Ftplectures Hematology system Lecture Notes

HEMATOLOGY

Medicine made simple

Ftplectures Clinical Medicine
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The field of Medicine is an ever-changing profession and as new evidence based studies are conducted, new knowledge is discovered. Ftplectures has made tremendous effort to deliver accurate information as per standard teaching of medical information at the time of this publication. However, there are still possibilities of human error or changes in medical sciences contained herein. Therefore, ftplectures is not responsible for any inaccuracies or omissions noted in this publication. Readers are encouraged to confirm the information contained herein with other sources.

Anemia part-1 The red blood cell

Structure

- Biconcave
- Microscopic- 6 to 8 μm
- Volume- 90 fentolitre
- Diameter – 2 μm
- No nucleus
- Small
- Few organelles
- Haemoglobin – can carry 270millionmolecules inside a single RBC
- Cytoskeleton- spectrin
- Cell membrane is bilayered with cholesterol and phospholipids
- Phosphotydylserine (PS)
- RBC is red because of haemoglobin= heme (porphrin ring + Fe2+) + globin (2αglobin + 2βglobin= 4 polypeptide chains)
- Histidine holds the Fe molecule in the centre so that O_2 can bind to the Fe.
- Mainly the RBC is red due to iron in heme group.

Functions

- Carry oxygen but do not use it
- Undergo anaerobic respiration- use glucose to form pyruvate.
- Pyruvate forms lactate and releases 2ATP which is used by the Na+/K+ ATPase pump to maintain electroneutrality.

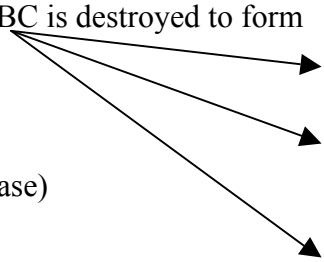
Production

- They are made in bone marrow of large bones like femur, radius or ulna.
- Stem cells – haematocytoblast - proerythroblast (committed stem cell) – erythroblast – normoblast – the nucleus is ejected to form – reticulocyte – a red blood cell/ erythrocyte formed finally
- Erythropoesis- it is the formation of RBC from stem cells
- Erythropoietin- produced from kidneys has the enhancing effect of erythropoesis
- Testosterone has enhancing effect on erythropoietin.

Lifecycle

- It has a life span of 120 days.
- An erythrocyte completes a round in circulatory system within every 20 seconds
- After 120 days the RBS gets weakened plasma membrane.
- Spleen, liver and bone marrow - area where RBCs are destroyed.
- Reticuloendothileal system- consists of macrophages
- Phosphatidyl serine is in the inner core membrane of RBC. When they are exposed and perceived by macrophages, they are destroyed.

- The process of destruction is called phagocytosis.
- The RBC is destroyed to form



Heme-it releases Fe3+ which binds to transferrin

Rest of the RBC- biliverdin– bilirubin (b v reductase)

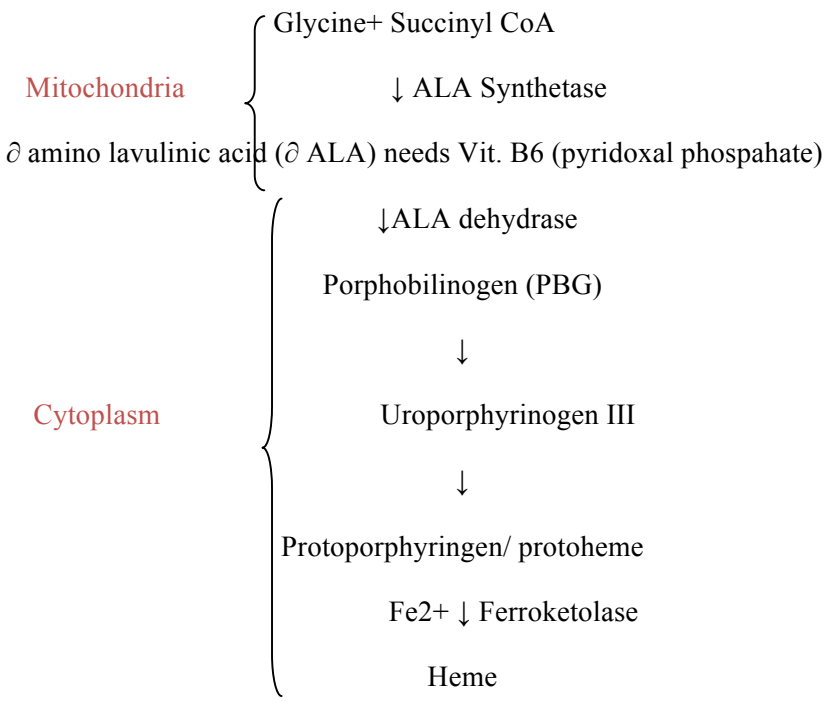
Albumin binds to bilirubin and takes it back to liver

4 polypeptide chains-

- Through urine and faeces, RBC is eliminated.
- The red blood cell can undergo hemolysis by itself. Hemolysed haemoglobin forms haptoglobin.

Anemia part 2- Heme synthesis

Heme is made inside the liver and bone marrow.



- Heme has a negative effect on ALA synthase to regulate the pathway
- Glucose has a negative effect also

Porphyrias

1. **Acute intermittent porphyria –**
   - Uroporphrinogen I synthetase deficiency
   - UPSI converts porphybilinogen to uroporphyringen III

   Labs
   - High levels of PBG
   - High levels of ∂ALA

   Symptoms
   - 5 P's
   - Painful abdomen
   - Neuropathy
   - Psychological problems
   - Paranoid, depressed
   - Portwine urine which turns pink in the presence of oxygen
   - Barbiturates, hypoxia and alcohol have the inhibitory effect on the pathway
   - Do not give barbiturates because they worsen abdominal pain by activating cytochrome P450 system found in liver. This system causes more and more of the functioning of the heme synthesis pathway resulting in an increase in PBG levels.
2. **Porphyria Cutenea Torda**
   - Most common
   - Deficiency of uroporphyrinogen decarboxylase which converts UPSIII to core porphyrinogen which gets converted to heme.

Symptoms

- Sensitive to light- very very photosensitivie
- Inflammation and blistering of the skin

Treatment

- Give beta carotene.

Vit. B6 deficiency

- Causes sideroblastic anemia
- Ringed sideroblast seen in peripheral smear.

Lead poisoning

- Lead inhibits ALA dehydrase and ferroketolase
- Microcytic sideroblastic anemia

Symptoms

- Headaches
- Nausea
- Memory loss
- Lead lines in the gums
- Lead deposition in abdomen and epiphyses of bone
- High levels of ALA in urine
- Abdominal pain, diarrhoea

Anemia

Definition

It is the decrease in hematocrit/haemoglobin concentration.

Hematocrit is the volume % of RBC in bloodstream. It is also called as PCV or packed cell volume.

Compensation of anemia

1. Heart rate increases
2. Cardiac output increases
3. Stroke volume increases
4. Increased extraction of oxygen to tissues

The Hb dissociation graph shifts to the right.

2,3 Diphosphoglycerate decreases the affinity of Hb to oxygen so the curve shifts again to right.

On doing CBC, if Hb<7g/dl, 2 units of PRBCs are given.

Those who are old or cardiopulmonary problems PRBCs must be given when Hb is below 10g/dl.

