Disseminated Intravascular Coagulation

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Background

**Definition**- Subcommittee on DIC of the International Society on Trombosis and Hemostasis

**DIC**- 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 small vessels, which if sufficiently severe, can produce organ dysfunction.


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**Background**

- **Consumption and exhaustion of coagulant proteins and platelets**, due to ongoing activation of the coagulation system, may induce severe bleeding complications.

- Derangement of the fibrinolytic system further contributes to intravascular clot formation.

- Accelerated fibrinolysis due to consumption of alpha 2-antiplasmin may cause severe bleeding.

- A patient with DIC can present with a simultaneously occurring thrombotic and bleeding problem, which complicates treatment.

Common clinical conditions associated with DIC

- **SIRS/sepsis/severe infection** (any microorganism)
- **Trauma** (polytrauma, neurotrauma especially in childhood, fat embolism, burns)
- **Organ destruction** (severe pancreatitis, severe hepatic failure)
- **Malignancy** (solid tumors, myeloproliferative and lymphoproliferative malignancies)
- **Obstetric events** (amnionic fluid embolism, abruptio placentae, dead fetus syndrome)
- **Vascular abnormalities** (large hemangioma or aortic aneurysm)
- **Severe toxic or immunologic reactions** (snake venom, drugs, amphetamines, severe allergic reaction, hemolytic transfusion reaction, transplant rejection)
Common clinical conditions associated with DIC
Pearls 2006

Two major pathways
- SIRS, cytokine network, activation of coagulation (infection)
- Release or exposure of procoagulant material in to the bloodstream (trauma)
- Both pathways (severe necrotizing pancreatitis)

**Infection:** any microorganism, G +ve; G -ve; viruses; rickettsiae; parasites

**Cell membrane components** (lipopolysaccharide or endotoxin) or exotoxin, proinflammatory cytokines: IL6, TNF, tissue factor, neutrophils secretory products

**Severe trauma:** release of tissue material such as fat and phospholipids, hemolysis, endothelial damage, proinflammatory cytokines; incidence of DIC-trauma+SIRS 50-70%

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Common clinical conditions associated with DIC
Pearls 2006

**Malignancy**: solid tumors cells can express different procoagulant molecules: tissue factor, a cystein protease with factor X-activating properties.

Some tumors are associated with a form of DIC with severe hyperfibrinolysis (acute promyelocytic leukemia, prostatic cancer); 10-15% of patients with metastatic tumor have DIC.

**Obstetric**: amniotic fluid is able to activate coagulation in vitro; 50% of patients with this conditions have DIC.

Degree of placental separation correlates with the extent of DIC suggesting that leakage of tromboplastin like material from placenta is responsible for DIC.

Common clinical conditions associated with DIC

Pearls 2006

Vascular disorders: may result in local activation of coagulation

Activated coagulation factors can overflow to the systemic circulation and cause DIC

Systemic depletion of coagulation factors and platelets as a result of local consumption

25% of patients with giant hemangiomas have DIC

0.5-1% of patients with large aortic aneurysms

Common clinical conditions associated with DIC

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**Frequency:** no age or gender predilection is known
DIC may occur in 30-50% of patients with sepsis

**Mortality:** depend on underlying disease and is directly related to the severity of coagulopathy
Idiopathic purpura fulminans + DIC mortality rate 18%
Septic abortion with clostridial infection and shock + DIC mortality rate 50%

**Major trauma + DIC and severe sepsis + DIC** approximately double the mortality rate


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Pathophysiology of DIC

Tissue factor + factor VIIa

Factor IXa (+ factor VIII) → Factor Xa (+ factor V)

Factor IIa (thrombin)

Fibrinogen → Fibrin

Generation of thrombin mediated by tissue factor

Cytokines

Low levels of antithrombin III
Impaired function of protein-C system
Insufficient TFPI

Factor IIa (thrombin)

Formation of fibrin

Inadequate removal of fibrin

Thrombosis of small and midsize vessels

Impairment of anticoagulation pathways

Suppression of fibrinolysis by PAI-1

Plasminogen activators

Plasminogen

PAI-1

Plasmin

Fibrin → FDPs


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Pathophysiology of DIC
Generation of thrombin mediated by tissue factor

Tissue factor mediated thrombin generation is detectable 3-5 hours after the occurrence of bacteremia or endotoxemia.

Tissue factor + factor VII system; whereas the intrinsic pathway of coagulation does not play important role.

