Anemia

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Abnormal red blood cell

- Variation in size: Anisocytosis
- Variation in shape: Poikilocytosis
- Abnormal in staining: Hypochromic, Polychromasia
- Abnormal in size:
  - Microcyte: RBC < 6 µm or MCV < 80 fl
  - Macrocyte: RBC > 9 µm or MCV > 100 fl

Signs and symptoms

- Fatigue
- Dizziness
- Pallor
- Cold, clammy skin
- Brittle or broken nails
- Reduced exercise tolerance
- Dyspnea
- Depression
- Headaches
- Impaired cognition
- Menstrual irregularities
- Loss of appetite
- Tachycardia
- Rales, peripheral edema, tachypnea

ภาวะโลหิตจางหรือภาวะซีด หมายถึง การที่มี hemoglobin (Hb) หรือ hematocrit (Hct) หรือ red cell mass น้อยลง

ตาม WHO classification ได้กำหนดค่ามาตรฐานดังนี้

- ผู้ชาย มีระดับ Hb < 13 g/dl หรือ Hct < 39%
- ผู้หญิงและเด็กโต < 12 < 36%
- หญิงมีครรภ์ < 11 < 33%
- เด็ก 3 เดือนถึง 4 ขวบ < 11 < 33%
Consequences of chronic anemia

- Reduced function and quality of life
- Decreased survival (< 65 year-old)
- Increased risk of heart failure
- Changes in neurological function
- Increased risk of complications from surgery and anesthesia
- Increased risk of coronary death
- Decreased tolerance of chemotherapy

Etiology

1. Blood loss
2. Hemolytic anemia
3. Impaired red cell formation

Classification of Anemia

1. Etiologic classification
2. Morphologic classification

<table>
<thead>
<tr>
<th>Severity</th>
<th>WHO</th>
<th>NCI</th>
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<tbody>
<tr>
<td>Grade 0 (WNL)*</td>
<td>≥11.0 g/dL</td>
<td>WNL</td>
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<tr>
<td>Grade 1 (mild)</td>
<td>9.5–10.0 g/dL</td>
<td>10.0 g/dL to WNL</td>
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<tr>
<td>Grade 2 (moderate)</td>
<td>8.0–9.4 g/dL</td>
<td>8.0–10.0 g/dL</td>
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<tr>
<td>Grade 3 (serious/severe)</td>
<td>6.5–7.9 g/dL</td>
<td>6.5–7.9 g/dL</td>
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<tr>
<td>Grade 4 (life threatening)</td>
<td>&lt;6.5 g/dL</td>
<td>&lt;6.5 g/dL</td>
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WHO, World Health Organization; NCI, National Cancer Institute.
*Within normal limits: female 12.0–16.0 g/dL, male 14.0–18.0 g/dL.
Etiologic classification

1. Blood loss:
   acute; GI hemorrhage, accident
   chronic; hook worm, hypermenorrhea

2. Hemolytic anemia:
   2.1 intracorpuscular
      1) membrane defects e.g. spherocytosis, elliptocytosis
      2) enzymatic defects e.g. pyruvate kinase deficiency, G6PD deficiency
      3) hemoglobin defects e.g. thalassemia

2.2 extracorpuscular
   1) immune
      - isoimmune
      - autoimmune e.g. autoimmune hemolytic anemia (AIHA)
   2) nonimmune (idiopathic, secondary)

3. Impaired red cell formation
   3.1 nutritional deficiency e.g.
      - iron
      - folic acid
      - vitamin B12
      - vitamin C
      - protein
      - vitamin B6
3.2 bone marrow failure

1) failure of all cell lines
   - congenital e.g. Fanconi’s anemia, dyskeratosis congenital
   - acquired e.g. aplastic anemia

2) failure of a single cell line e.g.
   - congenital pure red cell aplasia
   - acquired red cell aplasia

3.3 dyshematopoietic anemia (decreased erythropoiesis, decreased iron utilization)

1) infection
2) renal failure and hepatic disease

3.4 infiltration of bone marrow e.g. leukemia, lymphoma, disseminated carcinoma

Morphologic classification

1. MCV (Mean corpuscular volume)
2. MCHC (Mean corpuscular hemoglobin concentration)

Microcytic (MCV < 80 fl)

