Objectives

- Coagulation factor disorders and treatment
- Disorders of platelets and platelet transfusion
- Adjunctive drug therapy for bleeding
Coagulation factor disorders requiring blood products
# Coagulation factor disorders

## Inherited bleeding disorders
- Hemophilia A and B
- von Willebrand’s disease
- Other factor deficiencies

## Acquired bleeding disorders
- Liver disease
- Vitamin K deficiency/warfarin overdose
- DIC
Ecchymoses

(typical of coagulation factor disorders)
## Hemophilia A and B

<table>
<thead>
<tr>
<th></th>
<th>Hemophilia A</th>
<th>Hemophilia B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coagulation factor deficiency</strong></td>
<td>Factor VIII</td>
<td>Factor IX</td>
</tr>
<tr>
<td><strong>Inheritance</strong></td>
<td>X-linked recessive</td>
<td>X-linked recessive</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>1/10,000 males</td>
<td>1/50,000 males</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td>Related to factor level</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;1% - Severe - spontaneous bleeding</td>
<td></td>
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<tr>
<td></td>
<td>1-5% - Moderate - bleeding with mild injury</td>
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<tr>
<td></td>
<td>5-25% - Mild - bleeding with surgery or trauma</td>
<td></td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>Soft tissue bleeding</td>
<td></td>
</tr>
</tbody>
</table>
Hemophilia

Clinical manifestations (hemophilia A & B indistinguishable)

Hemarthrosis (most common)
  Fixed joints
Soft tissue hematomas (e.g., muscle)
  Muscle atrophy
  Shortened tendons
Other sites of bleeding
  Urinary tract
  CNS, neck (may be life-threatening)
Prolonged bleeding after surgery or dental extractions
Treatment of hemophilia A

- **Intermediate purity plasma products**
  - Virucidally treated
  - May contain von Willebrand factor

- **High purity (monoclonal) plasma products**
  - Virucidally treated
  - No functional von Willebrand factor

- **Recombinant factor VIII**
  - Virus free/No apparent risk
  - No functional von Willebrand factor
Factor VIII Infusion

Pharmacokinetics of Factor VIII Infusion

Time (hours)

Plasma Factor VIII (%)
Dosing guidelines for hemophilia A

- **Mild bleeding**
  - Target: 30% dosing q8-12h; 1-2 days (15U/kg)
  - Hemarthrosis, oropharyngeal or dental, epistaxis, hematuria

- **Major bleeding**
  - Target: 80-100% q8-12h; 7-14 days (50U/kg)
  - CNS trauma, hemorrhage, lumbar puncture
  - Surgery
  - Retroperitoneal hemorrhage
  - GI bleeding

- **Adjunctive therapy**
  - amino caproic acid (Amicar) or DDAVP (for mild disease only)
Complications of therapy

- Formation of inhibitors (antibodies)
  - 10-15% of severe hemophilia A patients
  - 1-2% of severe hemophilia B patients

- Viral infections
  - Hepatitis B
  - Hepatitis C
  - HIV
  - Human parvovirus
  - Hepatitis A
  - Other
Treatment of hemophilia B

- **Agent**
  - High purity factor IX
  - Recombinant human factor IX

- **Dose**
  - Initial dose: 100U/kg
  - Subsequent: 50 U/kg every 24 hours
# von Willebrand Disease

## Clinical features

- **von Willebrand factor**
  - Carrier of factor VIII
  - Anchors platelets to subendothelium
  - Bridge between platelets

- **Inheritance**
  - Autosomal dominant

- **Incidence**
  - 1/10,000

- **Clinical features**
  - Mucocutaneous bleeding
Laboratory evaluation of von Willebrand disease

Classification

- **Type 1** Partial quantitative deficiency
- **Type 2** Qualitative deficiency
- **Type 3** Total quantitative deficiency

Diagnostic tests:

