Anemia

- Anemia is defined as the reduction in one or more of the major RBC measurements: Hb, PCV or RBC count
- Anemia thresholds:
  - Women: 12
  - Men: 13
  - Pregnant: 11
- Causes of anemia:
  - Decreased production
  - Blood loss
  - Hemolysis
- Any anemia history should include:
  - Bleeding history
  - Systemic illness
  - Dietary history
  - Family history
  - Surgical history
  - Drug history
- Anemia syndrome (due to tissue hypoxia)
  - Dizziness
  - Fatigue
  - Shortness of breath
  - Headaches
  - Palpitations
- Any exam of anemic patient should include:
  - Liver and spleen exam
  - Signs of systemic disease
- Blood parameters:
  - MCV = PCV/# RBC 88±8
  - MCH = Hb/#RBC 28±2
  - MCHC MCH/MCV 34±2
- Corrected reticulocytes count: actual PCV/Normal PCV x reticulocyte correction factor
- Serum iron: amount of iron bound to transferrin
- TIBC: amount needed to bind all transferrin
- Percent saturation: amount of transferrin bound to iron expressed as a percentage
- Ferritin: amount of iron in the stores
<table>
<thead>
<tr>
<th></th>
<th>Iron def. anemia</th>
<th>Anemia of chr. Dis.</th>
<th>thalassemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCV</td>
<td>Low</td>
<td>Normal/low</td>
<td>low</td>
</tr>
<tr>
<td>Serum iron</td>
<td>Low</td>
<td>low</td>
<td>Normal/high</td>
</tr>
<tr>
<td>TIBC</td>
<td>High</td>
<td>low</td>
<td>normal</td>
</tr>
<tr>
<td>% saturation</td>
<td>Low</td>
<td>low</td>
<td>Normal/high</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Low</td>
<td>Normal/low</td>
<td>Normal/high</td>
</tr>
</tbody>
</table>

- Ferritin is one of the best markers of iron deficiency anemia
- RDW: RBC distribution width; it measure variation in RBC volume, it ranges from 11/5% to 14.5%
- Follow up for IDA:
  - CBC every 3 months
  - Ferritin every 3 months
- Pathogenesis of anemia of chronic disease:
  - Decrease erythropoietin production
  - Suppression of erythroid progenitors
  - Blockade of reticulo-endothelial iron release
- Anemia is not a final diagnosis
- Hb electrophoresis does not give good results unless IDA is corrected
- Rule of 3:
  - Hb x 3 = PCV
  - #RBC x 3 = Hb
- Clues to macrocytic anemia:
  - Large beefy tongue
  - Associated autoimmune diseases such as vitilligo, TIDM, and autoimmune thyroid disease.
  - Neurological symptoms are more common with B12 deficiency (compared to folate deficiency)
  - Pernicious anemia is an autoimmune disease that is the end result of atrophic body gastritis
  - Positive parietal cell and intrinsic factor antibodies
  - The schilling test: test used to diagnose pernicious anemia
  - Causes of macrocytic anemia:
    - B12 deficiency
    - Folate deficiency
    - Chronic PPI use
    - Ileal disease or resection
  - Folate can correct B12 deficiency hematologically but not neurologically
  - Complications: subacute combined degeneration of spinal cord
  - Treatment:
    - No blood transfusion
    - Vitamin B12 injection daily for 7 days then monthly for life
- Thyroid function and DM monitoring
  o Response to treatment:
    ▪ Megaloblastic changes disappear in 2 days
    ▪ Fall of serum LDH in 2 days
    ▪ Reticulocytosis in 3-4 days
    ▪ Rise in Hb concentration in 10 days and normalization in 10 weeks
  o During early treatment, watch out for severe hypokalmia

- Myelodysplastic syndrome:
  o a spectrum of heterogenous myeloid clonal disorders characterized by:
    ▪ Ineffective hematopoeisis
    ▪ Dysmorphic cells
    ▪ Pancytopenia
    ▪ Frequent progression to AML
  o Increase in MCV and splenomegaly: think of MOS
  o Peak incidence occurs at age 60
  o 50% have cytogenic abnormality; most commonly deletion 5q
  o IPSS: international prognostic scoring system. It depends on:
    ▪ % of BM blasts
    ▪ Karyotype
    ▪ Cytopenia
  o The lesser the IPSS score, the better the prognosis
  o Survival ranges between 6 months and 6 years.
  o WHO classification based prognostic scoring system (WPSS): here, transfusion requirement is added as a prognostic variable
  o Treatment:
    ▪ Best supportive care including iron chelation
    ▪ Hemopoietic growth factor
    ▪ Immunomodulatory drugs
    ▪ Chemotherapy
    ▪ Stem cell therapy

- Hemolytic anemia:
  o Clues:
    ▪ Jaundice
    ▪ Increased LDH
    ▪ Indirect bilirubenemia
    ▪ Polycythemia
    ▪ Supravital stain
    ▪ Erythroid hyperplasia in bone marrow
  o Spherocytosis:
    ▪ Hereditary spherocytosis
- Autoimmune hemolytic anemia
  - If the RBC lifespan is >20 days, there will be no symptoms:
  - It can be classified into:
    - Congenital:
      - Membrane defects such as hereditary spherocytosis
      - Enzymopathies in cases of G6PD and PK deficiencies
      - Hemoglobinopathies: thalassemia and sickle cell anemia
    - Acquired:
      - Immune mediated
      - Non-immune mediated
  - A different classification:
    - Extravascular hemolysis: ingested by reticuloendothelial cells in the liver and spleen
    - Intravascular:
      - Very toxic metabolites
      - Decreased serum haptoglobin
      - Hemoglobinurea and hemosidenuria

- Consequences of hemolytic anemia:
  - Splenomegaly
  - Gallstones (small and multiple)
  - Dark urine
  - Increased folate requirement
  - Aplastic crisis due to parvovirus B19

- Warm autoimmune hemolytic anemia:
  - Causes extravascular hemolysis
  - IgG mediated
  - Positive Coomb’s test
  - Etiology:
    - Primary: 45%
    - Secondary: 40%:
      - Lymphoproliferative disease
      - Connective tissue disease
      - Infections
      - Drugs (especially methyldopa)
  - MCV: normal to high
  - Treatment:
    - Prednisone 1mg/kg/day for two weeks then taper
    - Rituximab
    - IVIG

