Objectives of This Presentation

- Identify and describe the critical elements of the hemostatic mechanisms of the body
- Develop and implement an effective diagnostic and therapeutic approach to the abnormally bleeding patient
Black Box View of Hemostasis

Platelet/coagulation factor activation

Lots of exciting biochemistry

CLOT!
Key Points

- Hemostasis requires the interaction of platelets, coagulation and fibrinolytic factors, endothelium, proinflammatory and anti-inflammatory mediators, and leukocytes.
- Clot formation is typically initiated by vascular injury, in which a platelet plug forms and is reinforced with fibrin produced via the extrinsic pathway.
- Physiologic anticoagulants such as AT-III and Activated Protein C oppose thrombosis, serving to localize it to sites of vascular injury.
- Clot formation is balanced by plasmin-mediated fibrinolysis, resulting in the formation of D-dimers and other fibrin degradation products.
Vascular Injury

First

- Vasoconstriction

Second

- Exposure of Subendothelial Collagen
- Platelet Adhesion, Aggregation, and Activation (Primary Hemostasis)

Third

- Release of Tissue Factor
- Coagulation Cascade (Secondary Hemostasis)
- Stable Fibrin/Platelet Clot
- Fibrinolysis [as needed]
Platelets

Receptor Exposure, Activation

Adherence

Thromboxane A₂

Activation

Bind Clotting Factors

Aggregation

Vasoconstriction

Platelet Plug (Surface)

Thrombosis

Granule Release

Fibrinogen

Collagen
Thrombin
ADP
Epi
TxA₂

ADP
PDGF
5-HT

vWF
GPIib

GPIIb
GPIIIa

PL
<table>
<thead>
<tr>
<th>Coagulation Factors</th>
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<tbody>
<tr>
<td>I  Fibrinogen</td>
</tr>
<tr>
<td>II Prothrombin</td>
</tr>
<tr>
<td>III Thromboplastin</td>
</tr>
<tr>
<td>IV Calcium</td>
</tr>
<tr>
<td>V  Proaccelerin</td>
</tr>
<tr>
<td>VI Same as V</td>
</tr>
<tr>
<td>VII Proconvertin</td>
</tr>
<tr>
<td>VIII Antihemophilic</td>
</tr>
<tr>
<td>IX Christmas</td>
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<tr>
<td>X  Stuart-Prower</td>
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<tr>
<td>XI Plasma thrombo-plastin antecedent</td>
</tr>
<tr>
<td>XII Hageman</td>
</tr>
<tr>
<td>XIII Fibrin stabilizing</td>
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# Coagulation Factor Fun Facts

<table>
<thead>
<tr>
<th>Factor</th>
<th>Production</th>
<th>T 1/2</th>
<th>Level for Surgery</th>
<th>Therapy</th>
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<tbody>
<tr>
<td>I</td>
<td>Liver</td>
<td>72-100 hr</td>
<td>&gt; 100 mg/dl</td>
<td>Cryoprecipitate</td>
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<tr>
<td>II</td>
<td>Liver*</td>
<td>50-80 hr</td>
<td>15% - 40%</td>
<td>Plasma</td>
</tr>
<tr>
<td>V</td>
<td>Liver, EC</td>
<td>15-36 hr</td>
<td>15 - 25%</td>
<td>Plasma, platelets</td>
</tr>
<tr>
<td>VII</td>
<td>Liver*</td>
<td>5 hr</td>
<td>10 - 15%</td>
<td>Plasma, rVIIa</td>
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<tr>
<td>VIII</td>
<td>EC</td>
<td>8-12 hr</td>
<td>100%</td>
<td>Factor concentrate, DDAVP</td>
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<tr>
<td>IX</td>
<td>Liver*</td>
<td>24 hr</td>
<td>50% - 70%</td>
<td>Factor concentrate</td>
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<tr>
<td>X</td>
<td>Liver*</td>
<td>25-60 hr</td>
<td>10% - 40%</td>
<td>Plasma</td>
</tr>
<tr>
<td>XI</td>
<td>Liver</td>
<td>40-80 hr</td>
<td>10% - 25%</td>
<td>Plasma</td>
</tr>
<tr>
<td>XII</td>
<td>?</td>
<td>60 hr</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>XIII</td>
<td>Liver</td>
<td>4-7 days</td>
<td>&lt; 10%</td>
<td>Plasma</td>
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</tbody>
</table>
“Classic” (Test Tube) Coagulation Cascade

