# Hematology

## Anemia, General Principles

- Definition → **Hb** < **13.5 g/dL** (Hct < 40) in **men** or **Hb** < **12 g/dL** (Hct < 37) in **women**
- Most useful **classification of anemia** (based on MCV or mean corpuscular volume):
    1. **Microcytic** (MCV < 80) → **Iron-deficiency** anemia**, sideroblastic** anemia, anemia of **chronic disease**, **lead** poisoning, **thalassemia**
    2. **Normocytic** (MCV 80-100) → **aplastic** anemia, anemia of **chronic disease**, **myelofibrosis**/bone marrow infiltration, **chronic renal** failure, **hemolytic** anemia, **early stages** of iron-deficiency anemia, **hemorrhage**
    3. **Macrocytic** (MCV > 100) → **megaloblastic** anemia (vitamin $B_{12}$ and/or folate deficiency; drug-induced), **liver** disease, **myelodysplasia,** reticulocytosis
- Clinical features → **fatigue,** malaise, **weakness**, poor exercise tolerance, **tachycardia**/palpitations, **dyspnea** on exertion, **dizziness**/syncope, **chest pain**, **pallor**, **systolic** ejection **murmur**, wide pulse pressure, **orthostatic hypotension**
- Presentation **depends** on:
    1. **Degree** of anemia
    2. **Rapidity** of onset of anemia
    3. Age/**health status**
- **Best initial** diagnostic tests → **CBC** with **RBC indices** (e.g. MCV), **reticulocyte** count, blood **smear**
- Management → **etiology**-dependent ± packed **RBC transfusion**
- **Indications** for **RBC transfusion** →
    1. **Acute blood loss** > **30%** (> 1500-2000 ml)
    2. **Hb < 7 g/dL**
    3. **Hb < 8 g/dL** (Hct < 26) + **age > 65, cardiovascular/pulmonary** disease and/or **acute bleed**
    4. Overtly **symptomatic** (e.g. chest pain, respiratory distress, CNS symptoms/signs)

## Microcytic Anemia

### Iron-deficiency Anemia

- **Most common** cause of **anemia**
- **Females** > Males
- Etiology:
    1. Chronic **blood loss** → **most common** cause; e.g. **GI cancer, PUD, menorrhagia**
    2. ↓ **dietary** intake/**malabsorption** → e.g. **celiac** disease**,** post-**gastrectomy**, **cow's milk** diet in infants, achlorhydria
    3. ↑ **requirements** → e.g. **pregnancy,** growth spurt
    4. Chronic **intravascular hemolysis** → hemoglobinuria, hemosiderinuria
- **Promoters** of iron **absorption** → ↓ gastric **pH** and **ascorbic acid**
- Clinical features **specific** for **iron-deficiency** anemia →
    1. **brittle nails/koilonychia** (spoon-shaped nails)

2. **glossitis**/angular **cheilitis**
3. **pica** (craving for non-nutritive substances)
4. **dysphagia** (Plummer-Vinson syndrome)

- Initial lab results (CBC, reticulocyte count, etc.) → **low Hb** and/or Hct, **low MCV,** ↑ **RDW** (**r**ed blood cell **d**istribution **w**idth), ↓ **reticulocyte** count, possible **thrombocytosis**
- Blood smear → **hypochromic, microcytic RBCs** ± poikilocytosis (abnormal shapes)
- Best **next step** → perform **iron studies**:
  1. ↓ serum **ferritin** → **most specific** laboratory test; **lacks sensitivity** (falsely elevated in inflammatory conditions, liver disease and/or malignancies)
  2. ↓ serum **iron**
  3. ↑ **TIBC** (total iron binding capacity)
  4. ↓ transferrin **saturation** (serum iron/TIBC ratio, expressed as %)
- **Most accurate** diagnostic test → **bone marrow** biopsy + **Prussian blue** stain
- Best **next step** in **men > 50** and/or **postmenopausal** women → **colonoscopy** to rule out **colon cancer**
- Management:
  1. **Treatment**/correction of any **underlying** abnormality
  2. Packed **RBC transfusion**, when indicated (*see above*)
  3. **PO ferrous sulfate** (or ferrous gluconate) replacement → **continued until** serum **ferritin** becomes **normal,** indicating replenishment of iron stores (~ 3-12 months)
  4. **Parenteral** iron replacement, if **malabsorption**/intolerance to oral medications
- **Adequate** iron **replacement** indicated by →
  1. **Reticulocytosis** after ~ **1 week**
  2. **Rise** in **Hb** of ~ **1g/week**
  3. **Normalization** of **Hb** after ~ **1 month**

## Anemia of Chronic Disease

- **Anemia** that **accompanies** any **chronic inflammatory** (e.g. RA, IBD, etc.), **infectious** (e.g. TB, bacterial endocarditis, etc.) and/or **malignant** condition
- Pathophysiology →
  1. ↓ **sensitivity** to **erythropoietin**
  2. **Impaired utilization** of **stored iron** → due to ↑ levels of **TNF-α** and **IL-6**
- Clinical features → symptoms/signs of **anemia** + that of the **underlying disease**
- Initial lab results → **low Hb** and/or Hct, **low** or **normal MCV,** ↓ **reticulocyte** count, normal **RDW**
- Blood smear → **hypochromic, microcytic** or **normochromic, normocytic RBCs**
- Best **next step** → perform **iron studies**:
  1. ↓ serum **iron**
  2. ↓ **TIBC**
  3. **Normal** transferring **saturation**
  4. **Normal** or ↑ serum **ferritin**
- Bone marrow biopsy + **Prussian blue** stain → ↑ stainable **iron**
- Management → **treatment**/correction of any **underlying** abnormality ± **large doses** of exogenous **erythropoietin** ± iron replacement

## Sideroblastic Anemia

- A group of disorders of **heme** (protoporphyrin) **synthetic pathway** characterized by **iron accumulation** in the **perinuclear mitochondria** of nucleated RBCs → "**ringed**" **sideroblasts**
- May be **hereditary** (e.g. X-linked; defective **δ-aminolevulinic acid** (ALA) **synthase**) or **acquired** (e.g. **alcohol, isoniazid, lead** poisoning, **myelodysplastic** syndrome)
- Sideroblastic anemia associated with **myelodysplasia** may progress to **acute myelogenous leukemia** (AML)
- Clinical features of **lead** poisoning → abdominal **colicky** pain, peripheral **neuropathy** (e.g. wrist drop, foot drop), **encephalopathy**, **gingival** lead lines, developmental delay + symptoms/signs of **anemia**
- Initial lab results → **low Hb** and/or Hct, **low MCV,** ↓ **reticulocyte** count
- Blood smear → **dimorphic** (both normocytic and microcytic) population of **RBCs** ± **basophilic stippling** (with **lead** poisoning)
- Best **next step** → perform **iron studies**:
    1. ↑ serum **iron**
    2. ↑ serum **ferritin**
    3. **Normal TIBC**
    4. ↑ transferrin **saturation**
- **Most accurate** diagnostic test (**required** for diagnosis) → bone marrow biopsy + **Prussian blue stain** showing ↑ iron **stores** and **ringed sideroblasts**
- Management → **removal** of any underlying **drug/toxin** + **trial** of vitamin B6/**pyridoxine** (successful in some forms of hereditary sideroblastic anemia) ± lead **chelation** (e.g. EDTA, dimercaprol)
- Packed RBC transfusion, as indicated

## Thalassemia

- A group of **hereditary** (autosomal **recessive**) disorders characterized by **decreased** to absent **globin** chain (α and/or β) **synthesis** → **hypochromic, microcytic** anemia
- **α-thalassemia** (common in **Asians** and **African**-Americans) →

| | | |
|---|---|---|
| **Silent α-thalassemia** (carrier state) | Deletion of **one** gene | **Asymptomatic**<br>**Normal** CBC, Hb and MCV |
| **α-thalassemia trait** (minor α-thalassemia) | Deletion of **two** genes:<br>**Asian** variant → - - / α α<br>**African** variant → α - / α - | **Mild** anemia<br>↓**Hb**, ↓**MCV, normal RDW**<br>Smear → **hypochromic, microcytic** RBCs ± **target** cells |
| **HbH** (tetrads of β-chains) **Disease** | Deletion of **three** genes<br>More common in **Asians** | **Severe** anemia with **splenomegaly**<br>↓**Hb**, ↓**MCV, normal RDW**<br>Smear → **hypochromic, microcytic** RBCs with **HbH** (children/adults) or **Hb Barts** (neonates/infants) **inclusions** ± **target** cells |
| **Hb Barts** (tetrads of γ-chains) **Disease** | Deletion of all **four** genes<br>More common in **Asians** | **Hydrops fetalis**<br>**In utero** fetal demise |

- **β-thalassemia** (common in people of **Mediterranean** origin; also seen in **Asians** and/or **African-**Americans) → **unbalanced** production of **α-chains** leads to **ineffective erythropoiesis,** chronic **hemolysis** and **extramedullary** hematopoiesis

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| **β-thalassemia minor** | Mutations involving **one** gene | Asymptomatic to **mild** anemia ± splenomegaly<br>**↓Hb**, **↓MCV, normal RDW**<br>Smear → **hypochromic, microcytic** RBCs with **basophilic** stippling ± **target** cells ± poikilocytosis |
| **β-thalassemia major** (Cooley's anemia) | Mutations involving **both** genes | **Presentation** at ~ **3-6 months** of age (switch from γ to β chain synthesis) with **severe** anemia, **growth retardation, hepatosplenomegaly, jaundice**, bone **deformities** (principally involving the **face** and **skull,** e.g. frontal bossing, maxillary hyperplasia), possible **gallstones**, leg **ulcers** and/or pathologic **fractures**<br>**↓Hb**, **↓MCV, normal RDW**<br>Smear → **hypochromic, microcytic** RBCs with **basophilic** stippling ± **target** cells ± poikilocytosis<br>**Skull X-ray → "crew-cut"** appearance |

- **Best initial step** → perform **iron studies** to rule out **iron-deficiency** (should be **normal** in both forms of thalassemia)
- **Best next** and the **most sensitive** test → hemoglobin **electrophoresis:**
    1. **α-thalassemia** → normal levels of **$HbA_2$** and **HbF**
    2. **β-thalassemia minor** → ↑ **$HbA_2$** ± ↑ HbF
    3. **β-thalassemia major** → ↑ **$HbA_2$** and **HbF**
- **Most accurate** diagnostic test → **Genetic** analysis
- Management:
    1. **α-thalassemia trait/ β-thalassemia minor** → genetic **counseling** ± **folate** supplementation
    2. **β-thalassemia major**/HbH disease → daily **folate** supplementation + chronic blood **transfusions** + **iron-chelation** to **prevent** secondary **hemochromatosis** (e.g. deferoxamine and/or **deferasirox**) + **splenectomy** (improves anemia, decreases transfusion requirements) ± **bone marrow transplantation** (possibly curative)
    3. **Experimental** therapy → **hydroxyurea,** cytarabine and/or butyrates (↑ **HbF production**)
- **Major cause** of **death** → secondary **hemochromatosis**

* Note → **Thalassemia** may present with ↑ **Hct**

# Normocytic Anemia

## Hemolytic Anemia, General Principles

- Anemia resulting from ↑ **premature destruction** of **RBCs**
- May be **classified** according to:
    1. **time-course** → acute vs. chronic
    2. **site** of **hemolysis** → intravascular vs. extravascular
    3. **causative** factor → intrinsic vs. extrinsic (intracorpuscular vs. extracorpuscular)
- Clinical features **suggestive** of **hemolysis** → **acute** onset, **jaundice** with **dark urine**, **gallstone** disease, chronic **leg ulcers**, hepato**splenomegaly** + symptoms/signs of **anemia**
- Lab findings → ↓ **Hb**, ↓ **Hct**, **normal MCV** (possible ↑ MCV due to reticulocytosis), ↑ **reticulocyte** count, ↑ serum **LDH**, ↑ serum **indirect bilirubin**, ↓ serum **haptoglobin** (binds free hemoglobin; more **prominent** with **intravascular** hemolysis)
- Lab findings consistent with **intravascular** hemolysis → ↓ **haptoglobin,** presence of serum **free hemoglobin**, **hemoglobinuria,** possible **hemosiderinuria**
- Management → **etiology**-dependent + adequate **hydration** (with **intravascular** hemolysis to **prevent** renal **tubular damage** → acute **renal failure**) ± packed **RBC** **transfusion**, as indicated

