Hematology Summary

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L63- Introduction To Cancer Diagnosis & Treatment

Cancer Definition:

- **A term used for diseases in which abnormal cells divide and escape the body control, these cells are able to:**
  - Invade surrounding tissues (benign tumors like lipoma and fibroma cannot invade. Locally malignant tumors like Osteoclastoma can invade locally but cannot send distant metastasis. The ture malignant tumors can both invade locally and send metastasis.).
  - Send distant metastases
  - Lose their functions.
- **Primary tumors:**
  - Represent de novo tumors in their initial site e.g. Breast cancer inside the breast tissue.
- **Metastatic tumors:**
  - Originate from the distant growth of the primary tumors to lymph nodes or other organs like liver, lung, bone, brain, etc..

Causes of Cancer

- **DNA Mutations:**
  - Cancer arises from the mutation of a normal gene.
  - Mutated genes that cause cancer are called oncogenes.
  - Radiation and other environmental factors (Tobacco, Alcohol, Radon, Asbestos, etc).
  - Random somatic mutations.
  - Inherited germline mutations.
- **Genetic Predisposition**
  - Retinoblastoma, p53 (tumor suppressor gene), APC, CDKN2A, BRCA1, BRCA2
- **Infectious agents**
  - **Viral:** HPV – cervical cancer, Hepatitis – liver cancer, EBV - Lymphoma
  - **Bacterial**: H. pylori – stomach cancer

Hallmarks of Cancer:

- Self-sufficiency in growth signals, Insensitivity to growth inhibitory signals, Absence of apoptosis, Limitless proliferative capacity, Sustained angiogenesis, Tissue invasion and metastasis.

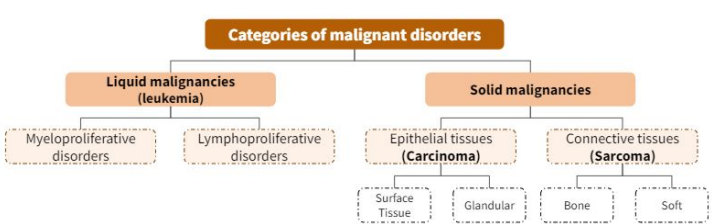
Q1: When to suspect cancer?

- Cancer Signs and Symptoms:
  - Cancer gives most people no symptoms or signs that exclusively indicate the disease.
  - Unfortunately, every complaint or symptom of cancer can be explained by a harmless condition as well.
  - **Do not forget the constitutional symptoms:**
    - Fatigue, fever, sweating, weight loss.
  - **What are the clues?**
    - Persistent, Progressive, Disabling and prevents it's patients from doing daily activity.
    - Symptoms & Signs changes according to the site of origin.
  - **Think about the pathology and site:**
    - The Mass is able to <u>invade locally</u> and <u>spread distantly</u> → To bone, brain, lung, liver .

Q2: How to diagnose cancer?

1	• **IT IS NOT A CLINICAL DIAGNOSIS**
2	• **IT IS NOT A RADIOLOGICAL DIAGNOSIS**
3	• **IT IS NOT SEROLOGICAL DIAGNOSIS**
4	• **IT IS A PATHOLOGICAL DIAGNOSIS**
5	• **IT IS A TISSUE DIAGNOSIS**

Categories of malignant disorders



L63- Introduction To Cancer Diagnosis & Treatment

Q3: What the essential work up for staging?

- **TNM** (T= tumor, N= Node, M= Metastases)
  - Clinical TNM
  - Radiological TNM
  - Pathological TNM
- **Radiology:**
  - XRay, MRI, CT, US, PET scan.
- **Surgical staging.**

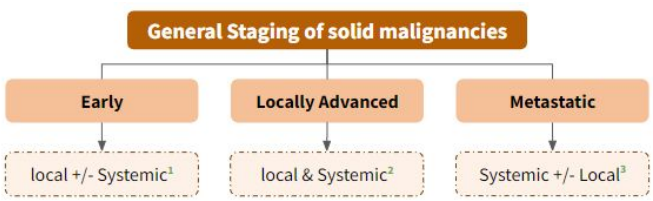
Q4: How to treat cancer?

