# Histology of Lymphatic system

## White Blood Cells

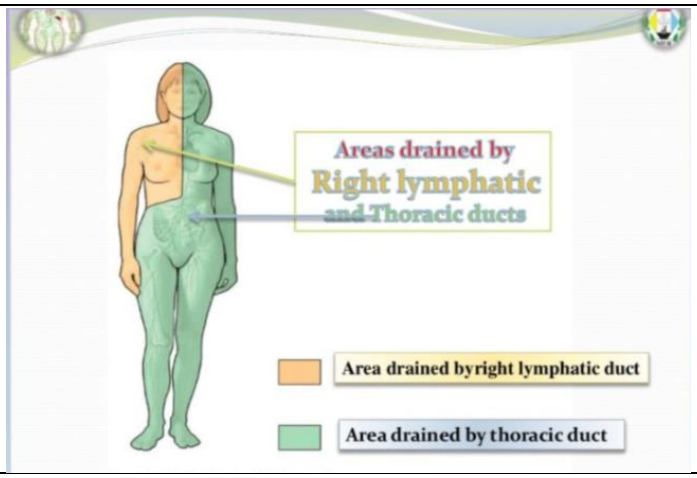
All blood cells come from Hematopoietic stem cells which gives rise to 2 different lineages: Myeloid, and Lymphoid.

- Lymphoid lineage gives rise to WBC, where they develop in the bone marrow
- B-Lymphocytes released into blood as mature b-cells with Ag receptor for a specific non-self Ag.
- T-Lymphocytes released into blood as immature cells and transport to Thymus for maturation where they will also be prototypic to a very specific antigen.
- Lymphocytes are not activated until they encounter their specific antigen first

## Lymphocyte Circulation

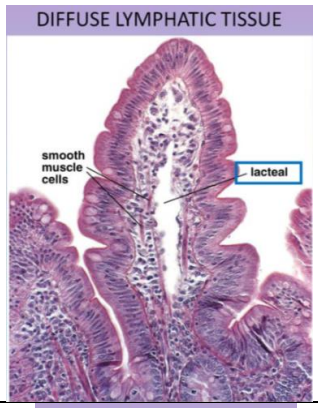
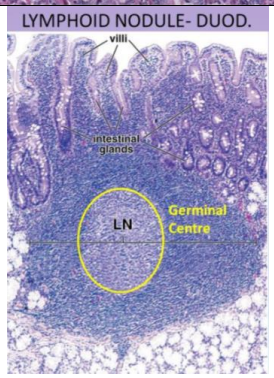
- Cycle: Leave blood/lymph -> Enter lymphatic tissue -> survey secondary tissue -> Return to blood/lymph
- Secondary/Peripheral Tissues:
    - MALT (Mucosa Associated Lymphoid Tissue)
        - Diffuse Lymphatic Tissue – Cells diffusely arranged throughout lamina propria
        - Lymphoid Nodules – Distinct boundaries and structure within lamina propria or submucosa
        - Aggregations of Nodules – Peyer's Patches, GALT (gut), BALT (Bronchi), NALT Nasal), VALT (Vulvo-vaginal)
    - Spleen
    - Lymph Nodes
- Once lymphocytes reach the peripheral organs/tissues they squeeze out of the capillaries to enter the tissues
    - Once finished checking out the tissues they enter the lymphatic vessels and return directly to the blood through the spleen
- Lymph = Fluid removed from extracellular spaces in connective tissues to carry Ag to lymph nodes. Gets filtered like a Brita filter in lymph notes before it enters lymphatic vessels again to return to blood.

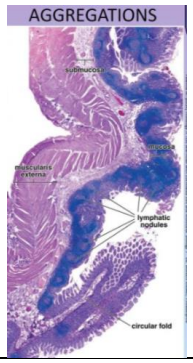
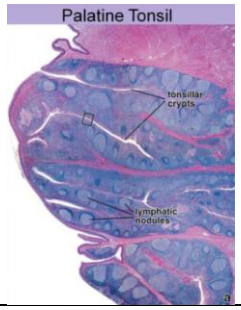
| Right Lymphatic Duct | Left Lymphatic Duct/Thoracic Duct |
|---|---|
| Drains right side of head, right upper abdomen and right arm<br><br>Empties into junction of right subclavian and internal jugular veins. | Drains rest of the body (much more)<br><br>Empties into junction of left internal jugular and subclavian veins |




- When lymphocytes bump into its specific Ag in the secondary lymphoid organs they become activated and remain in that tissue where they will multiply to fight the infection.
    - This activation can also occur via presentation of Ag by macrophages and dendritic cells. APC will move from site of infection to peripheral lymphoid tissue to find T and B lymphocytes to activate.

## GALT

| | | |
|---|---|---|
| **Diffuse Lymphatic Tissue** | Small Intestine – Villus with dilated lacteal in center |   |
| **Isolated Lymphoid Nodule** | Small Intestine – Duodenum<br>Lymphatic nodules in lamina propria extending into submucosa.<br><br>Lymphocytes are contained within a sharply defined specific meshwork<br><br>Nodules with paler center = Germinal Centre<br>- Indicative of activation and proliferation of lymphocytes, differentiation of B cells and Ab production<br><br>Ring of small lymphocytes encircle germinal centre |   |

| | | |
|---|---|---|
| **Lymphoid Aggregations** | Locations where multiple lymphatic nodules are all located in one area.<br><br>Eg:Peyer's Patches, or Appendix |  |
| **Waldeyer's Ring of Tonsils** | Stratified Squamous epithelium dips into connective tissue to form "Tonsillar Crypts"<br>- Lymphoid nodules under epithelium line these crypts<br><br>Crypts not supplied by afferent vessels but are drained by efferent lymphatic vessels |  |

## Lymph Node Structure

- Small bean-shaped encapsulated organ
- 1mm – 2cm long
- Found along lymphoid vessels to filter the lymph

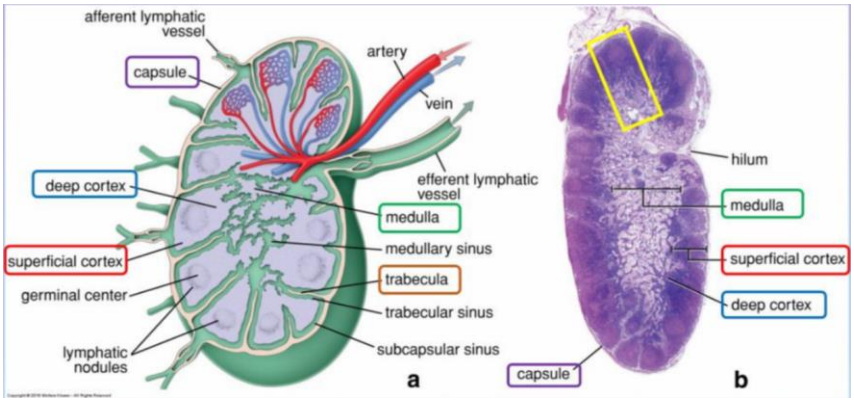
**2 routes of entry:**

1. Via lymph from one of many afferent lymphatic vessels entering node (1 efferent vessel leaves)
2. Via blood by crossing membrane of High Endothelial Venule (capillary bed within node)

**1 Route of exit:**

- Lymphocytes passing through node will exit via the efferent lymphatic vessel at hilum of the node (the depression on one side). They will eventually enter circulation again at the junction between subclavian and Internal jugular veins.

**Structure:**



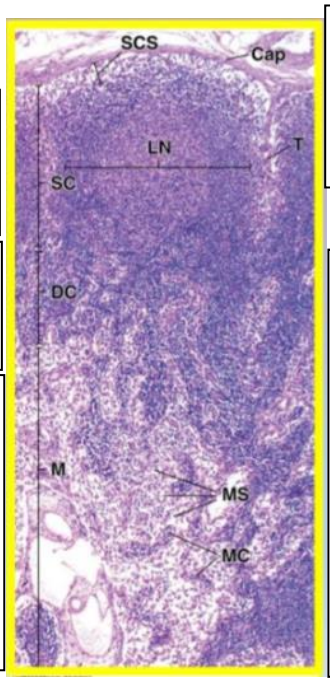
- Encapsulated by dense connective tissue, with projections, “trabeculae” running from outside towards inner medulla.
    - Function: Supportive framework

- Outermost Layer = ***Superficial Cortex***
    - Appears thick and dark purple on stain
- Middle Layer = ***Deep Cortex***
    - Innermost portion of the dark purple stain
- Innermost Layer = ***Medulla***
    - Lighter, unconsolidated stain in the middle.
    - Lymph from trabeculae sinuses drain in to medullary sinuses before leaving via efferent lymphatic vessel

Superficial Cortex: Contains lymphatic nodules

Deep Cortex: Contains densely packed lymphocytes

Medulla: Arranged in narrow strands (medullary chords) flanked by medullary sinuses. Lots of sinuses make it appear paler.




Cap + T = Capsule + Trabeculae
- Provide structure and support

SCS = Subcapsular Sinus + Trabecular Sinus
- Lymph from vessels flow into these sinuses and enter down into medulla

Reticular cells: Help provide structure and support by producing reticular fibres (Type III collagen).

- Surface molecules and secretions attract Lymphocytes and Dendritic cells

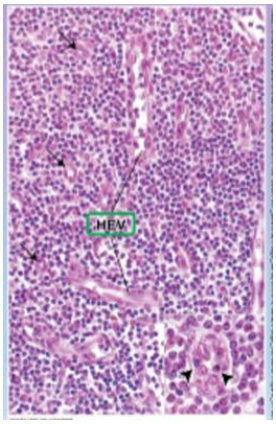
Dendritic cells found in T-cell rich areas, and are more efficient APC’s than macrophages.

Follicular dendritic cells: Numerous thin “arms” that reach into germinal centers to interact with B cells. Arms bind to Ag-Ab complexes for weeks-years.

- Don’t produce MHC II Therefore arnt APC’s

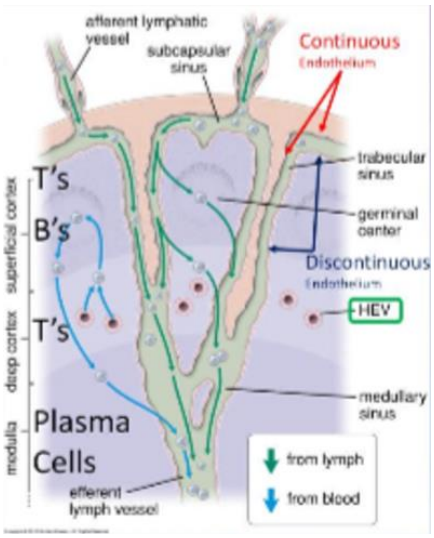
Sinuses are lined with endothelial cells and filled with meshwork of macrophage pseudopods, reticular cells and reticular fibres…acts as a filter to slow down lymph and allow immune cells to act.

- Endothelium of trabeculae is continuous with the outer connective tissue capsule
- Endothelium on side of sinus next to parenchyma of node is discontinuous. Macrophages and lymphocytes pass freely between parenchyma and sinus.
- Macrophages in parenchyma send projections through gaps in discontinuous to monitor lymph




**High Endothelial Venules**

- Main port of exit from node. Lined with Columnar or Cuboidal epithelial cells instead expected simple squamous.
- Have lots of $H_2O$ channels to allow resorption into interstitial fluid. Returns 35% of fluid and electrolytes back into circulation.



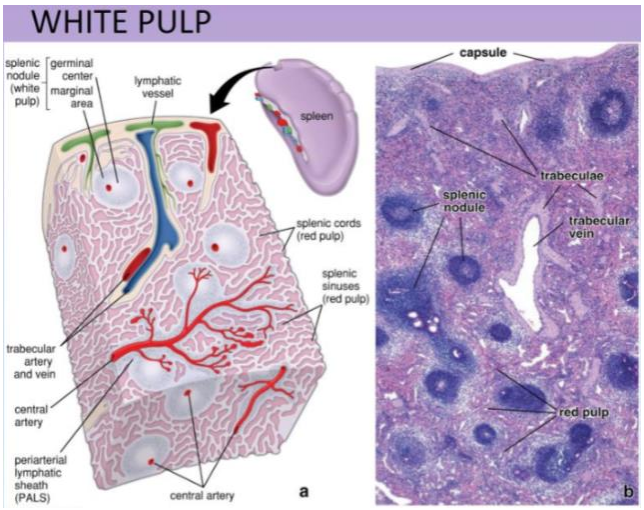

## Spleen

- Upper left quad of abdomen, size of clenched fist
- Largest lymphatic organ
- Filters blood and reacts immunologically to blood borne Ag
    - APC presents Ag
    - B & T cells activate
    - Removes macromolecular Ag from blood
- Removes and destroys RBC and platelets, Retrieves Iron from Hb

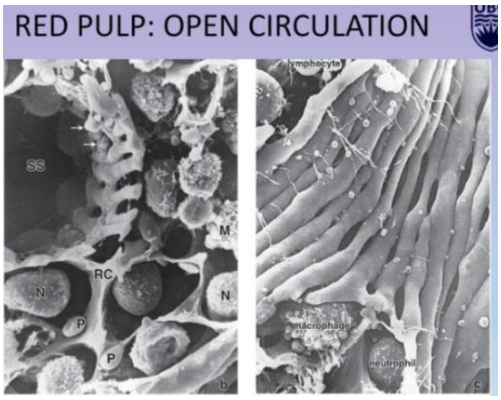
**Structure**

- Dense Connective tissue capsule and trabeculae extending into parenchyma.
    - CT and T contain myofibroblasts with ability to contract
- Hilum = area where artery, vein, nerve, and lymph vessels enter and leave
- Consists mainly of Splenic Pulp with 2 areas
    1. **White Pulp**

- Branches of splenic artery supply capsule, trabeculae and enter white pulp
- Consists of lymphocytes surrounding a central artery = Periarterial lymphatic sheath (PALS).
  - Appears similar to splenic nodule, but central artery gives it away
  - Lymphocytic expansion of splenic nodules (site of B lymph.) pushes artery to one side. PAL and lymphocytes surrounding nodules = T lym.




2. **Red Pulp**
   - Contain RBC to be broken down




- Sinuses are separate by Splenic Cords (like a bead curtain…for your spleen)
  - Meshwork of reticular cells and fibers (same and lymph nodes) suspends RBC, Macrophages, Lymphcytes, dendritic cells, plasma cells and granulocytes.
  - Lined by rod shaped endothelial cells with limited contact. Blood passes between these gaps to be carried to veins.
- Arterioles off the central artery dump blood directly onto splenic cords. Blood filters through mesh before collecting in sinuses
  - **Not a closed system!**

## Lymphatics System

- Vessels connect parts of immune system to vasculature, and transports lymph and lymphocytes
  - Lymph = fluid removed from extracellular spaces in connective tissue
  - Small lymphatic vessels drain into larger ones that drain into Thoracic Duct located at junction of left subclavian and Internal Jugular veins (largest lymphatic vessel, on left side of body)- Drains most of the body
  - Right arm and right side of the head drains lymph to bloodstream at junction of Right subclavian and Internal Jugular veins
  - One-way flow, propelled by muscle contraction throughout the system
- Lymph nodes filter out cellular material as lymph moves from either capillaries into the main venous system, or from afferent lymphatic veins entering the node before exiting as one main efferent.

