Disseminated Intravascular Coagulation (DIC)

ISTH Advanced Course
Cascais, Portugal
Sun 16 Mar 2014

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## Disclosures

<table>
<thead>
<tr>
<th>Organization</th>
<th>Description</th>
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<tbody>
<tr>
<td>GlaxoSmithKline</td>
<td>research funding</td>
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<tr>
<td>W. L. Gore</td>
<td>consulting, research funding</td>
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<tr>
<td>Taylor &amp; Francis</td>
<td>royalties</td>
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<tr>
<td>Instrumentation Laboratory</td>
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<td>Pfizer Canada</td>
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<td>Law firms</td>
<td>medical-legal testimony</td>
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- Specific therapeutic recommendations that are not FDA-labeled indications (**treatment of HIT with fondaparinux**)
HIGHLIGHTS

• MYTHS of DIC
  — Hypofibrinogenemia is a common feature of DIC (wrong)
  — DIC is characterized by simultaneous clotting and bleeding (usually one or the other predominates)
  — Some causes of DIC not listed in standard tables

• Describe how venous limb gangrene complicating HIT provides insight into the pathogenesis of ischemic limb necrosis (“symmetrical peripheral gangrene”) in DIC

• Potential for PTT confounding if therapeutic-dose heparin is given to treat/prevent thrombosis in DIC
Overview of DIC (or “Consumptive Thrombohemorrhagic Disorder”)

• A heterogeneous group of disorders that have in common increased consumption of coagulation factors and/or platelets.

• Like anemia, is not a “diagnosis,” but rather a clinicopathologic syndrome that begs the question, “what is the underlying diagnosis?”

• Wide spectrum of clinical consequences, ranging from nil to generalized bleeding to widespread microvascular thrombosis (predisposing to multi-organ dysfunction and acral thrombosis)

Pathologic Thrombin Generation

Tissue factor + Factor VIIa

Factor IXa (factor VIIIa)

Factor Xa (factor Va)

Factor XIII

Tissue Factor Pathway Inhibitor (TFPI)

Protein C System

Antithrombin (AT3)

Unchecked plasmin

Excess PAI-1

Impaired Natural Anticoagulant Mechanisms

Platelet activation

Platelet

Fibrinogen

fDP’s

Soluble fibrin

X-FDP’s (D-dimer)

THROMBOSIS

THROMBIN

α2-Antiplasmin (α2AP)

α2AP Depletion (unchecked plasmin)

Bleeding

Plasminogen activator

Plasminogen

Cross-linked (X) fibrin

FDP’s

β2AP

Depletion

Natural anticoagulant depletion

Warkentin (Ch. 22.6.5). Oxford Textbook of Medicine, 2010
Some Causes of DIC

- Infection/sepsis *
- Shock (e.g., cardiogenic)
- Obstetrical *
- Malignancy *
- Trauma *
- Hemolysis *
- Envenomations *
- Hepatic failure *
- Organ destruction *(e.g., pancreatitis)*
- HIT
- ARDS/SIRS
- Pulmonary embolism
- Intracardiac thrombosis
- Vascular abnormalities *
- Transplant rejection *
- Recreational drugs *
- Purpura fulminans
- PCC’s

Clinical Relevance of DIC......

...... is quite variable among patients

Often, lab evidence for **low-grade DIC**, e.g., ICU patients with multi-organ system failure, septicemia, etc., with low platelets, elevated D-dimer, but normal INR/APTT/fibrinogen:

Hemostatic intervention is **not** usually needed.