- Cold autoimmune hemolytic anemia:
Rare
- Signs and symptoms exacerbated by cold
- IgM mediated
- Associated with mycoplasma infection
- Therapy is ineffective
- It is more severe than the warm type because it is intravascular.
- It is caused by:
  - Mechanical damage: microangiopathic hemolytic anemia
  - Chemical damage
  - Infection
  - Transfusion reaction
- Differential diagnosis of microangiopathic hemolytic anemia:
  - TTP
  - HUS
  - DIC
  - Pre-eclampsia/HELLP
  - Vasculitis
  - Malignant hypertension
- Congenital hemolytic anemias:
  - G6PD deficiency:
    - Ranges from asymptomatic to severe intravascular hemolysis
    - Triggers:
      - Drugs: primaquine, sulphamide antibiotics, sulfur-containing drugs, Henna in infants.
      - Infections
    - Mediterranean and African (A') are the most clinically significant
    - Enzyme activity is scarcely detectable in the Mediterranean type, but is normal in the African type
    - X-linked caused by single point mutations
    - G6PD Mediterranean is caused by 563 C->T
    - If there is red urine, think of hemolysis
- Hereditary spherocytosis:
  - Autosomal dominant
  - Clinical severity is highly variable
  - Presents with gallbladder stones
  - No consensus for splenectomy indications
  - Increased osmotic fragility
  - -ve DAT
  - Mutation in ankyrin
Mutation in spectrin

Sickle cell:

- Autosomal recessive
- Point mutation in beta globin gene (Glu → Val)
- Common in blacks
- Hb electrophoresis confirms the diagnosis and distinguished between SS, AS, and other variants

Consequences:
  - Chronic hemolytic anemia
  - Increased susceptibility to infections
  - Vaso-occlusive crisis: most common complication

Organs susceptible to vascular injury:
  - Lung
  - Brain
  - Ankle
  - Penis

Crises:
  - Vaso-occlusive crisis
  - Aplastic crisis
  - Sequestration crisis

Predisposing factors:
  - Hypoxia
  - Cold
  - Acidosis
  - Stress
  - Fever
  - Infection
  - Dehydration

50% of vaso-occlusive pain occurs in the lumbar spine.

Management of painful events:
  - Use hypotonic fluid and limit volume to avoid overhydration
  - Treat any underlying illness
  - Opioids (pethidine is not recommended)
  - Blood transfusion is indicated in uncomplicated pain episode

Prevention of pain episodes: Hydroxyurea: increases fetal hemoglobin. Side effects: leukopenia

Pain episodes last 5-7 days

Avascular necrosis of the hip occurs in 33%
• May have abnormal finger shape
• Acute chest syndrome:
  o Emergency
  o Can lead to death
  o Multifactorial: rib infarcts, pulmonary fat embolism, anf infection
  o 6% mortality rate
  o Treatment:
    ▪ Incentive spirometry
    ▪ Treat possible infection
    ▪ Bronchodilators and oxygen
    ▪ RBC transfusion
• Indications for transfusion in sickle cell patients:
  o Stroke
  o Acute chest syndrome
  o Aplastic crisis preoperative treatment
  o Splenic sequestration
  o Symptomatic anemia

- Thalassemia:
  o Beta thalassemia: chromosome 11
  o (B)→ normal, (B+)→ mutated with some activity, (B0) mutated with no activity
  o Features:
    ▪ Bosssing
    ▪ Expansion of bone marrow
    ▪ Hair on end sign
    ▪ Stunted growth
    ▪ Iron overload: heart, liver, endocrine gland, and skin
  o Treatment:
    ▪ Blood transfusions (more than sickle cell patients)
    ▪ Iron chelation (deferroxamine, oral deferasirox)
    ▪ Allo-bone marrow transplant (curative)
    ▪ Diagnosis by Hb electrophoresis: increase HgA2

- Aplastic anemia:
  o Severe life threatening syndrome
  o Characterized by peripheral pancytopenia and accompanied hypocellular bone marrow
  o Etiology:
    ▪ Acquired:
      • Idiopathic: most cases
      • Drugs: chloramphenicol

- Chemicals
- Infections: infectious mononucleosis
  - Congenital:
    - Fanconi anemia
    - Familial aplastic anemia
  - Features:
    - Anemia syndrome
    - Neutropenia syndrome
    - Thrombocytopenia syndrome
    - No splenomegaly
  - Treatment:
    - Remove causative agent
    - Supportive:
      - Treat infections
      - Treat bleeding
      - Transfusion
    - Immune-suppressants
    - Bone marrow transplant in patients <50
    - Delay transfusion due to possible graft vs host disease
Bleeding disorders

- Extrinsic pathway: tissue factor increases the activity of factor VII
- Intrinsic pathway: factor XII $\rightarrow$ XI $\rightarrow$ IX
- Common pathway: factor X $\rightarrow$ V $\rightarrow$ II (thrombin)
- Factor XIII stabilizes fibrin
- Factor VII can be activated by factor IX
- Gamma carboxylase is dependent on vitamin L
- Warfarin blocks vitamin K dependent factors
- PT $\rightarrow$ extrinsic pathway
- PTT $\rightarrow$ intrinsic pathway
- Thrombin time (TT) $\rightarrow$ common pathway
- Hypocalcemia does not cause bleeding; very low levels of calcium are enough
- BT (bleeding time) VWD and thrombocytopenia
- Prolonged bleeding time does not predict excess surgical blood loss
- The most important thing before a surgery is a good history
- Hemophilia:

<table>
<thead>
<tr>
<th>Factor deficiency</th>
<th>Hemophilia A</th>
<th>Hemophilia B</th>
</tr>
</thead>
<tbody>
<tr>
<td>inheritance</td>
<td>VIII</td>
<td>IX</td>
</tr>
<tr>
<td>Incidence in males</td>
<td>1/10,000</td>
<td>1/50,000</td>
</tr>
</tbody>
</table>
| complications     |              | Soft tissue bleeding and compartment syndrome

