Disseminated Intravascular Coagulation (DIC)

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Disclosures for

In compliance with COI policy, ISTH requires the following disclosures to the session audience:

<table>
<thead>
<tr>
<th>Category</th>
<th>Disclosures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Support/P.I.</td>
<td>No relevant conflicts of interest to declare</td>
</tr>
<tr>
<td>Employee</td>
<td>No relevant conflicts of interest to declare</td>
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<td>Consultant</td>
<td>No relevant conflicts of interest to declare</td>
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<td>Major Stockholder</td>
<td>No relevant conflicts of interest to declare</td>
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<td>Speakers Bureau</td>
<td>No relevant conflicts of interest to declare</td>
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<td>Honoraria</td>
<td>No relevant conflicts of interest to declare</td>
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<tr>
<td>Scientific Advisory Board</td>
<td>No relevant conflicts of interest to declare</td>
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</table>
Definition

- DIC is an acquired syndrome characterized by the **intravascular activation of coagulation** without a specific localization and arising from different causes. It can originate from and cause damage to the **microvasculature**, which if sufficiently severe, can produce **organ dysfunction**.

Figure 5. The patient counts and mortality rates according to the categories of the original and simplified versions of Japanese Society on Thrombosis and Hemostasis (JSTH) disseminated intravascular coagulation (DIC) diagnostic criteria. The bar graph shows the number of patients in each category, and the line graph represents the mortality rate. The mortality rate increased linearly for scores of 3 to 7 and exceeded 30% based on the simplified JSTH-DIC score of 4.

Published in: Toshiaki Iba; Marcello Di Nisio; Jecko Thachil; Hideo Wada; Hidesaku Asakura; Koichi Sato; Daizoh Saitoh; Clin Appl Thromb Hemost Ahead of Print DOI: 10.1177/1076029617720069 Copyright © 2017 SAGE Publications
### Clinical conditions most frequently complicated by DIC

<table>
<thead>
<tr>
<th>Sepsis / severe infection</th>
<th>Severe allergic / toxic reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma / Burn / Heat stroke</td>
<td>Severe immunologic reactions e.g., transfusion reaction</td>
</tr>
<tr>
<td><strong>Malignancy:</strong> Solid tumors,</td>
<td><strong>Obstetric conditions:</strong></td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>Amniotic fluid embolism</td>
</tr>
<tr>
<td><strong>Vascular abnormalities:</strong></td>
<td>Abruptio placentae</td>
</tr>
<tr>
<td>Kasabach-Merritt Syndrome</td>
<td>HELLP syndrome</td>
</tr>
<tr>
<td>Other vascular malformations</td>
<td>Retained dead fetus</td>
</tr>
<tr>
<td>Aortic aneurysms</td>
<td></td>
</tr>
</tbody>
</table>
Bacteria, Cancer, Trauma, Burns, Placenta

Monocyte

P-selectin

PLT

NFκB

TF

(IL)-1b, IL-8, MCP-1, TNF-α, IL-1, IL-6, Adhesion protein

TFPI, APC, Antithrombin

Multiorgan ischemia, e.g. ATN, Acute lung injury

Microvascular thrombi

Coagulopathy, Thrombocytopenia

Fibrinolysis: tPA, uPA, PAI-1

Bleeding

Coagulopathy, Thrombocytopenia

Bleeding
Clinical Manifestations of DIC

Vary depending on Underlying disorder

<table>
<thead>
<tr>
<th>Acute severe DIC</th>
<th>Chronic DIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sepsis, major trauma, Obstetric, severe immunologic response</td>
<td>• Malignancy, retained dead fetus, aneurysm</td>
</tr>
<tr>
<td>• Diffuse multiorgan bleeding, hemorrhagic necrosis, thrombi in small to medium/large blood vessels</td>
<td>• Mucin-producing AdenoCA – venous thrombosis, NBTE  →  arterial embolism</td>
</tr>
<tr>
<td></td>
<td>• APL - bleeding</td>
</tr>
</tbody>
</table>
DIC in Infectious Disease

- Risk: immunocompromised, asplenia, newborns, (major trauma/active malignancy)
- Gram-negative bacteria e.g. *P. aeruginosa*, *E. coli*, *Proteus vulgaris*, Meningococcemia
- Gram-positive bacteria e.g. *Streptococcus* A toxic shock syndrome
- Others: virus (e.g. Dengue), malaria, fungi
- Vary from Lab abnormalities ➔ severe DIC ➔ Purpura fulminans
DIC in Trauma, Brain injury, Burns, Heat Stroke

- **Time interval** between Trauma and medical intervention (e.g. evacuation, resuscitation) correlates with development and magnitude of DIC. ... Rx: ↓ TF exposure, prevent shock
- **Trauma**: early phase – hyperfibrinolysis; later phase – hypercoagulable from ↑ PAI-1
- **Head injury**: Lab DIC score predicts prognosis
- **Heat stroke**: endothelial cell damage, TF from heat-damaged tissues
DIC in Obstetric Complications