- **Types of oncology problems:**
  - Patient with Suspected Cancer diagnosis
  - Patient with Established Cancer diagnosis (Answer the following questions):
    - Does the patient have cancer?
    - What type of cancer?
    - What stage of cancer?
- **Management Multidisciplinary:**
  - Surgery, Radiation, Medical.
  - Others Disciplines: Radiology, Pathology, Lab, Combined clinics, Tumor board.
- **Determine the treatment Objective:**
  - Either Curative or Palliative

Curative	Palliative
Therapy: • Aggressive, Expensive, recent, updated, complex. **Toxicity:** • Long term, irreversible	**Therapy:** • Simplest , Avoid hospitalization, Availability Least toxic **Toxicity:** • Short term, acute, quality of life

Different Treatment Modalities	
Local therapy: • Surgery & Radiation therapy	**Systemic therapy:** • Chemotherapy • Hormones • Biologicals • Immune therapy

- **Mechanism of Action of Immunomodulators**
  - Blocking the PD-1 or PDL-1 pathway would restore/promote the function of chronically exhausted tumor-specific T cells and decrease tumor-induced immune suppression
- **Liquid malignancies:**
  - Treated systemically
- **Solid malignancies:**
  - Treated according to stage



Q5: What is the prognosis of your patient?

- **What can medicine offer the cancer patient?**
  - The cancer type & extent (stage)
  - The host factors (age, sex, comorbidities)
  - The available tools

1 Tumors that can be cured	2 Tumors that can have prolonged survival	3 Tumors that can be palliated
• lymphomas, leukemia, early solid tumors.	• Locally advanced and some of the metastatic tumors.	• Metastatic solid tumors.

L64- Lymphomas

Lymphoma is a **cancer of the lymphatic system.** **It is of two main subtypes:**

	Hodgkin lymphoma	Non-Hodgkin lymphoma
Age	**aged 20-30 years** and **those 55 years of age**	**aged 60 years** and older. However, some types are more likely to develop in children and young adults.
Sex	**More common in males**.	**More likely in women** in most types.
Chemicals & Radiation	-	**Nuclear radiation and certain agricultural chemicals have links to non-Hodgkin lymphoma.**
Immunodeficiency	**HIV infection** can weaken the immune system and increase the risk	A person with a less active immune system has a higher risk.
Infectious factor	**Infectious mononucleosis:** The **Epstein-Barr virus (EBV)** can cause mononucleosis. This disease increases the risk of lymphoma.	Certain viral and bacterial infections that transform lymphocytes, such as the **EBV,** increase the risk. This virus causes **glandular fever**.

Grouping/ subtypes	• Nodular lymphocyte-predominant HL
	• Classical HL:
	  ○ **Nodular sclerosis HL (most common)**
	  ○ Lymphocyte-rich classical HL **(best prognosis)**
	  ○ Mixed cellularity HL
	  ○ Lymphocyte depletion HL **(worst prognosis)**
		• Indolent
		• Aggressive
		• Highly aggressive

Signs and symptoms

The definition, presentation, diagnostic tests, "B" symptoms, and staging of Hodgkin disease (HD) are the same as NHL. HD has Reed-Sternberg cells on pathology.

