Clinical Evaluation of the Bleeding Patient
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Objectives
1. Articulate the differential diagnosis of a patient with a bleeding disorder.
2. Name several causes of a quantitative platelet disorders.
3. Describe a couple causes of qualitative platelet disorders.
4. Identify clues in the history, physical exam and laboratory data that suggest a bleeding disorder.

Objectives
5. Understand that in bleeding disorders stemming from defects in one or more of the coagulation factors, the prothrombin time (PT), partial thromboplastin time (PTT), or both can be prolonged.
6. Explain how to interpret a mixing study.
7. Formulate a clinical hypothesis from the history and physical exam for a patient with a bleeding disorder.
8. Choose appropriate laboratory testing for cases of bleeding disorders and interpret results.
References

• * Powerpoint slides – focus of test questions
• Handouts
• Robbins Basic Pathology

Outline

I. Bleeding Disorder Review

II. Illustrated Case Studies
Bleeding Disorders: Differential Diagnosis

<table>
<thead>
<tr>
<th>Platelet Disorders</th>
<th>Clotting Factor Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia (Quantitative Platelet Disorders)</td>
<td>Inherited</td>
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<tr>
<td>• Idiopathic Thrombocytopenic Purpura (ITP)</td>
<td>• Factor VIII deficiency (Hemophilia A)</td>
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<td>• Drug-induced thrombocytopenia</td>
<td>• Factor IX deficiency (Hemophilia B)</td>
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<tr>
<td>• Hypersplenism</td>
<td>• Other Factor deficiencies (less common)</td>
</tr>
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<td>• Marrow infiltration by neoplasia</td>
<td>Acquired</td>
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<td>• Viral infections (e.g., HIV, EBV, Rubella)</td>
<td>• Vitamin K deficiency</td>
</tr>
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<td>• DIC</td>
<td>• Factor inhibitors</td>
</tr>
<tr>
<td>• ITP-HUS</td>
<td>• Failure of Synthetic Function of the Liver</td>
</tr>
<tr>
<td>• Autoimmune condition (e.g., Lupus)</td>
<td>• Drugs</td>
</tr>
<tr>
<td>• Geriatric thrombocytopenia</td>
<td>• DIC</td>
</tr>
<tr>
<td>Qualitative Platelet Disorders</td>
<td>Inherited</td>
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<tr>
<td>• Inherited</td>
<td>• Factor VIII deficiency (Hemophilia A)</td>
</tr>
<tr>
<td>• Von Willebrand’s Disease</td>
<td>• Factor IX deficiency (Hemophilia B)</td>
</tr>
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<td>• Glanzmann Thrombasthenia</td>
<td>• Other Factor deficiencies (less common)</td>
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<td>• Bernard-Soulier Syndrome</td>
<td>Acquired</td>
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<td>• Vitamin K deficiency</td>
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<td>• Factor inhibitors</td>
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<td></td>
<td>• Failure of Synthetic Function of the Liver</td>
</tr>
<tr>
<td></td>
<td>• Drugs</td>
</tr>
<tr>
<td></td>
<td>• DIC</td>
</tr>
</tbody>
</table>

History is Key!

- Surgeries, tooth extraction, childbirth
- Bleeding that required surgical intervention, blood transfusion, or replacement therapy
- Positive family history (especially in children without a history of hemostatic challenge)
- Circumcision in boys
- Menorrhagia in women
- Medications (e.g. warfarin, heparin, aspirin, plavix, other anticoagulants)
- Viral illness, malnutrition, liver disease, malignancy

Physical Exam

- Epistaxis, bruising, petechiae, hematomas
- Oral cavity bleeding
- Hematemesis, hematochezia, melena
- Hemarthrosis
- CNS bleeding
- Lymphadenopathy
- Splenomegaly, hepatomegaly
Some Clues