Nodes categorized as:

1. **Superficial Nodes**
   - Associated with skin and superficial fascia, particularly in neck, under the arms, and in groin
2. **Deep Nodes**
   - Associated with abdominal and thoracic cavity and main arteries

## Lymphadenopathy

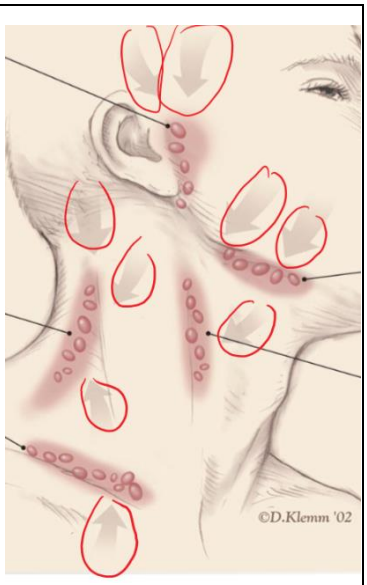
= Lymph nodes abnormal in size or consistency (infection or malignancy)

Lymphadenitis = inflammation of the lymph node (from infection)

| **Lymphadenopathy** | |
|---|---|
| **Etiology** | Infection<br>Autoimmune disorder<br>Medication<br>Iatrogenic causes<br>Malignancy<br><br>Infectious = Fever, Fatigue, Malaise<br>Autoimmune = Joint pain, Muscle weakness, Rash<br>Malignancy = Fever, Night Sweats, Weight Loss<br><br>Chance of malignancy ↑ w/ Age, Male, Caucasian, Supraclavicular nodes |
| **Diagnostics** | Blood Test<br>Imaging<br>Biopsy (fine needle aspiration, Core sample, Excisional removal) |

## Head and Neck Lymphadenopathy

| **Location** | **Differential** | **Malignancies** | |
|---|---|---|---|
| **Submental/Submandibular**<br>- Drain oral cavity | Upper Resp Infection<br>Dental Infection<br><br><2cm = Insignificant | Squamous Cell Carcinoma of head and neck<br>Lymphoma<br>Leukemia | |
| **Anterior Cervical**<br>- Drain Larynx, Oropharynx, Anterior neck | Same as submental/mandibular | | |
| **Posterior Cervical**<br>- Drains scalp, Neck, Upper thoracic skin | Scalp infection, mycobacterial infection | Skin neoplasm, Lymphomas, Head and | |

| | | | |
|---|---|---|---|
| | <2cm = Insignificant | Neck Squamous Cell Carcinoma |   |
| **Preauricular**<br>- Drains Scalp, and Skin | Same and Posterior Cervical | Same and Posterior Cervical | |
| **Supraclavicular Nodes**<br>- Drain GI, Genitourinary, Pulmonary tracts | Thyroid disease, fungal infections<br><br>>1cm significant | Abdominal/Thoracic | |

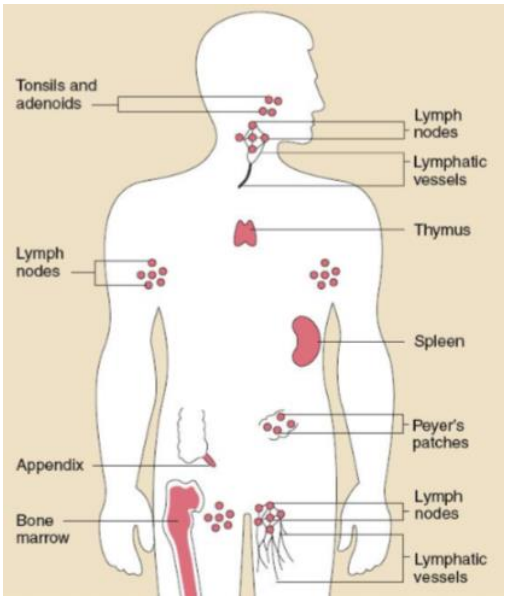
| | |
|---|---|
| **Size** | <2cm = Insignificant<br>Supraclavicular Node: >1cm significant |
| **Consistency** | Soft: Insignificant<br>Rubbery: Lymphoma<br>Hard: Malignancy & Granulomatous Infection |
| **Tender** | Tender: Infection<br>Non-Tender: Malignancy |

**Primary Lymphoid Organs**

- Bone Marrow
- Thymus (maturation site of T-cells)
    - Loss or lack of thymus = severe immunodeficiency

**Secondary Lymphoid Organs**

- Spleen
- Lymph Nodes
- Tonsils
- Appendix
- Peyer's Patches (small intestine)
- MALT
- GALT



## Spleen

= Largest Lymphoid organ

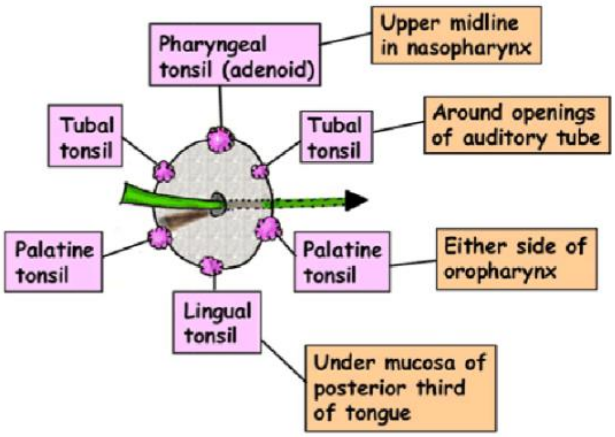
- Major Function = Remove opsonized bacteria, and Ab-coated cells from circulation

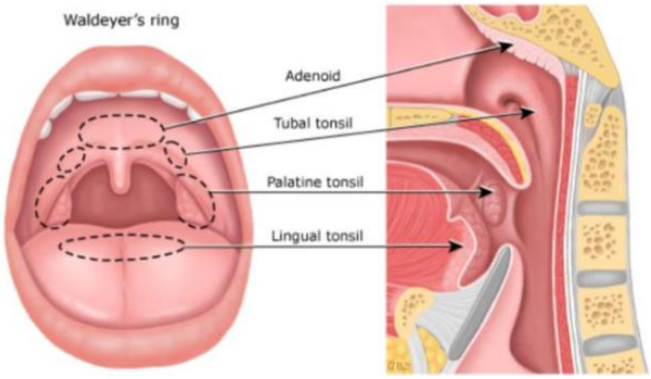
| Red Pulp | White Pulp |
|---|---|
| - (75%-80%)<br>- Splenic sinuses separated by splenic cords<br>  ○ Suspends RBC, Macrophages, Dendritic cells, platelets, granulocytes<br>- Stores RBC for Emergencies<br>- Stores 33% of total platelets<br>- Stores 50% monocytes (turn into dendritic cells and macrophages) | - (20%-25%)<br>- Aggregations of lymphocytes (mainly B lymphocytes<br>- Surrounded by Red Pulp<br>- Stores 25% lymphocytes |

## Waldeyer's Ring

= Ring of lymphatic tissue in nasopharynx and oropharynx

2 Palatine Tonsils + 2 Tubal Tonsils + Pharyngeal Tonsil + Lingual Tonsil



# Histology of RBC

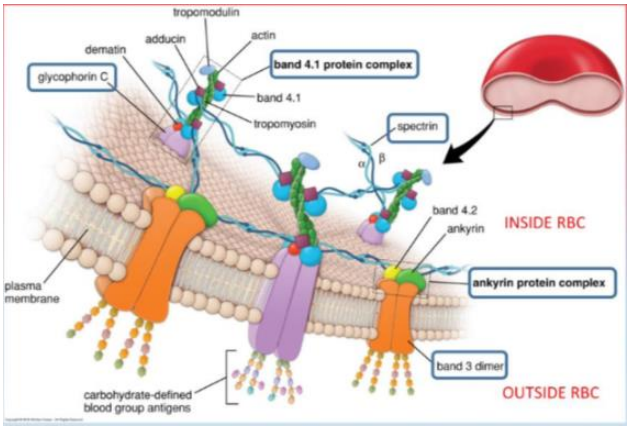
- Of the two main components of connective tissue (Cells, ECM – Amorphous and fibers) red blood cells fall under the Cells umbrella as a specialized connective tissue.
- Fibrinogen (and fibrin) are also connective tissue, under the Extracellular matrix umbrella.

**Characteristics of RBC**

- Produced in bone marrow
- Biconcave disk shape with no nucleus or organelles
    - Allows more hemoglobin to be closer to plasma membrane to trap $O_2$ and $CO_2$
- Contains mainly hemoglobin and enzymes
- 7-8um diameter
- Lives 120 days in circulation

## Structure of RBC

- 2 essential categories of proteins that aid in the structural flexibility characteristics and biconcave shape of RBC




| Integral Transmembrane Proteins | |
|---|---|
| **Glycophorin C** | Binds band 4.1 complex inside RBC |
| **Band 3 Protein** | Binds Ankrin complex inside RBC |
| Peripheral Membrane Proteins (α- & β- Spectrin) | |
| **Band 4.1 Complex** | Anchors Spectrin filaments to cell membrane to form hexagonal lattice |
| **Ankrin Complex** | |

- When RBC passes through tiny capillary bonds between spectrin molecules break and reform with new shape (one that will allow it to squeeze through). Allows membrane to be highly elastic and pop back to normal shape.

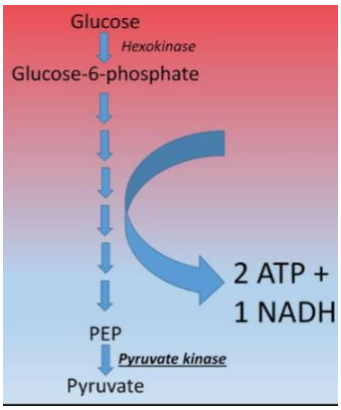
**Mutations**

| | Hereditary Spherocytosis | Hereditary Elliptocytosis |
|---|---|---|
| Inheritance | Autosomal Dominant | Autosomal Dominant |
| Affected Units | Band 3, 4.2, and Spectrin | Spectrin lateral bonds between α- & β subunits and bonds to Ankrin Complex |
| Results | Spherical RBC (destruction) | Elliptical RBC (destruction) |

**Contents**

- 66% $H_2O$, 33% Hemoglobin, 1% enzymes, lipids, ions etc

**Metabolism**

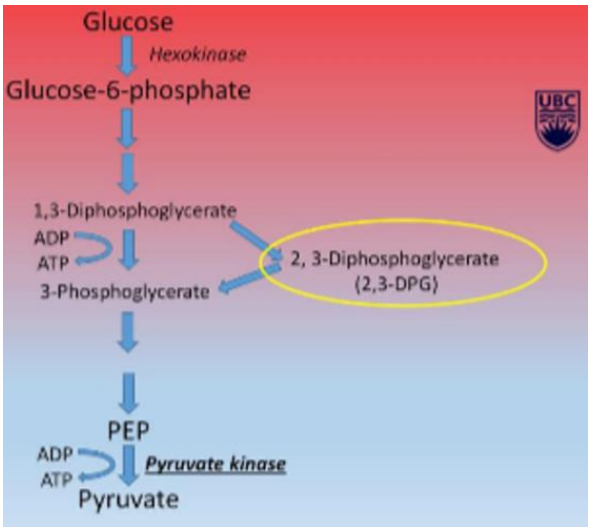



Energy comes from glycolytic pathway (no mitochondria needed)

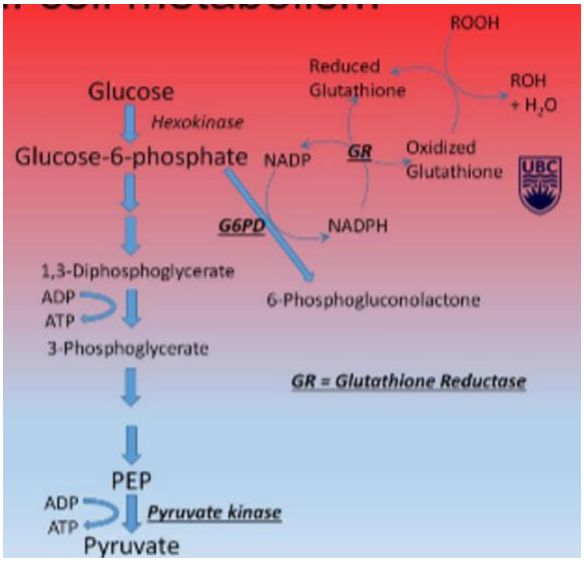
- NADH (Keeps iron reduced and prevents oxidative stress of membrane and Hb)
- ATP
    - NOT needed for $O_2$ or $CO_2$ transport
    - IS needed to maintain shape, flexibility

*Glycolytic Shunts*

1. **2, 3 – DPG shunt (Rapoport-Luebering)**
    - Contain equimolar hemoglobin:2,3-DPG ratio (unique to RBC)
    - 2,3 – DPG concentration is controlled by pH (Low pH = loss of 2,3-DPG, High pH = maintenance and production of 2,3-DPG)
    - Unbound 2,3-DPG binds with cytoskeletal proteins (Spectrin, Band 3 etc) and permits cellular shape change to squeeze through capillaries for gas exchange, and into spleen
    - 2,3-DPG binds deoxyhemoglobin = conformational change to have less affinity for $O_2$ causing the release of $O_2$




2. **Pentose shunt (hexose monophosphate shunt)**
    - Uses Glucose 6 Phosphate Dehydrogenase (G6PD), which is also the rate limiting step
    - Results in production in NADH, which keeps glutathione reduced
        - Reduced glutathione is a major antioxidant that eliminates peroxide, detox. Oxidants, prevents membrane lipid oxidation, and prevents globin oxidation.




Mutation in Pyruvate Kinase = Na-ATP pumps stop function, K+ then leaks out of cell, water follows causing the cell to shrink and die of dehydration.

## Hemoglobin

**Metabolically Active tissue** --> $CO_2$ diffuses into RBC --> Converted to $H_2CO_3$ (carbonic acid) by Carbonic Anhydrase --> $H_2CO_2$ ionizes to $H^+ + HCO_3^-$

- Ionization drops intracellular pH (acidic) which shifts EQ and favours $O_2$ release.

**Lungs:** Deoxyhemoglobin picks up $O_2$ and releases $CO_2 + H^+$ causing rise in pH and affinity for more $O_2$

**2, 3 – DPG:** Binds deoxyhemoglobin, changes its shape and decreases affinity for $O_2$**.** Hb releases 10% more $O_2$ in presence of 2, 3, - DPG.

- Production increases during respiratory alkalosis at high altitude, anemia, cardiac and pulmonary disease.

***Structure:***

| | |
|---|---|
| **Globin** | Metalloprotein<br>Tetromer consisting of:<br>- 2α and 2β subunits |
| **Heme** | Porphyrin ring with iron in centre ($Fe^{2+}$)<br>$O_2$ Binds reversibly to ferrous iron |

## Erythropoiesis and Bone Marrow

Monophyletic Theory = All cells develop in bone marrow from one common Hematopoietic Stem Cell (HSC)

Gives rise to 2 pathways:

1. Myeloid Progenitor
    a. Influence of EOP, IL-3, IL-4= Megakaryocyte/Erythrocyte Progenitor (MEP) -> Megakaryocyte (and platelets) or RBC via erythropoietin-sensitive erythrocyte-committed progenitor
    b. Granulocyte lineage
2. Common Lymphoid Progenitor (CLP)
    a. T-Cells, B-Cells, NK Cells, Dendridic Cells

**RBC Differentiation**

| | |
|---|---|
| 1. Pro-erythroblast | -1st recognizable precursor<br>-Basophilic (stains blue) due to many free ribosomes making Hb<br>-As grows and matures slowly turns red from eosin stain binding to more Hb and Hematoxylin to less Ribosomes |
| 2. Erythroblast | Polychromatic blue-red colour |
| 3. Normoblast | -Cell Division stops<br>-Lots of Hb causing cytoplasm to be eosinophilic |
| 4. Reticulocyte | -Nucleus is lost and mitosis is stopped<br>-Remains in bone for 5 days |
| 5. Erythrocyte | -Mature RBC develops in circulation over course of 1 day<br>-Lifespan = 120 days |

**Erythropoietin**

- Produced in Kidney in response to hypoxia (low $O_2$ concentration)

Acts on:

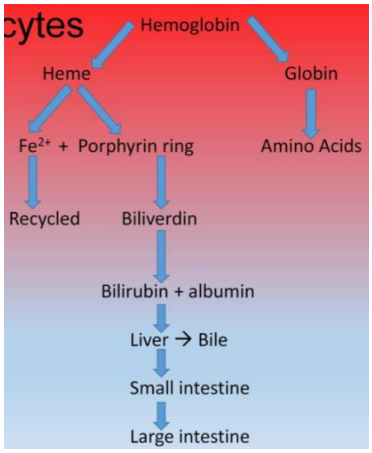
1. CMP cells
    - EPO + IL-3 + IL-4 stimulatees differentiation into MEP
2. Receptor found on Erythropoietin-sensitive erythrocyte-committed progenitor (ErP) cells

## Lifecycle of RBC

| Embryo/Fetus | Children | Adult |
|---|---|---|
| 1. Yolk Sac<br>Primitive nucleated Erythroid cell -> Loses nucleus in circ.<br><br>2. Yolk Sac + Placenta<br>Differentiated Erythroid prog. -> Migrate to liver -> Lose nucleus (Definitive RBC)<br><br>3. Aorta-Gonad-Mesonephros<br>HSC seeds Liver and Spleen -> Colonizes bone marrow at birth | Axial Skeleton and bones of extremities | Axial skeleton and proximal ends of femur and humerus<br><br>-Lasts 120 days (4months)<br>-1% replaced daily<br>-Eryptosis = programmed RBC death<br><br>Senescent RBC:<br>Low pH, Increase $Ca^{2+}$, Low ATP<br>Loss of membrane, shape change<br>Band 3 shape change exposes senescence-specific Ag<br>Internal facing lipids flip to outside to bind receptors on macrophages<br>Removed by phagocytes in spleen, liver and marrow |

**Hemoglobin Breakdown:**

1. Splits into Globin -> Heme + amino acids
2. Heme oxidised by heme oxidase -> opens porphyrin Ring and exposes Iron (recycled to RBC)
3. Heme comverted to biliverdin -> converted to bilirubin
4. Bilirubin bind albumin -> picked up in Liver and secreted into bile



# Components and Major Functions of Blood

**Blood has 4 main components:**

1. Plasma
2. Red Blood Cells
3. White Blood Cells
4. Platelets

**Functions of Blood:**

1. *Transport $O_2$*, and nutrients to lungs and throughout body
2. *Waste delivery* to kidneys and liver for detoxication and excretion
3. *Coagulation* to prevent blood loss
4. Transport *cells and antibodies* for immunity
5. Maintain *Acid-Base* equilibrium
6. Maintain *homeostasis* of:
    a. Temperature
    b. Electrolytes
    c. Intravascular Volume

