HEMOSTASIS/THROMBOSIS II

Congenital/Acquired Hemorrhagic Disorders & Their Treatment
COAGULATION TESTING

- Bleeding time primary screening test for platelet function
  - If bleeding time abnormal
    - Platelet Aggregation Studies
      - ADP, Epinephrine, Collagen, Ristocetin as agonists
      - Difficult to standardize

- PT/aPTT screens for clotting studies
  - If PT/aPTT abnormal
    - Clotting factor assays (depending on which test is abnormal)
    - Inhibitor screen (If more than one clotting factor is abnormal)
PLATELET FUNCTION DEFECTS

Prolonged Bleeding Time

- Congenital
- Drugs
- Alcohol
- Uremia
- Hyperglobulinemias
- Fibrin/fibrinogen split products
- Thrombocythemia
- Cardiac Surgery
PLATELET FUNCTION DEFECTS

Platelet Adhesion

• Bernard Soulier Disease
  - Abnormal GPIb-IX Complex
  - Receptor for von Willebrand factor
  - Only adhesion mediator @ high shear stress
  - Tested by ability to aggregate platelets in presence of ristocetin

• Von Willebrand disease
  - Reduced or dysfunctional von Willebrand factor
PLATELET FUNCTION DEFECTS

Platelet Release Defects - Congenital

- δ-storage pool disease
  - Failure to form dense granules
  - Do not release ADP, serotonin, calcium on activation
  - Fail to recruit platelets for aggregation

- Gray platelet syndrome
  - Failure of packaging of α-granules
  - Do not release protein mediators of platelet aggregation

- Decreased platelet aggregation
- Mild bleeding disorder
PLATELET FUNCTION DEFECTS

Aggregation-Congenital

- Glanzmann's thrombasthenia
  - Autosomal recessive
  - Lack of fibrinogen receptor, GP IIb/IIIa
- Platelets cannot aggregate in response to usual stimuli
- Bleeding sometimes severe
PLATELET FUNCTION DEFECTS

Scott Syndrome

- Defect in platelet microparticle formation
- Loss of shufflase, an enzyme that shuffles phospholipid species within the cell membrane
- Fail to produce receptors for Factors VIIIa & Va on the surface of activated platelets
PLATELET FUNCTION DEFECTS

Prolonged Bleeding Time

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PLATELET FUNCTION DEFECTS

Acquired - Drug Induced

- Alcohol
- Prostaglandin Synthetase Inhibitors
  - Aspirin
  - Non-Steroidal Antiinflammatory Drugs
  - Phenylbutazone
  - ? Dipyridamole ?
- ADP receptor inhibitors
  - Clopidogrel
  - Ticlopidine
- Beta-lactam antibiotics
- Heparin
PLATELET FUNCTION DEFECTS

Prolonged Bleeding Time

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- Cardiac Surgery
Platelet Function Disorders

**Treatment**

- DDAVP often useful to correct bleeding time & (probably) to decrease bleeding
- Need to avoid drugs that inhibit platelet function &/or lower platelet number
- Platelet transfusion only sure method to decrease bleeding; should reserve for procedures only
- ε-amino caproic acid (Amicar®) sometimes useful to limit bleeding
THROMBOCYTOPENIA

Decreased production

- Decreased megakaryocytes
  - Normal platelet life span
  - Good response to platelet transfusion

- Neoplastic Causes
  - Leukemias
  - Aplastic Anemia
  - Metastatic Carcinoma
  - Drugs
  - Radiotherapy

- Primary Marrow Disorders
  - Megaloblastic Anemias
  - Myelodysplastic syndromes
  - Myeloproliferative diseases
  - Some congenital syndromes
THROMBOCYTOPENIA

*Increased Destruction*

- Shortened platelet life span
- Increased megakaryocytes
- Macroplatelets
- Poor response to platelet transfusion
THROMBOCYTOPENIA

*Increased Destruction - Causes*

- **Immune**
  - ITP
  - Lymphoma
  - Lupus/rheumatic diseases
  - Drugs
- **Consumption**
  - Disseminated intravascular coagulation
  - Thrombotic thrombocytopenic purpura
  - Hemolytic/uremic syndrome
- **Septicemia**
IDIOPATHIC THROMBOCYTOPENIA PURPURA

- IgG autoantibodies bound to platelets
- Platelets removed by macrophages
- Antibodies can act on marrow
- No good diagnostic test
- Treatment - Inhibit macrophage clearance
  - Corticosteroids
  - High dose gamma globulin
  - Splenectomy
HIV-ASSOCIATED THROMBOCYTOPENIA

• Early
  - Immune mediated
  - Often in absence of AIDS
  - Remainder of marrow WNL
  - Treatment - Antiretroviral therapy

