DISCLOSURE

- Relevant Financial Relationship(s)
  None
Objectives

• Provide a brief overview of biology of hemostasis

• Review the common causes of congenital and acquired bleeding disorders

• Discuss value-based algorithmic approach for laboratory testing of bleeding disorders
Hemostasis

• Primary Hemostasis
  • Platelet Plug Formation
  • Platelet, VWF, subendothelium
  • Initial manifestation of clot formation
  • Provide a binding site for phospholipid-dependent coagulation complexes

• Secondary Hemostasis
  • Activation of clotting cascade

• Tertiary Hemostasis
  • Dissolution of fibrin clot
  • Dependent on plasminogen activation
Primary Hemostasis

Vascular injury / high shear stress

Endothelial damage and exposure of subendothelial matrix protein (collagen, fibronectin, vitronectin, thrombospondin, and laminin)

↓

Platelet adhesion to subendothelium (Platelet GPIb/IX/V-VWF-collagen)

↓

Platelet activation, shape change, degranulation

↓

Platelet auto-activation by endogenous activators

↓

Platelet Aggregation (GPIIb/IIIa-Fibrinogen complex)

Secondary Hemostasis
Coagulation Cascade

**Intrinsic**
- Prekallikrein
- HMW-Kininogen
- Surface

**Extrinsic**
- Tissue factor
- Phospholipid
- Ca++

**Common**
- Prothrombin (II)
- Thrombin (IIa)
- Fibrinogen
- Fibrin

**Coagulation Cascade Diagram**

- XII
- XIIa
- HMW-K
- Phospholipid
- Ca++/Zn++
- XI
- Xla
- ?
- Phospholipid
- Ca++
- IX
- IXa
- VIII
- VIIa
- Phospholipid
- Ca++
- VII-Vila
- Tissue factor
- Phospholipid
- Ca++
- X
- Va
- Phospholipid
- Ca++
- Vila
- Phospholipid
- Ca++
<table>
<thead>
<tr>
<th>Abnormalities</th>
<th>Primary Hemostasis</th>
<th>Secondary Hemostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormalities</td>
<td>Platelets; VWF; vascular</td>
<td>Coagulation factors</td>
</tr>
<tr>
<td>Site</td>
<td>Mucocutaneous</td>
<td>Deep tissues</td>
</tr>
<tr>
<td>Pattern of bleeding</td>
<td>Petechia, ecchymosis, menorrhagia</td>
<td>Hematomas, hemarthrosis</td>
</tr>
<tr>
<td>Other sites</td>
<td>Rare</td>
<td>Joint, muscle, CNS, retroperitoneum</td>
</tr>
<tr>
<td>Onset</td>
<td>Spontaneous, immediate after trauma</td>
<td>Delayed after trauma</td>
</tr>
<tr>
<td>Example</td>
<td>Thrombocytopenia, platelet functional defect, VWD, scurvy</td>
<td>Factor deficiency (congenital or acquired); acquired inhibitors</td>
</tr>
</tbody>
</table>
Evaluation of Bleeding Diathesis

- History, History, History
  - Presence or absence of bleeding diathesis
  - Acquired vs. congenital
  - Primary vs. secondary hemostasis abnormality
- Physical examination
- Laboratory tests
Evaluation of Bleeding Diathesis

- Surgical history, including dental procedures
- Nature of bleeding: epistaxis, petechiae, purpura, menorrhagia, hemathrosis, hematomas
- Family history of bleeding: negative family history does not rule out a congenital bleeding disorder
- Medication: warfarin, heparin, factor Xa inhibitor, director thrombin inhibitor aspirin or other NSAIDs, antibiotics (affecting vitamin K dependent clotting factors), herbal medications, nutritional supplements
- Medical problems: severe liver disease, malabsorption syndromes, renal failure
Screening Tests of Primary Hemostasis

• Platelets
  • Platelet count
  • Platelet functional analysis (PFA)
  • Platelet aggregation assay

• VWF
  • VWF Antigen
  • VWF Activity
  • Factor VIII
Platelet Surface Receptors and Glycoproteins

Glanzmann thrombasthenia

Reduced response to collagen

Altered response to stimuli: ADP (P2Y₁₂), TXA₂ (TPα)

Bernard-Soulier syndrome

Modified diagram used with permissions from Thromb Haemost 99:253, 2008
PFA-100

• Newer automated whole blood platelet function test
  • Measures shear-induced primary hemostasis
  • Agonist-coat cartridges
    • Collagen/Epinephrine
    • Collagen/ADP
  • Whole blood sample
    • In Collagen/Epi cartridge only: Aspirin and NSAIDs
    • In both cartridges: VWD, intrinsic platelet dysfunction, thrombocytopenia, decreased hematocrit, and other drug effects
Sensitivity of PFA-100 for Detecting Hereditary Platelet Disorders