**Major Plasma Proteins:**

1. Transport Proteins (albumin, transferrin, apolopoproteins)
2. Protease Inhibitors (Antitrypsin)
3. Coagulation Proteins (Fibrinogen, Prothrombin)
4. Gamma Globulins (IgG, IgA, IgM, IgD, IgE)
5. Compliment system Proteins (20 diff.)
6. Peptide Hormones (IGF-1, Angiotensinogen, Thrombopoietin)

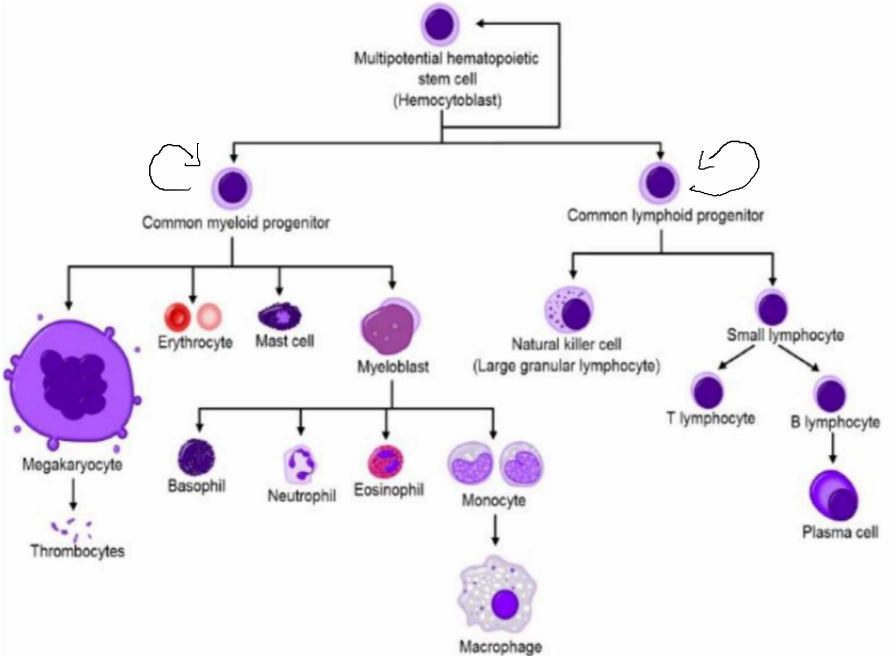
**Fluid Compartments:**

- Intracellular Fluids: 65%
- Extracellular Fluids: 35%
    - Interstitial Fluid
    - Plasma: 55% of blood
        - 91.5% water
        - 7% Protein
        - 1.5% Electrolytes, Nutrients, Vitamins, Hormones
    - Transcellular Fluid

**Plasma Vs Serum**

- Both non-cellular components of blood
- Serum = Plasma without any clotting factors
    - Centrifuge without anticoagulant to separate out clotting factors

## Hematopoiesis




All blood cells come from hematopoietic stem cells in bone marrow

-Hematopoietic stem cells are multipotent (turn into different cells) but not pluripotent because cant turn into EVERYTHING.

- Many maturation steps along the different differentiation lineages

## Erythropoiesis

- Occurs in the bone marrow, controlled by erythropoietin (EPO)
    - EPO is endocrine hormone from Kidney (and a little in liver) in response to low $O_2$ in blood relative to metabolic activity
- Requires: **Iron, Vitamin B12, and Folate**
- Takes 8 stages to produce a mature RBC (we are only focused on the last 2 stages)
    - Step 7: Reticulocyte (Direct precursor to mature RBC) matures in bone marrow for 5 days, and moves to peripheral blood for 1 day
    - Step 8: Maturing Erythrocyte.
        - RBC loses nucleus and organelles and adopt high surface area biconcave shape.
        - Defective (senescent) erythrocytes are removed from circulation by macrophages in spleen, liver, and marrow. Called **Mononuclear Phagocyte System**

### Red Blood Cells

- Flexible, membrane composed of protein and lipids with large surface area for maximum $O_2$ and $CO_2$ binding
- Lack nucleus, mitochondria, and Endoplasmic Reticulum
- Flexibility allows them to squeeze through small tight capillaries in single file
- Most numerous cells in blood
- Cytoplasm rich in **Hemoglobin**
    - Gives RBC red colour due to Iron content
    - Heme + Globin = Hemoglobin chain (α or β).
        - 4 (2x α and 2x β) hemoglobin chains = Hemoglobin molecule

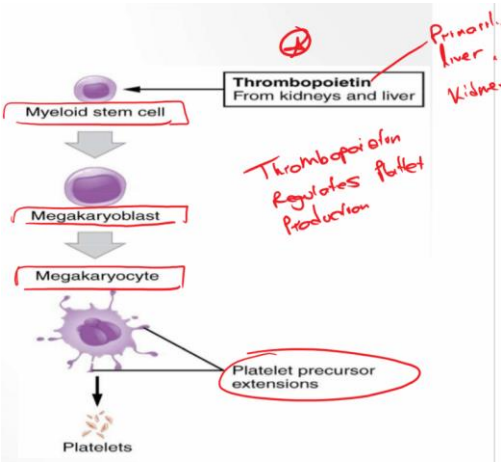
        - 4 Pyrole molecules + Iron = heme
    - Binds $O_2$ (which is released in pattern characteristic of oxyhemoglobin dissociation curve)

## Platelets

- Mediators of **Primary Hemostasis**
    - Gather at site of injury, adhering to subendothelium (via collagen and von Willebrand Factor) and produce 1st unstable plug to help seal the vessel
    - Release substances from granules to promote further clotting
    - Phospholipid membrane of platelets form platform on which coagulation can occur (stable fibrin clot)

| **Granules** | |
|---|---|
| **α-granules** | **Dense Granules** |
| Fibrinogen (CF 1), Clotting Factor V, von Willebrand Factor (vWF), Growth Factor, Heparin antagonist (PF-4) | ADP, Serotonin (5-HT), Clotting Factor IV (Ca++) |
| **Surface Receptors** | |
| **Glycoprotein Ib (GPIb)** | **GPIIb/IIIa** |
| Attaches via vWf to subendothelial collagen (GP VI binding) | Binds fibrinogen, allows platelet aggregation |

- Production controlled by Thrombopoietin (from Liver, and a little bit from kidney)




- Produced by megakaryocyte cells
- Lifespan: 10-12 days, ~1/3 of all platelets are found in the spleen

**Thrombocytopenia** = Platelet # too low (increased bleeding time and increased bruising)

**Thrombocythemia** = Platelet # too high (Increased clotting, higher risk of cardiovascular accident, cerebrovascular accident, pulmonary embolism etc)

## Primary Hemostasis

1) **Adhesion:**
    a. Damaged endothelial cells decrease platelet inhibition, and exposes vWF and collagen in subendothelium
    b. Platelets recruited to exposed subendothelium and bind to vWF and collagen to adhere to vessel
2) **Activation**
    a. Binding vWF activates platelets causing a change in shape (from disk shape to spiney shape)
    b. Activation turns on receptors (GP IIb/IIIa) to allow aggregation, and chemical messenger secretions (Granules release contents) to recruit more platelets
3) **Aggregation**
    a. Activated platelets bind to fibrinogen via GP IIb/IIIa. Multiple platelets can bind to the same fibrinogen, and different fibrinogens across their surface, creating a mat of platelets at site of injury

## White Blood Cells

- Presence of nucleus distinguishes them from other blood cells (anuclear RBC and platelets)
- Respond to Chemotaxis to squeeze through capillaries into extravascular space

| **Polymorphonuclear Leukocytes (PMN's)** | |
|---|---|
| Neutrophils | 55-70% of total WBC<br>Immediate response cells (1st line of cellular defence, major phagocytic cells)<br><br>Highly Mobile – migrate from small vessels to tissue damage to engulf microbes and cell debris<br><br>Die after engulfing (main component of pus) |
| Eosinophils | 1-6% of leukocytes<br><br>Kill bacteria primarily (also immobilize and kill parasites, or foreign bodies too big to ingest)<br><br>Contain toxic granules, and cause epithelial cell lysis (therefore proper control is important)<br><br>Involved with IgE in allergy reactions<br><br>Phagocytic to Ag-Ab complexes<br><br>Helps destroy cancer cells |
| Basophils | 0.4-1% of WBC (least common)<br><br>Participate in allergic response (type I reactions, immediate hypersensitivity and anaphylacsis)<br><br>Release chemokines to recruit more WBC's to infection/inflammation |

| | |
|---|---|
| | Granules contain Heparin (anticoagulant), Histamine, Vasoactive amines (vasodilators to increase capillary permeability)<br><br>Functionally similar to Mast cells<br><br>Protection against parasitic infection |
| **Round Cell Leukocytes (non-segmented nuclei)** | |
| Lymphocytes | Primary Mediators of Adaptive immunity<br><br>T Cells:<br>- Mature in Thymus gland<br>- Distinguish self from non-self<br>- Cells act directly on infectious and foreign agents<br><br>B Cells:<br>- Mature in Bone Marrow<br>- Develop into plasma cells to produce Ab specific to Ag<br><br>Natural Killer Cells:<br>- Protect against viral infections<br>- Detect and destroy some cancers |
| Monocytes | Phagocytose dead or damaged cells, and defend against microbes<br><br>Become macrophages once move extravascularly<br><br>Macrophages:<br>- Engulf foreign agent into phagosomes<br>- Help T-cells identify things to be destroyed<br>- Contain lysosomal enzymes to destroy engulfed things |

Mononuclear Phagocytes

| Location | Cells |
|---|---|
| **Brain** | Microglial cells |
| **Skin** | Langerhans cells |
| **Lung** | Alveolar Macrophages |
| **Liver** | Kupffer cells |
| **Kidney** | Mesangial cells |
| **Lymph Nodes** | Lymph node macrophages and dendritic cells |
| **Joint fluid** | Synovial A cells |
| **Spleen** | Splenic macrophages |

## Pathology

| | |
|---|---|
| **Thrombocytopenia** | Low platelet #<br>Bruising and abnormal bleeding likely (mostly bleeding gums) |

| | |
|---|---|
| | Not often large hematomas<br><br>*Caused by:*<br>Decreased Production<br>- Aplastic Anemia<br>- Bone neoplasm<br>- Drug induced (often chemotherapy)<br>Decreased platelet survival<br>- Immunologically mediated destruction (Idiopathic thrombocytopenic purpura (ITP)<br>- Disseminated intravascular coagulopathy (DIC)<br>Sequestration<br>- Splenomegaly |
| **Thrombocythemia** | High platelet #<br>Excessive clotting<br>Risk of cardiovascular incident, pulmonary embolism, cerebrovascular accident |
| **Leukopenia** | Low Leukocyte #'s<br>Prone to infection |
| **Leukocytosis** | Increased leukocyte #'s<br>Indicative of underlying infection, inflammation or leukemia |
| **Anemia** | Low RBC #'s<br>Can be malnutrition, low iron, low RBC production, increased RBC destruction, or low $O_2$ binding capacity |
| **Polycythemia** | High RBC #'s<br>Found in people blood doping with EPO |
| **Pancytopenia** | Reduction in all blood cell lines (RBC, Platelets, WBC) |

# Hemostasis

- First sign of coagulopathy (bleeding disorder) = spontaneous gingival hemorrhage and/or prolonged bleeding after tooth extraction or surgery
- Constantly happening with low level trauma (bumps and scrapes)

- Blood vessels lined with **endothelial cells**:
    - Enable passage of gases and soluble nutrients into and out of blood
    - VERY active
    - Barrier against blood contact with subendothelial space (prevents unnecessary clot formation). When this is breached hemostasis is initiated with exposure of subendothelial space

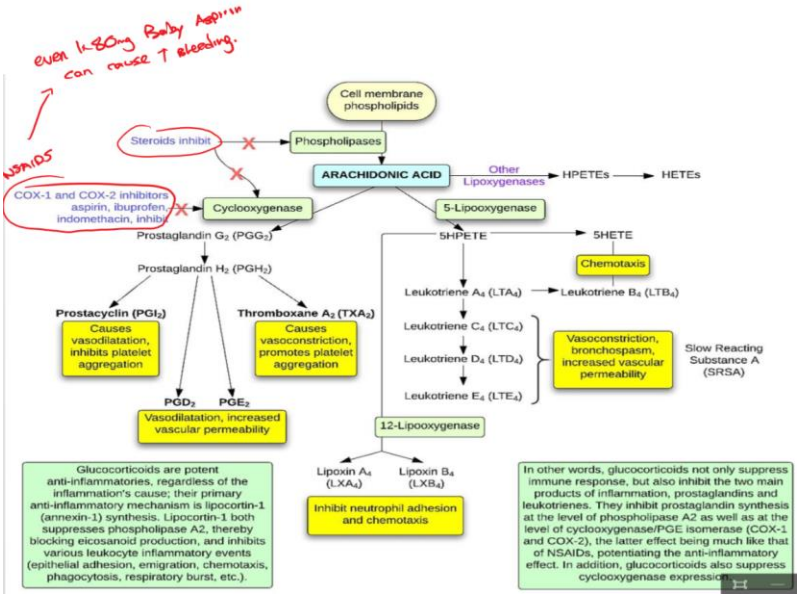
## 3 Major Processes

1) **Vasoconstriction**

a. Initial vasoconstriction: Local contraction: short lasting (60sec) neurogenic spasm followed by myogenic spasm (20-30 mins) which causes further constriction and tissue pressure.
b. Secondary vasoconstriction: Release of humoral substances from platelets (Serotonin 5-HT and Prostaglandin Thromboxane A-2. Endothelin is released by injured endothelial cells.

2) **Platelet Adhesion**
   a. ***Adhesion***: Attachment to damaged and exposed subendothelium. GP Ib binds vWF, and GP VI binds collagen.
      i. vWF is the glue that holds platelets to vessel walls and is produced both by endothelium and megakaryocytes (released by endothelial cells and platelets)
      ii. vWF promotes platelet adhesion and aggregation and is a carrier for factor VIII to increase its ½ life preventing its destruction
   b. ***Activation***: Binding to vWF and collagen activates the platelet.
      i. This changes platelet shape (Disk – spiny), turns on GP IIb/IIIa receptor, and secretes chemical messengers
      ii. Dense granules release: ADP (activates and recruits other platelets to area), Serotonin (vasoconstriction), clotting factor IV (Ca++, for clotting cascade)
      iii. Alpha granules release Fibrinogen (CF I) for aggregation, Clotting factor V (Clotting cascade), vWF, growth factors
   c. ***Aggregation***: GP IIb/IIIa – fibrinogen binding allows platelets to aggregate around fibrinogen at site of injury forming unstable initial plug
      i. ADP stimulates synthesis and release of thromboxane A-2 from platelets. **Thromboxane A-2** formed from phospholipids in plasma membrane

1. Phospholipse A2 mediates conversion of platelet membrane phospholipids to arachidonic acid. COX -1 and COX -2 converts arachidonic acid to thromboxane A2.
2. ADP and thromboxane A2 stimulate and activate neighbouring platelets, amplifying response, and also acts as vasoconstrictor to decrease local blood flow and loss.
      ii. Tissue Factor CF III from subendothelium + Ca++ (CF IV) converts prothrombin to thrombin, allowing for aggregation and further activation
      iii. Primary plug localized. ADP by activated platelets promotes prostacyclin and NO release from neighbouring intact cells (inhibits platelet aggregation when it doesn't need to be).