**Normochromic**
- Iron deficiency; early
- Thalassemia trait
- Some hemoglobinopathies; Hb E
- Anemia of chronic disease*

**Hypochromic**
- Iron deficiency; late
- Thalassemia trait
- Sideroblastic anemia
- Anemia of chronic disease*

* most commonly normochromic/normocytic.
Macrocytic (MCV > 100 fl)
- B12 and folate deficiency
- Liver disease
- Alcoholism
- Myelodysplastic syndrome
- Blood loss #
- Hemolysis #
- Hypothyroidism
- Some drugs

Normochromic/Normocytic (MCV 80-100 fl)
- Anemia of chronic disease
- Anemia of renal failure
- Marrow infiltration
- Aplastic anemia
- Blood loss #
- Hemolysis #

Evaluation of Anemia
A. Hematologic
   1. Complete blood cell count (CBC)
   2. RBC indices : MCV, MCH, MCHC
   3. Reticulocyte count
   4. ESR (Erythrocyte sedimentation rate)
   5. Stained blood smear : RBC morphology

Complete blood cell count
- White blood cell count; 5,000 -10,000/cu.mm
- Red blood cell count; 4.0-6.0 x10¹² /l
- Hematocrit (Hct) or pack cell volume (PVC); 35-45%
- Hemoglobin (Hb); 12 - 17.5 g/dl
- WBC differential; PMN, lymphocyte, monocyte, RBC morphology
- **MCV;** Mean corpuscular (cell) volume; 80-100 fl
  \[
  \text{MCV} = \frac{\text{Hct} \times 10}{\text{RBC} \times 10^{12}/\text{l}}
  \]

- **MCH;** Mean corpuscular hemoglobin; 26-36 pg
  \[
  \text{MCH} = \frac{\text{Hb} \times 10}{\text{RBC} \times 10^{12}/\text{l}}
  \]

- **MCHC;** Mean corpuscular hemoglobin concentration; 32-36 fl
  \[
  \text{MCHC} = \frac{\text{Hb} \times 100}{\text{Hct} \times \%}
  \]

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**Reticulocyte count**

- เป็นค่าที่บอกถึงความสามารถในการสร้างเม็ดเลือดแดงของไขกระดูก
  - **Reticulocyte /1,000 RBC >> %**
  - **Automation >> absolute reticulocyte count**
  - **Normal value of reticulocyte count**
    - **1.65±0.82 % in male**
    - **2.45±0.82 % in female**
  - **Absolute reticulocyte count = 30-85 \times 10^3/\text{ul}**

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**Reticulocyte production index (RPI)**

- สามารถบอก erythropoietic activity ในไขกระดูกสูงเป็น ค่าเท่าใด
  \[
  \text{RPI} = \frac{\% \text{ reticulocytes} \times \text{patient Hct}/45}{\text{correction factor}}
  \]

 โดยทั่วไป correction factor จะมีค่าเท่ากับ 2 ถึง 3 แล้ว

  - ถ้าค่า reticulocyte อยู่ในภาษาปกติ ต้องใช้ Hct น้อยกว่า 15% จะใช้ correction factor 3 แทน

  **RPI > 2** - effective erythropoiesis
### B. Urine analysis
1. Appearance: Color, pH, Clarity, specific gravity
2. Test for protein, Bence Jones protein
3. Bilirubin, Uribilinogen
4. Occult blood
5. Microscopic examination

### C. Stool
1. Appearance: Color, consistency
2. Occult blood
3. Examination for ova, parasites

### D. Serum or Plasma
1. BUN
2. Creatinine
3. Bilirubin: Direct, indirect
4. Protein
5. SI (Serum iron), TIBC (Total iron binding capacity)

### E. Special tests in hematology
- Hb typing / Ham acid test / Coombs' test, G-6PD, Ferritin, Sucrose test, Autohemolysis test, Haptoglobin, Flow cytometry, etc.