<table>
<thead>
<tr>
<th>Reference</th>
<th>Glanzmann thrombasthenia</th>
<th>Bernard Soulier</th>
<th>Storage Pool</th>
<th>Hermansky-Pudlak</th>
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<tbody>
<tr>
<td>Fressinaud, 1998</td>
<td>2/2</td>
<td></td>
<td>4/4</td>
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<td>Mammon, 1998</td>
<td>5/5</td>
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<td>Harrison, 1999</td>
<td>6/6</td>
<td>2/2</td>
<td>2/5</td>
<td>4/6</td>
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<td>Kerenyi, 1999</td>
<td>1/1</td>
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<td></td>
<td>3/5</td>
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<td>Cattaneo, 1999</td>
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<td>0/6</td>
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<td>Harrison, 2002</td>
<td></td>
<td></td>
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<td>13/19</td>
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<tr>
<td>Posan, 2003 (Mayo)</td>
<td>3/3</td>
<td></td>
<td>1/1</td>
<td>1/1</td>
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<tr>
<td>Total</td>
<td>15/15</td>
<td>2/2</td>
<td>7/16</td>
<td>21/31</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>100</td>
<td>100</td>
<td>44</td>
<td>68</td>
</tr>
</tbody>
</table>
Platelet Aggregation Assay

- Measures the ability of agonist to induce in vitro platelet activation and platelet-platelet binding
  - In whole blood: impedance technique; can be combined with luminometer to monitor dense granule release (ATP)
  - In platelet rich plasma (PRP): turbidimetric techniques

- ADP
- Arachidonic acid (AA)
- Collagen (Co)
- Epinephrine (Epi)
- Ristocetin (Rc)
# Platelet Aggregation Assay Interpretation

<table>
<thead>
<tr>
<th>Normal/Disease</th>
<th>AA</th>
<th>U$_{46619}$</th>
<th>ADP 5 µN</th>
<th>ADP 20 µM</th>
<th>EPI</th>
<th>COL low</th>
<th>COL high</th>
<th>Ristocetin</th>
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<tbody>
<tr>
<td>Normal</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N/↓</td>
<td>N</td>
<td>N</td>
<td>N</td>
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<tr>
<td>SPD</td>
<td>N/↓</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N/↓</td>
<td>N/↓</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>BSS or VWD</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>↓↓</td>
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<tr>
<td>GT</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>N/↓</td>
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<tr>
<td>P2Y12</td>
<td>V</td>
<td>V</td>
<td>↓↓</td>
<td>↓↓</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>N/V</td>
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<tr>
<td>GPIIa</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>↓</td>
<td>N/↓</td>
<td>N</td>
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<td>GPVI</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>↓↓</td>
<td>N/↓</td>
<td>N</td>
</tr>
<tr>
<td>TXA2 synthesis</td>
<td>↓↓</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>TXA2 receptor</td>
<td>↓↓</td>
<td>↓↓</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

N: Normal    V: Variable    ↓: Decreased  
BSS: Bernard Soulier Syndrome (GP Ib/IX/IV)  
GT: Glanzmann’s Thrombasthenia (GPIIbIIIa)
Von Willebrand Factor (VWF)

- D', D3, A1, A2, A3, D4
- FVIII, GPIb, Collagen
- Multimer S-S, Ristocetin
- Dimer S-S, GPIIb-IIIa, RGDS
von Willebrand Disease (VWD)

• Clinical Features
  • Prevalence ≈ 1%
  • 0.1% (1:1000) symptomatic
  • Female: Male ≈ 2:1

• Classification
  • Type 1: partial quantitative deficiency (≈70%)
  • Type 2: qualitative abnormalities (≈25%)
  • Type 3: complete deficiency (<5%)
VWD Subtypes

• Type 1 and 3 VWD: quantitative

• Type 2 VWD: qualitative
  • Defective platelet adhesion
    • 2A: Selective deficiency of HMW multimers
    • 2B: Increased platelet affinity
      loss of HMW multimers
    • 2M: Decreased platelet or matrix binding
      normal multimers
  • Defective FVIII binding
    • 2N: Normal multimers, decreased factor VIII binding,
      normal platelet adhesion
VWD Testing – Laboratory

- **Initial testing**
  - VWF:Antigen
  - VWF activity (VWF:Rco, or other method)
  - FVIII:C

- **Additional Testing**
  - VWF multimer analysis
  - Ristocetin-induced platelet aggregation (RIPA)
  - VWF:CB (collagen binding activity)
## Expected Laboratory Values in VWD

