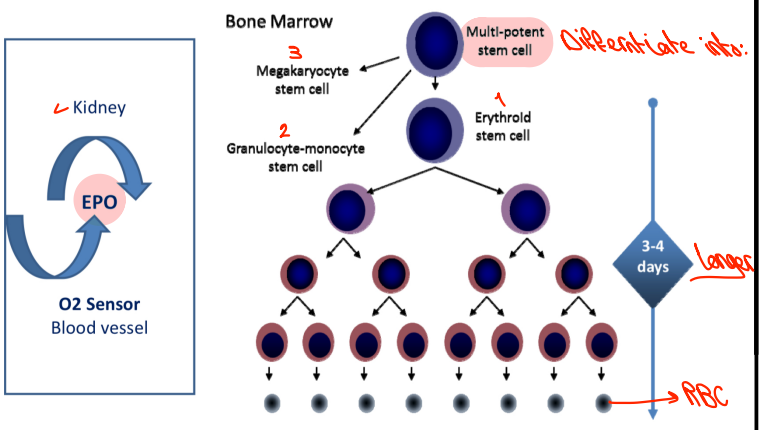
Approach to anemia



#Our Bone marrow responsable producing RBC & Platlets & WBC.

#EPO: released from Kidey upon hypoxia.

#Patient with high EPO: Bone marrow is hyperactive due to hemolysis or Bleeding (anemia) → hypoxia main stimulous.

Definition:

Anemia is operationally defined as a reduction in one or more of the major RBC measurements:

Hemoglobin concentration, → O2-carrying capacity ↓ clinical anemia

Hematocrit, RBC count

These are all concentration measures

Anyone whose hemoglobin is below the level found in the lowest 2.5% of healthy individuals is considered to have anemia.

The cut-off value defining anemia has been determined by convention as the value at -2 SD from the mean or the 2.5th percentile of the normal distribution of a healthy iron-replete population.

WHO's Hemoglobin thresholds used to define anemia in adults (g/dl)

Women, non-pregnant (>15yrs) 12. < 12

Women, pregnant 11. < 11

Men (>15yrs) 13. < 13

Severity of Anemia/g/dl/WHO Classification

	Mild	Moderate	Severe
Non-pregnant women (15 yrs and above)	**11-11.9**	**8-10.9**	**< 8**
Pregnant women	**10-10.9**	**7-9.9**	**<7**
Men (15 yrs and above)	**11-12.9**	**8-10.9**	**<8**

Anemia

- Understanding anemia # Primary anemia (Treat anemia itself).
- Disease - to be treated on its own merits
- Condition - a secondary manifestation of another disease (Secondary anemia treat the cause)
- Causes
- Decreased production — The bone marrow is not making enough red blood cells. This can happen due to iron deficiency, vitamin B12 deficiency, chronic diseases, bone marrow disorders.
- Blood loss — Losing blood leads to losing red blood cells. Examples: bleeding from the stomach, heavy periods, trauma, surgery.
- Hemolysis — Red blood cells are being destroyed faster than the body can replace them. Causes include autoimmune diseases, genetic conditions (like sickle cell), infections, or certain medications.

Factors that influence symptomatology and severity of symptoms :

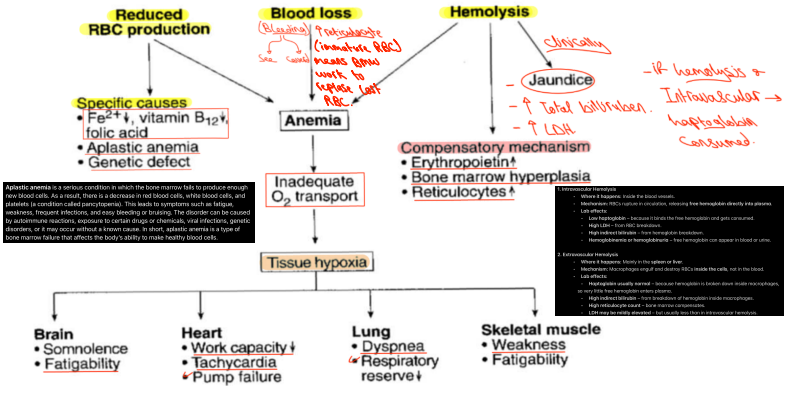
- Acute or chronic
- Cardiovascular status
- Additional symptoms related to cause

PATHOLOGY, SYMPTOMS, AND SIGNS OF ANEMIA

Hemolysis is the destruction or breakdown of red blood cells (RBCs) before their normal lifespan ends. Normally, RBCs live about 120 days, but in hemolysis, they are destroyed prematurely.

Here's a clearer breakdown:

- Causes of hemolysis:
  1. Intrinsic (problem within the RBC itself) – e.g., sickle cell disease, hereditary spherocytosis, enzyme deficiencies like G6PD deficiency.
  2. Extrinsic (outside factors) – e.g., autoimmune reactions (autoimmune hemolytic anemia), infections, certain medications, mechanical damage (like artificial heart valves).



Aplastic anemia is a serious condition in which the bone marrow fails to produce enough new blood cells. As a result, there is a decrease in red blood cells, white blood cells, and platelets (a condition called pancytopenia). This leads to symptoms such as fatigue, weakness, frequent infections, and easy bleeding or bruising. The disorder can be caused by autoimmune reactions, exposure to certain drugs or chemicals, viral infections, genetic disorders, or it may occur without a known cause. In short, aplastic anemia is a type of bone marrow failure that affects the body's ability to make healthy blood cells.

The "Anemia Syndrome" due to **tissue hypoxia**

1- Dizziness
2- Fatigue
3- Shortness of breath especially on exertion
4- Headaches
5- Chest pain/ palpitations
6-? Heart Failure in severe anemia - tachypnea - hypotention.

Clinical evaluation of anemia: **Physical Examination**

- **Look for signs of anemia** → Pale
- **Look for signs suggestive of type & anemia**
- **Examine for splenomegaly/ Hepatomegaly**, Lymphadenopathy
- **Look for signs suggestive of cause**
- **Examine for signs of systemic disease**

Reticulocyte count, which reflects bone marrow response.
- Purpose: To see whether anemia is caused by decreased production of RBCs or increased loss/destruction.

Anemia Classification: Two main approaches

1- Biologic or kinetic approach

-Determined by reticulocyte count If ↑: anemia of Peripheral Loss (Bone marrow work properly).
Bleeding
Hemolysis

2- Morphology.

-Determined by MCV

- Based on: MCV (mean corpuscular volume) – the average size of RBCs.
- Purpose: To classify anemia by RBC size (helps narrow down the cause).

If normal OR low → unreproductive RBC (Bone marrow not produced enough RBC.)
Lasting MCV.

Acute vs. chronic

-Signs and symptoms

#If MCV- high (>100) → Macrocytic anemia. Due to ↓vit.B12 like: ↓fe

#If MCV- Normal (80-100) → Primary or 2ndary bone marrow failure (normocytic)

- Primary BMF & aplastic anemia.
- 2ndary BMF & Drugs, infection, infiltration.

Low MCV (<80): microcytic Due to Iron (thalassemia).

Laboratory Evaluation of Anemia

- **Complete blood count** including HB, RBC, MCV, RDW
- **Reticulocyte count**
- **Peripheral smear**

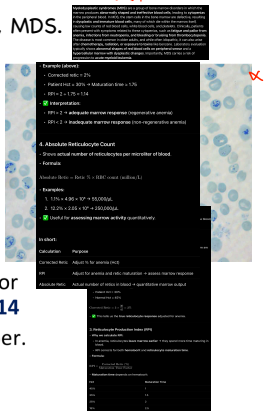
MCH (Mean Corpuscular Hemoglobin) is a measure of the average amount of hemoglobin in a single red blood cell (RBC).

Morphological Classification of Anemia

A - Normocytic/normochromic (normal MCV &MCH): acute blood loss, Hemolysis, ACD, BM failure → Causes of Blood loss.

B- Microcytic/hypochromic (MCV<78, MCH <26): IDA, Thalassemia

C- Macrocytic (MCV>98): megaloblastic anemias , MDS. Liver.dis, alcohol, hypothyroidisim .

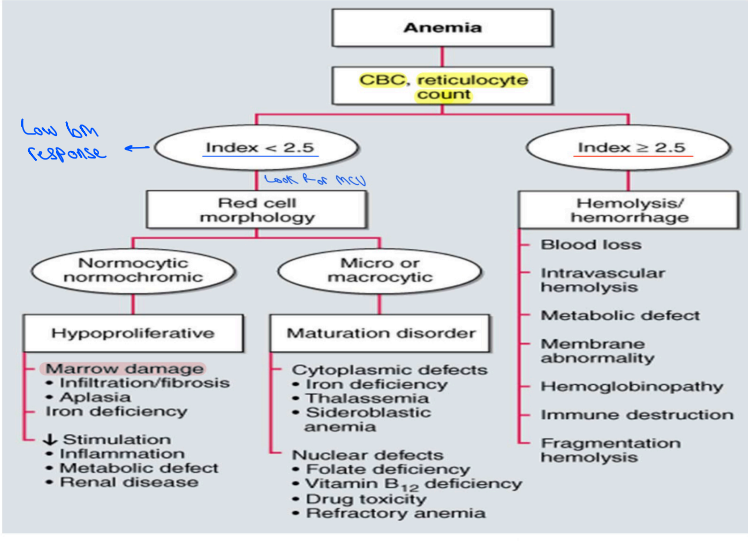


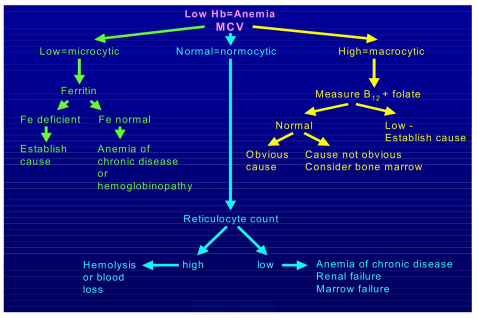
The reticulocyte count

- Hematocrit = (volume of RBCs ÷ total blood volume) x 100

- **Corrected retic.** = Patients retic.(3%) x (Patients Hct(30)/45) : 3(%)x30/45 = 2%
- **Retics index (RPI)** = corrected retic. count/Maturation time
  (Maturation time = 1 for Hct=45%, 1.5 for 35%, 2 for 25%, and 2.5 for 15%.) example above: 2/1.75= **1.14**
- Absolute reticulocyte count = retics % x RBC number.

Example: 1.1% x 4.96 x10^6 = 55,000/µl
12.2% x 2.05 x10^6 = 250,000/µl





Microcytic Hypochromic Anemia: Diagnosis #Causes

- Mild (MCV > 70 fl)
  - Iron deficiency
  - Thalassemia
  - Lead toxicity
  - Sideroblastic anemia
  - Anemia of chronic disease

- Severe (MCV < 70 fl)
  - Iron deficiency
  - Thalassemia

Evolution of Iron Deficiency Anemia

- **Depletion of body Iron stores only but No anemia** (not eat / Losing Blood / not absorbed)
  - most common cause of IDA in Female (bearing age) - menstrual
  - most common cause of IDA in Young - Inadequate diet
- **Iron Deficiency with anemia**
- **Ferritin: The Best Marker for Iron Deficiency in "adults"**

What is HEPICIDIN??

- ❑ HEPICIDIN is the key regulator of iron in our body.
- ❑ Is a peptide hormone.
- ❑ Its molecular weight is 25 Kda.
- ❑ Highly folded structure.
- ❑ Present in inactive form;prohepcidin(60aa) and its active form is hepicidin(25aa).

* Test it sometimes in order to differentiate ACD anemia of chronic disease VS Iron deficiency anemia.

Mechanism of action of hepicidin

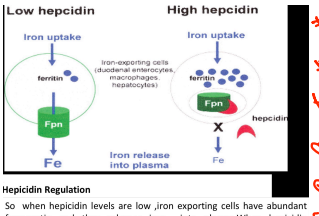
The major mechanism of hepicidin is THE REGULATION OF TRANSMEMBRANE IRON TRANSPORT.

TRANSPORT PROTEINS/Fe

DMT1 (Divalent Metal Transporter 1)
(Tranports from lumen into the enterocytes(small intestine))

FERROPORTIN1
(Transports from enterocytes to circulation)

Hepicidin It binds to FERROPORTIN, forms hepicidin-ferroportin complex, which is degraded in the lysosomes and iron is locked inside the cells(mainly enterocytes,hepatocytes and macrophages).



Hepicidin Regulation

So when hepicidin levels are low ,iron exporting cells have abundant ferroportin and thus releases iron into plasma.When hepicidin concentration increases it binds to ferroportin and thus iron is retained in the cells.

* Hepicidin is elevated in Inflammation.
* ↑ Hepicidin level → reduce iron intake to tissue. That's why Patient with anemia of CKD :- have hypocrytic anemia. Not due to iron-def - BUT related to poor iron handeling RCS & high hepicidin level.

Hypoxia/ Anemia leads to decrease in hepcidin .
Inflammation leads to increase in hepcidin .

- Hepcidin lowers iron absorption in the intestine ,lowers iron releasing from hepatocytes and macrophages

→ Serum iron is decreased

Regulation of Hepcidin synthesis by anemia and hypoxia

- Oxygen ↓ → Hepcidin ↓

→ Uptake of diet iron
→ Iron release from hepatocytes
→ Iron release from macrophages

Regulation of Hepcidin synthesis by inflammation

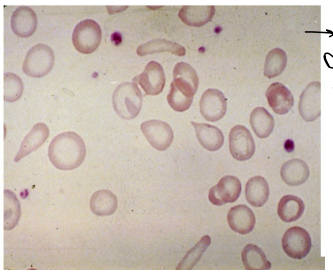
❖Interleukin-6 ↑ → Hepcidin ↑

→ iron ↓ → anemia of chronic disease.

Disease States

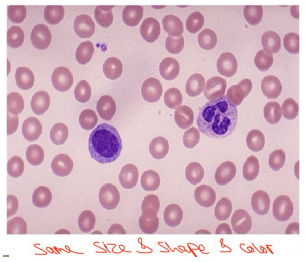
Hemochromatosis is a medical condition in which your body **absorbs too much iron from the diet**. Normally, your body regulates iron absorption carefully, but in hemochromatosis, this regulation fails, leading to **iron overload**. Over time, excess iron gets deposited in organs like the **liver, heart, pancreas, and joints**, which can cause serious complications

Hepcidin deficiency, physiological = Haemochromatosis
Hepcidin excess - anaemia of chronic disease



→ Iron Deficiency Anemia

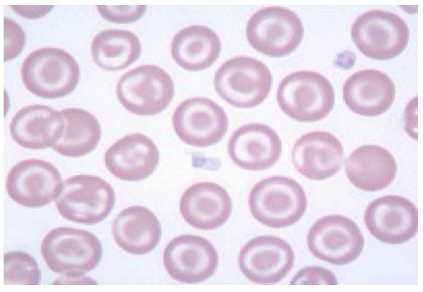
Normal Smear



Same Size & Shape & color

- **Hypochromia** means red blood cells (RBCs) have less color than normal, which usually reflects low hemoglobin content inside the cells.
- **Anisocytosis** : Different sizes of RBCs , indicates various degrees of maturity .
- **Poikylocytosis:** Indicates different shapes .

Hypochromia with target cells but without Anisocytosis: Thalassemia Trait

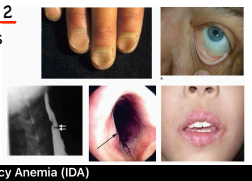


Major Categories of the cause of IDA

1- Nutritional: poor or absent red meat consumption
2- Blood loss: GI/GU/: benign or malignant lesions. Hemosiderinuria (iron in urin)
3- Malabsorption: Gluten enteropathy = celiac dis
4- Repeated pregnancies

Case one

24 yr old female complains of
Dizziness, Fatigue, Shortness of breath especially on exertion and Headaches for the last 4 months. She has been losing scalp hair.
She does not eat red meat and has reported heavy menstrual bleeding.
Her physical exam is shown
Lab and Xray test are shown
Lab: Hb 8, MCV 72, RDW 19, MCH 20pg. WBC 8000/Normal dif.Plts 380000
Bld Film: microcytic, hypchromic, anisocytosis, poikilocytosis, Retics (corrected) 0.8%
Serum Ferritin 2
Likely Diagnosis



Diagnosis: Iron Deficiency Anemia (IDA)

Reasoning:

- **Microcytic, hypochromic anemia** → typical of iron deficiency or thalassemia
- **Very low ferritin (2 ng/mL)** → confirms **iron deficiency** (ferritin <15 strongly suggests IDA)
- **Symptoms & history** → chronic blood loss (menorrhagia) + dietary deficiency (no red meat)
- **Low reticulocyte response** → marrow not producing enough RBCs due to iron deficiency

Conclusion: Classic **iron deficiency anemia in a young female.**

Treatment / Follow-up

Treatment:

1. Oral iron therapy:
   - Ferrous sulfate / ferrous gluconate / ferrous fumarate
   - Usually 100–200 mg elemental iron daily in divided doses
2. Education:
   - Take iron on an empty stomach if tolerated
   - Avoid tea, coffee, or calcium with iron (reduces absorption)
3. IV iron (if oral not tolerated or absorption issues):
   - Iron sucrose, ferric carboxymaltose, IV dextran

Follow-up:

- CBC every month: Hb should rise ≈1 g/dL every 10 days
- Ferritin after 3 months to check iron store repletion
- Monitor underlying causes (gynecology consult for menorrhagia)

Differential Diagnosis of Microcytic Anaemia

- Thalassaemia syndromes
- Certain haemoglobinopathies (Hb C)
- True (classical) iron deficiency secondary to blood loss, iron-poor diet, increased iron needs, Helicobacter pylori infection or gastric pathology
- Anaemia of chronic inflammatory diseases
- Certain forms of sideroblastic anaemia
- Genetic forms of iron deficiency anaemia

Sideroblastic anemia is a type of anemia in which the body has **enough iron but cannot properly use it to make hemoglobin**. In the bone marrow, immature red blood cells called **sideroblasts** accumulate iron in their mitochondria. When the iron forms a **ring around the nucleus**, these cells are called **ringed sideroblasts**, which is the hallmark of the disease. This leads to **ineffective red blood cell production** and anemia, which can be caused by genetic defects, alcohol, certain drugs, vitamin B6 deficiency, or lead poisoning. Lab findings often show microcytic or normocytic anemia with high iron and ferritin, and treatment focuses on addressing the underlying cause and sometimes giving vitamin B6 or supportive care.

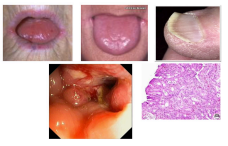
Case one B

60 yr old male complains of :Dizziness, Fatigue, Shortness of breath especially on exertion and Headaches for the last 2 months. He has constipation and weight loss 5 kg over 2 months.
Lab: Hb 8, MCV 72, RDW 19, MCH 20pg. WBC 8000/Normal dif.Plts 380000
Bld Film: microcytic, hypchromic, anisocytosis, poikilocytosis, Retics (corrected) 0.8% Serum Ferritin 2.
FOB x 3 positive in 2.

FOB (Fecal Occult Blood) test

- Purpose: To detect hidden (occult) blood in the stool that you cannot see with your eyes.
- How it works: Usually, 3 separate stool samples are tested on different days to improve accuracy.

Findings:



Diagnosis: Colon adenocarcinoma Mod. dif.

Always Look for a cause for IDA. Anemia must have a full identification

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Anemia is **not a final diagnosis**

IRON DEFICIENCY ANEMIA **IS NOT** A DIAGNOSIS PER SAY.
ALWAYS PUT A LABEL TO IT:
IDA DUE TO UPPER GI BLEEDING DUE TO GASTRIC CANCER

Megaloblastic anemia

OVERVIEW

- Megaloblastic anemia (MA) encompasses a heterogeneous group of anemias **characterized by the presence of large red blood cell precursors called megaloblasts in the bone marrow.** and on blood film (peripheral smear).

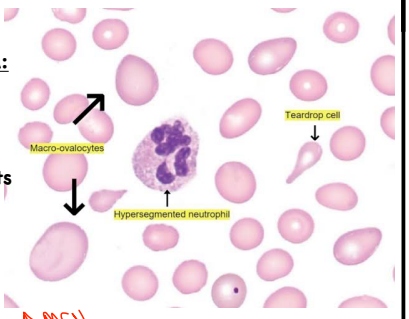
This condition is due to impaired DNA synthesis, which inhibits nuclear division. Cytoplasmic maturation, mainly dependent on RNA and protein synthesis, is less impaired.

This leads to an asynchronous maturation between the nucleus and cytoplasm of erythroblasts (precursor of RBCs), explaining the large size of the megaloblasts.

• The nucleus develops slowly, while the cytoplasm develops faster

On blood film Of Megaloblastic Anemia:

- **Macro-ovalocytes** → non-specific sign
- **Hypersegmented neutrophils > 5 segments**
- **Tear drop cell** → non-specific sign



- Most important sign: macrocytosis: ↑ MCV

ETIOLOGY

Megaloblastic anemia is most often **due to hypovitaminosis, specifically vitamin B12 (cobalamin) and folate deficiencies, which are necessary for the synthesis of DNA.** Copper deficiency and adverse drug reactions (due to drug interference with DNA synthesis) are other well-known causes of megaloblastic anemia. A rare hereditary disorder known as thiamine-responsive megaloblastic anemia syndrome (TRMA) is also identified as a cause of megaloblastic anemia.

Severe anemia
↓WBC: Leukopenia
High → cell destruction

#Copper deficiency in → hemodialysis, Poor nutrient state, Alcohol.
Impaired iron mobilization and reduced enzyme activity for DNA synthesis

Confirm Pernicious anemia

#Ex: Drug → Chemotherapy & Antifolastic (methotrexate, sulphamethoxazol)

VITAMIN B12 DEFICIENCY

- The primary dietary sources of cobalamin are meats, fish, eggs, and dairy products.
- Vitamin B12 is first bound within the duodenum and jejunum to **the intrinsic factor (IF)** produced by gastric parietal cells and is then absorbed in the terminal ileum. The body stores 2 to 3 mg of vitamin B12 in the liver (sufficient for 2 to 4 years).
- The most frequent cause of vitamin B12 deficiency is pernicious anemia caused by autoimmune gastric atrophy, leading to decreased intrinsic factor production. Vitamin B12 deficiency may also develop following gastrectomy, ileal resection, or ileitis of any cause. Other causes of impaired vitamin B12 absorption include Zollinger-Ellison syndrome, blind loop syndrome, fish tapeworm infestation, and pancreatic insufficiency, Corpus-predominant H pylori gastritis, Long-term proton pump inhibitor therapy.

