My Child Bruises Easily...so does his Uncle: A Tale of Losses and Victories!

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Hemostasis

- Platelets
- VWF
- Clotting factors
- Vessel wall

The diagram illustrates the interactions between platelets, VWF, clotting factors, and the vessel wall in the process of hemostasis. The arrows indicate the direction of interaction or regulation.
Hemostasis

- Primary – involves platelets and vWF
- Secondary – involves the clotting factors
Evaluation of the bleeding/bruising child

• Medical history
  – Bleeding history
  – Constitutional history
  – Family history

• Physical examination

• Laboratory examination
Medical history

• Bleeding history \(\rightarrow\) features of abnormal bleeding include:
  – Epistaxis unrelieved by 15 minutes of pressure
  – Menstrual bleeding lasting longer than 7 days
  – Bleeding from dental procedures lasting beyond the day of the procedure or requiring a blood transfusion
  – Ecchymoses inconsistent with the degree of reported trauma

• Type of bleeding
  – Mucosal/petechia \(\rightarrow\) think platelet disorder or von Willebrand disease
  – Muscle/joint \(\rightarrow\) factor deficiency

• Time of onset of symptoms
  – Acute onset \(\rightarrow\) suggestive of acquired disorder
  – Longer duration \(\rightarrow\) congenital disorder
  – Mild bleeding disorders may not become apparent until a patient experiences a challenge to their hemostatic system

• Overall health
  – Congenital bleeding disorders and ITP occur in children who are otherwise well
  – DIC occurs in sick children with co-morbid conditions
• When a child has had previous surgery or dental extractions without bleeding complications, it is unlikely there is an underlying congenital hemorrhagic disorder
Laboratory examination

• First line testing
  – Complete blood count
  – Review of peripheral smear
  – Prothrombin time
  – Partial thromboplastin time
  – Fibrinogen
  – Thrombin time
  – von Willebrand panel
    • factor VIII activity
    • vWF activity
    • vWF antigen
  – PFA, platelet aggregation studies

• Subsequent testing-repeat all abnormal testing!
  – FXIII screen
  – Fibrinolytic screen
  – PTT abnormal
    • PTT mixing study
    • Factors 8, 9, 11, 12
    • Antiphospholipid syndrome
  – PT abnormal
    • PT mixing study
    • Factor VII
    • Protein S and C activity
  – vWF panel abnormal
    • Repeat testing
    • vWF multimers
    • DDAVP challenge testing
## Normal PT, PTT, and platelet count

<table>
<thead>
<tr>
<th>PT</th>
<th>PTT</th>
<th>Plt</th>
<th>DDx</th>
<th>Follow-up labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N</td>
<td>N</td>
<td>von Willebrand disease</td>
<td>PFA-100 von Willebrand panel including multimers</td>
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<tr>
<td></td>
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<td>Platelet function disorder</td>
<td>Platelet aggregation studies</td>
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<td></td>
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<td>Factor XIII deficiency</td>
<td>Urea clot lysis test</td>
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<td></td>
<td></td>
<td></td>
<td>Fibrinolytic defect</td>
<td>Alpha-2-antiplasmin, PAI-1, TPA</td>
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</tbody>
</table>
# Isolated prolongation of the PTT

<table>
<thead>
<tr>
<th>PT</th>
<th>PTT</th>
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<th>Follow-up labs</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>↑</td>
<td>N</td>
<td>PTT inhibitor</td>
<td>PTT mixing studies, lupus anticoagulant, cardiolipin Ab’s</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>von Willebrand disease</td>
<td>Von Willebrand panel including multimers</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Hemophilia A or B</td>
<td>Factor VIII and Factor IX activity</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Factor XI deficiency</td>
<td>Factor XI activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Heparin contamination</td>
<td>Thrombin time</td>
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</table>
### Isolated prolongation of the PT

<table>
<thead>
<tr>
<th>PT</th>
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</thead>
<tbody>
<tr>
<td>$\uparrow$</td>
<td>N</td>
<td>N</td>
<td>PT inhibitor</td>
<td>PT mixing study</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vitamin K deficiency</td>
<td>Factors II, VII, IX, X, protein C and protein S</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Warfarin</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Factor VII deficiency</td>
<td>Factor VII activity</td>
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</table>
# Prolongation of PT and PTT

<table>
<thead>
<tr>
<th>PT</th>
<th>PTT</th>
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<th>DDx</th>
<th>Follow-up labs</th>
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<tbody>
<tr>
<td>↑</td>
<td>↑</td>
<td>N</td>
<td>Circulating inhibitor</td>
<td>PT and PTT mixing studies; lupus anticoagulant; cardiolipin Ab’s</td>
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<tr>
<td></td>
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<td></td>
<td>Liver dysfunction</td>
<td>Liver enzymes; thrombin time, reptilase time</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Vitamin K deficiency</td>
<td>Factors II, VII, IX, X, protein C and protein S</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Factor II, V, and X deficiency</td>
<td>Factor activity assays</td>
</tr>
</tbody>
</table>
# Prolonged PT/PTT and decreased platelets