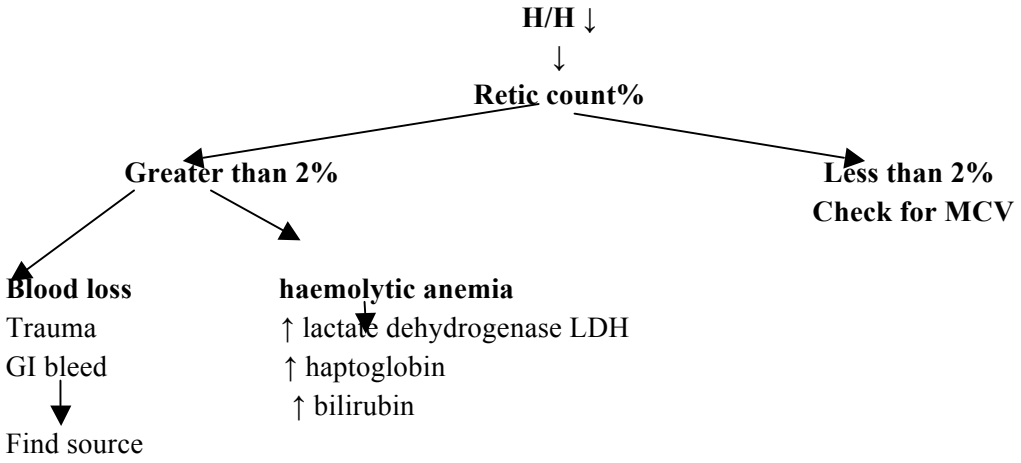
Clinical features

1. Pallor in Eyes- pale conjunctiva
2. Fatigue, weakness, poor concentration
3. Nausea, vague abdominal discomfort
4. Hypotensive (80/40) and tachycardiac
5. Jaundice – yellow eyes+ yellow skin- haemolytic anemia – due to excess of bilirubin spilled in the blood stream

Diagnosis

1. CBC- complete blood count- check Hb level and hematocrit (H/H)
   Hb *3= hematocrit
   1 unit of PRBCs= Hb increases by 1
   Hematocrit increases by 3
   Side note- pseudo anemia (dilutional anemia)- when 0.9% normal saline is given, Hb concentration gets diluted so gives the impression of anemia.
2. Reticulocyte index – to check if erythropoesis is going on. It can be
   a. Greater than 2%- making a lot of reticulocytes- indicates excess destruction or loss of blood
   b. Less than 2%- no production of RBCs from the bone marrow
3. Blood smear for mean corpuscular volume (MCV)
   Average volume of RBC= 90Fl

Approach to anemia



MCV

<70- microcytic anemia	**80-99- normocytic anemia**	**>100 macrocytic anemia**
Iron studies	**Aplastic anemia**	**Vitamin B12 dficiency**
Thalassemias (Alpha and Beta)	**Bone marrow fibrosis**	**Folate**
Anemia of chronic disease	**Tumour**	**Liver disease**
Iron deficiency	**Anemia of chronic disease**	
Lead poisoning	**Renal failure**	
Sideroblastic anemia		

In case of emergency, resuscitation is done.

Iron deficiency anemia

Definition

- It is the most common type of microcytic anemia

- MCV<70

- ferrochetolase brings fe for conversion of protoporhyrin to heme.

Causes

- Chronic blood loss by far
- Menstrual blood loss by far
- Any male of age 40 years with iron deficiency anemia secondary to GI bleed, rule out colon cancer.
- Inadequate supplementation of iron in diet.- like infants growing in breast milk and toddlers (6monts to 3 years)
- Adolescent females
- Pregnant women

Clinical features

1. Fatigue/tired
2. Pallor- conjunctiva and hands
3. Dyspnoea on exertion
4. Orthostatic hypotension or lightheadedness
5. Hypotensive and tachycardia in acute GI bleed.

Diagnosis

1. Ferritin level- Ferritin is a form of iron storage.- level is **low**
2. TIBC – total iron binding capacity- level is **high**
3. Transferrin levels- It transfers iron from ferritin to bone marrow for erythropoesis- level be **high**
4. Iron levels- level is **low**
5. **Peripheral smear-** microcytic, hypochromic RBC
6. **Stool Guaic test-** check your finger inserted in stool with stool Guaic, if it turns blue, it indicates blood loss.

Treatment

1. Ferrous sulphate- oral supplements- ADR- nausea, constipation and dyspepsia
2. Parentral IV Iron
3. Packed Red Blood Cells- hemodynamic instability in case of high heart rate and low BP.

Sideroblastic anemia

- It occurs due to Vit B6/ pyridoxal phosphate deficiency
- The peripheral smear shows ringed sideroblasts.
- Vit B6 is important for the action of ALA synthetase for the formation of delta ALA which if not formed causes non-formation of heme thereby causing anemia.

Thalassemia

Definition

It is a disorder where the globin component of haemoglobin is affected. There is ainadequate production of alpha or beta globin chain.

Types

Beta thalassemia	**Alpha thalassemia**
Beta globins are missing	Alpha component is missing
More in Indians, Mediterranean's, Middle Eastern people	Beta tetramers are formed
	Severity depends on the number of globin chains missing.

Beta thalassemia

Major	Minor	Intermedia
Homozygous beta chain mutation **Also called Cooley's anemia**	Heterozygous beta chain mutation	It affects the 2 genes that code for the beta globin chains
More common in Mediterranean people	It is the most common type of thalassemia	
Symptoms - **Microcytic and hypochromic anemia** - **MCV<70 Fl** - **Massive splenomegaly** - **Bone marrow expansion to make more RBC, and bone looks rugged** - **Growth retardation** - **Failure to thrive** - **Death within first year if left untreated**	**Symptoms** - Asymptomatic - MCV<70Fl - Mild microcytic and hypochromic anemia	**Symptoms** - Intermediate type of anemia
Diagnosis - **Haemoglobin electrophoresis- Elevated level of HbF (fetal)** - **Peripheral blood smear- microcytic and hypochromic**		
Treatment **Blood transfusion- PRBCs have to be given** **Due to lots of transfusion, there may be iron overload causing hemochromatosis-**	Treatment No treatment required	Treatment No treatment required

Deferoxamine (iron chelating agent)

Alpha thalassemia

For 1 alpha sub-unit 2 genes are required. So in total 4 genes needed for 2 alpha chains.

1. **Silent carrier**- (α-/αα)- If only 1 gene is affected, no treatment is required. Normal Hb/Haematocrit
2. **Alpha thalassemia minor**- (α-/α-)- two gene mutations are missing

- Mild Microcytic and hypochromic anemia
- Common in African American patients
- No treatment required

3. Haemoglobin H disease

- --/α-
- Severe haemolytic anemia
- Splenomegaly
- Diagnosis by Hb electrophoresis- we find Hb H.
- Treatment-

i. Blood transfusion
ii. Splenectomy

4. Mutations in all 4 genes

- --/--
- They develop Hydros fetalis
- They do not survive

Anemia of Chronic Disease

-microcytic hypochromic anemia

Definition

A patient is anemic while he has a chronic disease like tuberculosis.

Causes

- Tuberculosis
- Lupus
- Lung abscess (parapneumonic effusion- pneumonia)
- Cancer-Hodgkin's disease, lung cancer and breast cancer
- Inflammatory pathologies- Rheumatoid arthritis, lupus , Sjogren's syndrome
- Trauma

Chronic infection- releases inflammatory cytokines- inhibits erythropoesis

Lab

- Ferritin- high level
- TIBC- low level
- Serum Fe – low level
- Serum transferrin- low level

During chronic disease, the body does not like releasing iron and keeps it away from bacteria

Treatment

Treatment of underlying cause is done.

Aplastic anemia

It is normocytic normochromic anemia. Bone marrow fails to do its function of production of RBCs, WBCs and platelets. It is called pancytopenia (anemia, thrombocytopenia and neutropenia).