## Hereditary Spherocytosis

- **Most common hereditary** hemolytic anemia
- Autosomal **dominant** (more **common**, **less** severe) or autosomal **recessive** inheritance
- Etiology → **spectrin deficiency** resulting from various genetic defects, with **mutations** involving the **ankyrin** gene being **most common**
- Pathophysiology: RBC **membrane defects/**instability → assumption of a **spherical shape** → ↓ **elasticity** → inability to traverse **splenic cords** → **extravascular** (principally splenic) hemolysis
- Clinical features → **family history** + **triad** of mild/moderate **anemia** + **splenomegaly** + **jaundice/gallstone** disease (e.g. biliary colic, acute cholecystitis)
- **Aplastic crisis** → **worsening** of **anemia** characterized by ↓ **reticulocyte** count, secondary to **parvovirus B19** infection and/or concurrent **folate** deficiency
- Lab findings → consistent with **extravascular** hemolysis (*see above*) + ↑ **MCHC** (mean corpuscular hemoglobin concentration)
- Blood smear → **normochromic, normocytic** RBCs + presence of **spherocytes** (**small**, hyperchromic RBCs with **loss** of normal **central pallor**)
- **Most accurate** diagnostic test → **osmotic fragility test** (RBC susceptibility to hemolysis when placed in hypotonic solutions)
- Management:
    1. **Mild** anemia → daily **folate** supplementation
    2. **Severe** anemia → **splenectomy** (**symptomatic** improvement; **persistence** of spherocytosis) + daily **folate** supplementation

* Remember → administer **Pneumococcal vaccine before** performing **splenectomy**
* Remember → **Never** perform **cholecystectomy** in suspected/confirmed hereditary spherocytosis **before removing** the **spleen** (↑ risk of intahepatic stone formation)

# Sickle Cell Anemia

- Autosomal **recessive** chronic **hemolytic** anemia resulting from **substitution** of **valine** for **glutamic** acid at **position 6** of the **β-globin** gene → **HbS**
- **Most common** in people of **African** descent (**8%** of **African-Americans** are **heterozygous** for HbS → sickle cell **trait**)
- Both sickle cell **trait** and **anemia** (homozygous for HbS) **protect** against falciparum **malaria**
- Pathophysiology: **deoxygentated HbS** tends to **polymerize** forming **rigid crystals** → "**sickling"** of RBCs (**irreversible** with time) + **membrane damage** → abnormally **sticky** and **non-deformable** RBCs → principally **extravascular** hemolysis + **vaso-occlusion** of small **arterioles** and/or larger **arteries**
- Factors that **promote**/precipitate **sickling** →
    1. ↓ **$pO_2$**
    2. **acidosis** (both metabolic and respiratory)
    3. **dehydration**
    4. ↑ **temperature**
    5. ↑ **Hb** concentration
- **Inhibitor** of HbS **polymerization** → **HbF** (**no** clinical **manifestations** until **6-12 months** of age)
- Clinical manifestations:
    1. chronic hemolytic **anemia**
    2. **jaundice**
    3. bilirubin **gallstones**/acute **cholecystitis**
    4. chronic **leg ulcers**
    5. **avascular necrosis** of the **femur**/humerus
    6. **growth** and/or **developmental delay**
    7. splenomegaly followed by **autosplenectomy**
    8. **susceptibility** to **infections** with **encapsulated** bacteria (e.g. Streptococcus *pneumonia,* Heamophilus *influenzae*, Neisseria *meningitidis*)
    9. **osteomyelitis** caused by **Salmonella** (**most common**) and/or **S. *aureus***
    10. **hyposthenuria** (renal concentrating defects) → **nocturia**, enuresis
    11. renal **papillary necrosis** → **hematuria** and/or acute renal **failure**
    12. **retinopathy** (non-proliferative or proliferative)
    13. **acute** painful **crisis** (vaso-occlusive crisis):
        - **dactylitis** (painful, swollen digits) → common in **children**
        - **pain** involving the **ribs, back, elbows** and/or **knees**
    14. **acute chest syndrome**:
        - **chest pain, tachypnea/**dyspnea, ↑ **temperature,** ↑ **WBC** count, **hypoxia**
        - **infiltrates** on chest **X-ray**
        - **indistinguishable** from **pneumonia**
        - **most common** cause of **mortality**
    15. **priapism** (painful, prolonged erection)
    16. transient ischemic attacks (**TIA**) and/or **stroke**
    17. **myocardial infarction,** cardiomyopathy
    18. **aplastic crisis:**
        - secondary to **Parvovirus B19** infection and/or **folate** deficiency
        - **worsening** anemia with ↓ **reticulocyte** count
    19. **hemolytic crisis:**
        - in patients with **concurrent G6PD** deficiency
        - **worsening** anemia with ↑ **reticulocytosis**

20. **splenic sequestration crisis**:
    - massive **splenomegaly, hemodynamic instability**
    - develops only in **children < 5 years** of age (before autosplenectomy)
21. ↑ rate of **spontaneous abortion** and/or **preterm** delivery

- Lab findings → ↓ **Hb**, ↓ **Hct**, ↑ **reticulocyte** count (unless in aplastic crisis), ↑ **indirect bilirubin**, ↑ **LDH**, ↑ **WBC** count (in the absence of infection) with **eosinophilia**
- Blood smear → normochromic, normocytic RBCs, "**sickled**" RBCs, **target** cells, **Howell-Jolly** bodies (post-splenectomy)
- Urinalysis → microscopic **hematuria**
- X-ray → "**fish-mouth**" vertebrae
- **Best initial** (screening) test → **sickle solubility test** or sickle cell prep or Sickledex (**cannot differentiate** between **trait** and **disease**)
- **Most accurate** diagnostic test → **Hb electrophoresis** with **HbS > 80%**
- Management:
    1. **chronic** management → daily **folate** supplementation, **vaccination** against **Pneumococcus** and Haemophilus; possible **daily penicillin V** prophylaxis
    2. **acute vaso-occlusive crisis** → adequate **hydration, analgesia** and **oxygen** supplementation; **antibiotics** if ↑ **temperature** (e.g. **3rd-generation** cephalosporins, **newer fluoroquinolones**)
    3. **acute chest syndrome** → as above + **RBC exchange transfusion** (goal HbS level of < 30%)
    4. **indications** for **exchange transfusion** (other than acute chest syndrome) → **stroke**/TIA**, priapism,** retinopathy, **cardiac** involvement
    5. **splenic sequestration crisis** → hemodynamic **stabilization** followed by **splenectomy**
    6. **recurrent** vaso-occlusive **crisis** and/or **single** episode of **acute chest syndrome** → **hydroxyurea** (increases HbF → ↓ HbS polymerization → ↓ frequency of vaso-occlusion → ↓ mortality)
    7. **recurrent acute chest syndrome** and/or **stroke** → consider **bone marrow transplantation** (possibly curative)
- **Top 3** causes of **mortality**:
    1. **acute chest syndrome**
    2. **stroke**
    3. **infections**

*** Sickle Cell Trait → asymptomatic** to **hyposthenuria** with nocturia/enuresis, **hematuria** from renal **papillary necrosis**, asymptomatic **bacteriuria**/↑ risk of **pyelonephritis** (especially during pregnancy), possible PE and/or glaucoma ± **acute** vaso-occlusive **crises** in periods of **extreme hypoxia** and/or **acidosis**; Lab findings → **normal**; Blood smear → **normal**; **most accurate** diagnostic test → **Hb electrophoresis** with **HbS** > 35% but < 50%; **treatment** not required

## Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

- **X-linked** recessive
- Most common in **African-Americans**
- G6PD deficiency **protects** against **malaria**
- Pathophysiology: **G6PD** deficiency → ↓ **NADPH** → ↓ reduced **glutathione** → susceptibility to **oxidant stress** → self-limited **acute intravascular hemolysis** (reticulocytes have normal G6PD activity)
- Oxidant stress → **infections** (e.g. pneumonia, hepatitis, typhoid fever), **drugs** (e.g. primaquine, sulfonamides, nitrofurantoin, dapsone, quinidine, aspirin) and/or **fava beans** ("**favism" → limited** to patients with the **Mediterranean variant** of G6PD deficiency)
- Clinical features → **previously asymptomatic** (Mediterranean variant → mild/moderate chronic hemolytic anemia) + **sudden onset** of fever/**chills**, **backache**, tachycardia/**palpitations**, weakness, **dizziness**, **jaundice** and/or **dark urine** within **several days** of **oxidant** exposure
- Lab findings → suggestive of **intravascular hemolysis** (*see above*)
- Blood Smear → **normochromic, normocytic** RBCs with **Heinz bodies** (denatured, oxidized Hb) + **bite cells** (remnants of RBCs after removal of Heinz bodies by splenic macrophages) ± **spherocytes**
- **Most accurate** diagnostic test → **G6PD assay** (**not performed** until acute episode subsides → ↑ **reticulocyte** count → **false-positive** results)
- Management → Adequate **hydration** ± alkalinization of urine, **removal** of **oxidant stress** (e.g. treatment of infections, stopping offending medications, etc.), **transfusion**, as indicated
- **Prevention** of future attacks (**most important**)

## Paroxysmal Nocturnal Hemoglobinuria (PNH)

- **Acquired stem cell** disorder characterized by the **triad** of **chronic hemolytic anemia** with **superimposed** attacks of **intravascular hemolysis**, **hypercoagulability** and **ineffective hematopoiesis**
- Pathophysiology: **stem cell somatic mutation** → ↓ **synthesis** of the **GPI** (glycosylphosphatidylinositol) **anchor** → **absence** of **CD55/DAF** (decay-accelerating factor) and **CD59** on RBC plasma membranes → ↑ **complement** binding/activation → **hemolytic anemia**
- **PNH** may **progress** to **aplastic anemia** and/or **leukemia**
- Clinical features →
    1. Asymptomatic to **chronic hemolytic anemia**
    2. **Intermittent** attacks of intravascular hemolysis → **dark urine** (e.g. in the **morning**, during **infection**, etc.)
    3. **Intra-abdominal** venous **thrombosis** (hepatic, portal, etc.) → **Budd-Chiari syndrome** (hepatic vein thrombosis)
    4. Possible **cerebral venous sinus** thrombosis
- Lab findings → suggestive of **intravascular hemolysis** (*see above*) + ↓ **WBC** count and/or **thrombocytopenia** + ↓**LAP** (leukocyte alkaline phosphatase)
- **Most accurate** diagnostic test → **flow-cytometric** demonstration of the **absence** of **CD55/DAF** and/or **CD59**

- Previously used diagnostic tests (commonly tested on exams) → **sucrose lysis** and/or **acidified serum lysis**/Ham **test**
- Standard Management →
    1. **Periodic** washed **RBC transfusions** and/or **steroids** ± **iron replacement** (chronic hemoglobinuria/hemosiderinuria → iron-deficiency)
    2. **Treatment** of **thrombotic** complications (e.g. thrombolysis, chronic anticoagulation, etc.)
    3. **Bone marrow transplantation** (possibly curative)
- **Most common** cause of **mortality** → intra-abdominal and/or cerebral **thrombosis**

