Disseminated Intravascular Coagulation (DIC) and Thrombosis: The Critical Role of the Lab

Paul Riley, PhD, MBA, Diagnostica Stago, Inc.
Learning Objectives

- Describe the basic pathophysiology of DIC
- Demonstrate a diagnostic and management approach for DIC
- Compare markers of thrombin & plasmin generation in DIC, including D-Dimer, fibrin monomers (FM; aka soluble fibrin monomers, SFM), and fibrin degradation products (FDPs; aka fibrin split products, FSPs)
- Correlate DIC theory and testing to specific clinical cases
DIC = Death is Coming
What is Hemostasis?
Blood Circulation

- Occurs through blood vessels
- The heart pumps the blood
- Arteries carry oxygenated blood away from the heart under high pressure
- Veins carry de-oxygenated blood back to the heart under low pressure
Hemostasis

- The mechanism that maintains blood fluidity
- Keeps a balance between bleeding and clotting

2 major roles
- Stop bleeding by repairing holes in blood vessels
- Clean up the inside of blood vessels
- Removes temporary clot that stopped bleeding
- Sweeps off needless deposits that may cause blood flow blockages
Two Major Diseases Linked to Hemostatic Abnormalities

- **Bleeding** = Hemorrhage
- **Blood clot** = Thrombosis
Physiology of Hemostasis
Wound

PRIMARY HEMOSTASIS

break in vessel

strong clot

wound sealing → blood flow ± stopped

PLASMATIC COAGULATION

FIBRINOLYSIS

clot destruction

Sealing
The Three Steps of Hemostasis

❖ **Primary Hemostasis**
  - Interaction between vessel wall, platelets and adhesive proteins → platelet clot

❖ **Coagulation**
  - Consolidation of the platelet thrombus → insoluble fibrin net
    - Coagulation factors and inhibitors

❖ **Fibrinolysis**
  - Clot lysis → clot is digested
    - Fibrinolytic activators and inhibitors
Vessel Wall

Intact endothelium ➞ non thrombogenic

- Synthesis of vasodilators (prostacyclin)
- No reaction either with platelets or factors
When a vessel wall is damaged

- Exposure of the subendothelium
- Platelet adhesion
- Initiation of the mechanisms of coagulation and fibrinolysis
Primary Hemostasis

Aim is to clog the damaged vessel

(≈ bricks without cement)
Platelet Structure: Unactivated/Activated

α granules (raw materials)
PF4, β-TG, Fibrinogen, VWF, Factor V, and PAI-1

dense granules (energy and glue)
ATP, ADP, Serotonin, Ca\(^{2+}\), Mg\(^{2+}\), P
Primary Hemostasis

- Vasoconstriction occurs first
- Platelets then aggregate on the break in the vessel wall

![Diagram showing the stages of primary hemostasis: platelet at rest, adhesion, first shape change, activation, second shape change & release, aggregation (not reversible)]
Primary Hemostasis Assays

- **Routine**
  - Platelet count
  - PT
  - APTT
  - TT

- **Follow-up**
  - von Willebrand Factor
  - Antigen determination
  - Activity
  - Factor VIII
  - PFA-100 / Platelet aggregation studies

- **Specialized/Send Out**
  - Activation markers (b-TG, PF4, GPV)
  - Specialized tests for platelet function
Aim is to strengthen the platelet plug
Coagulation is a balance between pro- & anti-coagulant mechanisms → bleed & clot, → hemorrhage & thrombosis

- Triggering agents
- pro-enzyme → enzyme
\(\text{serine-protease: FIIa, FVIIa, FIXa, FXa}\)
- Cofactors (FVa & FVIIIa)

- Serine-protease inhibitor: Antithrombin (AT)
- Cofactors/inhibitors: Protein C / S
- Tissue factor pathway inhibitor (TFPI)
Coagulation Cascade Schematic

## Coagulation factors

<table>
<thead>
<tr>
<th>Historic name</th>
<th>Factor</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>I</td>
<td>Substrate</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>II</td>
<td>Pro-enzyme</td>
</tr>
<tr>
<td>Proaccelerin</td>
<td>V</td>
<td>Pro-cofactor</td>
</tr>
<tr>
<td>Proconvertin</td>
<td>VII</td>
<td>Pro-enzyme</td>
</tr>
<tr>
<td>Anti-hemophilic factor A</td>
<td>VIII</td>
<td>Pro-cofactor</td>
</tr>
<tr>
<td>Anti-hemophilic factor B</td>
<td>IX</td>
<td>Pro-enzyme</td>
</tr>
<tr>
<td>Stuart factor</td>
<td>X</td>
<td>Pro-enzyme</td>
</tr>
<tr>
<td>Rosenthal factor</td>
<td>XI</td>
<td>Pro-enzyme</td>
</tr>
<tr>
<td>Hageman factor</td>
<td>XII</td>
<td>Pro-enzyme</td>
</tr>
<tr>
<td>Fibrin Stabilizing Factor</td>
<td>XIII</td>
<td>Pro-enzyme</td>
</tr>
</tbody>
</table>

Pro-enzyme = Zymogen ➡️ activation ➡️ Active Enzyme
Coagulation Assay Mechanisms

**Intrinsic (Contact) Pathway**
- Damaged Surface
- XII → XIIa
- XI → XIa
- IX → IXa
- VIII → VIIIa

**Extrinsic (Tissue Factor) Pathway**
- Trauma
- VIIa → VII
- Tissue Factor
- Trauma

**PT Based**
- X → Xa
- Va → IIa
- Thrombin
- II → Prothrombin
- I → Ia
- Fibrinogen → Fibrin
- Cross-linked fibrin clot

**Common Pathway**
Fibrin Under Microscope

Fibrin Formation

Fibrinogen → Thrombin → FM + fibrinopeptides

Thrombin → XIII → XIIIa

Soluble Fibrin Polymer

Stabilized Fibrin clot (not soluble)
Fibrinolysis

(Digestion of Fibrin)
Fibrinolysis Overview

- Destroys fibrin fibers
- Destroys the scab (*dried wound*)
- Maintains vessel integrity
Fibrinolysis Overview

Plasmin digests fibrin

Plasmin
Fibrinolysis Cascade

Extrinsic pathway
(endothelial cells)

1st Step

Pro Urokinase

PK → Kallikrein

Urokinase

PAI-1

Plasminogen

Plasmin

2nd Step

Fibrin clot

Fibrin degradation products

D-dimer


Intrinsic pathway
(plasma)

Pro Urokinase

PAI-1

Plasminogen

Plasmin

Antiplasmin (& a2-MG)
Fibrinolysis Releases D-dimers

D-dimer presence: fibrin has been formed and digested in patient’s body

Normal D-dimer level: no thrombosis occurred in the patient
Basic Pathophysiology of DIC
Disseminated Intravascular Coagulation (DIC)