Causes

1. Idiopathic
2. Radiation
3. Medication- Gold, chloramphenicol, sulphonamides
4. Viruses-Parvo viruses, HepB and C and Epstein Barr virus, CMV, HZV and HIV
5. Chemicals – insecticide

Symptoms

1. Anemia-Fatigue. Tired, Dyspnoea
2. Thrombocytopenia- easy bruising, petechiae
3. Neutropenia- more predisposed to infection
4. Acute leukemia

Diagnosis

Bone marrow biopsy- hypocellular marrow, absence of progenitor cells.(haematopoetic cell lines)

Treatment

1. Bone marrow transplant
2. PRBCs- blood transfusion
3. Immunosuppressive drugs

Vitamin B12 deficiency

Macrocytic anemia

1. Odd chain fatty acids/ cholesterol- propionyl CoA (in presence of PCA carboxylase)- methylmelonyl coA (in presence of MMA mutase which is activated by Vitamin B12)- succinyl CoA- myelin synthesis and Kreb's cycle
2. N5-methylTHF in presence of methinine synthase (MS) gets converted to THF (active form of folate). B12 gets converted to Methyl B12.
3. In the presence of methinne synthase homocysteine gets converted to methinine. Me-B12 gives methyl group to homocysteine
4. dUMP is converted to dTMP then to thymine
5. THF is converted to 5 10 methylene THF which catalyses the reaction 4 and gets converted to DHF.
6. DHF is converted to THF in the presence of dihydrofolate reductase.
7. Thymine is converted to DNA

What does Vit B12 deficiency cause?

1. Increased level of methyl malonyl coA
2. Neuropathy due to non-formation of myelin sheath
3. Homocysteine level is high
4. Cells do not proceed in their cell cycle.

Liver stores Vit B12 for a period of 3 years

Source- meat and fish

Causes for VitB12 deficiency

1. Perinicious anemia- antibodies are produced against parietal cells which produce IF that is responsible for Vit B12 deficiency.
2. Gastrectomy
3. Strict vegetarian/ poor nutrition
4. Diseases affecting terminal ileum like Crohn's disease
5. Terminal ileum resection
6. Fish tapeworm (Diphylobothrium Latum) or bacterial overgrowth - Impaired absorption of Vit. B12

Clinical features

1. Anemia- Megaloblastic anemia, macrocytosis because cells stuck in G2 phase of mitosis. There is impaired DNA synthesis.
2. Neuropathy- nerves of spinal cord affected.
3. Loss of vibration and position sense
4. Ataxia
5. Upper motor neuron lesions- increased deep tendon reflexes, weakness and spasticity
6. Positive Babinski's sign

Diagnosis

1. Peripheral blood smear- Megaloblastic anemia, MCV >100, hypersegmented neutrophils
2. Serum VitB12 level- low in this case <100pg/ml
3. Levels of methylmalonic acid and homocysteine is very very high.
4. Schilling's test- VitB12 is injected IM which saturates the liver.

Radioactive B12 is given and plasma and urine are checked. If the levels are similar, it is normal. If there is reabsorption problem, B12 is excreted in feces and not present in urine or plasma. Now give intrinsic facto, B12 is found in plasma and urine. So in short, the person has perinicious anemia.

Treatment

Vit B12 supplements given and IV once a month.

Folate deficiency

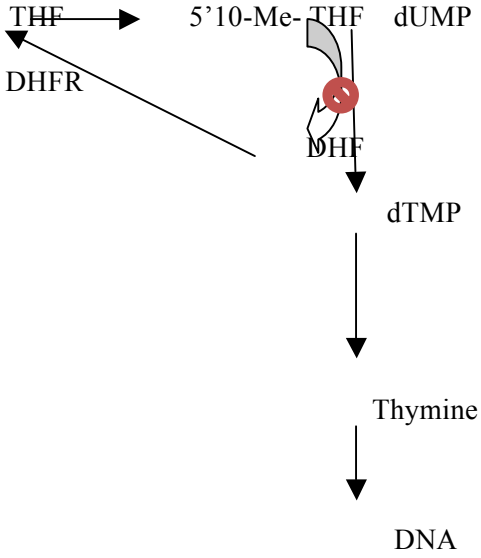
- Liver can store folic acid only for 3 months so there is a high chance of developing folate deficiency
- Folate comes from foliage-green leaves/ green vegetables- best source for folate.
- Do not overcook your vegetables as the folate is lost.

Causes

- Insufficient dietary intake – old people who are in "tea and toast diet".
- Alcoholics- they do not feel hungry do have poor diet
- Long term use of antibiotics
- High demand for folate in pregnancy.
- Hemolysis
- Drugs like methotraxate.

Clinical features

- Similar to Vit. B12 deficiency.
- Macroytic anemia
- Megaloblastic anemia with MCV>100
- CH3-THF → THF → 5'10-Me- THF dUMP



-DNA synthesis does not occur so sells are stuck at G2 phase.

- Folate **does not** cause neurologic symptoms.

- Stomatitis and glossitis.

- High levels of homocysteine and no MMA produced (unlike Vit B12 deficiency)

Treatment

- Give folate supplements.

Haemolytic anemia- hereditary spherocytosis

Definition

It is caused by destruction of red blood cells.

Intravascular	Extravascular
Wihin blood vessels	In spleen or liver

Clinical features

- Can be mild, moderate or severe
- Tired and fatigued
- Weakness
- Dyspnoea
- Dark urine due to haemoglobinuria
- Jaundice – release of unconjugated bilirubin.

Diagnosis

1. MCV- usually normal, may be high sometimes
2. Reticulocyte count is high >2%
3. LDH level in haemolytic anemia
4. Indirect bilirubin level is going to be elevated.>4
5. Haptogobin level- low levels
6. Peripheral blood smear – Schistocytes, spherocytes

Treatment

1. Blood transfusion
2. IV fluids

Classification of haemolytic anemia

Intravascular	Extravascular
Within blood vessels	In spleen or liver- reticuloendothileal sytem
- **Calcified aortic valve**	Hereditary spherocytosis
- **Prosthetic valve**	Sickle cell anemia
- **IgM**	Autoimmune hemolysis (IgG)
Symptoms- dark urine due to hemoglobinuria	Symptoms- jaundice - splenomegaly

Intrinsic red cell membrane defect	Extrinsic RBC membrane defect
Inherited	**Acquired**
Hereditary spherocytosis- autosomal dominant disorder with loss of spectrin/band 3.1/Ankrin	
Splenomegaly	
Severe anemia due to Pavo virus B19 or folate deficiency	
Pigmented stones – acute cholecystitis	

Diagnosis

- **high LDH**
- **retic count is high**
- **indirect bilirubin is high**
- **Comb's test- negative**
- **Osmotic fragility test- positive**
- **MCHC is high**

Treatment

- **Folate supplements**
- **Splenectomy in acute cases**
- **Symptoms of jaundice prevail.**

PNH

Hemolytic anemia- paroxysmal nocturnal hemoglobinuria

- Intermittent dark urine
- They lack PIG-A phoaphatidyl inositol glycogen- which protects a RBC from complements.
- PIG-A is a decay accelerating factor (DAF)- CD55/CD59
- At night we have hypoventilation – so we become acidotic- then complements attack the RBC- results in hemolysis.