DIC is ‘**clinically-important**’ when it causes **bleeding** and/or **thrombosis**
Routine Laboratory Investigation

1. CBC, blood film (RBC fragments, nucleated RBCs)

2. INR, APTT

3. Fibrinogen, thrombin clotting time

4. Fibrin-related marker: e.g., fibrin D-dimer, fibrin monomer, fibrin split products
TESTS for DIC

Highest Sensitivity for DIC

D-dimer
FDP
Platelet count
INR
aPTT
Fibrinogen

Lowest Sensitivity for DIC
ISTH Criteria for DIC (2001)

- Does patient have disorder associated with overt DIC? (if yes, proceed; if no, do not use this algorithm)
- **Order**: Plt, PT, Fgn, Fbn marker (Fbn monomer, FDP’s, D-dimer)
- **Score**:
  - Platelet count: >100=0, 50-100=1, <50=2
  - ↑Fbn marker: none=0, moderate=2, strong=3
  - ↑PT: <3 sec=0, 3-6 sec=1, >6 sec=2
  - Fgn: >100 mg/dl=0, <100 mg/dl=1
- **Interpret**:
  - If ≥5: compatible with overt DIC
  - If <5: suggestive (not affirmative) for non-overt DIC (repeat next 1-2 d)

64 y.o. F
NIDDM
*Klebsiella urosepsis*

DIC?
- Platelet (Plt) 40
- INR 1.8
- PT 16 s
- APTT 42
- Fibrinogen (Fibr) 8.0 g/L (800 mg/dL)
- D-dimer >5000

Days after Starting Heparin
- Right femoral vein line
- UFH flushes

Day 0
**Scoring System for Overt Disseminated Intravascular Coagulation (DIC)**

1. **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

2. **Order global coagulation tests**
   - Platelet count: 150-450
   - D-dimer: < 551
   - Prothrombin time: 9.4-11.6 sec
   - Fibrinogen: 170-330

3. **Score global coagulation test results:**
   - **Platelet count:**
     - >100 = 0
     - <100 = 1
     - <50 = 2
   - **Elevated Fibrin related markers** (Fibrin split products & D-dimer):
     - no increase = 0
     - moderate increase = 2
     - strong increase = 3
   - **Prothrombin time:**
     - <3 sec = 0
     - >3 but <6 sec = 1
     - >6 sec = 2
   - **Fibrinogen level:**
     - >100 mg/dL = 0
     - <100 mg/dL = 1

4. **Calculate score:**
   - If ≥ 5: Compatible with overt DIC
   - If < 5: Suggestive (not affirmative) for non-overt DIC

**Tests for DIC ordered**

<table>
<thead>
<tr>
<th>Normal</th>
<th>Pt “X”</th>
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<tbody>
<tr>
<td>Platelet count: 150-450</td>
<td>40</td>
</tr>
<tr>
<td>D-dimer: &lt; 551</td>
<td>&gt; 5000</td>
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<td>Prothrombin time: 9.4-11.6 sec</td>
<td>16 sec</td>
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**Diagnosis = “DIC”**

TOTAL [Maximum, 8 points] 6
64 y.o. F
NIDDM
*Klebsiella urosepsis*

**DAY 4: PHLEGMASIA CERULEA DOLENS**
R femoral/popliteal DVT

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Days after Starting Heparin

UFH flushes

R femoral vein line

Platelet Count (x10^9/L)
Fibrinogen Values in DIC

Per ISTH DIC criteria:
Median (25%ile-75%ile) = 203 (115 – 334 mg/dL)

Per JMHW criteria:
Median (25%ile-75%ile) = 191 (120 – 345 mg/dL)

Per JAAM criteria:
Median (25%ile-75%ile) = 254 (150 – 365 mg/dL)

Levi & ten Cate (Blood Rev 2002) = “the sensitivity of a low fibrinogen level for the diagnosis of DIC was only 28%”
DAY 4: PHLEGMASIA CERULEA DOLENS
R femoral/popliteal DVT

Klebsiella urosepsis

DIC:

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- UFH flushes
- FFP
- Therapeutic-dose UFH

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Phlegmasia Resolved
64 y.o. F
NIDDM
*Klebsiella urosepsis*

