The Child with a Bleeding Disorder

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Objectives

• Understand the basics of hemostasis
  — Platelets
  — Clotting Factors
  — Blood Vessel
• Clinical features of a bleeding disorder
• Laboratory evaluation
• Common bleeding disorders
  — von Willebrand Disease
  — Hemophilia

Hemostasis

• Primary Hemostasis
  — Involves platelets, vWF, and vessel wall
  — Goal is platelet plug formation at site of injury
  — Platelet plug stops bleeding, but is unstable

• Secondary Hemostasis
  — Involves the clotting factors
  — Goal is stabilization of platelet plug
  — Leads to fibrin clot formation

The Platelet “Plug”

Coagulation Cascade

New View: Interacting Systems

Adapted from Hoffman R, Monroe DM, III, Roberts HR. Blood Coag Fibrinol 1998;9:561-564; Used by Permission
### Evaluation of the bleeding child

- **Medical history**
  - Bleeding history
  - Constitutional history
  - Family history

- **Physical examination**

- **Laboratory examination**

### Bleeding History

- **Varies with patient age and gender**

- **Type of bleeding**
  - Platelet / blood vessel disorders: mucosal bleeding, petechiae
  - Clotting factor deficiency: soft tissue, muscle and joint bleeds
  - Bleeding with other invasive, dental or surgical procedures

### Features of Abnormal Bleeding

- **Epistaxis**
  - Unrelieved by 15 minutes of pressure
  - Requiring ED visit

- **Menorrhagia**
  - Frequent pad changes (< 2 hour frequency)
  - Menses lasting > 7 days
  - >1 menstrual period in a month

### Features of Abnormal Bleeding

- **Post-surgical / dental**
  - Uncontrolled bleeding in the field
  - Bleeding lasting beyond the day of dental work
  - Requiring a blood transfusion

- **Bruising**
  - Bruises other than on distal extremities
  - Larger than a quarter
  - Associated with hematoma
  - Out of proportion to mechanism of injury

### Other Pertinent History

- **Family history**
  - Transfusions for minor surgery or menses
  - Post-partum hemorrhage
  - Chronic iron deficiency anemia

- **Medications**
  - ASA, ibuprofen, herbal medications

### Most Important

When a child has had previous surgery or dental extractions without bleeding complications, it is unlikely there is an underlying congenital bleeding disorder.
Laboratory examination

- First line testing
  - CBC
  - Peripheral smear
  - Prothrombin time (PT)
  - Partial thromboplastin time (PTT)
  - Fibrinogen
  - Thrombin time
  - von Willebrand panel
    - Factor 8 activity, vWF antigen, vWF activity
    - PFA-100

Laboratory Examination

- Subsequent testing - repeat all abnormal tests
  - Factor XIII test
  - PTT abnormal
    - PTT mixing study
    - Factor VIII, IX, XI, XII levels
    - Lupus anticoagulant, Antiphospholipid testing
  - PT abnormal
    - PT mixing study
    - Factor 7
    - Protein C and S activity
  - vWF panel abnormal
    - Repeat testing
    - vWF multimers

Normal PT, PTT and platelet count

<table>
<thead>
<tr>
<th>PT</th>
<th>PTT</th>
<th>PR</th>
<th>DDx</th>
<th>Follow-up labs</th>
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Isolated prolongation of PTT

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<td>Hemophilia A or B</td>
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Isolated prolongation of PT

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<td>Vitamin K deficiency</td>
<td>Factors II, VII, IX, X, protein C and protein S</td>
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Prolongation of PT and PTT

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<td>Factor II, V, and X deficiency</td>
<td>Factor activity assay</td>
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Prolonged PT/PTT and decreased platelets

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<td>Liver dysfunction</td>
<td>Liver enzymes, thrombin time, reptilase time</td>
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<td>Kasabach-Merritt syndrome</td>
<td>Physical exam, imaging to look for hemangiomas</td>
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Common inherited bleeding disorders
- Hemophilia A
- Hemophilia B
- von Willebrand disease

