I have no conflicts of interest to disclose.
HEMOSTASIS

- Vascular phase
  - Blood vessel damage results in vasoconstriction
- Platelet phase
  - Platelets adhere to damaged vessel surface forming a temporary platelet plug
- Coagulation phase
  - Clotting pathways lead to conversion of fibrinogen to fibrin
- Fibrinolytic phase
  - Anticlotting mechanisms allow for clot dissolution and vessel repair

PLATELET PLUG FORMATION

HEMOSTASIS IS DEPENDENT UPON...

- Vessel wall integrity
- Adequate number of platelets
- Proper function of platelets
- Appropriate clotting factor levels
- Proper function of the fibrinolytic pathway
The patient’s report of symptoms is subjective!

**Surgical challenges**
- Dental procedures
- Anemia
  - Iron responsive
  - Transfusion requirement
- Menses
  - Soaking feminine product every 2 hours
- Medications
- Comorbid conditions
  - Liver or renal disease
- Age of onset
- Family history
- Superficial vs. deep tissue bleeding

**Primary Hemostasis**
- Primary hemostasis = blood vessel + platelets

Petechiae  Purpura  Ecchymosis
**SECONDARY HEMOSTASIS**

- Secondary hemostasis = coagulation factors

- Hematoma
- Hemarthrosis

**VESSEL ABNORMALITY**

- Scurvy = vitamin C deficiency
  - Gum bleeding
  - Poor wound healing
- Ehlers-Danlos syndrome
  - Easy bruising
  - Joint hypermobility
  - Skin hyperelasticity

**LABORATORY EVALUATION**

- Complete blood count
- Platelet
- Peripheral smear
- Bleeding time
  - Limitations: labor intensive, operator dependent
- Prothrombin time (PT)
  - Extrinsic pathway
- Partial thromboplastin time (PTT)
  - Intrinsic pathway
- Thrombin time
  - Time to convert fibrinogen to fibrin
- Additional testing:
  - Closure time
  - Platelet aggregation studies
  - Mixing studies
**PLATELETS: THESE LITTLE CELLS ARE A BIG DEAL!**

**PLATELET DISORDERS**
- Thrombocytopenia
  - Pseudothrombocytopenia
  - Idiopathic thrombocytopenia purpura (ITP)
  - Thrombotic microangiopathy
    - Thrombotic thrombocytopenic purpura (TTP)
    - Hemolytic uremic syndrome (HUS)
  - Heparin induced thrombocytopenia (HIT)
  - Pregnancy
  - Marrow failure
  - Hypersplenism
- Dysfunction
  - Drugs
  - Renal dysfunction
  - Congenital disorders
  - Von Willebrand disease

**PSEUDOTHROMBOCYTOPENIA**

EDTA is the enemy!
Bleeding Problems: Causes and Cures
Melissa M. Cyr, D.O.

IDIOPATHIC THROMBOCYTOPENIA PURPURA
- Isolated profound thrombocytopenia
  - Normal red and white blood cell counts
- Antibody mediated platelet destruction
  - Testing for anti-platelet antibodies not useful
- Associated disorders
  - Infection
    - H. pylori
  - Malignancy
  - Diagnosis of exclusion
  - Acute versus chronic

ITP TREATMENT
- Watchful waiting
- Address the underlying cause
- Platelet transfusion
- Corticosteroids
- IVig
- Anti-Rh(D) immunoglobulin
- Rituximab
- Thrombopoietin receptor agonists
  - Romiplostim (Nplate)
  - Eltrombopag (Promacta)
- Splenectomy

THROMBOTIC MICROANGIOPATHY
- Thrombocytopenia
- Microangiopathic hemolytic anemia
  - Intravascular hemolysis
  - Renal and neurologic dysfunction
- Neurologic symptoms
  - Vision loss
  - Other dysfunction
Thrombotic Microangiopathy (TMA)
- Thrombocytopenic purpura (TTP)
- Hemolytic uremic syndrome (HUS)
- HELLP syndrome
  - Hemolysis
  - Elevated liver enzymes
  - Low platelets
- Drug-induced microangiopathy
- DIC
  - Disseminated intravascular coagulation