FOLIC ACID DEFICIENCY less common

- Folic acid is present in food such as green vegetables, fruits, meat, and liver. Daily adult needs range from 50 to 100 mcg The recommended dietary allowance is 400 mcg in adults and 600 mcg in pregnant women.
- Folic acid is mainly absorbed in the jejunum and the body stores around 5 mg of folate in the liver, which is enough for 3 to 4 months.
- Folic acid deficiency may be related to decreased intake in the case of alcohol use disorder or malnutrition (elderly patients, institutionalized patients, poverty, special diets, etc.), increased demand particularly in case of pregnancy, hemolysis, hemodialysis, and malabsorption (tropical sprue, celiac disease, jejunal resection, Crohn disease, etc.). In some cases, medications like anticonvulsants and anticancer agents cause megaloblastic anemia related to folate deficiency by affecting folate metabolism.

Severe in severe cases
anticonvulsants

COPPER DEFICIENCY

Clinical copper deficiency can cause microcytic, normocytic, or macrocytic anemia and neutropenia.

Copper deficiency also causes myelopathy and peripheral neuropathy.

in macrocytic anemia

Bone marrow evaluation can reveal myelodysplasia and megaloblastic anemia. Treatment with copper replacement promptly reverses hematologic manifestations of the disease, although neurologic manifestation may take longer.

#Copper Deficiency → more common in End stage renal disease with hemodialysis & in very poor oral intake & alcohol

RARELY, MA IS DUE TO INHERITED PROBLEMS:

- Thiamine-responsive megaloblastic anemia syndrome: An autosomal recessive disease characterized by megaloblastic anemia associated with diabetes mellitus and early-onset sensorineural hearing loss. Mutations in the gene encoding a thiamine transporter (SLC19A2) are thought to be the cause of this disorder. The disease manifests in early infancy and is treated with high-dose thiamine.

- Inherited deficiency of intrinsic factor or the receptor in the intestines: Imerslund-Grasbeck syndrome or juvenile megaloblastic anemia is caused by biallelic mutations affecting the ileal receptor for the vitamin B12-IF complex. These patients also have proteinuria and abnormal vitamin D metabolism.
- Some infants have congenital folate malabsorption syndrome.

DRUG-INDUCED MEGALOBLASTIC ANEMIA Don't need to memorize it.

- Bone Marrow Effect (DNA Synthesis):

Allopurinol, Azathioprine, Capecitabine, Cladribine, Fludarabine, Fluorouracil, Gadolinium, Gemcitabine, Hydroxyurea, Lamivudine, Leflunomide, Mercaptopurine, Methotrexate, Mycophenolate mofetil, Trimethoprim, Zidovudine.

- Reduce the intestinal absorption or metabolism of these vitamins:

Aminosalicylic acid, Antacids and proton pump inhibitors, Penicillin antibiotics, Chloramphenicol, Erythromycin, Oral contraceptives, Metformin, Phenytoin, Tetracyclines, Valproic acid.

Case 2

Strange

65 yr old male had gradual onset of "odd" behavior with psychotic symptoms, irritability and parasthesia in hands and feet He was noticed to have imbalanced gait.

Examination showed loss of vibration and proprioception in lower limbs.

Laboratory tests

High (macrocytic: megaloblastic anemia)

Hb 5 g/dl , MCV 112, Retics (corrected)0.009

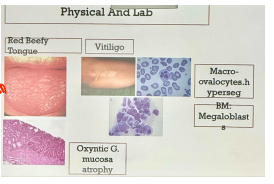
WBC 3.3k, Platelets 112k → ↓ Thrombocytopenia (platelets low)

LDH 1900, Serum B12 =30 pg/ml (low) ↓RBC Production

IF Ab +PCA+ Positive intrinsic factor & parietal cell antibodies → pernicious anemia

Achlorhydria+

Gastric Biopsy: atrophic gastritis.



Pathogensis of Pernicious Anemia (PA)

1-PA is the end-stage of Atrophic Body Gastritis (ABG) causing oxyntic gastric mucosa damage: achlorhydria.

2-It is considered an autoimmune disease (AID).

3-AID theory is based on the presence of parietal cell and/or intrinsic factor autoantibodies.

Frequent association with other autoimmune disorders: autoimmune thyroid disease (ATD), type 1 diabetes, and vitiligo

Epidemiology

The incidence of megaloblastic anemia increases with elderly, (> 60 years of age) Especially those living in retirement facilities.

Pernicious anemia is the most frequent cause of anemia related to cobalamin deficiency and usually occurs in individuals older than 40 years.

The incidence of folate deficiency is low, especially in countries with universal supplementation of folate in dietary products, but increases with alcohol use disorder, malabsorption syndromes, and decreased oral intake due to mental health diagnoses as the identified causes.

PATHOPHYSIOLOGY

- Ineffective erythropoiesis secondary to intramedullary apoptosis of hematopoietic cell precursors, which results from DNA synthesis abnormalities.

- Both vitamin B12 and folate deficiencies may cause defective DNA synthesis. Subsequently, the nucleus and cytoplasm in RBC do not mature simultaneously. The cytoplasm (in which hemoglobin synthesis is unaltered) mature at the normal rate, and the nucleus (with impaired DNA synthesis) is not fully mature.

→ Here's why big cytoplasm & small nucleus → see macrocytes

- The cells arrest in the DNA synthesis (S) phase and make DNA replication errors, which eventually leads to apoptotic cell death

CLINICAL PRESENTATION

The most common presentation of megaloblastic anemia is an asymptomatic incidental finding on routine laboratory testing. Usually, anemia develops gradually, and symptoms are present only in severely anemic patients.

Common symptoms include weakness, shortness of breath (primarily with exertion), palpitation, and lightheadedness. Physical examination may reveal pallor, tachycardia, functional heart murmur, Hunter glossitis, and splenomegaly. Jaundice can occur from intramedullary hemolysis.

There are some minor differences between the clinical manifestations caused by cobalamin deficiency and folic acid deficiency.

In vitamin B12 deficiency, neurological manifestations are observable. The main symptoms are paresthesia and balance disorders. Lancinating pains caused by peripheral neuropathy.

Less frequently, there may be a development of visual disturbances caused by optic atrophy.

The clinical exam usually shows a loss of **vibratory sense** and **proprioception** with a **positive Romberg test**. **Babinski reflex**, hyporeflexia, and clonus are less frequent. Moreover, there are **psychological disturbances** that include a form of **dementia**. These neurological disorders may not be completely reversible after replacement therapy.

EVALUATION

- Clinical suspicion for megaloblastic anemia should be high in patients with unexplained macrocytic (mean corpuscular volume [MCV] greater than 100 fL) anemia or hypersegmented neutrophils on a peripheral smear.
- An MCV of greater than 115 fL is more specific for vitamin B12 deficiency or folate deficiency than other causes of macrocytosis, however, a normal MCV does not rule out megaloblastic anemia.
- A reticulocyte count is also indicated in the workup of this disease.

Retic-count differentiate between megaloblastic anemia & anemia Due to blood loss (bleeding, hemolysis). BCS both are macrocytic.

- Retic-count in MA → Low BL → high

EVALUATION

- A B12 level above 300 pg/mL (above 221 pmol/L) is considered normal. A level between 200 to 300 pg/mL (148 to 221 pmol/L) is considered borderline and additional testing should be obtained to verify the diagnosis and elucidate the cause. A level below 200 pg/mL (below 148 pmol/L) is consistent with deficiency and further testing is only indicated if the route of administration of B12 supplementation needs clarification.

- A folate level of 2 to 4 ng/mL (from 4.5 to 9.1 nmol/L) is considered borderline. A level below 2 ng/mL (below 4.5 nmol/L) is consistent with folate deficiency.

- Spuriously **low serum vitamin B12 levels** can occur in patients with multiple myeloma, HIV infection, pregnancy, oral contraceptive use, and diphenylhydantoin administration.
- Falsely elevated B12 levels may be seen in patients with myeloproliferative neoplasm, alcoholic liver disease, and renal disease.
- Homocysteine is elevated in both vitamin B12 and folate deficiencies.
- Methylmalonic acid can also help differentiate between vitamin B12 and folate deficiency as it is elevated in vitamin B12 deficiency but not in folate deficiency.

helpful marker → common Question.

- It is imperative to remember that vitamin B12 and folate deficiency testing should be done simultaneously to ensure both deficiencies are diagnosed if present. In cases where folate is replaced without vitamin B12 supplementation and underlying B12 deficiency, the neurologic manifestations of vitamin B12 deficiency will not be treated and may potentially get worse.

TREATMENT

- If there is no evidence of malabsorption, the generally preferred route for supplementation is oral.
- In asymptomatic cases, oral supplementation is sufficient. In patients with neurologic symptoms or those with increased demand such as pregnancy and in infancy, vitamin B12 and folic acid supplementation should be initiated parenterally.
- Patients with symptomatic anemia may require a blood transfusion to relieve symptoms, as vitamin B12 and folic acid supplementation do not correct anemia rapidly.
- Vitamin B12 is also available in a sublingual formulation, which may be appropriate for patients with intestinal malabsorption syndromes.

- The duration of treatment is dependent on the cause of the deficiency. If the root cause is correctable, supplementation can be stopped after serum B12 levels normalize. However, in cases with expected life-long deficiency (gastric bypass surgery patients, pernicious anemia, etc.) indefinite supplementation is warranted.

- With adequate supplementation and bone marrow response, hemolytic markers (if intramedullary hemolysis is present) will improve within 1 week and serum hemoglobin/hematocrit levels will completely normalize within 1 to 2 months. The bone marrow will produce normal RBCs with normal DNA, so correction of anemia ,correction of size ,shape also improvement of neurological abnormality .

DIFFERENTIAL DIAGNOSIS

- The complete blood count may show macrocytosis in non-megaloblastic macrocytic anemias. Reticulocyte count will help distinguish between two primary conditions. If reticulocytosis(high retic count)is present, hemolytic anemia and acute hemorrhage are the two main conditions for which the clinician must look. If a reticulocytopenia is present, the underlying conditions may be evident in some cases, such as hypothyroidism, alcoholism, liver dysfunction, and certain drugs. In other cases, one should perform bone marrow aspiration provided that the investigations to exclude vitamin B12 or folate deficiency are carried out. Indeed, myelodysplastic disorders and sideroblastic anemia can manifest as refractory megaloblastic anemia.

DIFFERENTIAL DIAGNOSIS

- Common clinical conditions to consider in patients who present with megaloblastic anemia include conditions that present with macrocytosis such as:
- Alcoholic hepatitis
- Atrophic gastritis
- Gastric cancer
- Celiac sprue
- Tropical sprue
- Myelodysplastic syndrome
- Aplastic anemia
- Acquired sideroblastic anemia
- Homocystinuria

PROGNOSIS

- The prognosis for megaloblastic anemia is favorable with proper identification of the precise etiology and the institution of appropriate treatment. Hematologic abnormalities recover with adequate supplementation although neurologic manifestations show some delay in improvement. Timely recognition and supplementation improve the prognosis of this disease, which may have little to no morbidity or mortality associated with it. There are some complications of the disease that can lead to poor outcomes in patients, such as gastric malignancy in patients with pernicious anemia as the cause of megaloblastic anemia.

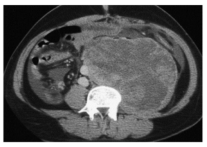
COMPLCATIONS

- The most concerning complication of patients with megaloblastic anemia secondary to pernicious anemia are gastric malignancy. The incidence of gastric malignancy in patients with pernicious anemia was reported as 0.27% per patient-year and a sevenfold relative risk of gastric cancer in patients with pernicious anemia.
- Folate deficiency is associated with neural tube defects in the fetus. This is a highly preventable complication via, adequate supplementation during pregnancy.

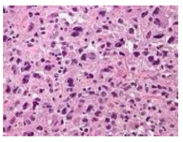
Case 2 B

65 yr old male had "anemia syndrome" over the last 6 weeks. He noticed abdominal swelling and weight loss.
He had mild fever and night sweats for 2 weeks. No neurological symptoms or signs.
Hb 9, MCV 106, WBC 5.3, Plt 142, Retics (corrected)0.1%. Serum B12 normal. LDH 1100. serum folate was 0.2

Abdominal Ct



Biopsy (undif. sarcoma)



Causes of Folic acid deficiency

1. Inadequate intake
- diet lacking fresh, uncook food; chronic alcoholism, total parenteral nutrition,

2. Malabsorption
- small bowel disease (sprue, celiac disease,)
- alcoholism

3. Increased requirements:
- pregnancy and lactation
- infancy
- chronic hemolysis
- **malignancy**
- hemodialysis

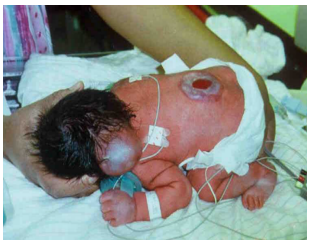
4. Defective utilisation

Drugs: folate antagonists(methotrexate, trimethoprim, triamteren), purine alogs (azathioprine), primidine analogs (zidovudine), RNA reductase hibitor (hydroxyurea), miscellaneous (phenytoin, N,).

Treatment and follow-up

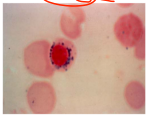
Treat the original Cause
Oral administration of folic 5 mg x2daily, for 3 months, and maintenance therapy if it is necessary.
Retics after 5-7 days.
Correction of anaemia after 2 months therapy.

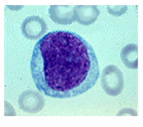
 # Folic acid has role in neural tube closure in foetus, a pregnant woman should have enough folate to protect her foetus from having neural tube defects



Case 2 C

48 yr old lady presented with "anemia syndrome" for 3 months. She was found to have splenomegaly. Hb 8g, MCV 107fl, WBC 3.6, plt 95k, retics 0.6%. LDH350 BM: ringed sideroblasts, blasts 8%. Cytogenetics by FISH 11 q del.





Diagnosis: MDS: RARS/RAEB type I with ring sideroblasts

What are MDS?

- **MDS: a spectrum of heterogeneous malignant hematopoietic stem cell disorders characterized by ineffective and dysplastic changes in BM with**
- ineffective haemopoiesis
- Bone marrow cells cannot mature properly → low counts of red cells, white cells, or platelets in blood.
- dysmorphic cells in blood.
- Variable cytopenia
- Patients may have anemia, leukopenia, and/or thrombocytopenia.
- frequent progression to AML.

→ acute myloid leukemia

- MDS may occur
1) de novo: primary MDS
2) as a result of haemopoietic stem cell injury: secondary or treatment-related MDS

- MDS is associated with significant morbidity and mortality due to
- cytopenias
- impaired quality of life
- risk of transformation to AML

- **Typical MDS patient**
- elderly (occurs at 60-90 years of age)
- slight male preponderance
- approximately 50% have a cytogenetic abnormality

Pathogenesis Of MDS

1. Clonal disorder

- MDS arises from a single hematopoietic stem or progenitor cell that has acquired multiple genetic mutations.
- All the abnormal blood cells in the patient originate from this mutated clone.

2. Genetic and epigenetic changes

- Global DNA hypomethylation:
- Leads to genomic instability and abnormal cell function.
- Promoter hypermethylation of specific genes:
- Silences tumor suppressor genes, contributing to ineffective hematopoiesis.

3. Specific gene mutations

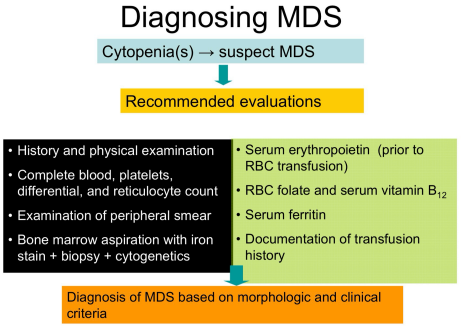
- Mutations in genes encoding enzymes that regulate DNA modification and cell metabolism, such as:
- TET2
- IDH1 / IDH2
- These mutations disrupt normal differentiation and maturation of blood cells.

4. Immune system involvement

- Some patients respond to immunosuppressive therapy, suggesting:
- The immune system may attack hematopoietic stem cells.
- This contributes to marrow hypocellularity (low cellularity) and cytopenias in some cases.

Clinical features in MDS

- **Anaemia**
- > 80% of patients with MDS are anaemic at diagnosis
- Granulocytopenia
- 50-70% of patients
- predisposition for infections
- **Thrombocytopenia in 30% of patients**
- **In MDS**
- **chronically low Hb levels associated with cardiac remodelling and increased incidence of heart failure**



MDS: therapeutic options

- "Best supportive care"including iron chelation

Purpose: Manage symptoms rather than cure.
- Methods:
- Blood transfusions for anemia.
- Platelet transfusions if bleeding risk is high.
- Iron chelation (e.g., deferasirox) to prevent iron overload from repeated transfusions.
- Goal: Improve quality of life and prevent complications.

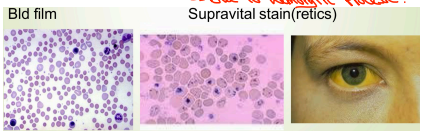
- Haemopoietic growth factors
- Immunosuppressive treatment
- Differentation induction
- Immunomodulatory drugs
- Arsenic trioxide
- Low-dose chemotherapy
- Epigenetic treatment
- Intensive chemotherapy
- Allogeneic SCT (stem cell transplant)

Hemolytic Anemia

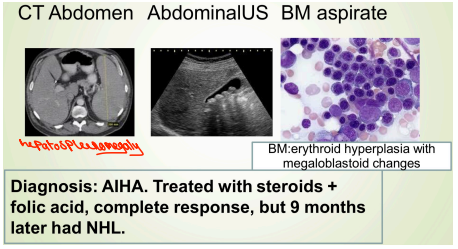
Case 3

24 yr old female presented with "anemia syndrome" and jaundice. She was found to have splenomegaly.

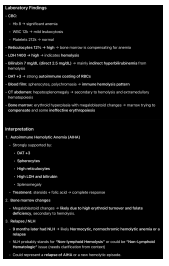
Hb 8, wbc 12k, Plt 212k, retics© 12%, LDH 1400, bilirubin 7 mg/dl, d 2.5mg/dI, DAT +3. Bld film spherocytes, polychromasia.



- Spherocytes are RBCs that are rounder and smaller than normal (no central pallor).
- DAT stands for Direct Antiglobulin Test (also called the Coombs test).
- A positive DAT means that antibodies (usually IgG) or complement proteins are coating the patient's red blood cells (RBCs).
- +3 is a semi-quantitative grading, meaning a strong positive reaction.
- Clinical implication: Suggests immune-mediated hemolysis, i.e., the body is attacking its own RBCs.
- Polychromasia means RBCs are slightly bluish on the blood film, which indicates immature red blood cells (reticulocytes).
- It shows that the bone marrow is responding by producing more RBCs to replace the ones being destroyed.



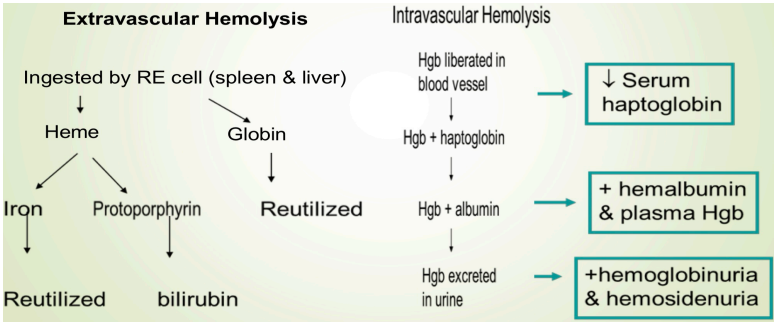
Diagnosis: AIHA. Treated with steroids + folic acid, complete response, but 9 months later had NHL.



Hemolysis= RBC destruction= Shortend RBC Survival with or without anemia

Hemolytic Anemias -Classification:

- **By sites of red cell destruction:** intravscular VS extravascular
- **Acquired** (immune, Non-immune) VS **congenital** (membrane: HS, Enzymopathies: G6PD def/PK, Hb-pathies: Thal, ss)
- **By mechanism of red cell damage:**



#Workup of hemolytic anemia require Tests:
- Serum haptoglobin → consumption of haptoglobin indicates Intravascular hemolysis
- hemoglobin urea & hemosiderinuria → indicates presence & Product of Distructed RBC in urin.

Evidence for increased red cell production #Marker:

- **In the blood:**
  - Elevated reticulocyte count (corrected/RPI)
  - Circulating NRBCs may be present → immature
- **In the bone marrow:**
  - erythroid hyperplasia
  - reduced M/E (myeloid/ erythroid ratio)
    - Normally, there are more myeloid (white cell) precursors than erythroid.
    - In hemolytic anemia, erythroid precursors dominate → M/E ratio decreases.
- **In the bone:**
  - Seen in chronic hemolytic anemia (like thalassemia major)
  - Bone marrow expands to produce more RBCs → bones thicken and deform, especially skull and facial bones.
  - Deforming changes in the skull and long bones (" frontal bossing ")

↳ especially happen in long-term - Particularly in chronic congenital anemia such as Thalassemia & ...

General Clinical Features

1 Anemia syndrome
2 Spleenomegaly
3 gallstones.
4 Dark urine (tea-colored or red)
5 Patients may have chronic ankle ulcers.
6 Aplastic crises associated with Parvovirus B19, may occur
7 Increased requirement for folate

Gallbladder stones/ biliary/ pigment stones

In people with congenital or long standing hemolytic anemia such as: hereditary Spherocytosis

Parvovirus B19

- Non-encapsulated DNA virus.
- Infects and lyses RBC precursors in marrow, causing 7-10d cessation of erythropoiesis. which reduce bone marrow capacity to produce normal RBC.
- Normal individuals have no significant hematologic effect, since RBCs have normal life span.
- In pts with hemolytic anemias, loss of red cell production causes Aplastic Crisis

Autoimmune Hemolytic Anemia

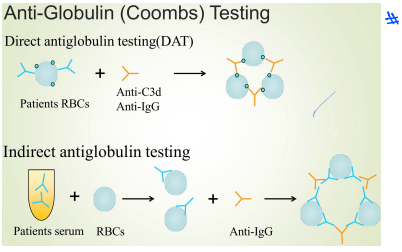
Subdevided depends on cause of Antibody :

- **Warm antibodies (IgG-mediated)**
  - Primary 45%
  - Secondary 40%
- **Cold antibodies (IgM-mediated)**

---> warm antibody (warm autoimmune hemolytic anemia) resuts from causes:

- Lymphoproliferative disease → CLL
- Connective tissue disease → SLE
- Infectious disease
- Drug-induced 15%
- Idiopathic

Laboratory testing - Normocytic/macrocytic anemia
Peripheral smear - spherocytosis



#Direct Coombs Test: +ve in most cases.