Diagnosis

- **High** Hb in urine
- High LDH, indirect bilirubin
- Sugar water test
- Acidified hemolysis test (ham test)
- Low DAF

Treatment

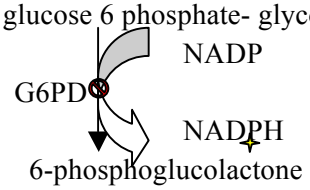
- Fe supplements
- Corticosteroids

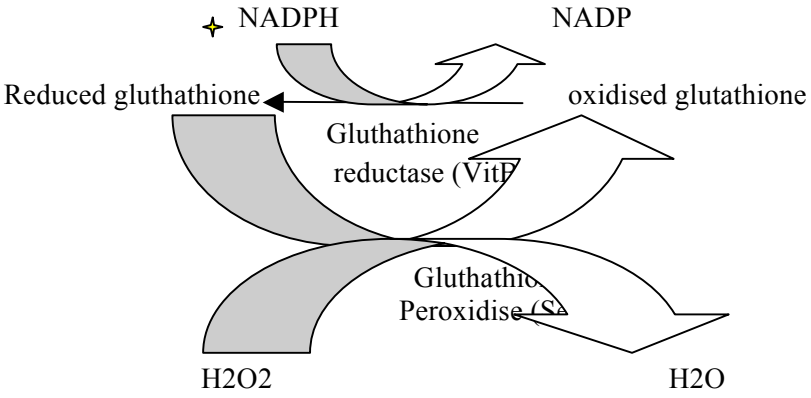
Complications

- Venous thrombosis
- Budd-Chiari syndrome- hepativ vein thrombosis- put on anticoagulant like Warfarin

G6PD (glucose 6 phosphate dehydrogenase) deficiency

- A type of extravascular Hemolytic Anemia
- Glucose- glucose 6 phosphate- glycolysis





- Predisposed to high levels of oxidative stress- free radicals
- Origin- X linked recessive disease- so in males more commonly
- Asian and African people
- Oxygen can form free radicals
- Free radicals cause clumping of Hb molecules and they appear in the form of Heinz bodies which appear as blue dots in the peripheral blood smear.

Causes for high levels of oxidative stress

I. Drugs
1. Antimalarial drugs like primaquine, cloroquine
2. Sulpha drugs like sulfamethoxizole
3. Nifuratine
4. Nalidixic acid

II. Fava beans

III. Infections- HepB, diabetic ketoacidosis

Clinical features

1. Jaundice – bite cell in peripheral blood smear
2. They have protection against malaria.

Diagnosis

1. High LDH
2. Indirect bilirubin high
3. Heinz bodies in PBS
4. Low haptoglobin
5. Negative Comb's test
6. Buetler fluorescent spot test.

Treatment

1. Prevention- stay away from fava beans
2. Vaccinations like HepB.
3. Vit E/Selenium
4. Severe anemia- blood transfusion
5. Acute renal failure- dialysis
6. Splenectomy
7. Folic acid replacement.

Autoimmune haemolytic anemia

Extrinsic defects (Acquired)- IgG/IgM/C3

Autoimmune – IgG	Cold agglutinins disease-IgM	Drugs
Extravascular	Extravascular	Extravascular
- Systemic lupus - Lymphoma - Viruses - Leukemia	- Mycoplasma pneumonia - Infectious mononucleosis	- Penicillin – BPO group - Alpha methyl DOPA - Quinidine - Cephalosporins, - sulpha drugs, - procainamide - rifampicin
		Spider bite (Brown Recluse) **Snake bite**

Clinical features

- fever
- syncope
- congestive heart failure
- Hb in urine
- Mild splenomegaly
- Weakness, pale conjunctiva,

Diagnosis

- Coombs test- posistive
- Normocytic anemia
- Increased LDH, Retic
- Decreased haptoglobin

Treatment

- No treatment usually
- Steroids can be given
- Stay away from cold for cold agglutinin disease- steroids and splenectomy will not affect this disease.
- Stop giving causative drugs
- Retoximab – anti CD20 antibody

Sickle Cell Anemia

Definition

It is an autosomal recessive genetic mutation. They have HbS instead of HbA. Electerophoresis differentiates between HbA and HbS.

Pathophysiology

The 6^{th} position of Hb chain has valine instead of glutamic acid in HbS.

The folding of the globin chain is affected thereby giving a sickle shape to the RBC.

Conditions like-

1. Low oxygen conditions
2. Acidosis
3. Dehydration
4. Change in temperature
5. Infections

They cause Hb polymerisation (RBC gets clumped) causing sickling- increased traffic of RBC in blood vessels- causing ischemia in various organ- decreased blood flow- decreased oxygen to tissues- infarction- tissue necrosis

Population- It affects African people more, one in 12 people have sickle cell trait (HbA/S). Only one gene is mutated. It affects Italians, Greeks and Saudi Arabians.

- Sickle cell trait remains asymptomatic.
- Problem arrives at marriage of two heterozygous people because there is 25% chances for a baby with sickle cell anemia.
-
- **Prognosis**
-
- Vaso-occlusive crisis- obstruction of blood vessels- the more the crisis the shorter is the life span. 3 crisis in 1 year-average life of 35years.

Clinical features

- Lifelong chronic haemolytic anemia
- Jaundice, pallor
- Gall stones- pigmented
- Aplastic anemia- due to infection from Human Parvovirus B19- pRBCs transfusion required
- High output heart failure due to loss of cardiac myocytes.- most common cause of death is CHF.
- Bone infarction- due to decreased blood flow. Extremely painful. Affected bones- humerus, tibia and femur. Painful crisis- it resolves by itself within 2-7 days.
- Hand foot disease- painful swelling on the dorsum of hand and feet. Firts seen in 4 to 6 months.
- Avascular necrosis in metacarpal, metatarsals - ductylitis
- Chest pain- due to pulmonary infarction and a lot of pneumonia

- Spleen- breaking down sickle red blood cells- splenic infarct- becomes small, calcified- autosplenectomy by 4 years
- Joints- avascular necrosis of joint- on femoral and humeral heads.
- Priapism – painful erection episode – 30mins to 3 hours-elf-resolving- drugs given are hydrazaline, nifedepine
- Brain stroke- cereral vascular accident.- more in children
- Eyes- retinal infarct and vitreous hemorrhage
- Proliferative retinopathy- chronic obstruction causes creation of new blood vessels
- They can go blind.
- Chronic leg ulcers
- Predisposed to infections caused by encapsulated bacteria like
    1. Streptococcus pneumonia
    2. Neisseria meningiis
    3. Haemophilus influenza
    4. Kleibsella
    5. Salmonella osteomyelitis

  These encapsulated bacteria are removed by spleen which is not present in these patients.

- Delayed growth in boys
- Sexually not mature like normal people.

Diagnosis

1. Anemia
2. Peripheral smear- sickle shaped RBCs
3. Hb electrophoresis to diagnose HbS.

Treatment

1. Avoid high mountain due to low oxygen tension
2. Drink a lot for oral hydration
3. Treatment of infections
4. Vaccination for- S. Pneumonia, H.influenza, meningitis.
5. At 4 months Penicillin prophylaxis – 6year old.
6. Folate supplements- chronic hemolysis

Treatment of painful crisis

1. Hydration (oral)-normal saline
2. Morphine-pain
3. Oxygen- keep patient warm
4. Hydroxyurea- increases production of HbF, reduce the occurrence of leg ulcers.
5. Blood transfusion- cardiac decompensation
6. Bone marrow transplant

Disseminated intravascular coagulopathy DIC

Definition

It is the formation of blood clots in blood vessels all over the body.

Pathophysiology

It is due to the abnormal activation of the coagulation cascade.

Endothileal cells of blood vessels - trauma – collagen fibres sticking out – release of endotoxin from gram-ve bacteria like E. Coli – glycoprotein 1A attached to exposed collagen fibres – expression of Von Willebrand factor – glycoprotein 1B – platelets bind together – primary hemostatic plug formed.