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Type 1</th>
<th>Type 2A</th>
<th>Type 2B</th>
<th>Type 2M</th>
<th>Type 2N</th>
<th>Type 3</th>
<th>PLT-VWD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>VWF: Ag</td>
<td>N</td>
<td>L, ↓ or ↓↓</td>
<td>↓ or L</td>
<td>↓ or L</td>
<td>N or L</td>
<td>Absent</td>
<td>↓ or L</td>
<td></td>
</tr>
<tr>
<td>VWF: Rco</td>
<td>N</td>
<td>L, ↓ or ↓↓</td>
<td>↓↓↓ or ↓↓↓</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
<td>N or L</td>
<td>Absent</td>
<td>↓↓</td>
</tr>
<tr>
<td>FVIII</td>
<td>N</td>
<td>N or ↓</td>
<td>N or ↓</td>
<td>N or ↓</td>
<td>↓↓↓</td>
<td>1-9 IU/dL</td>
<td>N or L</td>
<td></td>
</tr>
<tr>
<td>RIPA</td>
<td>N</td>
<td>Often N</td>
<td>↓↓↓</td>
<td>Often N</td>
<td>↓↓↓</td>
<td>Absent</td>
<td>Often N</td>
<td></td>
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<tr>
<td>LD-RIPA</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>↑↑↑</td>
<td>Absent</td>
<td>Absent</td>
<td>↑↑↑</td>
<td></td>
</tr>
<tr>
<td>PFA-100® CT</td>
<td>N</td>
<td>N or ↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>N</td>
<td>↑↑↑</td>
<td></td>
</tr>
<tr>
<td>BT</td>
<td>N</td>
<td>N or ↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>N</td>
<td>↑↑↑</td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>↓ or N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td></td>
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<tr>
<td>VWF multimer</td>
<td><img src="image" alt="Pattern" /></td>
<td><img src="image" alt="Pattern" /></td>
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</tbody>
</table>

NHLBI Guidelines 12/2007
# Acquired von Willebrand Syndrome (AVWS)

<table>
<thead>
<tr>
<th>Pathophysiologic Category</th>
<th>Disease or Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibodies to VWF</td>
<td>Monoclonal Gammopathies; Lympo-prolif. Dz; Autoimmune Dz (SLE etc.)</td>
</tr>
<tr>
<td>Shear-induced VWF proteolysis (ADAMTS13)</td>
<td>AS/R; MS/R; VSD; LVAD; HOCM; Primary Pulmonary Hypertension</td>
</tr>
<tr>
<td>Thrombocytosis (marked) &amp; proteolysis</td>
<td>Essential Thrombocytemia; P. vera; AMM + Myelofibrosis; other MPN</td>
</tr>
<tr>
<td>(ADAMTS13)</td>
<td></td>
</tr>
<tr>
<td>Aberrant VWF binding to tumor cells</td>
<td>Wilm’s tumor; certain plasma cell or lymphoproliferative disorders</td>
</tr>
<tr>
<td>Decreased VWF synthesis</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Drug-related AVWS</td>
<td>Ciprofloxacin, valproic acid, hydroxyethyl starch, griseofulvin</td>
</tr>
</tbody>
</table>
Secondary Hemostasis Screening Tests

**Intrinsic**
- Surface activator
- Phospholipid
- Ca²⁺

**Extrinsic**
- Tissue thromboplastin (tissue factor and phospholipid)
- Ca²⁺

### Pathway Diagram

- **VIII** → **IX** → **X** → **XIII**
- **APTT**
- **Thrombin time (TT)**
- **Fibrinogen (I)**

- **TF/VIIα**
- **PT**
- **Fibrin**

**Notes:**
- Fibrinogen (I) → Fibrin
Thrombin Time (TT) and Reptilase Time (RT)

**Thrombin time**: sensitive to heparin or director thrombin inhibitor

![Thrombin time diagram](image)

- TT prolonged, RT normal:
  - Heparin
  - Director thrombin inhibitor (DTI)

- TT and RT both prolonged:
  - Hypofibrinogenemia
  - Dysfibrinogenemia
  - Interference from elevated fibrin degradation product, paraprotein
  - Anticoagulant artifact

**Reptilase time**: insensitive to heparin or director thrombin inhibitor

![Reptilase time diagram](image)
Prolonged Clot Time

- Factor deficiency
- Factor inhibitors
- Dysfunctional factors
- Pre-analytical artifact
## Congenital Coagulation Factor Deficiencies