- Clinically, they are the same
- Severity is related the factor level
- We administer factor 8 at a lower dose, it has a short t $\frac{1}{2}$
- We administer factor 9 at a higher dose, it has a long t $\frac{1}{2}$

Clinical features of bleeding disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Platelet</th>
<th>Coagulation factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petichiae</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Site of bleeding</td>
<td>Skin, mucus membranes</td>
<td>Deep in soft tissues</td>
</tr>
<tr>
<td>Ecchymoses</td>
<td>Small, superficial</td>
<td>Large, deep</td>
</tr>
<tr>
<td>Hemarthrosis</td>
<td>rare</td>
<td>common</td>
</tr>
<tr>
<td>Bleeding after injury</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Bleeding after surgery</td>
<td>Immediate, usually mild</td>
<td>Delayed, often severe</td>
</tr>
</tbody>
</table>

- Coagulation factor disorders:
  - Inherited:
    - Hemophilia A and B
    - VonWillebrand’s disease (manifests as a platelet disorder)
    - Other factors deficiency
  - Acquired:
    - Liver disease
- Vitamin K deficiency or warfarin overdose
- DIC

- F8 gene on chromosome X
- F8 intron 22 inversion is responsible for 45% of cases of hemophilia A
- Severity is related to factor level
  - <1%: severe spontaneous bleeding
  - 1-5%: moderate bleeding with mild injury
  - 5-25%: mild bleeding with surgery or trauma

- Management of hemophilia A
  - Treat acute attacks with factor replacement
  - Analgesics
  - Evacuate for synovectomy (chemical, surgical)
  - Long term prophylaxis
  - Education, genetic counseling
  - Screen for inhibitor twice yearly since therapy is different
  - FVIII: recombinant or plasma derived
  - Complications of therapy (formation of inhibitors)
    - 10-15% of severe hemophilia A patients
    - 1-2% of hemophilia B patients

- VonWillebrand’s disease:
  - Labs:
    - Bleeding time: increased, normally below 10
    - PTT: increased
    - Factor VIIIc decreased, reduced because vWF is needed to carry it
    - vWFAg: decreased
    - INR: normal
    - Platelets: normal
    - Clot retraction: normal; used to exclude Glanzmann thromb.
  - vWFactor:
    - synthesized in endothelium and megakaryocytes
    - forms large multimer
    - carries factor VIII
    - anchors platelet to subendothelium
    - bridge between platelets
  - vWD
    - autosomal dominant
    - incidence: 1/10,000
    - causes mucocutaneous bleeding, but may manifest like hemophilia A
  - lifespan of factor VIII is reduced from 12-20 hours to <2 hours
  - Types:
- Type 1: partial quantitative deficiency (most common)
- Type 2: qualitative
  - Type 2A
  - Type 2B:
    - Here only the large multimers are absent
    - Association with hyperaggregation. Here, we also have thrombocytopenia, so we cannot give DDAVP.
- Type 3: total quantitative deficiency

<table>
<thead>
<tr>
<th>vWF assay</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>vWF antigen</td>
<td>decreased</td>
<td>normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>vWF activity</td>
<td>decreased</td>
<td>decreased</td>
<td>Decreased0</td>
</tr>
<tr>
<td>Multimer analysis</td>
<td>normal</td>
<td>Normal/abnormal</td>
<td>Absent</td>
</tr>
</tbody>
</table>

- Acquired vonWillebrand syndromes:
  - Immune mediated
  - Proteolysis
- Treatment:
  - Cryoprecipitate: fibrinogen, factor VIII, and vWF
  - DDAVP (vasopressin, antidiuretic hormone)
    - Stimulates vWF secretion from endothelium
    - Used for mild type 1
  - Factor VIII concentrate (Humate P): used for types 2 and 3

- DIC:
  - Mechanism is through systemic activation of coagulation which leads to:
    - Intravascular deposition of fibrin which leads to thrombosis of small vessels with organ failure
    - Depletion of platelets and coagulation factors which leads to bleeding
  - Circulatory thrombin is responsible for the consumption of all the factors
  - Increased PTT, PT, TT, and increased dimmers.
  - Increased fibrin degradation products
  - Schistocytes
  - Decreased fibrinogen, decreased platelets, and increased BT
- Triggers:
  - Sepsis
  - Trauma
  - Malignancy
  - Obstetric complications
  - Vascular disorders
  - Toxins
- Immunological disorders
  - These triggers work by:
    - Release of tissue factor or thromboplastic substances into the circulation
    - Widespread injury to endothelial cells
  - Treatment:
    - Treat the underlying cause
    - Platelet transfusion
    - Fresh frozen plasma
    - Coagulation inhibitor concentrate (antithrombin)
    - Anticoagulation with heparin
    - Monitor PT, PTT, DD, fibrinogen degradation products, and platelet count
- Thrombophilia workup:
  - Mutations: methyldihydrofolate reductase (the most common)
  - Factors:
    - Factor V laden
    - Protein C, S
    - Antithrombin 3 (most severe)
    - Factor VIII
    - Antiphospholipid antibody
- Glanzmann throbasthenia
  - Defect of platelet aggregation
  - Life-long mucosal bleeding
  - Ovarian bleeding bleeding in closed spaces
  - Treatment is supportive (transfusion)
  - Labs:
    - Normal platelet count and morphology
    - Prolonged bleeding time
    - Absent or impaired clot retraction
    - No aggregation with physiological aggregating agent (light doesn’t pass through the plasma mixture). These agents include ADP, thrombin, and collagen
    - Absent or reduced GPIIb-IIIa
    - Normal PT, PTT, and TT
  - Common in Jordan
  - Autosomal recessive
  - no binding of fibrinogen
**Platelet disorders**

- **Types:**
  - Quantitative:
    - Abnormal distribution
    - Dilution effect
    - Decreased production
    - Increased destruction
  - Qualitative:
    - Inherited:
      - Defects of platelet adhesion: Bernard Soulier disease, von Willbrand disease
      - Defects of platelet secretion
      - Defects of platelet aggregation (thrombasthenia)
    - Acquired:
      - Medications (aspirin, NSAID’s)
      - CKD
      - Cardiopulmonary bypass