Treatment of Autoimmune Hemolytic Anemia (Warm Antibody type)

- **Treat underlying disease if indicated**
- Prednisone
- Splenectomy ?? less commonly.
- Other:
  - Immunosuppressive agents
  - IVIG 'intravenous immunoglobulin'

#Steroids are backbone therapy for these Problem.

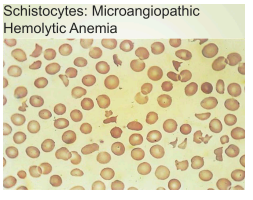
Hemolytic Anemia with Intravascular Hemolysis

Usually results from :

- Mechanical damage (Microangiopathic hemolytic anemia) ex: TTP, HUS.
- Chemical damage (Burns) or trauma
- Infection (Malaria or Babesiosis)
- Transfusion reaction (ABO incompatibility)

Differential Diagnosis of Microangiopathic Hemolytic Anemia → Patient present with HA that result from RBC distruction inside small BV.

- Thrombotic thrombocytopenic purpura (TTP)
  Anemia , thrmbocytopenia ,renal impairment, CNS problem and fever .
- Hemolytic uremic syndrome (HUS)
  Same , but have renal impairment and less CNS involvment.
- Disseminated intravascular coagulation (DIC)
  Common cause of Microangiopathic Hemolytic Anemia.
- Vasculitis
- Malignant hypertension
- Metastatic neoplasm with vascular invasion
- Preeclampsia/HELLP syndrome of pregnancy

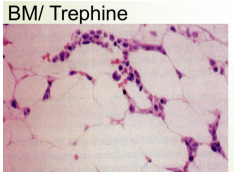


Case 3 B

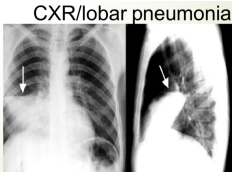
19 yr old male presented with "anemia syndrome", fever and easy bruising.
No splenomegaly
Hb 6 g/di, WBC 1500 : N10%, L 80%, others 10%.
Retics© 0,001% MCV 105fl, PIt 20k → Pancytopenia & hemolysis.

fever anemia

BM/ Trephine



CXR/lobar pneumonia



APLASTIC ANEMIA

- Aplastic anemia is a severe, life threatening syndrome in which production of erythrocytes, WBCs, and platelets has failed.
- Aplastic anemia may occur in all age groups and both genders.
- The disease is characterized by peripheral pancytopenia and accompanied by a hypocellular bone marrow.

- The primary defect is a reduction in or depletion of hematopoietic precursor stem cells with decreased production of all cell lines

- This may be due to quantitative or qualitative damage to the pluripotential stem cell.
- In rare instances it is the result of abnormal hormonal stimulation of stem cell proliferation
- or the result of a defective bone marrow microenvironment
- or from cellular or humoral immunosuppression of hematopoiesis.

Causes of Bone Marrow Failure

Acquired

-Idiopathic

-PNH: Paroxysmal Nocturnal Hemoglobinuria

Secondary

-Drugs

-radiation

-Viruses

Inherited

-Fanconi anemia

-Diamond-Blackfan Anemia

Clinical manifestations of AA

»Anemia syndrome → The consequences of Hbase, fatigue and infections & bleeding are Expected.

»Neutropenia syndrome

»Thrombocytopenia syndrome

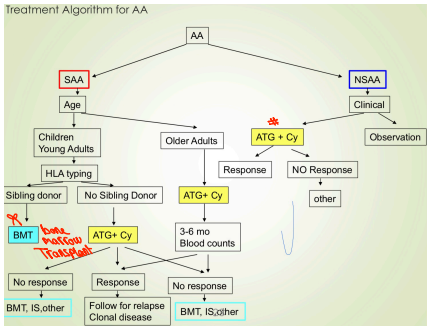
»Combination of the above

Classification of aplastic anemia

Depends on cellularity/activity of Bone marrow:

Classification	Criteria
Severe	BM cellularity < 25% (or < 50% if < 30% of BM is hematopoietic cells) AND ≥ 2 of the following: • Peripheral blood neutrophil count < 0.5×10^9/L • Peripheral blood platelet count < 20×10^9/L • Peripheral blood reticulocyte count < 20×10^9/L
Very severe	As above, but peripheral blood neutrophil count must be < 0.2×10^9/L
Nonsevere	Hypocellular BM with peripheral blood values not meeting criteria for severe aplastic anemia

also for determin risk of AA.



ATG: anti-Thymocyte Globulin
Cy: Cyclophosphamide (immunosuppressive Therapy)

Don't need to Memorise

Treatment of AA

» **Remove causative agent, if known** if AA Secondary

» **Supportive care** if not Enough.

✓RBC transfusions

✓Treat infections

✓Treat Bleeding

» **Bone marrow transplant** → for Severe form of AA.

» **Immune suppression**

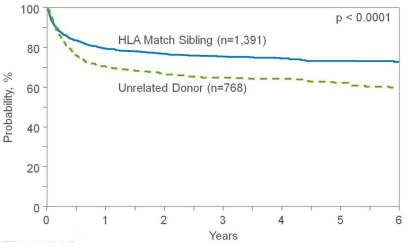
_ CSA

_ ATG

Combination of the above

Survival after Allogeneic Transplants for Severe Aplastic Anemia, ≥ 20 Years, 2002-2012

#There's an survival advantag from Bm Transplant.

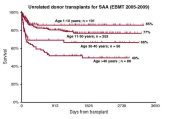


Intensive immunosuppression (ATG plus cyclosporme) for severe aplastic anemia

A strong age effect in patients with aplastic anemia, after transplantation from an HLA identical sibling.

In patients with severe aplastic anemia who undergo bone marrow transplantation from an **HLA-identical sibling**—meaning a brother or sister whose human leukocyte antigens (HLA, proteins that help the immune system recognize self versus foreign cells) perfectly match—the patient's **age strongly affects the outcome.** Younger patients generally have better survival, lower complication rates, and faster recovery, while older patients face higher risks of transplant-related complications and mortality. This emphasizes the importance of considering age when planning sibling donor transplants.

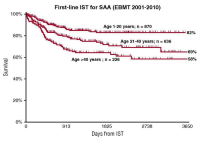
The age effect in UD (unrelated donor) transplants: best outcome is seen for very young patients, for whom first-line UD BMT may be considered.



The age effect in patients receiving first-line IST

(Immuno Supressive Therapy)

- This is the first-line treatment for severe aplastic anemia when a matched sibling donor is not available.



RELATED DISORDERS that can be missdiagnosed with AA

1 Disorders in which there is peripheral pancytopenia, but the bone marrow is normocellular, hypercellular, or infiltrated with abnormal cellular elements (Myelopthesic anemia)

- replacement of bone marrow by fibrotic, granulomatous, or neoplastic cells

2 Pure red Cell aplasia

3 Myelodysplastic syndrome (MDS)

⚠ 4. Clinical Scenario Clues

📌 **MDS**

- Older patient 👴
- May mention:
  - "dysplastic cells"
  - "ring sideroblasts"
  - risk of → Acute Myeloid Leukemia

📌 **Aplastic anemia**

- Often younger patient
- History of:
  - Drugs (chloramphenicol, chemo)
  - Radiation
  - Viral infection (e.g., hepatitis)
- Symptoms:
  - Severe fatigue + infections + bleeding
  - **NO splenomegaly**

🚫 **5. Splenomegaly Trick**

- **MDS** → may have splenomegaly (sometimes)
- **Aplastic anemia** → **NO splenomegaly**

🔥 **If you see:**

- Pancytopenia + **hypercellular marrow** + abnormal cells
  ➡ **MDS**

❄ **If you see:**

- Pancytopenia + **hypocellular fatty marrow** + very low retics
  ➡ **Aplastic anemia**

Congenital Hemolytic Anemias

Congenital Hemolytic Anemias: # Intrinsic causes : leads to premature RBC.

Subtypes

1- Membrane defects (membranopathy) : HS & Electrocytosis
2- Enzymopathies: G6PD Deficiency, PK Def
3- Hemoglobinopathies: B-Thal, SS

] Patient born with these condition.

Extrinsic causes :

- RBC is ok, has normal bicancave disk shape, functionaly normal ; BUT there external factor leads to destruction.

Autoimmune Hemolysis : immune destruction of RBCs such as Hypersplenism & Portal hypertention, mechanical valve, Thrombotic microangiopathic Hemoglobinopathies.

- When patient become anemic due to hemolysis The RBC have short survival time - Days to week. The Bone marrow have Very Good ability to compensate for hemolysis by ↑Erythropoiesis Provided that healthy BM, BUT if hemolysis Significant or continues, if RBC life span < 1-2 weeks Patient will be anemic.

- Patient with acute hemolysis, expected to have Burden of symptoms, It's mimic bleeding BCS; hemoglobin concentration drop quickly.

Acute hemolytic episod = (mimic) Bleeding.

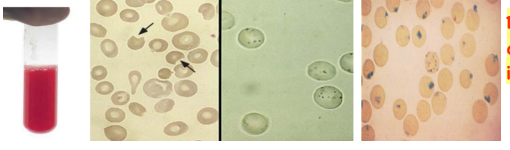
Anemia (4): Congenital Hemolytic Anemias

18 yr old male presented to ER with headches, dizziness, red urine and severe loin pain few hours after he ate fresh "fool" beans. He looked jaundiced and sweaty. His BP 90/60, Pulse rate 120.He had no splenomegaly. Hb 9 g/dl, WBC 16K, Plt 280K. Retics 9%. LDH 3000, Bilirubin 5 mostly indirect.

↑ due to infection

Urine | Bite cells (Bld film) | Heinz Bodies

oxidize RBC.



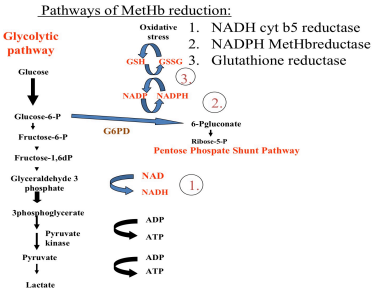
Diagnosis of case 4: G6PD deficiency: hemolytic anemia induced by fava beans

- Anemic Patient with Jaundic : you should think hemolysis.
- Red Urin : Usually seen when hemolysis Predominantly Intravascular.
- not all condition of hemolysis presented Splenomegaly.

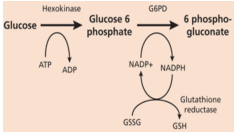
G6PD defiency , in which patient develop episodic hemolytic anemia . So its comes in episode , normaly they dont have a chronic hemolytic processe , usually they have episodic hemolytic that comes 2ndary to certain triggers : medications, stress, infection . The typical patient is a male BCS its X-linked recessive disease **(so patient usually have maternal history of disease)**, they tends to be normal between attacks but the become suddenly symptomatic when they develop hemolysis .

- high LDH & Billirubin = hemolysis

Pathways of MetHb reduction:



Why they have hemolysis when G6PD deficient ?
BCS , RBC dont have other source to reduce NADP other than use G6PD . Having NADPH in reduced form important to restore Glutathion levels , and having restored Glutathion levels are imprtant to avoid destruction of cells .



The cells that usually destoyed are relativly older cells, that have less G6PD in them .

The insedance of disease increases in area where malaria more

Clinical Features:

- **Disease from completely asymptomatic to severe intravascular hemolysis upon exposure to oxidant stress.**

- **Common precipitating factors:**

- Drugs: Primaquine(antimalarea) - Methylene Blue - Nalidixic acid - sulpha drugs - pyridium .
- Infections
- Diabetic ketoacidosis
- Soia
- Favism: hemolysis after exposure to Fava beans, occurs in GdMed variant

Gd MED variant means Glucose-6-Phosphate Dehydrogenase – Mediterranean variant, which is a type of G6PD deficiency commonly found in people from the Mediterranean region (e.g., Middle East, North Africa, Southern Europe).

Clinical Syndromes: G6PD Deficiency

1- **Neonatal Jaundice:** severe/ Kernicterus (bilirubin deposit in brain) / 1-3 day after birth.
2- **Favism:** acute intravascular Hemolysis after exposure to broad bean (Vicia fava), the offending agent is divicine, it produces free Oxygen radicals on autoxidation.
3-**Infection** which promote the formation of H_2O_2, following oxygen burst in neutrophils and macrophage may result in hemolysis
4- **Drug induced hemolysis**
G6PD Med : whites Mediterranean Kurdish severe def

Drug-Induced Acute Hemolysis → مما

- Drugs that have been linked to G6PD
  - Primaquine
  - Sulphonamide antibiotics
  - Sulphones e.g. dapsone used against leprosy
- Other sulphur-containing drugs: glibenclamide (an anti-diabetic drug
  - Nitrofurantoin
- Vitamin K analogues
- Several others
  - Henna can cause a hemolytic crisis in G6PD deficient infants

Genetics → مما

- Majority of the variants - from a single point-mutation resulting in amino acid substitution in gene encoding for G6PD located at the Xq28 region on the tip of the long arm of theX-chromosome
- G6PD Mediterranean is caused by mutation (563 C-->T)

Therapy

- Avoid precipitating factors.
- Blood transfusion in severe hemolysis.
- Maintenance of good urine output during hemolytic episodes Via hydration

Hemolysis releases free hemoglobin → can block renal tubules → acute kidney injury.

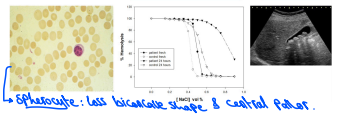
- Folic acid.
- Exchange transfusion in newborn

Dont check for G6PD levels in acute hemolysis BCS will show high level due to reticulocytosis (reticulocyte having high G6PD) so falls negative .

Case 4 B

36 yr old lady presented with "anemia syndrome" and splenomegaly ,She was mildly jaundiced. Hb 8g/dl, retics 10%, WBC, PIt were normal. LDH 1160, Bilirubin 3mg/dId 1.DAT -ve.

Bld film | Osmotic fragility test | Abd. US

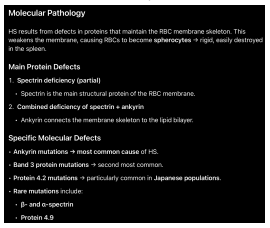


↳ Spherocyte : less bicancave shape & central Pallor.

Membranopathies : Abnormal RBC have abnormal membrane , so loss ability to go throgh smaller vessles and they recognised as abnormal cell in spleen and get destoroyed .
The patient alwayse have defect all the time , these cells get destroyed all time so not episodic .
The hemolysis mainly extravascular
And BCS the hemolysis occure in spleen leads to spleen enlargment , as spleen enlarge more and more the distruction get worsen and anemia also worsen .مهم
Aotosomal dominant
The gene defect can involve many proteins BCS the cell structure has more than one protein .

Hereditary Spherocytosis

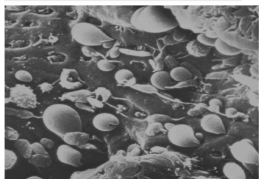
- **Clinical severity is highly variable, but uniform within a given family** (similar within same family)
- **Typically the autosomal dominant homozygous is very severe or lethal**
- some recessively inherited
- No consensus for splenectomy indications



The charactaristic of disease : continouse hemolytic processe

in order to diagnose or secreen patient if you suspect spherocytosis : **Osmotic fragility test**
Incupate cells in hypertonic solution and then change concentration of solution , BCS cells have abnormal membrane they cant handle the change salts concentration during test , so they tends to lyse prematurly BCS, their membrane not adabtive as normal cells

Splenic Conditioning



If the pateint have sever anemia do spleenectomy
Some of them they dont need spleenectomy if the dont have sever anemia .
If hemolysis is compensated and not anemic you just observe them & provide them with folate .
All pateint with hemolytic anemia have increased risk of folate deficiency .

G6PD or spherocytosis or hemoglobenopatheis ---> you observe if not anemic, if anemic and spleen enlargment due to anemia ---> spleenectomy is treatment of choice

Case 4 C

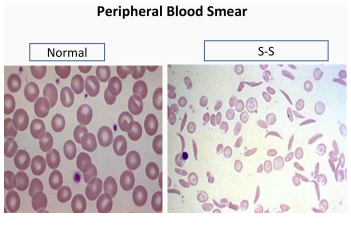
18 yr old male complains of acute pain in his back, Dizziness, Fatigue, Shortness of breath and Headaches for the last 6 hours. He has had similar attacks. P/E

Xray spine

Hemoglobinopathis : due to abnormal hemoglobin (either structurally abnormal or quantitavly low bcs of gene defect)
1) **Sickle cell disease** : Abnormally structured hemoglobin , so gene defect that resposable is point mutation in beta chain and this point mutation leads to abnormal hemoglobin , and that abnormal hemoglobin tends to form polymers in hypoxic events and these polymers leads to sickiling in RBC . And those RBCs not functional; they dont delever oxygen to tissue (compromize o2 delevary), also cause obstruct smaller blood vessles leading to complication .
-> patient with SS are expect to have short life span than healthy pop, bcs of sig complication and organ damage happen 2ndary to sickiling .can affect retina, bones, liver , kidneys also can leads to repeating thrombi in lungs leading to repeating thromboembolic event in lung , pulmonary hypertention , if sickling occure in the brain vessles leads to arterial ischemai and arterial stroke , if sickling occure in the lungs leads to sever hypoxia & respiratory faliar .
SH or G6PD -> doesnt usually affect life span

SS is inhereted in autosomal rececive , the carriers are usually asymptomatic (not easly to identify them)

- **Point mutation in beta globin gene (36 Glu →Val)**
- **Gene occurs in 8% of African-Americans**



Called : boat cells or cresent shape cells

Sickle Cell Anemia Clinical Effects

- **Chronic hemolytic anemia**
  - Gallstones (bilirubin)
  - Risk of red cell aplasia (Parvovirus)
  - Decreased vascular tone: chronic anemia and hemolysis can impair nitric oxide availability, reducing blood vessel dilation.
- **Susceptible to infection**
  - Functional asplenia: develops due to repeated splenic infarctions, leaving patients prone to infections by encapsulated bacteria (e.g., Streptococcus pneumoniae).
  - Infarcted tissue
  - Numerous manipulations: Frequent hospital interventions and transfusions increase infection risk.
- **Vaso-occlusion**

The sickiling becomes worse due to certain triggers, bcs the sickiling becomes worse and diffuse. Pateint with SS have acute sickiling crisis depends on organ that involves in sickiling and these crisis are usually triggered - any thing that cause hypoxea will leads to acute sickiling .

what we can do ? You may try to increase hemoglobin-F production bcs hemoglobin-f doesnt have beta chain , it has alpha and gamma chains , if you able to increase hemoglobin-F production littel bit you may have to decrease their sickiling crisis , one way to do that by using medication called: **hydroxycarbamide** .

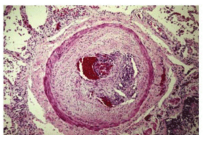
Transcranial doplerultrasound mainly for young patient mainly pediatric group : observe blood velocity(flow) in their brain vessles, if there is an increase blood flow in brain vessle means this vessle getting tight and there is risk of stroke ,so in order to prevent strok try do **exchange transfusion program** (removal of patient's sickelled blood and introducing donor's blood) that called **profilatic exchange.**

#introduce genetic changes through vector that would do excess hemoglobin-f
can do BoneM transplant with similar HLA donor .
#supportive care , bcs they are at High risk of infection, BCS they loose their spleen function overtime bcs due to repeate thrombotic episodes in spleen . So need vaccines and regular monitoring to argan that may be affecting by sickiling even if dont have symptoms.

Vascular beds susceptible to injury

- Brain
- Lung
- Ankle
- Erectile vasculature of the penis

End-stage vascular lung disease



Infectious complications of Sickle cell anemia

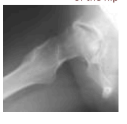
- **Related to absent spleen**
  - Pneumococcus infections
  - Hemophilus infections
  - Dramatically improved with the use of prophylactic penicillin in childhood
- **Related to frequent instrumentation**
  - Staphyloccocal infections
- **Related to tissue infarction**
  - Osteomyelitis

Auto-splenectomy occurs in sickle cell disease, bcs spleen gets smaller and smaller with repeated thrombotic events until shricks and disapearance or having little voleum of what was usualle spleen.

Sickle Cell Anemia Vaso-occlusion: Unique pathophysiologic feature

- Causes acute and chronic organ damage
- **Acute complications:** These result from sudden blockage of blood vessels by sickled RBCs.
  - Sickle cell vaso-occlusive pain crisis (most common)
  - Hepatic crisis
    - Severe bone, back, or abdominal pain
    - Triggered by dehydration, infection, cold, or stress
  - Splenic crisis
  - Priapism: Vaso-occlusion in penile blood vessels, Painful, prolonged erection → risk of impotence

Sickle cell: avascular necrosis of the hip



- **Chronic organ damage**
  - Stroke
  - Chronic lung disease with pulmonary hypertension
  - Renal failure
  - Avascular necrosis of bone

- **The Serious complication of sickle cell anemia**
- **Most Serious Acute Complications ("< 48 Hours" Risk)**
  - Acute chest syndrome
  - Splenic sequestration
  - Massive hemolysis
  - Risk of sudden death

The Vaso-occlusion crisis , the most common crisis that seen in SS and it happen bcs there are sickling in vessles of bone which carachtarizes by pain.

Sickle Cell Anemia Painful Events:Management Principles

1. Correct fluid and electrolyte abnormalities
   - Patients are often mildly dehydrated, which worsens sickling.
   - Use hypotonic IV fluids (e.g., 0.45% saline).
   - Avoid overhydration, because too much fluid can cause pulmonary edema and may worsen acute chest syndrome.
2. Treat any underlying illness
   - Pain crises can be triggered by infection, fever, dehydration, stress.
   - Identify and treat infections early (antibiotics if needed).
3. Opioid analgesics
   - Moderate to severe pain requires strong opioids such as morphine or hydromorphone.
   - Meperidine (pethidine) is not recommended due to the risk of neurotoxicity from its metabolite (normeperidine → seizures).
4. Blood transfusion
   - NOT indicated in typical, uncomplicated painful crises.
   - Transfusions are reserved for complications such as acute chest syndrome, stroke, severe anemia, or multiorgan failure.
5. Incentive spirometry
   - Should be used regularly during waking hours.
   - Prevents atelectasis and decreases the risk of acute chest syndrome, a major complication during painful crises.
6. Hydroxyurea Therapy
   - Increases fetal hemoglobin (HbF).
   - HbF reduces sickling.
   - Benefits:Fewer painful episodes, Lower rates of acute chest syndrome, Reduced need for transfusions, Fewer hospitalizations
7. Non-pharmacologic approaches
   - Techniques like heat pads, relaxation, massage may help, but they haven't been fully studied or proven.
8. Pregnancy
   - Prophylactic transfusions in pregnant women with sickle cell disease have shown reduced painful crises and improved outcomes.