<table>
<thead>
<tr>
<th>Assay</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>vWF antigen</td>
<td>↓</td>
<td>Normal</td>
<td>↓↓</td>
</tr>
<tr>
<td>vWF activity</td>
<td>↓</td>
<td>↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Multimer analysis</td>
<td>Normal</td>
<td>Normal</td>
<td>Absent</td>
</tr>
</tbody>
</table>
Treatment of von Willebrand disease
Varies by Classification

- **Cryoprecipitate**
  - Source of fibrinogen, factor VIII and VWF
  - Only plasma fraction that consistently contains VWF multimers
  - Correction of bleeding time is variable

- **DDAVP (Deamino-8-arginine vasopressin)**
  - Increases plasma VWF levels by stimulating secretion from endothelium
  - Duration of response is variable
  - Used for type 1 disease
  - Dosage 0.3 µg/kg q 12 hr IV

- **Factor VIII concentrate (Humate-P)**
  - Virally inactivated product
  - Used for type 2 and 3
# Vitamin K deficiency

- **Source of vitamin K**
  - Green vegetables
  - Synthesized by intestinal flora

- **Required for synthesis**
  - Factors II, VII, IX, X
  - Protein C and S

- **Causes of deficiency**
  - Malnutrition
  - Biliary obstruction
  - Malabsorption
  - Antibiotic therapy

- **Treatment**
  - Vitamin K
  - Fresh frozen plasma
Vitamin K deficiency due to warfarin overdose

Managing high INR values

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR therapeutic-5</td>
<td>Lower or omit next dose; Resume therapy when INR is therapeutic</td>
</tr>
<tr>
<td>INR 5-9; no bleeding</td>
<td>Lower or omit next dose; Resume therapy when INR is therapeutic</td>
</tr>
<tr>
<td></td>
<td>Omit dose and give vitamin K (1-2.5mg po)</td>
</tr>
<tr>
<td></td>
<td>Rapid reversal: vitamin K 2-4 mg po (repeat)</td>
</tr>
<tr>
<td>INR &gt;9; no bleeding</td>
<td>Omit dose; vitamin K 3-5 mg po; repeat as necessary</td>
</tr>
<tr>
<td></td>
<td>Resume therapy at lower dose when INR therapeutic</td>
</tr>
</tbody>
</table>

*Chest 2001:119;22-38s (supplement)*
# Vitamin K deficiency due to warfarin overdose

*Managing high INR values in bleeding patients*

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR &gt; 20; serious bleeding</td>
<td>Omit warfarin</td>
</tr>
<tr>
<td>Any life-threatening bleeding</td>
<td>Vitamin K 10 mg slow IV infusion</td>
</tr>
<tr>
<td></td>
<td>FFP ± factor rhVIIa (depending on urgency)</td>
</tr>
<tr>
<td></td>
<td>Repeat vitamin K injections every 12 hrs as needed</td>
</tr>
</tbody>
</table>
Disseminated Intravascular Coagulation (DIC) Mechanism

Systemic activation of coagulation

- Intravascular deposition of fibrin
  - Thrombosis of small and midsize vessels with organ failure

- Depletion of platelets and coagulation factors
  - Bleeding
Common clinical conditions associated with DIC

- Sepsis
- Trauma
  - Head injury
  - Fat embolism
- Malignancy
- Obstetrical complications
  - Amniotic fluid embolism
  - Abruptio placenta
- Vascular disorders
- Reaction to toxin (e.g. snake venom, drugs)
- Immunologic disorders
  - Severe allergic reaction
  - Transplant rejection
DIC

Treatment approaches

- Treatment of underlying disorder
- Anticoagulation with heparin
- Platelet transfusion
- Fresh frozen plasma
Liver Disease

Decreased synthesis of II, VII, IX, X, XI, and fibrinogen
Prolongation of PT, aPTT and Thrombin Time

