Benign Hematology: Bleeding Disorders

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Learning Objectives

1. Identify common algorithms for the evaluation of patients with bleeding disorders including inherited and acquired disorders
2. Discuss current recommendations for the evaluation and treatment of idiopathic thrombocytopenia purpura (ITP)
3. Discuss current recommendations for the evaluation and treatment of patients with von Willebrand disease
4. Outline strategies to reduce the risk of bleeding during surgical procedures for patients with bleeding disorders
Financial Disclosure

Dr. Krishnadasan has no potential conflicts of interest.
Outline

- Review of hemostasis
- Workup and laboratory testing
- Primary hemostasis
  - von Willebrand disease
  - Immune thrombocytopenia
- Secondary hemostasis
  - Hemophilies
  - Acquired hemophilia
  - Lupus anticoagulant
Primary Hemostasis

Primary Hemostasis (cont)
Primary Hemostasis (cont)
Primary Hemostasis (cont)
Primary Hemostasis (cont)

Formation of Platelet Plug!
Secondary Hemostasis
Secondary Hemostasis

[Diagram showing the process of secondary hemostasis, including factors, von Willebrand factor, platelets, collagen, and fibrin clot.]
Primary Hemostasis (cont)

1. Vascular injury exposing collagen and tissue factor
2. vWF binds collagen to platelets (GPIb-IX); collagen also binds platelets directly
3. Platelets adhere; then release ADP and thromboxane A2, causing platelet aggregation and plug formation
4. Platelets adhere to each other with GPIIb-IIIa
Platelets

- Megakaryocytes are their progenitor cells in the bone marrow
- Lifespan in peripheral blood 8–10 days
- Normal values between 150K and 400K
- Important in primary hemostasis—form the platelet plug
- Important for secondary hemostasis—provide surface and phospholipid for coagulation cascade
- Contain granules that are released with activation: ADP, platelet factor 4, factor V
Secondary Hemostasis
Coagulation Factors

- Normally circulate as zymogens (inactive precursors)
- Vitamin K–dependent factors: II, VII, IX, X
  - Also protein C and protein S, which are natural anticoagulants
- Intrinsic and extrinsic pathways
- Ultimately lead to fibrin-stabilizing clot
Coagulation Cascade

PTT

PT/INR
Platelet Phospholipids Play Central Role in Blood Coagulation
Fibrinolysis

- In equilibrium with hemostasis
- Removes fibrin deposits and prevents formation of unnecessary fibrin clots
- In event that lysis of clot occurs rapidly, could see bleeding; often delayed
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History

- Decipher whether pattern is consistent with primary vs. secondary hemostasis
  - Or delayed bleeding
- History of transfusions
- History of procedures
- Family history
- Time/age of onset
- Changes with estrogens, or pregnancy
History: Primary Hemostasis

- Mucocutaneous bleeding (microhemorrhage)
  - Gum bleeding
  - Nose bleeds
  - Bruising: Spontaneous vs. with trauma
    - VERY subjective
  - Petechiae
  - Menorrhagia (How many days? Pads?)
  - Bleeding history with dental extractions
    - Wisdom teeth
Petechiae
Petechiae

Vascular-platelet defect
- Petechiae, purpura
- Skin and mucous membrane bleeding
- Spontaneous
- Bleeding immediate, prolonged

Purpura
History: Secondary Hemostasis

- Hemarthrosis (macrohemorrhage)
  - Knees/elbows > ankles > shoulders > hips
  - Early sensation of stiffness, or aura
- Muscle bleeds
  - Flexors > extensors (iliopsoas, quads, gastrocnemius)
  - May require prolonged therapy
- May also see some bruising
Hemarthrosis (joint bleed)

Iliopsoas bleed

Muscle bleed
Laboratory Testing: Primary Hemostasis

- Platelet function
  - Bleeding time
  - Platelet aggregation
  - PFA-100
  - Thromboelastogram (TEG)

**Make sure patient is not on NSAIDs or aspirin and is not thrombocytopenic!!**
PFA-100

Platelet

Platelet Agonists
ADP
EPI

? Platelet Closure Time
Laboratory Testing: Primary Hemostasis (cont)

- Von Willebrand
  - von Willebrand antigen (vW Ag)
  - von Willebrand activity
    - Ristocetin cofactor activity
  - Factor VIII activity
  - von Willebrand multimers
  - Collagen-binding activity
  - Ristocetin-induced platelet aggregation
  - Genetic testing
Laboratory Testing: Secondary Hemostasis

- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)
- Mixing study
- Factor activities
- Factor XIII
- Factor inhibitor
- Lupus anticoagulant studies
  - DRVVT, anticardiolipin, and antibeta 2 glycoprotein I antibodies

DRVVT = dilute Russell’s viper venom time.
Mixing Study

- Also known as a 1:1 mix
- Two steps
  1. Mix patient’s serum with normal serum and measure PT or aPTT
  2. Incubate sample for 1 hour and recheck PT and aPTT

*This will differentiate a factor deficiency vs. an inhibitor*
Coagulation Cascade