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- Iron deficiency anemia
- Vitamin B12 deficiency anemia
- Folate deficiency anemia
- Anemia of chronic disease
- Aplastic anemia
- Hemolytic anemia

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**Iron Deficiency Anemia**
The multiple forms of iron in the body

- **Iron in food:**
  - Heme sources: meat
  - Non heme sources: beans, clams, vegetables
- **Iron in storage:**
  - Ferritin: liver, spleen, skeletal muscle, BM
  - Hemosiderin: macrophages
- **Iron in circulation:**
  - Iron and globin are recycled as a result of red cell senescence

Enhancers of iron absorption

- Orange juice
- Vitamin C
- Pickles
- Soy sauce
- Vinegar
- Alcohol
Inhibitors of iron absorption

- Tea
- Coffee
- Oregano
- Milk

Iron Metabolism

- Iron is absorbed primarily in Duodenum
  - 25% of Heme-Bound Iron (Red Meat)
  - 1-2% of Non-Heme Iron
- Body Losses of Iron are Limited
  - 1-2 mg/Day by Epithelial Cell Shedding
- Mucosal Block - Maintains Balance

Causes of Iron Deficiency

- External Blood Loss - Most Common
  - Female Genital Tract
  - Gastrointestinal Tract
- ↑ Demand - Infancy, Pregnancy
- Dietary Deficiency - Rare (Vegetarian Diets)
- Intestinal Malabsorption Syndrome
Iron Deficiency Clinical Manifestations

- Anemia - Non-Specific Findings
- Koilonychia
- Plummer-Vinson Syndrome
  - Hypochromic Microcytic Anemia
  - Atrophic Glossitis
  - Esophageal Webs (Dysphagia)

Iron Deficiency Anemia Laboratory Findings

- Hypochromic Microcytic Anemia
  (↓ RBC Count, ↓ MCV)
- ↓ Serum Ferritin Levels
- ↓ Transferrin Saturation
  (↓ Serum Fe, ↑ Transferrin)
Megaloblastic Anemia

Treatment:
- Correct causes
- Iron supplement
- Breast feeding

Megaloblastic Anemia:
- Impaired DNA Synthesis (Nucleus)
- Affects All Rapidly Dividing Cells
  - Mouth - Atrophic Glossitis
  - Gastrointestinal tract - Intestinal Malabsorption
Causes of megaloblastic anemia

- Vitamin B12 deficiency
- Folate deficiency
- Miscellaneous: orotic aciduria, liver disease, drugs e.g. purine analogues (6MP, 6TQ or 5FU)

Vitamin B12 deficiency

- Prevalence: 15-25% of population
- Functions of cobalamin: Coenzyme for 13 enzymes
- RDI = 2.4 ug/d
- Sources: Meat, liver, Kidney, oyster, clams, fish, eggs, cheese and other dairy products

Cobalamin

- Cobalamine
- Prevalence: 15-25% of population
- Functions of cobalamin: Coenzyme for 13 enzymes
- RDI = 2.4 ug/d
- Sources: Meat, liver, Kidney, oyster, clams, fish, eggs, cheese and other dairy products
Vitamin B₁₂ Deficiency

Causes:
- Dietary deficiencies in vegans
- Malabsorption States: Gastric Atrophy, Pernicious anemia (absence of IF), Gastrectomy, ileal resection
- Food-cobalamin maldigestion: Achlorhydria, acid suppressive drugs
- Diphyllobothrium Latum - Fish Tapeworm

Vitamin B₁₂ Deficiency - Cause

Western World - Pernicious Anemia
- Autoimmune Disorder
  - Autoantibodies to IF and Parietal Cells
  - Chronic Atrophic Gastritis
  - Achlorhydria - Absent HCL

Signs & Symptoms

- Additional signs & symptoms
  - Sore, smooth, beefy red tongue
  - Numbness and parenthesis, weakness, ataxia
  - Cognitive disturbances (forgetfulness, dementia, psychosis)
  - Increased risk for venous and arterial thrombosis and cardiovascular disease
Glossitis with cobalamin deficiency. The smooth shiny tongue results from loss of papillae over the lingual surface. Thinning of the epithelium sometimes give the tongue a red "beefy" appearance.