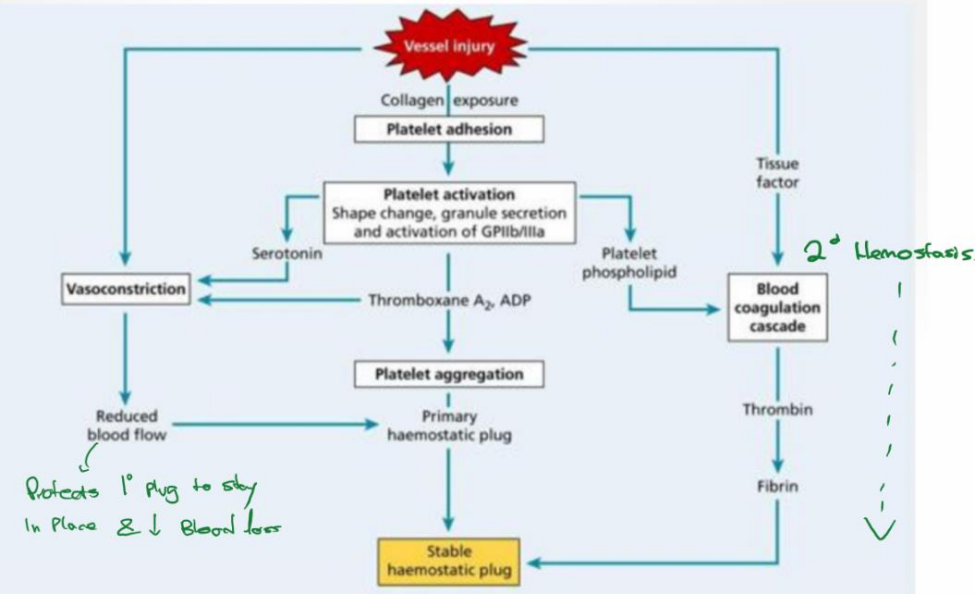

- ASA (Aspirin) inhibits COX. Preventing production of Thromboxane AS (TXA2), increasing bleeding. Action lasts 7-10 days (life of the platelet)

## Thrombocytopenia Pathogenesis

1. Decreased production of platelets
    - Generalized diseases of bone marrow
        - Aplastic Anemia
        - Bone Neoplasm
        - Drug Induced
2. Decreased platelet survival
    - Immunologically mediated destruction
        - Idiopathic Thrombocytopenic Purpura (ITP)
        - Disseminated Intravascular Coagulopathy (DIC)
            - Clotting happens all throughout vasculature, using up all the coagulation factors, leading to increased bleeding time
3. Sequestration
    - Splenomagely
        - Spleen hold more platelets than it should

**Summary:**

1. Vasoconstriction (Reflex and endothelin)
2. Structural and functional changes in activated platelets (granule contents expelled)
3. 5-HT and ADP recruit more platelets to area
4. Activated platelets synthesize TXA2 to amplify platelet response (via COX 1)
5. TXA2 activates, aggregates and vasoconstricts




## Clotting Factors

- Coagulation proteins for secondary hemostasis
- All are produced in Liver except Ca++ (Clotting Factor IV)
- Vitamin K dependant clotting factors (II, VII, IX, X, Proteins C and S).
    - Can be produced in absence of Vitamin K, but wont be able to bind to phospholipid surface (non-functional)

| Factor | Name |
|---|---|
| **I** | Fibrinogen |
| **II** | Prothrombin |
| **III** | Tissue Factor/Thromboplastin |
| **IV** | Calcium |
| **V** | (don't need to know name) |
| **VII** | (don't need to know name) |
| **VIII** | Antihemophilic Factor A |
| **IX** | Antihemophilic Factor B |
| **X** | (don't need to know name) |
| **XI** | (don't need to know name) |
| **XII** | (don't need to know name) |
| **XIII** | Fibrin Stabilizing Factor |
| **vWF** | Von Willebrand Factor |
| **Prekallikrein** | (don't need to know name) |
| **HMWK** | High-molecular-weight kininogen |
| | |

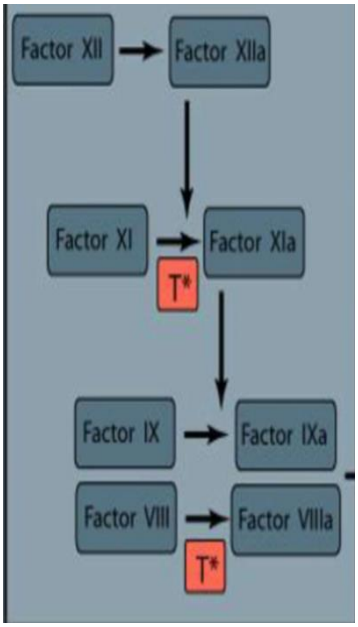
## Coagulation Cascade

- 3 main components: Extrinsic pathway, Intrinsic pathway, Common pathway
    - Extrinsic pathway initiates the cascade and Intrinsic amplifies it, Common pathway is where they merge to one in order to create a fibrin clot.
- Cascade occurs on the phospholipid surface of platelets in the instable clot
- **Critical feature: Sequential activation of many proenzymes to active enzymes. Stepwise amplification**
- **Clotting factors generate thrombin which converts fibrinogen to fibrin to create the insoluble stable clot.**

### Extrinsic Coagulation Cascade

### Intrinsic Pathway

- Initiated by High-Molecular-weight kininogen (HMWK), Prekallikrein, and Factor XII

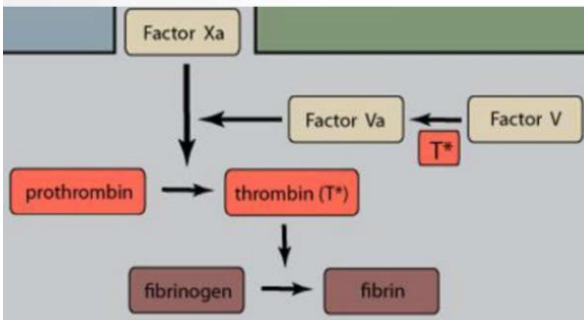



1. Prekallikrein converted to Kallikrein
2. Kallikrein activates Factor XII
3. Factor XII activates Factor XI
4. Factor XI activates Factor IX
5. Factor IXa + Factor VIIIa + Factor IV (Ca++) activates Factor X
6. Factor X activates Thombin, Factor II (from prothrombin)
7. F IIa activates V, VIII, and XI to amplify cascade

Prekallikrein circulates bound to High Molecular Weight Kininogen (HMWK)

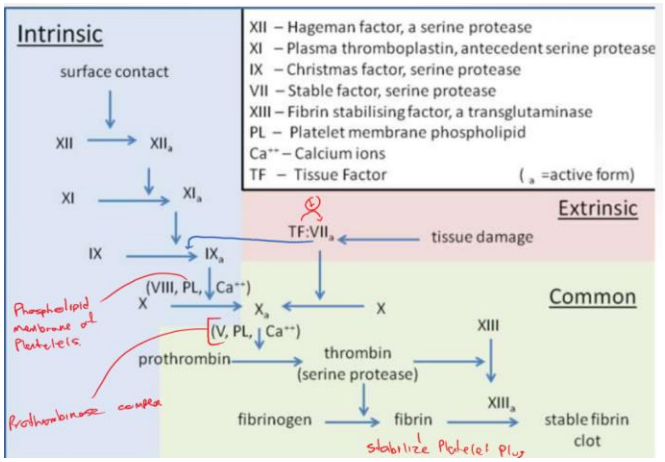
Reciprocal reaction: Prekallikrein activated to Kallikrein by Factor XIIa. Kallikrein then further activates Factor XII (positive feedback loop)

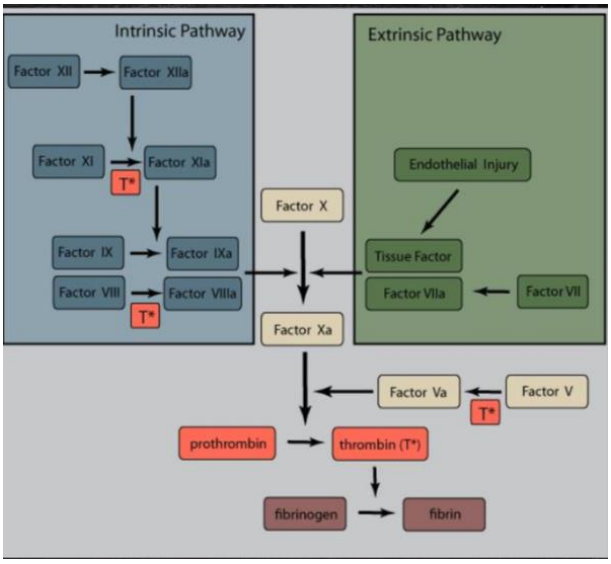
### Common Pathway




1. Prothrominase Complex (Xa-Va) on surface of activated platelets and tissue cells produces MUCH more thrombin than Xa alone
2. Factor V amplifies production of thrombin big time

## Clotting Cascade



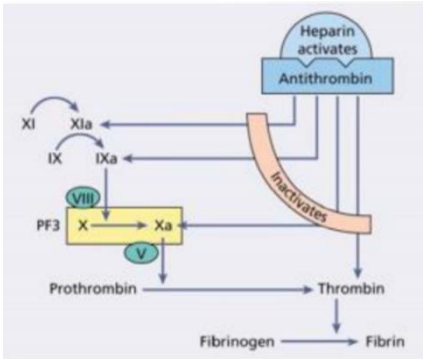




Thrombin:

- Enhances aggregation
- Converts Fibrinogen to Fibrin
- Activates Factors: V, VIII, XI, XIII
- Feedback to regenerate Factor Va and VIIIa
- Binds thrombomodulin to activate protein C (turning off coagulation)

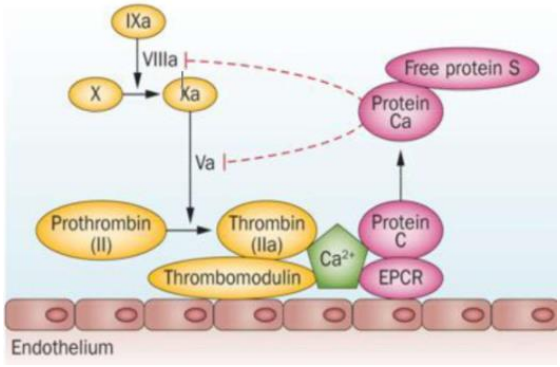
## Regulation of Coagulation

1. **<u>Inactivation of procoagulant enzymes</u>**
    a. Antithrombin
        - Degrades thrombin, Factor IXa, Factor Xa, Factor XIa, and Factor XIIa
        - Action enhanced by heparin




    b. Proteins C and S
        - C: Inhibits Factors VIIIa and Va, activated by thrombin bound to thrombomodulin, Vitamin K

- S: Cofactor for activated protein C, Vitamin K dependant




c. Heparin
   - Enhances antithrombin activity

d. Tissue Factor Pathway Inhibitor (TFPI)
   - Limits the action of tissue factor and the factors it produces

e. Prostacyclin
   - Released by endothelium to inhibit platelet activation
   - Vasodialator
   - Keeps clot formation localized to site of injury only

f. Thrombomodulin
   - Endothelial cell surface binding site for thrombin when bound to thrombomodulin activates protein C

**2. <u>Hepatic Clearance of activated clotting factors</u>**

**3. <u>Fibrinolysis</u>**

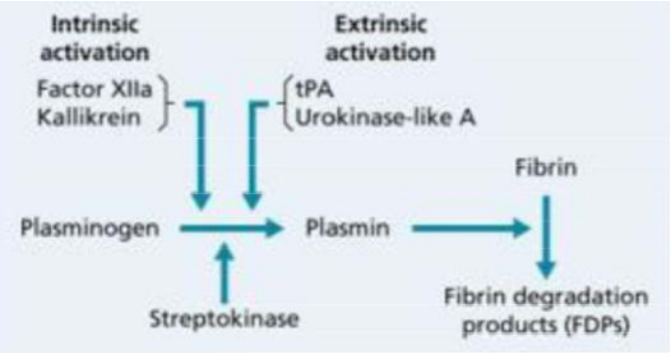
a. Plasminogen
   - Activators from endothelial cells to activate plasminogen into plasmin

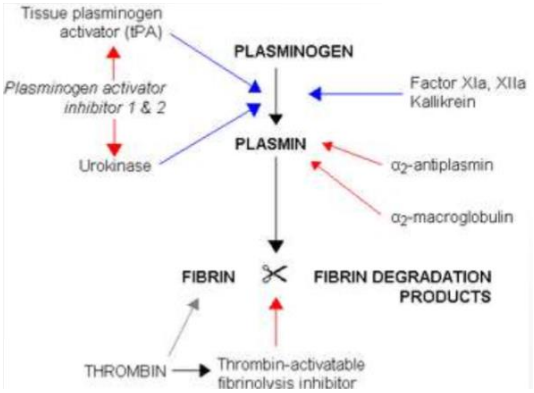
b. Plasmin
   - Degrades fibrin to form Fibrin degradation products (FDPs); One major FDP is D-dimer

c. Tissue Plasminogen Activator (tPA)
   - Poor activator from endothelial cells, but become efficient with bound to fibrin with plasminogen around
   - Given endogenously by Dr's to dissolve clots

d. Urokinase
   - Activator of fibrinolysis in excretory passages, secreted by endothelial cells

e. Streptokinase
   - Bacterial product that is a potent plasminogen activator.
   - Given endogenously by Dr's to prevent clotting



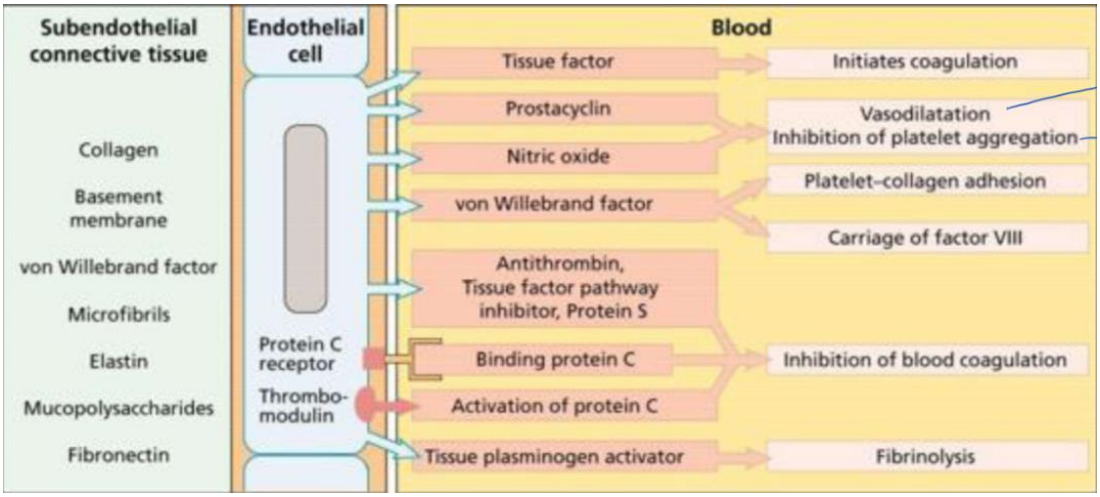




Fibrinolysis is regulated by Plasminogen Activator Inhibitors (PAI's) and Plasmin Inhibitors

- Slow down fibrinolysis
- Inactivate tPA and urokinase (which are rapidly cleared by liver)
- Secreted by vascular endothelial cells and activated platelets

Clot retraction occurs in the first 24 hours of initial clot formation and is dependant on Factor XIIIa crosslinking and twisting/knotting to condense the size of the clot.

- After clot retraction, fibrinolysis occurs




## Wound Healing

- Stimulated by platelet derived growth factor (PDGF)
- After clot retraction, true repair begins with tissue proliferation and collagen forming ECM in the wound
- New blood vessels grow into healing tissues (Angiogenesis), stimulated by vascular endothelial growth factor (VEGF)
- Wound contracts and epithelial cells grow and cover wound

## Coagulopathy

= impaired ability of blood to clot

**Classic symptoms:**

- Spontaneous gingival hemorrhage
- Petechia of skin/mucosa
- Purpura
- Ecchymosis
- Epistaxis

**1. Coagulation Abnormalities**

- Congenital or acquired clotting factor deficiency
- Impaired hepatic function
- Malabsorption syndromes (Vit. K deficiency)
- Medications (Heparin, Warfarin)

**2. Platelet Disorders**

A. Quantitative (thrombocytopenia)
   - Decreased production in bone marrow (Aplastic anemia, drug induced, neoplasm)
   - Increased Destruction (Immune thrombocytopenic purpura (ITP), Disseminated intravascular coagulopathy (DIC))
   - Sequestration (Splenomegaly)

B. Qualitative
   - Abnormal platelet function

**3. Non-hematologic defects**

- Trauma to blood vessel
- Local/systemic infections (Upper Resp Infections, Hemorrhagic fever, GI Infection)
- Decreased Vessel Integrity

| Bleeding Disorders | |
|---|---|
| **Hereditary** | **Acquired** |
| Von Willebrand Disease (vWD) | Liver Disease |
| Hemophilia A | Vitamin K Deficiency |
| Hemophilia B | Disseminated Intravascular Coagulation (DIC) |
| Factor V Deficiency | Drug-Induced Platelet Dysfunction |
| Factor XIII Deficiency | Idiopathic Thrombocytopenic Purpura (ITP) |
| Hereditary Hemorrhagic telangiectasia | |
| Protein C Deficiency | |
| Antithrombin III Deficiency | |

| Bleeding Disorder Symptoms | |
|---|---|
| **Petechiae** | Pinpoint capillary hemorrhages <2mm |
| **Purpura** | Small hemorrhages 2mm-1cm diameter |
| **Ecchymoses** | Hemmorhages >1cm |
| **Mucosal Bleeding** | Epistaxis, gingival bleeding, hematuria (bloody urine), Hematochezia (blood from anus), Melena (black bloody stool) |
| **Hemarthrosis** | Bleeding in joints |
| **Deep Hematoma** | Bleeding into epidural or subdural spaces. Around esophagus, retroperitoneal, intramuscular |