• Late
  - Usually marrow infiltration
  - Often pancytopenia
  - Often associated infection or neoplasm
  - Poorly responsive to all treatments
CONGENITAL CLOTTING DISORDERS

- Von Willebrand disease
- Hemophilia
- Factor XI deficiency
- Other clotting protein deficiencies
- Acquired factor inhibitors
  - Factor VIII, vWF most common
COAGULATION TESTING

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Clotting Factor Deficiency

Determination of missing factor

- Done only if one of screening tests is abnormal
- Run panel of assays corresponding to the abnormal screening test, using factor deficient plasmas
  - PT abnormal - Factors II, V, VII, X
  - aPTT abnormal - Factors XII, XI, IX, VIII
- For all but the deficient factor, there will be 50% of normal level of all factors, & clotting time will be normal
- For missing factor, clotting time will be prolonged
- If more than one factor level abnormal, implies inhibitor
VON WILLEBRAND DISEASE

- Autosomal Dominant inheritance with variable penetrance
- Distinct variability in severity even within same family
- Prevalence: 0.8–2% (probable underestimate)
- Generally mild bleeding disorder
- Lack of von Willebrand Factor causes
  - Decreased Factor VIII Activity
  - Defect in Platelet Adhesion
VON WILLEBRAND FACTOR

- Large Adhesive Glycoprotein
- Polypeptide chain: 220,000 MW
- Base structure: Dimer; Can have as many as 20 linked dimers
- Multimers linked by disulfide bridges
- Synthesized in endothelial cells & megakaryocytes
- Constitutive & stimulated secretion
- Large multimers stored in Weibel-Palade bodies
VON WILLÉ BRAND DISEASE

Diagnostic Studies

- aPTT - Prolonged
- vWF Activity Level (Ristocetin Cofactor Activity) - Decreased
- vWF Antigen Level ("Factor VIII Antigen") - Decreased
- Factor VIII Activity - Decreased
- Bleeding Time - Increased
- Ristocetin-Induced Platelet Aggregation - Decreased
- Multimer Structure - Variable
VON WILLEBRAND DISEASE

Classification

- Type I - Quantitative Defect
- Type II - Qualitative Defect
  - Type IIa - No multimer formation
  - Type IIb - Decreased multimers, decreased platelets
  - Type IIc - Other Protein Defects
- Type III - Severe Quantitative Defect
VON WILLEBRAND DISEASE

Treatment

• DDAVP – Releases vWF from stores
  – 70% respond; must test prior to use in critical situation

• Humate-P – Factor VIII concentrate rich in vWF; approved for Rx of vWD; 40-50 u/kg vWF activity for Type I vWD; 60-80 u/kg vWF activity for Type II or III vWD

• Cryoprecipitate – Gold standard; 40 units/kg for 0-100% of normal; ½ life 12-24 hours
HEMOPHILIA A

- Sex-linked recessive disease
- Disease dates at least to days of Talmud
- Incidence: 20/100,000 males
- 85% Hemophilia A; 15% Hemophilia B
- Clinically indistinguishable except by factor analysis
- Genetic lethal without replacement therapy
HEMOPHILIA

Clinical Severity - Correlates with Factor Level

• Mild – > 5% factor level – Bleeding only with significant trauma or surgery; only occasional hemarthroses, with trauma
• Moderate – 1–5% factor level – Bleeding with mild trauma; hemarthroses with trauma; occasionally spontaneous hemarthroses
• Severe – < 1% factor level – Spontaneous hemarthroses and soft tissue bleeding
• Within each kindred, similar severity of disease
• Multiple genetic defects
  - Factor IX > 1000
  - Factor VIII > 1000
PLATELET ACTIVATION

Platelet Activation

II $\rightarrow$ IIa

X $\rightarrow$ Xa

VIIa-TF
Tenase/Prothrombinase complex assembly (Hemophilia)

- $X \rightarrow Xa$
- $\text{VIIIa/IXa}$
- $\text{VIIIa R}$
- $\text{II } \rightarrow \text{IIa (burst formation)}$
- $\text{Va/Xa}$
- $\text{Va R}$
# FACTOR VIII vs. VWF

<table>
<thead>
<tr>
<th></th>
<th>Von Willebrand Factor</th>
<th>Factor VIII</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Function</strong></td>
<td>Platelet adhesion, Factor VIII stability</td>
<td>Fibrin Clot Formation</td>
</tr>
<tr>
<td><strong>Site of synthesis</strong></td>
<td>Endothelial cells, Megakaryocytes</td>
<td>Hepatocytes</td>
</tr>
<tr>
<td><strong>Genetic control</strong></td>
<td>Autosomal dominant</td>
<td>X-linked recessive</td>
</tr>
<tr>
<td><strong>Hemophilia</strong></td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Von Willebrand Disease</strong></td>
<td>Low</td>
<td>Low</td>
</tr>
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## HEMOPHILIA vs. VON WILLEBRAND DISEASE

