Coagulation, Coagulopathy, and Anticoagulants

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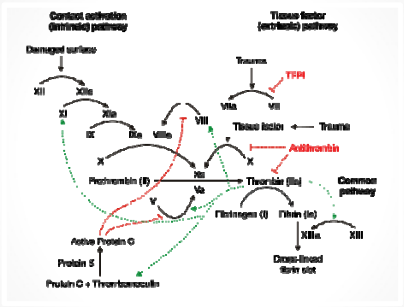
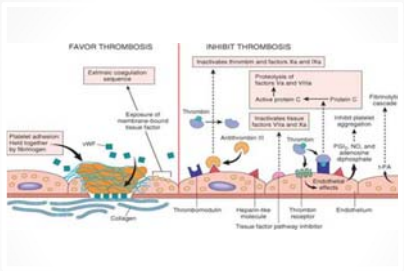
The Coagulation System: An outdated model



Disclosures

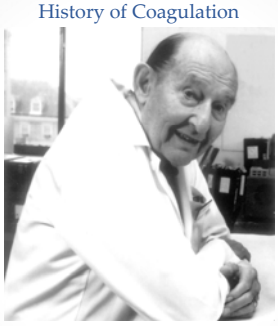
- I have nothing to disclose,
- not even my age or my handicap.

The Vascular Endothelium



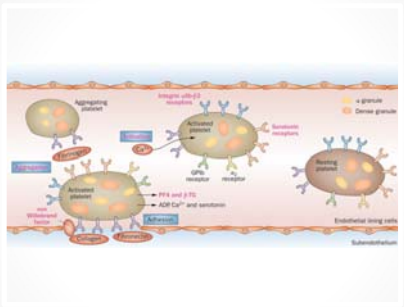
Why don't clots form when we DON'T want them to form, and how do they form when we DO want them to form

History of Coagulation



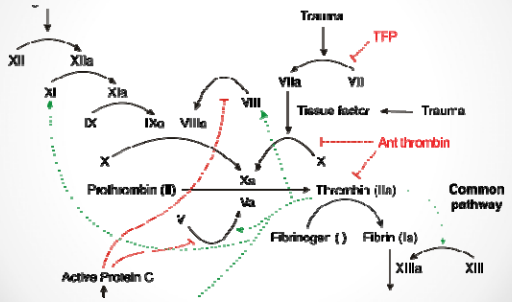
Professor Oscar D. Ratnoff

The Role of Platelets



Adhesion, activation, aggregation

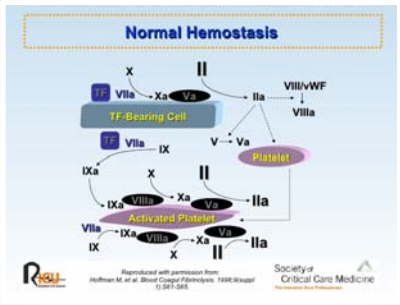
The Coagulation Cascade: Then ….



Inflammation and Coagulation

"Every time you have inflammation, you have coagulation"

The coagulation cascade



…. And Now

Inflammation and Coagulation

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

Sources of Tissue Factor

- Vascular injury
- Malignancy
- Circulating Monocytes

Inflammation and Coagulation

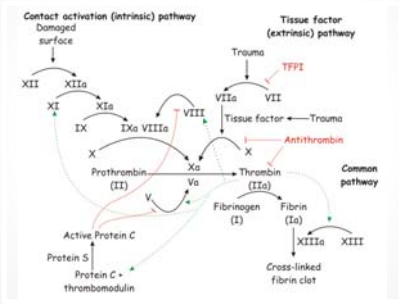
- Activation of coagulation and deposition of fibrin as a result of inflammation leads to extensive organ dysfunction
- The most important initiator of inflammation-induced coagulation is the expression of

tissue factor

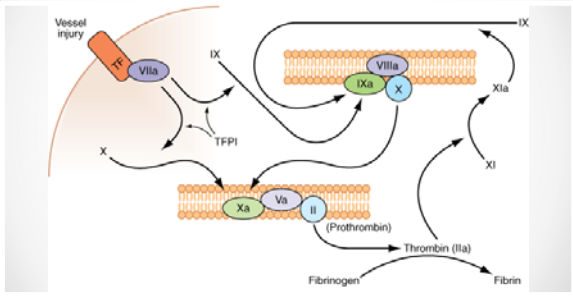
Tissue Factor

- 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

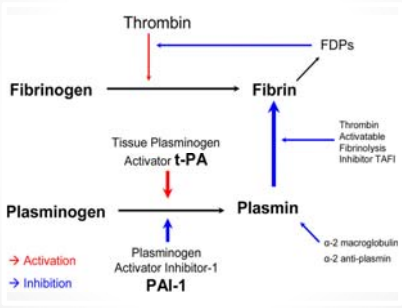
Endogenous Anticoagulants: Checks and Balances