* Recently updated test Qs may offer **eculizumab** (Soliris) as the **treatment of choice** for **PNH; monoclonal antibody** directed against **C5 complement** protein → ↓ **hemolysis**, ↓ **transfusion** requirements, ↓ **thrombotic** complications, **improved quality** of life; DO NOT STOP **anticoagulation** in patients on **eculizumab**; **vaccinate** against **meningococcus** before initiating therapy

## Immunohemolytic Anemia, Warm-Antibody Type

- **Autoimmune**-mediated **hemolytic anemia** secondary to production of "**warm" antibodies** of the **IgG** type (react at body temperature)
- Most commonly seen in **adult females**
- Usually **idiopathic**
- **Secondary causes** include →
    1. **Drugs:**
        - **α-methyldopa** (production of anti-Rh autoantibodies)
        - **penicillins/cephalosporins** (stable hapten)
        - **quinidine**, **sulfonamides**/other sulfa derivatives (unstable hapten)
    2. **NHL** (non-Hodgkin lymphoma), Hodgkin's lymphoma
    3. **CLL** (chronic lymphocytic leukemia)
    4. **SLE**/other collagen-vascular disorders
    5. **Viral** infection (usually **transient**; predominantly in **children**)
- Pathophysiology: **IgG** and/or **complement coating** of RBCs → **Fc** fragment and/or **complement-**mediated **adherence** to **splenic macrophages** → **extravascular** (principally splenic) **hemolysis** ± intravascular hemolysis (from complement activation)
- Clinical features →
    1. **Mild/moderate** anemia + **splenomegaly**
    and/or
    2. **Sudden onset** of fever/**chills**, **dark urine**, weakness, **tachycardia**, **dizziness**/syncope, acute **CHF** → **shock** (with massive intravascular hemolysis)
- Lab findings → consistent with **hemolysis** (*see above*)
- Blood Smear → **normochromic, normocytic** RBCs + **spherocytes**
- **Most accurate** diagnostic test → **direct Coombs' test** showing reaction with **anti- IgG ± anti-C3** antibodies:
    1. **Both** reactive → consider **SLE**
    2. **Only anti-C3** reactive → consider **quinidine-type** drug-induced **hemolysis**
- Management:
    1. **Mild** hemolysis → treatment **not required**
    2. **Severe** hemolysis → **IVIG** (intravenous immunoglobulin) + **steroids**

3. **Moderate** hemolysis → systemic **steroids** with **gradual taper** (after normalization of Hb levels)
4. **No response** to **steroids** → **splenectomy**
5. Intolerance to steroids → **splenectomy**
6. **Relapse** → **splenectomy**
7. **No response** to **splenectomy** → **cyclophosphamide**, azathioprine or **rituximab** (anti-CD20 antibodies)

* **Evans Syndrome** → **Autoimmune** hemolytic **anemia + ITP**

## Immunohemolytic Anemia, Cold-Antibody Type (Cold Agglutinin Disease)

- **Autoimmune-**mediated **hemolytic anemia** secondary to production of "**cold**" **antibodies** of the **IgM** type (react at temperatures < 37ºC)
- **Classification:**
    1. **Chronic** → idiopathic, **CLL, lymphoma**, **Waldenstrom's** macroglobulinemia
    2. **Acute**/transient → **Mycoplasma** *pneumoniae*, infectious **mononucleosis**, **adenovirus**
- Pathophysiology: **IgM coating** of RBCs + **activation** of **complement** cascade → **agglutination** of **RBCs** ± **hemolysis** (usually **intravascular** and/or intra-**hepatic**)
- Clinical features → **acrocyanosis** (ears, nose, fingers) on **cold exposure** that **disappears** with **re-warming** ± symptoms/signs of **anemia**
- Lab findings → consistent with **hemolysis** *(see above*)
- Blood Smear → **normochromic, normocytic** RBCs ± **agglutination**
- **Most accurate** diagnostic test → **direct Coombs' test** showing reaction with **anti-C3** antibodies
- Management:
    1. Associated with **infections** → treatment **not required**
    2. **Mild** disease → **avoidance** of **cold** exposure + **treatment** of **underlying** disease
    3. **Severe** disease → **immunosuppressive** medications (e.g. cyclophosphamide, azathioprine) and/or **rituximab + treatment** of **underlying** disease

* **Paroxysmal Cold Hemoglobinuria (PCH)** → due to the presence of **anti - P antigen IgG** antibodies (Donath-Landsteiner antibodies); secondary to → tertiary **syphilis,** post-**viral** (e.g. measles, mumps) or **autoimmune**; **asymptomatic** with **episodes** of **intravascular hemolysis** on **cold exposure** (fever/chills, backache, weakness, dark urine, etc.); management → **steroids** and/or **immunosuppressive** medications

* **Schistocytes** or fragmented RBCs (e.g. **helmet** cells, **triangle** cells) on blood **smear** → look for **traumatic** causes of **hemolysis** (macro- and/or microangiopathic), such as **DIC, TTP/HUS, malignant hypertension, HELLP** syndrome, **prosthetic** heart valves, disseminated cancer, renal graft rejection

* Anemia due to **chronic renal failure** → treat with **erythropoietin** (side effects → **↑BP** (most common), **flu-like** symptoms, skin irritation/**rash**, and headache)

# Aplastic Anemia

- **Pancytopenia** associated with **bone marrow hypocellularity** secondary to failure of hematopoietic **stem cells**
- Etiology →
    1. **Idiopathic** (most common)
    2. **Radiation**
    3. **Drug-** and/or **chemical**-related
        - Anticipated reaction → **chemotherapeutic** agents, **benzene,** etc.
        - Idiosyncratic reaction → **chloramphenicol. NSAIDs,** phenytoin, carbamazepine, cimetidine, gold, etc.
    4. **Infectious → hepatitis** virus (so called non-A, non-B, non-C), **HIV**, infectious **mononucleosis**, **parvovirus** B19
    5. **Congenital** (Fanconi's anemia)
    6. Other → **PNH,** eosinophilic fasciitis, **transfusion**-related **GVH** disease
- Clinical features → symptoms/signs of **thrombocytopenia** (e.g. easy bruising, nose-bleeds, petechiae, etc.) + **anemia** (e.g. pallor, weakness, dyspnea, etc.) ± **neutropenia** (e.g. ↑ fever, pharyngitis, sepsis, etc.) in the **absence of** systemic manifestation, splenomegaly/lymphadenopathy and/or weight loss
- Lab findings → ↓ **Hb** (and Hct), ↓ **reticulocyte** count, ↓ **WBC** count, ↓ **platelet** count
- **Most accurate** diagnostic test → **bone marrow biopsy** showing ↓ and/or **absent hematopoietic precursors** with marked **fatty replacement** and some residual stromal and/or lymphoid cells (**note** → remaining precursor cells should be **morphologically normal**)
- Management →
    1. **removal** of any offending **drug/toxin**
    2. **supportive** measures (e.g. **antibiotics** for infection/↑ **fever** (*see neutropenic fever)*, **single** donor, **leuko-depleted platelet** transfusions, packed **RBC** transfusion)
    3. **bone marrow transplantation (BMT) → curative**; suitable for otherwise healthy **young adults** with a histocompatible **donor**
    4. BMT not possible → **immunosuppression** using a combination of **ATG** (anti-thymocyte globulin) and **cyclosporine**; future risks → high **relapse** rate, **MDS** (myelodysplastic syndrome), possible **leukemia** and/or **PNH**

* **Neutropenic Fever** requiring treatment → Temperature > **38.3 ºC** (**single** reading) or > **38.0 ºC** (**> 1 hour**) in the presence of **ANC** (absolute neutrophil count) < **500**

- **Low risk** (outpatient, no comorbidities, serum creatinine < 2 mg/dL, normal-slightly increased LFTs, neutropenia of short duration, normal BP) → **PO ciprofloxacin + PO amoxicillin-clavulanate** or **IV ceftazidime** (usually not tested on exams)
- **High risk**:
    1. Step 1 → evaluate for indications for **vancomycin** (e.g. **catheter-**related infection, ↓ **BP**, previous known **colonization** with **MRSA** (methicillin-resistant S. aureus) and/or **penicillin-resistant pneumococcus**)
    2. Vancomycin **not needed** → IV **ceftazidime** (or cefepime or imipenem) (most common test Q answer) or **combination** of IV **aminoglycosides** with **piperacillin/tazobactam** (or ceftazidime, cefepime or imipenem)
    3. Vancomycin **needed** → IV **vancomycin** + IV **ceftazidime** (or any of the above mentioned drugs/combinations)
- **Afebrile** within **3 days** → switch to **PO antibiotics** (e.g. cefixime or fluoroquinolones) if **low-risk** (otherwise continue the same antibiotics)
- **Febrile** on **days 5-7** → add **antifungal** agents (possible Candida, Aspergillus) → **posaconazole, voriconazole, echinocandins** (e.g. caspofungin) or amphotericin B

# Macrocytic Anemia

## Megaloblastic Anemia

- Pathophysiology: Vitamin **B12** and/or **folate** deficiency → ↓ **DNA synthesis** → **arrested nuclear** maturation + **normal cytoplasmic** maturation → **large, nucleated** RBC **precursors** (megaloblasts)
- Etiology:
    1. **Vitamin B12** deficiency → **pernicious anemia** (most common), total **gastrectomy**, atrophic gastritis**, malabsorption** syndromes (e.g. Crohn's disease, celiac disease, chronic pancreatitis, bacterial overgrowth), **resection** of the **ileum, fish tapeworm** (Diphillobothrium latum), strict **vegetarianism,** chronic **$N_2O$** inhalation
    2. **Folate** deficiency → ↓ **dietary intake** (most common; seen in **alcoholism, poverty** and/or infancy), ↑ **requirements** (e.g. pregnancy, rapid growth, chronic hemolysis, hemodialysis, psoriasis, dermatitis), **malabsorption** syndromes (especially celiac disease), **drug/**chemical induced (e.g. **phenytoin, barbiturates, methotrexate, trimethoprim, pyrimethamine, alcohol**)
- Clinical features (common to both forms of disease) → symptoms/signs of **anemia**, mild **jaundice** (due to ineffective hematopoiesis → intramedullary hemolysis), atrophic **glossitis,** diarrhea, abdominal pain, ± symptoms/signs of **thrombocytopenia**
- Clinical features suggestive of **vitamin B12** deficiency → **neurologic** manifestations:
    1. **Distal**, **symmetric**, predominantly **sensory**, peripheral **neuropathy** (prominent **paresthesias**, pain, etc. predominantly affecting the **lower limbs**)

2. **Subacute combined degeneration** (involvement of **posterior columns** and **corticospinal** tracts) → ↓ **proprioception** (**ataxia** with positive **Romberg's sign**) and vibratory sense ± **spastic paralysis**
3. **CNS** involvement → confusion, delirium, **dementia** (commonly **reversible**)
4. Other → cranial nerve involvement, sexual dysfunction, loss of bladder/bowel control, autonomic neuropathy

- Lab findings → ↓ **Hb,** ↓ **Hct,** ↓ **reticulocyte** count, ↑ **MCV**, ↓ WBC and/or platelet count, ↑ **LDH,** ↑ **indirect bilirubin**
- Blood smear → **macrocytic** RBCs (**oval** macrocytes), **hypersegmented neutrophils** (>**50%** with **4 lobes**, or >**5%** with **5 lobes**, or at least **one** with **6 lobes**)
- Bone marrow biopsy → **hypercellularity** + prominent **arrest** in **nuclear maturation**
- **Most accurate** diagnostic test → serum **vitamin B12** and RBC **folate** levels, respectively
- **Suspected** vitamin **B12 deficiency** with **normal** vitamin **B12 levels** → order serum **methylmalonic acid** (MMA), which should be **high**
- **Best next step** in confirmed B12 deficiency → **anti-intrinsic factor** and/or **anti-parietal cell** autoantibodies (to confirm the diagnosis of pernicious anemia)
- **Best next step** if **antibodies negative** (or not offered as one of the answer choices) → **Schilling test**
- Management:
    1. vitamin **B12** deficiency → usually lifelong **IM** vitamin **B12 replacement** (clinical improvement within hours, brisk reticulocytosis within 5-7 days, normalization of hematologic picture within 2 months, neurologic manifestations ± reversible)
    2. **folate** deficiency → **PO folate** replacement