PTT ➔ INTRINSIC PATHWAY
PK
HK
XII ➔ XIIa
HK
XI ➔ Xla
EXTRINSIC PATHWAY
IX ➔ IXa
Villa
TF
X ➔ Xa
Va
prothrombin ➔ thrombin ➔ XIII
fibrinogen ➔ fibrin ➔ XIIIa
fibrin ➔ cross-linked fibrin

PT/INR ➔
Outline

- Review of hemostasis
- Workup and laboratory testing
- **Primary hemostasis**
  - von Willebrand disease
  - Immune thrombocytopenia
- **Secondary hemostasis**
  - Hemophilias
  - Acquired hemophilia
  - Lupus anticoagulant
von Willebrand Disease

- Most common bleeding disorder
- Prevalence of 1/100 to 1/10,000
- Autosomal inheritance: Seen equally in males and females
- Involved with both primary and secondary hemostasis
von Willebrand Disease

- Carrier protein for factor VIII
- So with certain types (IIN, III), may see factor VIII deficiency; similar clinical presentations
- But mainly key factor in primary hemostasis with key interactions with platelets and endothelium, so may see clinical similarities to platelet disorders
Simplified Model of von Willebrand Factor Functions in Platelet-Plug Formation

# Types of von Willebrand Disease

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Mechanism of Disease</th>
<th>Genetic Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Partial quantitative deficiency of von Willebrand factor (and factor VIII)</td>
<td>Autosomal dominant*</td>
</tr>
<tr>
<td>2</td>
<td>Qualitative defects of von Willebrand factor</td>
<td>Autosomal dominant†</td>
</tr>
<tr>
<td>A</td>
<td>Defective platelet-dependent von Willebrand factor functions, associated with lack of larger multimers</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Heightened platelet-dependent von Willebrand factor functions, associated with lack of larger multimers</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>Defective platelet-dependent von Willebrand factor functions, not associated with multimer defects</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Defective von Willebrand factor binding to factor VIII</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Severe or complete deficiency of von Willebrand factor and moderately severe factor VIII deficiency</td>
<td>Autosomal recessive</td>
</tr>
</tbody>
</table>

* This mode of transmission is sometimes not evident because of reduced penetrance and varied expressivity.
† Rare cases are characterized by autosomal recessive transmission.
von Willebrand Disease: Treatment

- DDAVP
  - Desmopressin acetate (intranasal)
  - IV
- Antifibrinolytic drugs: Aminocaproic acid, tranexamic acid
- Plasma-derived products
  - Humate-P
  - Antihemophilic factor/von Willebrand factor complex [human]
  - von Willebrand factor, factor VIII complex
- Oral contraceptive pills
Platelet Disorders

- Thrombocytopenia
  - Platelet count less than 150,000/mm$^3$
- Platelet dysfunction
- Thrombocytosis
  - Platelet count greater than 450,000/mm$^3$
  - Essential thrombocytosis - ? Bleeding defect
# Thrombocytopenia

<table>
<thead>
<tr>
<th>Platelet Count (mm$^3$)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>150,000–400,000/mm$^3$</td>
<td>Normal range</td>
</tr>
<tr>
<td>&gt; 100,000/mm$^3$</td>
<td>No abnormal bleeding</td>
</tr>
<tr>
<td>&gt; 40,000/mm$^3$</td>
<td>No spontaneous bleeding; abnormal bleeding with trauma</td>
</tr>
<tr>
<td>&lt; 20,000/mm$^3$</td>
<td>Spontaneous bruising common</td>
</tr>
<tr>
<td>&lt; 1,000–5,000/mm$^3$</td>
<td>Severe spontaneous bleeding</td>
</tr>
</tbody>
</table>

Immune Thrombocytopenia

- Presentation
- Definition
  - Platelets < 100,000/mm$^3$
  - Diagnosis of exclusion
  - No robust clinical or laboratory parameters are currently available to establish its diagnosis with accuracy
- Primary vs secondary

Immune Thrombocytopenia (cont)

- Phases of disease
  - Newly diagnosed: Within 3 months of diagnosis
  - Persistent ITP: Between 3 to 12 months from diagnosis
  - Chronic ITP: Lasting for more than 12 months
  - Severe ITP: Presence of bleeding symptoms at presentation sufficient to mandate treatment or occurrence of new bleeding symptoms requiring additional therapeutic intervention

<table>
<thead>
<tr>
<th>Treatment type</th>
<th>Initial response, days</th>
<th>Peak response, days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-D</td>
<td>1–3</td>
<td>3–7</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>30–90</td>
<td>30–180</td>
</tr>
<tr>
<td>Danazol</td>
<td>14–90</td>
<td>28–180</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>2–14</td>
<td>4–28</td>
</tr>
<tr>
<td>Eltrombopag</td>
<td>7–28</td>
<td>14–90</td>
</tr>
<tr>
<td>IVlg</td>
<td>1–3</td>
<td>2–7</td>
</tr>
<tr>
<td>Prednisone</td>
<td>4–14</td>
<td>7–28</td>
</tr>
<tr>
<td>Rituximab</td>
<td>7–56</td>
<td>14–180</td>
</tr>
<tr>
<td>Romiplostim</td>
<td>5–14</td>
<td>14–60</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>1–56</td>
<td>7–56</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>7–14</td>
<td>7–42</td>
</tr>
<tr>
<td>Vincristine</td>
<td>7–14</td>
<td>7–42</td>
</tr>
</tbody>
</table>