Sickle Cell Pain Episodes

- Average duration 5-7 days
- 30-50% of patients seen in ER are admitted

Acute Chest Syndrome: Clinical-Findings

- Etiology - multifactorial
- Rib infarct causing splinting/atelectasis
- Pulmonary fat embolism
- Infection (mycoplasma, chlamydia, viral)
- Indistinguishable from pneumonia
- Pleuritic chest pain, fever, cough, tachypnea, hypoxia & abnormal chest x-ray & abnormal respiratory exam.
- Laboratory diagnosis
- Worsening anemia
- Infiltrate on chest radiograph

Acute Chest Syndrome: Outcome

- Complete recovery 91%
  - Weaned of supplemental O_2 3.1±1.9 days
  - Hospital discharge 5.4±2.3 days
- Chronic respiratory disease 3%
- Death 6%

Acute Chest Syndrome: Prevention and Treatment

- Incentive spirometry
- Treat possible underlying infection
- Bronchodilators and supplemental oxygen
- RBC transfusion therapy

Indication for RBC transfusions in sickle cell disease

Indication	--->	Outcom
Stroke		decrease recurrence by 90%
Acute chest syndrome		rapid improvement
Aplastic crisis		may be life saving
Pre-operative treatment		decrease post-operative complications
Symptomatic anemia		clinical improvement
Splanic/hepatic sequestration		clinical improvement

Sickle Cell Trait

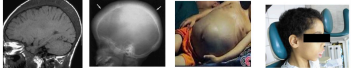
- Protection against malaria
- Genitourinary complications
- Hyposthenuria/ papillary sloughing
- Painless hematuria
- UTI during pregnancy
- **Vaso-occlusive complications :**
- Splenic infarction with hypoxia
- Sudden death
- Rhabdomyolysis

Case 4 D

13 yr old male complains of skin pigmentation, abdominal swelling and pallor. He has been receiving blood transfusions since the age of 9 months. Stunted growth. Hb 6, MCV 55, retcs16%,s.Ferritin 5000.

P/E

Xray



Thalasemea : autosomal recesive

Its hemoglobinopathy , but hemoglobin not structurally abnormal as much as low in production so we have a reduced part of hemoglobin result in abnormal shape of hemoglobin called hemoglobin inclusion, leads to distruction of cells .

So its an hemolytic anemia caused by hemoglobinopathy

One of complicatiom : Bone marrow expans leads to charactaristic facial featur .

Clinical Syndrome	Genotype	Hb	Hb analysis
Minor (Trait)	β/β^+ or β/β^0	10-13	↑ Hgb A2, ↑ Hgb F
~~Intermedia~~	~~β^+/β^+~~	~~7-10~~	~~↑ Hgb A2, ↑↑ Hgb F~~
Major (Cooleys)	β^+/β^0 or β^0/β^0	< 7	↑ Hgb A2, ↑↑↑ Hgb F

+ : reduced production
0 : absent production

At least should have one healthy copy gene on one allel , dont need blood transfusion .

Defect on both alleles --> sever anemia
Need regular blood transfusion at early gene , called transfusion dependent : cant survive without BT.

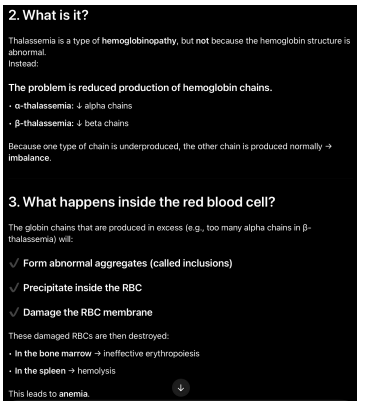
Beta Thalassemia: Clinical Manifestations/complication

Osteoporosis
Extramedullary erythropoiesis/ tumor effect
Iron overload:affect skin, heart, liver, endocrine organs
Dilated cardiomyopathy secondary to severe anemia
Growth and development delayed
Large splenomegaly

Avoid having child with thalasemia , so secreening for thalacenia carriers and try to identify them in order to prevent having a thalacemia patient .

Treatment/ Prevention of B thal major

- **Blood Transfusion** the only curative way.
- Iron chelation: deferroxamine (parenteral)
- ?splenectomy
- Allo-BMT
- Supportive
- Prevention



Bleeding Disorders 1

Classification bleeding disorder into :

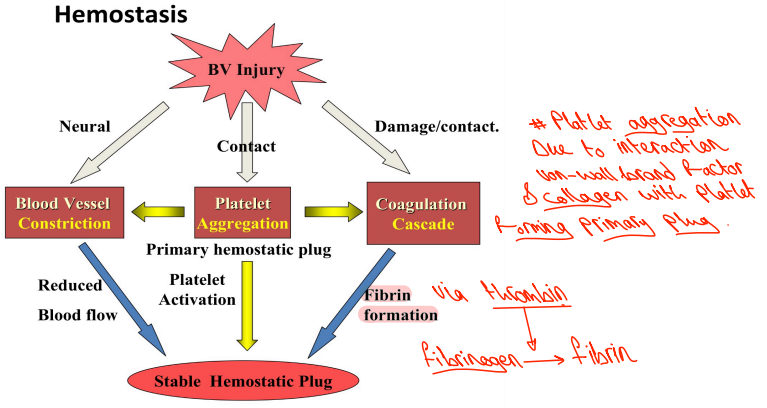
-congenital ex: hemophelia, von-wellbrand disease(most common)

-Aquiered (most common)

mainly due to medication via anti-platlets , anti-coagulant, sometimes thrombolytics.

Systemic conditions like liver, kidney disease .

Hemostasis



Disorder that affect function of platlet and von-wall brand factor ,usually results in **immediate bleeding** and that bleeding usually in skin and mucosal memb.

- The bleeding that is related to coagulation factor, initially alot of bleeding more in joints and deep muscles .

Feature	Platelet/VWF disorders	Coagulation factor disorders
Onset of bleeding	Immediate	Delayed
Type of bleeding	Skin, mucosa	Joints, muscles, internal
Common signs	Petechiae, epistaxis, gum bleeding	Hemarthrosis, large hematomas
Lab clues	Low platelets or prolonged bleeding time	Prolonged PT or aPTT

"Coagulation Screen"

A- common screening tests:

To assese bleeding risk for patient undergo surgery, or if patient that presents of bleeding symptoms .

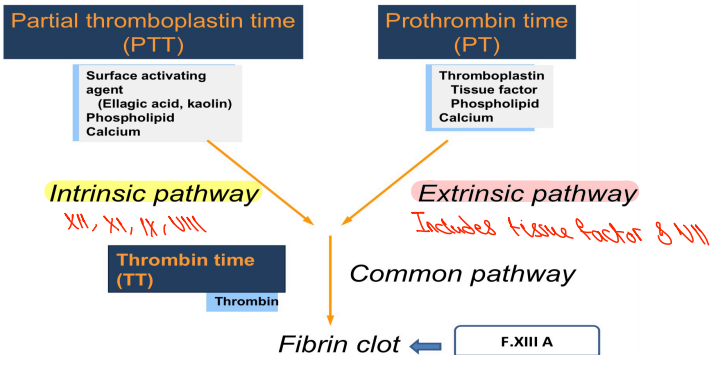
1- Platelet count and morphology
2- Bleeding time (plt count must be normal)
3- Partial Thromboplastin Time (PTT)
4- Prothrombin Time (PT)
5- Thrombin time (TT)

B- Specialized tests:

1- FXIIIA quantitative test
2- Clot retraction
3- Mixing studies
4-Factors assay
5-VW Factor quantitative assay
6- Platelet aggregation

C- Other rare tests

Laboratory Evaluation of the Coagulation Pathways



PT : assese the extrinsic pathway & common pathway

PTT : assese the intrinsic pathway or common pathway

TT : assese the common pathway

In hemophelea : isolated factor VIII(coagulation factor) defeteincy , the PT should be normal , they tends to bleed in joints(hemarthrosis) espcially weight bearing joint :knees .

- Hemophilea-A : factor VIII
- Hemophilea-B : factor IX

Dont usually heve petichiae (small skin pinpoint bleeding) ; usually seen petichiae in platelet disorders and VW-factor disorder .

Dont bleed after cuts, will be delayed later bleeding

Clinical Features of Bleeding Disorders

	Platelet	Coag Factors Disorders
Site of bleeding	Skin Mucous membranes (epistaxis, gum, vaginal, GI tract)	Deep in soft tissues (joints, muscles)
Petechiae	Yes	No
Ecchymoses ("bruises")	Small, superficial	Large, deep
Hemarthrosis / muscle bleeding	Extremely rare	Common
Bleeding after cuts & scratches	Yes	No
Bleeding after surgery or trauma	Immediate, usually mild	Delayed (1-2 days), often severe

Coagulation factor disorders

- **Inherited bleeding disorders**
  - Hemophilia A and B
  - von Willebrands disease
- **Acquired bleeding disorders**
  - Liver disease
  - kidney disease
  - Vitamin K deficiency/warfarin overdose
  - DIC (dissaminated intravascular coagulation)

	Hemophilia A	Hemophilia B
Coagulation factor deficiency	Factor VIII	Factor IX
Inheritance	X- linked	X-linked
Incidence	1/10,000 males	1/50,000 males
Complications/clinical	Soft tissue bleeding	

Severity of bleeding is related to factor level

<1% - Severe - spontaneous bleeding
1-5% - Moderate - bleeding with mild injury
5-25% - Mild - bleeding with surgery or trauma

Both Associated with hemarthrosis mainly & inhereted as X-linked recessive mainly seen in male .

The less factor activity the more symptoms are .

- If it sever the patient tends to bleed when they start to move & put wight on joint (arround age 6month up to 2years) .

-If it moderate to mild, many of these patient dont bleed spontanously ,only bleed after surgical or after chalange to his system .

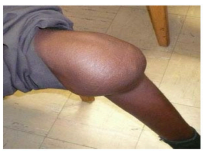
Case 5

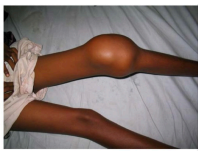
19 yr old male complains of repeated attacks of large joint painful swelling especially in his knees for several years, with limitation of movement of the knee joint. P/E shown. His maternal uncle has similar condition.

PT 14/14 s, PTT 80/31s, with mixing 40/32s. TT 12/12s, Plt 220K, BT 5mnts. F VIII <1%. F IX 100%.No VIII inhibitors.

Genetic testing INT 22 INVS.

Hemophelea A





Case 5: Management & Follow-up

Treat acute attack: give F-VIII supplement in regular programe (pro-prophylactic)

***F-VIII: recombinant derived (genetic engeneer) not via plasma derived**

Factor IX def leads to hemophelia B and treated by supplement of factor IX .

Geneting test to conferm

The F8 gene

Human F8 gene maps to the most distal band (Xq28) of the long arm of the X chromosome.

- An **intron 22 inversion is responsible for 45% of severe hemophilia A** .
- intron 1 inversion is responsible for 3 %of severe hemophilia A.

other reported mutation include **deletion**, insertion and point mutations causing nonsense, missense or splice site mutation.

H-A : usually caused by inversion or deletion .

H-B : usually caused by point mutation .

Treatment of Severe/ Moderate hemophilia A&B

A-Factor Replacement

1- On demand/hospital based
2- On demand/home based
3- Prophylactic/ home/ intermittent X 2 per week

B-Treatment of target joint
C- Physiotherapy/rehabilitation
D-Genetic counseling
E- Education

Dosing guidelines for hemophilia A

- **Mild / Moderate bleeding**
- **Desmopressin (DDAVP) → Releases stored factor VIII and vWF**
  - Works only in mild disease (baseline FVIII > 5%)
  - Not effective in moderate or severe cases

- Target Factor VIII Level: 30% dosing.

- Hemarthrosis, oropharyngeal or dental, epistaxis, hematuria

- **Major bleeding**

- Target level: 80-100%

Ex: CNS hemorrhage, lumbar puncture, Surgery, Retroperitoneal & GI bleeding.

- **Adjunctive therapy (supprative)**

— Tranexemic acid (Cyclokapron): Antifibrinolytic → stabilizes clot/Useful for mucosal bleeds (mouth, nose, dental work)

or DDAVP (for mild disease only)

Treatment of hemophilia B

- Agent
  - High purity factor IX
  - Recombinant human factor IX

Complications of therapy

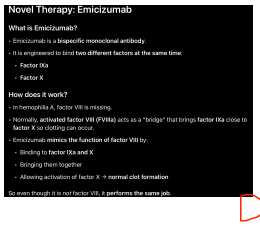
- They are IgG antibodies formed by the patient's immune system.
- These antibodies neutralize factor VIII or IX.

- **Formation of inhibitors (antibodies)** important BCS, it makes treatment difficult & loss response to treatment.
  - 10-15% of severe hemophilia A patients
  - 1-2% of severe hemophilia B patients
- **Viral infections/ Transmissible disease (when use Plasma Derived factor)**
  - Hepatitis B
  - Hepatitis C
  - HIV
  - Human parvovirus
  - Hepatitis A
  - Others (Prion disease or BSE)

Novel therapies

- **Emicizumab:** Bispecific (factor IXa and Factor X-directed antibody)that bridges activated factor IX and factor X in order to restore the function of missing activated factor VIII necessary for effective hemostasis.

- used with patient with hemophelia A & inhibitor : usefull treatment & change outcome of patient with inhibitor



Treatment of Inhibitors

1-Recombinant factor VIIa

2-By-Passing Agents (Mixture of partially activated vitamin K-dependent clotting factor including VIIa.

3-Porcine factor VIII (if available)

4-High dose factor VIII (if low titre inhibitor)

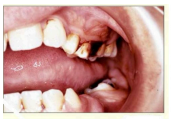
5-ITT (Immune Tolerance Therapy)

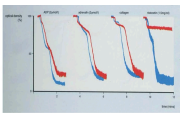
Case 5 B

27 yr old male patient was brought to E/R for prolonged bleeding after tooth extraction. He had epistaxis, gum bleeding and prolonged bleeding from wounds ever since he remembers. He was admitted several times because of bleeding. His father is reported to have epistaxis and several hospital admissions for bleeding. P/E: Pallor. P 120, BP 95/60 lying, no fever, bleeding from mouth and extraction socket.

Hb 7, WBC 13000, PIt 280k, PT 13/13, PTT 39/31, TT 12/11.

BT > 15 mints. Bld group, O Pos.





FVIII 48%, VWF 15%. Clot retraction: Normal.

Diagnosis: VWD Type I

VWD : most common inhereted bleeding disorder

Patient usually early in their life with bleeding symptoms from mucocotanous areas: gum bleeding, epistaxis, menorragea, skin bleed.

Family-history is common bcs the disease is inhereted mostly **autosomal dominant**.

The caractaristic feature in blood test is prolonged bleeding time.

- Bleeding time: test used to asses platlet & VW-factor function .

VWD type II :the quantitation of VW-factor is normal but the defect in interaction, so detect platelet aggregation via **platelt agrometry** not by quantitation of VWF.

Give your pateint VWF-consentrate after you diagnose the disease.

- Patient are usually symptomstic they have bleeding symptoms, sometimes Subclinical meaning that the deffeint in VWF is littele amount and usually seen in type one disease.

Management of Case 5 B

1- Cryoprecipitate.
2- Dental consultation/ mouth hygiene & care.
3-Education and counseling.
4- Screening of family.
5- **DDAVP for therapy of mild bleeding**

von Willebrand Disease: Clinical Features

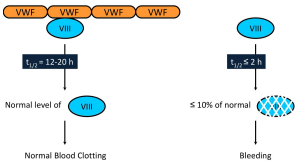
- **von Willebrand factor**
  - Synthesis in endothelium and megakaryocytes
  - Forms large multimer
  - Carrier of factor VIII
  - Anchors platelets to subendothelium
  - Bridge between platelets

Von Willebrand Disease

- Inheritance - autosomal dominant
- Clinical features - mucocutaneous bleeding, prolonged bleeding from wounds/cuts

Not only VWF-consentrate that you can give but also dismoprosen bcs it increase factor VIII & VWF, its useful in milder conditions and if procedure is not associated with increasing risk of bleeding.

VWF and Factor VIII Survival



Laboratory evaluation of von Willebrand disease Classification

- Type 1 --> Partial quantitative deficiency
- Type 2 --> Qualitative deficiency
- Type 3 --> Total quantitative deficiency

Diagnostic tests:

Von Willebrand type Assay	1	2	3
vWF antigen	⇓	Normal	⇓⇓
vWF activity	⇓	⇓	⇓⇓
Multimer analysis	Normal	Normal?abnormal	Absent

Treatment of von Willebrand disease

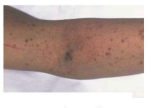
Varies by Classification

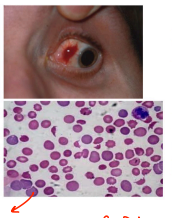
- **Cryoprecipitate**
  - Source of fibrinogen, factor VIII and VWF
  - Only plasma fraction that consistently contains VWF multimers
  - Correction of bleeding time is variable
- **DDAVP**
  - Increases plasma VWF levels by stimulating secretion from endothelium
  - Duration of response is variable
  - Used for type 1 disease
- **Factor VIII concentrate (Humate-P)**
  - Virally inactivated product
  - Used for type 2 and 3

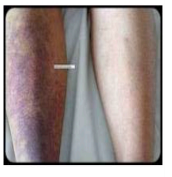
Case 5 C

37 yr old lady was admitted with high fever, chills, rigors and severe dysuria.P/E shown. Temp 40.5,BP 80/50, P122 regular, low volume.

Bleeding from needle puncture sites and bruising. Hb 9g/dl, retcs 6%, bilirubin 5 (d1), WBC 19k, Plt 25k, PT >50s, PTT > 100s, TT >30s, D-Dimer +++, Creatinine 2.3. Bld film shown. Fibrinogen. 30mg/dl.







Schistocyte & Polychromasia for DIC.

Common clinical conditions associated with Disseminated Intravascular Coagulation

Activation of both coagulation and fibrinolysis tiggered by

- **Sepsis**
- **Masive Trauma**

- Head injury

— Fat embolism

- **Malignancy**
- **Obstetrical complications**

- Amniotic fluid embolism, Abruption placentae

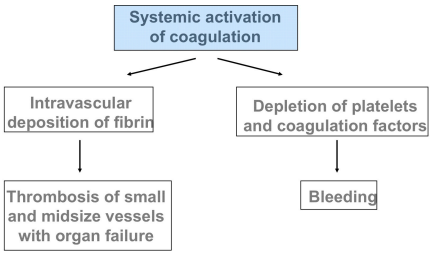
- **Vasculitis**
- **Reaction to toxin** (e.g. snake venom, drugs)
- **Immunologic disorders**

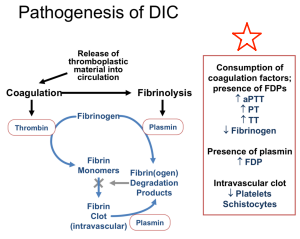
- Severe allergic reaction
- Transplant rejection

 # main reason for DIC is sepsis & systemic inflammatory response.

You have to look for underlying cause; BCS if treat underlying cause succecfully you will cotrol DIC , also you need to support patient bcs there is risk of thrombosis espacially in early phase so give them blood theners (anticoagulation) & try to support them with **platlet & clotting product** as much as you can in order to keep their coagulation in reasonable level to prevent them from bleeding symptoms.

Disseminated Intravascular Coagulation (DIC) Mechanism





Case 5 C: treatment and follow-up

1- Treat vigorously with IV antibiotics after blood, urine culture and septic work-up
2- Hydrate and ensure adequate urine output
3- ICU care, if unstable
4- Replace missing clotting factors: FFP.
5-Plt replacement
6- Monitor PT, PTT, D-Dimer and fbgn, Plt count
7- Investigate cause of uro-sepsis.
8- TTP can easily be excluded.

Disseminated Intravascular Coagulation: Treatment approaches

- Treatment of underlying disorder
- Platelet transfusion
- Fresh frozen plasma
- Coagulation inhibitor concentrate (ATIII)

Fresh Frozen Plasma is the liquid part of human blood that contains all the clotting factors, but no platelets and no red blood cells.
It is collected from donated blood, then frozen to preserve the clotting factors.
FFP includes:

- All clotting factors (II, V, VII, VIII, IX, X, XI, XII)
- Fibrinogen
- Proteins (albumin)
- Natural anticoagulants (Protein C, S, antithrombin)

Step-by-Step Pathophysiology of DIC

Step 1: Trigger

Something triggers your **blood clotting system** too much:

- Severe infection (sepsis)
- Trauma / burns
- Obstetric issues (placental abruption)
- Cancer (especially leukemia)

This trigger causes **widespread release of tissue factor or endothelial injury**.

Step 2: Excess clotting activation

- Tissue factor → activates **clotting cascade** → thrombin is produced.
- Thrombin converts **fibrinogen → fibrin** → tiny clots (microthrombi) form in small blood vessels everywhere.

Effect: Organs start getting **blocked**, leading to ischemia.

- Kidneys → acute kidney injury
- Lungs → trouble breathing
- Brain → confusion

Step 3: Consumption of clotting factors

- All the clotting factors (fibrinogen, prothrombin) and **platelets** are used up forming clots.
- Body **runs out of clotting resources**, so bleeding starts in **other places**.

Think of it like: you're trying to plug holes in a dam with limited sandbags → you run out and water leaks everywhere.

Step 4: Secondary fibrinolysis

- Body notices all the clots → starts breaking them down.
- This produces **fibrin degradation products (FDPs)** → these **inhibit clotting even more**.
- Result → **more bleeding**.

Step 5: Clinical result

You now have the paradox:

- **Clots** in small vessels → organ damage
- **Bleeding** from skin, gums, IV lines, or internal organs

Why the diagnosis is DIC? (Based on the case)

✓ **1. Severe infection trigger**
- High fever 40.5°C
- Rigors, chills
- Severe dysuria
- Hypotension BP 80/50
- Tachycardia HR 122

➡️ This is **septic shock**, the most common cause of acute DIC.

✓ **2. Bleeding from puncture sites**
- Oozing from needles
- Bruising
- Skin petechiae and purpura (shown in images)

➡️ These are hallmark signs of **consumption of clotting factors + platelets**.

✓ **3. Lab Findings = DIC fingerprint**

Let's break them down:

Platelets ↓
- Plt 25,000 → severe thrombocytopenia

➡️ Platelets are being *used up in widespread clotting*.

PT ↑, PTT ↑, TT ↑
- PT > 50 sec
- PTT > 100 sec
- TT > 30 sec

➡️ Clotting factors II, V, VIII, fibrinogen = **consumed** → prolonged times.