How common are bleeding disorders?
- von Willebrand disease
  - 1 in every 100 births = approximately 280,000
- Hemophilia
  - 20,000 males in the US
  - 80% hemophilia A
  - 20% hemophilia B
  - All racial and socioeconomic groups equally affected
  - Approximately 1 out of 7,500 live male births (CDC)
  - About 30% cases result from spontaneous mutation

Types of Hemophilia
- Hemophilia A
  - Classical type = Factor VIII deficiency
  - X-linked inheritance; 1:5000-10,000
- Hemophilia B
  - Christmas disease = Factor IX deficiency
  - X-linked inheritance; 1:30,000
- Hemophilia C
  - Factor XI deficiency
  - Autosomal inheritance, Ashkenazi Jews

Defect in Hemophilia
- Primary hemostasis is normal
  - Immature platelet plug is formed and bleeding stops
- Clotting protein deficiency
  - formation of mature fibrin clot is disrupted
- Platelet plug breaks
  - bleeding resumes
- Process repeats again
  - Repeated cycles of bleeding and stopping

Classification
- Severity classified by patient’s baseline level of factor
  - Levels often expressed as percentage of activity
- Mild hemophilia
  - 5-25% factor activity
- Moderate hemophilia
  - 1-5% factor activity
- Severe hemophilia
  - <1% factor activity
  - Experience the most morbidity and mortality
Evaluation

- Patient History
  - Neonatal
    - Prolonged bleeding with circumcision (30%)
    - Intracranial hemorrhage (1-2%)
  - Infant to Toddler
    - Easy bruising
    - Oral bleeding (especially torn frenulum)
    - Hemarthroses—ankles and knees once ambulatory
    - Intramuscular hemorrhages
  - Family History
    - Male relatives with histories of bleeding
    - Female carriers can also have bleeding
    - Skewed Lyonization
    - Turner's syndrome
    - 1/3 of new cases will have a negative family history

Complications of Hemophilia

- Joint bleeding
  - Knees>elbows>ankles>shoulder
  - Leads to chronic synovitis
- Muscle bleed
  - Leads to fibrosis and atrophy
  - Can lead to compartment syndrome
- Pseudotumors
- Subdural hemorrhage
- Inhibitors
  - HIV/ Hepatitis C — 90% if Rx started before 1994

Hemarthrosis

Treatment

- Replacement of missing clotting factor
- Most important—give factor before any imaging or testing
- Early administration decreases the total number of factor infusions required to treat a bleed
- When in doubt—GIVE FACTOR!

Factor Replacement

- Multiple factor preparations available
  - Plasma-derived and recombinant
  - Factor VIII—half life 8-12 hours
  - Humate-P—also has Von Willebrand's Factor
  - Factor IX—half life 18-24 hours
- Infused in peripheral vein
- Goal is to increase factor levels to stop bleeding
  - Each unit/kg of Factor VIII increases levels by 2%
  - Each unit/kg of Factor IX increases levels by 1%
- Expensive—approximately $1 per unit

Inhibitors

- 25% of severe hemophiliacs
- When to suspect an inhibitor?
  - Factor isn’t working
- Most common in the first 15 factor exposures
- Increased risk if +FHx of inhibitor
- Expressed in Bethesda Units (B.U.)
  - <10 BU low responder
  - >10 BU high responder
Pediatrics Grand Rounds
22 July 2011

Approaches to inhibitors

- Overcome the inhibitor with high doses of Factor
  - Only effective in low titer patients
  - Double doses or continuous infusions
- Use agents that can bypass inhibitor
  - FEIBA
  - Recombinant Factor VIIa (Novo7)
- Immune tolerance to decrease titers
  - Expose patient to Factor frequently to induce tolerance by immune system and decrease inhibitor titer
- Immune modulation to decrease titers
  - Rituximab

von Willebrand Disease

- Most common inherited bleeding disorder
  - Seen in 1% of population
  - <10% have bleeding problems
- Autosomal dominant
  - Men and women affected equally
  - Tends to cause greater morbidity in women of childbearing age
- Prevalence
  - referral based: 23-113 cases per million
  - population based: 8,200-16,000 per million

von Willebrand Factor

- VWF synthesized in megakaryocytes and endothelial cells
  - Stored in Weibel-Palade bodies in endothelial cells and alpha granules in platelets