- **Painless swelling of lymph nodes (most common)**
- **B symptoms**: Persistent Fever without infection, Night sweats, Unexplained Weight loss and reduced appetite.
- Persistent fatigue
- Itchy skin
- shortness of breath

Diagnosis

- **Biopsy:**
  - **FNA: Tells you there is a malignancy but doesn't tell you what type.**
  - **Tru-Cut Biposy: This is the one used for the diagnosis of lymphoma because it gives you more details.**
    - **If biopsy is +ve, perform bone marrow aspiration/biopsy next (to make sure it hasn't reached the bone marrow).**
- **PET Scan: Before and after treatment, PET scan can differentiate between fibrosis/necrosis from treatment, and active cancer**

Staging

I	• Involvement of a **single lymph-node region or lymphoid structure.**
II	• Involvement of **two or more lymph node regions on the same side of the diaphragm**.
III	• Involvement of **lymph node regions on both sides of the diaphragm**.
IV	• **Extensive extranodal disease** (more extensive than "E").

L64- Lymphomas *(cont.)*

Staging (Cont.): Designations applicable to any disease stage	
A	• Asymptomatic
B One is enough	• **Fever:** > 38°, recurrent (Spiking up and down, not stable.) • **Night sweats:** Drenching (Excessive sweating), recurrent. • **Weight loss:** unexplained loss of >10% of body weight within the previous 6 months
X	**Bulky disease:** (If you see the letter X in the description of lymphoma → Bulky) • **Mediastinal:** ≥ 10 cm or > 1/3 internal transverse diameter at T5/6 on PA CXR. • **Non-mediastinal:** ≥ 5cm
E	• **Limited** extranodal extension from **adjacent** nodal site

Hodgkin's lymphoma (HL)		

Subtypes	• Nodular lymphocyte-predominant HL
	• Classical HL:
	  ○ **Nodular sclerosis HL (most common)**
	  ○ Lymphocyte-rich classical HL **(best prognosis)**
	  ○ Mixed cellularity HL
	  ○ Lymphocyte depletion HL **(worst prognosis)**	

Treatment	**Very favourable prognosis**	**Favourable prognosis in Stages 1A & 2A**
	• **Stage 1A NLPH, high neck NS & LRCHL.**	• **1-3 sites** • **Age ≤ 40** • **ESR < 50** • **Nodular sclerosis, Lymphocyte-rich classical HL**
	(Local radiation only)	**(Chemotherapy 3-4 cycles followed by radiation)**
	Unfavourable prognosis in Stages 1A & 2A	**Advanced stage**
	• **>3 sites** • **Age >40** • **ESR >50** • **Mixed cellularity**	• **Stages 3 & 4** • **B symptoms** • **Bulky disease**
	(Chemotherapy 4-6 cycles followed by radiation)	**6 cycles if stage A, 8 cycles if stage B. followed by radiation**

Feel free to vent here, no one will read it..

L64- Lymphomas *(cont.)*

Non-Hodgkin's lymphoma (NHL)

Clinical grouping

Indolent	• **Follicular lymphoma Grade 1,2. (Most common indolent).**
	• **Marginal zone lymphoma**
	  ○ Nodal
	  ○ **Extranodal (MALT): may regress with treatment of H.pylori**
	• Small lymphocytic lymphoma
	• Lymphoplasmacytic
	  ○ asociación with Waldenstrom's macroglobulinemia

Aggressive	• **Diffuse large B-cell lymphoma (Most common)** • Primary mediastinal large B cell lymphoma • Anaplastic large T / null cell lymphoma • Peripheral T cell lymphoma • Extranodal NK / T cell lymphoma, nasal type • **Follicular lymphoma Grade 3** • **Mantle cell lymphoma**
Highly Aggressive	Lymphoblastic lymphoma **Burkitt's lymphoma** Burkitt's like lymphoma

Treatment

Indolent lymphoma
e.g. Follicular Grad ½, small lymphocytic, marginal zone

Limited disease (Stage 1A, 2A if 3 or less adjacent node regions)	Advanced stage (some Stage 2, Stage 3, 4)
IFRT 30-35 GY **(Local radiotherapy only)**	• Palliative radiation therapy for localized symptomatic disease • Palliative chemotherapy for disseminated symptomatic disease • Observation only if low bulk, asymptomatic ○ Treat when symptomatic