Fibrinogen ↓
- **Fibrinogen 30 mg/dL** (normal 200–400)

➡️ Extremely low = **key marker of DIC**

D-Dimer +++
- Very high

➡️ Indicates **massive fibrin breakdown** → strong evidence of DIC.

Blood film

The image shows **schistocytes** (fragmented RBCs)

➡️ Due to **microangiopathic hemolytic anemia** caused by fibrin clots shearing RBCs.

Reticulocytes ↑ (6%)

➡️ Bone marrow trying to compensate for hemolysis.

Bilirubin ↑ (5 mg/dL)

➡️ Breakdown of RBCs → indirect hyperbilirubinemia.

Creatinine ↑ (2.3 mg/dL)

➡️ Due to **renal ischemia** from microthrombi (organ damage in DIC).

Images Explanation

The images show:
- **Petechiae, purpura, ecchymosis**
- **Purpura fulminans** (severe form of DIC)
- **Subconjunctival hemorrhage**
- Blood film with **schistocytes**

These are all classical for **acute consumptive coagulopathy**.

Pathophysiology (simple): What happened in this patient?

Step 1 — Sepsis activates clotting everywhere

Bacteria release endotoxins → huge release of **tissue factor** → activates the clotting cascade.

Step 2 — Blood forms tiny clots everywhere

Microthrombi form in small vessels of:
- Kidney
- Skin
- Liver
- Brain

This causes **organ ischemia** (↑ creatinine, bruising).

Step 3 — Platelets and clotting factors are used up

So now the body **runs out** → bleeding starts.

Step 4 — Body tries to break the clots

→ Massive fibrinolysis
→ ↑ D-dimer
→ Even more bleeding

➡️ This explains **why she has both clotting + bleeding at the same time**.

Why is this Glanzmann Thrombasthenia?

Let's break down the evidence one by one.

Bleeding history strongly suggests a congenital platelet function disorder
- Bleeding **since childhood**
- **Heavy menstrual bleeding** >1 week every cycle
- **Gum bleeding**, **epistaxis** every summer
- **Mucosal bleeding** (classic for platelet disorders)
- **Parents are first-degree relatives** → **autosomal recessive disease** becomes very likely.

This fits **Glanzmann Thrombasthenia**, not VWD, not coagulation factor defects.

Platelet COUNT is normal (240,000)

➡️ So this is **not thrombocytopenia**.
The problem is **platelet function**, not number.

GT = normal platelet count + severe bleeding.

PT, PTT, TT are all normal

These tests measure **clotting factor pathways**, not platelet function.

In Glanzmann:
- Platelet plug formation = defective
- Coagulation cascade = normal

➡️ This again fits GT perfectly.

Bleeding Time >15 minutes

Bleeding time becomes **very prolonged** when platelets cannot aggregate.

GT = one of the most prolonged bleeding times in hematology.

VWF 105% (normal)

→ This EXCLUDES von Willebrand Disease.

If VWF is normal and PT/PTT normal → think platelet function disorder.

Glanzmann Thrombasthenia (often called "Glanzmann thrombocytopenia")

Big idea (in one line)

Platelets are present, but they cannot stick to each other (aggregation defect).

What is the defect?
- Problem in platelet receptor:
  - **GPIIb/IIIa (integrin αIIbβ3)**
- This receptor normally binds **fibrinogen** to link platelets together

In this disease:
- Platelets **can't aggregate**
- So no proper platelet plug forms

Cause
- Usually **autosomal recessive**
- Congenital (present from birth)

Clinical presentation (platelet-type bleeding)
- Easy bruising
- Epistaxis (nosebleeds)
- Gum bleeding
- Menorrhagia
- Bleeding after surgery

Mucocutaneous bleeding (not deep bleeding like hemophilia)

Lab findings (VERY HIGH-YIELD)

Test	Result
Platelet count	✅ Normal
PT	✅ Normal
PTT	✅ Normal
Bleeding time	⬆️ Increased

Clot retraction: Absent → THE KEY CLUE

Clot retraction requires **GPIIb/IIIa receptors** on platelets.

In GT:
- GPIIb/IIIa = absent or defective
- → fibrinogen cannot bind
- → no clot retraction

This finding is classic for GT and almost diagnostic.

Platelet Aggregation Study (the graph in the image)

In Glanzmann:
- No aggregation with **ADP**, **collagen**, or **epinephrine**
- But normal aggregation with **ristocetin**

This EXACT pattern is shown in the image.

➡️ Ristocetin tests GPIb (Bernard-Soulier) — normal in GT
➡️ ADP/collagen/epinephrine test GPIb/IIa — defective in GT

Ultrasound shows ovarian cysts → likely hemorrhagic cysts

Women with GT get repetitive **ovarian bleeding** during ovulation.
This is supportive evidence of a serious platelet function disorder.

Putting it ALL together

Finding	Interpretation
Normal platelet count	NOT thrombocytopenia
Severe mucosal bleeding	Platelet function disorder
Normal PT/PTT	Coagulation cascade normal
Bleeding time ↑↑↑	Platelet problem
VWF normal	Not VWD
Clot retraction absent	**Glanzmann hallmark**
Aggregation abnormal except ristocetin	**Diagnostic for GT**
Consanguineous parents	Autosomal recessive disease

TTP can be easily excluded

Why?

TTP (Thrombotic Thrombocytopenic Purpura) and DIC can look similar but differ in key ways.

TTP usually shows:
- *Normal PT & PTT* ❌
- Severe thrombocytopenia
- Schistocytes
- Neurological symptoms
- ADAMTS13 deficiency

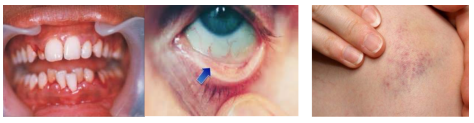
But in THIS case:
- **PT > 50 sec** → prolonged
- **PTT > 100 sec** → prolonged
- **Very low fibrinogen (30 mg/dL)**
- **D-dimer extremely high**

➡️ PT/PTT are **normal in TTP**, so this cannot be TTP.
➡️ This is classic **acute DIC**.

Bleeding Disorder 2

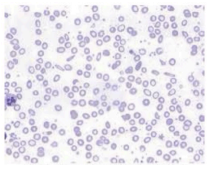
Case 6: GT

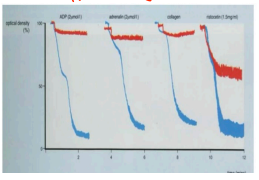
18 yr old female was admitted with pallor, abdominal pain and gum bleeding. She has been complaining of mucosal bleeding ever since she remembers. Her periods have always been heavy lasting more than 1 wk. She was admitted before and received bld TX for bleeding. She has summer epistaxis and bad bleeding gums. Her parents are 1st degree relatives.

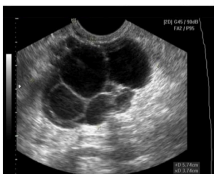


Hb 6, MCV 62, Retcs 0.9% WBC 16k, PIt 240k, PT,PTT, TT: Normal. Bld film shown. BT >15 mnts. VWF 105%. Clot retraction: Absent.

Diagnosis: Glanzmann Thrombasthenia







ex on congenital bleeding disorder for platelet disfunction (primary hemostatic disease) : The bleeding is more in mucocutanous area(gum bleed, conjunctival hemorrage, bleeding under skin(bruzes), menorrhagea, requiering hospitalization/blood transfusion indication a sever phenotype of bleeding .

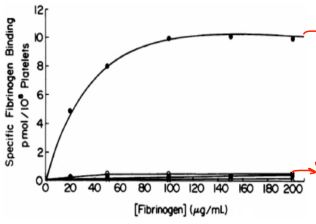
Relative ; increase autosomal recesive disease.

Glanzmann Thrombasthenia: platelets disorder caused by defeincy in glycoprtein 2B3A complex that is essential for normal platelets function and fibrinogen formation .

So those patients have abnormal bleeding time.

Imortant to asses VWF bcs its one of defferential.

Fibrinogen Binding of Platelet in GT



Case 6: Treatment & Follow-up

1- Bld TX (transfusion) : Packed RBC or washed RBC

2- Local dental measures

3- Iv Tranexemic acid (Cyclokapron)--> antifibrinolytic

4- Symptomatic for the ovarian cyst

5- If bleeding is not controlled: PIt TX if antibodies are -ve, if antibodies are +ve, use recombinant factor VIIa (activated factor 7) (Novoseven) used in sever bleedin that not response to several messures. until bleeding stops.

7- Long term contraceptives.(hormonal therapy: estrogen, to control abnormal menestural bleeding)

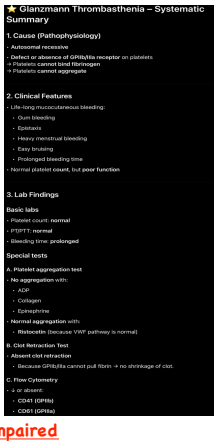
6- Education and counseling.

Clinical Manifestations of GT

- Life long mucosal bleeding
- Prolonged bleeding from cuts/wounds
- Purpura, menorrhagia
- Gastritestinal bleeding
- Intracranial haemorrhage (~1%)

GT Laboratory/ Diagnostic tests

- Normal platelet count and morphology, but disfunctional.
- Prolonged bleeding time
- Absent or impaired clot retraction
- Absent or reduced plt fibrinogen
- No aggregation with physiological aggregating agents
- Absent or reduced GPIIb-IIIa
- Treatment is supportive



 # Clot retraction test: messures fuction of fibrinogen , will be impaired

- The disease is diagnosed depends on abnormal platelets aggregtion , asses glycoprotein on surface of platelet by flow cytometry shows that absent CD-41 & CD-46 & 61

#Conferm the diagnosis by platelets aggregation & flow cytometry

Platelet transfusions - complications

- **Transfusion reactions**
- Higher incidence than in RBC transfusions
- Related to length of storage/leukocytes/RBC mismatch
- Bacterial contamination
- **Platelet transfusion refractoriness, not responed.**
- Alloimmune destruction of platelets (HLA antigens)
- Non-immune refractoriness: risk of bacterial contamination
- Microangiopathic hemolytic anemia
- Coagulopathy
- Splenic sequestration
- Fever and infection
- Medications (Amphotericin, vancomycin, ATG, Interferons)

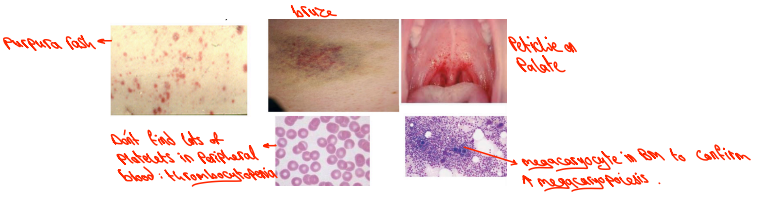
Classification of platelet disorders

- Quantitative disorders
  - Abnormal distribution
  - Dilution effect
  - Decreased production
  - Increased destruction
- Qualitative disorders
  - Inherited disorders (rare)
  - Acquired disorders
    - Medications
    - Chronic renal failure
    - Cardiopulmonary bypass

Case 6 B: ITP imune thrombocytopenia

23 yr old female presented with purpuric skin rash, PV bleeding and easy bruising for 5 days. She was previously healthy and she takes no medications.P/E.No LN,no splenomegaly .

Hb 10.5, WBC 10k, plt 10k. Pt, PTT, TT were normal. DAT -ve. ANA, >DNA -ve .



Immune thrombocytopenia charactarazed by low platelet count, the platelets destroyed by autoantibody (anti-body causting platelets) resulting in phagocytosis by mononeuclear cell in spleen this result in significant shortening of life span of platelets, the bone marrow normally response by increase platelets porduction (increasing megacareopoiesis) and leads to more release relatively younger platelts.

The bleeding symptoms limited to mucocutanous area.

The disease is more common in female, sometimes disease present with other autoimmune disease such as thyroiditis or vitiligo .

The examinatiom should be normal from having lymphnode enlargment, spleenomegaly , hemolysis , pt and ptt should be normal

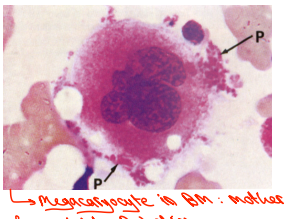
Case 6 B: Management & Follow-up

1- Start oral Prednisolone. If no response or relapse: IVIG, New TPO (Thrombopoietin receptor agonists), ???splenectomy.

2- Follow up for additional immune disease (SLE, APS) or lympho-proliferative neoplasms.

3- Careful monitoring during pregnancy & delivery (post delivery care of the baby).

1. Production
   - Platelets are made by megakaryocytes in the bone marrow.
   - Each megakaryocyte produces roughly 3,000 platelets.
   - In adults, the bone marrow produces around 100 billion platelets per day to maintain normal levels.
2. Distribution
   - About 20–30% of platelets are stored (pooled) in the spleen.
   - The rest circulate in the blood.
3. Lifespan
   - Platelets normally live 7–10 days in the peripheral blood.
   - After this, they are removed mainly by the spleen and liver.



imune thrombocytopenia
Is as a disease of execlusion

In ITP/ immune distruction of platelet perepheraly , usually bone marrow responds by increasing megacayopoiesis and releasing relativly younger platelets to blood film, these younger platelets looks larger on blood film even low platelets

Thrombocytopenia associated with shortened survival (increased destruction)

- **Immune mediated thrombocytopenia**
- Drug-induced thrombocytopenia
- Heparin induced thrombocytopenia
- ITP
- TTP
- **Non-immune destruction**
- DIC
- Sepsis-associated
- **Multifactorial thrombocytopenias**
- Hospital (ICU)-associated thrombocytopenia
- Cancer associated thrombocytopenia

Acquired thrombocytopenia with shortened platelet survival

Associated with bleeding	Associated with thrombosis
– Immune-mediated thrombocytopenia (ITP) – Most drug-induced thrombocytopenias – Most others	Thrombotic thrombocytopenic purpura DIC Heparin-associated thrombocytopenia

Pathogenesis of ITP

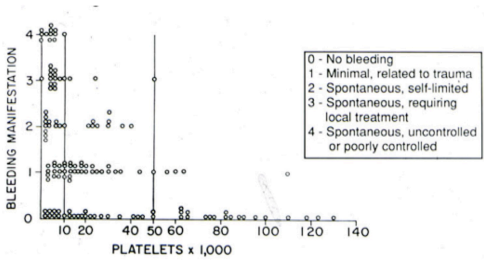
- Increased platelet destruction mediated by autoantibodies
- Auto-antibodies that react with major membrane glycoproteins can be identified in ~80% of patients
- Antibody concentrations diminish with effective treatment and increase with relapse
- Decreased production despite the increase in megakaryocytes in BM

Sites of bleeding in thrombocytopenia

- **Skin and mucous membranes**
  - Petechiae
  - Ecchymosis
  - Hemorrhagic vesicles
  - Gingival bleeding and epistaxis
- **Menorrhagia**
- **Gastrointestinal bleeding**
- **Intracranial bleeding**

The patient have healthy bone marrow and megacaryopoiesis function normal and platelets usually larger than usuall platelets so these patient not expected to have sig.bleeding, rarely seen bleeding in GI or CNS however, if platelets count drop verly low the risk increase espeacially if have other risk factor : alderly, other medications, truma .

Bleeding Manifestations in Relation to Platelet Count



having plt count below 10, is consederd strong risk factor for having spontanouse or uncontrolled bleeding . We prephere plt counte >20

Initial Treatment or No treatment of ITP

Platelet Count (per µl)	Symptoms	Treatment
> 50,000	None	None
30-50,000	Not bleeding Bleeding Mild & self limited	None Glucocorticoids
< 30,000	Not bleeding Bleeding	Glucocorticoids ? Glucocorticoids Hospitalization

Approach to the Treatment of ITP

Initial treatment	Glucocorticoids IVIG Not all patient response on steroid
Curative therapy	Glucocorticoids ✓Splenectomy ✓Rituximab
Rescue therapy	High dose glucocorticoids IVIG
Chronic therapy	Many agents **Thrombopoietin receptor agonists**

 # Important point: we dont to normalized plt.count in ITP, just need to keep it in safe value which > 30-40.
- Should avoid platelets transfusion in ITP , bcs its not usefull bcs having immune antibody destroying platelets.

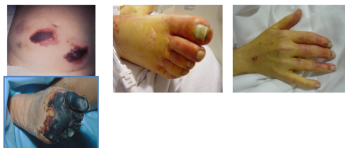
Summary: Thrombopoietin-receptor agonists

	Romiplostim	Eltrombopag
Mechanism	TPOR: active site	TPOR: TM domain
Indications	Chronic ITP	Chronic ITP
Route	SQ	PO
Initial dose	1 mcg/kg/wk	50 mg/day
Overall response	~80%	~80%
Immunogenicity	Yes	No
Hepatic toxicity	No	Yes
Response in splenectomized pts.	Yes	Yes

usually ITP is transient, like 2ndary to infection called acute ITP لحد ٣ شهور ،
ITP > 3 months is likely to persist not to recover (chronic) .

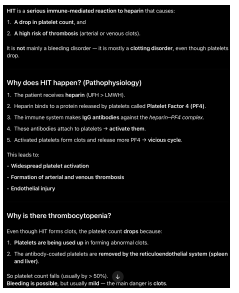
Case 6 C: HIT: heparin induced thrombocytopenea

56 yr old F underwent open heart surgery 6 days ago. She was given Unfractionated heparin. Her **pre-operative plt 300K.**
Patient developed signs of ischemia involving fingers and toes. **Plt count 80K**, PT 16/12, PTT 65/32. Suspected to have HIT. UFH was stopped and warfarin was given, serious complication happened.



Not all patient that take Heparin will develope HIT , some risk factor:
- type of heparin (as high molecular wieight heparin as high risk of develop autoantibody)
- host factor (gender: high in F) , (age: alderly),
- Inflammatory processe in time of intake heparin : **recent sugery** , truma .

#The disease charactarized by drop in platelets count , clinical manifistation : even bleeding or arterial or venous thrombosis(leads to akral eschemia or compromised blood supply to limbs), thrombosis occurr bcs antibody thought to activate platelets and injury to edothelial cells .
- why having thrombocytopenea? Bcs antibody caute the platelets will be recognised and removed by reticulendothelial sys .so may develope bleeding .


HIT is a serious immune-mediated reaction to heparin that causes:
1. A drop in platelet count, and
2. A high risk of thrombosis (arterial or venous clots).

It is not mainly a bleeding disorder — it is mostly a clotting disorder, even though platelets drop.

Why does HIT happen? (Pathophysiology)
1. The patient receives heparin (UFH > LMWH).
2. Heparin binds to a protein released by platelets called Platelet Factor 4 (PF4).
3. The immune system makes IgG antibodies against the heparin–PF4 complex.
4. These antibodies attach to platelets → activate them.
5. Activated platelets form clots and release more PF4 → vicious cycle.

This leads to:
- Widespread platelet activation
- Formation of arterial and venous thrombosis
- Endothelial injury

Why is there thrombocytopenia?
Even though HIT forms clots, the platelet count drops because:
1. Platelets are being used up in forming abnormal clots.
2. The antibody-coated platelets are removed by the reticuloendothelial system (spleen and liver).

So platelet count falls (usually by > 50%).
Bleeding is possible, but usually mild — the main danger is clots.

Clinical Suspicion of HIT
- Normal platelet count prior to heparin with a decline to < 100,000/ul - (or reduction of platelet count by >50%)
- Onset of thrombocytopenia by day 14
- Exclusion of other causes of thrombocytopenia
- Any new thrombotic event while on heparin
- Skin inflammation or necrosis at heparin injection site

Clinical sequelae of HIT

Outcome	Incidence
New thrombosis	up to 50%
Amputation	~10% Associated with arterial thrombosis Associated with venous limb gangrene
Death	10-20%

Typical-onset HIT (plt. Count drop within 4-14 days)

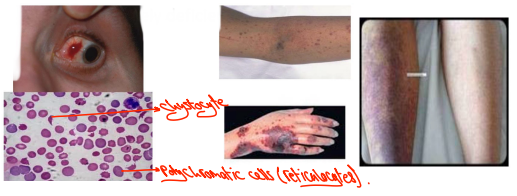
The confirmatory test: heparin-pf4 Anti-body, ELISA-test to detect antibody
Functional test: seretonin release assay

Six treatment principles of HIT
- Two Do's
  *Stop heparin
  *Start Alternative anticoagulation
- Two Don'ts
  *No warfarin until substantial platelet count recovery
  *No platelet transfusions

Not all thrombocytopenea having bleeding tendancy :
thrombocytopenea in ITP have bleeding tendancy but not thrombotic tendancy
thrombocytopenea in **HIT** have bleeding tendancy & thrombotic tendancy
thrombocytopenea in **liver disease(in portal HT)** have bleeding tendancy & thrombosis.
TTP have bleeding tendancy & thrombosis.

Case 6D: TTP

37 yr old lady was admitted with high fever, seizure and confusion for 3 dyas.P/E shown. Temp 40.5,BP 80/50, P122 regular, low volume. Bleeding from needle puncture sites and bruising. Hb 9g/dl, retcs 6%, bilirubin 5 (d1), WBC 19k, PIt 25k, LDH 1400, PT 14/12s, PTT 35/32s, TT 13/11s, Creatinine 2.3. Bld film shown. Fibrinogen 140mg/dl. **ADAM-ST 13 severly deficient.**



TTP is another autoimmune disease charactrarized by bleeding , its aquired , more in young Femal, may present with another Autoimmune dis, patient become unwell during short period of time , bleeding symptoms, febrile, renal faliar, sezure, neurological symptoms , thrombosis(DVT, PE, skin necrosis).
The disease charactarized by thrombocytopenea & intravascular hemolytic anemia this combination called microangiopathic hemolysis this seen mainly in TTP.
Normal PT, PTT, low Plt.count & hgb , positive hemolytic marker (high LDH, reti, indirect bilirubin)
- High mortality if untreated .
Aquierd Autoimmune disease: antibody against enzyme called ADAM-ST 13, this enzyme resposable for normally cleave altralarge VWF, if this enzyme inhibited the altralarge VWF accummulate leads thrombotic in veins or occlusion to organ mainly (brain, kidney) .