Source of the tissue factor?

May be expressed on mononuclear cells in vitro, circulating monocytes of patients with severe infection, endothelial cells in vitro, endothelial cells in vivo?

Polymorphonuclear cells? “Blood born” tissue factor may be transferred between cells through microparticles derived from activated mononuclear cells.
Pathophysiology of DIC

Impairment of anticoagulation pathways

- Plasma levels of AT III are usually markedly reduced in DIC
- It may be combination of consumption, degradation by elastase released from activated neutrophils, and impaired synthesis
- Depression of the protein C system may occur
- Downregulation of thrombomodulin expression on endothelial cells by proinflammatory cytokines (TNF-α and IL-1β) results in diminished protein C activation
- Tissue factor pathway inhibitor TFPI-pharmacologic doses of rTFPI block inflammation-induced thrombin generation in humans
- Endogenous concentration?

Pathophysiology of DIC

Suppression of fibrinolysis by PAI-1

Bacteremia and endotoxemia result in increase in fibrinolytic activity due to the release of plasminogen activators from endothelial cells.

The process is immediately followed by suppression of fibrinolytic activity due to increase in plasma levels of plasminogen activator inhibitor type 1 (PAI-1).

Anti-tissue factor antibodies and recombinant hirudin, that are able to block endotoxin-induced thrombin generation, are without any effect on activation and inhibition of fibrinolysis.

An independent regulation of these two processes.

Severe hyperfibrinolytic state in AML M-3 and prostatic cancer result with severe bleeding.

Physical findings

DIC occurs in acute and subacute or chronic forms

Acute DIC: signs of underlying etiology + petechiae on soft palate and legs from thrombocytopenia and ecchymosis at the venipuncture sites and traumatized areas

Subacute or chronic DIC: signs of underlying etiology + signs of venous thromboembolism from excess thrombin formation

Physical findings
Physical findings

- Symptoms and signs suggestive of DIC
- Bleeding from at least 3 unrelated sites
- Microvascular deposition of fibrin with signs of organ dysfunction and/or failure or acral cyanosis, hemorrhagic skin infarcts, or limb ischemia
- Thrombosis in large vessels

Diagnosis of DIC

Underlying disease, physical findings and laboratory test.

No single available laboratory test is sufficiently sensitive or specific for diagnosis of DIC.

**Specialized tests:** soluble fibrin in plasma has 90-100% sensitivity for diagnosis of DIC, specificity is low.

Prothrombin activation fragment F 1+2 (F1+2), marker that is released upon the conversion of a coagulation factor zymogen to an active protease; low specificity.

**Routine test:** platelet count, aPTT, PT, antithrombin III, fibrinogen, fibrin degradation products (FDPs) or D-dimer.

It should be emphasized that serial measurements and trends with reduction on platelets count and clear downward trend in coagulation tests are more helpful in establishing the diagnosis of DIC.

Diagnosis of DIC

Measurement of fibrinogen has been widely advocated for the diagnosis of DIC, but it is not helpful.

As an acute-phase reactant, despite ongoing consumption, plasma levels remain normal or high for a long time.

Test sensitivity is about 28%.

Tests for FDPs or D-dimer may be helpful to differentiate from other conditions associated with low platelets count and prolonged PT.

Elevated in inflammation and recent surgery.

Cross-react with fibrinogen degradation products which may cause high results.

5 steps DIC risk assessment

1. Does the patient have any underlying disorder known to be associated with DIC
   if YES if NO STOP

2. Check coagulation tests:
   Platelet count PV Fibrinogen FDPs

3. Score global coagulation test results:
   \[ \begin{array}{cccccc}
   P > 100 & 0 & P < 100 & 1 & P < 50 & 2 \\
   FDPs \leq 0 & 0 & FDPs \uparrow & 2 & FDPs \uparrow\uparrow \uparrow & 3 \\
   PT < 3s & 0 & PT 3-6s & 1 & PT > 6s & 2 \\
   FIB > 1g/L & 0 & FIB < 1g/L & 1 \\
   \end{array} \]

4. Calculate score

5. $\geq 5$ Compatible with overt DIC $< 5$ repeat after 1-2 day
5 steps DIC risk assessment

- Sensitivity of the DIC score for diagnosis of DIC is 91%, and the specificity 97%
- DIC scoring system is a strong independent predictor of a fatal outcome in ICU patients
- Patients with sepsis+DIC, according to 5 steps scoring system have mortality of more than 40% compared with about 25% in patients with sepsis alone
- For each DIC point in the system, the odds ratio for mortality is 1.29
- For each APACHE II point the odds ratio for mortality is 1.07

Differential diagnosis of DIC

- **Microangiopathic hemolytic anemias:**
  - TTP (thrombocytopenic thrombotic purpura)
  - Hemolytic-uremic syndrome
  - Chemotherapy induced microangiopathic hemolytic anemia
  - Malignant hypertension
  - **HELLP syndrome** (hemolysis, elevated liver-enzyme levels, low platelet count in association with preeclampsia).

