The Clotting Cascade and DIC

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Coagulation

Coagulation is a host defense system that maintains the integrity of the high pressure closed circulatory system.

To prevent excessive blood loss after injury the hemostatic system:

- Endothelial cells
- Platelets
- Plasma coagulation proteins
Coagulation

Immediately after injury, primary hemostasis occurs

- Vascular constriction
- Platelet activation
Platelet Aggregation

- Flowing disc-shaped platelet
- Rolling ball-shaped platelet
- Hemisphere-shaped platelet
- Spreading platelet

Firm, but reversible adhesion

Irreversible adhesion

Scanning electron micrograph of discoid, dormant platelets
Activated, aggregating platelets illustrating fibrin strands

Coagulation

Secondary hemostasis
- Stabilizes an otherwise unstable platelet plug by adding fibrin to the clot
Intrinsic Pathway
Vascular Surface Changes

Kallikrein + HMWK

HMWK

VIIIa → VIIIa/I Xa

Ca2+

Extrinsic pathway

Tissue thromboplastin

VII → VIIa

Common pathway

Prothrombin (II)

Xa + V

Xa + V

Thrombin

Fibrinogen (I) → Fibrin monomer → Fibrin polymer → Stable fibrin

Clot formation
Extrinsic Pathway

Tissue Factor

VIIa/TF
Fibrinolytic System

- Dissolves the occlusive fibrin clot
  - Restores vessel patency
  - Allows normal healing of vessel
Intrinsic pathway

Vascular surface changes

XII → XIIa

X → Xla

IX → IXa

Xla

Extrinsic pathway

Tissue thromboplastin

VII → VIIa

Common pathway

Prothrombin (II)

X ↘

Xa + V

Thrombin

Fibrinogen (I) ↘

Fibrin monomer ➔

Fibrin polymer ➔

Stable fibrin

Clot formation

Plasminogen

TPA/Uro

Plasmin

Fibrin Split Products + D-Dimer
Anticoagulants

Several natural anticoagulants exist

- Prevents “over” coagulation
- Deficiencies result in prothrombotic states
Laboratory Evaluation of Coagulation

- **aPTT**
  - Pt plasma incubated with surface-active powder (silica)
  - Measures intrinsic pathway and common pathway
Laboratory Evaluation of Coagulation

Evaluate abnormal PTT with 1:1 mixing study

- Clotting times remain prolonged = Inhibitor
- vs
- Clotting times normalize or decrease to near-normal = Factor deficiency
Laboratory Evaluation of Coagulation

**PT**
- Pt plasma incubated with source of tissue factor
- Extrinsic Pathway and Common Pathway
Laboratory Evaluation of Coagulation

Both PT/PTT elevated, typically common pathway deficiency or disease state like liver dsx/DIC
Disseminated Intravascular Coagulation

Consumption coagulopathy, Defibrination syndrome

Systemic activation of coagulation

- Intravascular deposition of fibrin
  - Microvascular occlusion/thrombosis and organ ischemia
  - Thromboembolic disease
- Consumption of coagulation factors and platelets
  - Bleeding if exhausted
Disseminated Intravascular Coagulation

Pathophysiology

- Tissue factor activation and coagulation
- Impaired fibrinolysis
- Defective anticoagulation pathways
Pathophysiology of DIC

- Fibrin deposition
  - Intravascular fibrin formation
  - Insufficient fibrin removal

- Mononuclear cells
- Proinflammatory cytokines
- Tissue factor expression
- Impairment of anticoagulant mechanisms
- PAI-1-mediated inhibition of fibrinolysis

- Vascular endothelial cells
Tissue Factor Activation

- Extrinsic pathway exclusive as etiology of fibrin deposition in DIC

- Activated by multiple pathologic states
  - Infection/sepsis
  - Trauma/head trauma
  - Malignancy
  - Vascular abnormalities
  - Obstetric complications
Impaired Fibrinolysis

- Bacteremia results in rapid increase in fibrinolytic activity due to endothelial cell release of plasminogen activators.
- Rapid decline in fibrinolytic activity due to sustained increase of plasminogen activator inhibitor, type 1.

Diagram:
- Plasminogen
- PAI-1
- TPA/Urokinase
- Plasmin
- Fibrin degradation products/D-Dimer
Defective Anticoagulation Pathways
Clinical Manifestations

No clinical manifestations with just abnormal labs to suggest diagnosis

Bleeding- 70-90%

Thromboembolic- 10-40%
Diagnosis

International Society on Thrombosis and Hemostasis, subcommittee on DIC

Box 2. Diagnostic algorithm for the diagnosis of overt disseminated intravascular coagulation (DIC)

Step 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.

Step 2. Order global coagulation tests: platelet count, prothrombin time (PT), fibrinogen, soluble fibrin monomers, or fibrin degradation products.

Step 3. Score global coagulation test results:
  - platelet count (> 100 = 0, < 100 = 1, < 50 = 2)
  - elevated fibrin-related marker (eg, soluble fibrin monomers/fibrin degradation products) no increase: 0; moderate increase: 2; strong increase: 3*
  - prolonged prothrombin time (< 3 sec. = 0, > 3 but < 6 sec = 1, > 6 sec = 2)
  - fibrinogen level (> 1.0 g/L = 0, < 1.0 g/L = 1)

Step 4. Calculate score.

Step 5. If ≥5: compatible with overt DIC; repeat scoring daily. If <5: suggestive (not affirmative) for non overt DIC; repeat next 1–2 days.

* In the prospective validation studies, D-dimer assays were used and a value above the upper limit of normal was considered moderately elevated; whereas, a value above five times the upper limit of normal was considered a strong increase.
Treatment

- Treat the underlying disease process!!!!
- Replace platelets, FFP, cryoprecipitate, Vitamin K
Treatment

Heparin

- Subacute/chronic DIC as in malignancy as more likely to have thromboembolic phenomenon
- Acute DIC less commonly; consider if intensive replacement therapy doesn’t alleviate bleeding/correct coags
- 80u/kg bolus then 18u/kg/hr
Treatment

Recombinant tissue pathway factor inhibitor

- Inhibits VIIa/TF binding to factor X
- OPTIMIST trial
  - 96 hr continuous infusion of rTPFI vs placebo
  - Efficacy end point 28 day mortality
  - Additional analysis of organ dysfunction, biomarkers of inflammation and coagulation
Treatment

Recombinant tissue pathway factor inhibitor

- OPTIMIST trial
  - rTPFI mortality 34.2%, placebo mortality 33.9%
  - Trend toward mortality benefit in pts with documented bloodstream infections or documented PNA
Treatment

Antithrombin III

- Inhibits multiple clotting factors; most potently thrombin
- First transfused in pts with DIC in 1978 by Schipper
- Multiple animal studies with improved lab parameters, shortened duration of DIC, improved organ fxn, AND improved mortality
Treatment

Antithrombin III

- Fourrier et al, 1993
  - 35 pts septic shock, DIC
  - 44% relative risk reduction in sepsis mortality

- Inthorn et al, 1997
  - 45 pts septic shock, DIC; co-adm with heparin gtt
  - 14% relative risk reduction in mortality

- Schuster et al, 1998
  - 42 pts septic shock, DIC
  - 39% relative risk reduction in mortality
Treatment

Antithrombin III

- Large phase III multinational sepsis study
  - 2314 patients worldwide
  - No improvement in 28 day mortality compared to placebo
    - Study population not as sick as they had hoped to enroll
    - Failure to achieve target blood level of ATIII
    - SIGNIFICANT bleeding risk if co-administer of even low dose heparin