**DAY 4: PHLEGMASIA CERULEA DOLENS**
R femoral/popliteal DVT

**DIC:**
- Plt: 40
- INR: 1.8
- PT: 16 s
- APTT: 42
- Fibr: 8.0
- D-dimer: >5000

**DIC:**
- Plt: 23
- INR: 1.3
- PT: 12 s
- APTT: 30
- Fibr: 4.9
- D-dimer: >5000

Phlegmasia Resolved

Acquired Natural Anticoagulant Failure

AT3: 0.68 (0.77-1.30)
Prot C: 0.38 (0.65-1.80)

DIC:
- Plt: 40
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*UFH flushes*

**R femoral vein line**

**0 1 2 3 4 5 6 7 8 9**

**Days after Starting Heparin**

**Therapeutic-dose UFH**

**FFP**
64 y.o. F
NIDDM
*Klebsiella* urosepsis

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Acquired Natural Anticoagulant Failure

Phlegmasia Resolved

UFH flushes

Therapeutic-dose UFH

FFP

Days after Starting Heparin:
0 1 2 3 4 5 6 7 8 9

Platelet Count (x10^9/L):
0 50 100 150 200

R femoral vein line

DIC:
- Platelet (Plt)
- INR
- PT
- APTT
- Fibrinogen (Fibr)
- D-dimer
“Symmetric peripheral gangrene” – pulses present!
DIC & Ischemic Limb Loss

- Disseminated intra-vascular coagulation (DIC)
- Hypotension
- Vasopressor use
- Multi-organ failure

QUESTION:
Why do only some ICU patients with shock & DIC develop ischemic limb loss?
Natural Anticoagulant Failure in Setting of DIC (↑IIa Generation)
Ischemic Limb Necrosis and Amputations in HIT
Amputation Frequencies in HIT

- Fonaparinux 3/60 = 5%
- Danaparoid 9/182 = 5%
- Lepirudin 12/214 = 6%
- Warfarin 8/66 = 12%
- Argatroban 51/373 = 14%

Limb Artery Thrombosis in HIT

“White clot syndrome”

Limb artery thrombosis

Acral necrosis

Warkentin  *J Crit Illn* 2002
54 y.o. M
Coronary artery bypass surgery
Pulmonary embolism
Symptomatic left proximal DVT
Left foot gangrene when INR = 4.5

Pulses palpable !!!

Platelet Count (x 10^9/L)

Days after Starting Heparin

UFH
Warfarin
Limb Loss from Venous Limb Gangrene

HIT-associated deep-vein thrombosis (DVT)

Elevated INR (> 4.0) secondary to warfarin

Surrogate marker for very low Protein C levels

Venous Limb Gangrene: Role of DVT

HIT-associated DVT helps to localize microthrombosis to same limb as DVT!

? Venous stasis

? Contiguous spread of thrombosis

How could warfarin therapy *cause* microthrombosis and hence limb gangrene with pulses?
Clot fibrinogen
Activate platelets

HIT DIC

Thrombin IIa
VIIIa

Antithrombin (AT)

Thrombin-antithrombin Complex (TAT)
Vitamin K-dependent Hemostatic Factors [$t_{\frac{1}{2}}$]

- **PROCOAGULANT**
  - Prothrombin (factor II) [60 hr]
    - Factor X [40 hr]
    - Factor IX [24 hr]
    - Factor VII [6 hr]

- **ANTICOAGULANT**
  - Protein C [9 hr]
    - Protein S [60 hr]
HIT-Associated Venous Limb Gangrene

palpable pulses

X X X

Hemostatic Profile in Venous Limb Gangrene

- Platelet Count ($x10^{-9}$/L)
- Thrombin-antithrombin complexes, TAT (ng/mL)
- Prothrombin activity (U/mL)
- Protein C activity (U/mL)

↑ TAT = more thrombin generation

↓ Protein C = more warfarin effect

TAT vs Protein C

HIT and Coumarin Necrosis

Thrombin-antithrombin (TAT) complexes (ng/mL)

Colored symbols: venous limb gangrene/skin necrosis patients
White circles: control patients

Profound Disturbance in Procoagulant-Anticoagulant Balance

HIT + Warfarin → ↓PC
Warfarin-induced Venous Limb Gangrene
(HIT $\rightarrow$ ↑↑ Thrombin; Warfarin $\rightarrow$ ↓↓ Protein C)

palpable pulses

Warfarin fails/worsens because:
1. Does not block IIa generation
2. Causes protein C depletion
3. Raises PTT (confounds PTT-adjusted anticoagulant therapy)
What is PTT Confounding?