- **Abruptio placentae**: 10% has DIC; risk: older multiparous, hypertension in pregnancy
- **Amniotic fluid embolism**: maternal mortality 26%; Pulmonary a. occlusion ... anaphylactoid response/DIC ... shock, convulsion ... bleeding
DIC in Malignancy

- Risk: Tumor (mucin-producing, AL), Host (old age), Rx (chemo), Complication (sepsis)
- **TF** + FVIIa $\rightarrow$ IXa, Xa
- **Cancer procoagulant** (cysteine protease) $\rightarrow$ Xa
- P-,L-selectin interact with mucin $\rightarrow$ PLT thrombi
- APL (>90%) > AML (32%) > ALL (15-20%)
DIC in APL

- **Annexin II**
  - Binds plasminogen and tPA
  - \( \uparrow \) Plasmin

- **TF**
  - Activate coagulation
  - Release IL-1\(\beta\), TNF-\(\alpha\)
  - \( \downarrow \) Endothelial thrombomodulin
  - \( \downarrow \) Protein C anticoagulant

**HyperFibrinolysis**

**DIC**

**Bleeding**
DIC in Vascular Disorders

- **Aortic aneurysm** – TF in atherosclerotic plaque
  - 40% had ↑FDP, 4% had DIC
  - Risk of DIC: large, dissected, expand

- **Kasabach-Merritt**
  - giant cavernous hemangiomas ➔ consume PLT and fibrinogen; tPA released from abnormal endothelium in tumor walls ➔ hyperfibrinolysis
DIC with Liver Disease

• Severe liver disease ➞ lab as DIC
  – ↓Coagulation factors
  – ↓Natural anticoagulants
  – ↓Clearance of IXa, Xa, Xla, tPA
  – Thrombocytopenia from hypersplenism, ↓TPO
DIC accompanies Liver Disease?

**PRO**
- ↓ Half-life of radiolabeled fibrinogen (reversed with heparin)
- Failure of replacement Rx to significantly increase level of hemostatic factors
- ↑ Markers of activation of coagulation

**CON**
- Microthrombi are found in only 2% of tissues from patients who die of liver dis.
- ↑ Fibrinogen turnover is from extravascular accumulation
DIC with Liver Disease

Current thinking

• DIC is rare in liver disease
• Patients with liver disease are sensitive to triggers of DIC
  – ↓Synthetic capacity
  – Inability to clear activated clotting factors
Laboratory Findings in DIC

• Low PLT
  — <100 x 10⁹/L: 50%-60% in critically ill patients,
    >80% in surgical or trauma patients
  — <50x 10⁹/L: 10%-15% in critically ill patients

• Prolonged PT or aPTT: >95%

• Factor VIII – mostly elevated due to massive release of vWF from endothelium and as acute-phase protein
Laboratory Findings in DIC

Fibrinogen concentration

• Fib. is an acute-phase protein $\rightarrow$ ↑↑ with inflammation
• Thus, Fib. level may remain normal for a long time despite ongoing consumption
• Sensitivity of low Fib. for Dx of DIC was 28%
• Hypofibrinogenemia only found in severe DIC
Laboratory Findings in DIC

Markers of fibrin generation and degradation

- **D-dimer** – sensitive but not specific
- Fibrin(ogen) degradation product (**FDP**) – metabolized in liver and cleared by kidney
- **Soluble fibrin** or fibrin monomer – theoretically useful, but no reliable quantitative test
Laboratory Findings in DIC

Endogenous coagulation inhibitors

• Protein C, Antithrombin
  – Reduced levels in 90% of DIC patients
  – Predictor of poor outcome and mortality
Laboratory Findings in DIC

Fibrinolytic markers

• Increased fibrinolytic activity
  – Plasma plasminogen and α2-antiplasmin: low levels may indicate consumption
  – Plasmin-α2-antiplasmin (PAP) complexes: increased
  – PAI-1: often elevated and correlate with unfavorable outcome
Laboratory Findings in DIC

Point of care tests

• Thromboelastography (TEG), ROTEM
  – Use whole blood → global assessment of PLT function, coagulation, and fibrinolysis
  – Correlate with morbidity and mortality
  – May be overly sensitive to fibrinogen administration
## Diagnostic Algorithm for Dx of Overt DIC

1. Presence of disorder associated with DIC: Yes → proceed

2. Score global coagulation test results

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platelet count, ( \times 10^9 /L )</strong></td>
<td>&gt;100</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td></td>
</tr>
<tr>
<td><strong>D-dimer or FDPs</strong></td>
<td>( \leq ) Upper limit of normal</td>
<td>&gt; ULN but &lt; 5x ULN</td>
<td>&gt; 5x ULN</td>
<td></td>
</tr>
<tr>
<td><strong>Prolonged PT, sec</strong></td>
<td>&lt; 3 sec</td>
<td>&gt; 3 but &lt; 6 sec</td>
<td>&gt; 6 sec</td>
<td></td>
</tr>
<tr>
<td><strong>Fibrinogen level, mg/dL</strong></td>
<td>&gt; 100</td>
<td>&lt; 100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Calculate score: \( \geq 5 \) overt DIC, \(< 5 \) suggest non-overt DIC