- Massive activation of coagulation leading to clots forming in multiple locations around the body
- Rapid consumption of clotting factors leading to bleeding
- Paradoxical condition leading to both clotting and bleeding
- A confusing disorder from both diagnostic and therapeutic standpoints
  - Many unrelated diseases can trigger DIC
  - Lack of uniformity in clinical manifestation
  - Lack of uniformity in the laboratory diagnosis
  - Lack of uniformity or consensus on management
Clinical Manifestations of DIC

<table>
<thead>
<tr>
<th>Organ</th>
<th>Ischemic</th>
<th>Hemorrhagic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Pupura Fulminans</td>
<td>Petechiae</td>
</tr>
<tr>
<td></td>
<td>Gangrene</td>
<td>Echymoses</td>
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<tr>
<td></td>
<td>Acral cyanosis</td>
<td>Oozing</td>
</tr>
<tr>
<td>CNS</td>
<td>Delirium/coma</td>
<td>Intracranial</td>
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<tr>
<td></td>
<td>Infarcts</td>
<td>Bleeding</td>
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<tr>
<td>Renal</td>
<td>Oliguria/Azotemia</td>
<td>Hematuria</td>
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<tr>
<td></td>
<td>Cortical Necrosis</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Myocardial dysfunction</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Dyspnea/Hypoxia</td>
<td>Hemorrhagic lung</td>
</tr>
<tr>
<td></td>
<td>Infarct</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Ulcers, infarcts</td>
<td>Massive hemorrhage</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Adrenal infarcts</td>
<td></td>
</tr>
</tbody>
</table>
Purpura Fulminans with DIC Due to Meningococcal Sepsis

Clinical Conditions Associated With DIC

- Sepsis and severe infection
- Trauma
- Organ destruction e.g. pancreatitis
- Malignancy
  - Solid tumours
  - Leukaemia
- Obstetric
  - Amniotic fluid embolism
  - Placental abruption
  - Pre-eclampsia
- Vascular abnormalities
  - Large haemangioma
  - Vascular aneurysm
- Severe liver failure
- Toxic and immunological insults
  - Snake bites
  - Recreational drugs
  - ABO transfusion incompatibility
  - Transplant rejection
# Frequency of DIC in Selected Disease States

<table>
<thead>
<tr>
<th>Disease</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Gram-negative sepsis</td>
<td>30-50%</td>
</tr>
<tr>
<td>Severe trauma and systemic inflammation</td>
<td>50-70%</td>
</tr>
<tr>
<td>Metastasized tumors</td>
<td>15%</td>
</tr>
<tr>
<td>Abruptio placenta/amniotic fluid embolism</td>
<td>50%</td>
</tr>
<tr>
<td>Severe preeclampsia</td>
<td>7%</td>
</tr>
<tr>
<td>Giant hemangioma</td>
<td>25%</td>
</tr>
</tbody>
</table>

In a Japanese survey from 1997 on incidence of DIC and underlying diseases in 652 divisions and departments of university hospitals, DIC occurred in 2,193 patients with the number of patient with infections (including sepsis) and hematologic tumors (including leukemia) accounted for 28% and 23%, respectively.

## Epidemiology of DIC

<table>
<thead>
<tr>
<th>Time frame*</th>
<th>Design</th>
<th>Setting</th>
<th>Centre</th>
<th>n</th>
<th>Criteria</th>
<th>Incidence (%)</th>
<th>Mortality (%)</th>
<th>Evaluation</th>
<th>Refs</th>
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<tbody>
<tr>
<td>Various underlying disorders</td>
<td>1992</td>
<td>Questionnaire survey</td>
<td>Ward</td>
<td>123,231</td>
<td>JMHW</td>
<td>1.04</td>
<td>65.2</td>
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<tr>
<td></td>
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<td>Ward</td>
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<td>JMHW</td>
<td>1.87</td>
<td>56</td>
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<td>2010–2012</td>
<td>Retrospective</td>
<td>Various</td>
<td>34,717*</td>
<td>Various</td>
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<td>2006</td>
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<td>ICU</td>
<td>1,461</td>
<td>ISTH</td>
<td>18*</td>
<td>76</td>
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<td>ICU</td>
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<td>ISTH</td>
<td>1.9</td>
<td>50.6</td>
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<td>ICU</td>
<td>217</td>
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<td>32</td>
<td>46*</td>
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<td>2005</td>
<td>Prospective</td>
<td>ICU</td>
<td>3,864</td>
<td>JAAM</td>
<td>8.5</td>
<td>21.9</td>
<td>28-day</td>
<td>8</td>
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<td>Severe sepsis</td>
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<td>Retrospective</td>
<td>Various</td>
<td>1,568</td>
<td>Modified ISTH</td>
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<td>30.5–43*</td>
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<td>1997–2000</td>
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<td>563</td>
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<td>25.4–40*</td>
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<td>2010–2011</td>
<td>Prospective</td>
<td>ICU</td>
<td>624</td>
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<td>46.8</td>
<td>38.4</td>
<td>Hospital</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ISTH</td>
<td>18.1</td>
<td>38.1</td>
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<td>Severe trauma</td>
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<td>ED or ICU</td>
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<td></td>
<td>ISTH</td>
<td>8.9</td>
<td>71.4</td>
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<tr>
<td></td>
<td>2014</td>
<td>Retrospective</td>
<td>ED or ICU</td>
<td>562</td>
<td>JAAM</td>
<td>54.2</td>
<td>25.2</td>
<td>Hospital</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ISTH</td>
<td>16.9</td>
<td>43.2</td>
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<tr>
<td>Obstetrical calamities</td>
<td>1980–2009</td>
<td>Retrospective</td>
<td>Ward</td>
<td>151,678</td>
<td>ISTH</td>
<td>0.03</td>
<td>6.1</td>
<td>Hospital</td>
<td>21</td>
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</table>

Patients with positivity of DIC tend to have worse mortality outcomes compared to negative patients or those with pre-DIC.

Patients with positivity of either Overt or Non-Overt DIC tend to have worse mortality outcomes compared to negative patients

Impact of Age on Mortality in DIC Patients

Older patients with DIC (black bars) generally tend to have worse outcomes compared to non-DIC patients (grey bars).

Pathophysiology of DIC

Bacteria in sepsis infections cause release of TF from immune cells, leading to coagulation activation, and proinflammatory cytokines cause endothelial cell activation, impairing the anticoagulation and fibrinolysis process, resulting in DIC.

Host Response in Severe Sepsis

Exaggerated inflammation as a result of the host response to sepsis is collateral tissue damage and cell death further resulting in release of danger molecules, continuing the inflammatory process in a downward spiral.

Organ Failure in Severe Sepsis

Sepsis associated with microvascular thrombosis as a result of TF mediated coagulation activation results in release of neutrophil extracellular traps (NETs), tissue hypoperfusion, and mitochondrial damage resulting in a downward spiral leading to organ failure.
Mechanism of DIC in Organ Failure

Underlying condition (sepsis, trauma) → Cytokines

- TF-mediated activation of coagulation
- Depression of inhibitory systems
- Reduces fibrinolysis

Fibrin formation → Fibrin deposition → Organ failure

Note: impaired fibrinolysis in relation to the clinical need, not in absolute value (FDPs are ↑↑↑)

Interaction of Inflammation and Coagulation in Sepsis

Binding of TF, thrombin, and other activation coagulation factors to PARs and fibrin to TLRs on inflammatory cells results in inflammation through release of proinflammatory cytokines and chemokines.