Senile Ecchymosis/Purpura

- Age-related
- Especially on forearms/sun-exposed regions
- Related to sun damage, increased vascular fragility
- Worsened by steroids and antiplatelet agents
- Benign: No treatment necessary
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Hemophilia

- Factor VIII or IX deficiency
- X-linked recessive (males)
- Occasional symptomatic carriers (females)
<table>
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<tr>
<th>Laboratory defect</th>
<th>Clinical manifestation</th>
<th>Bleeding symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1%</td>
<td>Severe</td>
<td>Early childhood spontaneous</td>
</tr>
<tr>
<td>1%–5%</td>
<td>Moderate</td>
<td>Usually only after trauma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May be spontaneous</td>
</tr>
<tr>
<td>5%–30%</td>
<td>Mild</td>
<td>After trauma</td>
</tr>
</tbody>
</table>
Hemophilia: Treatment

- Factor replacement
- Fibrinolysis inhibitors: Aminocaproic acid
- Desmopression (DDAVP)
- Bypassing agents
  - Activated factor VIIa
  - FEIBA (activated prothrombin complex concentrate [PCC])
- On demand vs. prophylaxis
Additional Factor Deficiencies

- Elevated PTT
  - Factor XI deficiency
  - Factor XII deficiency
- Elevated PT
  - Factor VII deficiency
  - Vitamin K deficient (poor nutrition, Abx)
Acquired Hemophilia

- Seen in pregnant females, elderly, patients with autoimmune or lymphoproliferative diseases; can also been seen with hepatitis C/interferon therapy
- Present with significant hematomas and bruising, instead of joint or muscle bleeds
- High morbidity and mortality (22%)

Acquired Hemophilia (cont)

Acquired Hemophilia (cont)

- **Diagnosis**
  - Mixing study: Partial correction, then prolongation with 1-hour incubation
  - Factor studies: Identify type

- **Additional studies**
  - Inhibitor titer (Bethesda units [BUs])

Acquired Hemophilia (cont)

- **Treatment**
  - Stop bleeding
    - Low titer (< 5 BUs): High-dose factor
    - High titer (> 5 BUs): Bypassing agent
      - Activated factor VIIa
      - Prothrombin complex concentrate (PCC): FEIBA
      - More recently porcine factor VIII
  - Suppress antibody production
    - Prednisone with or without cyclophosphamide
    - Rituximab
    - IVIG and other immunosuppressants

Case Study

A 32-year-old female presents for surgery and is incidentally found to have an elevated PTT on preoperative labs. The surgeon refers the patient to your clinic on Monday for a surgery that they would like to perform on Friday.
What is the first step in the evaluation of this patient?

A. von Willebrand studies  JL410
B. PFA-100  JL411
C. A bleeding history  JL412
D. Mixing study  JL413
Questions for the Patient

- **Bleeding questions**
  - Do you have a history of easy bruising or bleeding?
  - Have you ever had any procedures in the past?
  - Do you/did you have heavy periods?
  - Have you ever needed a blood transfusion?

- **Clotting questions**
  - Have you ever had any blood clots, strokes, or heart attacks?
  - Have you had any miscarriages?
Lupus Anticoagulant

- Clinicopathologic diagnosis
  - Clinical: Clotting, miscarriages, thrombocytopenia
  - Pathologic:
    - Lupus anticoagulant (DRVVT)
    - Anticardiolipin antibody
    - Antibeta 2 glycoprotein I antibody

- 12 weeks apart
What is the first lab test you would order?

A. von Willebrand studies JL414
B. PFA-100 JL415
C. Lupus anticoagulant JL416
D. Mixing study JL417
Test results show partial correction with prolongation. What does this patient have?

A. Lupus anticoagulant  JL418
B. Factor VIII deficiency  JL419
C. Factor VIII inhibitor  JL420
D. Both A and C  JL421
The patient never had a history of clotting or bleeding. What is your recommendation for surgery?

A. Observation, with appropriate deep vein thrombosis prophylaxis after surgery  JL422
B. Desmopressin acetate  JL423
C. Factor VIII replacement  JL424
D. Surgery is bad  JL425
Clinical Pearls

- History is most important part of bleeding history
- Primary hemostasis: You see mucocutaneous bleeding
  - What are the main components of primary hemostasis?
- Secondary hemostasis: Macro, joints, muscle bleeds
- Most important test in secondary hemostasis for elevated PT/PTT is *mixing study* to distinguish deficiency from inhibitor
- Acquired factor VIII inhibitors: Prolonged PTT, partial correction with prolongation
Primary Hemostasis

Formation of Platelet Plug!
Secondary Hemostasis

Factors

Platelets

Von Willebrand

Blood Vessel

Collagen

Fibrin Clot