## Lab Tests

| Test | Description | Normal Range |
|---|---|---|
| **CBC w/platelet count** | -Count of all RBC, WBC, and Platelets in a blood sample<br>-Used to quantify different levels for diagnoses of infection, bleeding disorders, or anemia | Platelets: 150,000 – 400,000/uL |
| **Peripheral Blood Smear** | -Evaluated size and shape of RBC to qualify types of anemia | |
| **Mean Corpuscular Volume (MCV)** | -Evaluates the mean volume of RBC, can determine size of RBC for anemia typing | |
| **Prothrombin Time (PT)** | -Measures **Extrinsic and Common** Pathways (Factors I, II, V, VII, X)<br>-Measures Vitamin K dependant Factors (II, VII, X)<br>-Elevated during Warfarin therapy | 11-15sec |
| **Activated Partial Thromboplastin Time (aPTT)** | -Measures **Intrinsic** (Factors XII, XI, IX, VIII and **Common** Pathway (Factors V, X, II, I)<br>-Elevated in Hemophilia, vWD, and during Heparin Therapy | 27-36sec |
| **Thrombin Time (TT)** | -Measures effectiveness of thrombin (II) to convert fibrinogen to fibrin (I)<br>-Normal in patients with defects in pathway prior to fibrinogen conversion (primary hemostasis)<br>- Prolonged in patients with low fibrinogen or with Heparin | 24-35sec |
| **Fibrinogen** | -Low when consumption is increased (DIC, Hemorrhage), or function in impaired<br>-Elevated during reactive conditions (Inflammation, Infection, Malignancy) | |
| **D-Dimer** | -Proof of thrombus formation and clot breakdown/resorption<br>-Positive value indicative of clotting | |

**BLEEDING TESTS DIFFERENTIAL**

| PT result | PTT result | Common Conditions Present |
|---|---|---|
| Prolonged | Normal | • Liver disease<br>• Decreased vit K<br>• Decreased or defective CF VII |
| Normal | Prolonged | • Hemophilia A (CF VIII def.) / B (CF IX def.)<br>• CF XI/XII deficiency<br>• Von Willebrand disease |
| Prolonged | Prolonged | • Severe liver disease<br>• Decreased/defective CFs I (fibrinogen), II (prothrombin), V / X<br>• DIC (disseminated intravascular coagulation) |
| Normal | Normal | • Normal hemostasis<br>• Mild forms of CF deficiency or von Willebrand disease (further tests required) |

## Oxygen Transport

- $O_2$ carried in blood in 2 forms
    1. Plasma dissolved (2%)
    2. Bound to hemoglobin (98%)

- 1 Hemoglobin binds 4 $O_2$
    - Contains 4 heme subunits (1 $O_2$ per heme)
    - 2 α- chain globulin and 2 β- chain globulins per heme + 1 Iron
- **$O_2$ Saturation** = amount of $O_2$ bound to Hb relative to the max that can bind.
    - **Oxyhemoglobin** = With $O_2$ bound
    - **Deoxyhemoglobin** = Partially or fully unloaded.
- $O_2$ bound to oxyhemoglobin is function of partial pressure (pp) of $O_2$ in blood and tissues
    - Lungs with high $ppO_2$ = lots of oxyhemoglobin
    - Exercising muscle with low $ppO_2$ = lots of deoxyhemoglobin

### Cooperativity

= Feedforward mech for $O_2$ binding to Hb

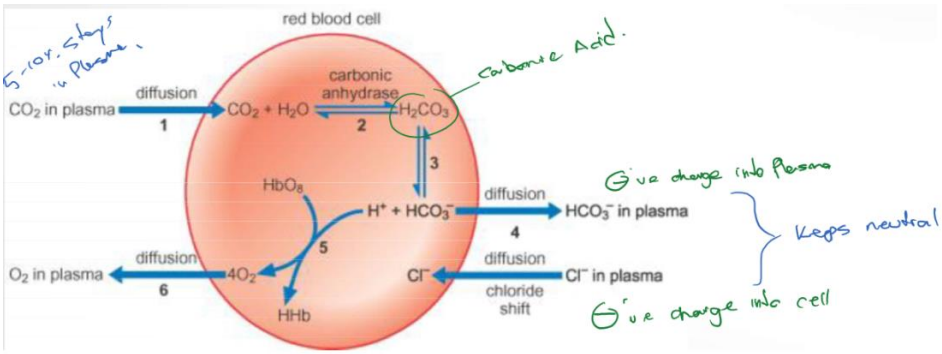
- Hb molecule undergoes subtle intramolecular changes during $O_2$ loading/unloading
    - Changes increase/decrease $O_2$ binding strength for subsequent $O_2$ molecules.
    - 1st loaded/unloaded $O_2$ makes 2nd easier to bind/dissociate
    - 2nd will associate after smaller change in $ppO_2$ than 1st etc etc etc

### $CO_2$ Transport

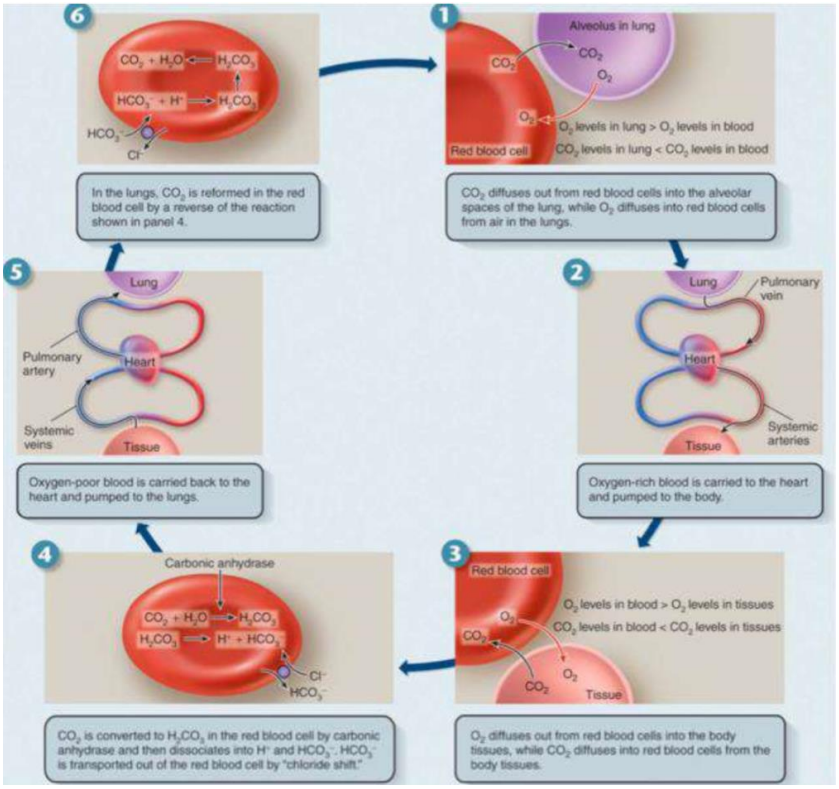
- 20x more soluble than $O_2$, so we see more dissolved in plasma
- **Carbaminohemoglobin** = $CO_2$ bound hemoglobin
- 3 Methods of transport:
    1. Dissolution into plasma (5-10%)
    2. Hemoglobin Binding (20%)

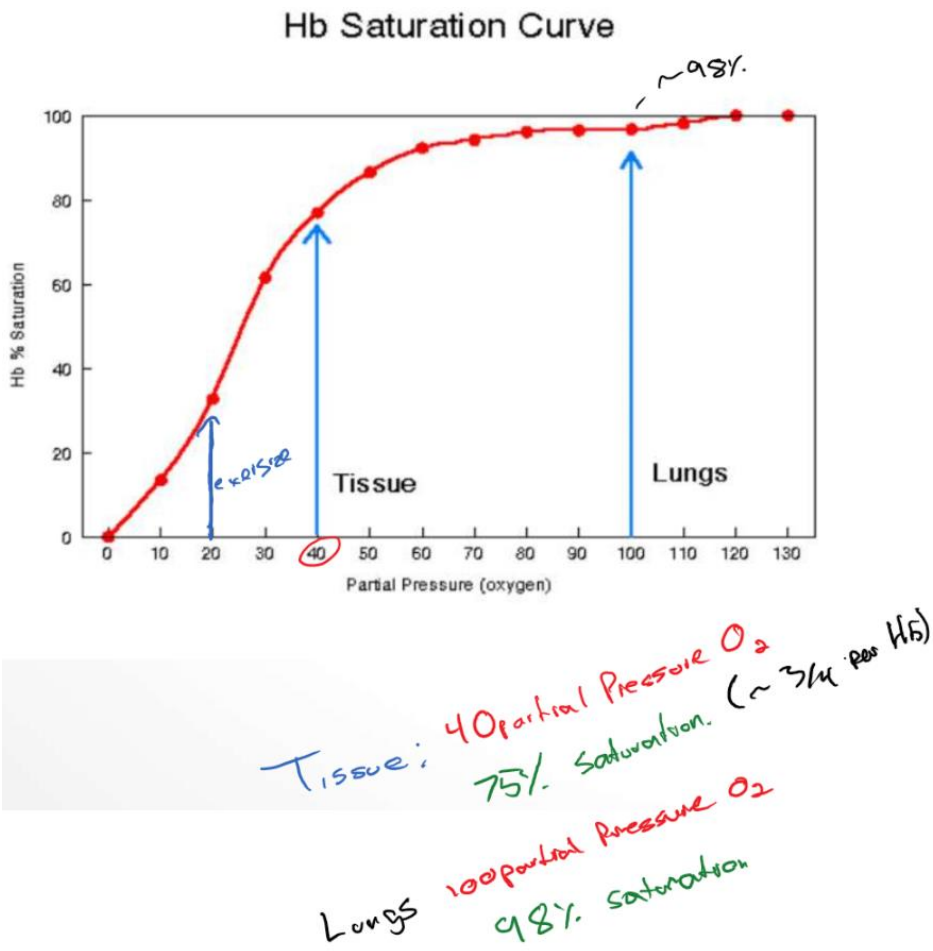
3. Conversion to bicarbonate (70%)

- Carbonic Anhydrase (CA) within RBC converts $CO_2 + H_2O$ into carbonic acid ($H_2CO_3$) which dissociates into $HCO_3^- + H^+$ ions
    - Quick conversion allows continued uptake along concentration gradient




$$H_2O + CO_2 \rightarrow H_2CO_3 \rightarrow HCO_3^- + H^+$$






| | |
|---|---|
| **Hypoxemia** | Inadequate $O_2$ in arterial blood |
| **Hypoxia** | Deficiency in $O_2$ throughout body.<br>- Tissue Hypoxia<br>- Cerebral Hypoxia<br>Extremities appear cyanotic (blue-gray) |

## Sepsis

- Inflammation resulting in systemic response to BACTERIAL infection
    - Fever (<36 or >38)
    - Tacchycardia (<90)
    - Hypotention
        - ↓$O_2$ to tissues = acute organ failure (lungs, liver, kidney)
    - Confusion
    - Tachypnea (>20)
    - Diaphoresis
- **<u>Central to the pathophysiology is altered endothelial cell function</u>**
    - Increased permeability (loss of barrier function)
        - Mediated by IL-1, IL-6, TNF-α, Nitric Oxide

- Movement of fluid out of the vasculature can result in severe hypotension

**Septic Shock** = Sepsis with refractory (resistant to treatment) hypotention and impaired organ perfusion

- Cardiovascular failure
- Respiratory Failure
- Renal Failure
- Hematologic failure (coagulopathy)

**SIRS (Systemic Inflammatory Response Syndrome)** = Systemic inflammation that may or may not have infectious cause.

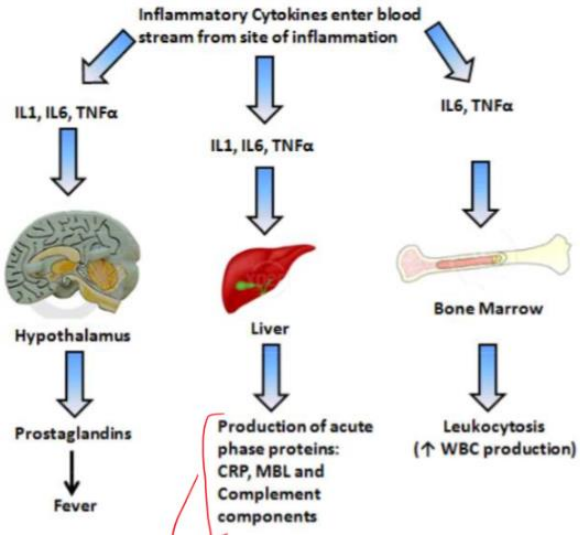
- Same diagnostic characteristics as sepsis, minus the bacterial culture.

## Cytokines and Chemokines

- Cell signalling and activating function of immune cells
- Produced by activated macrophages and T-cell
  - Chemokines – stimulate leukocyte movement

**Acute Inflammatory mediators**: *TNF-α, IL-1, IL-6*

- Release of these mediators induce:
  - Hypothalamus release of prostaglandins = Fever
  - Liver release of Acute Phase Proteins (C-Reactive Protein, Compliment)
  - Bone marrow release of WBC

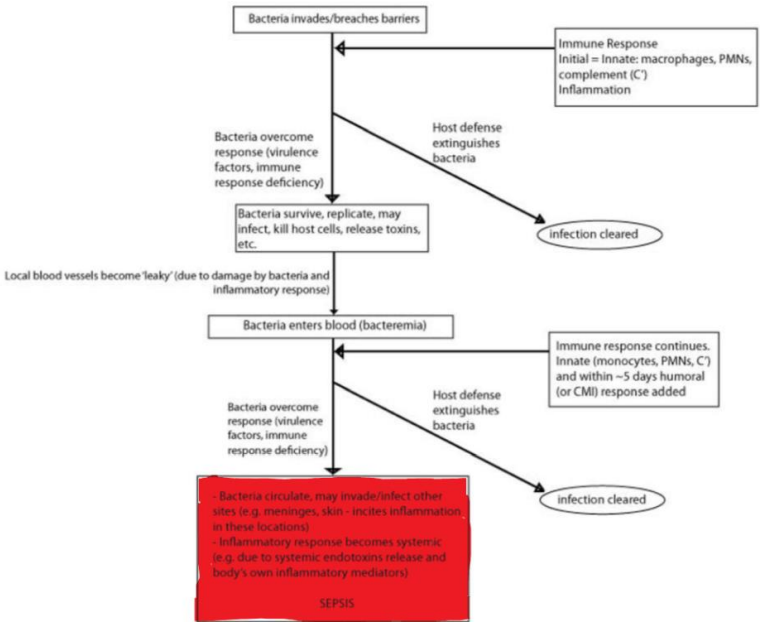


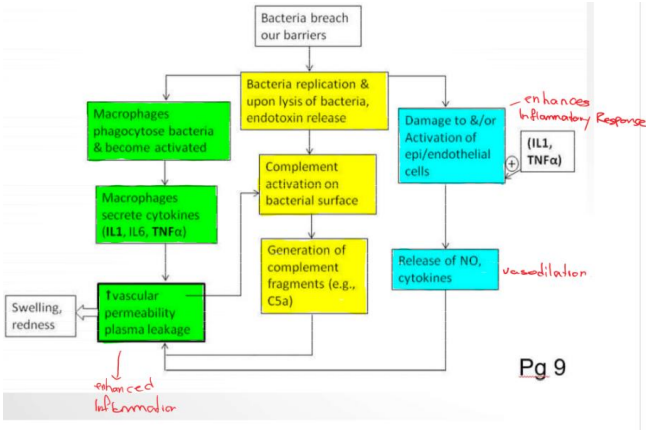

## Bacteremia

- Bacteria in blood, confirmed with culturing

| Systemic Responses to diagnose Sepsis (need 2+ of these) | |
|---|---|
| **Temperature** | >38°C or <36°C |
| **Heart Rate** | >90 bpm |
| **Respiratory Rate** | >20 breathes per minute or $ppCO_2$ <32 mmHg |
| **WBC Count** | >12,000/uL or < 4000/uL, or >10% immature blasts |

- Via trauma, vessel damage, adhesion to endothelial cells, increased permeability of endothelial cells.