Inflammatory activation and microvascular thrombosis contributes to multiple organ failure in DIC.

Mechanism of Multiple Organ Failure in DIC

lipopolysaccharides

mononuclear cell

cytokines

cougulation activation

tissue factor
Diverse and Opposing Effects of Thrombin

Coagulation and Fibrinolysis in DIC

Fibrinogen

Thrombin

Soluble FM Complexes

FM + fibrinopeptides

Soluble fibrin Polymer

XIIIa

Fibrin clot

D-Dimer

Fibrin Degradation Products

Mechanism of DIC

Blood activation
Endothelial lysis
TF expression

THROMBOSIS

Fibrin

Plasmin

FDPs
D-Dimer

BLEEDING
Pathophysiology of DIC

**1st step: abnormal activation of coagulation**
- Injury of vessel wall cells, venous stasis, release of large quantities of thromboplastin, influx of activated cells (monocytes, macrophages)
- Results in an intravascular deposition of fibrin
- Morbidity from disseminated microthrombosis in small and midsize vessels; leading to multiple organ failure

**Second step:**
- Consumption and depletion of coagulation factors, inhibitors (Protein C, Protein S, AT) and platelets
- Local fibrinolytic response
  - Local plasmin generation, dissolves the thrombus
  - Disseminated overwhelming fibrinolytic response leading to production of FDP and D-Dimer

**Bleeding**
Pathophysiology of DIC - Mechanism

Systemic activation of coagulation

- Intravascular deposition of fibrin
  - Thrombosis of small and midsize vessels and organ failure

- Depletion of platelets and coagulation factors
  - Bleeding

Pathophysiology of DIC – 2 Types of Clinical pictures

- **Chronic** = non-overt DIC
  - May be unrecognized clinically

- **Acute** = overt DIC
  - Life threatening bleeding
  - Or multiple organ failure
Sub-Acute and Non-Overt DIC Clinical Findings

Compensated non-overt DIC

- Steady low level or intermittent activation
  - Compensated by increased production of coagulation components and platelets

- Few or no clinical signs, or multiple microvascular thrombosis, sometimes not clinically obvious

- Risk of decompensation leading to overt DIC
Pathophysiology of Overt DIC

- Massive activation of coagulation and fibrinolysis
- Does not allow for compensatory efforts
- Rapid depletion of coagulation factors, inhibitors and platelets
- Thrombosis: multiple organ failures
- Bleeding complications and shock
Physiopathology of DIC – Overt DIC Findings

- **Thrombin generation**
  - **Thrombosis**
    - Renal, liver, respiratory failures, coma, skin necrosis, gangrene, venous thromboembolism, hypotension, edema

- **Cytokine and kinin generation (shock)**
  - Tachycardia, hypotension, edema

- **Plasmin generation**
  - **Hemorrhage**
    - Spontaneous bruising, petechiae, intracranial, gastrointestinal and respiratory tract, bleeding, persistent bleeding at venipuncture sites, at surgical wounds
    - Tachycardia, hypotension, edema

Pathogenesis Pathways in DIC

Cytokines

- TF-mediated thrombin generation
- dysfunctional anticoagulant mechanism
- impaired fibrinolysis due to PAI-1 deficiency
- inadequate fibrin removal
- fibrin formation

Fibrin deposition
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Monday, April 24th
Preanalytical Variables in Coagulation Testing and Troubleshooting: Views from a Reference Laboratory Practitioner

Presented by: John V. Milsic, PhD - Assistant Director, Special Coagulation Laboratory, St. John’s Reference Laboratories

Hemostasis testing quality is determined by preanalytical variables which encompass patient preparation, sample collection, handling, transportation, processing and storage. If any of the preanalytical variables are not properly adhered to, incorrect or uninterpretable results are reported resulting in possible adverse patient consequences or delays in treatment. This webinar will provide background on commonly performed coagulation screening tests but also discuss the impact of preanalytical variables on these tests.

Wednesday, April 26th
Direct Oral Anticoagulant Screening and Measurement for Challenging Patient Cases

Presented by: Michael P. Galazka, PharmD, BCPS, FASHP - Program Director for Anticoagulant Services, Sanford USD Medical Center & Clinical Associate Professor, Department of Internal Medicine, University of South Dakota Sanford School of Medicine

When patients taking direct oral anticoagulants (DOACs) are admitted into the hospital, there may be a need for bridging parental anticoagulants especially for those at high risk of thrombus recurrence. By presenting information on DOAC interference in laboratory assays, institutional experience, and case studies, this webinar will address questions surrounding management of patients on DOAC therapy.

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  - Apple and Android
  - Tablet or phone

- **iHemostasis**
  - Coagulation diagrams
  - Case studies
  - Apple & Android
  - Tablet only

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Break

Keep Calm
It's Break Time

Time for a Break
Diagnostic and Management Approach for DIC
Diagnosis of DIC

- Clinical diagnosis is obvious in cases of overt DIC

- Laboratory tests are necessary
  - To make/confirm the diagnosis
  - To assess stage of the patient
  - To assess the treatment efficacy
Lab Diagnosis of DIC – Markers of Factor Consumption

- Routine/screening assays
  - PT, APTT
  - Platelets
  - Fibrinogen
  - Thrombin time

- Other coagulation assays: Factor assays, Antithrombin

- Generation of Thrombin: FM/FSPs

- Generation of Plasmin: D-dimer, FDPs

- Important to recognize simultaneous formation of thrombin and plasmin

Lab Diagnosis of DIC – Screening Tests

- Platelet count: usually decreased
- PT abnormal in 70% of cases (short half-life of FVII)
- APTT abnormal in 50% of cases
- Thrombin time, usually prolonged, in overt DIC, normal in non-overt DIC and no relation with syndrome severity
- Fibrinogen low in < 50% of cases, sensitivity: 22%, specificity: 87%, overall predictive value: 64%
  - Normal fibrinogen level should not exclude DIC diagnosis (acute phase reactant: initial high fibrinogen level); repeat testing assesses progression

- Screening tests not clinically specific or sensitive for DIC

## Laboratory Changes in Overt DIC

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>Decreased—consumed</td>
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<tr>
<td>Activated partial thromboplastin time</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Thrombin time</td>
<td>Prolonged—due to low fibrinogen and elevated D-dimer</td>
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<tr>
<td>Fibrinogen</td>
<td>Decreased—consumed</td>
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<tr>
<td>Coagulation factors</td>
<td>Decreased—consumed</td>
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<tr>
<td>Fibrin degradation products</td>
<td>Increased</td>
</tr>
<tr>
<td>D-dimer</td>
<td>Increased</td>
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<tr>
<td>Thrombin generation markers</td>
<td>Increased</td>
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<td>Antithrombin</td>
<td>Decreased—consumed</td>
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<tr>
<td>Protein C</td>
<td>Decreased—consumed</td>
</tr>
<tr>
<td>Protein S</td>
<td>Decreased—consumed</td>
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<td>Thrombomodulin, endothelial</td>
<td>Decreased by neutrophil elastase + proinflammatory cytokines</td>
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<td>TPA trauma</td>
<td>Early DIC—increased</td>
</tr>
<tr>
<td></td>
<td>Late DIC—decreased</td>
</tr>
<tr>
<td>PAI-1 trauma</td>
<td>Early DIC—low levels</td>
</tr>
<tr>
<td></td>
<td>Late DIC—elevated</td>
</tr>
</tbody>
</table>
DIC Diagnostic Practices Over Time