<table>
<thead>
<tr>
<th>Congenital coagulation factor deficiency</th>
<th>Deficient factor</th>
<th>PT</th>
<th>APTT</th>
<th>Prevalence</th>
<th>Mode of inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia A</td>
<td>Factor VIII</td>
<td>Normal</td>
<td>Prolonged</td>
<td>1:5000†</td>
<td>X-linked recessive</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>Factor IX</td>
<td>Normal</td>
<td>Prolonged</td>
<td>1:30,000†</td>
<td>X-linked recessive</td>
</tr>
<tr>
<td>Hemophilia C</td>
<td>Factor XI</td>
<td>Normal</td>
<td>Prolonged</td>
<td>Up to 4%‡</td>
<td>Autosomal</td>
</tr>
<tr>
<td>von Willebrand disease</td>
<td>von Willebrand factor</td>
<td>Normal</td>
<td>Normal/prolonged</td>
<td>Up to 1%</td>
<td>Autosomal</td>
</tr>
<tr>
<td>Factor VII</td>
<td></td>
<td>Prolonged</td>
<td>Normal</td>
<td>1:500,000</td>
<td>Autosomal</td>
</tr>
</tbody>
</table>

**Rare coagulation factor deficiencies**

| Factor V                                 | Prolonged | Prolonged | 1:1 million | Autosomal |
| Factor II                                | Prolonged | Normal/prolonged | Rare§ | Autosomal |
| Factor X                                 | Prolonged | Normal/prolonged | 1:500,000 | Autosomal |
| Factor XIII                              | Normal    | Normal    | Rare§      | Autosomal |
| Combined factors VIII and V              | Prolonged | Prolonged | Rare§      | Autosomal |

*APTT = activated partial thromboplastin time; PT = prothrombin time. †Live male births. ‡Among Ashkenazi Jews. §Case reports.

Typical APTT Test Sensitivity coagulation Factor Deficiencies

- From highest to lowest sensitivity for deficiency
  - Factor XII (<40-50%)
  - Factor XI (<40-50%)
  - Factor VIII (<30-35%)
  - Factor IX (<20-25%)
  - Factor XIII (Insensitive)

- Note: APTT sensitivity to coagulation factor deficiency varies with differing APTT reagents and coagulation instrumentation; data shown are general approximations.
Typical PT test sensitivity coagulation factor deficiencies

- Factor VII (<45-55%)
- Factor V (<35-45%)
- Factor X (<25-35%)
- Factor II (<20-30%)
- Factor I (fibrinogen) (<50-75 mg/dL)

Note: PT sensitivity to coagulation factor deficiency varies with differing PT reagents and coagulation instrumentation; data shown are general approximations.
Approach to a Prolonged PT or APTT
Exclusion of Artifactual Results

Prolonged PT/APTT

Is abnormality artifactual?

Repeat testing

Normal

No further testing

Abnormal

Is patient receiving anticoagulants or does patient have systemic disease (eg. Liver disease)?

Yes

No further testing, unless clinically indicated

No

Mixing study with normal plasma

CBC to exclude erythrocytosis
Wrong Tube (EDTA)
Storage or Transportation

Images:
- Normal and high plasma levels with different anticoagulants
- Categorization of hematocrit levels
Prolonged PT/APTT

Mixing study with normal plasma

PT/APTT corrects

Clotting factor deficiency

Clotting factor assays to identify deficiency: clinical correlation to determine whether deficiency is congenital or acquired

PT/APTT inhibited

Inhibitor

Further testing to determine type of inhibitor

Drug: heparin, direct thrombin inhibitor, factor Xa inhibitor

Specific factor inhibitor (eg. Factor VIII or V)

Nonspecific inhibitor: lupus anticoagulant
APTT

Is result within normal range?

YES → STOP

NO →

APTT Mixing Test (1:1 mix with normal plasma)

Does result correct sufficiently?

YES

Is further clarification needed?

NO → STOP

NO → Platelet Neutralization Procedure (PNP)

Factor assays: XII, XI, IX

NO → STOP

STOP

Dilute Russell Viper Venom Time (DRVVT)

Is result within normal range?

YES

No heparin

STOP

NO

DRVVT Mixing Test (1:1 mix with normal plasma)

Does result correct sufficiently?

YES

Assays performed upfront

STOP

NO →

DRVVT Confirmatory Testing

PT

Is result within normal range

YES → STOP

NO →

PT Mixing Test (1:1 mix with normal plasma)

Is further clarification needed?

YES → STOP

NO

Reptilase Time

TT

Is TT normal?

YES

Factor assays: II, V, VII, X

STOP

NO →

STOP

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VWF antigen

Abnormal (<55)
- Ristocetin activity

Normal (55-200)
- VWF activity/antigen ratio <0.8
  - No
    - STOP
  - yes
    - VWF multimer analysis

VWF activity

Abnormal (<60)
- STOP

Normal (60-200)
- Ristocetin activity

Factor VIII

Normal (55-200)
- STOP

Abnormal (<55)
- Suspicion for Factor VIII inhibitor?
  - No
    - Inhibitor Screen
      - Bethesda titer
        - pos
        - Inhibitor Screen
          - Bethesda titer

Factor IX (male)
Fibrinogen
Fibrin D-dimer
Factor XIII screen

Assays performed upfront
Questions & Discussion