- Causes Acute inflammatory Response: Releases IL-1, IL-6 TNF – α, NO, and Histamine
  - Increases vascular permeability, and vasodilation = Hypotension (↑HR ↑RR)
  - Leads to multiple organ failure
  - IL-1, IL-6 TNF – α cause endothelial cells to lose anti-thrombogenic state = DIC

| | **Cause** | **Description** |
|---|---|---|
| **Disseminated Intravascular Coagulation (DIC)** | Massive tissue injury, pregnancy, sepsis<br>-IL-1, IL-6, TNF- α alter endothelial cells, prevent anticoagulation state | Widespread clotting throughout microcirculation (capillary blockage) = Ischemia, Hemolytic anemia<br><br>Increased expression of tissue factor (activate clotting), but decreased thrombomodulin (reduce protein C anticoagulation) |

## Neutropenia

| | |
|---|---|
| **Counts** | Normal: 2.5-7.5 x $10^9$/L<br>Mild: 1.0-2.0 x $10^9$/L<br>Moderate: 0.5 – 1.0 x $10^9$/L<br>Severe: <0.5 x $10^9$/L |
| **Etiology** | Decreased production in marrow<br>- Congenital<br>- Malignancy into bone marrow<br>- Chemotherapy<br>- Autoimmune attack<br>- HIV |

| | |
|---|---|
| | - Vitamin B12, Folate, Iron deficiency (required for neutrophil production)<br>Margination (Neutrophils bound to endothelial walls of vasculature, stopped from flowing in circulation)<br>Sequestration in spleen<br>Immune mediated destruction of neutrophils (drug or autoimmune) |
| **Dental Surgery Considerations** | >2000 x $10^9$ : No prophylaxis necessary<br>1,000-2,000 x $10^9$/L : Antibiotic prophylaxis needed<br><1000 x $10^9$/L : Postpone dental treatment |

= Decrease in Neutrophil count

## Neutrophilia

= Too many neutrophils

| | |
|---|---|
| **Etiology and Pathogenesis** | **Infection**<br>- ↑IL-1, ↑IL-6, ↑TNF = ↑ Neutrophil release<br>- ↑IL-1, ↑IL-6 = Delayed neutrophil apoptosis<br><br>**Acute inflammation** (tissue necrosis, Myocardial infarction, Burns)<br><br>**Glucocorticoids**<br>- ↑demargination of peripheral blood neutrophils<br>- ↓transmigration neutrophils into tissue<br>- ↑ immature bands neutrophils into circulation<br>- ↑ numbers in tests ↓ effectiveness<br><br>**Acute Stress**<br>- ↑demargination of peripheral blood neutrophils |

# Disorders of the Immune System

## Autoimmune Disorders

= Immune response of organism acting against its own cells/tissues (via autoantibodies or T lymphocytes)

- Type 1 diabetes Mellitis
- System Lupus Erythematosus (SLE)
  - Hypersensitivity with symptoms in every organ
- Sjorgen's Syndrome
  - Secretory gland impairment (lacrimal gland and salivary glands)
- Hashimoto's Thyroiditis
  - Hypothyroidism
- Graves Disease
  - Hyperthyroidism
- Idiopathic Thrombocytopenic Purpura
- Rheumatoid Arthritis
- Addison's Disease

**3 sets of genes that cause autoimmune diseases**

1. Immunoglobulin genes

2. T-cell Receptor genes
3. Human Leukocyte Antigen (HLA) or MHC

| Host antigen alterations | |
|---|---|
| **Chemical** | Chems bind with self antigens, making them immunogenic<br>(hemolytic anemia from cephalosporin antibiotics) |
| **Physical** | UV light cause keratinocyte apoptosis and lead to cutaneous lupus erythematosus |
| **Biologic** | Persistent RNA viral infection combines with host tissues and alter autoantigens |

## Immunodeficiency

### Primary Immunodeficiency

- Hereditary, typically X-linked (60% of cases are male) and often manifests during childhood as unusual and/or frequent infections

| Categories of Primary Immunodeficiencies | |
|---|---|
| **Humoral Deficiencies (B-Cell defects)** | 50%-60% of immunodeficiencies<br>↓Serum Ig<br>Commonly IgA deficiency |
| **Cellular Immunity Deficiency (T-cell Defects)** | 5%-10% of immunodeficiencies<br>↓ serum Ig also |
| **Combined Humoral and Cellular immune deficiency (B and T cell defects)** | 20% of primary immunodeficiencies |
| **Phagocytic Cell defects** | 10%-15% of primary immunodeficiencies<br>Commonly: Chronic granulomatous disease (↓ neutrophil phagocytic function) |
| **Complement Deficiencies** | <2%, very rare<br>Defective opsonization, phagocytosis and lysis of pathogens |

### Secondary Immunodeficiencies

**Caused by:**

- Systemic disorders (Diabetes, Leukemia, Malnutrition, HIV)
- Immunosuppressive treatments (chemotherapy, corticosteroids)
- Chronic illness

Treatment focuses on underlying disorder

## Hypersensitivity

- Allergic reaction because of exaggerated/inappropriate immune reaction

Allergens bind *IgE sensitized mast cells and basophiles* -> ***Histamine*** released -> Facilitates *inflammation*

**Mast Cells**

- Extravascular (not in circulation)
- *Produce*: Histamine, Heparin, Leukotrienes, Platelet Activating Factor
- *Contain*: Proteases, Anti-microbial Proteins

**Histamine**

- Causes:
    - Local vasodilation (Redness/erythema)
    - Increased capillary permeability and edema (swelling)
    - Vasodilation of surrounding arterioles
    - Stimulation of sensory nerves (Itchiness)
    - Bronchoconstriction
    - GI muscle contraction (↑motility)
    - ↑ Nasal, Salivary and Bronchial gland secretions

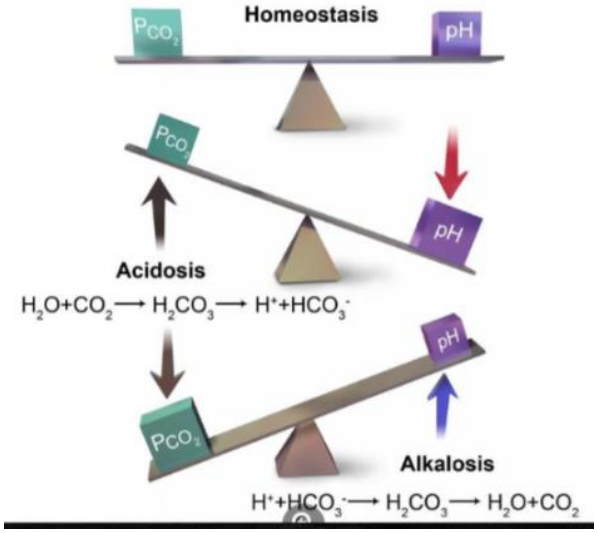
| Hypersensitivity Reactions | |
|---|---|
| **Type 1** (Immediate hypersensitivity, IgE- mediated) | -Most common forms of allergy (anaphylaxis, asthma, hay fever etc)<br><br>Atopy = Exaggerated IgE mediated response |
| **Type 2** (Antibody-dependent cytotoxic hypersensitivity)<br><br>***Non-circulating*** | -Ab binds to cell surface receptor in a tissue<br>-Ab-Ag complex activates cytotoxic cells (NK cells, eosinophils, macrophages), and compliment<br>- Results in cell death and tissue death<br><br>Eg: Graft rejections, Autoimmune Hemolytic Anemia, Hashimoto thyroiditis, Anti-glomerular Basement Membrane Disease |
| **Type 3** (Immune complex disease)<br><br>***Circulating in blood*** | -Inflammation response to **circulating** Ag-Ab immune complexes deposited in vessels<br>- Compliment systems activated = inflammatory mediator release<br>-Larger complexes deposit in various tissues (glomeruli, vessels) to cause systemic reactions<br><br>Eg: Systemic Lupus Erythematous, Rheumatoid Arthritis, Leukocytoclastic Vasculitis. |
| **Type 4** (Delayed Hypersensitivity)<br><br>T-cell mediated | -Ag specific T-cell mediated disorders<br><br>T cells sensitized after contact with Ag, reactivated upon re-exposure to Ag<br><br>-Appear after time lag (2-3 days), leads to tissue injury via direct toxic effect or activation of cellular response.<br><br>Eg: Contact dermatitis following exposure to metals and plants. |

Allergy = Broad term that encompasses all 4 hypersensitivities

Atopy = Specific for Type I only

## Acid-Base Balance

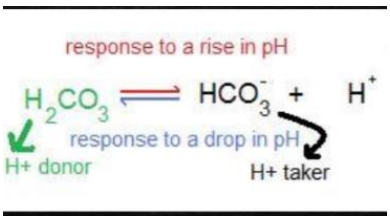
Blood pH typically between 7.35-7.45




- Balance based mostly on $H^+$ ion
- Most acids come from carbohydrate and fat metabolism = generates ↑ $CO_2$ which is converted to carbonic acid ($H_2CO_3$) by Carbonic anhydrase. Carbonic acid dissociates to form $H^+ + HCO_3^-$

### 1. Chemical Buffering (Immediate, Low capacity)

- Resist changes in pH, 1st line of defense
    - Release $H^+$ when pH ↑, and bind $H^+$ when pH↓
- Made of Weak Acid and its conjugate base
- Eg: Carbonic Acid Buffering System
- Eg: Bone Buffering System
    - During Acidosis: Releases $NaHCO_3 + Ca(HCO_3)_2$ for the $H^+$ ion binding
    - During Prolonged Acidosis: Releases $CaCO_3 + CaPO_4$
        - Results in demineralisation and osteoporosis in chronic acidosis

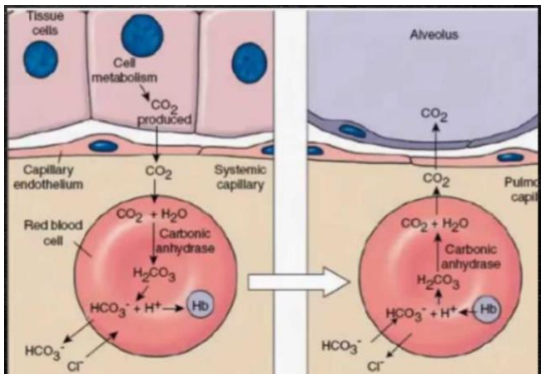



### 2. Pulmonary Buffering (Min-Hrs, 50-70% effective)

- $CO_2$ produced by cellular metabolism, leaves tissues and enters the blood. Carbonic Anhydrase produces carbonic acid from $CO_2$ and $H_2O$ which ionizes into $H^+$ and $HCO_3^-$
- $H^+$ binds hemoglobin, and travels from anaerobic tissue to the lungs where carbonic anhydrase reverses the rxn to create $H_2O$ and $CO_2$ to exhale.

### 3. Renal Regulation (Hrs.- Days, sustainable over longer periods)

- Controls amount of bicarbonate $HCO_3^-$ that is excreted or reabsorbed based on pH sensors in renal tubules
    - By reabsorbing $HCO_3^-$ we remove free $H^+$ -> ↑pH
    - $H^+$ is also actively excreted -> ↑pH




## Acidosis and Alkalosis

| | |
|---|---|
| **Metabolic Acidosis** | |
| **Causes** | -Diabetic Ketoacidosis<br>-Alcohol, Aspirin, Iron ingestion<br>-Lactic acidosis (lactic acid builds up after shock)<br>-Excretion of bicarbonate (diarrhea etc)<br>-Advanced Kidney disease<br>-Toxins: Carbon monoxide, cyanide, methanol |
| **Symptoms** | Nausea, Vomit, Fatigue, weakness, confusion<br>Deeper breathing, Faster Respiratory Rate<br>↓ B.P. = Shock, Coma, Death |
| **Metabolic Alkalosis** | |
| **Cause** | -Acid loss from vomit, stomach drainage, overactive adrenal gland, or diuretics |
| **Respiratory Acidosis** | |
| **Causes** | Elevated arterial $ppCO_2$ b/c ↓ breathing<br>- Sleep apnea, lung disorders, nerve/muscle impairment in chest, OD of alcohol, Opioids, or strong sedatives |
| **Symptoms** | Headache, Drowsiness, Stupor, Coma |
| **Respiratory Alkalosis** | |
| **Causes** | Anxiety<br>Aspirin OD<br>Fever (breathing off extra heat)<br>Hypoxemia<br>Pain |
| **Symptoms** | -Irritability<br>-Muscle Twitching<br>-Muscle Cramping<br>-Muscle Tetany in severe cases |

# Pharmacology of BL&I I

## RBC Disorders

### Anemia

- See PBL case wrap up for details

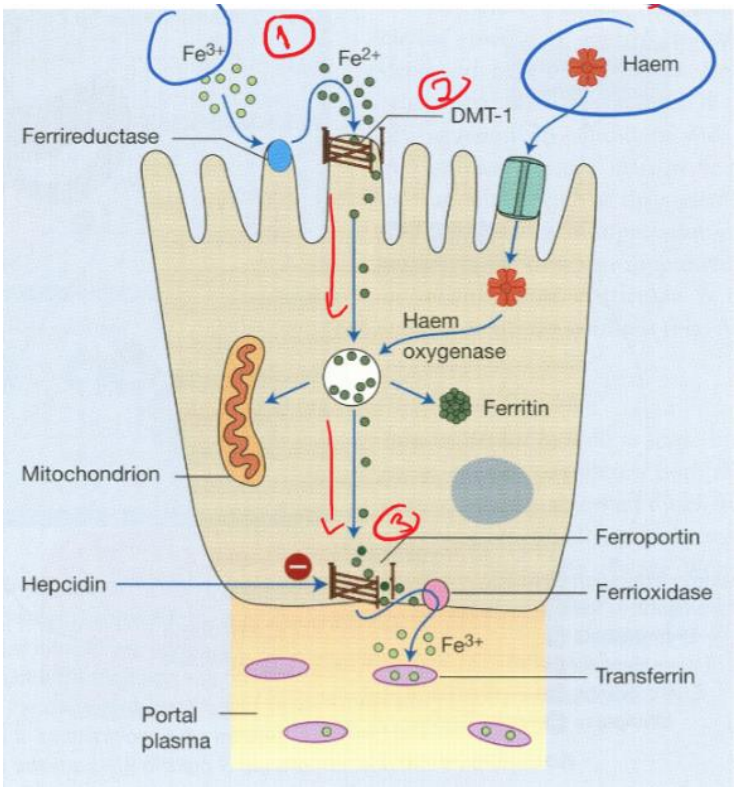
**Pharmalogical Considerations**

- General anaesthesia (with epinephrine) ↑H.R. and cardiac work load
    - $O_2$ transport is compromised
    - Vital to ensure full oxygenation!

### Iron Absorption/ Iron Deficiency Anemia

- 2 sources: from Heme in meat, and from Ferric iron supplements

1) $Fe^{3+}$ is reduced to $Fe^{2+}$
2) Divalent metal transporter 1 (DMT-1) transports $Fe^{2+}$ into cell from gut lumen, and Heme Carrier Protein 1 (HCP1) transports heme into the blood (or stored as Ferritin)
    - Occurs in duodenum
3) Ferroporin transports $Fe^{2+}$ out of the cell into blood
4) $Fe^{2+}$ oxidized to $Fe^{3+}$
5) Transferrin transports $Fe^{3+}$ within circulation to marrow for Hgb synthesis, or to liver for storage as ferritin




| | Etiology | Cause | Treatment | Side effects |
|---|---|---|---|---|
| **Iron Deficiency Anemia (Microcytic)** | | Deficiency in the absorption/uptake of iron | Iron Salt tabs<br>Ferrous Sulphate/Ferrous Gluconate)<br><br>For Malabsorption issues use Perenteral iron therapy | Nausea, Epigastric discomfort, Abdominal Cramps, Constipation, Diarrhea, Teeth Staining |
| **Vitamin $B_{12}$ Deficiency (Megaloblastic)** | From diet meat. Binds to intrinsic factor and absorbed into ileum for liver storage | Defect in Intrinsic Factor, vegan diet, ileal disease. | | Nitrous Oxide inhibits methionine synthetase (essential for B12 metabolism) and can lead |

| | | | | |
|---|---|---|---|---|
| | - GI symptoms, Neurologic symptoms | | | to impaired bone marrow function |
| **Aplastic Anaemia (pancytopenia)** | | Genetics, Autoimmune, Chemical, Virus<br><br>Drugs (NSAID, Phenylbutazone, Chloramphenicol, Sulphonamides,<br><br>Glue sniffing, heavy metals, benzene, Toluene | Remove cause (drug, or chem) if possible | |

**Glucose-6-Phosphate Dehydrogenase Deficiency:**

G6PD: Protects cells from oxidative stress, by producing NADPH, keeps Glutathione reduced (which can reduce oxidised things)

- Essential for normal life span of RBC

Deficiencies provoke destruction of RBC (leads to hemolytic anemia with Jaundice)

Drugs that cause haemolysis by G6PD deficiency: Aspirin, Sulphonamides, Anti-malarial,

- *Prilocaine* (common local anaesthetics without epinephrine) – Prevents $Fe^{3+}$-$Fe^{2+}$ Methemoglobulinemia -> cannot absorb Iron from gut

**Erythropoietin Treatment:**

2 forms:

1. Epoetin alfa – Recombinant form of the endogenous protein
2. Darbepoetin alfa - Modified form of Epoetin alfa

*Indications:*

- Anemia from chronic renal failure
- Anemia from Chemotherapy
- Increase blood yield prior to donation
- Cancer

***Local Anaesthetic Considerations:***

- *Limit use of Prilocaine and Benzocaine*
    - Prevents $Fe^{3+}$ - $Fe^{2+}$
    - Results in methemoglobin – unable to transport $O_2$

## Cancer Patients

| | Antineoplastic Drugs |
|---|---|

| | |
|---|---|
| **Side Effects** | Bone Marrow Suppression<br>GI Effects (due to fast replication, these cells are targeted)<br>Hepatotoxicity<br>Immunosuppression<br>Oral effects (ulceration, xerostomia) |
| **Clinical Management** | Before Chemo<br>- Eliminate/manage infections<br>- Control periodontal disease<br>- Educate on proper oral hygiene<br>- Extract non-vital teeth<br><br>During Chemo<br>- Consider hematologic status<br>- Consider immune status |