Intrinsic pathway 12- 11- 9- 8- 10- 5- 2- 1

Extrinsic pathway tissue factor-10- 5- 2- 1

Coagulation factors convert prothrombin to thrombin which converts fibrinogen to fibrin mesh.

Due to DIC numerous microthrombi are formed. This results in the wastage of a lot of platelets and coagulation factors, fibrin.

Causes of DIC- stop making thrombi

- Sepsis/snake bite
- Trauma
- Obstetrics- in case of dead foetus in uterus, and amniotic fluid embolism
- Placental abruption
- Malignancy
- Thrombi

Clinical features

- Patients have bleeding and clotting going on at the same time.
- ICU patients are predisposed to this problem.
- It can be fatal
- Development of petechiae, purpura, ecchymosis
- Bleeding from everywhere – GI tract, urinary tract
- Cerebral infarction
- Acute renal failure

Diagnosis

- Coagulation profile- PT- prothrombin time- it is to measure extrinsic pathway; normal is 10-15 secs.
- PTT - intrinsic pathway- 25-40 secs
- Bleeding time- 2-7 minutes
- D dimer- fibrin spilt by products- it is elevated.
- FIBRINOGEN- it is low
- Platelet count is low- thrombocytopenia
- Peripheral smear has Schistocytes

- Microangiopathic hemoltyic anemia (MAHA)

Complications

- Intracranial bleed- cause of death
- Tiny clots going to head- stroke
- To lungs- pulmonary embolism
- GI- mesenric ischemia- bowl infarction
- Renal – renal failure

Treatment

- Fix the underlying pathology
- FFP-fresh frozen plasma
- Platelet transfusion
- Low dose of heparin
- Cryoprecipitate- clotting factor and fibrinogen
- Oxygen and IV fluids.

Haemophilia A and B

Haemophilia A

Definition

It is an X-linked recessive disorder that often affects males. It is caused by Factor VIII deficiency. Factor 8 converts factor 9 to 10.

Clinical manifestations

1. Hemarthrosis- bleeding joints especially knees
2. Hematoma- Intracranial bleeding, retroperitoneal hematoma, anywhere bleeding can happen.

Diagnosis

1. PTT is prolonged because intrinsic pathway affected.
2. Factor VIII level is low
3. vWB factor is normal-rules out Von Willebrand's disease

Treatment

1. Acute hemarthrosis- analgesics like acetaminophen with or without codeine but no aspirin and NSAIDS because that affects platelet functioning by inhibiting thromboxane A2 production.
2. Immobilize the joints by ice packs
3. Factor VIII concentrate
4. Desmopressin (DDAVP)– increase the production of vWB factor and increase of Factor VIII.
5. Gene therapy- future

Haemophilia B

- Deficiency of Factor IX
- Similar clinical features
- Treatment- Factor IX concentrate
- Desmopressin cannot be given

Von Willebrand's disease

Definition

It is an autosomal dominant disorder caused due to deficiency of VW factor or antigen related to Factor VIII. VWF produced from megakaryocytes and endothelial cells.

A denuded surface on endothelial cells--- VWF are attached to it---- VWF expresses Glycoprotein 1B on its surface---- platelets attached to it------ platelets adhere with each other by Glycoprotein 3B and 2A----- primary hemostatic plug

Absence of VWF-------bleeding

Most common inherited bleeding disorder

1-3% population has it.

Types

1. Decreased VWF- most common
2. Functional dysfunction of VWF- Qualitative abnormality
3. No or absence of VWF

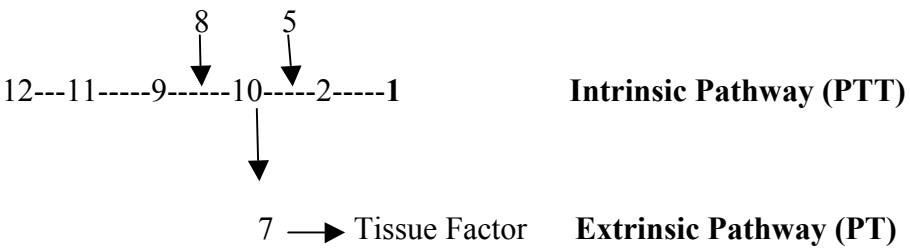
Clinical presentation

1. Cutaneous and mucosal bleeding.
2. Epitaxis- nose bleeds
3. Bleeding gums
4. Easy bruising- excess bleeding from scratch
5. Menorrhagea – heavy menstrual periods

Diagnosis

Usually diagnosed when patient comes in after trauma or has undergone major surgery, and the bleeding does not stop. Patient is not on warfarin or heparin as well.

1. PT- normal
2. PTT- prolonged
3. VWF- low in blood
4. Decreased activity of VWF in blood
5. Ristocetin induced platelet aggregation test



Treatment

1. DDAVP- Desmopressin- induces endothelial cells to produce more VWF.
2. Factor VIII concentrate.
3. Don’t give cryoprecipitate- because of viral transmission
4. Don’t give aspirin or NSAIDS- they inhibit the production of thromboxane A2.

Hodgkins Lymphoma

Objectives for learning: Learning about lymphatic system, histological classification of Hodgkin lymphoma, clinical signs and symptoms, diagnostic techniques, Staging and treatment.

Definition:

Lymphoma is the cancer of the lymph node.

Lymph nodes are the constituent of the lymphatic system. This system is responsible for the drainage of the lymph and by doing so it plays an important role in maintaining the immunity of the body. It has lymphoid tissues within the lymph nodes containing lymphocytes. Lymphocytes further consist of B and T cells. B cells upon encountering with an antigen or a foreign body can give rise to plasma cells which ultimately form antibodies. Thus, when antigens come to destroy the lymphoid tissue, it reacts by activating its cells and in turn lymph node gets enlarged, giving rise to lymphoadenopathy. All kinds of lymphoma show lymphadenopathy while the histological features help to differentiate them.

Causes/ Risk factors:

Pathophysiology

There are two kinds of lymphoma.

- Hodgkin Disease/ lymphoma
- Non- Hodgkin lymphoma

Hodgkin disease has a bimodel age distribution i.e. it occurs in two different age groups. The first age group is between 15 and 30 years of age and other group comprises of patients over 50 years of age.

The histological hallmark of the Hodgkin lymphoma is the Reedsternberg cells which are large cells containing two nuclei, giving an appearance like an owl's eyes. There are two forms of Hodgkin lymphoma, namely

- Nodular lymphocyte- predominant Hodgkin lymphoma (10 to 20%)
- Classical Hodgkin lymphoma which is histologically further classified as:
  - Nodular sclerosis Hodgkin lymphoma (It is basically band of collagen and occurs more in women with incidence of 40 to 60%)
  - Mixed cellularity Hodgkin lymphoma
  - Lymphocyte-rich Hodgkin lymphoma
  - Lymphocyte-depleted Hodgkin lymphoma (It has a poor prognosis)

Hodgkin lymphoma can be differentiated from non Hodgkin lymphoma on the basis of the presence of inflammatory cells. These inflammatory cells are present in case of Hodgkin lymphoma while in non Hodgkin lymphoma there is no inflammatory infiltrate.

Clinical symptoms and signs

- Patients are often asymptomatic or may have B symptoms such as fever, weight loss and night sweats.
- There is painless lymphadenopathy. The painless lymphadenopathy together with B symptoms exhibits a poor prognosis.
- There may be pruritus and cough due to the involvement of the mediastinal lymph nodes.

Diagnosis

- Lymph node biopsy
- Chest x-ray
- CT scan chest, abdomen and pelvis
- Bone marrow biopsy
- Laboratory tests reveal the presence of leukocytosis, eosinophilia and elevated erythrocyte sedimentation rate (ESR).