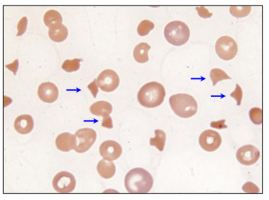
#Congenital TTP: born with deficient in ADAM-ST 13 (not common)

Case 6 D: Management & follow-up
1- **Plasma exchange daily until recovery**
2- Monitor LDH, Plt count and clinical status
3- Monitor ADAM TS 13
4- Careful follow-up post recovery for ?relapse

Thrombotic Thrombocytopenic Purpura :A Disorder of VWF Proteolysis

A classic pentad of signs:

- Microangiopathic hemolytic anemia ← mainly
- Thrombocytopenia
- (Neurologic dysfunction)
- (Renal disease)
- (Fever)

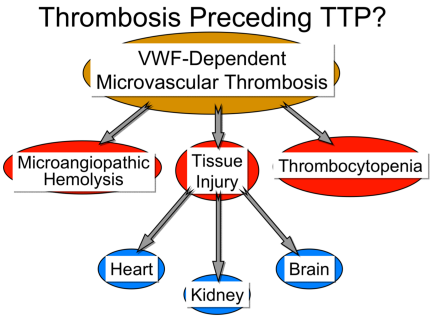


= 4 per million incidence

Strikes mainly young adult women

Untreated, mortality >90%

Treated with plasma exchange, mortality <20%



 # Confirme the disease via testing ADAMTS13 activity which is low in the disease or check antibody against ADAMTS13. بس غالباً بطول لذلك

= TTP is clinical diagnosis

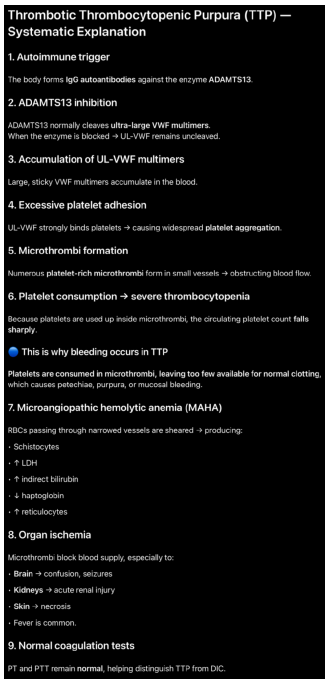
Thrombotic Thrombocytopenic Purpura:

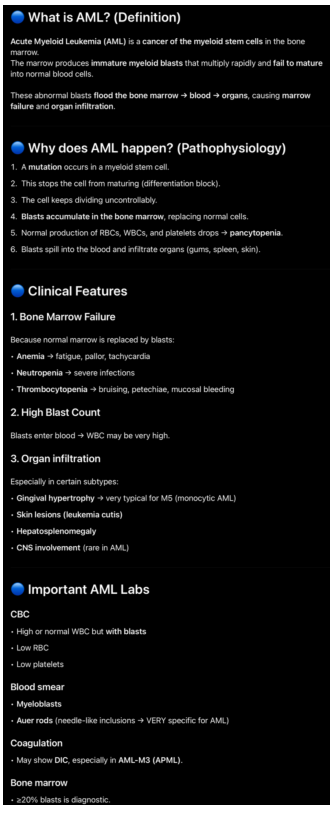
Treatment

- **Initial treatment:**
  - Plasma exchange (plasmapheresis) daily

Usually 4-5 session daily

- **Relapsed or refractory disease:**
  - Plasmapheresis(plasma exchange) +/- Rituximab immunosuppressive therapy
  - Other (Vincristine; Splenectomy)
- **Adjunctive therapy (unproven role)**
  - Glucocorticoids
  - Aspirin

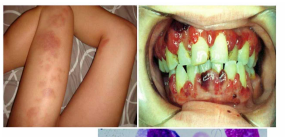


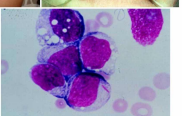


Acute Myloid Leukemia

Case 9: Acute Leukemia

29 yr old lady complains of fever and painful gums for 1 week.
She developed easy bruising and hemorrhagic spots on her trunk and limbs.
Physical findings shows Spleenomegaly, gingival hypertrophy & some Skin lesions, Fever 40,
BP 100/70 (stable) , Pulse: 102 (tachy) , Hb 9, WBC 54K, Blasts 80%, PIt 24K, PT 18/13, PTT 40/32 (Slightly prolonged) ,Urine: RBC +3(hematurea), WBC ++t in urin , Bacteria +++. **Bld culture + E.Coli.**

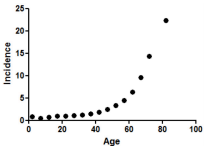




Typically pic of Acute myloid leakemis (AML), is disease of alderly, as you get older as increase risk, Survival Decreases with Age, Incidence of clonal hematopoiesis increases with age(those are sourse of oncogenic mutations leading to abnormal hematopoiesis)

Why do we develop AML as we get older?

Hematopoietic stem cells acquire mutations over their lifetime.
Most are benign (passenger).
Occasionally one leads to clonal hematopoiesis.
Each division within this clone results in further mutations, and facilitate subclonal evolution and progression to MPD/MDS/AML.



AML: Definition

- **De novo (primary) AML:** no identifiable triggers
- **Secondary AML**

- Clinical history of:
- Myelodysplastic syndrome
- Myeloproliferative disorder
- Prior exposure to radiation (both thuraputic or non), chemicals (benzene, pesticides, cigarette smoking) , or chemotherapy (Alkylating agents, Topoisomerase-II inhibitors, Anthracyclines, Epipodophyllotoxins Taxanes.

AML: Classification
French-American British (FAB)

Not widely used.

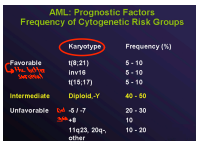
M0	Undifferentiated
M1	Myeloblastic without maturation
M2	Myeloblastic with maturation
M3	Promyelocytic
M4	Myelomonocytic
M5	Monocytic
M6	Erythroid
M7	Megakaryoblastic

*Added in 1985

- **AML with recurrent genetic abnormalities**
  - t(8;21)(q22;q22)
  - inv(16)(p13;q22) or t(16;16)(p13;q22)
  - t(15;17)(q22;q12)
  - 11q23 abnormalities
- **AML with multilineage dysplasia**
- **AML and myelodysplastic syndromes (MDS); therapy related**

AML: Prognostic Factors

- Age_ as age increase the propablity of survival decreases
- Cytogenetics_ detected through karyotyping
- Molecular mutation
- Secondary AML- better progonsis
- Performance status- the better PS the better prognosis
- Leukocyte count- the higher Leukocyte count the poorer prognosis



AML: Presenting Signs and Symptoms

Bone marrow failure

- Anemia (fatigue / pallor / DOE)
- Thrombocytopenia (bleeding / bruising)
- Neutropenia (infections / fever)

Leukemic infiltration of tissues

- Hepatomegaly
- Lymphadenopathy
- Splenomegaly
- Bone pain
- Leukemia cutis
- Gingival infiltration
- CNS infiltration

AML: Presenting Signs and Symptoms_ Oncologic Emergencies

- **Tumor lysis syndrome (TLS)**

Hyperuricemia
Hyperphosphatemia
Hyperkalemia
Hypocalcemia

- Acute renal failure
- Metabolic acidosis
- Cardiac arrhythmias

- **Hyper-leukocytosis (leukostasis syndrome)** → WBC Blast Flow
- Dyspnea
- Chest pain
- Headache
- Altered mental status
- Cranial nerve palsies

Hyperleukocytosis = very high WBC count (usually >100,000).
In AML, the blasts are large, sticky, and stiff, so when they become too many, they block small blood vessels.
This blockage is called leukostasis syndrome.

AML: Treatment Overview

Remission Induction

remission means to regain normal WBC-count

- Goal to reduce tumor burden & restore normal hematopoiesis
- **"7 + 3" (chemotherapy protocole)** : Continuous infusion cytarabine x 7 days and an anthracycline x 3 days remains standard of care.

Post-Remission (Consolidation) Therapy

- Once in Complete remission (after bonemarrow back to normal), long-term survival requires post-remission treatment
  - Chemotherapy versus
  - Allogeneic stem cell transplant (زراعة نخاع عظم من متبرع) versus
  - Autologous stem cell transplant

New approach in treating AML

1- Risk stratification
2- Incorporation of Monoclonal antibodies
3- Incorporation of small melcules and targeted therapy

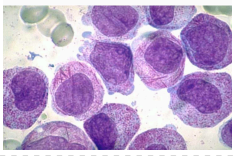
Promyelocytic leukemia M3 (specefic type of AML)

1. Associated with t (15;17) involving the retinoic acid receptor (RAR) gene.
2. Good prognosis category.
3. Commonly associated with DIC.

- It associated with Prominent Auer rods :

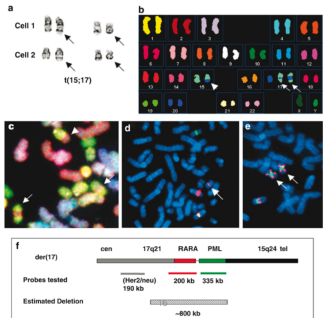
Auer rods are linear, red-pink, needle-shaped inclusions seen in the cytoplasm of myeloblasts in Acute Myeloid Leukemia (AML). They are formed by aggregated primary (azurophilic) granules containing enzymes like myeloperoxidase. Their presence is highly suggestive of AML, especially acute promyelocytic leukemia (APL).

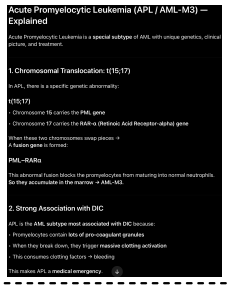
Auer rods in AML



t(15;17) translocation in AML

When there is a translocation between chromosome 15 & 17 , the fusion of RARA & PML proteins will take place resulting in AML-M3 .





M4: Myelomonocytic leukemia

- Usually associated With inverted 16 and associated eosinophilia this is a good prognostic category
- Associated with leukemia cutis like eschemic leukemic infiltration.
- CNS disease may occur.

Treatment aml/m3

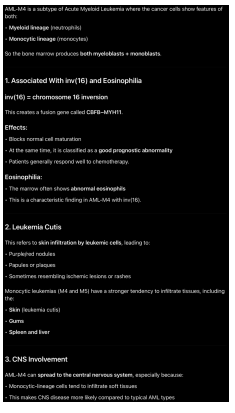
- **Tretinoin (all trans retinoic acid)** is an oral drug that induces the differentiation of leukemic cells bearing the t(15;17); it is not effective in other forms of AML.
- APL is responsive to **cytarabine and daunorubicin**, but about 10% of patients treated with these drugs die from DIC induced by the release of granule components by dying tumor cells.

ATRA Syndrome (All Trans Retenoic Acid)

- Tretinoin does not produce DIC but produces another complication called the **retinoic acid syndrome.**
- Occurring within the first 3 weeks of treatment, it is characterized by **fever, dyspnea, chest pain, pulmonary infiltrates, pleural and pericardial effusions, and hypoxia.**
- The syndrome is related to adhesion of differentiated neoplastic cells to the pulmonary vasculature endothelium.
- Glucocorticoids, chemotherapy, and/or supportive measures) can be effective.
- **The mortality of this syndrome is about 10%.**

Remember:

- leukocyte common antigen: **CD45**
- **Blasts**: CD34, CD123, CD117, HLA-DR
- **B-cell**: CD19, CD20, CD22, CD79a, PAX5
- **T-cell**: CD2, CD3, CD5, CD7, CD30
- **Myeloid**: CD13, CD33, MPO, CD11b
- ***APL**: HLA-DR-, CD34-, MPO+, CD33+*

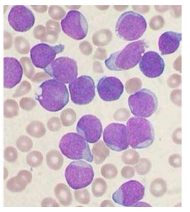


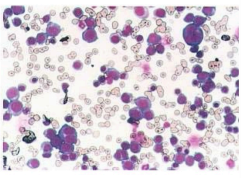
Case 9 B

A 19 yr old male has been complaining of fatigue, joint pain for 2 wks. He was admitted because he had a high fever.P/E he looked ill and pale, with Temp 40, BP 100/70, p 104, he had generalized LN enlargement, badly infected tonsil. His spleen was enlarged. Hb 9.5g/al, pIts 45k (low), WBC 90k: blasts 88%, other cells 12%. LDH 1600, Uric acid 13, Ca 7, PO4 5, Creat 3, K 6.1, PT, PTT, TT, Nml.

CD19(+),Tdt(+), CD10(+), CyIg(-), Karyotyping normal, PAS +++

This is Tumor Lysis Syndrome





Common manifestations of acute leukemia

1-Manifestations of BM replacement
Anemia
Thrombocytopenia
Neutropenia
2-Infiltration of extra BM tissues:
LN, Gums, skin, CNS, others
3-Release of granules/ metabolites:
DIC/ gout, ARF (acute renal faliar)
4-Hyperviscosity

Biology of Adult Acute- Lymphoblastic Leukemia

ALL

Classification based on :
-Morphologic Features
-Immunophenotyping

Morphologic subtypes of acute lymphoblastic leukemias (FAB classification)

Subtype	Morphology	Occurrence (%)
L1	Small round blasts clumped chromatin	75
L2	Pleomorphic larger blasts clefted nuclei, fine chromatin	20
L3	Large blasts, nucleoli, vacuolated cytoplasm	5

Immunologic classification of acute lymphoblastic leukemias

B- lineage (80%)	Markers
Pro-B	CD19(+),Tdt(+),CD10(-),CyIg(-),
Common	CD19(+),Tdt(+),CD10(+),CyIg(-),
Pre-B	CD19(+),Tdt(+),CD10(+),CyIg(+),SmIg(-)
Mature-B	CD19(+),Tdt(+),CD10(±),CyIg(±),SmIg(+)
T-lineage (20%)	
Pre-T	CD7(+), CD2(-), Tdt(+),
Mature-T	CD7(+), CD2(+), Tdt(+),

Chromosomal/molecular abnormalities with prognostic significance in ALL

Better prognosis
- normal koryotype
- hyperdiploidy

Poor prognosis
- t (8; 14)
- t (4; 11)

Very poor prognosis
- t (9; 22); BCR/ABL (+)

Philidelphia Chromosome.

#t(9;22) → Poor prognosis in ALL
→ excellent prognosis in CML

Risk classification in ALL

1. Standard risk
2. High risk
3. Very high risk

Feature	ALL	AML
Age	Children ✅	Adults
Lymphadenopathy	Common ✅	Less common
Down syndrome (age 9)	Common ✅	Less typical
Bone pain	Common ✅	Can occur

High-risk ALL/ very high risk

1. Pre - T
2. Pro - B
3. Age > 35 years,
4. WBC > 30 G/L in B-ALL
   > 100 G/L in T-ALL
5. No remission after 4 weeks of induction therapy
6. Chromosome Philadelphia - positive or BCR/ABL (+)

In ALL the choice of treatment-strategy depends on:

1. Risk Stratification
2. Immunophenotype of leukemic cells
- T lineage,
- early B lineage,
- mature B lineage,
3. Age and biological condition
4. Goal of treatment

Treatment Approach in ALL

CNS Prophylaxis

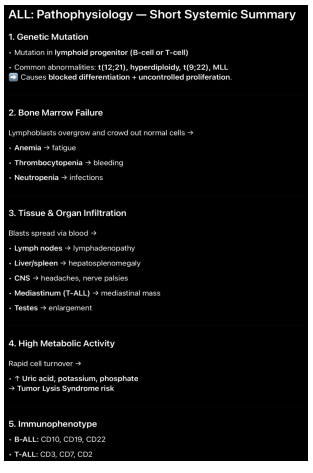
Intrathecal methotrexate, Ara-C, Steroids, Craniospinal irradiation

INDUCTION	CONSOLIDATION / INTENSIFICATION	MAINTENANCE
1 month	4-8 months	2-3years
Anthracycline Vincristine Cyclophosphamide L-asparaginase Methotrexate Ara-C Steroids	Chemotherapy Allogeneic Stem Cell Transplant	6-MP مركبتوبورين Methotrexate Vincristine Steroids
GOAL: rapidly restore normal	GOAL: prevent emergence of resistant clones eliminate residual disease	GOAL: eliminate residual disease

Allogeneic BMT for ALL

High risk ALL

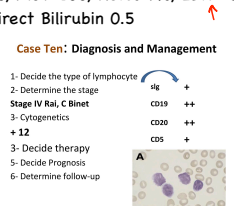
Unacceptable minimal residual disease
Depends on Availability of a donor
Good performance status
Aim to cure

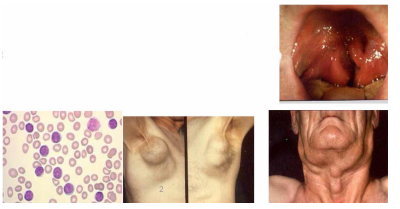


Chronic Leukemia

Case 10

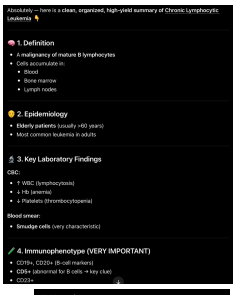
69 yr old man complains of fever and cervical and axillary swellig for several months with recurrent fever and productive purulent cough. P/E Splenomegaly, lymphadenopathy and pallor. Hb 10, MCV 100, Retcs 7%, LDH 680 U/ml, Blood film shown. WBC 123k, Plt 85k, DAT+3, Bilirubin 2, Direct Bilirubin 0.5

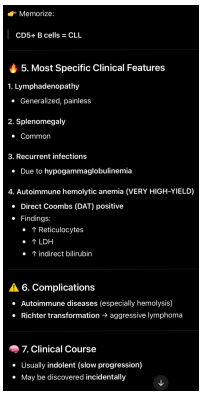




CLL Clinical Presentation

- **Lymphocytosis**
  - Morphologically mature
  - Immunologically immature
  - Accumulation in PB, BM and lymphatic tissues
- **Enlarged Lymph nodes**
- **Splenomegaly**
- **Hypogammaglobulinaemia** → ↑ infection





Estimating prognosis

- **Clinical staging systems - Rai/Binet**
  - Early disease: >10 years median survival
  - Intermediate: 5-7 years median survival
  - Advanced: 1-3 years median survival
- **Heterogeneity of disease**
  - doesnt present the same in all patient

Staging: Rai and Binet staging systems for CLL

Clinical staging systems for CLL

Value	Rai	Binet	Median survival
Lymphocytosis (>15,000/mm³)	0	-	150 months (12.5 years)
Lymphocytosis plus nodal involvement	I	A <3 node groups	101-108 months (8.5-9 years)
Lymphocytosis plus organomegaly	II	B >3 node groups	60-71 months (5-6 years)
Anemia (RBCs)	III PLT <1000/mm³	C Hgb <10 g/dL	19-24 months (1.5-2 years)

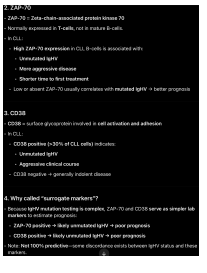
Genetic abnormalities in CLL

Genetic abnormaliity	Incidence (%)	Median survival (months)	Clinical correlation
13q14	55-62	133-292	Typical morphology Mutated V_H genes Stable disease
+ 12	16-30	114-122	Atypical morphology Progressive disease
del 11q23	18	79-117	Bulky lymphadenoathy Unmutated V_H genes Progressive disease Early relapse
p53 loss/mutation	7	32-47	Atypical morphology Unmutated V_H genes Advanced disease

* Poor prognosis

Mutation status of IgHV genes

- **Unmutated: (BAD)**
  - Pregerminal centre cell
  - Rapid progression
  - More aggressive
  - Surrogate markers: ZAP-70 & CD38 positive
- **Mutated: (GOOD)**
  - Postgerminal centre cells
  - Slow progression
- **Surrogate markers**
  - ZAP 70 and CD38



CLL treatment criteria:

Do we treat all patient with CLL ? No, only:

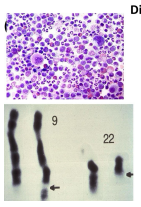
- Patient has symptoms
- Decline in Hb or Plt.
- Lymphadenopathy
- Hepatosplenomegaly
- Recurrent infections

Most recently targeted therapy is BTK inhibitor: Ibrutinib

Case 10 B: CML

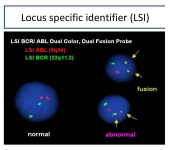
54 yr M, complains of Left abdominal discomfort, weight loss, sweating and headaches.P/E: signs of weight loss, temp 37.3, BP 135/85 (stable) . Spleenomegaly, Hb 13, mcv 88, Retcs. 0.9% PIt 800k, WBC 120k, uric acid 9.5.

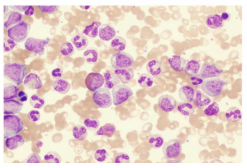
1- BM. 2-Karyotyping. 3- FISH.

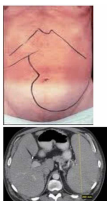


Diagnosis: CML in Chronic Phase

Locus specific identifier (LSI)







Epidemiology

- Incidence of CML is 1.5 / 100,000.
- Affects middle-aged individuals.
- CML accounts for 20% of all leukemias affecting adults.

Definition

- **Clonal expansion of a hematopoietic stem cell possessing a reciprocal translocation between chromosomes 9 and 22.**
- Fusion of BCR region on chromosome 22 with ABL gene from chromosome 9.
- Disease has three phases: chronic phase, accelerated phase, and blast crisis.

Pathophysiology

- BCR/ABL gene product plays central role.
- Bcr/Abl fusion proteins p210BCR/ABL and p230BCR/ABL can transform hematopoietic progenitor cells in vitro.
- Irradiated mice injected with BM cells infected with retrovirus carrying the BCR/ABL gene leads to CML-like picture.

Symptoms

- Insidious onset: accidental discovery
- Fatigue, malaise, weight loss
- Symptoms due to splenomegaly
- LUQ pain, early satiety, mass
- Infections, thrombosis, bleeding.
- ?Gout
- Worsening of symptoms heralds progression (fever, weight loss, decreased response to therapy, bone pain).
- Some patients may present in the accelerated or blastic phase.

Physical Findings

- Minimal to moderate splenomegaly
- Mild hepatomegaly
- Lymphadenopathy and myeloid sarcomas rare except in terminal stages of disease.

Hematologic Findings

- Elevated WBC, <5% blasts and <10% blasts and promyelocytes
- Elevated platelets
- Normochromic normocytic anemia
- Basophilia
- The cytogenetic hallmark of CML, found in 95% of patients, is the t(9;22)(q34;q11.2).
- Originally designated as the Philadelphia chromosome.
- All patients should have evidence of the translocation either by cytogenetics, FISH, or molecularly to make a diagnosis of CML.

Accelerated Phase is characterized by:

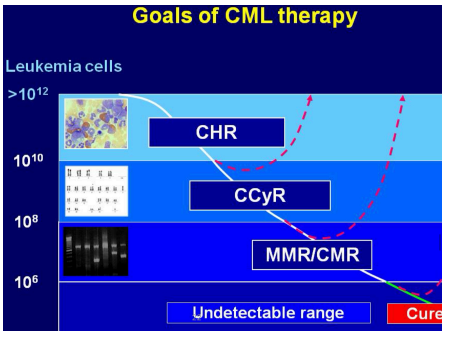
- Anemia, Blood or BM basophils ≥20%, Platelet count < 100,000/MI
- Cytogenetic clonal evolution, Blood or BM blasts between 10 and 20%

Blastic Phase (Crisis)

- resembel Acute leukemia, with blood or marrow blasts ≥ 20%.
- Hyposegmented neutrophils may appear (Pelger-Huet anomaly).
- Blast cells can be classified as myeloid, lymphoid, erythroid, or undifferentiated.