## Bleeding Disorders

| **Impair Platelet Function** | **NSAIDs, Aspirin**:Diclofenca, Ibuprofen, Difunial<br>**β-lactams/Broad Spectrum**: Ampicillin, Methicillin, Pen G, Rifampicin, Cephalosporin<br>**Psychoactives**: Antihistamine, Diazepam, Chlorpromazine<br>**Diuretics**: Acetazolamide, Chlorothiazide<br>**Cardiovascular**: Digitoxin, Heparin |
|---|---|

| | **Etiology** | **Pathophysiology** | **Management** |
|---|---|---|---|
| **Hemophilia A** | Most common<br>Sex linked (Males primarily) | Absence or ↓ Factor VIII, Common pathway of coagulation impaired | *Avoid:*<br>Local anaesthetics if no Factor VIII transfusion<br>(no Full Nerve blocks, ↑risk of severing nearby artery)<br>Aspirin/NSAIDs<br><br>Desmopressin: Induce release of Factor VIII from endothelial storage |
| **Hemophilia B** | Female carriers often have bleeding tendency as well | Factor IX deficiency<br>Presents similarly to Hemophilia A | Management similar to Hemophilia A |
| **Hemophilia C** | | Factor XI deficiency | Local haemostatic measures<br>Fresh Frozen Plasma |
| **vWD** | Most common inherited bleeding disorder | Deficiency in vWF<br>- Synthesizes in megakaryocytes and endothelial cells<br>- Carrier for Factor VIII<br>- Bridge between platelets and damaged vessel<br>Often find Factor VIII deficiency as well | Avoid Aspirin and NSAIDs<br>Use Desmopressin<br>- Stimulate release of vWF and Factor VIII |
| **Vitamin K deficiency** | | Malabsorption or low intake of Vitamin K (liver failure)<br>Prolonged broad spectrum antibiotic use kills Vit. K producing bacteria in gut | Phytomenadion (Vit. K1) IV prior to surgery |
| **Factor XII Deficiency** | Rare, inherited deficiency | Doesn't lead to abnormal bleeding despite prolonged aPTT test. | |

| | | | |
|---|---|---|---|
| | | Factor XII not essential for Intrinsic pathway function, because Extrinsic activated intrinsic at Factor IX step | |
| **Leiden Deficiency** | Single Gene defect (5% of Europeans) | Increased blood clotting, Factor V cannot be inactivated by anticoagulant protein C | Often on Warfarin |

## Anticoagulants

Red Flag conditions for when to prescribe:

- Atrial fibrillation
- Myocardial Infarction
- Cerebral thrombosis
- Deep vein thrombosis
- Heart valve replacements
- Renal dialysis

| Anti-Coagulation Cascade Drugs | |
|---|---|
| Drug | **Warfarin** |
| MOA | Interferes w/ synthesis of Vit. K dependant factors (II, VII, IX, X) -> Common and Extrinsic Pathways<br><br>Reversed by adding Vit K |
| Clinical use | Long term anticoagulation Therapy |
| Potentiation of Effects | Inhibits metabolism (Metronidazole)<br>Inhibit platelet function (Aspirin, NSAID, antibiotics)<br>Displacement of warfarin from albumin (NSAIDs, Chloral Hydrate)<br>Inhibition of Vit. K reduction (Cephalospirin)<br>Decrease Vit. K ability (Broad Spectrum Ab) |
| Reduction of Effects | P450 Metabolism induction (Barbituates, Rifampicin)<br>Increased Vit. K (Vitamin K)<br>Reduced warfarin absorption (Colestyramine) |
| | |
| Drug | **Heparin** |
| MOA | Catalyze antithrombin III activation (increases antithrombin III+thrombin complex)<br><br>Inhibits factors II, IX, X, XI, XII -> Intrinsic Pathway and common |
| Clinical Use | Rapid effects of anticoagulation |
| Toxicity | Increases Bleeding<br>Additive effects with other anticoagulants<br>Transient thrombocytopenia<br>Prolonged use associated with osteoporosis |
| | |
| Drug | **Low Molecular Weight Heparin (Lovenox)** |
| MOA | Inhibits activated Factor X (less effective on thrombin that heparin) |
| | |
| Drug | **Dabigatran (Praxada)**<br>**Lepirudin** |
| MOA | Direct Thrombin inhibitor<br>Doesn't depend on action of antithrombin |

| Antiplatelet Drugs | |
|---|---|
| **$TXA_2$ Inhibition** | |
| Drug | *ASA (Aspirin), NSAIDs* |
| MOA | Inhibits Thromboxane A2 synthesis via COX-1 pathway, therefore inhibiting platelet activation and aggregation<br><br>(ASA = Irreversible, NSAID = Reversible) |
| Drug | *Dipryridamole* |
| MOA | Inhibit phosphodiesterase (blocking adenosine uptake). This inhibits $TXA_2$ Synthesis |
| **ADP Inhibition** | |
| Drug | *Clopidogrel, Ticlopidine, Prasugrel, Ticagrelor* |
| MOA | Inhibit ADP-induced platelet aggregation by irreversible inhibition of $P2Y_{12}$ receptors |
| **GP IIb/IIIa Inhibition** | |
| Drug | *Abciximab* |
| MOA | Prevents GP IIb/IIIa from crosslinking with Fibrinogen between platelets |

| Thrombolytic Agents | |
|---|---|
| Direct Enzymes | |
| Agent | *Tissue Plasminogen Activator (tPA), Urokinase* |
| MOA | Directly converts plasminogen to plasmin |
| Indirect non-enzymes | |
| Agent | Streptokinase (from bacteria) |
| MOA | Bind circulating plasminogen, forming active complex. This complex is then catalyzed to activate plasminogen into plasmin |

# Pharmacology of BL&I II

## Hemostatic Agents

| Family | MOA | Contraindications |
|---|---|---|
| **Gelatin Sponges**<br><br>**Gelfoam** | $H_2O$ insoluble, porous and pliable. Can absorb 45x it's weight in blood<br>- Forms matrix that traps platelets and RBC's (scaffold for clot)<br>Completely resorbs in 4-6 weeks | Closure of skin incisions (interferes with healing of skin edges)<br><br>Don't place in intravascular compartments (inside vessels) -> risk embolization |
| **Denatured Celluose**<br><br>**Surgicel** | Meshwork of oxidized cellulose<br>- Forms physical plug<br>- Cellulosic acid release denatures hemoglobin to help plug up injured site (Tanic acid in tea bags does the same thing, ask patient to bite down on teabags) | Causes delayed healing of socket (interferes with bone regeneration and epithelialization) |
| **Bone Wax** | Mix of beeswax, paraffin, and isopropyl palmitate<br>- Used when bleeding is from a vessel within bone. Smeared across the hole to block blood loss. | NON-resorbable. Can have negative effects of osteogenesis<br>Prevents clearing of bacteria |
| **Topical Thrombin** | Direct action to clot the fibrinogen of blood | Surface use only -> IV use can cause extensive thrombosis and death<br><br>Doesn't work with massive rapid arterial bleeds |
| **Whiteheads Varnish** | Components:<br>- *Bismuth* -> ↓ blood flow from open blood vessel. Drying absorbent action<br>- *Iodoform* -> Antiseptic and anaesthetic to ↓ pain and ↓ infection<br>- Paraffin | |
| **Topical Epinephrine** | Vasoconstriction (adrenergic effects)<br>Used often in Epi soaked retraction cord | ↑ BP and tachycardia |
| **Astringents** | Cause contraction/shrinkage of tissues and dry up secretions (blood in this case)<br>- Used during gingival retraction<br><br>3 Groups:<br>1. ↓ blood supply via vasoconstriction (Epinephrine, cocaine)<br>2. Remove water from tissues (Glycerol, Alcohol)<br>3. Coagulate superficial tissue layers into crust (Metalics) | |

## Corticosteroids

Secreted by Adrenal Cortex

| | |
|---|---|
| **In dentistry** | Used topically or systemically as an inflammatory control against oral lesions |
| **Long Term Use** | Chronic systemic inflammatory diseases like arthritis or asthma |

| | **Glucocorticoids** | **Mineralocorticoids** |
|---|---|---|
| Example | Cortisol<br>Prednisone<br>Dexamethasone | Aldosterone |
| Effects | Carbohydrate Metabolism (main)<br>- Liver glycogen ↑<br>- Gluconeogenesis ↑<br>- ↑ Glucose output from liver<br>- Protein catabolism<br>- Bone Catabolism<br>Anti-inflammatory<br>Antiallergenic<br>↓ Prostaglandins and Leukotrienees | Affects water and sodium levels<br>↑ $K^+$ loss |
| Adverse Effects | Immunosuppression<br>Diabetes<br>Muscle Wasting<br>Growth Suppression<br>Osteoporosis<br>Psychosis<br>Peptic Ulceration | Hypertension<br>Hypokalemia<br>Muscle Weakenss<br>EDEMA |
| MOA | Steroid -> diffuses across membrane and binds cytoplasmic receptor -> enters nucleus and bind chromatin -> regulates gene $T^c$ and $T^L$. | |
| Dental Uses | *Oral Lesions*<br>- NOT herpetic lesions<br>- Only for non-infectious inflammatory diseases (lichen planus)<br>*Aphthous Stomatitis*<br>*TMJ pain*<br>- ↓ inflammatory effects of arthritis<br>*Oral Surgery*<br>- ↓ Post op edema, trismus and pain<br>- Must weight pros vs cons (risk of infection)<br>*Pulp Procedures*<br>- Pulp cap, pulpotomy, hypersensitivity, cervical dentin therapy | |

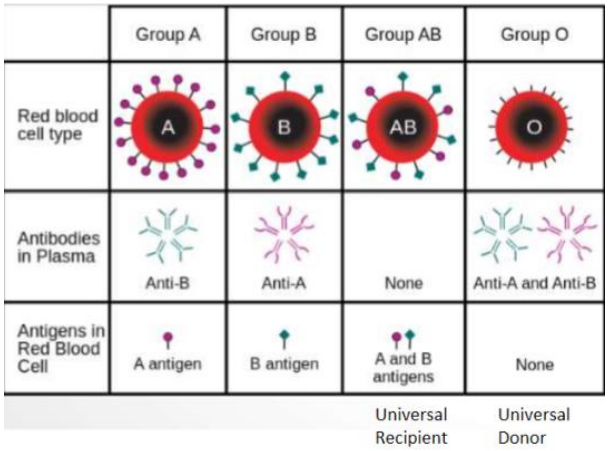
## NSAIDs

| | |
|---|---|
| Effects | Analgesic<br>Antipyretic<br>Anti-inflammatory |
| MOA | Inhibits Cyclo-Oxygenase (COX) -> inhibit prostaglandin synth<br>- Aspirin = irreversible inhibition<br>- Ibuprofen = Reversible inhibition |
| Adverse Effects | GI:<br>- Damages mucosa of GI (PG ↓ Acid secretion, ↓ blood in mucosa, and cytoprotection)<br>Blood:<br>- ↓ $TXA_2$ synth = ↓ platelet aggregation<br>Renal:<br>- ↓ Vasodilation of Afferent Arterioles in kidney = ↓ GFR |

# PBL I – Kourtney Love

## Blood Grouping

- Blood has 4 possible combinations of Ag on their surface (A, B, AB, O)
    - First detectable 3-6 months old
- Rhesus Factor (Rh) is another possible Ag on RBC.
    - Produced 30-45 days gestation
- Low numbers of ABO Ag in Fetal blood, few Ab bind therefore no significant immune activation.
    - IgM is main Ab class, and because its large cannot cross placenta.
    - ABO incompatibility isn't a major issue in pregnancy




## Rh in Pregnancy (Rh- mother, Rh+ fetus)

- Rh- mothers exposed to Rh+ RBC from fetus develop antibodies against Rh
    - Ab cross placental barrier and destroy Rh+ Fetal blood
- Initial exposure usually not problem because primary response takes time and fetus (in most cases) get born on exposure
    - Exposure due to transplacental fetal hemorrhage (late in preg. Or during birth), often during 3rd trimester. This is when mother is sensitized to Rh
- Sensitized mother (second pregnancy Rh+) can cause problems for fetus because Ab is IgG and is small enough to cross placental barrier, and immune response is faster

| | |
|---|---|
| Fetal Symptoms with Sensitized mother | Anemia associated heart failure<br>Liver failure<br>Kernicterus (Bilirubin-induced brain damage)<br>Erythroblastosis Fetalis (Hemolytic Disease of the Newborn) – Most severe |

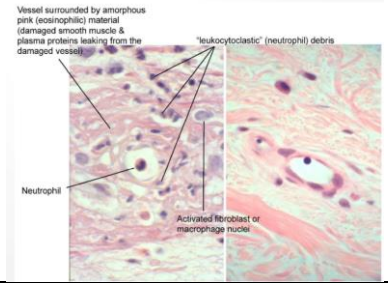
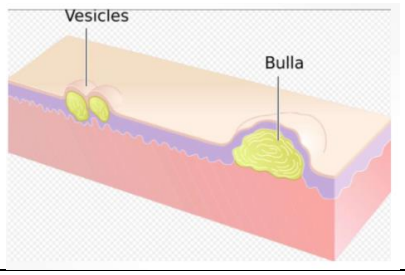
- Immunoprophylaxis injection of the Rh- mother used to prevent primary immune response
    - Injected Anti-Rh antibodies coat Rh+ Fetal RBC, opsonize and flag for rapid destruction before mothers immune system has opportunity to initiate primary response
        - Prevents sensitization
    - Given at 28 weeks (3rd trimester) AND at time of birth
    - Also important to give after miscarriage, or abortion in case fetus Rh+

## Hepatitis C

| | |
|---|---|
| **Severity** | Less severe than Hep B, often develops into asymptomatic chronic infection |
| **Associated Diseases** | -Sjogrens Syndrome (immune disorder, dry eyes, xerostomia)<br>-Lichen Planus (purplish, itchy flat-topped bumps on skin)<br>-Lymphoma<br>-Cryoglobulinemia<br>-Type III Hypersensitivity Rxn (Rash) due to Ag-Ab complexes depositing on blood vessel walls |
| **Diagnosis** | Anti-HCV IgG = Presence of infection at some point (can't tell acute or chronic)<br>HCV-RNA PCR = Presence of infection currently |
| **Transmission** | Blood Borne<br>Vertical transmission to newborn |

| | Acute HCV | Chronic HCV | Prior HCV* |
|---|---|---|---|
| Anti-HCV IgG | - | + | + |
| HCV-RNA (PCR) | + | + | - |

HCV = Hepatitis C virus; anti-HCV = antibody to HCV.
*Previous HCV infection with spontaneous recovery or successful treatment.

| | **Leukocytoclastic Vasculitis** | **Oral Pemphigoid (MMP)** |
|---|---|---|
| Etiology | Deposition of Ag-Ab complex along basal membrane of vessels of skin<br>(Type III Hypersensitivity) | Deposition of Ig + Complement against pemphigoid Ag along basal membrane of oral mucosa<br>-Considered Autoimmune |
| Pathophysioology | Neutrophils, Macrophages Complement destroys complexes but also damage vessels (creating rash) | Sub-epithelial clefting/separation between basement membrane and epithelium (blistering) |
| Lab Findings | Neutrophil (leuko) apoptosis with fragmentation (-cytoclasia) of the nuclei | Nikolsky Sign – top layer of skin easily rubs away from lower layers |
|  |  | |

# PBL II – Mrs. Robinson

**Blood Functions:**

- Transport $O_2$ and $CO_2$, Coagulate, provide immune response, delivery waste and drugs to liver and kidneys, maintain Acid-Base equilibrium, Temp, Electrolyte, and Volume

**Erythropoiesis**

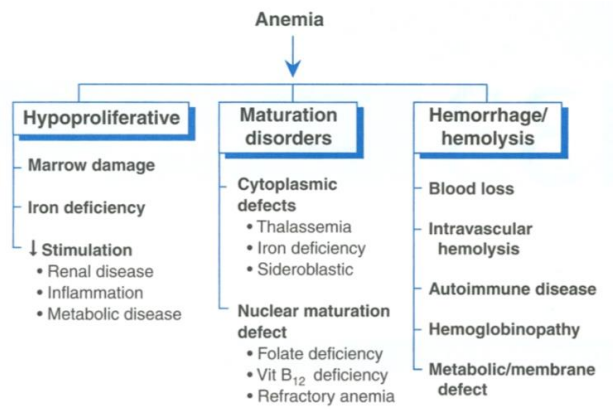
- 8 stages of differentiation and maturation between Pronormoblast stage and mature Erythrocyte
- 1st 7 stages occur in bone marrow to develop the Reticulocyte.
    - Reticulocyte develops for 4 days in bone marrow as more Hb is produce and Nucleus is lost
- Final maturation to Erythrocytes occurs when Reticulocyte is released into circulation, RBC matures for 1 day in circulation before development is complete

**Anemia = Decreased RBC, Hemoglobin, or Hematocrit ultimately resulting in decreased $O_2$ transport to tissues**

- Classified based on size of RBC or Mean Cell Volume (MCV)
- RDW (RBC Distribution Width) indicator of the variability of cell size, large RDW indicative of multiple causes (macrocytic AND microcytic)

