Coagulation, Coagulopathy, and Anticoagulants

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Disclosures

• I have nothing to disclose,
• not even my age or my handicap.

The Vascular Endothelium

Why don’t clots form when we DON’T want them to form, and how do they form when we DO want them to form?

History of Coagulation

Professor Oscar D. Ratnoff

The Role of Platelets

Adhesion, activation, aggregation
The Coagulation Cascade: Then ....

Inflammation and Coagulation

“Every time you have inflammation, you have coagulation”

Sources of Tissue Factor

- Vascular injury
- Malignancy
- Circulating Monocytes

Inflammation and Coagulation

- Trauma
- Surgery
- Sepsis
- Obstetric calamity
- Toxins and bites
- Cancer
- Burns

Inflammation and Coagulation

Activation of coagulation and deposition of fibrin as a result of inflammation leads to extensive organ dysfunction.

The most important initiator of inflammation-induced coagulation is the expression of tissue factor.
Tissue Factor

• The source of tissue factor is often different in different inflammatory conditions
  - Adventitial layer in injured vascular endothelium
  - Macrophages in unstable plaque rupture
  - Malignant cells
  - Circulating mononuclear cells

Endogenous Anticoagulants: Checks and Balances

Tissue factor, thrombin generation, and amplification

Fibrinolysis: clot stabilization

DIC: An elusive target

• Remains a diagnostic conundrum especially in the early stages
• Represents a continuum from non-overt DIC with early thrombosis to overt DIC with thrombosis and hemorrhage
• Novel therapies have been limited by our inability to recognize it early, therefore treatment remains directed at eliminating the inciting cause and supportive therapies
DIC: How it Happens

- Trigger (uncontrolled tissue injury)
- Activation of the coagulation cascade
- Formation of fibrin (fibrinogen conversion)
- Initiation of fibrinolysis

DIC: Diagnostic Tools

The ISTH Scoring System

- Exhibits superior prognostic value at predicting MODS and poor prognosis
- Selects more patients than the ISTH scoring system
- Dynamic scoring of the platelet counts contributes to the sensitivity
- Scoring should occur daily to evaluate the severity and development of DIC

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DIC: The JAAM Scoring System

The Discovery of Heparin

By Jay McLean, M.D.
Keeping up with Anticoagulants

- **Options for thromboprophylaxis**
  - ASA
  - Antiplatelet drugs and IIb-IIIa inhibitors
  - SQH
  - IV UFH
  - LMWH
  - VKA’s
  - Indirect Factor Xa inhibitors
  - Oral direct thrombin inhibitors
  - Parenteral direct thrombin inhibitors

Reversing Anticoagulants

- **Factor Xa inhibitors**
  - Indirect inhibitors
    - Idraparinux - half life 80 hrs, hold for 1 week
  - Direct inhibitors
    - Apixaban
    - Rivaroxaban

- **Oral direct thrombin inhibitors**
  - Dabigatran: CCl3 > 50 hold for 1-2 days minor Sx, 3-4 days major Sx
    - CCl3 < 50 hold for 3-4 days minor Sx, 6-8 days major Sx
    - PCC?

- **Parenteral direct thrombin inhibitors**
  - Argatroban: half life 40-50 min; will falsely elevate the INR

Novel Agents

- **Odiparcil**
  - An oral, indirect thrombin inhibitor which activates antithrombin II
- **RB006**
  - Direct factor X inhibitor which inhibits the factor VIII-X activation of factor X
  - Being developed in conjunction with its antidote, RB007
- **Recombinant human soluble thrombomodulin (ART-123)**
  - Binds to thrombin and activates protein C
- **SR123781A**
  - Inhibits both factor Xa and thrombin via antithrombin

Take Home Messages

- **Our concepts of the normal coagulation system continues to evolve, and includes the role of the vascular endothelium, the platelet, and the cell based model of coagulation**
- **Inflammation plays a critical role in activating the coagulation system**
- **DIC remains a diagnostic and therapeutic challenge**
- **The burgeoning array of anticoagulation poses new challenges for perioperative patients**