# Hematology

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**Edited by: Fareed Halteh**

# 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 transferrrin
- 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

| | Iron def. anemia | Anemia of chr. Dis. | thalassemia |
|---|---|---|---|
| MCV | Low | Normal/low | low |
| Serum iron | Low | low | Normal/high |
| TIBC | High | low | normal |
| % saturation | Low | low | Normal/high |
| Ferritin | Low | Normal/high | Normal/high |

- 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
    - 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
    - During early treatment, watch out for severe hypokalmia
- Myelodysplastic syndrome:
    - a spectrum of heterogenous myeloid clonal disorders characterized by:
        - Ineffective hematopoeisis
        - Dysmorphic cells
        - Pancytopenia
        - Frequent progression to AML
    - Increase in MCV and splenomegaly: think of MOS
    - Peak incidence occurs at age 60
    - 50% have cytogenic abnormality; most commonly deletion 5q
    - IPSS: international prognostic scoring system. It depends on:
        - % of BM blasts
        - Karyotype
        - Cytopenia
    - The lesser the IPSS score, the better the prognosis
    - Survival ranges between 6 months and 6 years.
    - WHO classification based prognostic scoring system (WPSS): here, transfusion requirement is added as a prognostic variable
    - Treatment:
        - Best supportive care including iron chelation
        - Hemopoetic growth factor
        - Immunomodulatory drugs
        - Chemotherapy
        - Stem cell therapy
- Hemolytic anemia:
    - Clues:
        - Jaundice
        - Increased LDH
        - Indirect bilirubenemia
        - Polycythemia
        - Supravital stain
        - Erythroid hyperplasia in bone marrow
    - 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
            - Hemoglobinpathies: 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-eclempsia/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:
    - Emergency
    - Can lead to death
    - Multifactorial: rib infarcts, pulmonary fat embolism, anf infection
    - 6% mortality rate
    - Treatment:
        - Incentive spirometry
        - Treat possible infection
        - Bronchodilators and oxygen
        - RBC transfusion
- Indications for transfusion in sickle cell patients:
    - Stroke
    - Acute chest syndrome
    - Aplastic crisis preoperative treatment
    - Splenic sequestration
    - Symptomatic anemia

- Thalssemia:
    - Beta thalassemia: chromosome 11
    - (B)→ normal, ($B^+$) → mutated with some activity, ($B^0$) mutated with no activity
    - Features:
        - Bossing
        - Expansion of bone marrow
        - Hair on end sign
        - Stunted growth
        - Iron overload: heart, liver, endocrine gland, and skin
    - 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:
    - Severe life threatening syndrome
    - Characterized by peripheral pancytopenia and accompanied hypocellular bone marrow
    - Etiology:
        - Acquired:
            - Idiopathic: most cases
            - Drugs: chloamphenicol

            - Chemicals
            - Infections: infectious mononucleosis
        - Congenital:
            - Fanconi anemia
            - Familial aplastic anemia
- Features:
    - Anemia syndrome
    - Neutropenia syndrome
    - Thromboccytopenia sydrome
    - 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 → XI → IX
- Common pathway: factor X → V → 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→ extrinsic pathway
- PTT → intrinsic pathway
- Thrombin time (TT) → 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:

| | Hemophilia A | Hemophilia B |
|---|---|---|
| Factor deficiency | VIII | IX |
| inheritance | X-linked recessive | X-linked recessive |
| Incidence in males | 1/10,000 | 1/50,000 |
| 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 ½
  - We administer factor 9 at a higher dose, it has a long t ½

| Clinical features of bleeding disorders | | |
|---|---|---|
| Disorder | Platelet | Coagulation factor |
| Petichiae | yes | no |
| Site of bleeding | Skin, mucus membranes | Deep in soft tissues |
| Ecchymoses | Small, superficial | Large, deep |
| Hemarthrosis | rare | common |
| Bleeding after injury | yes | no |
| Bleeding after surgery | Immediate, usually mild | Delayed, often severe |

- 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

| vWF assay | 1 | 2 | 3 |
|---|---|---|---|
| vWF antigen | decreased | normal | Decreased |
| vWF activity | decreased | decreased | Decreased0 |
| Multimer analysis | normal | Normal/abnormal | Absent |

    - Acquired vonWillbrand syndromes:
        - Immune mediated
        - Proteoloysis
    - 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: methylhydrofolate 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 districution
    - 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 (thrombastenia)
    - 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 thrombopoeitin 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
    - Anit-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 lymphoproliverative neoplasms.
    - If female, monitor during pregnancy and delivery. Make sure to provide adequate post-delivery care and avoid using forceps for delivery
- Flashback:
    - Thrombocytopenia associated with shortened survival:
        - Immune mediated thrombocytopenia:
            - ITP
            - TTP
            - Heparin induced thrombocytopenia (HIT)
            - Drug induced thrombocytopenia
        - Non-immune destruction of platelets:
            - DIC
            - Sepsis
        - Multifactorial thrombocytopenia:
            - Hospital associated
            - Cancer associated
- Thrombocytopenia:
    - Associated with bleeding:
        - ITP
        - Drug induced
    - Associated with thrombosis:
        - TTP