Aggressive lymphoma
(e.g. Diffuse large B cell)

Stage I, some Stage II	Stage III, IV, B symptoms or bulky disease
(Chemotherapy 3 cycles followed by radiation)	**(Chemotherapy: 6 cycles if stage A, 8 cycles if stage B. followed by radiation, only if bulky disease or there is residual cancer)**

MALT lymphoma

Stage IE (H. pylori +ve)	Stage IE (H. pylori -ve or antibiotic failure)	Stage 2 or higher
• **PPI, 2 antibiotics (e.g. clarithromycin, amoxicillin) (H.pylori eradication)** • Follow up gastroscopy with Biopsy every 6 month for 2 yrs, then every 1 year	• IFRT 30 Gy (95% local control) **(Local radiotherapy only)**	• Treat as indolent lymphoma + H. pylori eradication

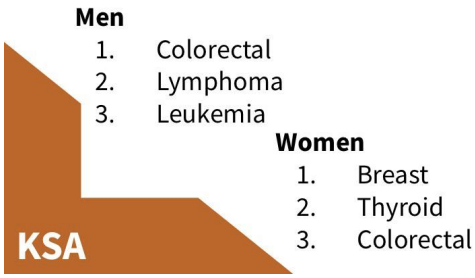
- **Stomach:** associated with **Helicobacter pylori infection** **Salivary Gland:** associated with **Sjogren's syndrome**
- **Thyroid:** associated with **Hashimoto's thyroiditis** **Orbital** (lacrimal, conjunctiva)

L65-Common solid tumors

◄ Classification of solid tumors

	Carcinoma	Sarcome	Germ cell tumor	Blastoma
Origin	**Epithelial cells**	**Connective tissue**	**Pluripotent cells**	Immature precursor **Embryonic tissue**
i.e.	Breast, prostate, lung, pancreas and colon	• Bone: osteosarcoma • cartilage: chondrosarcoma • fat: Liposarcoma • nerve	Testicular (seminoma), ovary (dysgerminoma)	Hepatoblastoma
Notes	Most common cancers	each of which develop from cells originating in mesenchymal cells outside the bone marrow.		Most common in children

◄ Cancer Statistics in KSA



◄ General principles of solid tumor treatments

- Early: Local & -/+ systemic
- Locally advanced: Local & systemic
- Metastatic: Systemic & -/+ Local
- Simple equation: Late presentation & Advanced stage= POOR OUTCOME. Early presentation+ Early stage= GOOD OUTCOME

Breast Cancer

Risk factors

- ❖ History of breast cancer
- ❖ Family history of breast cancer, especially in first-degree relatives
- ❖ Benign breast diseases / atypical hyperplasia
- ❖ Early menarche and late menopause
- ❖ Late first pregnancy and no pregnancy (Pregnancy suppress estrogen, and increase progestrone)
- ❖ Exogenous estrogens(HRT but not OCP)
- ❖ Radiation (HD) Hodgkin's disease

- **Self awareness(Monthly self exams):** Advised for all female >30.
- **Mammogram:** Every women aged 50-70, every 3 years.

Clinical features

- ❖ Painless lump or thickening of the skin (can be painful especially if infected.
- ❖ Thickening or swelling that persist.
- ❖ Nipple pain or retraction.
- ❖ Breast skin irritation or dimpling.
- ❖ Nipple discharge.
- ❖ Thickening or swelling that persist.

Staging of Breast Cancer

Stage 1 (early disease)	Stage ll (early disease)	Stage lll (locally advanced)	Stage IV (advanced)
Confined to the breast (**Node-negative**) (Tumor <2cm)	Spread to **movable ipsilateral axillary nodes (node-positive)** (Tumor 2-5cm)	Spread to the superficial structure of the **chest wall involvement** of ipsilateral internal mammary lymph node, or skin fixation, and/or **fixed axillary nodes**	**Metastasis** present at distant sites such as bone, liver, lungs and brain including supraclavicular lymph node involvement

L65-Common solid tumors *(cont.)*

Diagnosis:

➔ **Reasons to suspect breast cancer:**

Most common cancer in females, Wide age range 20 to +70y, Can occur during pregnancy & lactation, Can occur in pre, peri & post menopausal females.