- **Platelet transfusion complications:**
  - Transfusion reaction:
    - Higher than in RBC transfusions
    - Bacterial contamination
  - Platelet transfusion refractoriness:
    - Allo-immune
    - Non-immune:
      - Microangiopathic hemolytic anemia
      - Coagulopathy
      - Splenic sequestration
      - Fever and infection
      - Medications: vancomycin, interferons

- **ITP (AKA ATP)**
  - Increased platelet destruction mediated by autoantibodies
  - Characterized by decreased production of platelets despite increased megakaryocytes in bone marrow
  - Treatment:
    - 50,000 platelet count is considered the safe cutoff value; therefore, treatment depends on platelet count:
      - > 50,000: no symptoms, no treatment
      - 50,000: if the patient is not bleeding, no treatment. If the patient is bleeding administer steroids, IVIG, or antiD
• <20,000: if the patient is not bleeding, administer steroids. If the patient is bleeding, administer steroids, IVIG, antiD and admit.

Curative therapy:
• Splenectomy
• Rituximab

Rescue therapy:
• High dose steroids
• IVIG or anti-D

Chronic therapy: many agents including thrombopoietin agonists

• Steroids increased platelet count by increased apoptotic death of autoantibody producing lymphocytes and down regulation of macrophage activity responsible for platelet destruction

• IVIG increases the platelets by overwhelming the reticuloendothelial system. It interferes with platelet destruction

• Anti-D: is an Ig directed against the D antigen of RH blood group system, it raises platelet count by saturation macrophage Fc receptor with anti-D coated RBC’s

• Follow up for secondary causes of ITP such as SLE and lymphoproliferative neoplasms.

• If female, monitor during pregnancy and delivery. Make sure to provide adequate post-delivery care and avoid using forceps for delivery

  o Flashback:

   ▪ Thrombocytopenia associated with shortened survival:

     • Immune mediated thrombocytopenia:
       o ITP
       o TTP
       o Heparin induced thrombocytopenia (HIT)
       o Drug induced thrombocytopenia

     • Non-immune destruction of platelets:
       o DIC
       o Sepsis

     • Multifactorial thrombocytopenia:
       o Hospital associated
       o Cancer associated

  o Thrombocytopenia:

    ▪ Associated with bleeding:
      • ITP
      • Drug induced

    ▪ Associated with thrombosis:
      • TTP
- DIC
- Trousseau’s syndrome
- HIT

○ Heparin induced thrombocytopenia:
  ▪ Suspected in:
    - Normal platelet count prior to heparin with decline to <100,000 or reduction of platelet count by 50%
    - Onset of thrombocytopenia by day 14
    - Any new thrombotic event while on heparin
    - Skin inflammation or necrosis at heparin injection site
    - Exclusion of other causes of thrombocytopenia
  ▪ Outcome in HIT patients:
    - New thrombosis in up to 50%
    - Amputation in 10%
    - Death in 10-20%
  ▪ 6 principles of treatment in HIT:
    - 2 do’s
      - Stop heparin
      - Start new anticoagulant: donnaparoid, lepirudin, or argatroban
    - 2 don’t
      - No warfarin until substantial platelet count recovery
      - No platelet transfusion
    - 2 diagnostics:
      - Labs for HIT
      - Duplex for lower limb
  ○ TTP:
    ▪ Pentad of findings:
      - Fever
      - Neurologic changes
      - Renal impairment
      - Thrombocytopenia (<20,000)
      - Microangiopathic hemolytic anemia (schistocytes), Hgb <10, and lab findings of hemolysis
    ▪ Other findings:
      - Severe deficiency of ADAM-TS13
      - PT, PTT, TT are normal (unlike DIC)
      - MRI may show leukoencephalopathy or brain infarcts
- ADAM-TS13 is vWF protease; its deficiency causes ultra large multimer production which predisposes to thrombus formations
  - Differential: HUS; however, in HUS ADAM-TS13 is normal
  - Treatment:
    - Initial treatment: plasma exchange (plasmapheresis) daily
    - Relapse: plasmapheresis + rituximab (anti CD20)
    - Other treatment:
      - Vincristin
      - Splenectomy
      - Steroids
      - Aspirin
    - Monitor LDH, platelets, clinical status, and ADAM-TS13
    - LDH correlates with disease activity
  - Veno-thrombo embolism (VTE):
    - Causes:
      - Genetic
      - Environmental
      - Triggers
    - Risk factors:
      - Stasis
      - Hypercoagulability
      - Endothelial damage
    - Prophylaxis:
      - Pharmacological prophylaxis reduces DVT and PE by 50-65%
      - Bleeding risk is rare
      - HIT → 2.4% with unfractionated heparin, 0.06% with LMWH
      - Prophylaxis reduces VTE’s burden
    - Homozygous factor V laden patients have a very high risk for developing VTE (20-30%)
    - Importance of VTE:
      - Preventable
      - Life-threatening
      - Long term complications
      - Common
      - Costly
    - The burden of VTE:
      - DVT:
        - 40% develop post thrombotic syndrome
        - 30% develop PE:
- 3% death
- 5% pulmonary hypertension
- Patients >45 years of age are at a greater risk for VTE
- Post DVT syndrome:
  - Pain (aching and cramping)
  - Heaviness
  - Itching
  - Swelling
  - Varicose veins
  - Brownish skin discoloration
  - Ulcers
- Treatment:
  - Unfractionated heparin
  - LMWH
  - Overlap of heparin and warfarin
- Other medications:
  - Thrombolytic therapy
  - Thrombectomy
  - IVC filter
  - Embolectomy
- Duration of treatment is individualized
- Heparin’s side effects:
  - HIT (early and late)
  - Bleeding
  - Hypersensitivity
  - Osteoporosis
  - Increased thyroxin
  - Dermatologic (alopecia)
  - Metabolic (hypokalemia, hyponatremia, and hypertriglyceremia)
- Heparin’s antidote: protamine sulfate
- LMWH antidote: factor X + fresh blood
- Warfarin:
  - Plasma concentration peaks 2-8 hours after oral dose
  - 99% bound to albumin
  - T 1/2: 25-60 hours
  - Inhibits vitamin K dependent factors: prothrombin, factor VII, IX, and X.
  - Inhibits protein C and S
The 1st factors to decrease after warfarin administration are factor VII and protein C
It takes 3-5 days for warfarin to start working; we usually bridge the patients using heparin

