenia, a decrease in the numbers of fibrinogen, and increased FDP or D-dimer<sup>9</sup>

Non overt DIC is a state where there is a disturbance to the endothelial, but the body is still able to compensate and so the clinical manifestation is not seen. The diagnosis of non-overt DIC use a different set diagnostic algorithm scoring system (Table 4)<sup>10</sup>

1. Risk assessment: does the patient have an underlying disorder known to be associated with DIC?  
yes = 2, no = 0

2. Major criteria

Platelet Count	>100x10 <sup>9</sup> L <sup>-1</sup> = 0	<100x10 <sup>9</sup> L <sup>-1</sup> = 1	Rising = -1 Stable = 0 Falling = 1
PT Prolongation	<3 s = 0	>3 s = 1	Falling = -1 Stable = 0 Rising = 1
Fibrin related-markers	Normal = 0	Raised = 1	Falling = -1 Stable = 0 Rising = 1

3. Specific criteria

Antithrombin	Normal = -1	Low = 1
Protein C	Normal = -1	Low = 1
-----	Normal = -1	Abnormal = 1

4. Calculate score:

Figure 4. Scoring system for non-overt DIC.<sup>10</sup>

**Management**

The core treatment of DIC focuses on treating the underlying diseases, such as administering antibiotics to patients with infections, anti-cancer drugs or surgical treatment in patients with malignancy<sup>9</sup>. DIC can improve spontaneously when the underlying disease is treated, although in some cases additional supportive treatment is needed to correct abnormalities in the coagulation system<sup>4</sup>

Based on its type, treatment for BL, OF and NS type of DIC focus on treating the underlying diseases, whereas MB type of DIC is started with blood transfusion<sup>4</sup>

**Blood Transfusion**

Patient with low platelet and coagulation factors increase the risk of bleeding. However, transfusion therapy should not be based on laboratory results alone. Evaluation on the whole picture is a must, for example, in patients

with active bleeding, or patient who will undergo invasive procedures, or in high risk of bleeding complication<sup>5</sup>. General administration of platelet transfusion in patients with bleeding presentation starts at  $\leq 50 \times 10^9/L$ , whereas patients with no bleeding presentation starts at  $10 - 20 \times 10^9 /L$ . Platelet transfusion is generally given to BL or MB type of DIC<sup>4</sup>. Initial dose given is 0.1-0.2 units/kg<sup>9</sup>

Fresh Frozen Plasma (FFP) administration can be given to patients with several indications, such as prolonged PT-aPTT > 1.5 times normal, or fibrinogen <1.5 g / dL, or in patients KID with active bleeding and prolonged PT-aPTT<sup>4</sup>. Initial doses recommended is 15 ml/kg, although there is some evidence suggest that 30 ml/kg dose given may produce more satisfying results<sup>5</sup>. Correction with FFP administration needs to be observed, as it may exacerbate the state of excess fluid.

In this circumstance, consider administration of factor concentrates such as prothrombin complex concentrates instead. However, because there is a massive deficiency of the whole coagulation factors in DIC, giving this factor concentrates can only correct a deficiency of coagulation factors partially<sup>4,5</sup>. In some cases of DIC, hypo-fibrinogenemia (fibrinogen <1 g / dL) may occur. The fibrinogen deficiency can be corrected by using cryoprecipitate transfusion. 3 g dose of plasma fibrinogen is expected to increase as much as 1 g/L. PRC administration in patients with active and/or massive bleeding can also be done, with a target Hb >8<sup>5</sup>

The response of transfusion therapy should be observed and evaluated periodically<sup>4,5,9</sup>

**Anticoagulant**

Administration of anticoagulant to decrease the hyper-coagulation is still on debate<sup>9</sup>. However, in cases of DIC where hypercoagulable state predominates (severe purpura fulminant associated with acral ischemia or vascular skin infarction, arterial or venous thromboembolism), therapeutic doses of heparin should be considered. The therapeutic dose is 15.000-20.000 U/12 day or 8000-10.000 U/8 hr. If the patient is in high risk bleeding, continuous infusion 10 U/kg/h of Unfractionated Heparin should be considered. Cases where the DIC patients are critically ill with no bleeding presentation, prophylaxis doses of heparin or low molecular weight heparin for venous thromboembolism is recommended<sup>4,5,9</sup>

### Anticoagulant Factor Concentrates

Anti-thrombin (AT) concentrate administration has shown an improvement in the results of laboratory tests, but does not have a significant reduction in mortality. Decreased concentration of protein C in the DIC state is one of the reasons of Activated Protein C (APC) administration. A large randomized controlled trial showed that APC administration can effectively reduce mortality and organ failure in severe sepsis with DIC. Mortality percentage by administration of APC in a DIC patients group is 24%, while the placebo administration is 30%. Though it is reported that bleeding is more common in the group of patients with APC administration<sup>5</sup> Initial dose can be administered by continuous infusion, 24 g/kg/day for 4 days. This therapy is not recommended in patients with a high risk of bleeding and/or with platelet count  $\leq 30 \times 10^9/l^{5,9}$

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### Anti-fibrinolytic

Anti-fibrinolytic administration is not recommended in patients with bleeding presentation. In DIC where the state of dominant hyper-fibrinolysis (as in AML-M3 or prostate cancer) is exceptional. The recommendation dose for anti-fibrinolytic administration is tranexamic acid 1 g/8hrs. KID exception for cases where the state hyper-fibrinolysis more dominant (as in AML-M3 or prostate cancer), recommended the granting anti-fibrinolytic tranexamic acid dose of 1 g / 8 hours<sup>5</sup>.

### Acknowledgement

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### Conflict of interest

None