Often complicated by
Gastritis, esophageal varices, DIC

Treatment
Fresh-frozen plasma infusion *(immediate but temporary effect)*
Vitamin K (usually ineffective)
Coagulation cascade

Intrinsic system (surface contact)
- XII
  - XIIa
  - XI
  - Xla
  - IX
  - IXa
  - VIII
  - VIIIa
  - X
  - Xa

Extrinsic system (tissue damage)
- Tissue factor
- X
  - Xa
  - V
  - Va
  - II
  - IIa (Thrombin)

Fibrinogen

Vitamin K dependent factors

Washington University in St. Louis
School of Medicine
Laboratory Evaluation of the Coagulation Pathways

Partial thromboplastin time (PTT)
- Surface activating agent (Ellagic acid, kaolin)
- Phospholipid
- Calcium

Prothrombin time (PT)
- Thromboplastin
- Tissue factor
- Phospholipid
- Calcium

Intrinsic pathway

Extrinsic pathway

Common pathway

Thrombin time
- Thrombin

Fibrin clot
Pre-analytic errors

- **Problems with blue-top tube**
  - Partial fill tubes
  - Vacuum leak and citrate evaporation

- **Problems with phlebotomy**
  - Heparin contamination
  - Wrong label
  - Slow fill
  - Underfill
  - Vigorous shaking

- **Biological effects**
  - Hct ≥55 or ≤15
  - Lipemia, hyperbilirubinemia, hemolysis

- **Laboratory errors**
  - Delay in testing
  - Prolonged incubation at 37°C
  - Freeze/thaw deterioration
Initial Evaluation of a Bleeding Patient

Normal PT
Normal PTT

Urea solubility

Abnormal

Factor XIII deficiency

Consider evaluating for:
- Mild factor deficiency
- Abnormal fibrinolysis (α2 anti-plasmin def)
- Elevated FDPs

Normal

Abnormal
Initial Evaluation of a Bleeding Patient

Normal PT
Abnormal PTT

Repeat with 50:50 mix

50:50 mix is normal

50:50 mix is abnormal

Test for inhibitor activity:
Specific factors: VIII, IX, XI
Non-specific (anti-phospholipid Ab)

Test for factor deficiency:
Isolated deficiency in intrinsic pathway (factors VIII, IX, XI)
Multiple factor deficiencies (rare)
Initial Evaluation of a Bleeding Patient - 3

Abnormal PT
Normal PTT

50:50 mix is abnormal

50:50 mix is normal

Test for factor deficiency:
- Isolated deficiency of factor VII (rare)
- Multiple factor deficiencies (common)
  - (Liver disease, vitamin K deficiency, warfarin, DIC)

Repeat with 50:50 mix

Test for inhibitor activity:
- Specific: Factor VII (rare)
- Non-specific: Anti-phospholipid (rare)
Initial Evaluation of a Bleeding Patient

Abnormal PT
Abnormal PTT

Repeat with 50:50 mix

50:50 mix is normal

50:50 mix is abnormal

Test for inhibitor activity:
- Specific: Factors V, X, Prothrombin, Fibrinogen (rare)
- Non-specific: anti-phospholipid (common)

Test for factor deficiency:
- Isolated deficiency in common pathway: Factors V, X, Prothrombin, Fibrinogen
- Multiple factor deficiencies (common) 
  (Liver disease, vitamin K deficiency, warfarin, DIC)
Coagulation factor deficiencies

Summary

Sex-linked recessive

◆ Factors VIII and IX deficiencies cause bleeding
  Prolonged PTT; PT normal

Autosomal recessive (rare)

◆ Factors II, V, VII, X, XI, fibrinogen deficiencies cause bleeding
  Prolonged PT and/or PTT

◆ Factor XIII deficiency is associated with bleeding and impaired wound healing
  PT/PTT normal; clot solubility abnormal

◆ Factor XII, prekallikrein, HMWK deficiencies
  do not cause bleeding
Disorders of Platelets and Platelet Transfusion
Sites of bleeding in thrombocytopenia