- 1950: Pathological diagnosis
  - Proof of thrombosis
  - Scoring of underlying diseases, clinical symptoms and laboratory data

- 1970: Diagnosis by research laboratory
  - Colman’s criteria

- 1980: Diagnosis in general hospital
  - ISTH overt DIC diagnostic criteria
  - Scoring of laboratory data

- 2000: Early diagnosis
  - ISTH Non-overt DIC diagnostic criteria
  - Scoring of global coagulation tests, its change rate and hemostatic molecular markers

- 2010: Improve outcome
  - New diagnostic criteria for DIC
  - JAAM diagnostic criteria

**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 ($<3 \text{ s} = 0$, $>3 \text{ s but} <6 \text{ s} = 1$, $>6 \text{ s} = 2$)
- Fibrinogen level ($>1 \text{ g/l} = 0$, $<1 \text{ g/l} = 1$)

**Calculate score:**
- $\geq 5$ compatible with overt DIC: repeat score daily
- $<5$ suggestive for non-overt DIC: repeat next 1–2 d
 ISTH Step by Step DIC Algorithm

Algorithm

1. Presence of an underlying disorder known to be associated with DIC? 
   If yes: proceed. If no: do not use this algorithm

2. Global coagulation results:
   a. Platelet count (>100,000/µL = 0, <100,000/µL = 1, <50,000/µL = 2)
   b. Fibrin degradation products such as D-dimer (no increase = 0, 
      moderate increase = 2, strong increase = 3)
   c. Prolonged prothrombin time 
      (<3 seconds = 0, >3 seconds = 1, >6 seconds = 2)
   d. Fibrinogen level (>1.0 g/L = 0; <1.0 g/L = 1)

DIC, disseminated intravascular coagulation.

*a*Interpretation of algorithm: A score of 5 or higher is compatible with acute DIC.
The algorithm can be repeated on occasion if acute DIC remains a consideration and 
the laboratory values change. Modified from Taylor et al.*

146: 670-80.
When retrospectively comparing the ISTH score to a locally derived score in 2,136 DIC panels from 130 pediatric patients, the ISTH score had a higher AUC.
### Differential Diagnosis in DIC

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Platelet Count</th>
<th>PT</th>
<th>aPTT</th>
<th>Fibrinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIC</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>TTP, HUS, aHUS</td>
<td>↓</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>ITP</td>
<td>↓</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>N to ↓</td>
</tr>
<tr>
<td>Heparin</td>
<td>N</td>
<td>N to ↑&lt;sup&gt;a&lt;/sup&gt;</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td>Coumadin</td>
<td>N</td>
<td>↑</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td>HIT</td>
<td>↓</td>
<td>N to ↑&lt;sup&gt;a&lt;/sup&gt;</td>
<td>↑</td>
<td>N</td>
</tr>
</tbody>
</table>

- **aHUS**: atypical hemolytic uremic syndrome
- **HUS**: hemolytic uremic syndrome
- **HIT**: heparin-induced thrombocytopenia
- **ITP**: immune thrombocytopenic purpura
- **TTP**: thrombotic thrombocytopenic purpura

---

DIC and MAHA

< 3 schistocytes per high-power field considered normal; > 10 schistocytes apparent per high-power field (picture taken with oil emersion lens at x 100)

When RBCs pass through compromised vasoconstricted vessels, result is microangiopathic hemolytic anemia (MAHA); overt DIC is therefore a thrombotic MAHA because there is thrombocytopenia in addition to schistocyte formation.
DIC Management Goals

- Identify and correct the underlying cause
- Microclots preventing blood flow in organs may strongly impair the biosynthesis of new coagulation factors, inhibitors, fibrinolysis proteins leading to severe deficiencies
- Correct consumption and restore anticoagulation pathway with blood components
  - Fresh frozen plasma (preferred)
  - Coagulation factor concentrates, fibrinogen and/or cryoprecipitate
  - Antithrombin
  - Platelet concentrates
  - Monitor coagulation markers for correction
DIC Management and Treatment

- **Stop activation process: Thrombin and plasmin inhibitors**
  - Unfractionaed heparin (UFH) & low molecular weight heparin (LMWH); requires adequate AT levels; typically low dose
  - Monitor with anti-Xa activity, no APTT (if UFH)

- **Longer term once the patient stabilizes: oral anticoagulants**

- **Other supportive treatment**
  - Vitamin K for critically ill patients with acquired vitamin K deficiency
  - Oxygen to correct hypoxia

DIC Management Strategies

Anticoagulant factor concentrates (e.g. AT, TFPI, TM, aPC) target sepsis with DIC before DIC emergence leads to deterioration of physiological responses maintaining homeostasis.

## Anticoagulant Factor Concentrate Treatment Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial</th>
<th>Design</th>
<th>Subject</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin</td>
<td>KyberSept</td>
<td>Double-blind, placebo-controlled, multicentre</td>
<td>Severe sepsis</td>
<td>Failed</td>
</tr>
<tr>
<td></td>
<td>KyberSept</td>
<td>Retrospective subgroup analysis of the KyberSept trial</td>
<td>DIC in severe sepsis</td>
<td>Significant mortality reduction ($P = 0.024$)</td>
</tr>
<tr>
<td></td>
<td>JAAMDICAT</td>
<td>Prospective multicentre</td>
<td>DIC in sepsis and severe sepsis</td>
<td>Significant improvement of DIC ($P = 0.015$) and doubling the recovery rate of DIC without risk of bleeding</td>
</tr>
<tr>
<td>Tissue factor pathway inhibitor</td>
<td>OPTIMIST</td>
<td>Double-blind, placebo-controlled, multicentre</td>
<td>Severe sepsis</td>
<td>Failed</td>
</tr>
<tr>
<td>Recombinant activated protein C</td>
<td>PROWESS</td>
<td>Double-blind, placebo-controlled, multicentre</td>
<td>Septic shock</td>
<td>Failed</td>
</tr>
<tr>
<td></td>
<td>PROWESS</td>
<td>Retrospective subgroup analysis of the PROWESS trial</td>
<td>DIC in severe sepsis</td>
<td>A trend towards greater risk reduction in mortality</td>
</tr>
<tr>
<td>Plasma-derived activated protein C</td>
<td>NA</td>
<td>Randomized, prospective, double-blind, multicentre</td>
<td>DIC in various underlying diseases</td>
<td>Significant mortality reduction without increasing bleeding ($P &lt; 0.05$)</td>
</tr>
<tr>
<td>Recombinant soluble thrombomodulin</td>
<td>NA</td>
<td>Randomized, prospective, double-blind, multicentre</td>
<td>DIC in haematological malignancy or infection</td>
<td>Significant improvement of DIC without risk of bleeding ($P$ value is not provided, but the resolution rate with 95% CI was described)</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>Double-blind, placebo-controlled, multicentre</td>
<td>Suspected DIC in sepsis</td>
<td>Evidence suggestive of efficacy supporting further development of this drug in sepsis-associated DIC</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>Double-blind, placebo-controlled, multicentre</td>
<td>Severe sepsis and coagulopathy</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

Recombinant aPC, AT, and TFPI have been attempted for treatment of DIC in large clinical trials with mostly failures; recombinant TM trials have shown promise.