- DIC
- Trosseau'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 laiden 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: (<2mg 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 allo0immunization, 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

    - With adenine: 42 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 reacts 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 $O_2$ 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:
    - The most common adult leukemia
    - 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
    - Clinical presentation:
        - Lymphocytosis:
            - Morphologically mature
            - Immunologically immature
            - Accumulation in blood, lymphatics, and bone marrow
        - Enlarged lymph nodes
        - Splenectomy
        - Hypogammaglobinemia: mucosal infections
    - Approach:
        - Decide the type of lymphocyte T Vs B
        - Determine the stage (Rai Vs Binet systems)
        - Cytogenetics
        - Decide therapy, prognosis, and follow-up
    - Staging (Rai/Binet systems)
        - Early: 10 year median survival
        - Intermediate: 5-7 years median survival
        - Advanced: 1-3 years median survival
    - It is a heterogenous disease:
    - 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 hematopooetic 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%
            - Hyposegmented 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
                - $2^{nd}$ 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 daunorubcin, 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 rretinoic acid syndrome(ATRA syndrome):
    - In the first three weeks of treatment
    - Characterized by fever, dyspnea, chest pain, pulmonary infiltrates, effusion and hypoxia
    - Treatment: steroids, chemotherapy, supportive measures
    - Mortality rate: 10%
  - Other side effects:
    - Nasal stuffiness
    - Dry, red skin
    - Transient increase in ALT, AST, bilirubin and triglycerides. They rarely require any attention during treatment

- ALL:
  - 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
  - Classifications:
    - Morphological (FAB)
      - L1 → 75%
      - L2 → 20%
      - L3 → 5%
    - Immunological classification:
      - B lineage (80%)
        - Pro-B: CD19, TdT
        - Common: CD19, TdT, CD10
        - Pre-B: CD19, TdT, CD10, cyIg (cytoplasm Ig)
        - 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, asparginase, 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-mercatopurine, methtroxate
        - 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)
    - Acute
    - Blast predominance
    - Children
    - Drastic course
    - Elderly
    - Fever
- Chronic leukemias:
    - Mature predominance
    - Middle age
    - Less drastic course
    - Usually no fever
- Summary of treatment:
    - ALL: vincristin, prednisone, laspraginase, anthracyclin
    - AML: anthracyclin, cytarabin
    - Acute pro-myelocytic leukemia: all trans retinoic acid
    - CLL: no treatment if asymptomatic; clorambucil and rituximab
    - CML: imatinib, gamma intereferon
    - Hodgkin (IA, IB): radiotherapy

# Lymphomas

- Common features:
  - Painless lymph node enlargement
  - B-symptoms (fever, night sweats, weight loss)
  - Compression symptoms secondary to enlarged lymph nodes
  - Extra-nodal involvement
  - Needs lymph node biopsy for diagnosis
  - Each have different histology types
  - Both have similar staging systems
- Non-Hodgkin lymphoma (NHL):
  - Each type of lymphoma can be viewed as a lymphocyte arrested at a certain stage of development and transformed into a malignant cell
  - 85% are of a B-cell origin
  - 15%: T-cell or null all
  - Etiology:
    - Idiopathic: most common
    - Immune suppression:
      - Congenital (Wiskott Aldrich)
      - Organ transplant (cyclosporine)
      - AIDS
      - Aging
    - DNA repair defects:
      - Ataxia telangectasia
      - 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
  - 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)
  - 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, vincrystin, 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

| Comparison between HD and NHL | |
|---|---|
| HD | NHL |
| Reed strengberg cells | No Reed strengberg cells |
| Single group of axial LN | Multiple groups of peripheral LN |
| Contagious spread of LN | No contagious spread to LN |
| More constitutional symptoms | Less constitutional symptoms |
| Bimodal age (young and elderly) | 20-40 year |

- When you encounter and 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: roloux 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 Jone's 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 $B_2$ microglobulin <3.5 mg/dL
        - II: between I and III
        - III: $B_2$ microglobulin >5 mg/dL
    - Treatment:
        - Standard chemotherapy:
            - Dexa and thalidomide
            - Dexa and Bartezomib (Velcade)
            - Melphalane 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 $O_2$ saturation and EPO
            - A3: palpable spleen
            - A4: no BCR-ABL fusion (absent Philadelphia chromosome)
        - B criteria:
            - B1: thrombocytosis >400 x $10^9$
            - B2: neutrophilia: >10 x$10^9$
            - B3: radiological splenomegaly
            - Endogenous erythroid colonies
    - Treatment of PRV:
        - Phlebotomy (Hct <45%)
        - Low dose aspirin
        - Hydroxyurea or interferon gamma
        - Busulphan in elederly
        - Manage CVS risk factors
        - Allopuranol
        - 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