- Skin and mucous membranes
  - Petechiae
  - Ecchymosis
  - Hemorrhagic vesicles
  - Gingival bleeding and epistaxis

- Menorrhagia

- Gastrointestinal bleeding

- Intracranial bleeding
Petechiae

- Do not blanch with pressure (cf. angiomas)
- Not palpable (cf. vasculitis)
Classification of platelet disorders

- Quantitative disorders
  - Abnormal distribution
  - Dilution effect
  - Decreased production
  - Increased destruction

- Qualitative disorders
  - Inherited disorders (rare)
  - Acquired disorders
    - Medications
    - Chronic renal failure
    - Cardiopulmonary bypass
Acquired thrombocytopenia with shortened platelet survival

<table>
<thead>
<tr>
<th>Associated with bleeding</th>
<th>Associated with thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Immune-mediated thrombocytopenia (ITP)</td>
<td>• Thrombotic thrombocytopenic purpura</td>
</tr>
<tr>
<td>• Most drug-induced thrombocytopenias</td>
<td>• DIC</td>
</tr>
<tr>
<td>• Most others</td>
<td>• Trousseau’s syndrome</td>
</tr>
<tr>
<td></td>
<td>• Heparin-associated thrombocytopenia</td>
</tr>
</tbody>
</table>
Approach to the thrombocytopenic patient

- History
  - Is the patient bleeding?
  - Are there symptoms of a secondary illness? (neoplasm, infection, autoimmune disease)
  - Is there a history of medications, alcohol use, or recent transfusion?
  - Are there risk factors for HIV infection?
  - Is there a family history of thrombocytopenia?
  - Do the sites of bleeding suggest a platelet defect?

- Assess the number and function of platelets
  - CBC with peripheral smear
  - Platelet function study
Platelet function screen

- Replaces the *bleeding time* as a test of platelet function
- PFA-100; ordered as “platelet function screen”
- Blue top tube
- Measures the time it takes for blood to block membrane coated with either collagen/epinephrine or collagen/ADP
<table>
<thead>
<tr>
<th>Epi</th>
<th>ADP</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal platelet function</td>
</tr>
<tr>
<td>Abnormal</td>
<td>Normal</td>
<td>“Aspirin effect”</td>
</tr>
<tr>
<td>Abnormal</td>
<td>Abnormal</td>
<td>Abnormal platelet function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valvular heart disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Von Willebrand disease</td>
</tr>
</tbody>
</table>
Platelet transfusions

■ Source
  • Platelet concentrate (Random donor)
    Each donor unit should increase platelet count ~10,000 /µl
  • Pheresis platelets (Single donor)

■ Storage
  • Up to 5 days at room temperature

■ “Platelet trigger”
  • Bone marrow suppressed patient (>10-20,000/µl)
  • Bleeding/surgical patient (>50,000/µl)
Platelet transfusions - complications

- Transfusion reactions
  - Higher incidence than in RBC transfusions
  - Related to length of storage/leukocytes/RBC mismatch
  - Bacterial contamination

- Platelet transfusion refractoriness
  - Alloimmune destruction of platelets (HLA antigens)
  - Non-immune refractoriness
    - Microangiopathic hemolytic anemia
    - Coagulopathy
    - Splenic sequestration
    - Fever and infection
    - Medications (Amphotericin, vancomycin, ATG, Interferons)
## Laboratory Evaluation of Bleeding