Markers of Thrombin & Plasmin Generation in DIC
D-dimer, FDPs, and DIC

- **D-Dimer sensitive test for DIC, but not specific**
  - Elevated D-Dimer: Thrombin + Plasmin activity
  - Negative D-Dimer: low probability for DIC

- **Fibrin monomers (FM; aka soluble fibrin monomers, SFM), and fibrin degradation products (FDPs; aka fibrin split products, FSPs)**
  - Manual FDP/FSP detects both fibrin and fibrinogen degradation products
  - Sensitive assay typically with cutoff adapted for DIC

Cut-off value??
D-Dimer and FDPs in DIC

- Detects both fibrin and fibrinogen degradation products
- Sensitive, cut-off adapted to DIC


<table>
<thead>
<tr>
<th>Tests</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Efficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (n = 82)</td>
<td>91</td>
<td>27</td>
<td>57</td>
</tr>
<tr>
<td>PTT (n = 82)</td>
<td>91</td>
<td>42</td>
<td>57</td>
</tr>
<tr>
<td>TT (n = 43)</td>
<td>83</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>Fibrinogen (n = 71)</td>
<td>22</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>Platelet count (n = 82)</td>
<td>97</td>
<td>48</td>
<td>67</td>
</tr>
<tr>
<td>Schistocytes (n = 80)</td>
<td>23</td>
<td>73</td>
<td>51</td>
</tr>
<tr>
<td>FDP (n = 71)</td>
<td>100</td>
<td>67</td>
<td>87</td>
</tr>
<tr>
<td>D-dimer (n = 44)</td>
<td>91</td>
<td>68</td>
<td>80</td>
</tr>
<tr>
<td>AT (n = 21)</td>
<td>91</td>
<td>40</td>
<td>70</td>
</tr>
<tr>
<td>PT + PTT + TT (n = 43)</td>
<td>83</td>
<td>11</td>
<td>51</td>
</tr>
<tr>
<td>PT + PTT + fibrinogen (n = 71)</td>
<td>22</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>PT + PTT + FDP (n = 71)</td>
<td>91</td>
<td>71</td>
<td>86</td>
</tr>
<tr>
<td>FDP + D-dimer (n = 39)</td>
<td>91</td>
<td>94</td>
<td>95</td>
</tr>
</tbody>
</table>

PT: prothrombin time; PTT, partial thromboplastin time; TT, thrombin time; FDP, fibrinogen/fibrin degradation products; AT, antithrombin.
Follow Up of DIC State of Disease

Coagulopathy continuing or worsening during the first day of severe sepsis (followed by PT, AT, and D-dimer) was associated with development of organ failure and 28 day mortality.

FM/D-Dimer in DIC: Major Differences

**FM: may be predictive**
- Appear 0-3 days after the onset of thrombosis; typically prethrombotic
- Short half-life (6 - 8 hrs)

**D-Dimer (a specific FDP): well-established DIC**
- Appear 2-10 days after the onset of thrombosis; typically postthrombotic
- Longer half-life (4 - 11 hrs)

% Positivity of Test Results, ISTH Score, and Disease State

Markers in Patients with or without DIC


HT: hematopoietic tumor
IF: infection
SC: solid cancer
In a study of ED patients, automated FM assays exhibit much better inter-assay agreement compared to automated FM vs. a manual FSP assay from Stago.
Baseline Characteristics in Study of Diagnostic Performance of FM and D-dimer in DIC

<table>
<thead>
<tr>
<th>Parameters, Units</th>
<th>Overt DIC, Group 1 (n = 32)</th>
<th>Nonovert DIC, Group 2, (n = 24)</th>
<th>Non-DIC, Group 3, (n = 14)</th>
<th>Chi-Square P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT, seconds</td>
<td>24 (16-70)</td>
<td>18.5 (14-30)</td>
<td>17 (13-31)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>APTT, seconds</td>
<td>40.5 (30-74)</td>
<td>38.5 (28-50)</td>
<td>37.5 (28-74)</td>
<td>.015</td>
</tr>
<tr>
<td>TT, seconds</td>
<td>19.5 (15-79)</td>
<td>19 (13-68)</td>
<td>18 (15-46)</td>
<td>.004</td>
</tr>
<tr>
<td>Platelet count, $10^3$/L</td>
<td>28.5 (7-190)</td>
<td>90 (25-331)</td>
<td>40 (9-260)</td>
<td>.0002</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>225 (60-700)</td>
<td>335 (120-650)</td>
<td>490 (110-800)</td>
<td>.0005</td>
</tr>
<tr>
<td>$^a$D-Dimer, $\mu$g/mL</td>
<td>6.55 (0.51-25)</td>
<td>2.84 (0.66-17)</td>
<td>2.35 (0.14-5.8)</td>
<td>.0001</td>
</tr>
<tr>
<td>$^b$Fibrin monomer, $\mu$g/mL</td>
<td>55.6 (6.32-195)</td>
<td>9.65 (6.1-189)</td>
<td>5.98 (3.1-9.88)</td>
<td>.0001</td>
</tr>
<tr>
<td>Antithrombin (%)</td>
<td>41 (22-76)</td>
<td>55.5 (28-78)</td>
<td>82.5 (33-134)</td>
<td>.0002</td>
</tr>
</tbody>
</table>

In comparing Non-Overt to Non-DIC patients, FM far outperforms D-dimer on the ROC.
In comparing DIC positive to Non-Overt DIC patients, D-dimer outperforms FM on the ROC.
In comparing Overt to Non-DIC patients, FM is more comparable to D-dimer on the ROC
## Diagnostic Performance of FM and D-dimer in DIC