- Warfarin resistance (>20 mg per day with subtherapeutic INR)
  - Non-compliance
  - Lab errors
  - Excessive vitamin K intake
  - Mutations (rare)

- Warfarin sensitivity: (<2 mg per day with high INR)
  - 15% of Caucasians
  - Cytocrome p450 polymorphism that decreases the rate of metabolism

- Side effects of warfarin:
  - Bleeding (treated with vitamin K or fresh frozen plasma)
  - Birth defects and abortion
  - Skin necrosis
Blood transfusion

- ABO system:
  - O antigen is made of H substance
  - A antigen is made of H substance + N-acetylgalactosamine
  - B antigen is made of H substance and galactose

- Blood types, antibodies and antigens:
  - A: A antigen on RBC, serum anti B
  - B: B antigen on RBC, serum anti A
  - AB: A and B antigen on RBC, no serum antibodies
  - O: no antigens on RBC, serum anti A and anti B

- O plasma is not a common donor because it has anti-A and anti B while O RBC is a common donor

- Blood donor criteria:
  - Age (17-65)
  - Weight >50
  - Contact with infection
  - General health
  - Specific illness

- Whole blood donation (500 mL); then it can be centrifuged:
  - 200 mL of packed RBC
  - Platelets with plasma (can be centrifuged)
    - Platelet concentrate (50 mL): 5 days shelf life
    - Plasma (fresh frozen): 250 mL; one year shelf life

- Leukodepletion:
  - Universal leukodepletion introduced in 1999 to reduce the risk of vCJD transmission by blood
  - Other benefits: less febrile reaction, less alloimmunization, less GVHD, and less CMV

- Blood donation testing:
  - Microbiology markers
  - Blood grouping and screening for high titer antibodies
  - Quality monitoring

- Washed RBCs:
  - Prevents hemolysis and anaphylaxis
  - For PNH patients and IgA deficient patients

- Irradiated RBCs:
  - Prevents GVHD
  - For immune-deficient patients

- RBCs shelf life:
  - With citrate: 28 days
- Transfusion reaction:
  - Acute:
    - Immunologic:
      - Hemolytic
      - Febrile
      - Allergic
      - TRALI
    - Non-immunologic:
      - Circulatory overload
      - Hemolytic
      - Air embolism
      - Metabolic
  - Delayed (>24 hours)
    - Immunologic:
      - Allo-immunization (HLA)
        - Hemolytic
        - Post transfusion purpura
        - Graft Vs Host disease (GVHD)
        - Immunedulation
      - Non-immunogenic:
        - Iron overload
        - Viral infections
        - Other infections
  - Protocol for all transfusion reactions:
    - Stop transfusions immediately
    - Maintain IV access with 0.9% NaCl
    - Check blood components for patient’s ID
    - Notify blood bank
    - Send blood sample and urine to blood bank
    - Keep blood unit in case culture becomes necessary
    - Support patient as necessary
  - Transfusion transmitted disease:
    - HIV: 1/500,000
    - Hep C: 1/600,000
    - Hep B: 1/500,000
    - CMV: 50% of donors are sero-positive
    - Bacteria: 1/250 with platelet transfusion
  - Platelet transfusion:
    - Platelet concentrate (random donors)
- Pheresis platelets (single donor)
  - Target levels:
    - Bone marrow suppressed patients >20,000
    - Bleeding/surgical patients >50,000
- Platelet transfusion complications:
  - Higher incidence than in RBC transfusions
  - Related to length of storage, leukocytes, or RBC mismatch
  - Bacterial contamination
- Patients with frequent platelet transfusions become refractory to transfusion because:
  - Allo-immune destruction of platelets (HLA antigen)
  - Non-immune refractoriness:
    - Microangiopathic hemolytic anemia
    - Coagulopathy
    - Splenic sequestration
    - Fever and infection
    - Medications (amphotericin, vancomycin, ATG, and interferones)
- Fresh frozen plasma:
  - Content: plasma with low factor V and VIII
  - Indications:
    - Coagulation deficiencies (liver disease and trauma)
    - DIC
    - Warfarin reversal
    - Factor VII and XI deficiencies
  - Dose: 10-15 mL/kg
- TRALI:
  - Transfusion related acute lung injury
  - Not rare, but underdiagnosed
  - Potentially fatal
  - Presents as pulmonary edema
  - Occurs within 1-4 hours of starting the transfusion
  - Clinical features:
    - Acute respiratory distress
    - Fever with chills
    - Non-productive cough
    - Cyanosis
    - Hypotension
    - Chest pain
    - Chest X-ray shows bilateral pulmonary infiltrates in the hilar region
  - Pathogenesis:
- Classical theory (immune TRALI)
  - Donor’s antibodies react with patient’s neutrophils
  - Neutrophils sequestrate in pulmonary vasculature
  - Cytokine and components are liberated
  - Damage to endothelium leading to pulmonary edema

- Two-hit theory (non-immune TRALI)
  - Predisposing condition (sepsis, surgery, trauma, or malignancy)
  - Pulmonary endothelial activation and neutrophil sequestrations
  - Lipids and WBCs antibodies activate neutrophils which causes endothelial damage

  - TRALI management:
    - Non-specific
    - Largely supportive
    - Respiratory support with \( \text{O}_2 \) and mechanical ventilation
    - Steroids

  - Note: females with previous pregnancy are not allowed to donate blood because all females produce antibodies against their husbands’ and babies’ antigens
Leukemias