Since 1961
“New” (in vivo) Coagulation Cascade

Tissue Factor + VII

PL

TF-VIIa

IX

IXa

PL Ca²⁺

VIIIa

X

Xa

Prothrombin (II)

PL

Va

Thrombin (IIa)

XIII

Fibrinogen (I) → Fibrin (weak)

XIIIa → Fibrin (strong)
Factor VII – Tissue Factor “two-unit enzyme”

- Factor VIIa – catalytic component
- Tissue factor – regulatory component (not on EC or circulating blood cells)
- TF-VIIa (extrinsic Xase) complex catalyzes X to Xa
- Extrinsic Xase activates IX
- Factor VIIa + IXa form the intrinsic factor Xase
  - Intrinsic Xase 50x more effective at catalyzing factor X activation than extrinsic Xase
The Many Roles of Thrombin

Coagulation System
Clot formation:
- Fibrinogen → Fibrin
- F XIII → F XIIIa
Amplification/Activation
- F V → F Va
- F VIII → F VIIIa

Platelets
Aggregation
Release reaction
- TxA2-synthesis

Leukocytes
Chemotaxis
- Cytokine production

Macrophages
Chemotaxis

Tumor cells
Adhesion
- Metastasis
- Cell growth

Neurons
Neurite growth regulation

Endothelial Cells
Synthesis and release:
- Prostacyclin
- EDRF, t-PA
- Endothelin
- Tissue factor
Activation:
- Protein C → PCa
- Thrombomodulin

Fibroblasts
Proliferation

Smooth Muscle
- Contraction
- Mitogenesis

Heart
Positive inotrope
Physiologic Anticoagulant Mechanisms

Tissue Factor + VII → TFPI

PL

TF-VIIa → IX

IXa → PL

IX

VIIIa → Xa

PL

VIIa → Prothrombin (II)

Antithrombin III

Thrombin

Proteins C & S (+ thrombomodulin)

Fibrinogen → Fibrin (weak) → Fibrin (strong)

Fibrinolysis
Today’s Rehearsals

- Will my patient bleed?
- Why am I seeing excessive intraoperative or post-operative bleeding!
- I think my patient has HIT!
Will my patient bleed?

- “Are you a bleeder?” is not enough
  - Hx of prolonged or frequent bleeding
    - Biting lip or tongue, gums bleed with brushing
    - Nosebleeds (excessive and recurrent)
  - Bruises without apparent injury
  - Prolonged bleeding after dental extraction
  - Excessive menstrual bleeding
  - Previous operative bleeding
  - Relative with a bleeding problem
  - Medications (ASA, Plavix, “alternatives”)
Platelet Defect or Factor Deficiency?

- Platelet defect or von Willebrand disease
  - Mucocutaneous bleeding
  - Excessive bruising, gingival bleeding, frequent nose bleeds
- Coagulation factor defects
  - Muscle and joint bleeds
- Both groups will bleed excessively from injuries and at the time of surgery!
Inherited Defects of Platelet Function

- **Platelet function disorders with normal platelet numbers**
  - Collagen aggregation defects (variable inheritance)
  - Glanzmann thrombasthenia (AR)
  - Dense body deficiency (AR)
  - Secretion defect (varies)

- **Thrombocytopenia (large platelets)**
  - Alport’s syndrome (AD)
  - Autosomal dominant thrombocytopenia (AD)
  - Bernard-Soulier (AR)
  - Gray platelet syndrome (AD)
  - May Hegglin anomaly (AD)
  - Fechnter syndrome (AD)
  - Montreal giant platelet syndrome (AD)

- **Thrombocytopenia (normal sized platelets)**
  - Chédiak-Higashi syndrome (AR)
  - Thrombocytopenia with absent radius (TAR, AR)
  - Factor V Quebec (AD)

- **Thrombocytopenia (small platelets)**
  - Wiskott-Aldrich syndrome (X-linked)
Acquired or Inherited Factor Disorder?