**3 Mechanisms of Anemia:**

1. *Decreased RBC Production*
    - Deficient blood forming components
    - Bone Marrow Failure
    - Decreased EPO (renal failure)
2. *Increased RBC Destruction*
    - Hemolysis
3. *Blood Loss*
    - Hemorrhage (Acute or Chronic)




| | General Signs and Symptoms |
|---|---|
| **Anemia** | -Pallor (skin, and mucous membrane)<br>-Weakness<br>-Fatigue<br>-Lightheaded<br>-Cold extremities<br>-Headaches<br>-Malaise<br>-Dyspnea (Out of breath)<br>-Tachycardia (Increased Heart Rate)<br>-Angina Pectoris (Radiating pain in left chest, arms, back and mandible) |

| | Microcytic (Low MCV) | Normocytic (normal MCV) | Macrocytic |
|---|---|---|---|
| **Cause** | -Iron Deficiency<br>-Thalassemia (abnormal Hb)<br>-Chronic Illness | -Hemorrhage<br>-Chronic Illness<br>-Hemolytic Anemia<br>-Neoplasm<br>-Marrow suppression (chemotherapy induced) | -B12 or Folate deficiency<br>-Chronic liver disease<br>-Alcohol Excess<br>-Myelodysplastic Syndrome (immature RBC produced)<br>-Hemolytic anemia with high Reticulocytes<br>-Aplastic Anemia |

| | Etiology | Mechanism |
|---|---|---|
| **Aplastic Anemia** | *1°:*<br>Unknown cause<br>Often young adults, leading to death<br>*2°:*<br>Caused by drug/chem. Ingestion or radioactive exposure<br>Occurs at any age<br>Better prognosis | Decreased production of all bone marrow products<br>- WBC, RBC, Platelets |
| **Anemia of Chronic Disease** | Chronic inflammatory diseases (infection, autoimmune, kidney disease, cancer)<br><br>Resembles Iron deficiency (reduced RBC production)<br><br>Normocytic early on, microcytic in later stages | Protective mech. To limit available iron during "attack"<br><br>Inflammation triggers Iron regulation.<br>IL-1, TNF-α, IF-β increase synthesis of Hepcidin (decrease Iron metabolism)<br>- ↓ Iron Absorption<br>- ↓ Iron release from macrophage<br>- ↓ Iron release from Liver<br><br>↓ Fe = ↓ Erythropoiesis |
| **Drug Induced** | Chronic Ibuprofen use = acute GI bleeding from ulceration<br><br>NSAIDs cause kidney damage | Fe deficiency leads to microcytic anemia<br><br>↓ kidney function = ↓ EPO and ↓ RBC |
| **Hemolytic Anemia** | **1. Intravascular vs Extravascular destruction**<br>Destruction occurs most often in Liver and Spleen (Extravascular) via mononuclear phagocyte system<br><br>**2. Intrinsic RBC Defect**<br>Cellular rigidity causes splenic sequestration<br>- Spherocytosis, Sickle Cell, Thalassemia, G6PD deficiency<br><br>**3. Extrinsic Defects – Most common**<br>Immune mediated destruction (autoimmune + allo-immune (transfusion rejection) = Ab coated RBC phagocytosis<br><br>Non-immune destruction in infection, or abnormal vasculature (synth hearth valve, TTP fragmentation) | |
| **Thrombotic Thrombocytopenic Purpura (TTP)** | Acquired and Inherited | Clots form in small vessels throughout body<br><br>Ab-inhibition of ADAMTS13, which is normally responsible for vWF cleavage into small subunits.<br>- Long vWF ↑platelet adhesion and RBC trapping |

| | Oral Manifestations |
|---|---|
| **Hemolytic Anemia** | -Mucosal Pallor or jaundice (tongue, sublingual, soft palate)<br>-Lamellar striations in radiograph due to enlarged medullary spaces in hyperplasia of erythrocytes<br>-Step-ladder trabeculae between roots in radiograph |
| **Autoimmune Hemolytic Anemia**<br>(Ab against own RBC either spontaneous or secondary to disease) | Splenomegaly (RBC-Ab transported to spleen, ↑ size to ↑ rate of destruction |
| **Pernicious Anemia**<br>($B_{12}$ malabsorption via ↓ Intrinsic factor by parietal cells) | Crohn's disease (terminal ileum)<br>Pancreatitis<br>Dysphagia (difficulty swallowing)<br>Dysguesia (altered taste)<br>Atrophic Glossitis<br>Angular Chelitis<br>Glossodynia (red dorsal tip of tongue w/ papillary atrophy)<br>Decreased muscle tone due to neurologic defects |
| **Folic Acid Deficiency** | Angular Chelitis<br>Atrophic Glossitis<br>Ulcerative Stomatitis<br>Pharyngitis<br><br>NO neurologic symptoms like in $B_{12}$ Deficiency |
| **Iron Deficiency**<br>(microcytic, hypochromic RBC) | Gingival/Mucosal Pallor<br>Atrophic Glossitis<br>Angular Cheilitis |
| **Plummer-Vinson Syndrome (Because of Iron Deficiency)**<br>(Pre-malignant condition) | Esophageal webs<br>Xerostomia<br>Atrophic changes in mucosa and pharynx<br>Dysphagia (muscular degeneration of esophagus)<br>Atrophic glossitis<br>Angular Cheilitis |
| **Sickle Cell Anemia**<br>(Autosomal Recessive, Abnormal Hb and RBC shape, ↓ RBC lifespan and ↑rigidity) | Pale Mucosa (possible jaundiced)<br>Orofacial pain (from bone infarcts)<br>Pulpal necrosis w/o dental disease<br>Enamel Hypomineralization<br>Step-ladder trabeculae between roots<br>Dense Alveolar bone with distinct lamina dura<br><br>Enlarged hematopoietic Maxilla (from marrow hyperplasia)<br>Excessive Overjet and Overbite delayed skeletal maturation<br><br>Risk of stroke<br>Pain<br>Tissue Damage |

## PBL III – Tyrone Bogue

| | Acute Myelogenous Leukemia | Acute Lymphoblastic Leukemia |
|---|---|---|
| **Incidence** | More common in adults<br><br>Successful Cure 50% | Most common malignancy in children <15<br><br>Incidence peaks between 2-5 years old<br><br>Successful remission >80%<br>Successful cure >70% |
| **Types** | 20% pediatric leukemia | 80% pediatric leukemia |
| **Etiology** | Mostly unknown<br>Increased incidence in Down Syndrome<br>No family history<br>Siblings are not at greater risk | |
| **Clinical Presentation** | Onset either slow and insidious or acute and fast<br>Bone Marrow Infiltration: Pallor, Fatigue – Anemia<br>Fever, Infection – Leukopenia<br>Purpura, Epistaxis, Bruising – Thrombocytopenia<br>Gingival Enlargement<br>Loss of appetite<br>Malaise<br>Bone and joint pain<br>Lymphadenopathy (30% of ALL)<br>Hepatosplenomegaly (10% of ALL)<br>Mediastinal mass (10% of ALL) | |
| **Oral Manifestations** | Gingival Enlargement (infiltration by blast cells)<br>Gingival ulceration<br>Gingival hemorrhage<br>Infection (Bacterial, Fungal, Viral)<br>Lymphadenopathy<br>Petechia<br>Purpura<br>Mucosal Pallor - anemia | |
| **Diagnosis** | > 20% nucleated Blasts present in marrow<br>- (normal is < 5%)<br><br>Immunotype blasts for CD markers to determine if Myeloid or Lymphoid lineage<br><br>Lumbar Puncture at time of diagnoses to determine any blast present in CSF<br>- Required extra treatment for CNS infiltration | |
| **Lab Findings** | Peripheral Smear: Anemia (75%)<br>Leukopenia (50%)<br>Thrombocytopenia (70%) | Peripheral Smear: Anemia (75%)<br>Leukopenia (50%)<br>Thrombocytopenia (70%)<br><br>Immature B-cell – 85%<br>Mature B-cell – 1%<br>T-cell – 15%<br><br>CSF infiltration: 5-10% of cases |
| **Treatment** | Combination chemotherapy<br>Possibly cranial radiation<br>Complete remission when marrow <5% blasts and no extramedullary evidence of leukemia<br><br>W/O therapy – Dead in 2-3 months | |

| Oral Complications of Chemo | |
|---|---|
| **Mucositis and Ulceration** | Inflammation of GI, mouth, pharynx, and esophagus (high cell turnover areas) |
| **Infection** | Immunosuppression from chemo ↑ risk of infection<br>- Usual signs of inflammation may not be present (red, pain, swelling, heat) |
| **Pain/Neurotoxicity** | Possible constant, deep pain as result of drugs. Bilateral and mimics toothache (no odontogenic source) |
| **Xerostomia** | Decreased or thickened saliva |
| **Dysgeusia (Taste alteration)** | Atrophy of tongue papilla? |
| **Bleeding** | Thrombocytopenia and clotting factor decrease due to marrow suppression ↑ bleeding time.<br>Platelet transfusion may be necessary |
| **Dental Developmental Abnormality** | Chemo during development may cause short malformed roots, enamel defects, disturbed crown development and eruption. |

**Prophylactic treatments prior to Chemotherapy:**

1. Thorough exam identifying: *Non-vital teeth, grossly carious teeth, gingivitis, periodontitis (5mm pocket depth)*
2. Educate on *proper oral hygiene* and its importance in relation to cancer treatment
3. *Warn about oral side effects* of chemo (xerostomia, mucositis etc)
4. Extract hopeless teeth
    a. *Minor surgery 2 weeks prior to chemo*
    b. *Major surgery: 4-6 weeks prior to chemo*
5. *Antifungal prophylaxis* (miconazole, fluconazole) when ↓WBC to prevent candidiasis
6. *No flossing* prior to treatment (eliminate laceration to gingiva)
7. *Frequent rinses* to debride mouth and reduce bacterial count (chlorhexidine)
8. Fluoride rinse
9. Remove orthodontic appliances, and ensure dentures are fitting well

**Managing Oral Complications during chemo:**

- Suck on ice chips and use Benzydamine 0.15% rinse (topical NSAID)
- 2% lidocaine with Maalox or Benadryl
- Chlorhexidine rise (0.12%)
- Surgilube or Lanolin to dry lips (NO Vaseline, bacteria and fungi can culture on oil based lube)

| Condition | History | Physical Exam | Lab Results |
|---|---|---|---|
| **Hemophilia A** | More prevalent in males<br>Presents in childhood<br>Deep tissue bleeds (joints, muscles)<br><br>Family Hx: Male relatives on mother side | Large bruises<br>Swollen joints (Hemarthrosis) (ankles, knees) | PTT: High<br>INR (PT): Normal<br>CBC: Normal<br>Factor 8: Low |
| **Von Willebrand Disease (vWD)** | Present in children or adults<br>Excessive bleeding with minor or no injury, superficial cuts<br>Spontaneous gingival and nose bleeds<br>"easy bruiser"<br><br>Autosomal Dominant | Mucosal bleeding<br>Petechiae | PTT: Normal<br>INR (PT): Normal<br>CBC: Normal<br>vWF: Low<br>Ristocetin cofactor : Low<br>- Tests vWF function |
| **Disseminated Intravascular Coagulopathy (DIC)** | Severely ill (sepsis, trauma, malignancy)<br>Multiple bleeding sites<br>Bleed from IV puncture | Bleeding from IV<br>Abnormal bleeding<br>Abnormal vitals due to illness | PTT: High<br>INR (PT): High<br>Fibrinogen: Low<br>D-dimer: High<br>CBC: Low platelets, anemia<br>Smear: RBC fragments |
| **Immune Thrombocytopenic Purpura (ITP)** | More common in children (in adults too)<br>Preceded by Viral infection<br>Abnormal bruising<br>Mucosal bleeding<br>Nose bleeds | Mucosal bleeding<br>Petechiae | PTT: Normal<br>INR (PT): Normal<br>CBC: Low Platelets |
| **Platelet reduction thrombocytopenia** | Mucosal bleeding<br>Nose bleeds<br>Fatigue<br>Medication use | Mucosal Bleeding<br>Petechiae<br>Possible splenomegaly or hepatomegaly | PTT: Normal<br>INR (PT): Normal<br>CBC: Low platelets, possible anemia |
| **Child Abuse** | Previous presentations for trauma<br>Inconsistent bruising<br>Inadequate explanation of bruising<br>Social, or familial risk factors | Multiple injuries at different stages of healing<br>Patterned injury (belt, hand)<br>Genetical injury | PTT: Normal<br>INR (PT): Normal<br>CBC: Normal |

## DALE I – Harry

| Von Willebrand Disease | |
|---|---|
| - Prolonged bleeding<br>- Inherited (Autosomal Dominant) defect of platelet adhesion. Deficiency of von Willebrand Factor | |
| **Type 1**<br>**Type 2**<br>**Type 3** | Not enough vWF<br>Malfunction vWF<br>Complete Deficiency |
| **Presentation** | Mucous membrane bleeding (gingiva, nose)<br>Excessive blood loss from superficial cuts<br>Operative and Post Operative Hemorrhage |
| **Treatment** | Desmopressin<br>- Stimulates vWF and Factor VIII release from endothelial cells. Acts in 30-60 mins for 6-12 hours<br>vWF replacement therapy<br>Antifibrinolytic agents<br>Topical thrombin or fibrin sealants |

# DALE II – Bleedin' Disorders

Effects of Primary and Secondary Hemostasis disorders

| Injury | Primary (platelet) Hemostasis | Secondary (Coagulation) Hemostasis |
|---|---|---|
| **Surface Cuts** | Excessive, Prolonged bleeding | Normal/Slightly prolonged bleeding |
| **Onset after Injury** | Immediate | Delayed |
| **Site of Bleeding** | Superficial (Mucosal, and skin) | Deep (Joints, Muscles) |
| **Lesions** | Petechiae, Ecchymosis | Hemarthroses, Hematoma |

Interpretation of Lab Findings

| Condition | INR (PT) – Extrinsic | PTT - Intrinsic | Platelet Count | RBC Count |
|---|---|---|---|---|
| **Haemophilia A/B** | N | ↑ | N | N |
| **vWD** | N | N | N/↓ | N |
| **DIC** | ↑ | ↑ | ↓ | N/↓ |
| **Liver Failure** | ↑ | N/↑ | N/↓ | N |
| **ITP** | N | N | ↓ | N |
| **TTP** | N | N | ↓ | ↓ |

| Hemostasis Type | Test | Normal Range | Purpose | Diagnostics |
|---|---|---|---|---|
| **Primary** | *Platelet Count* | 150-400 x $10^9$/L | Quantify Platelet Number | Low in ITP, DIC, TTP, HUS |
| **Secondary** | *aPTT* | 27-36 sec | Measure Intrinsic pathway (VIII, IX, XI, XIII, XII)<br><br>Monitor Heparin therapy | Prolonged in Haemophilia A/B |
| | *PT (INR)* | 11-24 sec | Measure Extrinsic pathway (VII, III)<br><br>INR standardises lab values<br><br>Used to monitor Warfarin Therapy | Prolonged in Factor VII Deficiency |
| | *Mixing Studies* | | Tests inhibitors of clotting factors by mixing patients plasm with normal plasma | Factor deficiency evident if test becomes normal,<br><br>Inhibition is test still abnormal |
| **Fibrinolysis** | *Euglobin lysis time* | >90min | Checks accelerated fibrinolysis | Accelerated in DIC, VIII Deficiency |

## DALE III – Ethel

| Name | Class | Indications | MOA | Effects on Dental Treatment |
|---|---|---|---|---|
| **Ramipril** | Angiotensin-Converting Enzyme Inhibitor (ACEi)<br><br>Anti-hypertensive | -Heart Failure after myocardial Infarction<br>-Hypertension<br>-↓ Risk MI, Stroke, Cardiovascular events | -Lower BP by reducing products of Angiotensin II, and thus recuding vasoconstriction | -Orthostatic hypotension<br>-Dry cough may interfere with longer appointments |
| **Hydrochlorothiazide** | Antihypertensive<br>Thiazide diuretic | -Hypertension<br>-Edema due to hear failure, liver cirrhosis, renal dysfunction | Blocks salt and fluid reabsorption from urine and kidneys.<br>Increasing urine output | Orthostatic hypotension |
| **Warfarin** | Vitamin K antagonist<br>Anticoagulant | -Thrombembolic disorders<br>-Complications from atrial fibrillation or valve replacement<br>-Pulmonary embolism<br>-Deep vein thrombosis (DVT)<br><br>Target INR:<br>2.5 (2.0-3.0)<br>3.0 (2.5-3.5) – Mechanical Heart Valve | Decreases Vit K factors (II, VII, IX, X) and Proteins C and S | Oral Ulceration<br>Dysguesia (Altered taste)<br>Possible gingival bleeding if over dosing<br><br>NOTE:<br>Avoid Metronidazole use<br>Corticosteroids enhance effects of Warfarin<br>Antibiotic use = 2 fold increase of bleeding with warfarin<br>Antifungal use = 4 fold increase in bleeding |
| **Dabigatran** | Direct thrombin inhibitor anticoagulant | Replacement of Warfarin | Binds reversibly to active site of thrombin, reduces activity ad fibrin formation<br><br>Increases TT test, no effect on INR like warfarin.<br><br>Increases aPTT (thrombin involved in feedback of intrinsic pathway | Procedures as late as possible after most recent dose<br>- Half life 12-14 hr<br>- Peak effect in 1-2hr<br><br>Local hemostatic measures |