<table>
<thead>
<tr>
<th>PT</th>
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<th>Plt</th>
<th>DDx</th>
<th>Follow-up labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>DIC</td>
<td>DIC panel including d-dimers</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Liver dysfunction</td>
<td>Liver enzymes; thrombin time, reptilase time</td>
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<td></td>
<td></td>
<td></td>
<td>Kasabach-Marrett phenomena</td>
<td>Physical exam and imaging looking for hemangiomas</td>
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</table>
Common Hemostatic bleeding disorders

- Hemophilia A
- Hemophilia B
- Von Willebrand disease
How Common Are Bleeding Disorders?

• Hemophilia
  – 20,000 males in U.S. have hemophilia
  – 80% have hemophilia A
  – 20% have hemophilia B
  – Affects all racial and socioeconomic groups equally
  – Occurs in approximately 1 out of 7,500 live male births (CDC)
  – About 30% of cases result from spontaneous genetic mutation

• von Willebrand Disease
  – 1 in every 100 births - approximately 280,000
Hemophilia Types

- **Hemophilia A** - Classical type; Factor VIII deficiency; X-linked; 1:5000-10,000
- **Hemophilia B** - Christmas Disease; Factor IX deficiency; X-linked; 1:30,000
- **Hemophilia C** - Factor XI deficiency; Autosomal; chromosome 4; Ashkenazi Jews
Defect in Hemophilia

- The first steps of hemostasis function normally – an immature platelet plug is formed and bleeding stops
- Deficiency of clotting proteins – disruption of the formation of a mature fibrin clot
- Platelet plug breaks – bleeding resumes
- Process repeats again – repeated cycle of bleeding and stopping
Hemophilia - Severity

- Severe: 0% - 1%; 60% of patients
- Moderate: 1% - 5%; 15% of patients
- Mild: 5% - 25%; 25% of patients
Genetics of Hemophilia
Physical Effects of Hemophilia

• Prolonged bleeding
• Potential for spontaneous bleeds
• Muscle bleeds
• Joint bleeds can cause significant orthopedic damage, arthritis and crippling
• Internal bleeding can also occur (organs and internal structures)
• Central nervous system bleeds are always life threatening and require emergency medical intervention
Joint Bleeding: Hemarthrosis

• The most common sites for hemarthrosis are:
  – Knees
  – Elbows
  – Ankles

• Bleeding also occurs in other joints, such as:
  – Hips
  – Shoulders
Hemarthrosis: Signs and Symptoms

• Signs and symptoms of a joint bleed include:
  – A tingling or bubbling feeling in the joint
  – Not wanting to move the joint
  – Limited mobility
  – Swelling
  – Pain (usually gets worse the longer the bleed goes untreated)
  – The skin around the joint feels warm to the touch
  – Decreased range of motion

Hemarthrosis: Effect of Repeated Bleeding in Joints

- Over time, the body breaks down the blood.
- Byproducts (iron, enzymes) damage cartilage and erode joint surfaces.

Target joints are the joints that have had repeated bleeding episodes.
Impact of Chronic Hemarthrosis

- Because of the frequent bleeding episodes in target joints, problems can arise:
  - Chronic pain
  - Disfigurement
  - Limited range of motion
    - (when left untreated)

In order to cope with the pain and limited mobility associated with chronic joint disease, people may sometimes need assistive devices such as crutches, canes, or other mobility-assistance devices.
What Is Hemophilic Arthropathy?

Is a permanent state of limited mobility in a joint caused by the wearing away of cartilage from repeated prolonged bleeding episodes in patients with hemophilia.
Hemophilic Arthropathy

- Initiated by several bleeds spaced close together
- Iron is toxic
- Vicious cycle of bleeding, synovitis, arthritis
- Radiographic changes similar to rheumatoid arthritis
- Ankle in young child absorbs stress and is particularly vulnerable.
Emergencies in Hemophilia

- Head bleeds – accounts for most of the death in these patients! Can occur without obvious external bruising or lacerations
- Bleeding around the neck
- Abdominal bleeding

- Note: These may occur without a known history of trauma!! Therefore Treat first and then call or take to the ER
Diagnosis

- Normal PT
- Prolonged APTT
- Normal Bleeding Time
- Low or Absent Factor VIII or IX levels (Nl 50% - 150%)
Some Major Complications of Bleeding Disorders

- Excessive bleeding
- Joint destruction
- Inhibitors
- Psychosocial aspects
- Economic impact
Complications - Inhibitors