Staging of Hodgkin lymphoma

The Hodgkin lymphoma is classified according to the Ann Arbor classification.

Stage I: Involvement of a single lymph node

Stage II: Involvement of two or more lymph nodes on the same side

Stage III: Involvement of lymph nodes on both sides or below the diaphragm

Stage IV: Wide spread, disseminated, involving extra lymphatic sites

Treatment

- Radiotherapy
- Chemotherapy

Radiotherapy is used to treat stage IA, IIA and IIIA. For stage III and stage IV chemotherapy is preferred. The combination of both radio and chemotherapy offers a good cure rate of 70%.

1. A -20-year female presents with night sweats, fever and weight loss. On examination, she is having an enlarged mandibular lymph node, which is non-tender and painless. What is the most probable diagnosis?
    a. Sarcoidosis
    b. Hodgkin lymphoma
    c. Systemic Lupus Erythematosus
    d. Non-Hodgkin lymphoma

The correct Answer is b.

The most probable diagnosis is Hodgkin lymphoma. This is because this lymphoma is usually presents with the painless enlargement of lymph nodes. Sometimes, it may accompany B symptoms such as weight loss, fever and night sweats. It shows bimodal age distribution with first peak between 20 and 35 years of age.

Sarcoidosis is a disease in which multisystem inflammation takes place. Its etiology is unknown and usually manifests as noncaseating granulomas, chiefly in the intrathoracic lymph nodes and lungs. It may therefore present with a number of symptoms depending upon the site of involvement.

Systemic lupus erythematosus (SLE) is a condition of inflammation of connective tissues demonstrating variable manifestations. It may affect several organ systems by means of immune complexes and a huge range of autoantibodies, predominantly antinuclear antibodies.

Non-Hodgkin lymphoma is usually widely disseminated on presentation and therefore presents with not only B symptoms and painless lymphadenopathy but also with the extranodal involvement such as bone marrow, brain, skin, lung, testes, thyroid, gut and bone.

2. A-52 -years old male presents with increasing weight loss, cough and abdominal pain. Chest X-ray shows mediastinal mass while CT scan of the abdomen shows enlargement of lymph nodes above and below the diaphragm. On the basis of lymph node biopsy Hodgkin lymphoma is diagnosed. What is the stage of this lymphoma in this patient?
    a. Stage I
    b. Stage II
    c. Stage III
    d. Stage IV

The correct Answer is C.

On the basis of clinical symptoms and investigations, the stage of Hodgkin lymphoma in this patient is III. This stage is characterized by the involvement of lymph nodes on both sides of the diaphragm with or without the involvement of extralymphatic sites. This patient shows dissemination of tumor to both sides of the diaphragm.

Stage I is the Involvement of a single lymph node. It therefore does not presents with abdominal pain along with cough. Either there is a complaint of cough or abdominal pain.

Stage II of Hodgkin lymphoma is basically the involvement of tumor to two or more lymph nodes on the same side.

Stage IV is the diffuse involvement of one or more extralymphatic tissues such as bone marrow or liver.

3. A-65-year old female presents with the complaints of low grade fever for four months. There is also a complaint of weight loss over the past four months. On examination, generalized lymphadenopathy is found which is non-tender and rubbery in consistency. A lymph node biopsy is taken and Hodgkin lymphoma is diagnosed. What is the characteristic histological finding of the Hodgkin lymphoma?
   a. Reedsternberg cells
   b. Starry sky pattern
   c. Smudge cells
   d. Myeloblasts

The correct Answer is a.

Reedsternberg cells are the characteristic histological finding of the Hodgkin lymphoma. These are large cancerous lymphoid cells of B cell origin. They are usually present in small numbers surrounded by large numbers of plasma cells, reactive T cells and eosinophils. Reedsternberg cells consist of abundant cytoplasm, two nuclear lobes and large inclusion-like nucleoli.

Starry sky pattern is the characteristic finding of the Burkitt lymphoma and this pattern is the result of interspersed benign tangible body macrophages. Burkitt lymphoma is the malignant tumor of the B lymphocytes.

Smudge cells are often found in chronic lymphocytic leukemia (CCL). In this malignancy, the peripheral blood comprises increased number of round, small lymphocytes with scant cytoplasm. These are very fragile and usually disrupted in the process of making smears, thus give rise to smudge cells.

Myeloblasts are the characteristic finding of acute myelogenous leukemia (AML). They have delicate nuclear chromatin, voluminous cytoplasm and two or four nuclei.

Non-Hodgkin's lymphoma

- Causes are not known
- Malignant transformation of Bcell and Tcell
- 85% Bcell lymphoma
- 15% Tcell lymphoma
- It starts inside lymph node- spreads to blood- then to bone marrow
- 6th most common disease in the U.S.

Risk factors

- HIV/AIDS
- Organ transplant- immunocompromised
- Viral infection- Ebstein-Barr virus, HTLV-1
- H.pylori infection induced
- Hashimoto's disease
- MALT

Classification

<table>
<tr><th>Low grade</th><th>Intermediate grade</th><th>High grade</th></tr>
<tr><td>- Bcell tumor
- Small lymphocytic lymphoma
- It is associated with CLL</td><td>- Diffuse large cell lymphoma
- 80% Bcell tumor and 20% T cell tumor</td><td>- Burkitt's lymphoma
- B cell tumor
- SMAL NON-CLEAVED CELL NHL</td></tr>
<tr><td>Occurs in older adults</td><td>Occurs in older adults, 20% of children are affected.</td><td>Occurs most commonly in children</td></tr>
<tr><td>Follicular lymphoma/small cleaved cell
- CD20 Bcell
- Most common type of Non-Hodgkin' s lymphoma
- Translocation (14:18)
- Overexpression of BCL2 which inhibits apoptosis and makes B cell immortal
- Treatment by Ritoximab which binds to CD20 on Bcell and help them destroy.</td><td>- Aggressive tumor but curable</td><td>-transolocation (8:14)- cmyc gene replaced by heavy chain Ig gene
- EBV
- African and American type
<table><tr><td>Large jaw/mandible</td><td>Adult AIDS</td></tr><tr><td></td><td>Abdomen affected</td></tr><tr><td></td><td></td></tr></table>WE ARE GOING TO C MICKEY AT 8:14 AT THE EPSTEIN BAR.</td></tr>
<tr><td></td><td></td><td>starry sky pattern</td></tr>
</table>

MISCELLANEOUS

Mantle cell NHL

- B cell tumor
- Found inadults
- Translocation (11:14)
- Overexpression of IgH
- Bcell – CD19: CD20 CD23-
- T cell – CD5- poor prognosis

Clinical features

1. Lymphoadenopathy- painless, firm, mobile, it grows in size quite fast.
2. B-symptoms- low-grade fever, night sweats, weight loss
3. Liver enlargement and splenic enlargement- hepatosplenomegaly
4. Abdominal pain and a lot of fullness
5. Infections and symptoms of anemia due to bone marrow involvement- fatigue
6. Thrombocytopenia
7. Obstruction of superior venacava
8. Respiratory involvement and bone pain

Diagnosis

1. Lymph node biopsy specially if more than 1 cm diameter within 4 weeks
2. Chest Xray, CAT scan of chest, abdomen and pelvis
3. Serum LDH and Beta 2 microglobulin
4. Alkaline phosphatase is elevated
5. Liver function test- AST and ALT will be elevated and bilirubin will be high
6. CBC
7. Bone marrow biopsy