“Situation where an underlying patient-related clinical factor (or factors) results in anticoagulant-induced changes in PTT values that are misleading with respect to indicating a patient’s true level of anticoagulation”

Anticoagulant failure in coagulopathic patients: PTT confounding and other pitfalls

Theodore E. Warkentin
Department of Pathology and Molecular Medicine, McMaster University and Hamilton Regional Laboratory Medicine Program, Hamilton Health Sciences (Hamilton General Site), Hamilton, Ontario, Canada

Introduction: Devastating thromboses can complicate heparin-induced thrombocytopenia (HIT) and disseminated intravascular coagulation (DIC). In these disorders, acquired abnormalities of the partial thromboplastin time (PTT) and international normalized ratio (INR) can confound monitoring of PTT- and INR-adjusted anticoagulant therapies, contributing to treatment failure.
Warfarin-associated Skin Necrosis
INR = 3.6

Vitamin K 10mg i.v.

PTT = 41 sec

PTT = 72 sec

PTT normal range

Heparin started (PTT nomogram)

Heparin re-started 3000 U/h

Anti-Xa level = 0.80 U/ml (PTT = 72 sec)

Therapeutic anti-Xa range for UFH

Anti-Xa level = 0.10 U/ml (PTT = 72 sec)

Therapeutic PTT range for UFH

Irony: therapeutic !!

53-y.o. F with AdenoCA and Ischemic Foot (+Pulses) on Warfarin

"PTT Confounding"

Simple Rule:
If “baseline” (pre-treatment) PTT is ↑, PTT-based nomogram is unlikely to be successful ("PTT confounding")
Limb Gangrene/
Microthrombosis
2° to Disturbed
Procoagulant-
Anticoagulant Balance
Shock & Ischemic Limb Loss

Why do some ICU patients with shock & DIC develop ischemic limb loss?  **SHOCK LIVER**
Acute Hepatic Necrosis – Acute Limb Necrosis

A

300,000

200,000

100,000

0

Platelets (per μm³)

0 1 2 3 4 5 6

Platelets

Norepinephrine/dopamine

Heparin

Cardiac arrest post-heart catheterization

Emergency cardiac surgery

Continuous renal replacement therapy

Platelet transfusions

Ischemic limb necrosis

Death

3-day gap

Admission for acute myocardial infarction

Acute ischemic hepatitis
(“shock liver”)

ALT = 2468 (peak)

AST = 3593 (peak)

### Figure A

- Admission for acute myocardial infarction
- Cardiac arrest post-heart catheterization
- Emergency cardiac surgery
- Continuous renal replacement therapy
- Platelet transfusions
- Ischemic limb necrosis

### Figure B

- Heparin
- Procoagulant markers:
- Anticoagulant markers:

Acute Hepatic Necrosis – Acute Limb Necrosis

*Disturbed Procoagulant – Anticoagulant Balance*

We found a highly significant positive association ($r^2 = 0.62; P = 0.001$), indicating that differing factor half-lives could help to explain the observed profile of reduced coagulation factors, particularly the very low levels of protein C activity. **We postulate** that a disturbance of procoagulant–anticoagulant balance — arising from the combination of greatly increased thrombin generation (DIC) with impaired hepatic synthesis of key natural anticoagulant factors (protein C, antithrombin) — can explain ischemic limb necrosis (with pulses) in patients with acute hepatic necrosis.