Treatment TMA
- TTP
  - ADAMTS13
  - Plasma exchange
- HUS
  - Shiga toxin-producing E Coli:
    - Intravascular volume expansion
    - Antibiotics should be avoided
  - Atypical:
    - Compliment testing
- HELLP
  - Delivery
- Drug-induced microangiopathy
  - Remove the offending agent
  - Plasma exchange
- DIC
  - Supportive therapy
  - Address the underlying disorder

Heparin Induced Thrombocytopenia (HIT)
- Risk of clotting not bleeding
- Immune mediated response to heparin causing a drop in platelet count:
  - Immune complex formation between heparin and platelet factor 4 (PF4)
  - Antibody binds to the complex and platelets are destroyed
- "50% drop" in platelet count
- Occurs 5-10 days after heparin exposure
  - "amnestic response"
- Nonimmune HIT
  - Not harmful
  - More common
  - Mild decrease in platelet count
**TREATMENT HIT**
- Discontinue all heparin products
- Avoid platelet transfusion
- Direct thrombin inhibitor (DTI)
  - Argatroban
  - Bivalirudin
- Factor Xa inhibitor
  - Fondaparinux
- Warfarin
  - Start after platelet count normalizes
- Novel anticoagulants
  - Not FDA approved

**PREGNANCY ASSOCIATED THROMBOCYTOPENIA**
- Gestational thrombocytopenia
  - Mild decrease in platelet count
  - Later in pregnancy
- Preeclampsia/eclampsia
  - Degree of thrombocytopenia correlates with severity of disease
- HELLP
  - Variant of severe preeclampsia
- ITP
  - Antiplatelet antibodies may cross the placenta causing significant fetal thrombocytopenia
- HIT
  - Consider if on therapeutic or prophylactic dose heparin
- Others

**TREATMENT OF PREGNANCY ASSOCIATED THROMBOCYTOPENIA**
- Gestational thrombocytopenia
  - Epidural anesthesia safe when platelet count >80,000 and stable
- Preeclampsia/eclampsia/HELLP
  - Delivery is the ultimate cure
- ITP
  - Corticosteroids, IVlg, anti-Rh(D) immunoglobulin, splenectomy, platelet transfusion
- HIT
  - Fondaparinux
- Others
**Thrombocytopenia Due to Marrow Failure**
- Viral
- Nutritional deficiency
- Chemotherapy
- Radiation
- Infiltration of abnormal cells
  - Aplastic anemia
  - Leukemia
  - Metastatic cancer

**Thrombocytopenia Due to Hypersplenism**
- Associated with:
  - Liver disease
  - Infection
  - Hemoglobinopathy
  - Malignancy
  - Autoimmune disorders
  - Infiltrative processes
- Increased spleen size leads to destruction of platelets
  - Normal size ~ 11 cm
- Sequestration
- Treatment:
  - Address the underlying disorder
  - Transfusion support
  - Splenectomy
  - Radiation

**Disorders of Platelet Function**
- Drugs
  - Aspirin
    - Irreversible binding to platelet for entire lifespan (7-10 days)
  - NSAIDS
    - Reversible binding to platelet (~6 hours)
  - Clopidogrel, ticlopidine
  - Antihistamines
  - Antidepressants
  - Ginkgo biloba
- Myeloproliferative disorders
- Renal dysfunction
  - Bleeding risk in uremia multifactorial
**DISORDERS OF PLATELET DYSFUNCTION CONTINUED**
- Congenital disorders
  - Disorders of platelet secretion
    - Storage pool disease
  - Disorders of platelet aggregation
    - Bernard Soulier syndrome
      - GpIb
    - Giant platelets
    - Glanzmann’s thrombasthenia
      - GpIIb/IIIa
  - Von willebrand disease

**TREATMENT OF PLATELET DYSFUNCTION**
- Remove the offending agent
- DDAVP
  - Releases vWF helping platelet adhesion
- Platelet transfusion
- Antifibrinolytic agents
  - Tranexemic acid
  - Aminocaproic acid
- Hormone therapy
  - Addresses menstrual dysfunction

**SECONDARY HEMOSTASIS: CLOTTING FACTORS**

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POMA District VIII 30th Annual Winter Seminar January 26-29, 2017
**Hemophilia A**
- 80-85% of all hemophiliacs
- Deficiency of factor VIII

**Hemophilia B**
- Deficiency of factor IX

**Hemophilia C**
- Deficiency of factor XI

**Von willebrand disease**
**TREATMENT OF HEMOPHILIA**

- DDAVP
- Replacement therapy
- Antifibrinolytics
- Physical therapy
- Surgery

LEAVE IT TO THE EXPERTS!!