Treatment

- No standard treatment
- 5 year survival rate is 5 to 7%
- Start with chemotherapy and then radiotherapy
- Treatment of intermediate or high grade
- Chop therapy and radiation therapy is used
  Cyclophosphamide
  Hydroxydaumycine/ doxorubicin
  Oncovin/vincristine
  Prednisone
- Bone marrow transplant
- Survival rate

- Low grade	- 5 to 7 years
- Intermediate	- 2 years
- High	- Few months

-

CML- CLL

Types	Chronic lymphocytic leukemia	Chronic myelogenous leukemia
Age	Most common type and occurs in 50 years or above	Around 40 years old
Cell lines	Rapid growth of mature lymphocytes >20,000 (50,000- 200,000)	Myeloid stem cell lines affected- granulocytes, erythrocytes and platelets
Symptoms	- Asymptomatic - Painless lymphadenopathy and splenomegaly - Predisposed to infection - Anemia and thrombocytopenia	- Begins as an indolent/chronic form - Then suddenly an acute phase occurs where there is blast crisis - T (9:22)- Philadelphia chromososme - Prediction is 3 years of survival - Asymptomatic generally - Fever - Weight loss - Anxiety - Hepatomegaly - splenomegaly
Detection	During routine lab work and ordering CBC- lymphocytosis seen Peripheral blood smear- smudge cell (beaten up leukemic cell) Bone marrow biopsy- infiltrating leukemic cells	- marked leucocytosis as WBC (50,000-200,000) - left shift towards granulocytes - small blast cells - eosinophils - myelocytes,metamyelocytes - low alkaline phophatase activity /low ALP
Stages	0- Elevated WBC 1- Lymphoadenopathy 2- Hepatosplenomegaly 3- Anemia 4- Thrombocytopenia	
Treatment	Stage 0,1- no treatment Stage 2, 3, 4 – chemotherapy Fludarabine and chlorambucil used.	Tyrosine kinase blocker- Imatinib Bone marrow and stem cell transplant The main aim to push back disease progress to chronic phase so that the acute phase never comes to scene.

Leukemia AML_ALL

Definition

It is the cancer of blood. It is the neoplastic proliferation of abnormal white blood cells.

Types

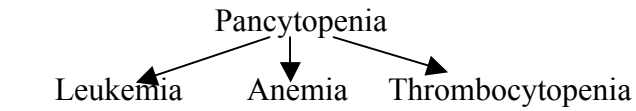
Acute-

1. Myelogenous – granulocytes, monocytes
2. Lymphocytic

Chronic-

1. Myelogenous
2. Lymphocytic

Immature WBC- blast cells



- Infection - Fatigue - petechiae, ecchymosis, purpura, bleeding

Types	Acute Lymphoblastic Leukemia	Acute Myelogenous lukemia
Age	<15 year old Most common leukemia	15-19 years old
Cell line	Precursors of B (CD 10,19,20) and Tcells(CD 2,3,4,5) affected Tdt + cells- terminal deoxynucleotidal transferase +- a specialised DNA polymerase- it is present in preB and preT cells CALLA+	Auer-rods cells **M3** type has numerous aeur-rods cells. In **M3** t(15:17)- retinoic acid (Vit.A) No chemo should be done because DIC development **M4** and **M5- nonspecific esterases** **M5-** acute monocytic (Gum infiltration) **M6**- RBC **M7**- Megakaryocytes
Response to chemotherapy	Good	
Risk factors	Down syndrome- we all fall down Radiotherapy	
Clinical presentation	Throat pain, fever, huge spleen	

Diagnosis	Bone marrow biopsy	
Treatment	Respond well to chemotherapy Prognosis is poor if age is less than 2 and more than 9 and WBC is more than 10 raised to the power 5/mm³	Methotraxate Does not respond well to chemotherapy

Clinical presentation

	Anemia	Leukopenia	Thrombocytopenia /low platelets
	Fatigue	Infections predisposition like	Mucosal bleeding
	Pallor	Pneumonia	Epistaxis /nasal bleed
	Dyspnoea	Urinary tract infection	Petechiae , ecchymosis
	Pale conjunctiva	Cellulitis	Purpura
		Pharyngitis	Splenomegaly, hepatomegaly, lymphadenopathy. Bone and joint pain
		Esophagitis	
Treatment After blood culture	Blood transfusion if Hb/HH<7 Bone marrow transplant	Antibiotics Bone marrow transplant	Platelets Bone marrow transplant

- In CNS- focal neurological dysfunction- meningitis
- Testicular infiltration in ALL
- Skin nodules AML
- Anterior mediastinal mass of Tcell

Diagnosis

- CBC- WBC is 1000 to 100,000mm³
- A lot of blast cells- immature WBC
- Electrolyte abnormalities
- Bone marrow biopsy

Multiple myeloma

Definition

- Neoplastic proliferation of a single type of plasma cells.
- Bone marrow produces B cells. They are of 2 types- memory B cells and plasma cells.
- Plasma cells make antibodies- IgG, IgA, IgM, IgE, IgD (GAMED)
- In multiple myeloma, monoclonal immunoglobulins are formed. (IgA or IgG)
- Antibody has a light chain and a heavy chain. Both chains are connected by disulphide bonds.
- In women more than 50 years
- More in African American (Caucasian)
- Cause unknown. Mutation in chromosome number 14.
- Pancytopenia- low WBC, platelets and low RBC- advanced stages

Clinical features

Hyper CRAB

1. Bone pain- osteolytic lesions due to over-expression of RANK L protein (receptor activator for nuclear K B ligand) which stimulate the function of osteoclasts
2. Hypercalcemia- Due to bone degradation
3. There is chest pain and rib pain.
4. Persistent localized pain- pathologic fracture
5. Renal failure-
   i. due to hypercalcemia, tubular damage from light chain proteins – Bence Jones proteins- they lead to acute tubular necrosis
   ii. Predisposition to amyloidosis
   iii. Infection due to pyelonephritis
6. Anemia – plasma cells produce cytokines which decrease RBC production. Normocytic and normochromic anemia
7. Predisposition to recurrent infections
   a. Pneumonia- Strep. pneumonia, Stap. aureus, Kleibsella pneumonia
   b. UTI- pyelonephritis- E. coli

Diagnosis

1. Serum protein electrophoresis- monoclonal M protein spike (IgG) in serum and urine
2. Plain X-ray- osteolytic lesions- MRI
3. Bone marrow biopsy- 10% plasma cells are abnormal

Labs

1. High level of calcium
2. Total protein in the serum – high

3. ESR- high
4. Peripheral smear- RBC like stack of coins-Roleaux formation
5. High levels of Bence-Jones proteins in urine
6. Tam Horsefull protein- found in DCT and CT – are IgG like chains like BJ proteins

Treatment

1. Systemic Chemotherapy and radiation
2. IV fluids
3. Pain medications
4. Watch out for spinal cord compression- loss of bladder and bowel control
5. Stem cell transplant
6. Poor prognosis- 2to 4 years survival rate.
7. X-ray- punched out lesions.