- Potentially serious complication of hemophilia treatment therapy
- The body’s immune system produces antibodies that interfere with the effectiveness of infused factor
- High cost to treat
- Difficult to treat bleeding

Inhibitors are most common in severe hemophilia
- Incidence of 6% to 21% in people with hemophilia A
- Incidence of 2% to 3% in people with hemophilia B
Psychosocial Effects of Hemophilia

• Lost time from school or work by patient and family members
• Compromised activities of daily living
• Social isolation
• Family and marital stress
• Quality of life issues
• Child care issues
• Parenting and discipline issues
• Sibling problems
• Financial burden
  – Among the five most costly diseases to treat
  – Exceed lifetime insurance maximums
  – Loss of insurance benefits
Goals of Hemophilia Care

• Treatment & prevention of severe bleeds
• Preservation of joint function
• Optimal quality of life
• Goals achieved through:
  – Patient and family education
  – Promotion of self-care and compliance
  – Prevention through use of protective devices
  – Monitoring and supporting treatment regimen
  – Enhancing communications... Completing the circle of care

Source of statistics national hemophilia foundation and CDC.
Hemophilia: Through the Years*

• Early Observations
• The Years of Hope (1948-1970)
• The Era of Opportunity (1965-1980)
• New Challenges (Early 1980s)
• New Horizons (1985-2001)
• The 21st Century and Beyond

Early Observations

• **1828**: The word “hemophilia” first appears in a description of the condition written by German Physician Frederick Hopff at the University of Zurich

• **1840**: First recorded case of hemophilia treatment by transfusion

• **1893**: First documentation of abnormal prolongation of coagulation in capillary tube in hemophilics

Early Observations: Other Highlights of the Early 1900s

- **1911**: Publication of “monumental review of pedigrees of families with bleeding disorders”¹
- **1920-1930**: Hemophilia treatments published; plasma for transfusions introduced
- **1937**: IV administration of redissolved plasma precipitate shown to shorten blood clotting time²
- **1937**: First permanent blood bank established in US

New Discoveries

- **1966**: Hyland announces commercial availability of FVIII concentrates
- **1969**: FIX concentrate licensed\(^1\)
- **1971**: von Willebrand’s factor identified\(^2\)

New-found Independence: 1966-1975

• **1970s:** Home infusion therapy: a common treatment practice

• **1973:** Hemophilia Act of 1973

• **July 29, 1975:** Public Law 94-63

• **1975:** Federally funded comprehensive hemophilia treatment centers initiated
The Price of Independence: 1975-1985

Transmission of blood-borne diseases:
- Hepatitis B: HBV
- Hepatitis non-A, non-B: Later called “C”
- HIV

New Horizons: 1985-2001

- New products
- Evolution and impact of HTCs
- New methods of administration of replacement products
## Hemophilia A: Evolution of Therapy

<table>
<thead>
<tr>
<th>Year</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950</td>
<td>Plasma (1-FVIII U/ml)</td>
</tr>
<tr>
<td>1966</td>
<td>Cryoprecipitate (5-FVIII U/ml)</td>
</tr>
<tr>
<td>1975</td>
<td>Lyophilized concentrates (30-FVIII U/ml)</td>
</tr>
<tr>
<td>1983</td>
<td>Heat treatment of lyophilized concentrates for viral attenuation</td>
</tr>
<tr>
<td>1985</td>
<td>Introduction of a solvent detergent for viral inactivation</td>
</tr>
<tr>
<td>1988</td>
<td>Monoclonal antibody-purified FVIII concentrates with heat or solvent detergent treatment</td>
</tr>
<tr>
<td>1992</td>
<td>Recombinant DNA products: 1st generation</td>
</tr>
<tr>
<td>2000</td>
<td>2nd Generation recombinant products (ReFacto®, Kogenate® FS, Helixate® FS)</td>
</tr>
<tr>
<td></td>
<td>3rd Generation recombinant products (Advate, Xyntha)</td>
</tr>
<tr>
<td>Year</td>
<td>Therapy</td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
</tr>
<tr>
<td>1950</td>
<td>Plasma (1-FIX U/ml)</td>
</tr>
<tr>
<td>1975</td>
<td>Lyophilized prothrombin complex concentrates or PCC (30-FIX U/ml)</td>
</tr>
</tbody>
</table>
| 1985 | Heat treatment of lyophilized concentrates for viral attenuation
Development of a solvent detergent for viral inactivation |
| 1992 | Chromatographic/monoclonal antibody-purified FIX concentrate with ultrafiltration and thiocyanate treatment (Mononine®) |
| 1997 | Recombinant DNA product (BeneFIX®) |
Causes of Death and Selected Standardized Mortality Rates Among 2,950 Males with Hemophilia in 6 States

Mortality decreased 40% in patients using a comprehensive hemophilia treatment center (HTC).