<table>
<thead>
<tr>
<th>Cutoff</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Negative Predictive Value (95% CI)</th>
<th>Positive Predictive Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overt-DIC vs non-DIC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d-Dimer, µg/mL, ≥3.34</td>
<td>81.25 (64.69-91.11)</td>
<td>85.71 (60.06-95.99)</td>
<td>92.86 (77.35-98.02)</td>
<td>66.67 (43.75-83.72)</td>
</tr>
<tr>
<td>Fibrin monomer, µg/mL ≥9.32</td>
<td>81.25 (64.69-91.11)</td>
<td>92.86 (68.53-98.73)</td>
<td>96.3 (81.72-99.34)</td>
<td>68.42 (46.01-84.64)</td>
</tr>
<tr>
<td><strong>Nonovert DIC vs non-DIC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d-Dimer, µg/mL, ≥2.2</td>
<td>70.83 (50.83-85.09)</td>
<td>42.86 (21.38-67.41)</td>
<td>68 (48.41-82.8)</td>
<td>46.15 (23.21-70.86)</td>
</tr>
<tr>
<td>Fibrin monomer, µg/mL, ≥7.2</td>
<td>83.33 (64.15-93.32)</td>
<td>78.57 (52.41-92.43)</td>
<td>86.96 (67.87-95.46)</td>
<td>73.33 (48.05-89.1)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DIC, disseminated intravascular coagulation.
Levels of D-dimer and FM generally rise going from no DIC, to non-overt, to overt DIC

Diagnostic Performance of FM and D-dimer in DIC

AUC in the ROC was higher for D-dimer (dashed line) in Non-overt but higher for FM (solid line) in Overt DIC

Sepsis patients have much higher levels of FDP, FM, and D-dimer compared to normal and systemic inflammatory response syndrome (SIRS) patients.

Trends in Markers of DIC for Different Patients

FDP, FM, and D-dimer all increase for patients with survival outcomes compared to those with death outcomes.

Determination of Cutoffs of FM and D-dimer in DIC

Analysis of D-dimer, FDP, and FM in DIC patients and classifying by outcome enables cutoff values to be determined

Analysis of D-dimer, FDP, and FM in DIC patients and classifying by outcome enables cutoff values to be determined in concordance with ISTH guidelines

DIC Case Studies
Case Study 1 - Presentation

- 18 year old male presented to the ED after 3 weeks of nosebleeds and increasing levels of severe fatigue.
- No medical history, born at term, all developmental milestones achieved.
- No family history of bleeding or thrombosis.
- No medications, denies recreational drugs/alcohol.
- Physical exam finds blood clots in both nostrils and petechial hemorrhages in mouth and lower extremities.
- Bleeding subsided but lab results were monitored closely during hospitalization while blood products were administered.

## Case Study 1 – Lab Results

<table>
<thead>
<tr>
<th>TEST</th>
<th>RESULT</th>
<th>REFERENCE RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC count</td>
<td>7.7 K/μL</td>
<td>4.23 – 9.07 x K/μL</td>
</tr>
<tr>
<td>RBC count</td>
<td>1.7 M/μL</td>
<td>13.7 – 17.5 x M/μL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>6.7 g/dL</td>
<td>13.7 – 17.5 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>19.5%</td>
<td>40.1 – 51.0%</td>
</tr>
<tr>
<td>MCV</td>
<td>95 fL</td>
<td>79.0 – 92.2 fL</td>
</tr>
<tr>
<td>MPV</td>
<td>12 fL</td>
<td>9.4 – 12.4 fL</td>
</tr>
<tr>
<td>Platelet count</td>
<td>9 K/μL</td>
<td>161 – 347 K/μL</td>
</tr>
<tr>
<td>PT</td>
<td>47 sec (corrected on mixing study)</td>
<td>11.6 – 15.2 sec</td>
</tr>
<tr>
<td>APTT</td>
<td>75 sec (corrected on mixing study)</td>
<td>25.3 – 37.3 sec</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>&lt; 76 mg/dL</td>
<td>177 – 466 mg/dL</td>
</tr>
<tr>
<td>D-dimer</td>
<td>9.00 μg/mL FEU</td>
<td>0 – 0.50 μg/mL FEU</td>
</tr>
</tbody>
</table>

Metamyelocytes, promyelocytes, myelocytes, myeloblasts all elevated above normal level of 0

Lymphocytes, monocytes, eosinophils, basophils, all below normal range

Case Study 1 – Microscopy

Case Study 1 – Diagnosis and Therapy

- Profound anemia, significant reticulocytosis, and increased mean corpuscular volume (MCV), decreased platelets with increased mean platelet volume (MPV), numerous promyelocytes, High D-dimer, with PT/APTT correcting on mixing study, along with low fibrinogen indicate disseminated intravascular coagulation (DIC) secondary to acute myelogenous leukemia (AML); most likely acute promyelocytic leukemia (APL).

- DIC due to TF release by APL blasts.

- Molecular studies of PML-retinoic acid receptor-alpha (RARA) gene fusion was positive; occurs in >95% of APL cases.

- Transfusions to replace factors, along with platelets and RBCs during APL treatment

Case Study 2 – Presentation

- 20-year-old male college student presenting to ED
- General malaise, hypotension (90/60 mmHg), high-grade fever, purplish discoloration on his body, pain in both legs, vomiting, and diarrhea on the preceding day
- Facial discoloration developed rapidly during the time from when he left house to the time he arrived at the emergency room
- Blood cultures started
# Case Study 2 – Lab Results

<table>
<thead>
<tr>
<th>TEST</th>
<th>RESULT</th>
<th>REFERENCE RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>67 x 10⁹/L</td>
<td>150-400 x 10⁹/L</td>
</tr>
<tr>
<td>PT</td>
<td>30 sec</td>
<td>11.3 – 14.6 sec</td>
</tr>
<tr>
<td>APTT</td>
<td>75 sec</td>
<td>25 – 34 sec</td>
</tr>
<tr>
<td>D-dimer</td>
<td>0.78 µg/ml FEU</td>
<td>&lt;0.50 µg/ml FEU</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>92 mg/dl</td>
<td>150-400 mg/dl</td>
</tr>
<tr>
<td>pH</td>
<td>7.28</td>
<td>7.38 to 7.42</td>
</tr>
<tr>
<td>PaO₂</td>
<td>57.0 mmHg</td>
<td>80-100 mmHg</td>
</tr>
<tr>
<td>WBC</td>
<td>3.3 x 10³/mm³</td>
<td>4.0-11 x 10³/mm³</td>
</tr>
<tr>
<td>ALT</td>
<td>111 IU/L</td>
<td>0–34 IU/L</td>
</tr>
<tr>
<td>AST</td>
<td>61 IU/L</td>
<td>0–34 IU/L</td>
</tr>
<tr>
<td>BUN</td>
<td>30.3 mg/dL</td>
<td>0.8-1.3 mg/dL</td>
</tr>
</tbody>
</table>
Case Study 2 – Diagnosis

- Pneumococcal infection
- Waterhouse-Friderichsen Syndrome with DIC
- Provide antibiotics with supportive measures
Case Study 3 – Presentation

- 60-year-old male, 4 day history of bleeding from the gums, diffuse spontaneous ecchymoses, mild fatigue, and bone pain
- 6-month history of pain localized to his right thigh with extension to the posterior part of his right leg
- Past medical history included atrial fibrillation, hypercholesterolemia, and hypertension, all well controlled with medication
- No history of smoking; moderate alcohol consumption until 1 year prior
# Case Study 3 – Lab Results