**Vitamin B\textsubscript{12} Deficiency**

- Clinical - Similar to Folate Deficiency, but also include Demyelinating Neurologic Disorder
  - Affects Both Sensory and Motor Tracts (subacute combined degeneration)
  - Lack of Correlation With Anemia

**Laboratory Findings:**

- Low Serum Vitamin B\textsubscript{12} Levels
- Normal RBC Folate Levels
- Abnormal Schilling Test - Impaired Absorption of Radioactive Vitamin B\textsubscript{12}, Correctable by Addition of IF
- Anti-Intrinsic Factor Antibodies (Anti-Parietal Antibodies Less Sensitive)
**Folic acid**

- **Purposes of folic acid**
  - Metabolism of serine, glycine, methionine, and histidine
  - Purine and pyrimidine synthesis

**Folic acid**

- RDI 400 ug/d
- Good sources: cereal, beef liver, cowpeas, spinach, asparagus, wheat germ, orange juice, baked beans, green peas, broccoli, egg noodles, white rice, avocado, peanuts, romaine lettuce, tomato juice, white bread, cantaloupe, papaya, banana, whole wheat bread

**Treatment:**

- Cobalamin
- Parenteral B₁₂ - Improves Anemia, +/- Resolution of Neurologic Symptoms
- Caution! Anemia of B₁₂ Deficiency Also Improves With Folate Supplementation

**Folate deficiency anemia**
Metabolism of folate

Causes of folate deficiency

- Dietary: general malnutrition, alcoholism
- Impair absorption: Tropical sprue, Celiac disease
- Increased requirements: infancy, pregnancy, lactation, anticonvulsant drugs, folate antagonist, chronic exfoliative dermatitis

Signs and Symptoms

- Additional signs & symptoms
  - Diarrhea
  - Cheilosis
  - Glossitis

Folate Deficiency

Laboratory Findings:
- Macrocytic anemia (MCV >100 fl)
- Decreased folic acid
- Increased homocysteine level
- Red Blood Cell Folate - Reflects Tissue Content of Folate Throughout Body
- Serum Folate - Levels Fluctuate Based on Recent Intake, Do Not Reflect Stores
Megaloblastic Anemia
Peripheral Blood

- RBCs - Large Oval: Macroovalocytes
  - MCV > 100 fl
- Hypersegmented Neutrophils
- Thrombocytopenia, Neutropenia (Severe)

Megaloblastic Anemia - Bone Marrow

Nuclear-Cytoplasmic Asynchrony:

- Erythroid Series (Hallmark Changes)
  - Megaloblasts
  - Erythroid Hyperplasia
- Myeloid Series
- Megakaryocytic Series - (Infrequent)
Treatment
- Folic acid 1 mg daily
- Treatment for 1-2 months
- Indefinite treatment may be necessary for cases of malabsorption and chronic malnutrition

Anemia of chronic disease

Anemia of Chronic Disease
- Normochromic Normocytic Anemia (or Hypochromic Microcytic)
- Chronic Disorders (Inflammation or Tissue Necrosis)
  - Chronic Microbial Illnesses
  - Chronic Immune Disorders
  - Neoplasms
- Often ↓ TIBC, ↑ Ferritin

Diseases associated with anemia of chronic inflammation
- Acute infections
- Chronic infections: TB, infective endocarditis, chronic UTI, chronic fungal infection, HIV
- Chronic inflammatory disorders: Rheumatoid arthritis, collagen vascular diseases, hepatitis, decubitus ulcer
Diseases associated with anemia of chronic inflammation:
- Chronic renal insufficiency
- Hypothyroidism
- Protein-energy malnutrition
- Malignancy: metastatic carcinoma, hematologic malignancy

Laboratory findings:
- Normochromic, normocytic
- Normal or increased ferritin (indicates increased iron stores)
- Decreased serum iron
- Decreased TIBC

Treatment of ACI:
- Correct or improve underlying abnormality
- Iron is not effective unless a true iron deficiency is also occurring
- Transfusions (for some indication)
- Erythropoietin (for some indication)
Aplastic Anemia

Acquired BM failure syndromes
- Aplastic anemia
- Pure red cell aplasia
- Paroxysmal nocturnal hemoglobinuria
- Myelodysplasia

Etiology of aplastic anemia
- Inherited:
  - Fanconi anemia
  - Dyskeratosis congenita

Etiology of acquired aplastic anemia
- Idiopathic
- Radiation: cancer irradiation
- Chemicals: chemotherapy drugs, benzene
- Chemicals (idiosyncratic):
  - chloramphenicol, gold, penicillamine,
  - NSAIDs, sulfonamides, propylthiouracil
Etiology of acquired aplastic anemia