What To do If you Suspect Breast Cancer?

- Do not just reassure the patient, Do not give hormonal therapy, Do not give antibiotics
- Take Careful history & physical examination:

If -ve: screening mammogram or US in young pt ➔ Suspicious? FNA

If +ve: Diagnostic Imaging Mammogram &US ➔ (Palpable mass/Equivocal or suspicious ➔ FNA.

- Perform Bilateral mammogram + breast US +/- Fine needle aspiration:

❖ Fine needle aspiration (FNA): The best initial biopsy. can differentiate between benign and malignant

❖ Core needle biopsy: Where cancer is considered likely, should follow FNA, assess for factors predictive of prognosis and response to treatment. These features include:

◄ Receptor status: ER, PR, HER2/neu, grade of tumour, Ki-67 proliferation index, molecular profiling.

❖ Open biopsy: The “most accurate diagnostic test” and allows for immediate resection.

Therapy (refer to the lecture for book details on breast cancer therapy)

1- Local therapy :

➔ Surgery

➔ radiotherapy

2- Systemic Therapy

➔ systemic therapy: (endocrine treatment and chemotherapy)

Indicated in: node-positive breast cancer, large primaries, oestrogen receptor-negative cancers and HER2 cancers .

➔ targeted: Hormonal and Biological therapy

Colon cancer:

Colorectal tube is a prime location for the development and growth of **small polyps or tumors.**

Risk factors

- Older age: older than 50 (Screening (**colonoscopy**) beginning at age 50).
- Personal history: colon cancer or adenomatous polyps, History of some other type of Cancer.
- Inflammatory intestinal conditions Ulcerative colitis and Crohn's disease
- Inherited syndromes Familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer (also known as Lynch syndrome).
- Family history of colon cancer and colon polyps.

Other risk factors: Low-fiber, high-fat1 diet (most important) because it leads to **Chronic constipation,** A sedentary lifestyle, Diabetes, Obesity, Smoking, Alcohol, Radiation therapy for cancer.

Symptoms

- Change in bowel habit
- A feeling of bowel not emptying completely
- Unexplained Weakness or fatigue
- Unexplained weight loss, Unexplained iron deficiency anemia
- Persistent abdominal discomfort
- Rectal bleeding:

Left colon:fresh blood, present early.

Right colon: Occult blood, present with anemia.

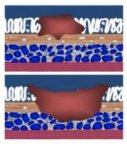
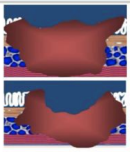
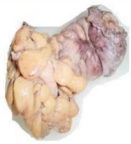
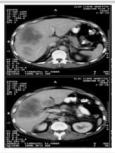
- **Post-menopausal females presenting with iron deficiency anemia should undergo a colonoscopy to rule-out colon cancer.**

L65-Common solid tumors *(cont.)*

Screening & early detection

- Population-based screening of people **over the age of 50 years** by regular faecal occult blood (FOB) testing
- **Colonoscopy: is the 'gold standard' for examination of the colon and rectum**
- other screening modalities: Flexible sigmoidoscopy: alternative option, CT colonography (imaging)

Staging

I	II	III	IV
Confined to wall	Beyond the wall	Nodal involvement	Metastasis
			
5 years Overall survival			
90%	60-80%	30-60%	<5%

Management

Depending on the location, options are:

- Surgery (mainly)
- Chemotherapy
- Radiation (if in the rectum)

Protective measures & prevention of colon cancer

- ❖ Decrease the risk: Vegetable, garlic,and fruits, Exercise, Milk, calcium consumption, Dietary fibre, Aspirin and other NSAIDs.
- ❖ Prevention: low-fat, high-fibre diet along with endoscopic screening.