“The finding that HTCs have a significant effect on reducing mortality in patients with hemophilia supports the effectiveness of such centers in providing specialized preventative care.”

Prophylaxis:

• Primary
  – Early institution ~ 1-2 years with the aim of maintaining trough > 1%
  – Longitudinal assessment of joint status essential

• Secondary
  – Appropriate for intervention to prevent joint and other disease associated morbidities

Genetic Therapies for Hemophilia

1. Translational readthrough therapy

2. Gene transfer
Hemophilia: Advantages for Gene Therapy

- Unequivocal single gene disorders
- Basic science knowledge is extensive
- Small increments in clotting factor levels will significantly improve clinical status
- Sensitive laboratory assays to measure transgene product
- Excellent animal models
- No requirement for stringent control of clotting factor level
- Site of transgene expression – only requires vascular access
Gene Discovery - 1982/1984

1989 - 1st rFVIII Trial

1998 - 1st rFIX Trial

Latest Hemophilia Gene Therapy Trials - 2010
Hemophilia Gene Transfer

Small Phase I/II Clinical Trials Involving a total of ~50 patients

- Ex vivo retroviral vector into autologous fibroblasts (FIX)
- Ex vivo electroporation into autologous fibroblasts (FVIII)
- IV retroviral vector (FVIII)
- IV adenoviral vector (FVIII)
- IM AAV vector (FIX)
- Hepatic artery AAV vector (FIX)
Will Gene Therapy Cure Hemophilia?

• The ultimate goal of gene therapy for hemophilia is to replace nonfunctional genes so the cells will produce normal levels of factor.
• Most gene therapies being studied today will insert or implant normal genes into the body rather than fix the existing nonfunctional genes.
The 21st Century and Beyond

• Gene transplantation
• Reduction of transfusion-associated infections
• Overcome and understand inhibitor development
  – Strategies to reduce the risk of inhibitor formation
  – Strategies to reduce the immunogenicity of factor products
  – Reducing bleeding complications with inhibitors
  – Prophylactic strategies
  – Improved bypassing agents
  – Eliminating inhibitors
    • Gene therapy
    • Immune tolerance
    • Alternative tolerogenic strategies

• Quality of life issues
  – Elimination of joint morbidity
  – Optimizing the individual’s social and academic performance
Severe Hemophilia A Therapy 2015-2020

- Plasma-derived FVIII
- Recombinant FVIII
- Recombinant FVIII + Recombinant VWF
- FVIII Conjugates (eg. PEG)
- Modified FVIII (eg. fusion proteins)
- FVIII Gene Transfer
- Novel Intrinsic tenase
- Novel Adjunctive Therapies
Mortality Among Males With Hemophilia: Relations With Source of Medical Care

Table 2. Causes of death and selected standardized mortality ratios (SMR)* among 2950 males with hemophilia in six US states, 1993-1995

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Number (%†) of persons (N = 236)</th>
<th>SMR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS/Infection</td>
<td>124 (52.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circulatory disease</td>
<td>43 (18.2)</td>
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</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>8 (3.4)</td>
<td></td>
<td></td>
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<tr>
<td>Respiratory disease</td>
<td>34 (14.4)</td>
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<td></td>
</tr>
<tr>
<td>Neoplasm</td>
<td>21 (8.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-HIV- or liver-related cancers</td>
<td>14 (5.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>20 (8.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraocular hemorrhage</td>
<td>6 (2.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>19 (8.1)</td>
<td>38</td>
<td>24.3-59.7</td>
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<tr>
<td>Central nervous system disease</td>
<td>17 (7.2)</td>
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<tr>
<td>Infections other than Pneumocystis or HIV</td>
<td>13 (5.5)</td>
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<tr>
<td>Renal disease</td>
<td>10 (4.2)</td>
<td>50</td>
<td>26.8-92.8</td>
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<tr>
<td>Other causes</td>
<td>7 (3.0)</td>
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</tr>
<tr>
<td>Trauma</td>
<td>5 (2.1)</td>
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<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (1.3)</td>
<td></td>
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</tr>
</tbody>
</table>

*The SMR is the ratio of the observed-to-expected number of deaths from this cause. An SMR >1.0 indicates that there were a greater number of deaths in the cohort than would be expected to occur in a cohort of similarly aged men without hemophilia. CI indicates confidence interval.
†Persons may have had more than one cause of death listed.


Atherosclerosis in Men With Hemophilia (MWH)

- Carotid and femoral IMT not significantly different from age matched controls*
- Study of intraluminal coronary stenosis (ICS) in autopsy study of MWH vs controls**
  - No difference in ICS
  - Fewer deaths due to CAD


IMT=Intima-Media Thickness
CAD=Coronary Artery Disease