- CLL:
  o The most common adult leukemia
  o Clues for diagnosis:
    ▪ Elderly >50
    ▪ Hypoglobinemia (IgA deficiencies to increased lymphocytes)
    ▪ Autoimmune hemolysis (DAT positive)
    ▪ CD19, CD 20
    ▪ Mostly asymptomatic
    ▪ Uncontrolled proliferation of mature defective B lymphocytes
  o Clinical presentation:
    ▪ Lymphocytosis:
      • Morphologically mature
      • Immunologically immature
      • Accumulation in blood, lymphatics, and bone marrow
    ▪ Enlarged lymph nodes
    ▪ Splenectomy
    ▪ Hypogammaglobulinemia: mucosal infections
  o Approach:
    ▪ Decide the type of lymphocyte T Vs B
    ▪ Determine the stage (Rai Vs Binet systems)
    ▪ Cytogenetics
    ▪ Decide therapy, prognosis, and follow-up
  o Staging (Rai/Binet systems)
    ▪ Early: 10 year median survival
    ▪ Intermediate: 5-7 years median survival
    ▪ Advanced: 1-3 years median survival
  o It is a heterogenous disease:
  o Prognostic factors:
    ▪ Lymphocytosis
    ▪ Lymph node involvement
    ▪ Organomegaly
    ▪ Anemia
    ▪ Thrombocytopenia
    ▪ Lymphocyte doubling time:
      • >1 year: good
      • <1 year bad prognosis
    ▪ VH gene mutation:
      • Unmutated: rapid progression
- Mutated: slow progression
  - Surrogate markers ZAP70 and CD38 carry a bad prognosis
  - Loss of P53 carries the worst prognosis
- Treatment criteria:
  - Symptomatic: if the patient is asymptomatic, wait until B cell symptoms appear
  - Decline in Hb or Platelets
  - Lymphadenopathy
  - Hepatosplenomegaly
  - Recurrent infections
- Treatment:
  - Rituximab- antiCD20
  - Chemoimmunotherapy
  - Chlorambucil
- CML
  - Clonal expansion of hematopoietic stem cells possessing a reciprocal translocation between chromosome 9 and 22 (Philadelphia chromosome)
  - Fusion of BCR region on chromosome 22 with ABL gene from chromosome 9
  - Has 3 phases:
    - Chronic
    - Accelerated
    - Blas crisis
  - Incidence is 1.5/100,000
  - Middle age (40-60)
  - Accounts for 20% of adult leukemias
  - Symptoms:
    - Insidious onset, accidental discovery
    - Fatigue, malaise, weight loss
    - Symptoms due to splenomegaly
    - Infections, thrombosis, bleeding
    - Gout
  - Physical examination:
    - Mild to moderate splenomegaly
    - Mild hepatomegaly
    - Rare to find lymphadenopathy except in terminal stages
  - Labs:
    - Elevated WBC’s
    - Elevated platelets
    - Normochromic, normocytic anemia
    - Basophilia
- The cytogenic hallmark t(9:22) in 95% of patients
- Accelerated phase:
  - Basophilia
  - Thrombocytopenia
  - Blasts between 10-20%
- Blastic phase:
  - Blasts >20%
  - Hypossegmented neutrophils (Petger-Het anomaly)
- Worsening of symptoms heralds progression (fever, weight loss, decreased response to treatment, and bone pain)
  - Treatment:
    - If not treated, converts into AML
  - Aims:
    - Reduce WBC: hematologic
    - Reduce gout
    - Target the molecular cause
  - Modalities:
    - Imatinib:
      - a targeted treatment; competitive inhibition of adenosine triphosphate binding site of the ABL kinase
      - 95% of patients achieved complete hematologic remission
      - 60% of patients achieved major cytogenic remission within few months
      - Side effects:
        - Main side effect is fluid retention, nauseam muscle cramps, diarrhea, and skin rashes
        - Myleosuppression is the most common hematological side effect
    - Stem cell transplant: the only definitive therapy
    - Others:
      - Gamma interferons
      - Chemotherapy
      - 2nd generation of tyrosine kinase inhibitors for failure or relapse
      - Bone marrow transplant for crisis
- Response to treatment:
  - We cannot detect any response beyond 5log ($10^{12}$-$10^{7}$)
  - PCR is the most accurate
- Mechanism of resistance to treatment:
  - Gene amplification
- Mutation at the kinase site
- Enhanced expression of multi-drug exporter proteins
- Alternative signaling pathways

- AML:
  - Clues:
    - Adult
    - Auer bodies
    - DIC – M3
    - No TdT markers
    - Blast with or without leukocytosis. The form with leukocytosis is the most common
  - Common manifestations:
    - Anemia
    - Thrombocytopenia
    - Neutropenia
    - Extramedullary infiltration: lymph nodes, skin, CNS
    - Hyperviscosity → associated with neurological symptoms
    - Release of metabolites: DIC, gout, ARF
  - Classification:
    - FAB: French-American-British classification; it is a morphological classification
    - WHO classification
    - Cytogenetic
  - Prognosis based on cytogenetics:
    - Favorable: t(15,17), PML-PARA (M3), t(8;21), inv(16), t(16;16)
    - Intermittent: t(9;11)
    - Unfavorable: t(6;9), inv(3)/t(3,3), d(7), complex karyotype
  - Promyelocytic leukemia (M3)
    - Associated t(15;17) involving the retinoic acid receptor (RAR) gene
    - Good prognosis
    - Commonly associated with DIC
    - Prominent Auer bodies
  - Treatment:
    - In general: correct Hb before chemotherapy, treated with anthracyclin and RCA
    - M3:
      - Tretinoin (all trans retinoic acid (ATRA)); an oral drug that induces the differentiation of leukemic cells bearing the t(15,17). It is not effective in other forms of AML.
• Acute M3 patients are responsive to cytarabine and daunorubicin, but about 10% of patients treated with these drugs die from DIC induced by the release of granule components by dying tumor cells.