Can we prevent Breast or Colon cancer?

Passive prevention :

- Discover Etiological factors Avoid theses factors eg. Smoking, Asbestos
- Avoid Breast cancer risk factors
- General health maintenance

Active prevention :

- Eliminate or prevent pre-invasive disease before invasion develops. (Chemoprevention,Surgery)
- Discover Pre malignant lesions Get rid of them before developing invasive cancer. (Colonic polyps & DCIS)

Feel free to vent here, no one will read it..

L66- Anemia

Definition: Anemia is a decrease in Hb in the blood below the reference level for the age and sex of the individual.

Mild anemia

- Few or no symptoms.
- Fatigue, Low exercise tolerance, SOB, palpitations, lightheadedness on arising, Sore tongue (glossitis), cracking mouth corners (angular cheilitis), peripheral paraesthesias (numb. toes..).
- **Clinical features:**
  - **Pica (pagophagia):** Desire to eat mud or ice. (in severe deficiency)
  - **koilonychia (with iron deficiency anemia)**
  - **Pallor**
  - **Neurological symptoms (severe B12/folate deficiency).**
  - **smooth tongue.**
  - **Orthostatic lightheadedness.**

Approach to Anemia

look at 3 CBC parameters and one additional test

1. The hemoglobin (Hb)
2. MCV (micro or normo or macro)
3. Reticulocyte count.

And the additional required test is the peripheral blood smear. Extremely important.

With the use of these 3 parameters your approach will be divided into 4 categories:

1. Low MCV (MCV <80 fL), **microcytic anemia.**
2. Normal MCV (MCV 80-100 fL)1 with low retic count, **normocytic anemia with inappropriately low bone marrow response.**
3. Normal MCV (MCV 80-100 fL) with high retic count, **normocytic anemia with appropriate marrow response.**
4. High MCV (MCV >100 fL), **macrocytic anemia.**

DDx of Anemia

MCV <80fL (TAILS)	MCV N, low retic count	MCV N, high retic count	MCV >100 fL[2]
1. Thalassemia[1] 2. Anemia of inflammation chronic disease[1] 3. Iron deficiency 4. Lead poisoning: Extremely rare 5. Sideroblastic anemia: Congenital, in paediatric	1. **BM failure:** a. Aplastic anemia: 2. **BM suppression:** a. Toxins, sepsis b. Organ failure: renal failure, liver failure, adrenal insufficiency c. Chronic inflammation d. Chronic diseases 3. **BM infiltration:** a. Lymphoma, leukemia b. Metastatic solid tumors c. Granulomatous disease (e.g.TB)	1. Bleeding 2. Hemolysis 3. Treated nutritional deficiency[3]	1. **Megaloblastic:** (impaired nucleic acid metabolism): a. B12 deficiency b. Folate deficiency c. Drugs: such as methotrexate and HU 2. **Non megaloblastic:** a. Liver disease b. Alcoholism c. Myelodysplasia (MDS) d. Thyroid disease (hypothyroidism)