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Disorders (Quantitative)</td>
<td>Mucosal bleeding, bruising, petechia, purpura</td>
</tr>
<tr>
<td>Platelet Disorders (Qualitative)</td>
<td>Consider in a patient with a lifelong history of bleeding despite negative laboratory work-up</td>
</tr>
<tr>
<td>Hemophilia type A or B (Factor VIII or IX Deficiency) or other Factor Deficiencies</td>
<td>Classically presents with joint or soft tissue bleeding; history of bleeding in men (skipped generations)</td>
</tr>
<tr>
<td>Factor Inhibitors</td>
<td>Presentation similar to hemophilia, but onset is typically sudden with no patient or family history of bleeding</td>
</tr>
<tr>
<td>DIC</td>
<td>Bleeding from multiple sites, prolonged PT and PTT</td>
</tr>
<tr>
<td>Vitamin K Deficiency</td>
<td>More common causes include malabsorption (bacterial overgrowth, celiac disease, inflammatory bowel disease), poor diet (alcohol, total parenteral nutrition) or drugs that bind vitamin K</td>
</tr>
</tbody>
</table>

CASE #1

Case #1: A. K.

- “I have a rash”
- 66 yo female, generally in good health
- Noted rash 1-2 weeks ago, seems a little worse now.
- I also had a cold – not too bad, but a sore throat – about a month ago
- Otherwise, no particular medical complaints
Case #1: A. K.

- **Characteristics**
  - Mucosal vs. Deep Tissue
  - Immediate vs Delayed
- **Associated conditions**
  - Epistaxis, hemoptysis, dark or tarry stool
  - Skin – bruising, purpura, petechiae, telangiectasias
  - Trauma/Accident
  - Childbirth
  - Circumcision
- **Social Exacerbations/Danger**

Case #1: A. K.

- Other bleeding?
  - Maybe a little bruising on her arms – doesn’t really think it’s too bad.
- **Characteristics**
  - No joint bleeds
- **Associated conditions**
  - Never had a history of easy bleeding, no blood transfusions
  - Never with excessive menorrhagia
  - 3 children, all vaginal deliveries, no complications
Case #1: A. K.

- PMH
  - High cholesterol
  - Hypertension
  - Thyroid disease
- Medications
  - Simvastatin
  - Metoprolol
  - Levothyroxine
  - No OTCs
- Social History
  - Docent at local museum
  - Retired banker
  - Divorced

- Family History
  - Mother died of breast cancer complications at 83
  - Father died of CAD at 68
  - Children are alive and well, no illnesses
  - 2 siblings, no bleeding history
- ROS
  - Fever 4 weeks ago with this “cold.” Only 1-2 days
  - No chills, no nausea, no vomiting, no change in energy level, no night sweats

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Case #1: A. K.

- Physical Exam
  - VSS
  - OP with petechiae
  - Legs as shown previously
  - No lymphadenopathy
  - One additional bruise on her thigh noted
  - Lungs Clear, heart RRR, no murmur
  - Nothing on palms or soles of feet
  - Mild splenomegaly

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Case #1: A. K.

- So far... full history and physical
  - Middle-aged woman with no prior history of bleeding or bruising
  - Now, a few weeks after a fever, has evidence of petechiae and bruising on PE
  - Otherwise feels well, no family history
Case #1: Work Up

<table>
<thead>
<tr>
<th>Test</th>
<th>A.K.</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>7.8 K/μL</td>
<td>4.0-10.0 K/μL</td>
</tr>
<tr>
<td>HGN</td>
<td>12.8 gm/dL</td>
<td>12.0-16.0 Gm/dL</td>
</tr>
<tr>
<td>MCV</td>
<td>89 FL</td>
<td>85-95 FL</td>
</tr>
<tr>
<td>PLT</td>
<td>8 K/μL</td>
<td>150-400 K/μL</td>
</tr>
<tr>
<td>PT/INR</td>
<td>12 sec (INR=1.0)</td>
<td>11-13 sec</td>
</tr>
<tr>
<td>aPTT</td>
<td>28 sec</td>
<td>25-32 sec</td>
</tr>
<tr>
<td>Bleeding Time</td>
<td>6.3 min</td>
<td>2-8 min</td>
</tr>
</tbody>
</table>

Bleeding Disorders: Differential Diagnosis

**Platelet Disorders**

- Idiopathic Thrombocytopenic Purpura (ITP)
- Drug-induced thrombocytopenia
- Immune thrombocytopenia
- Marrow infiltration by neoplasia
- Viral infections (e.g., HIV, EBV, Rubella)
- Inherited
- Acquired
- Bernard-Soulier Syndrome
- Glanzmann Thrombasthenia