- Acquired bleeding factor disorders will often present suddenly with severe bleeding and newly abnormal coagulation tests
  - Patients have other illnesses but autoimmune coagulation disorders can suddenly strike any previously healthy person
Acquired or Inherited Factor Disorder?

• Inherited bleeding factor disorders
  – Present from birth until old age
  – Mild hemophilia or von Willebrand disease patients may not have had troublesome bleeding until the first trauma or surgery
• Do not ignore an abnormal aPTT in an older patient
• Review family history
  – Hemophilia A/B are sex-linked - brothers, cousins, uncles
  – Von Willebrand disease may have variable penetrance within the family
Von Willebrand Disease (vWD)

• The most common inherited bleeding disorder
  – 1% of the population
  – Five forms or types are known and distinguishable
  – Classic – reduced VIII activity and decreased vWF
• vWF is crucial for the interaction of platelets with damaged vasculature
• vWF is also the carrier protein for factor VIII (otherwise, free VIII is labile in the plasma)
• vWD usually results from either a drop in vWF concentration or impaired vWF/VIII function
Von Willebrand Disease (vWD)

- Patients with vWD have “platelet-type” bleeding (nosebleeds and bruising)
  - Joint bleeding is rare
  - Bleeding as a child, less as an adult
  - Testing (a challenge)
    - Bleeding time (variable sensitivity)
    - Factor VIII level
    - Von Willebrand antigen
    - Ristocetin cofactor activity (binds vWF to platelets)
    - Crossed immunoelectrophoresis
- Therapy: DDAVP, Humate-P, cryoprecipitate
Will my patient bleed?

• Level I concern
  – History is negative
  – Procedure planned is relatively minor

✓ No screening tests are recommended
Will my patient bleed?

• Level II concern
  – History is negative
  – Screening tests have been negative in the past
  – **Major operation** is planned (procedure not usually attended with significant bleeding)

✔ Platelet count, peripheral smear, PT-INR, aPTT
Will my patient bleed?

• Level III concern
  – History is suggestive of poor hemostasis
  – Procedure may impair hemostasis (CPB or cell saver) or the procedure may leave behind a large, raw surface
  – Minimal post-operative bleeding will be injurious (craniotomy)

✓ Platelet count, PT-INR, aPTT,
✓ +/- bleeding time (PFA-100)
Will my patient bleed?

- Level IV concern
  - History highly suggestive of a hemostatic defect
  - Hematology consult
    - Platelet count, bleeding time, PT-INR, aPTT, euglobulin clot lysis analysis, factor assays
    - Bleeding time test + ASA provocative test
    - If emergent – platelet aggregation testing and thrombin time (TEG, if available)
Will my patient bleed?

• Patients with liver disease, renal failure, obstructive jaundice, possibility of disseminated malignant disease
  ✓ Platelet count, aPTT, PT-INR (uremic patients usually have a vitamin-K deficiency)

• Patients with uremia (qualitative platelet function abnormality)
  ✓ Bleeding time (improved with dialysis or administration of DDAVP)
Laboratory Monitoring of Coagulation

• Prothrombin Time (PT-INR)
  – Plasma + Calcium + Tissue Thromboplastin
    TF + VIIa → Xa + V → IIa → CLOT

• PT-INR only elevated
  – Factor VII deficiency
    • Congenital (very rare)
    • Acquired (Vit K deficiency, liver disease)
  – Factor VII inhibitor
  – Rarely in pts with modest decreases of factor V or X
Laboratory Monitoring of Coagulation

- Activated Partial Thromboplastin Time (aPTT)
  - Plasma + Calcium + Kaolin + Phospholipids
  - Contact → XIa → IXa + VIII → Xa + Va → IIa → CLOT

- PTT only elevated
  - Factor XI, IX, or VIII deficiency
  - Factor XI, IX, or VIII specific factor inhibitor
  - Heparin contamination
  - Antiphospholipid antibodies
Laboratory Monitoring of Coagulation