Platelet Adhesion

- PLT
- VWF
- Subendothelium

Without VWF

- Platelets are not targeted to areas of endothelial damage well
- Leads to insufficient formation of platelet plug and fibrin clot
- Secondary deficiency of factor VIII
  - Result of accelerated clearance
  - Half life of FVIII 2hrs vs 12-20hrs for the complex FVIII-vWF

von Willebrand Disease

- Type 1 (60-80%)—Autosomal dominant
  - Quantitative defect
  - Mild-moderate bleeding symptoms
  - Labs
    - Decreased VWF antigen—10-45% of normal
    - Decreased Ristocetin cofactor activity
    - Low-normal to mildly decreased Factor VIII level
    - Normal VWF multimers
    - Normal platelet count, PT, PTT
- Type 3—Autosomal recessive
  - Most severe form
  - Resembles severe Hemophilia A
  - No detectable VWF antigen and very low Factor VIII
    - May have severe mucosal bleeding
    - Can also have hemarthroses
    - Markedly decreased Ristocetin cofactor activity
    - Prolonged PTT, Normal platelet count
von Willebrand Disease

- Type 2 (20-30%)—Autosomal dominant
  - Normal levels of VWF
  - Multimers are structurally abnormal
  - Mild-moderate bleeding
  - Type 2A (10-15%)
    - Small multimer units in circulation
  - Type 2B (5%)
    - Large VWF multimers with "gain of function" defect
      - Spontaneous binding to platelets and rapid clearance can lead to thrombocytopenia
      - Multimers rapidly cleared as they bind platelets

- Type 3 (0-15%)
  - Low levels of VWF
  - Severe bleeding

Treatment: Desmopressin (Stimate®)

- DDAVP trial
  - Drug administered in clinic prior to using for bleeding symptoms
  - VWF antigen and activity obtained before administration and 1 hour after
  - Once adequate response is documented, patient may use medication
    - Nasal Spray (Stimate®)<50kg 1 nostril >50kg both nostrils
    - DDAVP IV=0.3 mcg/kg SC=0.4 mcg/kg

Treatment by Variant

<table>
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<tr>
<th>Variant</th>
<th>Response</th>
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<tr>
<td>Type 1</td>
<td>Yes: best if mild or moderate</td>
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<tr>
<td>Type 3</td>
<td>No: no response</td>
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<tr>
<td>Type 2A</td>
<td>±: poor response</td>
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<tr>
<td>Type 2B</td>
<td>No: decreases plts</td>
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<tr>
<td>Type 2M</td>
<td>±: poor</td>
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<tr>
<td>Type 2N</td>
<td>±: poor</td>
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<tr>
<td>Platelet type VWD</td>
<td>No: decreases plts</td>
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Treatment: Replacement Therapy

- Indicated in patients with severe disease
  - Type 3
  - Types 2A or 2B
- In type 1 patients who don’t respond to DDAVP or before serious surgery
- For prolonged treatment
  - Repeat doses q12-24 hrs.

- Factor VIII product rich in VWF (Humate P®): IV preparation that contains von Willebrand factor
  - Labeled with ristocetin cofactor units
  - 20-30 units/kg ristocetin cofactor raises blood levels to 50-100%
  - Cryoprecipitate
    - Only in extreme circumstances
    - Higher risk of viral transmission
Summary

• Consider all components of hemostasis when faced with a bleeding child
• Take a careful personal bleeding history
• Take a careful family history
• Consider bleeding disorder if amount of bleeding is unusual or prolonged
• When in doubt - give factor
• Consult Hemophilia Treatment Center or hematologist if any questions

Questions?

Thank you