- Viruses: Hepatitis; non-A, non-B, non-C, non-G, EBV, HIV
- Immune disorders: SLE, thymoma, transfusion-associated graft-versus-host disease, pregnancy

Bone Marrow Aplasia (Lack of Cells)
- Failure of Multipotent Stem Cell
  - T-cell Mediated Suppression or
  - Genetic Damage
- Bone Marrow - Markedly Hypocellular
- Peripheral Blood - Pancytopenia
  - Normochromic Normocytic RBCs

Characteristic features of aplastic anemia

- Peripheral blood pancytopenia
- Reticulocytopenia
- Bone marrow hypocellularity
- Depletion of hematopoietic stem cells

Normal BM

Aplastic Anemia
Myelophthisic Anemia

BM Replacement >> BM failure:

- Metastatic Carcinoma Most Common
- Destruction By Non-Neoplastic Process is Less Common i.e. Fibrosis, Infection
- Peripheral Blood Cytopenias, Immature Circulating Cells

Hemolytic Anemia

Definition of hemolytic anemia

- Short life span of RBC
- Defect in structure and metabolism >> destruction in RE system; spleen
- Hemolysis in RE system; extravascular hemolysis
Signs & Symptoms

- Pale, icteric
- Splenomegaly; prominent if chronic & EVH
- Gall stone; esp in the young
- Hx of drug intake of underlying disease

? Hemolytic anemia

- ↑ rbc destruction & production at the same time
- Persistent anemia despite increased erythropoiesis with out blood loss
- Hb drop ≥ 1 g/dl per week
- Hemoglobinuria or signs of IVH

Treatment

1. Splenectomy
2. Immunosuppressive agent
3. Prevent hemolytic reaction
4. Blood transfusion

Thalassemia and Hemoglobinopathy
โครงสร้างและการควบคุมการสร้างฮีโมโกลบิน

- hemoglobin = heme 4 molecules + globin chain 2 pairs (α globin : β globin : α : β)
- α chains; chromosome 16
- β chains; chromosome 11

การสร้างสายโกลบิน

- ภาวะที่ทำให้มีการสร้างสายโกลบิน (globin) ผิดปกติลดลงหรือไม่สร้างเลย ทำให้สร้างฮีโมโกลบินปกติลดลงหรือไม่สามารถสร้างฮีโมโกลบินปกติได้เลย
- ซึ่งสามารถถ่ายทอดทางพันธุกรรมได้, autosomal recessive
- แบ่งเป็นกลุ่มใหญ่ได้เป็น อัลฟาธาลัสซีเมีย (α thalassemia) และเบต้าธาลัสซีเมีย (β thalassemia)

Hemoglobinopathy

- ภาวะที่เกิดจากการเปลี่ยนแปลงของกรดอะมิโนบนสายโกลบิน ทำให้มีการเปลี่ยนแปลงของคุณสมบัติทางกายภาพหรือเคมีของสายโกลบิน ทำให้โครงสร้างของสายโกลบินผิดปกติไป
- การสร้างสายโกลบินยังคงเท่าเดิมหรือมีการลดลงของสายโกลบินร่วมด้วย
- ฮีโมโกลบินผิดปกติที่พบบ่อยในประเทศไทยคือ Hb E และ Hb Constant Spring; Hb CS
Clinical manifestations:

**β-Thalassemia**
1. Thalassemia major; homozygous
   - Severe, transfusion-dependent anemia
   - Hb 3-6 g/dl
   - Without transfusions, death occurs at an early age from profound anemia
2. Thalassemia minor; heterozygous
   - Usually asymptomatic
   - More common than Thalassemia major
3. Thalassemia intermedia; heterogenous

**α-Thalassemia**
- Severity is related to the number of α-globin genes deleted
1. Silent carrier state; asymptomatic
2. α-Thalassemia trait; clinical = β-thal minor
3. Hemoglobin H disease; deletion of three α-globin genes; clinical = β-thal intermedia
4. Hydrops fetalis; deletion of all four α-globin genes; Hb Barts, not compatible with life
Bleeding Disorders