**Clotting Factor Abnormalities**

- Inherited
  - Factor VIII deficiency (Hemophilia A)
  - Factor IX deficiency (Hemophilia B)
  - Other Factor deficiencies (less common)
- Acquired
  - Vitamin K deficiency
  - Factor inhibitors
  - Failure of Synthetic Function of the Liver
  - Drugs
  - DIC
Case #1: ITP

- Middle aged woman with
  - Petechiae, bruising
  - New onset severe thrombocytopenia
  - No additional complications in bone marrow
  - Ruled out all other causes

- ITP Treatment
  - Steroids
Case #2: J.B.

CC: History
- Routine blood work in a 36yo in the burn unit
- "Something's weird about the PT – INR is 5."
- Now needs skin grafting for lower extremity burn. Also with inhalation injury.

Important points in HPI
- Characteristics
  - Mucosal vs. Deep Tissue
  - Immediate vs Delayed
- Associated conditions
  - Epistaxis, hemoptysis, dark or tarry stool?
  - Skin – bruising, purpura, petechiae, telangiectasias?
  - Trauma/Accident
  - Childbirth
  - Circumcision
- Social Exacerbations/Danger

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Case #2: J.B.

- PMH
  - Elevated cholesterol
  - Apparently has had a blood transfusion in the past, after an automobile accident
- Medications
  - None
- Social History
  - Smoker X 20 years

- Family History
  - Adopted
- PE
  - VSS
  - Intubated for airway protection
  - 70% LE burns, wrapped
  - No other bruising, petechia are visible

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Case #2: J.B.

- So far… full history and physical
  - Young man with elevated PT/INR
  - Maybe lifelong
  - ?Familial
  - Not medication related
  - May or may not have been the reason for the need for his blood transfusion
Case #2: Work Up

<table>
<thead>
<tr>
<th>Test</th>
<th>J.B.</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>12.5 K/μL</td>
<td>4.0-10.0 K/μL</td>
</tr>
<tr>
<td>HGN</td>
<td>12.1 gm/dL</td>
<td>12.0-16.0 Gm/dL</td>
</tr>
<tr>
<td>MCV</td>
<td>98 FL</td>
<td>85-95 FL</td>
</tr>
<tr>
<td>PLT</td>
<td>230 K/μL</td>
<td>150-400 K/μL</td>
</tr>
<tr>
<td>PT/INR</td>
<td>28 sec, INR=3.1</td>
<td>10-11.7 sec</td>
</tr>
<tr>
<td>aPTT</td>
<td>28 sec</td>
<td>25-32 sec</td>
</tr>
</tbody>
</table>
Case #2: J.B.

- So far...
  - Young man with an isolated elevated PT but a NORMAL aPTT
  - Normal platelet count
- You check his Factor VII level – it’s 2%
- But does this discriminate between qualitative and quantitative abnormalities?
How To Approach An Increased PT/ or PTT Test

There are two basic reasons for elevated PT or PTT:
(1) Deficiency of a clotting factor
(2) Inhibitor of a clotting factor

Key Point: mixing study is used to differentiate between (1) and (2)

Mixing Study:

PROBLEM:  

TEST:
Mix Study  

Mix 1 part normal (NL) and 1 part patient (PT) plasma

TEST RESULT

 Correction
Deficiency of clotting Factor
Factor Assays

No Correction
Inhibitor
LA Testing
### Case #2: Work Up

<table>
<thead>
<tr>
<th>Test</th>
<th>J.B.</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VII level</td>
<td>4%</td>
<td>50-150%</td>
</tr>
<tr>
<td>PT/INR</td>
<td>28 sec</td>
<td>10-11.7 sec</td>
</tr>
<tr>
<td>INR=3.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixing Study</td>
<td>Corrects the PT to 12 sec</td>
<td></td>
</tr>
</tbody>
</table>

### Case #2: Factor VII Deficiency

- 95-97% of all Inherited Coagulation defects
  - X-linked inherited coagulation disorders:
    - hemophilia A (factor VIII deficiency)
    - hemophilia B (factor IX deficiency)
  - von Willebrand disease
- Remaining defects are VERY rare -- ranging from approximately 1 in 500,000 to 1 in 2 million
- Factor VII deficiency presents with a wide spectrum of clinical severity, correlating poorly with factor VII levels; some patients with undetectable levels are asymptomatic

### Case #2: Treatment

- Considerations
  - Fresh frozen plasma
  - But there is a very short half-life of factor VII (4 to 6 hours)
  - Recombinant activated factor VII is available – but very, very costly
Case #3: T.J.