* **Macrocytic** anemia due to **liver disease** → ↓ **LCAT** (lecithin-cholesterol acetyl transferase) **activity** → ↑ plasma **cholesterol** → **cholesterol deposition** on RBC membranes → ↑ membrane **surface area** → **round macrocytosis** (liver disease may also be associated with **spur cell anemia** (spur cells/acanthocytes → large **RBCs** covered with **irregularly-spaced spike-like** projections of variable **shapes** and/or **lengths**) Note: **Burr cells**/echinocytes → large **RBCs** covered with **uniformly** spaced **spike-like** projection of **similar shapes** and/or **lengths**

## Myelodysplasia (MDS)

- A group of **stem cell** disorders characterized by **anemia** ± other **cytopenias**, **dysmorphic** and frequently **hypercellular bone marrow** and **ineffective** hematopoiesis
- > **50%** of cases progress to **acute myelogenous leukemia (AML)**
- Etiology → **radiation, benzene, post-chemotherapy** (**latent** period of **2-7 years**; commonly implicated agents include → busulfan, procarbazine, nitrosureas, **topoisomerase II inhibitors**, such as etoposide, irinotecan), **aplastic anemia**
- **Most common** in persons **> 60 years** of age
- Common **cytogenetic** abnormalities → **del (5**q), **del 7**, **trisomy 8**, **del (20**q)
- **FAB** classification of MDS:
    1. **Refractory Anemia** → < 5% blasts, <15% ringed sideroblasts
    2. **Refractory Anemia** with **ringed sideroblasts** → < 5% blasts, > 15% ringed sideroblasts
    3. **Refractory Anemia** with excess **blasts** → > 5% but < 20% blasts
    4. **Refractory Anemia** with excess **blasts** in **transformation** → > 20% blasts and/or Auer rods
    5. **Chronic Myelomonocytic leukemia**
- Clinical features → Symptoms/signs of **anemia** ± **thrombocytopenia** and/or **neutropenia**; possible hepato**splenomegaly**
- **Fever** and/or **weight loss** → consider **CML** or other **myeloproliferative** disorders
- Lab findings → ↓ **Hb,** ↓ **Hct,** ↑ **MCV,** ↓ **reticulocyte** count, ↓ **WBC** and/or ↓ **platelet** count
- Blood smear → **macrocytic** and/or **dimorphic** population of **RBCs, large platelets** and **hypogranulated PMNs** with **hyposegmented** nuclei
- **Most accurate** diagnostic test → **bone marrow** examination showing:
    1. **hypercellularity**
    2. **ringed sideroblasts**
    3. **PAS-**positive **erythroblasts**
    4. asynchronous **nuclear/cytoplasmic** maturation
    5. **micromegakaryocytes** ± giant platelets
    6. pseudo-**Pelger-Huet** cells (hypogranulated, two-lobed PMNs/precursors)
- Management → **supportive** measures (blood transfusion, antibiotics, etc.), **G-CSF** and/or **erythropoietin, azacytidine** (inhibits DNA methylation), amifostine (inhibits apoptosis)
- **BMT** → possible **curative**; suitable for **younger** and otherwise **healthy** patients with **high-risk MDS**

# Myeloid Malignancies

## Acute Myelogenous Leukemia (AML)

- Hematopoietic **stem cell** disorder characterized by **clonal proliferation** of **immature myeloid precursors** (myeloblasts) secondary to **loss of ability** to **differentiate** → bone marrow **failure** + **peripheral myeloblasts**
- Risk factors → **benzene, petroleum** products, **radiation, post-chemotherapy** (**alkylating** agents → **del 5q** and/or **del7q**; **topoisomerase II** inhibitors → **11q** abnormalities; **faster** onset), **Down** syndrome, **Klinefelter** syndrome, ataxia-telangiectasia, Fanconi's anemia, Bloom syndrome
- Incidence **increases with age**
- **FAB** classification of **AML:**

| | |
|---|---|
| **M0:** minimally differentiated | **CD13** and **CD33** |
| **M1:** myeloblastic without maturation | |
| **M2:** myeloblastic with maturation | **Most common** AML; **t(8;21)**; **mass lesions** (granulocytoc sarcoma, also called **chloroma**) |
| **M3:** promyelocytic | **t(15;17)** involving the **retinoic acid receptor-α** gene; **Auer rods** most prominent; **DIC** |
| **M4:** myelomonocytic | **inv(16)** → **M4Eo** (subtype of M4 AML with abnormal marrow eosinophils); **tissue infiltration** (gums, skin → leukemia cutis, meninges, soft tissues, etc.) |
| **M5:** monocytic | **t(9;11)**; **tissue infiltration** |
| **M6:** erythroleukemia (DiGuglielmo's disease) | **Glycophorin A** and/or **ferritin receptor** expression |
| **M7:** megakaryoblastic | Prominent **myelofibrosis**; **CD41** and **CD61** |

- Clinical features → symptoms/signs of **anemia**, **thrombocytopenia** and/or **neutropenia** (e.g. weakness, fatigue, pallor, shortness of breath, easy bruising, bleeding gums, pharyngitis, skin infections, etc.), anorexia, **weight loss, fever, hepatosplenomegaly, lymphadenopathy, sternal** tenderness and/or diffuse **bone pain,** ± symptoms/signs of **tissue infiltration** and/or **mass lesions**
- Symptoms/signs of **leucostasis** if ↑↑**WBC** count → **headache**, **dyspnea**, **visual disturbances**, **retinal** and/or CNS **hemorrhage**
- Lab findings → normochromic, normocytic **anemia** with ↓ **reticulocyte** count, ↓ **platelet** count, ↓, normal or ↑ **WBC** count, circulating **blasts,** ↑ **LDH**, ↑ **uric acid**
- **Most accurate** diagnostic test (for leukemia **in general**)→ **bone marrow biopsy** showing > **20% blast** forms
- **Most accurate** diagnostic test to **differentiate** among **AML** and **ALL** and between **subtypes** of **AML** → **Cytogenetic**/molecular and **immunophenotypic** analysis
- Characteristics of **myeloblasts**:
    1. **fine**, reticular nuclear **chromatin**
    2. **large, multiple nucleoli**
    3. **larger cytoplasm**
    4. presence of **granules** and/or **Auer rods**
    5. positive for **meyloperoxidase, sudan black** and/or nonspecific **esterase** (seen with monocytic and/or myelomonocytic AML)

- Management:
    1. **Induction** therapy → combination of **cytarabine** (cytosine arabinoside) and **daunorubicin** (anthracycline) ± etoposide
    2. **Complete remission achieved** (< 5% marrow blasts, no peripheral blasts, no Auer rods, > 20% bone marrow tri-linage cellularity, etc.) → **high-dose cytarabine consolidation** therapy or **BMT** (preferred if available/suitable)
    3. **Complete remission not** achieved → **repeat induction** therapy
    4. **Failure** to achieve **complete remission** after two cycles of induction therapy → **BMT**
    5. **Relapse** after complete remission → **BMT**
    6. **BMT** not available or **age > 65-70** → consider **newer investigational** agents (e.g. **gentuzumab → anti-CD33** monoclonal antibody **linked to calicheamicin**, an anti-cancer antibiotic)
    7. **Supportive** measures → **leukodepleted** and **irradiated RBC** and/or **platelet** transfusions (keep **Hb > 8 g/dL**, and **platelets > 10,000**), **antibiotics** if ↑ temperature (*see neutropenic fever*), possible use of **G-CSF** and/or GM-CSF
    8. **IV**/PO **hydration** and **allopurinol** (xanthine oxidase inhibitor) ± urine **alkalinization before** initiating **chemotherapy** to **prevent** ↑ serum **uric acid** → **precipitation** of uric acid **crystals** → **acute renal failure** (uric acid nephropathy)
    9. **Induction** therapy for **M3 AML** → **ATRA** (tretinoin) in **combination** with **daunorubicin**
    10. **Consolidation** therapy for **M3 AML** → **cytarabine** and **daunorubicin**
    11. **Maintenance** therapy for **M3 AML** → **ATRA** (tretinoin) ± chemotherapy
    12. **Refractory** to **ATRA** → consider **arsenic trioxide**

* **ATRA** associated with **retinoic acid syndrome → fever, dyspnea,** pulmonary infiltrates on chest X-ray, pleural/pericardial **effusion, hypoxia**; treatment → **steroids** ± supportive measures

* symptoms/signs **of leucostasis →** IV hydration, allopurinol, platelet transfusion, **leukaphresis,** standard **chemotherapy** ± hydroxyurea

* **Alternative** to **allopurinol** in the management of **AML → rasburicase** (recombinant uric oxidase)

* **Tumor lysis syndrome → hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia,** hyperuricosuria, leading to **acute renal failure** and/or **arrhythmias;** prevention → **IV hydration** + **allopurinol** (or rasburicase); treatment → **IV hydration**, **loop diuretics**, **rasburicase** ± **hemodialysis**; **correction**/management of **electrolyte** abnormalities

## Chronic Myelogenous Leukemia

- **Myeloproliferative disorder** characterized by **clonal proliferation** of a myeloid **stem cell** harboring the **pathognomic t(9;22)** translocation (**Philadelphia** chromosome)
- Risk factors → high-dose **radiation** (e.g. atomic bomb survivor)
- Incidence **increases with age**
- Pathophysiology: **t(9;22)** → BCR/ABL **fusion protein** with **tyrosine kinase** activity → ↓ **apoptosis** → **transformation** of myeloid **stem cells** → **CML,** characterized by ↑↑ production of **mature myeloid** cells
- Clinical features → **asymptomatic** (e.g. detected on routine CBC) to **night sweats, fatigue,** weakness, **fever, weight loss, splenomegaly** (e.g. LUQ abdominal pain, early satiety), hepatomegaly, ± symptoms/signs of thrombocytopenia and/or neutropenia (uncommon), ± "**leucostasis"** (e.g. **priapism**, **dyspnea**, **visual** disturbances, ± arterial/venous **thrombosis** and/or **hemorrhages**)
- Possible manifestations of ↑ **histamine release** (secondary to peripheral **basophilia**) → **pruritus,** diarrhea**, PUD, flushing,** hypotension/tachycardia
- Possible manifestations of **hyperuricemia** → **gouty arthritis,** gouty nephropathy
- Lab findings → ↑↑ **WBC** count with prominent **left shift**, **blasts < 5%**, ↑ **basophils** and/or eosinophils, ↑ **platelet** count, normochromic normocytic **anemia**, ↑ vitamin **B12** level, ↓ **LAP** activity (**differentiates** from **other myeloproliferative** disorders and/or **reactive** leukocytosis ("**leukemoid reaction**")
- **Best initial** diagnostic test in suspected CML → **LAP** score
- Bone marrow biopsy → ↑ **cellularity** (predominantly **myeloid** and **megakaryocytic**), altered myeloid-to erythroid ratio, ↑ marrow **basophils** and/or eosinophils, ↑ **fibrosis**
- **Most accurate** diagnostic test (**mandatory** for diagnosis) → demonstration of **Philadelphia** chromosome (e.g. PCR, FISH, etc.)
- Natural course of CML: **chronic phase** → disease **acceleration** → **blast crisis**
- Acceleration/**blast crisis** → **worsening** symptoms/signs, significant **weight loss, bone** and/or **joint pain, bleeding,** ↑ **infections**