Hemostasis:
- A normal physiologic process maintaining blood in a fluid, clot-free state in normal blood vessels, while inducing a rapid, localized hemostatic plug at sites of vascular injury

Normal Hemostasis
- Blood vessel
- Platelet
- Coagulation System
- Fibrinolysis System
- Natural Anticoagulant

Blood vessel
- Endothelium
  - Maintain fluidity
  - Substrate release
    - Thrombogenesis
    - Antithrombotic
- Connective tissues
  - Collagen type III, IV etc.
  - Muscular layer
Normal Hemostasis—Platelet
- Platelet Adhesion
- Substrate Release
- Shape Change
- Platelet Aggregation
- Platelet plug formation and vasoconstriction
  = Primary hemostatic plug formation which is enough to stop bleeding from small and shallow wound.

Coagulation System
- To promote fibrin polymerization
- Secondary hemostatic plug formation = primary hemostatic plug + fibrin polymerization
  Classical Pathway
  - Intrinsic
  - Extrinsic
  - Common

Fibrinolysis
**Anticoagulant**

**Heparin**
- Action
  - Inhibit thrombin, Inhibit Factor Xa, Inhibit Factor IX and XI

**Caumadin**
- Action inhibit vitamin K epoxidase, Vitamin K dependent factor depletion (II, VII, IX and X)
- Dose adjustment by INR (adjusted PT ratio to ISI)

**Clinical Approach**
- History Taking
- Physical examination

"80% of correct diagnosis can be made by history taking and physical examination."
Questions
- Bleeding disorders VS Local bleeding?
- Hemostasis defects?
- Acquired VS Hereditary?

Most important questions
- Multiple bleeding sites
- Onset
- Familial history
- Prolonged bleeding, ↑ frequency
- Inappropriate with injuries
- Previous medical illness and medications

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<tr>
<th>Sites</th>
<th>Primary Hemostasis</th>
<th>Secondary Hemostasis</th>
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<tbody>
<tr>
<td></td>
<td>Onset</td>
<td>Immediate</td>
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<tr>
<td>Skin</td>
<td></td>
<td>Superficial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>petechiae, superficial ecchymosis</td>
</tr>
<tr>
<td>Mucosal</td>
<td></td>
<td>common</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td>rare</td>
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Laboratory Investigation
- CBC - the most informative test for thrombocytopenic bleeding
- BT - test primary hemostasis vascular defect and platelet function
- VCT - test intrinsic and common pathway
- aPTT - test intrinsic and common pathway
- PT - test extrinsic and common pathway
- Mixing - deficiency VS inhibitor
Bleeding time:
* Quantity of platelet
* Quality of platelet; adhesion, aggregation
* Vascular function
* Duke method (< 6 min), Ivy method (2-6 min)
* Abnormal Bleeding time:
thrombocytopenia (platelet < 100,000/ul)
von Willebrand disease
Drugs; aspirin
Glanzmann’s thrombasthenia

Activated partial thromboplastin time (APTT):
* intrinsic pathway
* normal value ~ 27 – 38 seconds
* prolonged APTT;
  - due to intrinsic pathway e.g. hemophilia A (F VIII), hemophilia B (F IX)
  - due to anti-coagulant, F VIII antibody, heparin and FDP
  - DIC (disseminated intravascular coagulation)

Prothrombin time (PT):
* extrinsic and common pathway
* report of PT
- second
- % activity
- prothrombin index
- prothrombin ratio
* international normalized ratio (INR); monitor
Rx with anticoagulant warfarin

International normalized ratio(INR) =
* normal value ; 0.75 – 1.3
* therapeutic level ; 2 - 4.5
* Prolonged prothrombin time
  - due to extrinsic pathway
  - oral anticoagulant
  - severe liver disease
  - due to vitamin K
Bleeding disorders

- Hemorrhagic diathesis may be caused by
  - Increased blood vessel fragility
  - Platelet disorders
  - Coagulation defects
- Laboratory testing:
  - Bleeding time - Prothrombin time
  - Platelet counts - Partial thromboplastin time
  - Special test (e.g. clotting factor levels)

Increased vascular fragility

- Petechial and purpuric hemorrhage
- Etiology:
  - Infections; meningococcus and rickettsia >>> vasculitis, or DIC
  - Poor vascular support; abnormal collagen, amyloidosis
  - Henoch-Schonlein purpura; purpuric rash, abdominal pain, polyarthralgia, acute glomerulonephritis