<table>
<thead>
<tr>
<th>Test</th>
<th>Hemophilia A</th>
<th>Von Willebrand Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding time</td>
<td>Normal</td>
<td>Prolonged</td>
</tr>
<tr>
<td>aPTT</td>
<td>Prolonged</td>
<td>Prolonged</td>
</tr>
</tbody>
</table>
HEMOPHILIA – General Rules RE: Rx

- Treat first; ask questions later
- Bleeding into closed spaces stops!!
- AVOID EMERGENT PROCEDURES IF POSSIBLE
- No procedures without replacement Rx
- Avoid weekend/night procedures
- No procedures without Hematology & Lab backup
## Initial Therapy of Hemophilia A

<table>
<thead>
<tr>
<th>Indication</th>
<th>Hemophilia A Factor VIII:C (u/kg)</th>
<th>Factor VIII Desired Level (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Hemorrhage</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Major Hemorrhage</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Life-Threatening Lesion</td>
<td>40-50</td>
<td>80-100</td>
</tr>
</tbody>
</table>
# Initial Therapy of Hemophilia B

<table>
<thead>
<tr>
<th>Indication</th>
<th>Hemophilia B Factor IX:C (U/kg)</th>
<th>Factor IX Desired Level (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Hemorrhage</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Major Hemorrhage</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Life-Threatening Hemorrhage</td>
<td>80</td>
<td>80</td>
</tr>
</tbody>
</table>

HEMOPHILIA Rx
Subsequent Treatment

• Dependent on:
  - Procedure being done
  - ½-life of factor VIII or factor IX IN THAT PATIENT!
    • Should be determined in each case
  - Generally, ½ life 8-12 hours for VIII, 24 hours for IX

• ε-amino caproic acid (Amicar®) – a plasminogen inhibitor sometimes useful to limit bleeding
Factor Concentrates

ALL FACTOR CONCENTRATES REQUIRE HEMATOLOGY APPROVAL!!
FACTOR XI DEFICIENCY

- Autosomal recessive; sometimes referred to as Hemophilia C
- >90% of cases Ashkenazi Jews
- Mild bleeding disorder; typically bleed only with procedures
- Levels of factor XI don’t correlate well with bleeding risk
- Rx: Fresh frozen plasma (5-10 ml/kg); good for c. 1 week (factor XI conc. available in Israel)
- #1 cause of lawsuits vs. coagulation experts
Other coagulation factor disorders

- Factor XII & above don’t cause bleeding
- Vitamin K dependent factor deficiency Rx with intermediate purity Factor IX concentrates
  - Different manufacturers have different levels of Factors II, VII, & X
- Factor V deficiency Rx with platelets (usually)
Clotting Factor Deficiency

Treatment

- For Factor XII & above, no treatment needed
- FFP for Factor XI deficiency, factor XIII deficiency
- Cryoprecipitate for low fibrinogen, factor XIII deficiency
- Primary Platelet disorders
  - Platelet transfusion, DDAVP
Clotting Factor Deficiency

Treatment

- Hemophilia A
  - Factor VIII Concentrate (Monoclonal Purified or Recombinant)
- Hemophilia B
  - Factor IX Concentrate (Recombinant or Monoclonal Purified)
- Von Willebrand Disease
  - Humate-P, Cryoprecipitate
- Antifibrinolytics often helpful to prevent late hemorrhage
CLOTTING DISORDERS

Acquired

- Vitamin K deficiency
- Liver disease
- Disseminated Intravascular Coagulation
- Coumadin therapy
- Heparin therapy
VITAMIN K DEFICIENCY

• Almost always hospitalized patients
• Require both malnutrition & decrease in gut flora
• PT goes up 1st, 2º to factor VII's short half-life
• Treatment: Replacement Vitamin K
• Response within 24-48 hours
CLOTTING DISORDERS

*Acquired*

- Vitamin K deficiency
- Liver disease
- Disseminated Intravascular Coagulation
- Coumadin therapy
- Heparin therapy
LIVER DISEASE

- Decreased synthesis, vitamin K dependent proteins
- Decreased clearance, activated clotting factors
- Increased fibrinolysis $2^\circ$ to decreased antiplasmin
- Dysfibrinogenemia $2^\circ$ to synthesis of abnormal fibrinogen
- Increased fibrin split products
- Increased PT, aPTT, TT
- Decreased platelets (hypersplenism)
- Treatment: Replacement therapy
  - Reserved for bleeding/procedure