<table>
<thead>
<tr>
<th>TEST</th>
<th>RESULT</th>
<th>REFERENCE RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>(107 \times 10^9/L)</td>
<td>150-400 (x) (10^9/L)</td>
</tr>
<tr>
<td>PT</td>
<td>22.8 sec</td>
<td>11.3 – 14.6 sec</td>
</tr>
<tr>
<td>APTT</td>
<td>45 sec</td>
<td>25 – 34 sec</td>
</tr>
<tr>
<td>D-dimer</td>
<td>0.80 µg/ml FEU</td>
<td>&lt;0.50 µg/mL FEU</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>82 mg/dL</td>
<td>150-400 mg/dL</td>
</tr>
<tr>
<td>FV</td>
<td>Normal</td>
<td>70-120%</td>
</tr>
<tr>
<td>FVII</td>
<td>Normal</td>
<td>55-170%</td>
</tr>
<tr>
<td>FVIII</td>
<td>Normal</td>
<td>60-150%</td>
</tr>
<tr>
<td>Protein C</td>
<td>Normal</td>
<td>70-130%</td>
</tr>
<tr>
<td>Hb</td>
<td>13.4 g/dL</td>
<td>14-16 g/dL</td>
</tr>
<tr>
<td>WBC</td>
<td>(8.1 \times 10^3/mm^3)</td>
<td>4.0-11 (\times) (10^3/mm^3)</td>
</tr>
<tr>
<td>ALT</td>
<td>32 IU/L</td>
<td>0–34 IU/L</td>
</tr>
<tr>
<td>AST</td>
<td>28 IU/L</td>
<td>0–34 IU/L</td>
</tr>
<tr>
<td>BUN</td>
<td>0.9 mg/dL</td>
<td>0.8-1.3 mg/dL</td>
</tr>
</tbody>
</table>
Case Study 3 – Diagnosis and Therapy

- Acute promyelocytic leukemia with DIC
- Transfusions to replace platelets and RBCs during APL treatment
Case Study 4 – Presentation

- Critical care transport arranged for 48 year old male admitted to the local hospital 3 days prior with weakness and hypotension.
- Four days prior, insect bite while hiking; large hematoma on left arm
- No prior medical history, no drug allergies, no current medications
- Upon arrival, patient is awake and alert in moderate respiratory distress, oozing blood from both vascular access sites, nose, and urinary catheter, skin is cool and mildly jaundiced
- Vital signs: heart rate 110 beats per minute, blood pressure 92/44, slightly labored respiratory rate 22 breaths per minute, pulse oximetry 91%
## Case Study 4 – Lab Results

<table>
<thead>
<tr>
<th>TEST</th>
<th>RESULT</th>
<th>REFERENCE RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>$70 \times 10^9$/L</td>
<td>150-400 $\times 10^9$/L</td>
</tr>
<tr>
<td>PT</td>
<td>28 sec</td>
<td>11.3 – 14.6 sec</td>
</tr>
<tr>
<td>APTT</td>
<td>71 sec</td>
<td>25 – 34 sec</td>
</tr>
<tr>
<td>D-dimer</td>
<td>3.1 µg/mL FEU</td>
<td>&lt;0.50 µg/ml FEU</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>92 mg/dL</td>
<td>150-400 mg/dl</td>
</tr>
<tr>
<td>FV</td>
<td>Normal</td>
<td>70-120%</td>
</tr>
<tr>
<td>FVII</td>
<td>Normal</td>
<td>55-170%</td>
</tr>
<tr>
<td>FVIII</td>
<td>Normal</td>
<td>60-150%</td>
</tr>
<tr>
<td>Protein C</td>
<td>Normal</td>
<td>70-130%</td>
</tr>
<tr>
<td>Hb</td>
<td>15.8 g/dL</td>
<td>14-16 g/dL</td>
</tr>
<tr>
<td>WBC</td>
<td>$7.1 \times 10^3$/mm$^3$</td>
<td>4.0-11 $\times 10^3$/mm$^3$</td>
</tr>
<tr>
<td>ALT</td>
<td>60 IU/L</td>
<td>0–34 IU/L</td>
</tr>
<tr>
<td>AST</td>
<td>47 IU/L</td>
<td>0–34 IU/L</td>
</tr>
<tr>
<td>BUN</td>
<td>38 mg/dL</td>
<td>0.8-1.3 mg/dL</td>
</tr>
</tbody>
</table>
Case Study 4 – Diagnosis

- Lyme disease with DIC
- Provide antibiotics with supportive measures
Case Study 5 – Presentation

- 55-year-old man 10 following months after thoracic endovascular aortic repair (TEVAR); multiple ecchymoses diffusely distributed in his torso along with upper and lower extremities
- Chronic type B aortic dissection and descending thoracic aortic aneurysm
- Persistent retrograde flow in false lumen with stable aneurysm diameter
- False lumen embolized with multiple Amplatzer plugs, which promoted false lumen thrombosis

Case Study 5 – Lab Results and Time Course

<table>
<thead>
<tr>
<th>TEST</th>
<th>RESULT</th>
<th>REFERENCE RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>33 x 10⁹/L</td>
<td>150-450 x 10⁹/L</td>
</tr>
<tr>
<td>PT</td>
<td>21.5 sec</td>
<td>10.3 – 12.8 sec</td>
</tr>
<tr>
<td>APTT</td>
<td>44 sec</td>
<td>26 – 36 sec</td>
</tr>
<tr>
<td>D-dimer</td>
<td>20 µg/mL FEU</td>
<td>&lt;0.25 µg/ml FEU</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>34 mg/dL</td>
<td>200-375 mg/dl</td>
</tr>
<tr>
<td>FII, FV, FVIII</td>
<td>Low</td>
<td>Not reported (NR)</td>
</tr>
<tr>
<td>FVII, FIX, FX, vWF</td>
<td>Normal</td>
<td>NR</td>
</tr>
</tbody>
</table>

Improvement in Plt and Fib after false lumen embolization with multiple endovascular plugs (arrows)

Case Study 5 – Diagnosis and Treatment

- DIC secondary to large type Ib endoleak
- UFH infusion, cryoprecipitate, partial improvement in platelet count and fibrinogen
- Rare case of DIC following TEVAR
  - (A) 3D CT reconstruction
  - (B) Illustration demonstrating chronic type B aortic dissection with associated aneurysmal dilatation of the descending thoracic aorta; patient treated with TEVAR
  - (C) Completion angiogram demonstrated patent supra-aortic vessels and thoracic stent-graft; no evidence of an antegrade endoleak but persistent distal type Ib endoleak (black arrow) into false lumen
  - (D) Illustration demonstrating repair

Case Study 6 – Presentation

- 29 year old female, 50 kg, hematuria and epistaxis, pregnant @ 37 weeks; no prior prenatal check ups; hematuria 10 days prior
- On examination, blood pressure 200/160, started on α-methyldopa.
- She developed profuse epistaxis, controlled after bilateral nasal packing.
- No history of blurring of vision or epigastric pain, denied history of prior abnormal bleeding episodes, ingestion of any medication except α-methyldopa.
- Examination revealed pallor and pedal edema, controlled with three 5 mg boluses of intravenous labetalol.
- Trachea was electively intubated under midazolam sedation for protection of airway and patient placed on ventilation with oxygen supplementation.
- Baby was monitored using cardiotocography and Doppler ultrasonography.