CC: History
- "Heavy periods"
- 16 yo
- Periods are 5-6 d in duration. Heavy tampon every couple of hours during d2-3.
- "Have to get up during the night and "can't make it through a movie without changing them."

Important points in HPI
- Characteristics
  - Mucosal vs. Deep Tissue
  - Immediate vs Delayed
- Associated conditions
  - Epistaxis, hemoptysis, dark or tarry stool?
  - Skin – bruising, purpura, petechiae, telangiectasias?
  - Trauma/Accident
  - Childbirth
  - Circumcision
- Social Exacerbations/Danger

Case #3: T.J.

- Menorrhagia?
  - Definition: More than 80 ml of blood/cycle

- Characteristics
  - No joint bleeds
  - Had to go back to dentist after excessive bleeding two days following an extraction

- Associated conditions
  - Also had two episodes of nose bleeding that required ER visits as a child. + Spontaneous. + packing, + cautery
  - No blood transfusions.
  - + gum bleeding
## Case #3: T.J.

**PMH**
- "They tell me I have anemia and have to take iron."

**Medications**
- Used to take a MVI
- No OCPs

**Social History**
- Planning a career in military
- No tobacco, occasional ETOH, + marijuana x 2
- Denies DV

**Family History**
- Mother
  - Blood transfusion after birth of second child
  - Menorrhagia → hysterectomy
- Father
  - HTN, Chol
- Younger brother
  - + nose bleeds
- MGF
  - Died in Korean war

### Physical Exam:
Paying special attention to the OP, teeth, skin, nails, joints, stool

## Case #3: T.J.

**So far... full history and physical**
- Young woman with a bleeding diathesis
- Appears lifelong
- Appears familial
- Not medication related
- Serious enough to cause anemia
- Possibly with impact on her professional function in the future
Case #3: Laboratory Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>What we can learn</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with differential</td>
<td>Platelet quantity. Is there involvement of the other cell lines? What do the</td>
</tr>
<tr>
<td></td>
<td>platelets look like? Is there evidence of a systemic disorder?</td>
</tr>
<tr>
<td>PT and aPTT</td>
<td>Is there abnormalities in the coagulation system? Will pick up BOTH qualitative</td>
</tr>
<tr>
<td></td>
<td>and quantitative defects, but won't differentiate which clotting factor is the</td>
</tr>
<tr>
<td></td>
<td>culprit</td>
</tr>
<tr>
<td>Bleeding Time</td>
<td>Defect in platelet plug formation. Imperfect test. Still discussed in the</td>
</tr>
<tr>
<td></td>
<td>literature, but rarely used clinically. New tests have been developed to look</td>
</tr>
<tr>
<td></td>
<td>at platelet function – PFA-100</td>
</tr>
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</table>

Case #3: Work Up

<table>
<thead>
<tr>
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<th>T.J.</th>
<th>Normal</th>
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<tbody>
<tr>
<td>WBC</td>
<td>6.3 K/ul</td>
<td>4.0-10.0 K/ul</td>
</tr>
<tr>
<td>HGN</td>
<td>10.8 gm/dL</td>
<td>12.0-16.0 Gm/dL</td>
</tr>
<tr>
<td>MCV</td>
<td>72 FL</td>
<td>85-95 FL</td>
</tr>
<tr>
<td>PLT</td>
<td>443 K/ul</td>
<td>150-400 K/ul</td>
</tr>
<tr>
<td>PT/INR</td>
<td>12 sec</td>
<td>INR=1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11-13 sec</td>
</tr>
<tr>
<td>aPTT</td>
<td>38 sec</td>
<td>25-32 sec</td>
</tr>
<tr>
<td>Bleeding Time</td>
<td>7.4 min</td>
<td>2-8 min</td>
</tr>
</tbody>
</table>
Case #3: T.J.