* Definition of disease **acceleration** → **blasts 10-20%,** worsening anemia, **thrombocytopenia,** and/or **basophils > 20%**

* Definition of **blast crisis** → **blasts > 20%**; most common variant is **AML** (with **ALL** in **second**)

* Definition of **complete response** → **WBC** count < **10,000/µL**, **normal RBC** and **platelet** counts, **normal spleen** size**, 0%** bone marrow cells with **t(9;22)**, **undetectable BCR/ABL** (using RT-PCR)

- Management:
    1. **Best initial therapy** → standard-dose **imatinib mesylate**/Gleevec (**inhibitor** of BCR/ABL **tyrosine kinase**)
    2. **Complete response** → **continue** same-dose imatinib
    3. **Partial**/minor **response** → ↑ imatinib **dose**
    4. **No response** → switch to **dasatinib** or **linotinib;** consider **BMT**
    5. **Accelerated phase** → **imatinib** (or dasatinib) followed by **BMT**
    6. **AML blast crisis** → **cytarabine** + **daunorubicin** + **imatinib** (or dasatinib) followed by **BMT**

7. **ALL blast crisis → daunorubicin + L-asparaginase + vincristine + prednisone + imatinib** (or dasatinib) followed by **BMT** (consider **CNS prophylaxis** using **intrathecal methotrexate**)
8. **Symptomatic** treatment → **antihistamines,** IV hydration**, allopurinol**

* **Interferon-α** ± cytarabine and/or **hydroxyurea** ± busulfan → **never** a **correct answer** in **test Qs** (not only in test Qs)

* **Management** of **thrombocytosis → anagrelide** (inhibition of **phosphodiesterase III → ↓ platelet** production); **second-line** therapy (**inferior** to **imatinib** and/or **hydroxyurea + aspirin** for CML and ET, respectively)

## Polycythemia Vera

- **Most common myeloproliferative** disorder characterized by **autonomous** overproduction of **eryhtroid** cells, secondary to ↑ **JAK2 kinase** activity
- **Males >** females; incidence **increases with age**
- Clinical features →
    1. ↑ blood **viscosity → headache, dizziness, blurry** vision, **tinnitus, hypertension**
    2. ↑ **histamine** release (secondary to ↑ **basophilia**) → **pruritus** (especially post-bathing), **PUD**, flushing, etc.
    3. **hyperuricemia → gouty** arthritis
    4. **splenomegaly**
    5. **plethoric** appearance
    6. fatigue, weakness, **weight loss**
    7. ↑ risk of **thrombosis** (e.g. stroke, MI, dural venous sinus thrombosis, etc.)
    8. ↑ risk of **hemorrhage** (secondary to platelet dysfunction)
    9. **erythromelalgia → dysesthesias, erythema** and/or **swelling** of the **lower extremities**, brought about by exposure to **heat, exertion** and/or **alcohol** consumption
- Lab findings → ↑↑ **Hct,** ↑ **WBC** count, ↑ **platelet** count, ↑ **basophils** and/or eosinophils, ↑ **vitamin B12** levels, ↑ **LAP** score
- Bone marrow biopsy → **trilineage hyperplasia,** ± marrow **fibrosis**
- Diagnosis → **exclusion** of secondary causes of **erythrocytosis**:
    1. **undetectable erythropoietin** levels
    2. **oxygen** saturation > **92%**
- Management:
    1. **symptomatic** therapy → **anti-histamines, allopurinol**, IV hydration
    2. **phlebotomy** (goal Hct of < 45%) → **mainstay** of therapy
    3. low-dose **aspirin**
    4. **indications** for **hydroxyurea** therapy → **age > 60**, history of **thrombosis**, extreme **thrombocytosis, intractable pruritus** (use **interferon** for **younger** patients)
- Complications → **myelofibrosis**, **AML, thrombotic** complications

* **Gaisböck syndrome** (stress erythrocytosis) → **obese, sedentary males** with **hypertension** and ↓ blood **volume** → **relative erythrocytosis**

* **Erythropoietin-secreting** tumors → **cerebellar/retinal hemangioblastomas, renal cell carcinomas, hepatomas,** uterine **fibroids**

## Essential Thrombocythemia (Essential Thrombocytosis)

- Chronic **myeloproliferative** disorder characterized by **autonomous platelet** overproduction → ↑↑ **platelet** count in the **absence** of **secondary causes** of thrombocytosis (e.g. iron-deficiency, infection, asplenia, etc.)
- Clinical features → **asymptomatic** (most common presentation) to ↑ risk of **thrombotic** and/or **hemorrhagic complications;** possible symptoms/signs of **histamine** excess and/or **hyperuricemia**
- Diagnosis → **platelet** count > **600,000,** bone **marrow megakaryocytic hyperplasia**, **absence** of **t(9;22)** + **exclusion** of **secondary** causes of thrombocytosis ± ↑ **JAK2** kinase activity
- Complications → **myelofibrosis, AML**
- Management →
    1. **Symptomatic** therapy + low-dose **aspirin**
    2. **Asymptomatic, young** → treatment **not required**
    3. **Age > 60** and/or history of **thrombosis** → **hydroxyurea**
    4. **Intolerance** to **hydroxyurea** → **anagrelide**
    5. **Young** + history of **thrombosis** → **interferon-α**
    6. **Pregnant** or contemplating pregnancy → **interferon-α**

## Primary Myelofibrosis (Idiopathic Myelofibrosis)

- Chronic **myeloproliferative** disorder characterized by **marrow fibrosis**, **extramedullary** hematopoiesis and varying degrees of **pancytopenia**
- Incidence **increases with age**
- Pathophysiology: **abnormal megakaryocytes** → ↑ **TGF-β** secretion → **recruitment**/activation of **fibroblasts** → **collagen** deposition
- Clinical features → **asymptomatic** to **massive splenomegaly, hepatomegaly,** lymphadenopathy, symptoms/signs of **anemia**, possible **gouty arthritis**
- Difficult to differentiate from other myeloproliferative disorders complicated with myelofibrosis
- **Clues → older** age, hepato**splenomegaly**, ↓ **Hct, teardrop**-shaped **RBCs** (dacryocytes), **leukoerythroblastosis** (blood smear showing **immature** RBCs and WBCs → **nucleated RBCs** and **myelocytes, promyelocytes** and/or **myeloblasts**), "**dry-tap"** on attempted marrow **aspiration**, bone **marrow biopsy** showing ↑ **collagen** deposition ± ↑ **megakaryocytes, absence** of **t(9;22)**
- Complications → **AML**
- Management → **symptomatic** therapy, possible **hydroxyurea** and/or **interferon**, ± **splenectomy**; consider **BMT**

# Lymphoid Malignancies

## Acute Lymphoblastic Leukemia/Lymphoma (ALL)

- **Most common** leukemia in **children**
- **Boys >** girls
- **Whites >** African-Americans
- **85%** of cases are of **B-cell origin**
- Risk factors → **radiation, benzene, genetic** syndromes (e.g. **Down** syndrome**, Bloom** syndrome, etc.)
- Clinical features → symptoms/signs of **anemia, thrombocytopenia** and/or **neutropenia, ↑ temperature**, severe **bone pain**, **arthralgias**, **lymphadenopathy, splenomegaly** ± hepatomegaly, **mediastinal mass** (especially with T-cell ALL) ± **respiratory distress**, possible **CNS** disease, **testicular enlargement** and/or tissue infiltration
- Lab findings → **pancytopenia** with ↓ **reticulocyte** count, circulating **lymphoblasts, ↑ LDH, ↑ uric acid**
- **Most accurate** diagnostic test **in general → bore marrow biopsy** showing > **20% marrow blasts**
- **Most accurate** diagnostic test to **differentiate** between AML and ALL and/or different forms of ALL → **immunophenotypic** and/or **cytogenetic** analysis
- Characteristics of a **lymphoblast →**
    1. **scant cytoplasm**
    2. **few, small nucleoli**
    3. **no** granules and/or Auer rods
    4. **positive** for **PAS** and/or **TdT** (terminal deoxynucelotidyl transferase)
- **Immunophenotypic** classification of **ALL →**
    1. **Pro-B-cell ALL → TdT +**, **CD 19 +**, CD 10 (CALLA) –
    2. **Pre-B-cell ALL → TdT +, CD 19 +, CD 10 +, cytoplasmic Ig +**
    3. **Mature B-cell (Burkitt) ALL →** TdT **-, CD 19 +, surface Ig +**
    4. **Pre-T-cell ALL → TdT +,** CD 3 -, **CD4+/CD8+** or CD4-/CD8-
    5. **Mature T-cell ALL → CD 3 +. CD4+**/CD8 – or CD4+/**CD8+**
- Common **genetic abnormalities** (associated with **poor prognosis) → t(4;11), t(9;22),** t(8;14), t(1;19)
- Management:
    1. **Induction** therapy → **vincristine, prednisone, daunorubicin** and **L-asparaginase**
    2. **Consolidation** therapy → **cytarabine** + daunorubicin
    3. **Maintenance** therapy → **2-3 years** of **methotrexate** and/or **6-marcaptopurine** (most commonly used agents)
    4. **CNS prophylaxis → intrathecal methotrexate**
    5. **Relapse** after complete remission → intensive chemotherapy + **BMT**
    6. **Relapse** at **"sanctuary"** sites (e.g. CNS, testes) → **radiation**
    7. **Complete remission** in ALL with **t(9;22)** or **t(4;11) → BMT**
    8. **Initial therapy** of ALL with **t(9;22) → Hyper-CVAD** regimen (cyclophosphamide, vincristine, Adriamycin, dexamethasone) ± **imatinib**
    9. **Supportive** measures
- **Poor prognostic** factors → **age < 2** or > **10**, **male** sex, **black** race, ↑ **WBC** count, **mature** phenotype, **mediastinal** mass, **T-cell** origin, **chromosomal** translocations

## Chronic Lymphocytic Leukemia/Small Cell Lymphoma (CLL/SCL)

- **Clonal** proliferation of **mature B lymphocytes**
- **Most common** form of **leukemia**
- **Age > 50**
- **Males** > Females
- Clinical features → **asymptomatic** (**most common**; e.g. detected on routine CBC, etc.) to fatigue, **splenomegaly, lymphadenopathy**, ↑ risk of **infections**, ± symptoms/signs of **anemia** and/or thrombocytopenia
- Complications → **autoimmune hemolytic anemia, immune-**mediated **thrombocytopenia**, **hypogammaglobulinemia**, **Richter syndrome** (transformation to high-grade large-cell lymphoma)
- Lab findings → ↑ **WBC** count with **absolute lymphocytosis** (lymphocyte count > **5000/µL**) ± ↓ RBC and/or platelet counts
- Blood smear → **small, mature** lymphocytes + "**smudge" cells**
- Bone marrow biopsy → **> 30% lymphocytes**
- **Most accurate** diagnostic test → **flow-cytometry** (**CD5+, CD19+, CD20**+ and **CD23**+)
- **Staging:**
    1. **Stage 0 → lymphocytosis**
    2. **Stage 1 →** lymphocytosis **+ lymphadenopathy**
    3. **Stage 2 →** lymphocytosis + lymphadenopathy **+ splenomegaly**
    4. **Stage 3 →** lymphocytosis **+ anemia** (excluding autoimmune etiology)
    5. **Stage 4 →** lymphocytosis + **thrombocytopenia**
- Management:
    1. **Stages 0-2** + **asymptomatic → observation**
    2. **Symptomatic** and/or **Stages 3-4 → fludarabine** ± rituximab (side effects → myelosuppression and immunosuppression, requiring PCP prophylaxis)
    3. **Alternative** for older individuals → chlorambucil ± prednisone
    4. **Relapse**/failure → **pentostatin, alemtuzumab** (anti-CD52 monoclonal antibody) or bendamustine
    5. **immune-**mediated hemolytic **anemia** and/or **thrombocytopenia → steroids**