  ▪ Tretinoin:
    • No DIC
    • Causes retinoic acid syndrome (ATRA syndrome):
      o In the first three weeks of treatment
      o Characterized by fever, dyspnea, chest pain, pulmonary infiltrates, effusion and hypoxia
      o Treatment: steroids, chemotherapy, supportive measures
      o Mortality rate: 10%
    • Other side effects:
      o Nasal stuffiness
      o Dry, red skin
      o Transient increase in ALT, AST, bilirubin and triglycerides. They rarely require any attention during treatment

- ALL:
  o Clues:
    ▪ Young
    ▪ Pancytopenia and bone marrow failure
    ▪ Immature B cells
    ▪ Positive TdT markers
    ▪ Blast → acute
    ▪ Positive periodic acid-Schiff stain (due to glycogen rich vacuoles), but negative peroxidase and negative non-specific esterase
    ▪ Can present with acute leukemia syndrome
  o Classifications:
    ▪ Morphological (FAB)
      • L1 → 75%
      • L2 → 20%
      • L3 → 5%
    ▪ Immunological classification:
      • B lineage (80%)
        o Pro-B: CD19, TdT
        o Common: CD19, TdT, CD10
        o Pre-B: CD19, TdT, CD10, cyIg (cytoplasm Ig)
        o Mature B: CD19, TdT, CD10, cyIg, smIg (surface Ig)
      • T lineage:
- Pre-T: CD7, TdT
- Mature T: CD7, TdT, CD2

- Molecular abnormalities with prognostic importance:
  - Better prognosis:
    - Normal karyotype
    - Hyperdiploidy
  - Poor prognosis:
    - t(8;14)
    - t(4;11)
  - Very poor prognosis:
    - t(9;22); Philadelphia chromosome

- Risk classification in ALL:
  - Standard risk
  - High risk
  - Very high risk

- High risk ALL:
  - Pre-T
  - Pro-B
  - Age >35
  - WBC >30 in B-ALL; >100 in T-ALL

- Treatment:
  - Determinant:
    - Risk qualification
    - Immunophenotype of leukemic cells
    - Age and biological condition
    - Goal of treatment
  - Remission induction treatment in ALL:
    - Anti-neoplastic treatment:
      - Drugs: steroid, vincristine, asparaginase, cyclophosphamide
      - Duration: 4-8 weeks
      - 1-2 courses
    - CNS prophylaxis: via methotrexate intrathecally
    - Supportive care
    - Treatment of complications
  - Post remission therapy in standard risk ALL:
    - Maintenance: 6-mercaptopurine, methotrexate
    - Intensification treatment periodically
    - CNS prophylaxis
  - Post remission therapy in high risk ALL:
    - Intensification treatment
• Hematopoietic stem cell transplant
  • Treatment results:
    • Complete remission in 80-85% of adults, and 95-99% of children
    • Leukemia free survival in 30-40% of adults and 70-80% of children
  • Splenomegaly is unusual in acute leukemias

- Acute leukemias (ABCDEF)
  o Acute
  o Blast predominance
  o Children
  o Drastic course
  o Elderly
  o Fever

- Chronic leukemias:
  o Mature predominance
  o Middle age
  o Less drastic course
  o Usually no fever

- Summary of treatment:
  o ALL: vincristin, prednisone, laspraginase, anthracyclin
  o AML: anthracyclin, cytarabin
  o Acute pro-myelocytic leukemia: all trans retinoic acid
  o CLL: no treatment if asymptomatic; clorambucil and rituximab
  o CML: imatinib, gamma interferon
  o Hodgkin (IA, IB): radiotherapy
Lymphomas

- Common features:
  o Painless lymph node enlargement
  o B-symptoms (fever, night sweats, weight loss)
  o Compression symptoms secondary to enlarged lymph nodes
  o Extra-nodal involvement
  o Needs lymph node biopsy for diagnosis
  o Each have different histology types
  o Both have similar staging systems

- Non-Hodgkin lymphoma (NHL):
  o Each type of lymphoma can be viewed as a lymphocyte arrested at a certain stage of development and transformed into a malignant cell
  o 85% are of a B-cell origin
  o 15%: T-cell or null all
  o Etiology:
    • Idiopathic: most common
    • Immune suppression:
      • Congenital (Wiskott Aldrich)
      • Organ transplant (cyclosporine)
      • AIDS
      • Aging
    • DNA repair defects:
      • Ataxia telangetasia
      • Xeroderma pigmentosa
    • Chronic inflammation and antigenic stimulation:
      • Helicobacter pylori- stomach
      • Chalmydia psittaci – ocular adnexia
      • Sjogren’s syndrome
    • Viral causes:
      • EBV and Burkitt lymphoma
      • HTLV-1 and T-cell leukemia
      • HTLV-V and cutaneous T cell lymphoma
      • Hepatitis C
  o Diagnosis:
    • Chromosome changes:
      • T(14:18) in follicular lymphoma (bcl oncogene)
      • T(8:14) and others in Burkitt lymphoma (c-myc oncogene)
      • T(11:14) in mantle cell lymphoma (cyclin D1 gene)
  o Staging:
Ann Arbor
- Same for NHL and HD
- I: 1 lymph node region or structure
- II: >1 lymph node region or structure; same side on diaphragm
- III: both sides of diaphragm
- IV: extra nodal sites, diffuse
- A: no systemic symptoms other than pruritis
- B: presence of B cell symptoms
- E: extra nodal extension

Revised European American lymphoma classification:
- Indolent: follicular
- Aggressive
- Very aggressive (Burkitt, lymphoblastic lymphoma)

- Frequency of NHL subtypes in adults:
  - 30% diffuse large B-cell
  - 20% follicular

- Prognostic factors in non-Hodgkin’s:
  - Adverse factors: age >60, stage III and IV
  - High serum LDH: indicating high turnover
  - Performance status (ECOG 2 or more)
  - More than one extra-nodal site involved

- Treatment options in advanced indolent lymphoma:
  - Observation only
  - Radiotherapy at the site of the problem
  - Systemic chemotherapy:
    - Oral agents: chlorambucil and prednisone
    - IV agents: CHOP, COP-R, FC-R
  - Anti-CD20: rituximab
  - Stem cell or bone marrow transplant