## DIC Scoring Systems

<table>
<thead>
<tr>
<th>Underlying condition</th>
<th>ISTH</th>
<th>JMHW</th>
<th>JAAM</th>
<th>CDSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential</td>
<td>Essential</td>
<td>0-1 point</td>
<td>Essential</td>
<td>0 – 2 points</td>
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</table>

<table>
<thead>
<tr>
<th>Clinical symptom</th>
<th>ISTH</th>
<th>JMHW</th>
<th>JAAM</th>
<th>CDSS</th>
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</thead>
<tbody>
<tr>
<td>Bleed, organ failure</td>
<td>-</td>
<td>Bleed, organ failure</td>
<td>SIRS</td>
<td>Bleed, organ dysfunction, microcirculatory disorder</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>PLT</th>
<th>ISTH</th>
<th>JMHW</th>
<th>JAAM</th>
<th>CDSS</th>
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<tbody>
<tr>
<td>0 – 2</td>
<td>0 – 3</td>
<td>0 – 2</td>
<td>0 – 2</td>
<td>0 – 2</td>
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</table>

<table>
<thead>
<tr>
<th>FDP,D-dimer</th>
<th>ISTH</th>
<th>JMHW</th>
<th>JAAM</th>
<th>CDSS</th>
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<tbody>
<tr>
<td>0 – 3</td>
<td>0 – 3</td>
<td>0 – 3</td>
<td>0 – 3</td>
<td>0 – 3</td>
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</table>

<table>
<thead>
<tr>
<th>Fibrinogen</th>
<th>ISTH</th>
<th>JMHW</th>
<th>JAAM</th>
<th>CDSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 1</td>
<td>0 – 2</td>
<td>-</td>
<td>0 – 1</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>PT</th>
<th>ISTH</th>
<th>JMHW</th>
<th>JAAM</th>
<th>CDSS</th>
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</thead>
<tbody>
<tr>
<td>0 – 2</td>
<td>0 – 2</td>
<td>0 – 1</td>
<td>PT or APTT: 0 – 2</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Dx, points</th>
<th>ISTH</th>
<th>JMHW</th>
<th>JAAM</th>
<th>CDSS</th>
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<tbody>
<tr>
<td>≥5</td>
<td>≥7</td>
<td>≥4</td>
<td>≥6 or 7</td>
<td></td>
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</tbody>
</table>

JMHW, Japanese Ministry of Health and welfare; JAAM, Japanese Association for Acute Medicine; CDSS, Chinese DIC Scoring System
DIC Score

• **ISTH**: Sensitivity 93%, Specificity 98%
• Related to the **mortality** in patients with sepsis.
• **Japanese** scoring system
  – Slightly higher sensitivity, probably from different population (more hematologic malignancies)
  – Simplified JSTH-DIC for Sepsis: with Antithrombin activity in score – sens. 80%, spec. 34%
• **Pregnancy** modified ISTH score of Erez, Clark: need more study
Treatment of DIC

SPECIFIC

• Sepsis: antibiotics, pus drainage
• Cancer: surgery, chemotherapy
• Abruptio placentae: uterus evacuation
• Aortic aneurysm: resection
• Trauma: debridement of crushed tissue
Treatment of DIC

SUPPORTIVE

- **Transfusion** if bleeding, requiring invasive procedure, at risk for bleeding
Treatment of DIC

**SUPPORTIVE**

- Transfusion
- **Heparin**: purpura fulminans, before surgery in chronic DIC (e.g. Aortic aneurysm), digital gangrene, failure of intensive transfusion to improve excessive bleeding
Treatment of DIC

SUPPORTIVE

• Transfusion
• Heparin
• Tranexamic acid in selected cases with refractory bleeding from primary hyperfibrinolysis e.g. metastatic CA prostate, APL, giant cavernous hemangioma, heat stroke, acute coagulopathy of trauma, massive postpartum hemorrhage
Types of DIC

Fibrinolysis

Bleeding
- APL, metastatic CA prostate, AAA, Early trauma

Asymptomatic

Massive Bleed/Consumptive
- Postpartum, etc.

Organ failure
- Sepsis CA pancreas

Microthrombi

Criteria for Dx of DIC with Enhanced Fibrinolysis

1. Prerequisite: TAT > 20 ug/L and PIC > 10 ug/L

2. Lab findings – at least 2 of followings:
   1. FDP > 80 ug/mL
   2. Fibrinogen < 100 mg/dL
   3. Increased FDP/D-dimer ratio

3. Reference findings – more severe bleeding is likely with the following findings:
   1. Decreased platelet count (< 50,000/uL)
   2. Decreased α2PI activity (< 50%)

PIC, plasmin-α2 plasmin inhibitor complex