## Hairy Cell Leukemia

- A **mature B-cell** neoplasm
- **Males >** Females; **middle age**
- Clinical features → **asymptomatic** to **splenomegaly,** progressive **fatigue**, symptoms/signs of **anemia, thrombocytopenia** and/or **neutropenia**
- In summary → **triad** of **middle** age, **splenomegaly** and **pancytopenia**
- Lab findings → consistent with **pancytopenia**
- Blood smear → WBCs with **"hair-like"** cytoplasmic **projections**
- Bone marrow **aspirate → "dry tap"**
- **Most accurate** diagnostic test → bone marrow **biopsy positive** for **TRAP** (tartrate-resistant acid phosphatase) **stain**
- Flow Cytometry → **CD19+, CD20+, CD11+, CD25+**
- Management:
    1. **Asymptomatic** + **normal/mildly** decreased **CBC → observation**
    2. **Best initial** therapy → **cladribine** or **pentostatin**
    3. **Relapse**/failure → **rituximab** (or alemtuzumab)
- **Most common** cause of **mortality → infections**

## Hodgkin Lymphoma (Hodgkin Disease)

- A **germinal center B-cell** neoplasm characterized by **contiguous spread** and presence of **Reed-Stenberg cells**
- Less common than NHLs
- **Males** > Females
- **Bimodal age** distribution → **15-25** and > **50**
- Risk factors → **EBV** infection, ↑ **SES,** family history
- Histologic Subtypes:

| | |
|---|---|
| Nodular Sclerosis | **Most common** variant; **females** > males**;** frequent **mediastinal** involvement |
| Lymphocyte Predominant | **Best prognosis** |
| Lymphocyte Depleted | **Worst prognosis** |
| Mixed-Cellularity | **Intermediate prognosis** |

- Clinical features → **painless,** rubbery **lymphadenopathy** (**cervical, axillary** and/or **supraclavicular**), possible **mediastinal** lymphadenopathy, **splenomegaly** (30% of cases at diagnosis), **B symptoms** (night sweats, fever, weight loss), generalized **pruritus**, **pain** on **alcohol consumption, cyclic fever** (Pel-Epstein fever), **cutaneous anergy**, possible **immune**-mediated hemolytic **anemia** and/or **thrombocytopenia**
- Spread → **contiguous** from one lymph node region to another
- Lab findings → **anemia** (of chronic disease)**,** ↑ WBC count, ↑ platelet count, **eosinophilia, lymphocytopenia,** ↑ **ESR**, ↑ **LDH**
- **Best initial** and **most accurate** diagnostic test → **excisional lymph node biopsy** showing **Reed-Stenberg** cells (large, **bi-nucleated cells** with **prominent nucleoli** → **"owl's eye**" appearance; **CD15+, CD30+**) admixed with **eosinophils, lymphocytes** and/or **plasma cells**
- **Best next step** → **Staging** (history and **physical examination**, **chest X-ray**, **CT** of the **chest, abdomen** and **pelvis**, blood tests, including **CBC**, **ESR**, **LFTs**, ± **PET** or **gallium scan** and/or bilateral **bone marrow aspiration/biopsy**)
- Staging System (simplified) →

| | |
|---|---|
| **Stage I** (IA or IB) | **Single** lymph node region ± **B symptoms** |
| **Stage II** (IIA or IIB) | ≥ **2** lymph node regions on the **same side** of the **diaphragm** ± **B symptoms** |
| **Stage III** (IIIA or IIIB) | Lymph node regions on **both sides** of the **diaphragm**, including the **spleen ± B symptoms** |
| **Stage IV** (IVA or IVB) | **Diffuse** involvement of **extralymphatic sites** (e.g. bone marrow, liver, etc.) ± **B symptoms** |

- **Poor prognostic** factors → age > **45, stage IV** disease, **male** gender, **B symptoms, mediastinal** involvement, ↑ **ESR**
- Management:
    1. **Stages IA** and **IIA** (limited disease) → **brief** course of **chemotherapy** (ABVD regimen) + **localized radiation**
    2. **Stages IA** and **IIA** documented by **laparotomy → radiation**
    3. **Stages III-IV** (extensive disease) and/or any **Stage B → full** course of **combination chemotherapy**:
        - **ABVD** (doxorubicin, bleomycin, vinblastine, dacarbazine)
        - **MOPP** (mechlorethamine, vincristine, prednisone, procarbazine)
        - **Stanford V → inferior** to ABVD

        - **BEACOPP** (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) → **superior** to ABVD
    4. **Best initial** therapy in **extensive** disease → **ABVD**
    5. **Relapse** after **radiotherapy** → **standard chemotherapy**
    6. **Relapse** after **chemotherapy** → high-dose chemotherapy + **BMT**
    7. **Acute, life-threatening** complications (e.g. SVC, spinal cord compression, airway obstruction, etc.) → **radiation**
- **Late complications** of therapy (more common with **MOPP** and **BEACOPP**) →
    1. **infertility**/amenorrhea
    2. radiation-induced **hypothyroidism**
    3. radiation-induced **pneumonitis** and/or **constrictive pericarditis**
    4. **doxorubicin-**induced **cardiomyopathy**
    5. **bleomycin**-induced **pulmonary fibrosis**
    6. secondary **AML** and/or **MDS**
    7. **aplastic anemia**
    8. radiation-induced **solid tumors** (e.g. breast cancer)

## Non-Hodgkin Lymphomas (NHLs)

- **Most common** hematologic **malignancy**
- **B-cell origin** > **85%** of cases
- **Males** > Females
- **Whites >** African-Americans
- **Age > 50** (exceptions → **Lymphoblastic** and/or **Burkitt** lymphomas; common in **children**/**young** adults)
- Risk factors → **EBV** infection (e.g. endemic Burkitt lymphomas), **HIV** infection (e.g. immunoblastic lymphomas, primary CNS lymphomas, Burkitt lymphomas), **HTLV-1** infection (e.g. adult T-cell leukemia/lymphoma), **H. pylori** infection (e.g. gastric MALTomas), **HHV-8** infection (e.g. body cavity-based lymphomas), **Hashimoto's** thyroiditis, **Sjogren** syndrome
- Clinically divided into **low-grade** (indolent), intermediate-grade and **high-grade** (aggressive) **lymphomas**
- Characteristics of NHLs →
    1. **Non-contiguous** spread
    2. **Diffuse lymphadenopathy** (including **retroperitoneal**) on presentation
    3. Common **extralymphatic** involvement, including the **CNS** and/or **Waldeyer** ring
    4. Common **bone marrow** involvement → **cytopenias**
    5. **No** pruritus
    6. **No** alcohol-induced pain
    7. **No** cyclic fever
- **Best initial** and **most accurate** diagnostic test → **excisional lymph node biopsy** ± immunophenotyping
- **Best next step** → **staging** (including **bilateral bone marrow aspiration/biopsy** ± **lumbar puncture**)
- **Best initial therapy** → **CHOP** regimen (cyclophosphamide, doxorubicin, vincristine, prednisone) or **R-CHOP** (**rituximab** + CHOP; **high-grade large-cell** lymphomas)

| Low-Grade NHLs | High-Grade NHLs |
|---|---|
| **Follicular** lymphoma, **small cell** lymphoma | **Diffuse large-cell** lymphoma, **immunoblastic** lymphoma, **Burkitt** lymphoma |
| **Non-curable** | **Curable** |
| **Longer survival** | **Shorter survival** if treatment-**resistant** |

* **Endemic Burkitt** Lymphoma → **EBV** infection; **African child** with **mandibular** enlargement

* **Sporadic Burkitt** Lymphoma → **most common** form in **USA**; possible **HIV** infection; **abdominal mass** ± bowel **obstruction**

* **Lymphoblastic** Lymphoma → commonly of **T-cell** origin; **mediastinal** adenopathy ± **respiratory** compromise and/or **SVC** in a **young adult**

* ↑ risk of **tumor lysis syndrome** upon initiation of **chemotherapy → prevent** with **IV hydration,** urine alkalinization and **allopurinol**

* **Bexxar (tositumomab) → anti-CD20** conjugated to **$I^{131}$** and/or **Zavalin (ibritumomab)→ anti-CD20** conjugated to **yttrium 90**; **low-grade refractory NHL**

# Plasma Cell Disorders

## Monoclonal Gammopathy of Undetermined Significance (MGUS)

- **Most common** monoclonal gammopathy
- Incidence **increases with age** (3-5% > 70 years of age)
- **Asymptomatic** to MGUS-associated **peripheral neuropathy**
- Detected as ↑ **total serum protein** on routine blood tests
- **Best initial** diagnostic test → **serum protein electrophoresis** (SPEP) showing **M-protein spike** < **3g/dL** (usually of **IgG type**)
- **Most accurate** diagnostic test → **bone marrow biopsy** showing < **10%** plasma cells
- Lab findings → **normal** serum **creatinine, normal Hb, normal** serum **Ca**
- Skeletal survey → **no** evidence of **lytic lesions**
- Management → **SPEP** every **12 months** (initially every 6 months for a total of one year)
- **1-2%** annual risk of **progression** to multiple myeloma

# Multiple Myeloma

- **Clonal** proliferation of **abnormal plasma cells** (CD19-, CD56+) characterized by **bone marrow infiltration** with varying degrees of **pancytopenia, bone destruction** and ↑ **paraprotein** production (**monoclonal** or **"M"** protein)
- Incidence **increases with age**
- More common in **African-Americans**
- **Second** most common **hematologic** malignancy
- **Most common primary bone** tumor (more common than osteosarcoma)
- Clinical features:
    1. **bone pain** (especially **back** and/or **ribs**) → **most common** manifestation
    2. pathologic **fractures** (e.g. vertebral, femoral neck) ± **deformities**
    3. symptoms/signs of **anemia**
    4. symptoms/signs of **thrombocytopenia**
    5. ↑ risk of **infections** (especially secondary to **Pneumococcus** and **Haemophilus**)
    6. spinal **cord compression** (severe back pain ± neurologic deficits)
    7. symptoms/signs of **hypercalcemia** → Nephrogenic **DI** (polyuria, polydipsia)
    8. **carpal tunnel** syndrome (**secondary amyloidosis**)
    9. slowly progressive **renal failure** (secondary to hypercalcemia, hyperuricemia, Bence-Jones proteinuria, and/or secondary amyloidosis)
    10. **hyperviscosity** syndrome → **blurry** vision, **headache, confusion, dyspnea**, etc.
- In summary → **older** patient with **back/chest pain** exacerbated by **movement** + **anemia** + ↑ ESR ± **renal failure** and/or **hypercalcemia**
- Lab findings → ↓ **Hb**, ↓ **Hct**, ± thrombocytopenia and/or leukopenia, ↑ **ESR**, ↑ serum **Ca**, ↑ serum **creatinine,** ↑ **total serum protein**, ↑ serum **$\beta_2$-microglobulin**
- Blood smear → "**Rouleaux"** formation
- **Best initial** diagnostic test → **skeletal survey** (not bone scan) looking for **"punched-out" osteolytic** lesions
- **Best next step** (or best initial step if skeletal survey not one of the answer choices) → **SPEP** showing **M-protein spike** > **3g/dL** (usually of **IgG type**)
- **Most accurate** diagnostic test → **bone marrow biopsy** showing > **10%** plasma cells
- **Best initial s**tep in suspected **cord compression → IV dexamethasone**
- **Best next** step in suspected **cord compression** → spinal **MRI**
- **Best initial** therapy in confirmed **cord compression → radiation**
- Management:
    1. **Young, healthy → thalidomide** (or lenalidomide) + **dexamethasone** followed by **BMT**
    2. **Older**, **asymptomatic, normal** skeletal survey and/or lab findings → treatment **not indicated**
    3. **Older, symptomatic** or **abnormal** skeletal survey and/or lab findings → **melphalan + prednisone** ± thalidomide
    4. **Relapse → VAD** regimen (vincristine, doxorubicin, dexamethasone)
    5. **Hypercalcemia → IV hydration + furosemide + bisphosphonates**
    6. **Hyperviscosity → plasmapheresis**
    7. **Light-chain nephropathy → plasmapheresis**
    8. **Vaccination** against **pneumococcus** and **haemophilus**