Thrombocytopenia

- Normal platelet count 140,000 – 400,000 /cu.mm
- Petechial hemorrhage
- Causes:
  - Decreased production; ineffective megakaryopoiesis, aplastic anemia, disseminated cancer
  - Decreased survival; immune-mediated platelet destruction, drug, HIV, systemic coagulopathies
  - Sequestration; retain in red pulp of enlarged spleen
  - Dilution; massive whole blood transfusion

Thrombocytopenia

- Plt > 100,000 : can surgery
- Plt < 100,000 : prolonged BT
- Plt < 50,000 : bleeding after trauma/Sx
- Plt < 10,000-20,000 : spontaneous bleeding
- Plt < 5,000 : increase risk ICH
Immune Thrombocytopenia Purpura (ITP)

- Acute ITP
  - Transient antiplatelet autoantibodies
  - Often in children after viral infection; rubella, CMV, viral hepatitis, infectious mononucleosis
- Chronic ITP
  - Platelet autoantibodies
  - Destruction occurs in the spleen
  - Splenectomy benefits 75% to 80% of patients.

Clinical features; adult, female, easy bruising or nosebleeds, petechial hemorrhage, internal hemorrhage (melena, hematuria)

Dx:
- Clinical; petechiae
- BM biopsy: increased megakaryocytes
- Bleeding time: prolong
- PT and PTT; normal

Drug-induced thrombocytopenia

- Immune-mediated platelet destruction
- Drug acting as hapten
- Drug withdrawal leads to clinical improvement

Hemorrhagic disorders related to defective platelet functions

- Congenital disorders;
  - Defective platelet adhesion
  - Defective platelet aggregation
  - Disorders of platelet secretion
- Acquired disorders;
  - Aspirin ingestion; suppress TXA₂ synthesis (necessary for platelet aggregation)
  - Uremia; defect in platelet function
Hemorrhagic diathesis related to abnormalities in clotting factors

- Clinical features;
  - Large ecchymoses or hematoma after injury, or prolonged bleeding after a laceration or surgical procedure
  - Bleeding of GI, urinary tracts, weight-bearing joints
- Hereditary deficiencies; hemophilia, von Willebrand disease
- Acquired deficiencies; vit. K deficiency, liver disease, DIC

von Willebrand disease

- Level of Factor VIII are often reduced because vWF stabilizes factor VIII in circulation.
- Defect in platelet function and coagulation pathway; prolonged bleeding time and partial thromboplastin time
- Clinical; spontaneous bleeding from mucous membranes, excessive bleeding from wounds, menorrhagia

Hemophilia A

- X-linked recessive disorder; male
- Factor VIII deficiency
- Clinical features develop only in the presence of severe deficiency (factor VIII levels < 1% of normal)
- Mild or moderate degrees of deficiency (levels 1%-50% of normal); asymptomatic
Clinically associated with
- Massive hemorrhage after trauma or operative procedures
- Spontaneous hemorrhages in regions of the body normally subject to trauma; joints (hemarthroses) progressive, crippling deformities
- Prolonged PTT and normal bleeding time
- Dx: factor VIII assay

Treatment
- Replacement therapy; recombinant factor VIII or factor VIII concentrates
- Factor VIII antibody
  - History of factor VIII replacement
  - Dx; Mixing test, factor VIII antibody

Hemophilia B (Christmas disease)
- X-linked recessive; male
- Factor IX deficiency
- Clinically indistinguishable from hemophilia A
- Dx; Factor IX assay

Hemophilia C
- AD
- Factor XI deficiency
Disseminated Intravascular Coagulation (DIC)

- DIC is an acute, subacute, or chronic thrombohemorrhagic disorder occurring as a secondary complication in a variety of diseases.
- Activation of the coagulation sequence >>> formation of microthrombi throughout the microcirculation.
- Consumption of platelets, fibrin, coagulation factors >>> activation of fibrinolytic mechanisms
- Clinical;
  - Signs and symptoms relating to infarction caused by microthrombi.
  - A hemorrhagic diathesis resulting from activation of fibrinolytic mechanisms and depletion of the elements required for hemostasis.