- Both PT-INR and aPTT are elevated
  - Factor(s) X, V, or II deficiency
  - Factor(s) X, V, or II inhibitor
  - Improper anticoagulation ratio (Hct >60 or <15)
  - High doses of heparin (↑ aPTT > ↑ PT-INR)
  - Large Warfarin effect ((↑ PT-INR > ↑ aPTT)
  - Low fibrinogen (<80 mg/dl)
Laboratory Monitoring of Coagulation

- Four causes of elevated aPTT and response to 50:50 mix
  - Factor XI, IX, or VIII deficiency
    - Corrects with 50:50 mix (normal pool plasma)
  - Factor XI, IX, or VIII specific factor inhibitor
    - May correct at time zero but then prolongs
  - Heparin contamination
    - Does not correct at all with normal pool plasma
  - Antiphospholipid antibodies
    - Does not fully correct at time zero or any time point
Laboratory Monitoring of Coagulation

- Thrombin Clotting Time (TCT)
  - Add thrombin to patient’s plasma
    - This should directly clot fibrinogen
  - Elevated in
    - Heparin use
    - DIC
    - Dysfibrinogenemia
    - Low fibrinogen levels
    - High fibrinogen levels
    - Uremia
Intraoperative Bleeding

**“Surgical”**
Discrete bleeding points
Obvious source
Typical scenario

Find it: Look at potential sites

(Get help, if needed)

Venous

Arterial

Pack
Get more help!
Direct suture
Ligate
Pack and close

**“Coagulopathic”**
Diffuse oozing

Late in case?

Early in case?

Pre-existing problem?

Suspect congenital or pre-existing problem

Sudden?

Progressive?

Hypothermia
Acidosis
DIC
Dilution
Primary fibrinolysis

Transfusion reaction
Medications

Treat as indicated
Hematology assistance?
HEROIC AWARD TIME!!

- Kaptain Koagulation
  - Brian Peyton
- Kid Clotter
  - Jayer Chung

- Infected aortic graft
  - Ax-bifem graft
  - Laparotomy
  - Pseudoaneurysm resection and aortic closure
- Extreme bleeding!!
- Extreme coagulopathy!!
- Couldn’t remove aortic X-clamp!!
Evaluation of Excessive Intraoperative or Postoperative Bleeding

- Ineffective or incomplete local hemostasis
- Complications of blood transfusion
  - Massive blood transfusion
  - Hemolytic transfusion reaction
- Previously undetected hemostatic defect
- Consumptive coagulopathy
- Fibrinolysis
Evaluation of Excessive Intraoperative or Postoperative Bleeding

- Ineffective or incomplete local hemostasis
  - √ Enough factor XV (Ethicon)?
  - √ CBC, platelet count
  - √ Bedside PT, aPTT
  - √ Blood transfusion record
  - √ Review patient’s history again (quickly)
Evaluation of Excessive Intraoperative or Postoperative Bleeding

• Complications of blood transfusion
  – Massive blood transfusion
    • Usually, patients who receive 10 units or more of banked blood within 24 hrs will be measurably thrombocytopenic, this is commonly not associated with a hemostatic defect
    • If there is diffuse bleeding, an 8- to 10-pack of fresh platelet concentrate should be given empirically (no clear association between the platelet count, bleeding time, and profuse bleeding)
Evaluation of Excessive Intraoperative or Postoperative Bleeding

• Complications of blood transfusion
  – Hemolytic transfusion reaction
    • First hint – diffuse bleeding in an operative field that had previously been dry
  • Pathogenesis –
    – release of ADP from hemolyzed rbcs, resulting in diffuse platelet aggregation, after which the platelet clumps are swept out of the circulation (relative thrombocytopenia)
    – Release of procoagulants – intravascular defibrination
    – Triggering of the fibrinolytic mechanism
Evaluation of Excessive Intraoperative or Postoperative Bleeding

- Previously undetected hemostatic defect
  - Congenital defects
    - Factor deficiencies
      - VIII (Hemophilia A, and/or von Willebrand’s disease)
      - IX (Hemophilia B or Christmas disease)
      - XI (Hemophilia C)
      - II, V, and X
      - VII
      - XIII
  - Transfusion purpura
    - Antibodies to donor platelets, which eventually destroy the host’s own platelets
Evaluation of Excessive Intraoperative or Postoperative Bleeding