Profound Disturbance in Procoagulant-Anticoagulant Balance

DIC + Shock liver → ↓PC
Limb Loss in ICU patients: HIT vs DIC

• HIT-related limb loss
  — Venous limb gangrene (DVT; gangrene with pulses)
    • Often related to warfarin therapy (onset ~3d after warfarin)
  — Arterial thrombosis

• DIC-related limb loss
  — Microvascular (gangrene with pulses)
  — Hypotension/vasopressors
  — Multi-organ failure (respiratory, renal, hepatic....)
    • Onset 3d after shock liver
  — Causes of DIC→ cardiogenic shock, septic shock, etc.

Warkentin TE. *Exp Opin Drug Saf* 2014
Wada et al. Guidance for Dx & Rx of DIC: harmonization of 3 guidelines


Quality of Evidence: Definitions

- **HIGH**: Further research unlikely to change confidence in the estimate of the effect
- **MODERATE**: Further research likely to have an important effect on confidence in the estimate of the effect, and may change the estimate
- **LOW**: Further research very likely to have an important effect on confidence in the estimate of the effect, and is likely to change the estimate

**Fbn marker:** 3↑↑; 2↑

**Diagnosis of DIC**

**Plt:** 2 <50; 1 50-100

**Recommendations:**

**PT:** 2 >6s↑; 1 3-6s ↑

There is no gold standard

**Fbg:** 1 <1.0

- Use of a DIC scoring system is recommended (*moderate*)
- DIC scoring system correlates with key clinical observations/outcomes (*moderate*)
- It is important to repeat lab tests to monitor dynamic changes (*moderate*)

DIC SSC (ISTH)→ Harmonization of (a) Br Cmte Standards Haematol; (b) Jap Soc Thromb Haemost; and (c) Italian Soc Thromb Haemost

**Treatment of DIC**

**Recommendation:**

The cornerstone of DIC treatment is the treatment of the underlying condition *(moderate)*

DIC SSC (ISTH) → Harmonization of (a) Br Cmte Standards Haematol; (b) Jap Soc Thromb Haemost; and (c) Italian Soc Thromb Haemost
Role of plts, FP, Fbg, and PCC

Recommendations:

• Plt tfn recommended in DIC pts with active bleeding and plt < 50; or pts with high bleeding risk and plt < 20 (low)

• FP may be useful in pts with active bleeding or who need invasive procedure with ↑PT/PTT (>1.5X N) or ↓Fbg (<1.5g/L) (low)

• Fbg concentrate or cryo may be recommended if active bleeding and persisting fbg < 1.5 g/L despite FP (low)

• PCC may be considered in bleeding pts if FP not possible
Role of Anticoagulants

Recommendations:

• Therapeutic-dose heparin should be considered where thrombosis predominates \( (low) \); LMHW is preferred over UFH \( (low) \)

• Prophylactic-dose heparin is recommended in critically-ill, non-bleeding patients with DIC \( (UFH-\text{moderate}; \text{LMWH-high}) \)

Anticoagulant factor concentrates

Recommendations:

• Further prospective evidence from RCTs confirming a benefit is required

• Administration of antithrombin, recombinant human TM (rhTM), or activated protein C (APC) may be considered in DIC patients
Antifibrinolytic treatment

**Recommendations:**

- Patients with DIC should generally not be treated with antifibrinolytic agents (*low*)
- DIC patients who present with bleeding and marked hyperfibrinolytic state such as leukemia (*low*) or trauma (*moderate*) could be treated with antifibrinolytic agents
HIGHLIGHTS

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  — DIC is characterized by simultaneous clotting and bleeding (usually one or the other predominates)
  — Some causes of DIC not listed in standard tables

• Describe how venous limb gangrene complicating HIT provides insight into the pathogenesis of ischemic limb necrosis (“symmetrical peripheral peripheral gangrene”) in DIC

• Potential for PTT confounding if therapeutic-dose heparin is given to treat/prevent thrombosis in DIC