### Overview

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Test Name</th>
<th>Pathological Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC and smear</td>
<td>Platelet count</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>RBC and platelet morphology</td>
<td>TTP, DIC, etc.</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Prothrombin time</td>
<td>Extrinsic/common pathways</td>
</tr>
<tr>
<td></td>
<td>Partial thromboplastin time</td>
<td>Intrinsic/common pathways</td>
</tr>
<tr>
<td></td>
<td>Coagulation factor assays</td>
<td>Specific factor deficiencies</td>
</tr>
<tr>
<td></td>
<td>50:50 mix</td>
<td>Inhibitors (e.g., antibodies)</td>
</tr>
<tr>
<td></td>
<td>Fibrinogen assay</td>
<td>Decreased fibrinogen</td>
</tr>
<tr>
<td></td>
<td>Thrombin time</td>
<td>Qualitative/quantitative fibrinogen defects</td>
</tr>
<tr>
<td></td>
<td>FDPs or D-dimer</td>
<td>Fibrinolysis (DIC)</td>
</tr>
<tr>
<td>Platelet function</td>
<td>von Willebrand factor</td>
<td>vWD</td>
</tr>
<tr>
<td></td>
<td>Bleeding time</td>
<td>In vivo test (non-specific)</td>
</tr>
<tr>
<td></td>
<td>Platelet function analyzer (PFA)</td>
<td>Qualitative platelet disorders and vWD</td>
</tr>
<tr>
<td></td>
<td>Platelet function tests</td>
<td>Qualitative platelet disorders</td>
</tr>
</tbody>
</table>
Adjunctive therapy for bleeding disorders
Adjunctive drug therapy for bleeding

- Fresh frozen plasma
- Cryoprecipitate
- Epsilon-amino-caproic acid (Amicar)
- DDAVP
- Recombinant human factor VIIa (Novoseven)
Fresh frozen plasma

- Content - plasma (decreased factor V and VIII)
- Indications
  - Multiple coagulation deficiencies (liver disease, trauma)
  - DIC
  - Warfarin reversal
  - Coagulation deficiency (factor XI or VII)
- Dose (225 ml/unit)
  - 10-15 ml/kg
- Note
  - Viral screened product
  - ABO compatible
Cryoprecipitate

- Prepared from FFP
- Content
  - Factor VIII, von Willebrand factor, fibrinogen
- Indications
  - Fibrinogen deficiency
  - Uremia
  - von Willebrand disease
- Dose (1 unit = 1 bag)
  - 1-2 units/10 kg body weight
Aminocaproic acid (Amicar)

- **Mechanism**
  - Prevent activation plaminogen -> plasmin

- **Dose**
  - 50mg/kg po or IV q 4 hr

- **Uses**
  - Primary menorrhagia
  - Oral bleeding
  - Bleeding in patients with thrombocytopenia
  - Blood loss during cardiac surgery

- **Side effects**
  - GI toxicity
  - Thrombi formation
Desmopressin (DDAVP)

- **Mechanism**
  - Increased release of VWF from endothelium

- **Dose**
  - 0.3µg/kg IV q12 hrs
  - 150mg intranasal q12hrs

- **Uses**
  - Most patients with von Willebrand disease
  - Mild hemophilia A

- **Side effects**
  - Facial flushing and headache
  - Water retention and hyponatremia
Recombinant human factor VIIa (rhVIIa; Novoseven)

- **Mechanism**
  - Activates coagulation system through extrinsic pathway

- **Approved Use**
  - Factor VIII inhibitors in hemophiliacs

- **Dose**: (1.2 mg/vial)
  - 90 µg/kg q 2 hr
  - “Adjust as clinically indicated”

- **Cost (70 kg person) @ $1/µg**
  - ~$5,000/dose or $60,000/day
Recombinant human factor VIIa in non-approved settings

- Surgery or trauma with profuse bleeding
  - Consider in patients with excessive bleeding without apparent surgical source and no response to other components
  - Dose: 50-100ug/kg for 1-2 doses
  - Risk of thrombotic complications not well defined

- Anticoagulation therapy with bleeding
  - 20ug/kg with FFP if life or limb at risk; repeat if needed for bleeding
Approach to bleeding: Summary

- Identify and correct any specific defect of hemostasis
- Use non-transfusional drugs whenever possible
- RBC transfusion for surgical procedures or large blood loss