## Case Study 6 – Lab Results

<table>
<thead>
<tr>
<th>TEST</th>
<th>RESULT</th>
<th>REFERENCE RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>109 x 10⁹/L</td>
<td>150-400 x 10⁹/L</td>
</tr>
<tr>
<td>PT</td>
<td>63 sec &gt; control</td>
<td>11.3 – 14.6 sec</td>
</tr>
<tr>
<td>INR</td>
<td>6.58</td>
<td>1 – 1.25</td>
</tr>
<tr>
<td>APTT</td>
<td>80 sec &gt; control</td>
<td>25 – 34 sec</td>
</tr>
<tr>
<td>D-dimer</td>
<td>&gt;200 µg/mL DDU</td>
<td>0.2 µg/mL DDU</td>
</tr>
<tr>
<td>Urine exam</td>
<td>Proteinuria and hematuria</td>
<td>150-400 mg/dl</td>
</tr>
<tr>
<td>Albumin</td>
<td>2.8 g/dL</td>
<td>NR</td>
</tr>
<tr>
<td>Hb</td>
<td>5.8 g/dL</td>
<td>NR</td>
</tr>
<tr>
<td>LDH</td>
<td>1196 U/L</td>
<td>NR</td>
</tr>
<tr>
<td>SGPT</td>
<td>144 IU</td>
<td>NR</td>
</tr>
<tr>
<td>SGOT</td>
<td>88 IU</td>
<td>NR</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>3.2 mg/dL</td>
<td>NR</td>
</tr>
</tbody>
</table>
Case Study 6 – Diagnosis and Treatment

- DIC complicating hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome in preeclampsia was made and C section planned.
- Intraoperative blood loss replaced with FFP, packed red blood cells (RBC), hexastarch, and crystalloids.
- Baby delivered successfully.
- Postop vaginal bleeding treated with intravenous TXA, platelets, and FFP.
- Patient remained haemodynamically stable and discharged on the 10th day postop.

HELPP syndrome complicates 0.2–0.6% of all pregnancies, 4–12% of cases with severe preeclampsia and 30–50% of eclamptic gravidas. Maternal and neonatal mortality 2–24% and 3–39%, respectively. HELLP syndrome may progress to DIC in 15–38% of patients. Patients with HELLP syndrome are at increased risk of abruptio placentae, pulmonary edema, ruptured liver hematoma, acute renal failure, cerebrovascular accident and multiorgan failure.
Case Study 7 – Presentation

- 44-year-old man with history of hepatitis C, cirrhosis, and chronic kidney disease presents to ED for altered mental status and ammonia level > 500 mM (RR 11-51 mM)
- Patient was given lactulose; however, his mental status worsened to require intubation
- Vital signs on admission to ICU on Oct 23: BP 120/84; heart rate 107 beats/min, respiratory rate 18/min, temperature, 97.8 °F
Case Study 7 – Presentation

♦ On Oct 23, patient started on vancomycin, piperacillin/tazobactam, and fluids because of concern for sepsis associated with systemic inflammatory response syndrome (SIRS) and multiorgan failure, as well as laboratory values showing a high WBC count and elevated lactate of 8 mM (RR 0.5-1.6mmol/L)

♦ Vital signs worsened over next 24 hours, became hypotensive, requiring treatment with norepinephrine and 6 L of normal saline on Oct 24

♦ Renal function continued to decline, received continuous renal replacement therapy on Oct 25

### Case Study 7 – Lab Results vs. Time

#### Laboratory values (reference range)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>October 23</td>
</tr>
<tr>
<td>WBC count (3.7-10.3), x $10^9$/L</td>
<td>20.1</td>
</tr>
<tr>
<td>Hemoglobin (13.7-17.5), g/dL</td>
<td>13.5</td>
</tr>
<tr>
<td>Platelet count (155-369), x $10^9$/L</td>
<td>253</td>
</tr>
<tr>
<td>International normalized ratio (0.9-1.2)</td>
<td>1.4</td>
</tr>
<tr>
<td>Prothrombin time (9.6-12.5), s</td>
<td>13.5</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (19-30), s</td>
<td>34</td>
</tr>
<tr>
<td>Fibrinogen (150-450), mg/dL</td>
<td>66</td>
</tr>
<tr>
<td>Lactate (0.5-1.6), mmol/L</td>
<td>8</td>
</tr>
<tr>
<td>pH (7.35-7.45)</td>
<td>7.18</td>
</tr>
<tr>
<td>Lactate dehydrogenase (140-280), U/L</td>
<td>412</td>
</tr>
<tr>
<td>Creatinine (0.8-1.30), mg/dL</td>
<td>5.8</td>
</tr>
</tbody>
</table>

#### Blood products, No.

<table>
<thead>
<tr>
<th>Type</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC units</td>
<td>3</td>
</tr>
<tr>
<td>Fresh-frozen plasma units</td>
<td>2</td>
</tr>
<tr>
<td>Apheresis platelet units</td>
<td>3</td>
</tr>
<tr>
<td>Cryoprecipitate units</td>
<td>10</td>
</tr>
</tbody>
</table>

*Note that the prothrombin time reagent contains a heparin neutralizer.*
Lab values from Oct 25 consistent with DIC; given packed RBCs, FFP, cryo, plts, and vit K to treat peritoneal bleeding, which stopped by Oct 26

Over next few days, continued to require norepinephrine, but eventually vital signs and laboratory values stabilized

During next few days, improvement was apparent, but found to have multiple infections, including vancomycin-resistant enterococcus (VRE) along with Stenotrophomonas maltophilia, peritoneal fluid growing Acinetobacter, and urinalysis growing Candida glabrata

Case Study 7 – Diagnosis and Treatment

- On Oct 29, started on daptomycin, linezolid, trimethoprim/sulfamethoxazole, and fluconazole, vancomycin and piperacillin/tazobactam were discontinued
- Hemodynamically stable, taken off pressors and extubated on Nov 1
- In process of transfer from ICU, became obtunded and hypotensive o/n
- FFP, cryo, platelets, and packed RBCs were ordered, but patient went into cardiac arrest and passed away

DIC: Take Home Messages

- Heterogeneous, rapidly fatal syndrome
- Etiology: sepsis, tumors, injuries or obstetric complications
- Simultaneous activation of coagulation and fibrinolysis
- Consumption of factors, anticoagulant proteins, fibrinogen and platelets
- Diagnosis not with a single test: panel including activation markers
- Screening coags, platelets, FM/FS and D-dimer
  - 1<sup>st</sup> consideration: treat the critical symptoms and underlying issue
  - 2<sup>nd</sup> consideration: compensation for the consumption and sometimes anticoagulation
- Monitor efficacy of therapy
  - Activation markers (D-Dimer, FM/FSP)
  - Normalization of coagulation markers
The bad news is...you have DIC disease. The good news is, I don't believe in that disease so you're fine!
Thank you! Questions?