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**FACTOR DEFICIENCY: ACQUIRED**

- Anticoagulants
  - Warfarin
  - Heparin
- Liver disease
  - Decreased production of clotting factors (1,2,5,7,9,10)
- Malabsorption
  - Intestinal diseases interfere with bile acid metabolism
  - Bile acids required for vitamin K absorption
- Factor inhibitors
  - Abnormal mixing study
- Broad spectrum antibiotics
  - Alter intestinal flora leading to decreased vitamin K production

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**“THE CROSS-OVER DISORDERS”**

- Involve disorders in both primary and secondary hemostasis
  - von Willebrand disease
  - Disseminated intravascular coagulation (DIC)
**VON WILLEBRAND DISEASE**

- vWF is carrier protein made for factor VIII important in platelet adhesion

**VON WILLEBRAND SUBTYPES**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Defect</th>
<th>vWF Ag</th>
<th>vWF RCoF</th>
<th>vWF von Willebrand multimers</th>
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<tbody>
<tr>
<td>1</td>
<td>Deficiency</td>
<td>↓</td>
<td>↓</td>
<td>↓ Normal distribution</td>
</tr>
<tr>
<td>2A</td>
<td>Mismutation</td>
<td>↓</td>
<td>↓</td>
<td>↑ Decreased high and intermediate molecular weight multimers</td>
</tr>
<tr>
<td>28</td>
<td>Decreased binding of high molecular weight multimers to platelets</td>
<td>↓</td>
<td>↓</td>
<td>↓ Decreased high molecular weight multimers</td>
</tr>
<tr>
<td>29</td>
<td>Decreased binding to platelets</td>
<td>Normal</td>
<td>↓</td>
<td>↓ Normal distribution</td>
</tr>
<tr>
<td>29*</td>
<td>Decreased binding to FVIII</td>
<td>↓</td>
<td>↓</td>
<td>↓ Normal distribution</td>
</tr>
<tr>
<td>3</td>
<td>Complete deficiency</td>
<td>↓</td>
<td>↓</td>
<td>↓ Decreased high molecular weight multimers</td>
</tr>
<tr>
<td>Paraplatelet</td>
<td>Decreased binding of high molecular weight multimers to platelets</td>
<td>↓</td>
<td>↓</td>
<td>↓ Decreased high molecular weight multimers</td>
</tr>
</tbody>
</table>

*Genes with type 2A are usually compound heterozygous for a type 1 mutation and therefore have low vWF Ag and RCoF.

vWF = von Willebrand factor; Ag = von Willebrand antigen.

**TREATMENT OF VON WILLEBRAND DISEASE**

- DDAVP
- Replacement therapy
  - Humate-P
  - Recombinant vWF product
- Antifibrinolytics
  - Aminocaproic acid
  - Tranexamic acid
- Contraceptives
- Fibrin glue
**DISSEMINATED INTRAVASCULAR COAGULATION (DIC)**

- Clotting (not bleeding) disorder
- Leads to consumption of platelets and clotting factors
- Lab abnormalities:
  - Elevated PTT
  - Elevated PT
  - Decreased platelet count
  - Elevated thrombin time
  - Elevated fibrin degradation products
  - Fibrinogen not reliable
    - Acute phase reactant

**TREATMENT OF DIC**

- Address the underlying disorder
- Transfuse blood products if bleeding or planned invasive procedures
  - Cryoprecipitate
    - Fibrinogen, vWF, factors VIII and XIII
  - Fibrinogen <100 mg/dL
- Heparin controversial
  - Active thrombosis
  - APML
- Fibrinolytic inhibitors
  - Can cause more clotting
  - Do not treat lab results!

**DISORDERS OF FIBRINOLYSIS**

- Congenital
  - Alpha-2-antiplasmin deficiency
  - Plasminogen activator inhibitor type 1 (PAI-1) deficiency
- Acquired
  - Liver disease
  - Amyloidosis
  - Leukemia (APML)
  - Solid tumors
  - Snake venom
- Treatment
  - Antifibrinolytic agents