- Consumptive coagulopathy (DIC) vs Fibrinolysis
  - No single test can confirm or exclude the diagnosis or distinguish between the two
    - Thrombocytopenia, positive plasma protamine test for fibrin monomers, a low fibrinogen level (<100), elevated FDPs argue for DIC
    - Positive euglobulin lysis time provides a method for detecting diffuse fibrinolysis
      (↑ plasminogen activator)
Life saver? rFVIIa

• Recombinant (activated) Factor VII
  – Initiates hemostasis at sites of bleeding
    • Directly activates thrombin on platelets
  – Used in various complex settings
    • Hemophilia, inhibitors to factors VIII or IX
    • Warfarin-associated bleeding
    • Massive transfusion coagulopathy
    • Acute intracerebral hemorrhage
    • Cardiac Surgery
    • Severe trauma
rFVIIa

• Anticoagulant reversal agent?
  – Hemorrhage due to LMWH – anecdotal
  – Potential reversal agent for most of the newer anticoagulant agents?
    • Reports of efficacy are derived from lab experiments or from healthy volunteers
      – Reversal of warfarin
      – Reversal of hirudin
      – Reversal of fondaparinux
    • Recommendations will require clinical data
Half of your patient’s platelets disappeared overnight! Where did they go?

- **HIT** = heparin-induced thrombocytopenia
  - Occurs in 0.6 to 30%* of patients who have received heparin

- **HITTS** = heparin-induced thrombocytopenia and thrombosis syndrome
  - Occurs in 3% with thrombosis in 0.9%
  - Morbidity and mortality reported at 61% and 23 %, respectively

*25-50% of post-cardiac surgery pts Ab (+) during the next 5-10 days!
Heparin- Induced Thrombocytopenia

- HIT begins 3 to 14 days after heparin exposure
  - Bovine, porcine, lmw heparins all guilty
- Suspect the diagnosis if…
  - 50% drop in platelet count [on heparin]
  - Fall in platelets below 100,000 [on heparin]
  - Thrombosis while on heparin
  - ? Sepsis or DIC
Heparin- Induced Thrombocytopenia

- **Treatment**
  - **Stop all heparin products**
  - Allow the heparin effect to wear off [ongoing prothrombotic state – micro-particles]
  - **Warfarin contraindicated** until adequate alternative anticoagulation established
    - Prothrombotic state similar to that of warfarin-induced protein C/S deficiency
    - May lead to venous gangrene or worse
## Anticoagulants Approved for Use by the FDA

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Mechanism</th>
<th>Indications</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Coumadin/Generic</td>
<td>Vitamin K</td>
<td>Art/Ven thrombosis</td>
<td>Oral</td>
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<tr>
<td>Anisindione</td>
<td>Miradon</td>
<td>Vitamin K</td>
<td>Art/Ven thrombosis</td>
<td>Oral</td>
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<tr>
<td>Unfractionated Heparin</td>
<td>Various agents</td>
<td>Thrombin/factor Xa antagonist</td>
<td>Art/Ven thrombosis</td>
<td>IV, SC</td>
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<td>Fractionated Heparins</td>
<td>Fragmin Lovenox</td>
<td>Factor Xa/thrombin inhibitor</td>
<td>VTE prophylaxis &amp; treatment, ACS</td>
<td>IV, SC</td>
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<td>Thrombate III</td>
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<td>VTE prophylaxis in Orthopedics</td>
<td>SC</td>
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<td>Xigris</td>
<td>Factor Va/VIIa inhibitor</td>
<td>Severe sepsis</td>
<td>IV</td>
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</table>
What if Surgery “Requires” Heparin?

- Consider status of HIT
  - Active HIT:
    - Avoid surgery
    - Avoid heparin
  - Subacute HIT
    - Avoid surgery
    - Consider alternatives to heparin
    - Heparin if absolutely necessary
  - History of HIT
    - Consider alternatives to heparin
    - Heparin, monitor closely
Black Box View of Hemostasis

Platelet/coagulation factor activation

Lots of exciting biochemistry that I now really understand!

CLOT!