### Waldenström Macroglobulinemia

- Synonyms → **lymphoplasmocytic** lymphoma
- Clinical features → **age > 60**, **hepatosplenomegaly,** generalized **lymphadenopathy, fatigue, nasal/**oral **bleeding**, peripheral **neuropathy**, recurrent infections, symptoms/signs of **hyperviscosity** syndrome (e.g. headache, blurry vision, dyspnea, retinal/cerebral hemorrhages, etc.); **renal** involvement **uncommon**
- Associations → **cold agglutinin** hemolytic anemia, **cryoglobulinemia, Raynaud's** phenomenon
- Diagnosis → **serum protein electrophoresis** showing **IgM spike** > 3 g/dL
- Management → **plasmapheresis** for hyperviscosity syndrome; **rituximab** + fludarabine or cladribine

* **POEMS** syndrome → **p**olyneuropathy + **o**rganomegaly **(**e.g. hepatosplenomegaly, lymphadenopathy) + **e**ndocrinopathy (e.g. amenorrhea, gynecomastia/impotence, DM type 2) + **m**ultiple **m**yeloma + **s**kin changes (e.g. hyperpigmentation, hypertrichosis)

* **Light Chain Disease → prominent renal** involvement, **normal** serum protein electrophoresis; diagnosis **→ urine protein electrophoresis**

## Platelet/Coagulation Disorders

### Idiopathic Thrombocytopenic Purpura (ITP)

- **Most common** cause of **thrombocytopenia**
- Pathophysiology: **anti-platelet IgG** production → **coating** of platelets → **destruction** by **splenic macrophages**
- ITP is a **diagnosis of exclusion**
- ITP is frequently **associated** with **SLE, HIV** infection and **hematologic malignancies**, e.g. CLL (known as **autoimmune** thrombocytopenic purpura; **not** ITP)
- **Females** > Males; **20-40 years** of age
- Clinical features → **epistaxis, menorrhagia,** easy **bruising**, **petechiae,** purpura**,** ecchymoses, possible **hematuria** and/or **GI** bleeding (so called "platelet-type" bleeding); **intracranial** hemorrhages in **severe** cases; **NO splenomegaly**
- **Best initial** diagnostic test → **CBC** showing ↓ **platelets** with **normal** RBC and WBC counts
- Other Lab findings → **normal** PT, PTT, blood smear and serum creatinine; ↑ **bleeding time**; presence of **antibodies** against **IIb/IIIa** receptor complex (not helpful)
- **Next step → exclusion** of secondary/known causes of thrombocytopenia:
    1. **Drug-induced** (e.g. quinidine, rifampin, **heparin, alcohol**)
    2. **SLE**/connective tissue disorders
    3. **HIV** infection
- **Bone marrow** examination (for definite diagnosis) indicated:
    1. If **age > 60**
    2. Before **splenectomy**

- Bone marrow findings → ↑ **megakaryocytes**
- Management:
    1. **Best initial** therapy → **prednisone**
    2. **Refractory** disease → **splenectomy** (vaccinate against Pneumococcus and Haemophilus)
    3. **No response** to steroids/splenectomy → **immunosuppressive** medications (e.g. cyclophosphamide, azathioprine) and/or **rituximab**
    4. **Platelet** count < **10,000** and/or **severe,** life-threatening **bleeding → IVIG** (intravenous immunoglobulin) or **RhoGAM** + high-dose steroids and/or platelet transfusions

*** Who needs steroids?**

1. patients with **platelet** counts < **30,000**
2. patients with **platelet** counts < **50,000** + **superficial** mucocutaneous **bleeding**
3. patients with **platelet** counts < **50,000** + ↑ **risk** of bleeding (e.g. hypertension, PUD)

*** Acute ITP** → common in **children 2-6 years** of age; usually **follows** a viral **URI** and/or **vaccinations; abrupt** onset of **"platelet-type" bleeding**; lab findings → ↓ **platelet** count + ↑ **bleeding time**; **spontaneous remission** within 6 months; average **duration 6-8 weeks;** treatment → **supportive**

## Type II Heparin-Induced Thrombocytopenia (HIT)

- Syndrome characterized by **thrombocytopenia** and ↑ **incidence** of **venous** and/or **arterial thrombosis**
- More common with **UFH** (unfractionated heparin)
- Pathophysiology: **anti - platelet factor 4–heparin** complex **IgG** production → **platelet aggregation** and **activation** → activation of **coagulation cascade → thrombocytopenia** with **thrombosis**
- Clinical features → **thrombocytopenia** and/or **venous**/arterial **thrombosis** developing **within 4-21 days** of **heparin** use
- Risk factors → **previous**, **high-dose** and/or **unfractionated** heparin use
- **Clue** to the presence of **HIT → dropping platelet** counts (do not order any other diagnostic test; **proceed to treatment**)
- **Most accurate** diagnostic test → **serotonin release** assay (**antibody assay** may also be used as a confirmatory test)
- Management:
    1. Step 1 → **stop heparin** administration
    2. Step 2 → administer **direct thrombin inhibitors** (**lepirudin**, bivalirudin, **argatroban**); monitor with **aPTT**
    3. Step 3 → **never** use **heparin** in the future (even **LMWH** → ↑ risk of **cross-reactivity**)

* **Bernard-Soulier** syndrome → autosomal **recessive deficiency** of glycoprotein **IB/IX** receptor complex; characterized by **thrombocytopenia**, **giant platelets** on blood smear, superficial **mucocutaneous bleeding**, ↑ **bleeding time** and **no aggregation** in response to **ristocetin** administration (not corrected by normal plasma); management → **ε-aminocaproic acid** (anti-fibrinolytic) and/or **platelet transfusions**

* **Glanzmann thrombasthenia** → autosomal **recessive deficiency** of glycoprotein **IIB/IIIA** receptor complex; characterized by **normal CBC**, superficial **mucocutaneous bleeding, ↑ bleeding time**, **normal** response to **ristocetin**, **no aggregation** in response to **ADP, epinephrine** and/or **collagen**; management → **platelet transfusions** and/or recombinant **factor VIIa**

## Thrombotic Thrombocytopenic Purpura/Hemolytic-Uremic Syndrome (TTP/HUS)

| **TTP** | **HUS** |
|---|---|
| More common in **adults; females** > males | More common in **children** |
| Etiology → **idiopathic**, associated with **HIV** infection, **ticlopidine, cyclosporine, pregnancy** | Etiology → associated with **E.coli O157:H7** infection (e.g. hamburgers at fast-food restaurants, apple cider), **Shigella** infection, **pregnancy** |
| **Pentad** of **thrombocytopenia** (with possible mucocutaneous bleeding), microangiopathic hemolytic **anemia** (e.g. helmet cells, triangle cells), acute **renal failure**/active sediment, **fever** and **neurologic** manifestations (e.g. headache, altered LOC, seizure, delirium) | **Triad** of **thrombocytopenia,** microangiopathic hemolytic **anemia** and **acute renal failure**/active sediment; possible **antecedent** hemorrhagic **gastroenteritis** |
| Pathology → **widespread hyaline thrombi** (platelets + fibrin without inflammation) | Pathology → **hyaline thrombi** limited to the **kidneys** |
| Lab findings → ↓ **Hb** and Hct, ↓ **platelet** count, ↑ **indirect bilirubin**, ↑ **LDH**, ↑ serum **creatinine** and **BUN**, **normal** PT and aPTT | Lab findings → **same** as with TTP |
| Pathophysiology → ↓ **ADAMTS13** activity (protease that cleaves large vWF multimers) secondary to **IgG autoantibody** production | **Normal** ADAMTS13 activity |
| Management → **plasma exchange** (plasmapheresis + fresh frozen plasma infusion) + **steroids** ± dipyridamole/aspirin | Management → **supportive** (e.g. dialysis) ± steroids ± anti-platelet agents; plasma exchange reserved for **severe cases** |

- **DO NOT** (may worsen the disease) →
    1. **Transfuse platelets**
    2. **Administer antibiotics**

## Von Willebrand's Disease (vWD)

- **Most common inherited** form of **coagulopathy**
- **Autosomal dominant** (most common) or autosomal recessive
- Secondary to **quantitative** or **qualitative** defects in **vWF**
- Pathophysiology: ↓ **vWF** → ↓ **platelet adherence** ± secondary **factor VIII deficiency**
- Clinical features → **positive family** history + **"platelet type"** bleeding (epistaxis, menorrhagia, petechiae, easy bruising, etc.), especially after **aspirin** administration; possible **hematuria** and/or **GI bleed**; soft tissue and/or intra-articular bleeding **uncommon**
- **Best initial** diagnostic test → **CBC** showing **normal platelet** counts (already performed in most test Qs)
- **Best next** diagnostic test (or best initial, if platelet count already known) → **bleeding time**, which should be **prolonged**

* Normal platelet count + ↑ bleeding time → consider **vWD, uremia**-associated **platelet dysfunction**, **anti-platelet agent** (e.g. aspirin) use and/or **Glanzmann** thrombasthenia.

- Other lab findings → ↑ **aPTT** (↑ aPTT + ↑ bleeding time = vWD)
- **Most accurate** diagnostic test → **vWF assay** (also known as factor VIIIag assay) showing ↓ **vWF levels**
- **Suspected vWD** + **normal vWF** levels → order **ristocetin cofactor assay:**
    1. ↓ **platelet aggregation** in response to ristocetin
    2. **Corrected** by mixing with **normal plasma**
- Management:
    1. **Best initial** therapy → **desmopressin**/DDAVP (releases subendothelial stores of vWF and factor VIII)
    2. **Desmopressin** not effective and/or contraindicated → **vWF concentrates**
    3. **Avoid anti-platelet** agents

## Hemophilia A

- **X-linked recessive** (hence **males >** females)
- **Deficiency** of **factor VIII** (also known as factor VIIIpro)
- Categorized as **mild**/subclinical (> 5%), **moderate** (1-5%) and **severe** (<1%) based on **factor VIII activity**
- Clinical features → **positive family** history + **asymptomatic** with **unexpected bleeding** following major **trauma** and/or **surgical** procedures to **hemarthrosis,** deep tissue **hematomas**, GI and/or urinary bleeding, **intracranial hemorrhage** with minor head trauma
- Repeated hemarthrosis → **disabling arthropathy**
- Lab findings → ↑ **aPTT** with **normal** PT, bleeding time, platelet count, etc.
- **Best next** diagnostic test → **mixing studies** (patient's plasma mixed with normal plasma) to differentiate between factor **deficiency** (**aPTT** should **normalize**) and factor **inhibitor** (e.g. antibodies against factor VIII, lupus anticoagulant)
- **Normal aPTT after mixing** with normal plasma → clotting **factor assay**, showing ↓ **factor VIII** levels

- Management → **desmopressin** for **mild** disease; otherwise recombinant **factor VIII concentrates**
- Treatment complications → transfusion-related **infections** (e.g. HBV, HIV), production of **anti-factor VIII antibodies** (**resistant** to standard therapy; use factor VIIa and/or prothrombin-complex concentrates)

* **Hemophilia B** (Christmas Disease)→ **X-linked** recessive deficiency of **factor IX**; otherwise **similar** to hemophilia A; treat with **factor IX concentrates**