Normal ranges in CBC

Test	Normal Range	Interpretation
Hemoglobin	Male: 13.5 (14)-17.5 g/dL Female: 11.5 (12.3)-15.3 (15.5) g/dL	**Low:** Anemia **High:** Polycythemia Hb 10 → mild Hb 7-10 → moderate Hb less than 7 → severe
Hematocrit (PCV) The volume of packed RBC in 100 ml blood	Male: 40-50% Female: 36-48%	
RBCs[1]	Male: 4.5-5.9 x10^6/mm3 Female: 4.1-5.1 x10^6/mm3	Measures the absolute RBC count: 1-**Low** 2-**Normal** 3-**High**
MCV	**80-96 IL**	**Low:** Microcytic **Normal:** Normocytic **High:** Macrocytic
MCH	34.4 ± 2.8 pg/RBC	**Low:** Hypochromic **Normal:** Normochromic
MCHC	34.4 ± 1.1 g/dL of RBC	**High:** Hereditary spherocytosis
RDW	**11.5 (11.7)-14.5%**	**High:** Increased: Many types of anemia (**Iron deficiency,** folate deficiency), liver disease
Reticulocytes	0.5-2.5% Males: 1.6 ± 0.5% Females: 1.4 ± 0.5%	
WBC	~4000-11000	**Low:** Leukopenia **High:** Leukocytosis *We are trying to avoid these terminology because they're not specific, you have to look for differential
ESR	2-12 mm/1sthour	

L66- Anemia *(cont.)*

Microcytic Anemia

Iron deficiency anemia.

Most common cause of anaemia in the world. Causes:

- Blood loss:
  - More common in female: heavy menses.
  - In males: always investigate for GI causes: Colon cancer, celiac disease(Most common in KSA).
- Increased demand: Growth, pregnancy.
- Decrease absorption
- Poor intake

Diagnosis

- Serum iron (Fe): Low.
- Ferritin level: The most accurate if it low (if high: exclude infection, because it's elevated in inflammation and infections.)
- Transferrin: the body produces transferrin in relationship to the need for iron, When iron stores are low, transferrin levels increase and vice versa.
- TIBC: Will be high

Treatment

- **Oral iron replacement** (ferrous sulphate or ferrous gluconate if patient has side effects)
- Parenteral iron replacement (In cases of malabsorption)
- Blood transfusion (If severe: Hb <7 g/dL)

Anemia of chronic disease

Etiology: Chronic infection, inflammation.

Pathophysiology

high levels of hepcidin expression play a key role. Cytokines released by inflammatory cells cause macrophages to accumulate iron and not transfer it to plasma or developing red cells. **Diagnosis:**

- Low serum iron but they are not deficient and don't need iron replacement, the defect is in the transportation.
- Low TIBC/serum transferrin.
- normal or raised serum ferritin.
- Peripheral blood smear usually reveals normocytic and normochromic anemia.'

Treatment: Correct underlying disease.

Normocytic Anemia: haemolytic anemias

Haemolytic anaemias are caused by increased destruction of red cells. any condition which leads to a reduction in the mean lifespan of the red cell is a haemolytic disorder.

How to differentiate between haemolytic anemia and anemia due to acute blood loss?

By clinical or laboratory findings, these 3 are haemolytic marker (high LDH and indirect bilirubin, low haptoglobin)

	Hemolysis	Bleeding
MCV	Normal or high	Normal or high
Retics	High	Normal or high
Bleeding	No	Yes, not always apparent
LDH	High	Normal
Haptoglobin	Low	Normal
Indirect bilirubin	High	Normal

L66- Anemia *(cont.)*

Normocytic Anemia: haemolytic anemias *(cont.)*

Diagnosis of haemolytic anemias

- Low Hb/Hct
- Elevated reticulocyte count
- Low haptoglobin (with intravascular hemolysis)
- Elevated LDH—released when RBCs are destroyed
- Elevated indirect (unconjugated) bilirubin

- **Autoimmune hemolytic anemia**

increased red cell destruction due to red cell autoantibodies. IgG or IgM labeled as "warm" or "cold" respectively. Cold hemolytic anemia often post-infectious, worsens with exposure of periphery to cold temperatures.

- **Diagnosis**
  - Coomb's test: Detects presence of either antibody on RBC.
- **Treatment:** Steroids/splenectomy– reduces immune function and RBC sequestration, respectively.

Lack of RBC enzyme makes cells very sensitive to oxidative stress the enzyme
G6PD oxidizing glucose-6-phosphate to 6-phosphoglycerate with the reduction of NADP to NADPH. The reaction is necessary in red cells where it is
the only source of NADPH, which is used via glutathione to protect the red cell from oxidative damage.