Bleeding disorders

Platelets	**Coagulation factors**
- *Skin*- Petechiae, ecchymosis, purpura - *Mucous membrane*- menorrhagia, epitaxis	Hematoma, hemarthrosis, coagulopathy
Labs- CBC-platelet count or bleeding time 1. *Low platelets*- ITP, TTP, HUS, HIT 2. *Normal platelets*- a. Patients on aspirin (non-release of TA2) b. Uremia c. Benard Solier- deficiency of GP1b d. Glanzmann thrombocytopenia- deficiency of GP2b/3a e. VWF- PTT high but PT is normal	Labs- PT and PTT Platelet count is normal. 1. Hemophilia A- def. of factor8, high PTT, normal PT. 2. Hemophilia B- def. of factor9 3. Hemophilia C-def. of factor11 4. Vitamin K deficiency or warfarin- PTT is slightly high but PT is very high. 5. Liver problem- lack of coagulation factors production

Thrombocytopenia

Normal platelet count = 150,000 to 400,000

<150,000- thrombocytopenia

Can be due to either decreased production or increased destruction

Decreased production	Increased production
Bone marrow failure- • Aplastic anemia • Fanconi's syndrome • Congenital rubella	Immune diseases like • ITP • TTP • HIT (Heparin induced thrombocytopenia)- i. Type I- no treatment required. Less than 48 hours of heparin admission in hospital ii. Type II- if on heparin for 3 to 12 days. Stop heparin.
Invasion of bone marrow- • Tumors • Leukemias • Fibrosis	HIV- thrombocytopenia may be the only symptom
Injury to bone marrow- • Drugs like chloramphenicol • Gold • chemotherapy	Non-immune- • Disseminated intravascular coagulopathy (DIC) • HIT and TTP
Chemicals- • benzene • insecticide all of them cause decreased production	Spleen - splenomegaly
Radiation	Pregnancy – eclampsia can cause HELLP syndrome. H= hemolysis EL= elevated LFTs LP= low platelets

Diagnosis

- get a complete blood count- low platelets
- bleeding time – increased
- prothrombin time - prolonged
- partial thromboplastin time- prolonged

Clinical presentation

- cutaneous bleeding

- petechiae, ecchymosis and purpura- the size of bleeding increase from petechiae to purpura
- mucosal bleeding so nose bleeds – epitaxis
- menorrhagia
- hemoptysis, GI bleed
- postoperative bleeding is high
- intracranial hemorrhage and GI bleed are life-threatening.
- Difference between coagulopathy and platelet disorders is that coagulopathy has hemarthrosis and hematoma.

Treatment

Platelet transfusion

Stop NSAIDS or aspirin- they inhibit thromboxane A2 inhibits platelets

Stop anticoagulants like warfarin.

Immune thrombocytopenic purpura ITP

Low platelets <20,000

It is an autoimmune disorder of the body where immune response of the body works against platelets by making IgG and skin manifestation like purpura is formed.

Spleen macrophages destroy the complex of IGG-platelets.

Acute form	**Chronic form**
In children due to infection	Adult (women 20-40yrs)
Self limiting disease and gets resolved by 6 months.	Spontaneous remission is very rare.

If platelet count is <100,000- primary hemostatic plug is not formed.

If platelet count is 20,000-100,000 – chances of hemorrhage are more.

If it is below 20,000 – minor injury also causes bleeding- ecchymosis, menorrhagia, petechiae, bleeding gums.

Clinical features

- Eccymosis
- Petechiae
- Mucosal membrane bleeding
- No splenomegaly

Diagnosis

- CBC- platelet low <20,000
- Hemoglobin and hematocrit value is lowered, Reticulocytosis is increased- only increase of heavy bleeding.
- Peripheral smear- decreased platelets
- Bone marrow aspiration- huge megakaryocytes

Treatment

1. Steroids- prednisone
2. Fool the spleen by showering free immune intravenous IgG (IVIG)- competitive inhibition.
3. Splenectomy – remember to give vaccines of H. influenza, strep. Pneumonia and Neisseria meningitis.

Thrombotic thrombocytopenic purpura (TTP)

Definition

It is rare disorder of platelet consumption clot formation disease in which red-purple discoloration is formed which are non blanchable with pressure and the size is 3-10mm under skin.

Cause is unknown.

Pathophysiology

Platelets attach to VWF. To prevent clumping of platelets body produces ADAMTS13 which is a metalloproteinase and breaks down Von Willebrand multimers. They prevent formation of microthrombi.

Antibodies can inhibit ADAMTS13 so clot formation occurs. The disease affects brain and kidney mainly. Fibrin gets activated to form platelet-fibrin complex. They get shredded on their way through small blood vessels, they form schistocytes or helmet cells and the condition is called MAHA (microangiopathic haemolytic anemia). Spleen has reticuloendothileal system removes schistocytes from the system.

Another form has low level of ADAMTS13.

Clinical features

- Haemolytic anemia- MAHA
- Jaundice, increased LDH, increased retic>2%
- High haptoglobin
- Brain:
  Headaches
  Strokes
  Hallucinations
  Altered mental status
- Kidneys:
  Acute renal failure- high BUN and creatinine- oligouria
- Fever

Labs

- PT/PTT- normal
- Bleeding time high
- Platelet count is low

Treatment

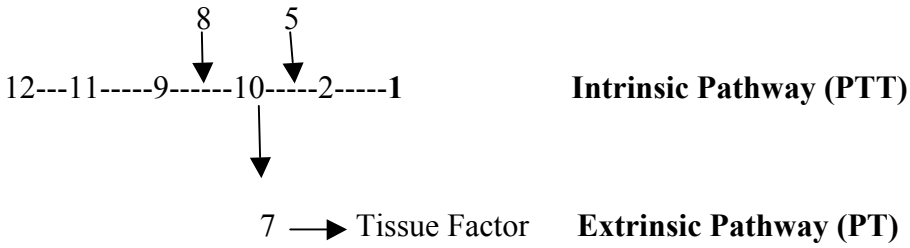
- Plasmaphoresis
- Corticosteroids

- Splenectomy
- **Do not** give platelets

Clotting cascade

When there is cut in our body, blood vessel gets ruptured

1. Denudation of endothileal cells
2. Subendothileal collagen deposited
3. VWF come to the site first. It is formed in endothileal cells which are not denuded.
4. Platelets run to the spot of cut- just like paramedics
5. **Adhesions** of platelets to VWF by GP1b
6. Platelets produce Thromboxane A2.
7. TA2 produced bring the rest of the platelets together. PGI2/NO prevent blood coagulation.
8. ADP produced activates the receptor on platelets to express GPIIb/IIIa.
9. Fibrinogen is attached to the GPIIa/IIb
10. Primary hemostatic plug is formed.



- Warfarin has to do with extrinsic pathway. It prevents activation of Vitamin K so extrinsic pathway does not happen.
- Vitamin K formed in gut, activated by epoxide oxidase.
- The activated Vitamin K activates factor 10, 9, 7 and 2
- Heparin is used to block intrinsic pathway. Antithrombin is helped by heparin to prevent activation of 12,11,10,9,2,1
- PTT is used to know if heparin is present or not.
- PT and INR (international ratio) are the same.
- Patients with DVT or myocardial infarction, heparin is given.
- Coagulation factors are produced by liver except Factor8.
- Factor 2 is prothrombin which gets converted to thrombin which converts fibrinogen to fibrin.
- The fibrin mesh forms the secondary hemostatic plug. Calcium ions come and settle over the mesh.

Waldenstrom's macroglobulinemia

It is a type of malignancy of plasmacytoid lymphocytes.

They produce Bcells which produce IgM in large numbers making blood viscous. It is called hyperviscosity of the blood.

Diagnosis

IgM>5gm/dl

Bence Jones proteins in urine-10%

Difference from multiple myeloma- **no bone/osteolytic lesions**

Lymphdenopathy

Splenomegaly

Anemia and abnormal bleeding

Hyperviscosity syndrome

Treatment

No cure as such

Chemotherapy

Plasmaphoresis to get rid of all IgM in blood

Hyperviscosity syndrome can cause obstruction of retinal blood vessels at the back of the eye- blinding due to massive bleeding.

Monoclonal Gammapathy of undetermined significance (MGUS)

- Asymptomatic
- >75 years old
- IgG<3.5g/dl
- Bence Jones proteins in urine- <1gm/24 hours
- No specific treatment
- Observation