Treatment

- Aim of treatment is to reduce WBC, prevent gout and target the molecular cause of the disease
- The treament has been revolutionized by imatinib mesylate, a targeted treatment. → Block BCR-ABL Tyrosin Kinase
- Stem cell transplant (SCT) is the only definitive therapy and treatment of choice in some patients. Especially in patient with no BCR/ABL



حكا بس ما فهمت

 # with Inrease months of treatment, there is reduction in amount of BCR-ABL transcript

Imatinib mesylate

Competitive inhibition at the adenosine triphosphate (ATP) binding site of the Abl kinase.
Rapid hematologic response.
95% of patients achieved complete hematologic remission, and 60% achieved major cytogenetic remission within few months.

Side effects of Imatinib

- The main side effects are fluid retention, nausea, muscle cramps, diarrhea, and skin rashes.
- Myelosuppression is the most common hematologic side effect.

Resistance to Imatinib

Mechanisms include
- Gene amplification
- **Mutations at the kinase site**
- Enhanced expression of multidrug exporter proteins
- Alternative signaling pathways functionally compensating for the imatinib-sensitive mechanisms

Other Treatment Modalities

- Alfa Interferons
- Chemotherapy (hydroxyurea, busulphan)
- Allogeneic BMT (SCT) for selected patients
- 2d generation TKI for failures or relapse or intolerance
- BMT for Crisis

1. What is CML? (Definition)

- CML is a **blood cancer** that starts in the **hematopoietic stem cells** (the cells in the bone marrow that make all blood cells).
- It is caused by a **genetic change: translocation between chromosome 9 and 22** → forms **BCR-ABL fusion gene** (called **Philadelphia chromosome**).
- This gene makes a protein called **BCR-ABL tyrosine kinase** → makes blood cells **grow uncontrollably**.

Key point: CML is a cancer of the bone marrow stem cells, not just white blood cells.

2. How it happens (Pathophysiology)

1. Normal stem cell → gets **BCR-ABL mutation**.
2. BCR-ABL protein **turns on growth signals constantly** → cells divide even when they shouldn't.
3. Consequences:
   - **Too many white blood cells (WBCs)** → seen as very high WBC in labs.
   - **Too many platelets** → thrombocytosis.
   - **Bone marrow overcrowding** → anemia (low Hb), sometimes low reticulocytes.
   - **Spleen enlarges** because it tries to help make blood cells (**extramedullary hematopoiesis**).
   - **High cell turnover** → uric acid rises → risk of **gout**.

3. Symptoms (Why patient feels them)

Symptom	Why it happens
Fatigue, malaise	Anemia or high WBC use up energy
Weight loss, sweating	Cancer metabolism & cytokines
LUQ discomfort	**Enlarged spleen** pressing on stomach
Early satiety	Spleen pushes on stomach → eat less
Headaches	Very high WBC → blood thickens → reduced oxygen delivery
Gout	Uric acid from cell breakdown

Tip: In chronic phase, patients may feel almost normal → symptoms appear slowly.

4. Physical Findings

- **Spleenomegaly** → LUQ mass, sometimes down to pelvis
- **Mild hepatomegaly**
- **Rare**: lymph node enlargement (lymphadenopathy) or leukemia deposits (myeloid sarcoma)
- **Vitals**: Usually stable in chronic phase

5. Labs (Explain each)

Lab	Case value	Why abnormal / meaning
WBC	120,000	Very high → uncontrolled growth of myeloid cells
Hb	13 g/dL	Normal → anemia not severe yet
Platelets	800,000	High → BCR-ABL also stimulates platelets
Reticulocytes	0.9%	Low-normal → bone marrow function okay but mostly producing WBCs
Uric acid	9.5	High → cell turnover → risk of gout
MCV	88	Normal → cells are normal size
Philadelphia chromosome	t(9;22)	Diagnostic hallmark of CML

Key point: High WBC + high platelets + Ph chromosome = typical **chronic phase CML labs**.

6. Disease Phases

1. **Chronic Phase**
   - WBC very high, <5% blasts
   - Usually mild or no symptoms
   - Patient in case: likely chronic phase
2. **Accelerated Phase**
   - Anemia develops
   - Basophils ≥ 20%
   - Platelets < 100k or > 1M
   - Blasts 10–19%
3. **Blast Crisis**
   - ≥20% blasts → behaves like **acute leukemia**
   - Can be myeloid, lymphoid, or undifferentiated
   - Severe symptoms, high risk

Important: Early treatment prevents progression from chronic → accelerated → blast crisis.

7. Treatment

Step 1: Target the BCR-ABL protein (Molecular Therapy)

- **Imatinib mesylate** → blocks BCR-ABL tyrosine kinase
- **Effects:**
  - Lowers WBC and platelets
  - Reduces spleen size
  - Prevents progression
- **Monitoring:** PCR for BCR-ABL transcript → should decrease over months
- **Side effects:** fluid retention, nausea, cramps, rash, myelosuppression

Step 2: Other supportive therapy

- Hydroxyurea → temporary cytoreduction
- Control uric acid → prevent gout
- Second-generation TKIs if resistant

Step 3: Stem cell transplant

- Only **curative** therapy
- Considered in patients with:
  - Blast crisis
  - TKI resistance
  - No BCR-ABL

8. Summary: Stepwise Understanding

1. **Mutation:** Stem cell gets BCR-ABL gene → produces uncontrolled kinase.
2. **Effect:** Too many WBCs and platelets, spleen enlarges, uric acid rises.
3. **Symptoms:** Fatigue, LUQ pain, weight loss, sweating, early satiety.
4. **Labs:** High WBC, high platelets, normal Hb early, Ph chromosome positive.
5. **Phase:** Chronic → can progress to accelerated → blast crisis.
6. **Treatment:** TKIs (imatinib), monitor BCR-ABL, stem cell transplant if needed.

Trick to remember:

- **C** for **Chronic** → mild, WBC high, asymptomatic
- **A** for **Accelerated** → anemia, more blasts, symptoms worsen
- **B** for **Blast crisis** → ≥20% blasts, looks like acute leukemia

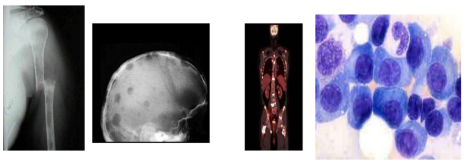
Multiple Myeloma

Case 11 B

67 yr old male has been complaining of back pain for several months. He recently noticed exertional dyspnea. He was admitted because of sever pain in his arm.

- having fracture in humerous , the bone is so hypodense , lytic lesion in skull, PET scan show active bony lesions, bld film showing plasma cell.

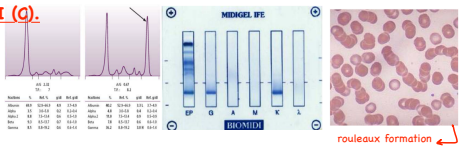
Hypodense bone & lytic lesions → areas where bone is being destroyed (common in multiple myeloma).



Investigation and Diagnosis

1 - Hb 8 g/dl, normocytic normochromic, WBC 8K, Plt 180K, ESR 112mm/1st hr. Bld film. B2-microglobulin 6mg/l, serum albumin 3 g/dl, P/E 1gG 15 g/dl and IF/ igGK(monoclonal protein)

2- Multiple myeloma igG/k stage III (G).



rouleaux formation

Clinical Features

- **Symptoms related to BM infiltration**: bone pain, osteolytic lesions and fractures, anemia, hypercalcemia
- **Secretion of abnormal proteins**: renal and neurological or visceral manifestations
- **Hyperviscosity syndrome** inform of headach, chest pain, blurring vision.
- **Recurrent infections**: •Plasma cells are abnormal → immune system compromised.
- **Amyloidosis**: • Deposition of abnormal proteins in organs.

Related organ or tissue impairment

MM is diagnosed either by haaving more than 60% of plasma cell in BM (Diagnostic) OR having plasma cell 10-59% with CRAB criteria

B$_{uy}$ – Lytic bone lesions – visible on x-ray in **85**% of patients. **Hint** – Osteoclasts activated, not osteoblasts.

C – Hypercalcemia (Ca > 11 mg/dL)

A – Anemia (Hb < 10)

V – Hyperviscosity – especially common in the IgM secreting myeloma rare

I – Bacterial infections (>2)

A – Amyloidosis

R – Renal (Crt > 1.96 mg/dL): **HINT** – occurs 50% of the time because most often the light chains are toxic to the tubules.

These are the end organ manifestations of myeloma

Clinical features

•CRAB helps distinguish active myeloma from smoldering/early disease.

- common tetrad of multiple myeloma is CRAB

-C = Calcium (elevated)

-R = Renal failure

-A = Anemia

-B = Bone lesions visible on X-ray , not show in bone-scan, bcs bone-scan detect osteoblastic activity rather than osteoclastic activity .

Active Multiple Myeloma

Both criteria must be met:

1- **Clonal bone marrow plasma cells >/= 10%** or **biopsy-proven bony or extramedullary plasmacytoma**

2- **Any one or more of the CRAB features**

Smouldering MM : early, silent, pre-cancer stage of multiple myeloma.

Both criteria must be met:

 # Serum monoclonal protein (IgG or IgA) >/=3 g/dL, or **urinary monoclonal protein 500 mg per 24 h and/or clonal bone marrow plasma cells 10%-60%**

 # Absence of myeloma defining events or amyloidosis : No CRAB features → asymptomatic

Diagnosis and Staging

- **Bone marrow biopsy and aspirate:→ confirm plasma cell infiltration**
- **Serum protein electrophoresis and immunofixation. Serum/urin free light chain → identify M protein type**
- **Skeletal survey/ MRI/PET Scan**

- Plain x-rays are better than bone scan.
- Lytic lesions do not show up well on bone scan.

- **Quantitative immunoglobulins → check M protein levels**

Prognostic Factors

International staging system

I (good prognosis)

Serum albumin > 3.5 g/dl

Serum β2 microglobulin < 3.5 mg/dl

II

Not I or III

III

β2 microglobulin: >5.5 mg/dl

Treatment of Multiple Myeloma

Standard Chemotherapy

- Dexamethazone (steroid) and Thalidomide
- Dexa and Bortezomib (Velcade/ Lenalidomide
- Melphalan and prednisone (steroid).
- High Dose Chemotherapy with Bone marrow transplant (auto)

Categories with Potential Prognostic Significance

Factor	Abnormality	Median Survival
	plasmablastic morphology	5 – 23 mos
Surface Markers	CD38+/CD45- Peripheral blood	>10 cells/uL 37 mos
Kinetics	S phase 1- 3% S phase > 3%	22 mos 12 mos
Conventional cytogenetics	Deletion 13	15 mos
FISH	t(4;14)	29 mos

1. Definition
   - **Multiple Myeloma (MM)** is a cancer of **plasma cells** in the bone marrow.
   - Plasma cells normally make antibodies to fight infection.
   - In MM, **abnormal plasma cells grow uncontrollably**, producing **a single type of antibody (M protein)**, damaging bones, blood, kidneys, and other organs.

2. Pathophysiology

Think of it in **three main mechanisms**:

A. Bone marrow infiltration
   - Abnormal plasma cells **replace normal marrow**, reducing production of RBCs, WBCs, and platelets.
   - **Result:** anemia, leukopenia (infection risk), thrombocytopenia (bleeding risk).

B. Bone destruction (osteolytic lesions)
   - Plasma cells **stimulate osteoclasts** (cells that break down bone) and **inhibit osteoblasts** (cells that make new bone).
   - Leads to:
     - Bone pain (back, ribs)
     - Pathological fractures (humerus, vertebrae)
     - Hypercalcemia (calcium released from bones → nausea, confusion, constipation)

C. Monoclonal protein (M protein) secretion
   - Plasma cells secrete **one type of antibody** (IgG, IgA, rarely IgM) or light chains (kappa/lambda).
   - Effects of M protein:
     1. **Kidneys:** Light chains clog renal tubules → kidney failure.
     2. **Blood viscosity:** Thick blood → headaches, blurred vision, heart strain.
     3. **Immune suppression:** Normal antibody production ↓ → infections.
     4. **Amyloidosis:** Protein deposits in heart, nerves, liver.

3. Clinical Features

MM symptoms come from **CRAB features** plus systemic effects:

CRAB:
- **C = Calcium ↑ (hypercalcemia)** → nausea, vomiting, confusion, constipation
- **R = Renal failure** → due to M protein deposition
- **A = Anemia** → fatigue, pallor
- **B = Bone lesions** → fractures, lytic lesions on X-ray

Other features:
- Recurrent infections (pneumonia, urinary tract)
- Hyperviscosity syndrome → headache, dizziness, blurred vision
- Weight loss, fatigue, night sweats

Key point:
- Bone pain + anemia + high ESR + M protein → **classic MM picture**

4. Investigations / Diagnosis

A. Blood tests
- **CBC:** anemia (normocytic, normochromic), normal/mildly low WBCs/ platelets
- **ESR:** very high
- **Calcium:** may be elevated
- **Renal function tests:** creatinine ↑ if kidney involved

B. Protein tests
- **Serum protein electrophoresis (SPEP):** detects M protein
- **Immunofixation (IF):** confirms type (IgG, IgA, kappa, lambda)
- **Serum free light chains:** measure light chains in blood

C. Bone marrow biopsy
- Shows **≥10% clonal plasma cells**

D. Imaging
- **X-rays / Skeletal survey:** lytic lesions (skull, spine, pelvis, ribs)
- **PET/CT or MRI:** detect active lesions
- **Note:** bone scan is usually **not sensitive**, because MM lesions are lytic (bone-destroying), not osteoblastic (bone-forming).

5. Disease Types / Staging

A. Active MM
- ≥10% plasma cells in marrow or plasmacytoma
- One or more **CRAB features**

B. Smoldering MM
- Serum M protein ≥3 g/dL or urine M protein ≥500 mg/24h
- Marrow plasma cells 10–60%
- **No CRAB features** → usually asymptomatic

C. Prognosis – International Staging System (ISS)
- **Stage I:** B2-microglobulin <3.5 mg/L, Albumin >3.5 g/dL → good prognosis
- **Stage II:** Neither stage I nor III
- **Stage III:** B2-microglobulin >5.5 mg/L → poor prognosis

6. Complications
- **Bone:** fractures, spinal cord compression
- **Blood:** anemia, bleeding
- **Kidneys:** myeloma kidney (cast nephropathy)
- **Infections:** bacterial pneumonia, UTI
- **Hyperviscosity syndrome:** headache, blurred vision
- **Amyloidosis:** heart failure, neuropathy

Lymphoma

NHL/ HD(Lymphoma): common features

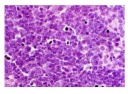
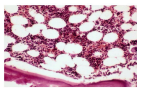
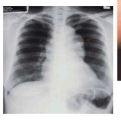
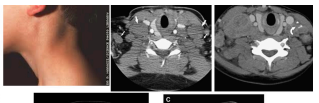
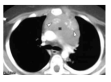
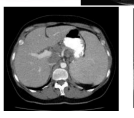
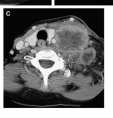
1- Lymph node enlargement: painless, decides stage
2- May be associated with B-symptoms: fever, night sweats, weight loss
3- Compression symptoms may occur due to comression of adjesent organs
4- Extra-nodal involvement, ex involvement of spleen or liver
5- **Needs LN Biobsy for diagnosis**
6- Each has different histology types
7- Both have similar staging system

6) Each has different histology types
- Hodgkin lymphoma → Reed–Sternberg cells
- NHL → many types (follicular, diffuse large B-cell, Burkitt's, mantle cell, T-cell types)

Case 11: NHL

27 yr old male, presented with weight loss, low grade fever and profuse sweating for the last 6 wks.P/E, he had generalized lymphadenopathy, hepato-splenomegaly and enlarged tonsils.

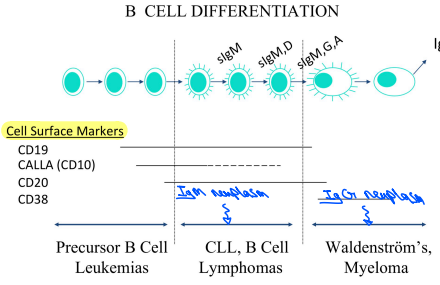
Hb 10g/dl, MCV 100, WBC 14k, Normal diff, PIt 196k, LDH 820, uric.a 7.5, Creat, Ca, PO4 NI.
LN.BX

NHL

- The types of non- Hodgkin's lymphoma reflect the developmental stages of lymphocytes.
- Each type of lymphoma can be viewed as a lymphocyte arrested at a certain stage of development and transformed into a malignant cell.
- 85% B cell origin, the rest T or null cell.

What does it mean "arrested at a developmental stage"?
A lymphocyte normally matures step-by-step.
NHL happens when the cell:
- stops maturing
- becomes malignant
- keeps multiplying at that "arrested" stage
→ leading to different lymphoma types (example: follicular, mantle cell, Burkitt's).



Etiology of NHL

- **Idiopathic**
- **Immune suppression**
- congenital immunodeficiencies (Wiskott-Aldrich)
- organ transplant (cyclosporine)
- AIDS
- increasing age
- **DNA repair defects**
- ataxia telangiectasia
- xeroderma pigmentosum
- **Chronic inflammation and antigen stimulation:**

Constant stimulation → lymphocytes keep dividing → mutations.

- Helicobacter pylori inflammation → stomach (gastric MALT lymphoma)
- Chlamydia psittaci inflammation → ocular lymphoma
- Sjögren's syndrome → salivary gland lymphoma
- **Viral causes**
- EBV → Burkitt lymphoma
- HTLV-I → adult T-cell leukemia/lymphoma
- HTLV-V → cutaneous T cell lymphoma
- Hepatitis C → some B-cell lymphomas

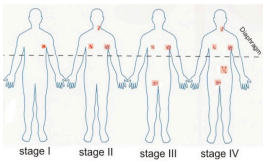
Diagnosis of NHL

Lymphoma Type	Translocation	Oncogene Activated
Follicular lymphoma	t(14;18)	BCL-2
Burkitt's lymphoma	t(8;14) (± t(2;8), t(8;22))	c-MYC
Mantle cell lymphoma	t(11;14)	Cyclin D1

Staging: Ann Arbor

I. 1 lymph node region or structure
II. >1 lymph node region or structure, same side of diaphragm
III. Both sides of diaphragm
IV. Extranodal sites diffuse, beyond "E" designation. Like: spleen, BM, liver.

Staging System for Lymphomas (ANN ARBOR CLASSIFICATION)



Revised European-American Lymphoma (REAL) Classification: B-Cell Neoplasms

based on clinical behavior (how fast they grow and how aggressive they are).

Indolent (slow-growing) (chronic, often long survival even without treatment)	Aggressive	Very Aggressive
•CLL/SLL (Small Lymphocytic Lymphoma, Chronic Lymphocytic Leukemia)	•PLL (Prolymphocytic Leukemia)	•Precursor B-lymphoblastic lymphoma/Leukemia
•Lymphoplasmacytic/ IMC/WM	•Plasmacytoma/ Multiple myeloma	•Burkitt's lymphoma/ B-cell acute leukemia
•HCL (Hairy Cell Leukemia)	•MCL (Mantle Cell	•Plasma cell leukemia
•Splenic marginal zone lymphoma	•Follicle center lymphoma, follicular, grade III	
•Marginal zone lymphoma – Extranodal (MALT) – Nodal	•DLCL (Diffuse Large B-Cell Lymphoma)	
	•Primary mediastinal large B-cell lymphoma	
•Follicle center lymphoma, follicular, grade I-II	•High-grade B-cell lymphoma/Burkitt's-like	

Prognostic factors in non-Hodgkin's lymphoma

- **Adverse factors:**
- Age > 60 years
- Stage III or IV, i.e. advanced disease
- High serum lactate dehydrogenase level
- poor Performance status (ECOG 2 or more)
- More than one extranodal site involved ex: spleen&BM or BM&CSF involvement.

Treatment Options in Advanced Indolent Lymphomas

- Observation only.
- Radiotherapy to site of problem.
- Systemic chemotherapy
- Oral agents: chlorambucil and prednisone
- IV agents: CHOP, COP-R, FC-R
- Antibody against CD20: rituximab
- Stem cell or bone marrow transplant.
- New monoclonal antibodies

Reasons to Treat in Advanced Indolent (slow growing) Lymphomas

- Constitutional symptoms (B-symptoms)
- Anatomic obstruction (Organ compression)
- Organ dysfunction/faliar
- Cosmetic considerations
- Painful lymph nodes
- Cytopenias

Treatment Options: Aggressive Lymphomas

Aggressive

- Diffuse large B-cell lymphoma, large cell anaplastic lymphoma, peripheral T cell lymphoma.

Very Aggressive

- Burkitt's lymphoma and lymphoblastic lymphoma.