A cardinal sign is the presence of fragmented red cells schistocytes in the blood smear.

Schistocytes are present in patients with severe form of DIC because of the presence of intravascular fibrin.

Treatment of DIC

- Treatment of DIC is controversial
- The first step is to treat the underlying disease
- The goals of pharmacotherapy are to reduce morbidity and to prevent complications

DIC treatment strategies are:
- Platelet and plasma (component) transfusion
- Anticoagulant therapy
- Restoration of anticoagulant pathways

Treatment of DIC

Platelet and plasma (component) transfusion

- Fresh frozen plasma (15-20 ml/kgBW) and/or platelet substitution (1-2 units/kgBW)
- Therapy is indicated in patients with DIC and active bleeding, at risk for bleeding complications or requiring an invasive procedure
- The statement that this can be “fuel to the fire” has never been proven in clinical or experimental studies
- The presumed efficacy of this treatment appears to be rational, but never proven in randomized controlled trial

Treatment of DIC

Platelet and plasma (component) transfusion

- Prothrombin complex concentrate
  (lack of factor V, and has small traces of activated factors)
- Specific deficiency in fibrinogen can be corrected with purified factor concentrates (2-3 g total dose)
- Vitamin K is indicated in case of vitamin K deficiency
- The threshold for platelet transfusion is 50 for patients with bleeding and 10-20 for those without bleeding; 1-2 units/kgBW
Treatment of DIC

Anticoagulant therapy

- Experimental studies have shown that heparin can at least partly inhibit the activation of coagulation in sepsis.
- Uncontrolled case series in patients with DIC have claimed to be successful.
- A beneficial effect of heparin on clinically important outcome in patients with DIC has never been demonstrated in controlled trials.

- The safety of heparin in bleeding patients with DIC is controversial; 5-10 units/kgBW/per hour.
- Therapeutic doses of heparin are indicated in patients with clinically overt thromboembolism or extensive fibrin deposition (purpura fulminans or acral ischemia).
Treatment of DIC

Anticoagulant therapy

Patients with DIC may benefit from heparin prophylaxis to prevent thromboembolism, no trials; doses???

Low molecular weight heparins are increasingly used, it is advisable to check anti-factor Xa levels in critically ill with serious renal failure.

The most logical anticoagulant agent to use in DIC is directed against tissue factor activity.
Treatment of DIC

Restoration of anticoagulant pathways

Recombinant human activated protein C has beneficial effect on mortality, organ failure, coagulation and inflammation compared with placebo group in sepsis studies.

Patients with DIC have the highest benefit of activated protein C treatment which was equally effective in patients with a protein C deficiency as well as ones who had normal protein C.

A large-scale multicenter randomized controlled trial showed no significant reduction in mortality of septic patients who were treated with antithrombin concentrate.

Treatment of DIC
Other/new agents

- Recombinant factor VII activated (rFVIIa) 60-120 microg/kgBW
- Antifibrinolitic agents: Epsilon-aminocapronic acid and tranexamic acid 10-15 mg/kgBW/per hour
- Danaparoid sodium, a low molecular weight heparinoid
- Recombinant hirudin
- Recombinant tissue factor pathway inhibitor TFPI
- Recombinant nematode anticoagulant protein c2 (Napc2) specific inhibitor of ternary complex between tissue factor/factor VIIa and factor Xa
- Anti-tissue factor/factor VII antibodies

**Conclusion**

DIC is a syndrome characterized by systemic intravascular activation of coagulation leading to bleeding and thrombosis.

The diagnosis of DIC is made by combination of routinely available laboratory test using a validated diagnostic algorithm.

The mechanism involved in pathological microvasculature deposition in DIC have become progressively clear, resulting in novel preventive and therapeutic approaches to patients with DIC.