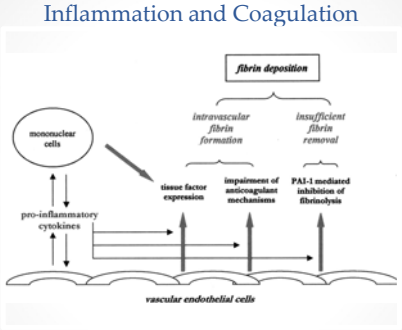
Tissue factor, thrombin generation, and amplification



Fibrinolysis: clot stabilization



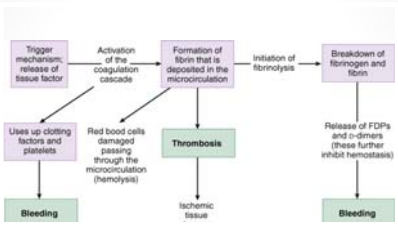
Inflammation and Coagulation



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



The JAAM 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

DIC: Diagnostic Tools

Table 1: International Society of Thrombosis and Haemostasis disseminated intravascular coagulation (DIC) scoring system

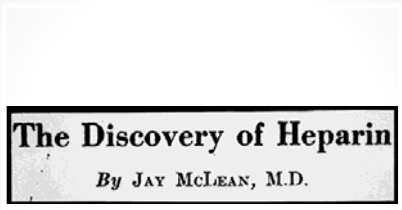
1. Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?
   If yes, proceed; if no, do not use this algorithm.
2. Order global coagulation tests (platelet count, prothrombin time, fibrinogen, soluble fibrin monomers, or fibrin degradation products).
3. Score global coagulation test results.
   - Platelet count (>100, 0; <100, 1; <50, 2)
   - Elevated fibrin-related marker (e.g., soluble fibrin monomers/fibrin degradation products) (no increase, 0; moderate increase, 2; strong increase, 3)
   - Prolonged prothrombin time (<3 secs, 0; >3 secs but <6 secs, 1; >6 secs, 2)
   - Fibrinogen level (>1.0 g/L, 0; <1.0 g/L, 1)
4. Calculate score
5. If ≥5, compatible with overt DIC; repeat scoring daily.
   If <5, suggestive (not affirmative) for nonovert DIC; repeat next 1-2 days.

The ISTH Scoring System

DIC: The JAAM Scoring System

Clinical conditions that should be ruled out
Thrombocytopenia Dilution and abnormal distribution Massive blood loss, massive infusion ITP, TTP-HUS, HIT, HELLP syndrome Disorders of hematopoiesis Liver disease Hypothermia Spurious laboratory results
Diagnostic algorithm for SIRS
Temperature >38°C or < 36°C Heart rate >90 beats/min Respiratory rate >20 breaths/min or $PaCO_2$ < 32 mm Hg [< 4.3 kPa] WBC count >12,000 cells/μL < 4000 cells/ μL or 10% immature (band) forms

Diagnostic algorithm *SIRS criteria*	Score
>3	1
0-2	0
Platelet count (× 10⁹/L)	
< 80 or >50% decrease within 24 hours	3
>80 and < 120 or >30% decrease within 24 hours	1
>120	0
Prothrombin time (ratio of patient/normal value)	
>1.2	1
< 1.2	0
Fibrin/FDPs (mg/L)	
>25	3
>10 and <25	1
< 10	0
Diagnosis **4 points or more**	**DIC**



Reversing Anticoagulants

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

  Hold for 1-2 days before minor Sx, 3-4 days before major Sx

  PCC?
- Oral direct thrombin inhibitors
  - Dabigatran: CrCl > 50 hold for 1-2 days minor Sx, 3-4 days major Sx
  - CrCl < 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
  - Bivalirudin: half life 25-35 min; will falsely elevate the INR

Keeping up with Anticoagulants

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

Novel Agents

- Odiparcil
  - An oral, indirect thrombin inhibitor which activates antithrombin II
- RB006
  - Direct factor IX inhibitor which inhibits the factor VIII-IX 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

Reversing Anticoagulants

- UFH: can be completely reversed with protamine
- LMWH: no reversal agents currently available, may be partially reversed with protamine
- Enoxaparin (single dose): factor Xa normal in 12h
- (twice daily): factor Xa normal in 24h
- Fondaparinux: 36h to 48h
- VKA's: Vitamin K for mildly increased INR
- PCC for life threatening conditions or intracranial hemorrhage
- FFP
- Off-label use of recombinant factor VII

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