- So far...
  - Young woman with a lifelong, likely familial bleeding diathesis
  - Microcytic anemia
  - Normal platelet number, prolonged aPTT, normal PT, prolonged bleeding time
- What’s my differential?
  - Common things are common

### Bleeding Disorders: Differential Diagnosis

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<td>- Hemolytic anemia</td>
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<tr>
<td>- DIC</td>
<td>Factor inhibitors</td>
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<tr>
<td>- TTP-HLS</td>
<td>Failure of Synthetic Function of the Liver</td>
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<td>- Autoimmune condition (e.g., Lupus)</td>
<td>Drugs</td>
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<td>- Glanzmann Thrombasthenia</td>
<td>Other Factor deficiencies (less common)</td>
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<tr>
<td>- Bernard-Soulier Syndrome</td>
<td>Acquired</td>
</tr>
<tr>
<td>- Acquired</td>
<td>Vitamin K deficiency</td>
</tr>
<tr>
<td>- Drugs</td>
<td>Factor inhibitors</td>
</tr>
<tr>
<td>- Chronic renal failure</td>
<td>Failure of Synthetic Function of the Liver</td>
</tr>
</tbody>
</table>

**Case #3: T.J.**

- Prolonged bleeding time, slightly prolonged PTT (normal platelet count, normal PT)

- Von Willebrand’s Disease
Case #4: F.C.

- 68 yo F underwent resection of a pancreatic tumor
- Excessive bleeding from the drain at her surgical site required blood transfusions; surgeon is concerned about a bleeding disorder
- Has had prior surgeries without bleeding complications. No family history of bleeding disorders. No history of liver disease.
- Prior to surgery, platelet count, PT, PTT all normal

**Laboratory Results**

- White blood cell count 15.5 K/µL [4.0-10.0 K/µL]
- Hemoglobin 8.7 g/dL [12.0-16.0 g/dL]
- Platelet count 90 K/µL [150-400 K/µL]
- PT 57 seconds [23-31 seconds]
- PTT 57 seconds [12-14 seconds]
- Fibrinogen 100 mg/dL [150-350 mg/dL]
- D-dimer >20 µg/mL [<5.0 µg/mL]
- AST 32 U/L [5-35 U/L]
- ALT 33 U/L [7-56 U/L]
- Alkaline phosphatase 57 U/L [20-140 U/L]
- Total bilirubin normal
- Occasional schistocytes
Case #4: DIC

Select Platelet Disorders Summary

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Platelet count</th>
<th>Bleeding Time</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITP</td>
<td>↓</td>
<td>↑</td>
<td>Anti-GPbetaII antibodies → splenic macrophage consumption of platelet-antibody complex.</td>
</tr>
<tr>
<td>Bernard-Soulier Syndrome</td>
<td>——</td>
<td>↑</td>
<td>Defect in platelet plug formation. ↓GP Ib loose bonds → defect in platelet-to-vWF adhesion.</td>
</tr>
<tr>
<td>Glanzmann Thrombasthenia</td>
<td>——</td>
<td>↑</td>
<td>Defect in platelet plug formation. ↓GP IIb/IIIa loose bonds → defect in platelet-to-platelet aggregation.</td>
</tr>
</tbody>
</table>

Mixed Platelet and Coagulation Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Platelet Count</th>
<th>Bleeding Time</th>
<th>PT</th>
<th>PTT</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Willebrand Disease</td>
<td>——</td>
<td>↑</td>
<td>——</td>
<td>↑/FE</td>
<td>Intracapillary coagulation defect. ↓vWF → ↑PTT (vWF acts to carry/protect factor VIII)</td>
</tr>
<tr>
<td></td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑/FE</td>
<td>Defect in platelet plug formation. ↓vWF → defect in platelet-to-vWF adhesion.</td>
</tr>
<tr>
<td>DIC</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Widespread activation of clotting → deficiency in clotting factors → bleeding state. Findings: ↑Fibrin degradation products (D-dimers), ↓Fibrinogen.</td>
</tr>
</tbody>
</table>
Bleeding Disorders Summary

• Bleeding history is key!
• Use this history and physical exam to guide laboratory testing and evaluation
• CBC, PT, and PTT and peripheral blood smear are useful tests
• Any questions?

THANK YOU!