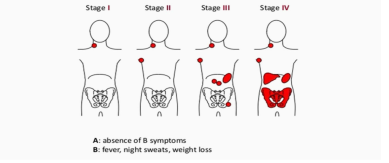
Treatment Options for Aggressive Lymphomas

*potentially curable
*disseminates through bloodstream early
***must use systemic chemotherapy**
CHOP-R x ?8 cycles
CHOP-R x 3 cycles followed by radiotherapy
*Bone marrow transplantation for some cases
* New monoclonal antibodies

Standard Treatment for Aggressive Lymphomas

- Systemic chemotherapy
- CHOP-R
- +/- Intrathecal chemotherapy
- AIDS patients and CNS involvement
- +/- Radiotherapy
- Spinal cord compression, bulky disease

??BMT



Burkitt's Lymphoma

- Treated with multidrug regimen chemotherapy similar to pediatric leukemia/ lymphoma regimens.
- BMT

Hodgkin's Disease/Lymphoma Treatment

With appropriate treatment about 85% of patients with Hodgkin's disease are curable

- I A,B — chemo.Radiation Therapy in selected cases
- II A — Chemo.XRT in selected cases
- IIB; IIIA,B; IVA,B — Chemo (+/- radiotherapy in selected cases)

Chemotherapy Regimens for Hodgkins disease

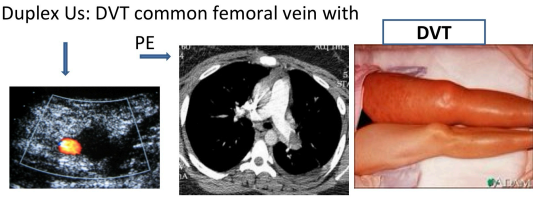
- MOPP
  - Mechlorethamine, Oncovin, Procarbazine, Prednisone
- ABVD
  - Adriamycin, Bleomycin, Vinblastine, Dacarbazine
- BEACOPP
- BMT for relapse or resistance

Chronic Myeloproliferative Disorders (VTE)

Case 7:

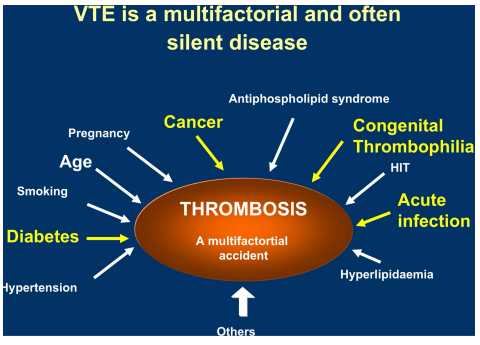
49 yr old lady complains of painful swelling and hotness of her L leg following coming back from visiting her relatives in USA. She had repeated attacks of cough with hemoptysis and shortness of breath. P/E

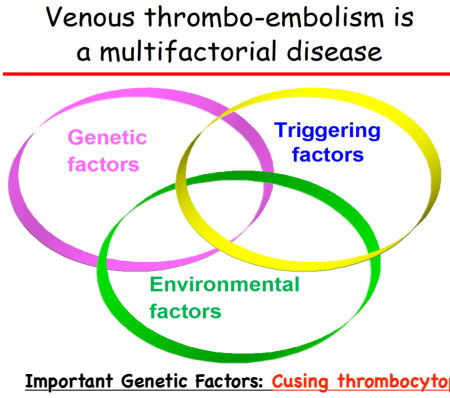
Duplex Us: DVT common femoral vein with



#Venous Thromboembolisim (VTE)
- lower limbs common site to have venous clot .
The blood clot that formed in lower limbs can traveled back to heart--> PE
- Doppler ultrasound : detect blood flow in vessele --> showing undetected Blood flow.
proximal venous thrombosis have MORE complications than DVT .
- compression ultrasound another way to detect DVT : showing the vein not compressable .
-CT scan with contrast to asses the pulmonary.A, if there a clot in pulmonary.A will show opacity in contrast .

Importance of VTE (DVT/PE)
A- PREVENTABLE
B- LIFE THREATENING
C- LONG TERM COMPLICATIONS
D- COMMON
E- COSTLY

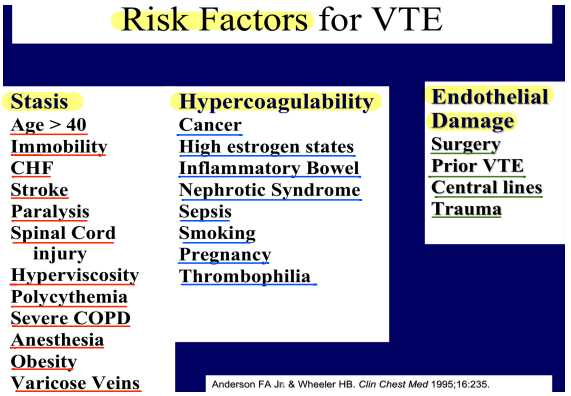




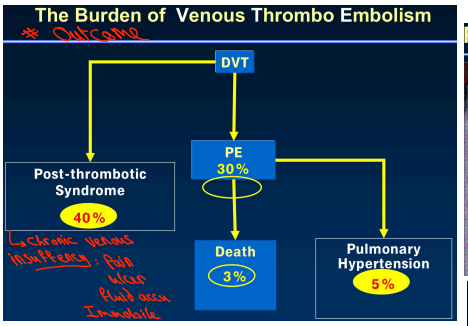
Important Genetic Factors: Cusing thrombocytopenia
1- Protein C defeiciency
2- Protein S deficiency
3- ATIII (anti-thrombin3) deficiency
4- Factor V Leiden mutation (most common inhereted thrombophilea)
5- Prothrombin (factor II) mutation

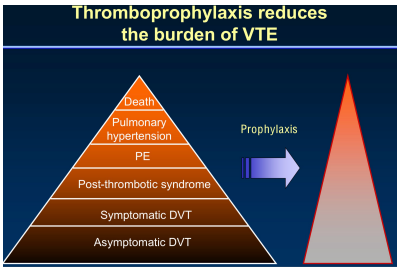
Unprovoked VTE & they leads to occure

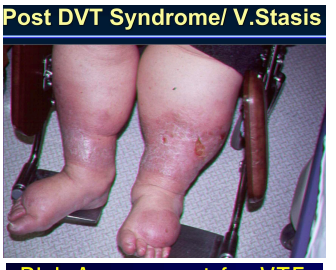
 # Combined risk factors (inherited + acquired) are key to high risk for VTE

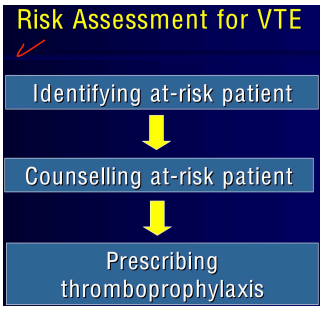


Most hospitalized patients have at least one risk factor for VTE









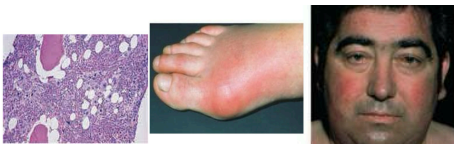
PULMONARY EMBOLISM and DVT TREATMENT (prevention)
INITIAL
Thrombolytic treatment
Heparin (UFH or LMWH)
Oral anticoagulant therapy (OAT) and new antithrombotics
LONG -TERM
OAT and new antithrombotics
LMWH
HOME
OAT and new antithrombotics
LMWH

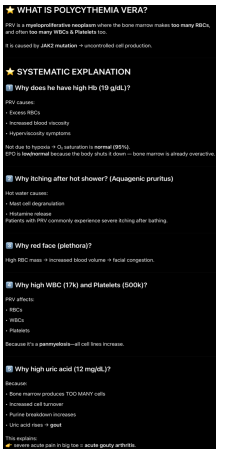
What if DVT happens?
Anti-coagulation (oral-warfarin) , (Injectable-LMWH)

Case 8

50 yr old man complains for several weeks of hotness in his face, itching and severe acute pain in his big toe.
Hb 19, WBC 17k, Platelets 500K, Serum Uric acid 12mg/dl, Po2 Saturation 95%, serum erythropoeitin 10 mU/ml. Jakll Mutation +.
Diagnosis: polycythemia rubra vera with acute gouty arthritis.

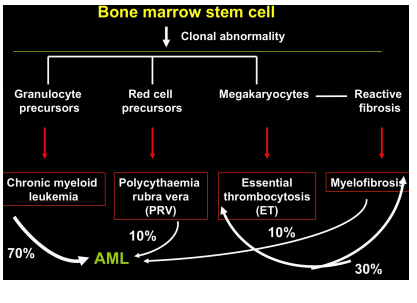
very high
low

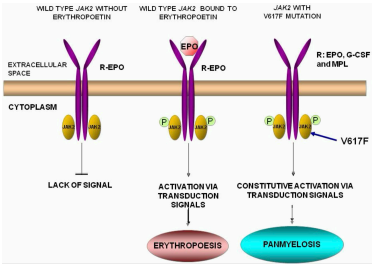




Myeloid Malignancies
1- CML
2- AML
3- CMPN (Chronic Myeloproliferative Neoplasms)/Disorders :
PRV - Polycythemia Rubra Vera
ET- Essential Thrombocythemia
MF- Myelofibrosis

Myeloproliferative Neoplasms (MPN)
Common features
- Specific clinco-pathologic criteria for diagnosis and distinct diseases, have common features • Each MPN (PRV, ET, MF) has distinct diagnostic features (e. g , high RBC for PRV, high platelets for ET). • Despite differences, they share core features due to clonal myeloid proliferation.
- Increased number of one or more myeloid cells • RBCs → polycythemia • Platelets → thrombocythemia • WBCs → leukocytosis
- splenomegaly due to: • Extramedullary hematopoiesis (marrow function overwhelmed) • Sequestration (trap) of excess blood cells
- Hypercatabolism: wt loss, gout • Hypercatabolism – increased metabolic activity due to excessive cell turnover.
- Clonal marrow hyperplasia without dysplasia
- Predisposition to evolve • MPNs can transform over time into: Acute leukemia (AML); Fibrotic marrow (MF from PRV or ET).
- Generalized pruritus (after bathing) • Seen especially in PRV. • Mechanism: histamine release from increased basophils and mast cells; worsens after warm baths.
- Unusual thrombosis (e.g., Budd-Chiari syndrome) • MPNs increase risk of clotting due to: High RBC mass (hyperviscosity), Abnormal platelets, Endothelial activation • Budd-Chiari – hepatic vein thrombosis, classic in PRV.





Janus Kinase 2 JAK2-V617F)

- Gain-of-function mutation is present in
- ~95% of cases of PV
- 23-57% of cases of ET
- 43-57% of cases of MF

Risk classification of PV and ET

High risk*	Low risk
• Age > 60 years	• Age ≤ 60 years
• Previous thrombosis	• No previous thrombosis

* For practical purposes, platelets > 1,500 x 10^9/L also considered high risk

Polycythemia Vera Diagnostic Criteria

Table 4. WHO diagnostic criteria for P-vera

Major Criteria

1. Elevated RBC mass > 25% above mean normal predicted value or, hemoglobin > 18.5 gm/dL (male) or 16.5 gm/dL (female)
2. Presence of JAK2 V617F

Minor Criteria

1. BM trilineage myeloproliferation
2. Low serum erythropoietin levels
3. Endogenous erythroid colony formation - RBC form without EPO

Diagnosis requires both major criteria or one major and two minor criteria

First-line therapy of PV

When:

- High-risk (age >60 years, thrombosis)
- Poor tolerance to or high need of phlebotomy
- Symptomatic or progressive splenomegaly
- Platelet >1.500 x 10^9/L
- Progressive leukocytosis
- Disease-related symptoms

How:

- Phlebotomy (Hct < 45%)
- Low-dose aspirin
- Hydroxyurea or IFN-α
  - Caveat on HU for young < 40 years
- Busulphan in elderly
- Manage generic cardiovascular risk factor

Essential Thrombocythemia: Diagnostic Criteria

- **Platelet count ≥ 450,000**
- **JAK2 V617F+ OR no evidence of reactive thrombocytosis**
- **Not meeting WHO criteria for other MPNs (e.g PV, CML)**
- **Megakaryocyte proliferation with large and mature morphology; no or little granulocyte or erythroid proliferation**

- ALL FOUR CRITERIA ARE "REQUIRED"

First-line therapy of ET

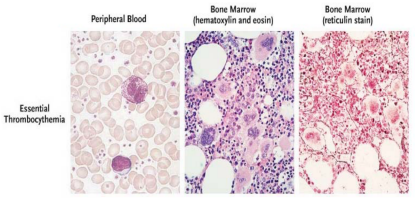
When:

- High-risk patients (age > 60 years, prior thrombosis)

How:

- Hydroxyurea at any age
- Manage generic cardiovascular risk factors
- Aspirin if microvascular disturbances

Essential Thrombocythemia



➢ **Bone marrow: Hypercellularity with marked megakaryocytic hyperplasia**

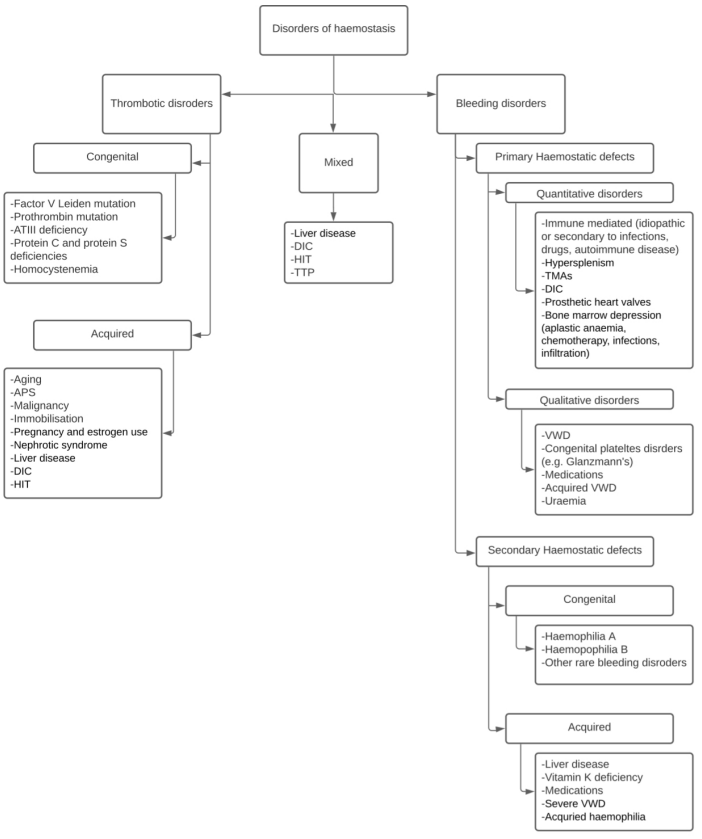
Ruxolitinib in the treatment of MPN

Selective JAK I & II inhibitor

Second line after hydroxyurea

Offers improvement of systemic symptoms, trx requirements.

No survival benefit as yet (limitation).



Blood Transfusion

RBC transfusion therapy Indications

- Improve oxygen carrying capacity of blood in patient :
- Acut Bleeding
- Chronic anemia that is symptomatic
- Peri-operative management ex: surgery, delivary.

Red blood cell transfusions Special preparation

If pateint is neunate or immuonocompromised : you should test blood for CMV to make sure give them CMV negative blood .

leukopoor (leukodepletion) : filter/remove resedual WBC from blood transfusion , the aim:
1) trying to prevent CMV infection .
2) prevent transfusion reaction: febril non-hemolytic rx .

WBCs are responsible for:
- CMV transmission
- Immune reactions
- Cytokine release → fever

Irradiate RBC : messure if you worried about patient from developing transfusion-graft VS host disease. Maimly the patient is immune compromised.

Blood is exposed to gamma radiation.
Why? To inactivate donor lymphocytes → stop them from dividing.
If donor lymphocytes survive, they can attack the host → Transfusion-Associated Graft-Versus-Host Disease (TA-GVHD).

Blood is washed with saline to remove plasma proteins, antibodies, complement.

Washed RBC : to prevent hemolysis & anaphylactic, used in patient with IgA deffeiecnt

Categories of Transfusion Reactions

Acute within 24h.

- **Immunologic**
  - ***Hemolytic***
  - ***Febrile***
  - ***Allergic***
  - Anaphylactic
  - ***TRALI***

Transfusion-Related Acute Lung Injury.

- **Non-immunologic**
  - ***Circulatory Overload***
  - Hemolytic
    - Physical
    - Bacterial contamination
  - Air embolus
  - Metabolic reaction

Categories of Transfusion Reactions Delayed (> 24 hours)

- Immunologic
- Alloimmunization --> RBC ,HLA
- Hemolytic
- GVHD
- Post-transfusion Purpura
- Immunomodulation
- Non-immunologic
- Iron overload
- **Viral infections**
- HCV
- HBV
- HIV
- HTLV
- Other organisms
- Malaria, Chagas, Babesiosis... .

Protocol for ALL acute transfusion reactions

- STOP THE TRANSFUSION immediately
- Maintain IV access with 0.9% NaCl
- Check blood component for patient ID
- Notify Blood Bank(BB)
- Send blood sample and urine to BB
- Keep blood unit in case culture becomes necessary
- Support patient as necessary by mantain BP & Air ways.

Transfusion-transmitted disease

Infectious agent	Risk
HIV	~1/4 million
Hepatitis C	1/ 1.4 million
Hepatitis B	1/ 3 million
Hepatitis A	<1/1,000,000
HTLV I/II	1/640,000
CMV	50% donors are sero-positive
Bacteria	1/250 in platelet transfusions
Creutzfeld-Jakob disease	Unknown

Platelet transfusions

- Platelet concentrate (Random donor)
- Platelets Pheresis (Single donor)

Platelet transfusions - complications

- Higher incidence than in RBC transfusions
- Related to length of storage/leukocytes/RBC mismatch
  - They are stored at room temperature → bacteria grow more easily
  - Platelets come with more leukocytes / cytokines
  - Platelets have shorter shelf life
- Bacterial contamination
- **Platelet transfusion refractoriness**
- Alloimmune destruction of platelets (HLA antigens) → Patient forms anti-HLA → transfused platelets destroyed → platelet count does not increase.
- **Non-immune refractoriness :**
- Microangiopathic hemolytic anemia (platelets used up in microthrombi)
- Coagulopathy Platelets are consumed in clotting/bleeding
- Splenic sequestration Hypersplenism → spleen traps platelets
- Fever and infection Acute infection lowers platelet survival
- Medications (Amphotericin, vancomycin, ATG, Interferons) → Drugs can directly destroy platelets.
  Anti-thymocyte globulin (ATG)

#when we give platelts ?
When we want platelets to be above certain value . (Give when plt.count <10,000)

Fresh frozen plasma

- its rich in clotting factor & fibrinogen so mainly given for coagulopathy patient.
- Indications
- Multiple coagulation deficiencies (liver disease, trauma)
- DIC
- Warfarin reversal effect
- Coagulation deficiency (factor XI or VII)

- **Note**
- Viral screened product
- ABO compatible (because FFP contains antibodies)

ABO blood types

Blood type	Antigens on RBCs	Serum antibodies
A	A	Anti-B
B	B	Anti-A
AB	A and B	Neither
O	Neither	Anti-A and anti-B

- The antibodies are induced by exposure to cross-reacting microbial antigens present on common intestine bacteria.
- ABO blood-group antigens have subtle differences in the terminal residues of the sugars on glyco-proteins in RBC.
- Providing the basis for blood typing test in blood transfusion

Aims of Transfusion Centre

- Provision of Blood of the best possible quality and safety for the patient receiving it
- To care for the donor - ensure act of donation does not harm donor

Blood Supply Chain

- Blood Donor Screening Criteria
  Goal: protect donor and recipient
  Screen for: Age,weight, General health, Infections, High-risk behaviors, Travel history, Medications
  → Ensures the donor is safe to give blood and the blood is safe for the patient.
- Donation Process- in monitor estting
- Donation Testing
  Every donated unit is tested for major infections: HIV-1/2, HBV, HCV, Syphilis, HTLV, West Nile Virus,Sometimes malaria, depending on region
  Also tested for: Blood group (ABO,Rh), Antibodies, Hemolysis, quality
  Unsafe units are discarded
- Component preparation- via centrifusion/separation of cells
- Plasma Products
  Plasma can be used as:
  - Fresh Frozen Plasma (FFP) → contains clotting factors
  - Cryoprecipitate → fibrinogen, FVIII, vWF
  - Fractionated products
  - Albumin
  - IV immunoglobulin (IVIG)
  - Coagulation factors (factor VIII, IX)

Blood Donor Criteria

- Age 17-65 (new donors accepted until 60)
- Weight > 50kg
- General health
  - Normal BP, pulse, temperature
  - Hb usually ≥ 12.5 g/dL
- Specific illnesses
- Contact with infection

Blood Donation

- **Volume collected : 475mls Blood + 63mls anticoagulant**

This prevents clotting and preserves RBCs.

After separation:

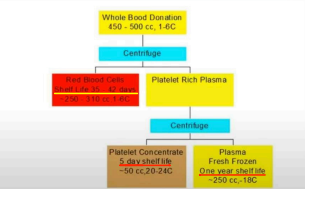
Red Cells
Plasma
Buffy Coat → used to prepare platelets

- **RBC Storage Additive Solution: Red Cells + Optimal Additive Solution:**

1. Saline → maintains osmotic balance
2. Adenine → helps RBCs produce ATP, extending life
3. Glucose → energy source
4. Mannitol → protects RBC membrane from damage

- **Expiry date 35 days**

Blood Collection and Manufacturing



Leucodepletion Removal of >99% of white blood cells from blood products using filters.

- introduced to reduce the risk of variant-CJD transmission by blood
- other benefits - less febrile reactions, less alloimmunisation, less GVHD, reduce immunosuppressive effects
- Less CMV

Blood Donation Testing Every donated unit is tested to keep blood safe:

- Microbiology markers
- Blood grouping and screening for high titre antibodies
- Quality monitoring

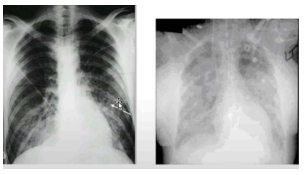
Transfusion Related Acute Lung Injury - TRALI

- Occurr when patient develope SOB or respiratory symptoms within 1-4h after recieving blood product transfusion.

- Not rare but under diagnosed
- A potentialy fatal condition
- Presents as pulmonary oedema
- Occurs within 1-4 hrs of starting transfusion

Clinical Features

- Acute respiratory distress
- Fever with chills
- Non productive cough
- Cyanosis
- Hypotension
- Chest pain
- Bilateral pulmonary oedema
- Chest X ray - **bilateral pulmonary infiltrates in hilar region**



Classical Theory (Immune TRALI)

- Donor antibodies react with patient neutrophils in pulmonary vessels of recepient.
- Neutrophils sequestrate in pulmonary vasculature Neutrophils get trapped in lung vessels Then release:
- Complement and cytokines liberated
- Damage to endothelium
- Results in pulmonary oedema

Two Hit Theory (Non-immune TRALI)

"High-risk recipient + trigger from transfusion"

1st hit: Patient already has inflammation

Conditions:

- Sepsis
- Trauma
- Major surgery
- Hematologic malignancies

→ Neutrophils already primed in the lungs

2nd hit: Transfusion product

Contains:

- Lipids
- Biologic response modifiers
- WBC-derived antibodies

These activate the primed neutrophils → endothelial injury → TRALI

The doners usually exposed to foreign blood / lady with multible pregnancy. (multi-Para)
Blood banks try to exceclude those patients.

Management - TRALI

- No specific treatment
- Largely supportive
- Respiratory support with 02
- Most cases require mechanical ventilation
- Steroids
- Clinical staff who administer transfusions must be aware how to diagnose & manage promptly

Implicated Donors and Prevention

- Implicated donors are usually "multipara" female due to exposure to paternal leucocyte antigens from the fetus during pregnancy.
- The percentage of women with antibodies increases with increasing number of pregnancies.

⭐ Prevention

- Avoid plasma from multiparous female donors
- Use male plasma if possible
- Screen donors for HLA antibodies
- Use leucodepleted products

فرح الكاسبي ♥