- Treatment options for aggressive lymphoma:
  - Potentially curable
  - Disseminate through blood stream: early
  - Must use systemic chemotherapy:
    - CHOP-R 8 cycles
    - CHOP-R 3 cycles followed by radiotherapy
    - Bone marrow transplant in some cases
  - CHOP-R: cycophosphamide, Hydroxydaunirubcin, vincristin, prednisone, Rituximab
  - Intrathecal chemotherapy for AIDS and CNS involvement
  - Radiotherapy for spinal cord compression and bulky disease
Hodgkin disease:
- With appropriate treatment about 85% of patients with Hodgkin’s disease are curable
- Treatment based on stage:
  - IA, IB: radiotherapy
  - IIA: chemotherapy + radiotherapy
  - IIB, IIIA, IIIB, IVA, IVB: chemotherapy with or without radiotherapy
- Chemotherapy (ABVD)
  - Adriamycin
  - Bleomycin
  - Vincristin
  - Dacarbazine

<table>
<thead>
<tr>
<th>HD</th>
<th>NHL</th>
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<tbody>
<tr>
<td>Reed strengberg cells</td>
<td>No Reed strengberg cells</td>
</tr>
<tr>
<td>Single group of axial LN</td>
<td>Multiple groups of peripheral LN</td>
</tr>
<tr>
<td>Contagious spread of LN</td>
<td>No contagious spread to LN</td>
</tr>
<tr>
<td>More constitutional symptoms</td>
<td>Less constitutional symptoms</td>
</tr>
<tr>
<td>Bimodal age (young and elderly)</td>
<td>20-40 year</td>
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</tbody>
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When you encounter an enlarged tonsil in an adult, think of NHL

Reed Sternberg cells: binucleated cells with mirror image nuclei

Multiple myeloma:
- CRAB:
  - Elevated Ca
  - Renal failure
  - Anemia
  - Bone pain
- Clinical features
  - Symptoms related to bone marrow infiltration: bone pain, osteolytic lesions and fractures, anemia, and hypercalcemia
  - Symptoms related to secretion of abnormal proteins: renal, neurological, or visceral symptoms
  - Hyperviscosity syndrome
  - Recurrent infection
  - Amyloidosis
- Mnemonic (Buy CAVIAR)
  - Lytic bone lesion visible on X-ray
  - Hypercalcemia
  - Hyperviscosity especially common in the IgM secreting myeloma
  - Bacterial infection
  - Amyloidosis
Renal failure: occurs in 50% of patients because most of the light chains are toxic to the tubules

Work-up:
- CBC and blood film: roux formation
- ESR, Ca, creatinine
- Albumin
- Bone marrow biopsy and aspirate
- Serum proteins and electrophoresis and immune-fixation
- Skeletal survey: plain X-ray better than a bone scan because lytic lesions do not show well on a bone scan
- Quantitative immunoglobulins
- Bence Jones protein

Durie-Salmon staging system for multiple myeloma disease burden (tumor load)

Stage I:
- Hb >10
- Normal bone or solitary plasmacytoma
- Low immunoglobulin spike (M-component)
  - IgG < 5, IgA <3
  - Bence Jones protein <4g/24 hours

Stage II:
- IIA: normal renal function (Cr <2)
- IIB: abnormal renal function (Cr >2)

Stage III:
- Hb <8.5
- Serum Ca >12
- Multiple lytic bone lesions on X-ray
- High M component
  - IgG >7, IgA >5
  - Bence-Jone’s protein >12g/24 hours

International staging system:
- I: good prognosis:
  - Serum albumin >3.5 g/dL
  - Serum B2 microglobulin <3.5 mg/dL
- II: between I and III
- III: B2 microglobulin >5 mg/dL

Treatment:
- Standard chemotherapy:
  - Dexamethasone and thalidomide
  - Dexamethasone and Bortezomib (Velcade)
  - Melphalan and prednisone for elderly
- High dose chemotherapy:
  - Bone marrow transplant
  - Peripheral stem cell transplant
Myeloproliferative neoplasms

- Myeloid malignancies:
  - EML
  - AML
    - Polycythemia rubra vera (PRV)
    - Essential thrombocytopenia (ET)
    - Myelofibrosis (MF)
- PRV, ET, and MF: compose the chronic myeloproliferative disorders (CMPN)
- Common features of CMPN:
  - Each has specific diagnostic criteria, but they share some characteristics
  - Increased number of one or more myeloid cells
  - Splenomegaly
  - Hypercatabolism: weight loss and gout (AML)
  - Clonal marrow hyperplasia without dysplasia
  - Predispose to evolve into AML
  - Generalized pruritis (after bathing)
  - Unusual thrombosis (Budd Chiari syndrome)
- Polycythemia rubra vera:
  - Clinical features:
    - Palpable spleen
    - Enlarged liver
    - JAKII mutation
    - Elevated leukocyte alkaline phosphatase (LAP)
    - Bone marrow shows erythroid hyperplasia and increased number of megakaryocytes
    - EPO is not diagnostic but suggestive
    - 10% converts into AML
  - Diagnostic tools:
    - JAKII mutation
    - Normal or decreased erythropoietin
    - Increased RBC with normal saturation
  - Mutations in CMPN (due to activation of STAT3/5)
    - Gain of function in JAKII, MPL, CBL
    - Loss of function in LNK and NF1
  - JAKII:
    - Gain of function presents in:
      - 95% of PRV
      - 23-57% of ET
      - 43-57% of cases of MF
Risk classification:
- Low risk:
  - Age <60
  - No previous thrombosis
- High risk:
  - Age >60
  - Previous thrombosis

Diagnostic criteria for PRV (you need A1 + A2 with one more A criteria or 2 more B criteria)
- A criteria:
  - A1: raised RBC mass
  - A2: Normal O₂ saturation and EPO
  - A3: palpable spleen
  - A4: no BCR-ABL fusion (absent Philadelphia chromosome)
- B criteria:
  - B1: thrombocytosis >400 x 10⁹
  - B2: neutrophilia: >10 x 10⁹
  - B3: radiological splenomegaly
  - Endogenous erythroid colonies

Treatment of PRV:
- Phlebotomy (Hct <45%)
- Low dose aspirin
- Hydroxyurea or interferon gamma
- Busulphan in elderly
- Manage CVS risk factors
- Allopurinol
- Increased water intake

- Treatment of ET:
  - Hydroxyurea
  - Aspirin if microvascular disturbance
  - Manage cardiovascular risk

- Myelofibrosis:
  - Teardrop cells
  - Bone marrow shows hypercellularity with grade II fibrosis