* **Factor VII** deficiency → **prolonged PT** with **normal** aPTT; **asymptomatic** to manifestations **similar** to **hemophilia A**; management → **factor VIIa** concentrates (alternative → fresh frozen plasma)

* **Hemophilia C** → **autosomal recessive** deficiency of **factor XI**; **prolonged aPTT** with normal PT; management → **fresh frozen plasma**

* **Factor XIII** deficiency → **autosomal recessive**; **normal** aPTT, PT and bleeding time; **umbilical cord bleeding**, delayed wound healing, **delayed bleeding** with trauma; management → **cryoprecipitate**

* **Factor XII, prekallikrein** and/or **HMWK** deficiencies → **no risk** of bleeding; **prolonged aPTT**

* **Factor II, V, X** deficiencies → ↑ **aPTT** + ↑ **PT**

## Vitamin K deficiency

- Etiology → **malabsorption** syndromes, prolonged **antibiotic** use, dietary deficiency, **warfarin** therapy, **liver disease** (*see below*)
- **Asymptomatic** to **bleeding** similar to hemophilia
- Lab findings → ↑↑ **PT**, ↑ **aPTT**, normal bleeding time
- Management →
    1. **vitamin K** supplementation (PT should normalize within 24 hours)
    2. **active bleeding → fresh frozen plasma** + vitamin K

## Liver Disease

- **Bleeding tendency** secondary to ↓ **production** of **all** clotting factors, **except** factor VIII and vWF ± **thrombocytopenia** and/or thrombocytopathia
- Most common site of bleeding → **GI tract**
- Lab findings → ↓ **factor V,** ↑↑ **PT,** ↑ **aPTT** (advanced disease), ± **thrombocytopenia** and/or ↑ bleeding time
- Management → **fresh frozen plasma** ± platelet transfusions

# Disseminated Intravascular Coagulation (DIC)

- **Acquired** consumptive **coagulopathy** that manifests as **bleeding** and/or **thrombosis**
- Etiology →
    1. **Gram-negative sepsis** (most common)
    2. **Meningococcemia**
    3. Massive **trauma**
    4. **Burns**
    5. **Obstetric complications** (abruptio placenta, amniotic fluid embolism)
    6. Severe **pancreatitis**
    7. **Adenocarcinomas** of the GI tract, **pancreas**
    8. Acute **promyelocytic leukemia** (M3)
    9. **Transfusion** reaction
    10. **Rhabdomyolysis**
    11. Large aortic **aneurysms** and/or giant **hemangiomas** (localized DIC)
    12. **Snakebites**
- DIC may be classified as **acute** (**most** causes of DIC) or **chronic** (e.g. **solid malignancies**, **retained** products of conception)
- Pathophysiology: **activation** of **coagulation cascade** → generation of **thrombin** → **diffuse microthrombi** formation → **consumption** of **platelets** and **coagulation factors** + microangiopathic **hemolytic anemia** + activation of **fibrinolysic system** → diffuse **combined-type bleeding** ± thrombosis
- Clinical features → symptoms/signs of **underlying disease** + **bleeding** from **venipuncture sites** and/or surgical wounds, **petechiae**, purpura, ecchymoses, **GI tract** and/or **GU tract** bleeding, **hematomas** ± evidence of **thrombosis** (e.g. **skin necrosis**, gangrene, stroke, MI, **DVT/PE**) ± manifestations of **acute hemolysis** (e.g. acute renal failure, jaundice)
- Lab findings → ↓ **platelet** count, ↑ **PT** and **aPTT**, ↓ **Hb** and Hct, ↓ **fibrinogen** and ↑ **D-dimer** levels (fibrin-split products)
- Blood smear → **evidence** of **traumatic hemolysis** (**schistocytes** → helmet cells, triangle cells, etc.)
- Management:
    1. **Treatment**/correction of **underlying** disease (**most important**)
    2. **FFP** (fresh frozen plasma) for ↑ **PT/aPTT**
    3. **Cryoprecipitate** for ↓ **fibrinogen**
    4. **Platelet** transfusions for **thrombocytopenia**
    5. **Heparin** only for **chronic DIC** with evidence of **thrombosis**

# Transfusion Reactions

## Acute Hemolytic Transfusion Reaction

- **Most life-threatening** of all transfusion reactions (but pretty **uncommon**)
- **Secondary** to **ABO incompatibility** (80% of cases)
- **Clerical errors** being the **most common** cause
- **Females** > Males
- Pathophysiology: **preformed IgM** antibodies against **donor RBCs** → coating of RBCs and **activation of complement** cascade → complement-mediated **intravascular hemolysis**
- Clinical features → **sudden onset** of fever/**chills**, **abdominal** and/or **back pain**, **hypotension**, **chest pain**, shortness of breath, **bleeding**/**pain**/discomfort at the **venipuncture site**, and/or **flushing**, developing **within minutes to hours** after **initiation** of transfusion
- Complications → **acute renal failure, DIC**
- Diagnosis → positive **direct Coombs** test
- Management:
    1. Step 1 → **stop transfusion**
    2. Step 2 → IV **fluids** and **furosemide** ± urine **alkalinization**
    3. Step 3 → **do not resume transfusion**

## Delayed Hemolytic Transfusion Reaction

- **More common** than acute hemolysis
- Secondary to **Rh** and/or **Kidd** antigen **incompatibility**
- **Females** > Males
- More common in patients with **sickle cell disease**
- Develops **1-4 weeks** after transfusion
- Pathophysiology: **preformed antibodies** at **low titers** → exposure to antigen → **anamnestic response** → **rise** in antibody **titer** → mild/moderate **hemolysis**
- Clinical features → **asymptomatic** (detected as **unexplained fall** in **Hb** and/or **Hct**) to symptoms/signs of **acute intravascular hemolysis**
- Management:
    1. **Mild** reaction → **identify** the cause; **avoid future** exposure to the offending antigen
    2. **Severe** reaction → as above + IV **fluids** and **furosemide** ± urine **alkalinization**

## Febrile Non-hemolytic Transfusion Reaction

- **Most common** transfusion reaction (3% of cases)
- Secondary to **preformed antibodies** against donor **WBC HLA** molecules ± release of **cytokines** from **stored WBCs**
- Clinical features → ↑ **fever**/**chills** ± headache, arthralgias, myalgias, developing ~ **1 hour** after **initiation** of transfusion
- Management:
    1. Step 1 → **stop transfusion**
    2. Step 2 → administration of **acetaminophen**
    3. Step 3 → **resumption** of transfusion
- Prevention → **acetaminophen** prophylaxis **before** transfusion ± **leukoreduction** (leukodepleted blood products)

## Allergic (Urticarial) Transfusion Reaction

- **Most common** transfusion reaction (3% of cases)
- Secondary to **preformed antibodies** against donor **serum proteins**
- Clinical features → **urticaria** (not generalized), **edema** developing **during** and/or **immediately** after transfusion
- Management:
    1. Step 1 → **stop transfusion**
    2. Step 2 → administer **diphenhydramine**
    3. Step 3 → **resumption** of transfusion
- Prevention → **diphenhydramine** immediately **before** transfusion

## Anaphylactic Transfusion Reaction

- Develops in persons with **IgA deficiency**
- Pathophysiology: presence of **anti-IgA** antibodies of **IgG type** → **complement** activation → generation of **anaphylatoxins**
- Clinical features → **similar** to acute hemolytic transfusion reaction ± **sudden onset** of **severe bronchospasm**, generalized **urticaria**, **hypotension**/shock
- Management:
    1. Step 1 → **stop transfusion**
    2. Step 2 → administer **epinephrine, IV fluids, diphenhydramine** and **steroids**
    3. Step 3 → **do not resume** transfusion
- Prevention → **use** of **washed** blood products and **IgA-deficient plasma**

## Other Transfusion Reactions

- **Volume overload** →
    1. Common in patients with **existing CHF**
    2. **Asymptomatic** to symptoms/signs of **acute pulmonary edema**
    3. Management → **Slow**/stop transfusion + **IV furosemide**
- **Acute lung injury** →
    1. **Second** most common cause of **mortality**
    2. **Acute** onset of **respiratory distress** + noncardiogenic **pulmonary edema**
    3. Management → **supportive** (oxygen, mechanical ventilation, etc.)
- **Post-transfusion purpura** →
    1. **Severe thrombocytopenia** developing **5-12 days** after transfusion
    2. Secondary to preformed **anti-HPA1a** (anti-platelet) antibodies
    3. **Sudden onset** of widespread **purpura** ± GI and/or GU **bleeding**
    4. Management → **IVIG** ± steroids
- **Graft-versus-Host Disease** →
    1. Secondary to transfusion of **non-irradiated** blood products to **immunocompromised** patients
    2. **Bullous** skin **rash** + fever + **watery**/bloody **diarrhea** + **pancytopenia**
    3. Prevention → use of **irradiated** blood products
- **Infectious** complications (e.g. **HBV, HCV**, **HIV,** HTLV-1, etc.)
- **Dilutional** thrombocytopenia →
    1. Secondary to **massive blood transfusion**
    2. **Bleeding** from **cut surfaces** and/or **venipuncture sites**
    3. Management → **platelet** transfusion
- **Hypocalcemia** → secondary to ↑ **citrate content**
- **Hypothermia** → prevent using the **heat-exchange** device to **warm blood**

# Anticoagulation, General Principles

## Heparin

- Mechanism of action → ↓ **thrombin** and factor **Xa activity** secondary to ↑ **inhibitory** action of **antithrombin III**
- Side effects → ↑ risk of **hemorrhage**, **thrombocytopenia**, ↑ LFTs, **hyperkalemia**, alopecia, **osteoporosis**
- Contraindications → **active bleeding** and/or bleeding **tendency**, history of **HIT**
- Overdose (usually **manifested as bleeding**) → **protamine** sulfate (side effects include **hypotension,** bradycardia, **anaphylactic** reaction)
- Monitoring → **aPTT** (target **1.5-2.5** times normal)
- Resistance → consider **antithrombin III deficiency**

## Warfarin

- Mechanism of action → ↓ **γ-carboxylation** of **vitamin K – dependent clotting factors** (**II, VII, IX** and **X**) and **anticoagulants** (proteins **C** and **S**) secondary to **functional deficiency** of **vitamin K** (warfarin → inhibition of vitamin K epoxide reductase)
- Side effects → ↑ risk of **hemorrhage**, **skin necrosis** (especially in patients with **protein C deficiency**), **teratogenic** (e.g. epiphyseal stippling)
- Contraindications → **active bleeding** and/or bleeding **tendency**, **pregnancy**
- Overdose → **vitamin K** ± **fresh-frozen plasma** (*see below*)
- Monitoring → **INR** or PT (*see below*)
- Resistance → consider **vitamin K** supplementation

## Target INR

| Target INR value/range | Medical Condition |
|---|---|
| **INR 2 (**range **1.5 – 2.5)** | **Primary prophylaxis** |
| **INR 2.5 (**range **2 – 3)** | **Most** warfarin **indications** |
| **INR 3 (**range **2.5 – 3.5)** | **Mechanical heart valves**<br>prophylaxis of **recurrent MI** |

## Supratherapeutic INR (warfarin overdose)

- **INR < 5 → lower**/omit **next** warfarin **dose** ± PO **vitamin K**
- **INR** > **5** but < **9 → omit next 1-2** warfarin **doses** + **resume** warfarin at a **lower dose**
- **INR > 9 → stop warfarin** + PO **vitamin K** + **resume** warfarin at a **lower dose**
- **Any INR** + active **bleeding → stop warfarin** + **fresh-frozen plasma** + IV **vitamin K**
- **Any INR** + **life-threatening bleeding →** as above ± recombinant **VIIa concentrates**