- **Sickle cell disease**

❖ one of the most common autosomal recessive gene defects.
❖ The specific Sickle cell mutation is substitution of hydrophobic valine for glutamic acid at position 6 of the beta-chain.

G6PD deficiency

Pathogenesis

In patients with sickle cell anemia, HbA is absent and completely replaced by HbS, whereas in heterozygous carriers, only about half is replaced.

Clinical features

- Anemia.
- Spleen: RBC destruction by the spleen، Splenic sequestration: Vaso-occlusion produces an acute painful enlargement of the spleen. Multiple infarctions: eventually leads to a fibrotic non- functioning spleen.
- Vascular features Arterial occlusion: leads to infarcts, pain crises, acute chest syndrome, stroke, MI, retinal and renal problems. Pulmonary hypertension
- Acute chest syndrome : pulmonary hypertension and chronic lung disease are the commonest causes of death in adults with sickle cell disease.
- Long-term problems: Growth and development

Diagnosis

Sickle solubility test: A mixture of HbS in a reducing solution such as sodium dithionite gives a turbid appearance because of precipitation of HbS, whereas normal Hb gives a clear solution.
Hb electrophoresis: always needed to confirm the diagnosis. There is no HbA, 80-95% HbSS and 2–20% HbF.
Management: Hydroxycarbamide (the first drug).

L66- Anemia *(cont.)*

Thalassemia

Characterized by hypochromic microcytic red cells

Beta Thalassemia

- **homozygous β-thalassaemia (major):** either no normal β chains are produced (β0) or β-chain production is very reduced (β+). There is an excess of α chains, which precipitate in erythroblasts and red cells causing ineffective erythropoiesis and haemolysis. The excess α chains combine with whatever β, δ and γ chains are produced, resulting in increased quantities of HbA2 and HbF

They are transfusion dependent, and they get iron overload and complication of it.

- **heterozygous β-thalassaemia:** Carrier of the trait "thalassemia minor" Or "thalassemia trait".

Beta Thalassemia major

Presentation: Prominent malar eminence and malalignment of the teeth, secondary to BM hyperplasia.
Extramedullary haemopoiesis (leads to hepatosplenomegaly and bone expansion → classical thalassaemic facies) chipmunk face. **Skull X-rays:** shows the characteristic 'hair on end' appearance.
Management : Long term folic acid supplements, regular transfusion: If transfusion requirements increase, splenectomy may help. The standard iron-chelating agent remains desferrioxamine
Ascorbic acid increases the urinary excretion of iron in response to desferrioxamine.

Beta Thalassemia intermedia

Symptomatic with moderate anaemia
Presentation: combination of homozygous mild β+- and α-thalassaemia leading to reduced α-chain precipitation(less hemolysis).

Alpha Thalassemia

- Often caused by gene deletions.

Four-gene deletion

- no α-chain synthesis and only Hb Barts (γ4) is present → Hb Barts cannot carry oxygen and is incompatible with life.
- Infants are either stillborn at 28–40 weeks or die very shortly after birth

Three-gene deletion (HbH disease)

- Has four β chains with low levels of HbA and Hb Barts.
- HbH does not transport oxygen and precipitates in erythroblasts and erythrocytes.
- Features: Moderate anaemia, Splenomegaly.

Two-gene deletion (α-thalassaemia trait)
One-gene deletion: blood picture is usually normal.

Iron Deficiency vs Thalassemia

	Iron deficiency anemia	Thalassemia
MCV	Low (80-70s)	Very low (70-60s)
RBC	Low	High or normal
RDW	High	normal
Ferritin/iron level	Low	High or normal

L66- Anemia *(cont.)*

Megaloblastic anemia

characterized by the presence in the bone marrow of erythroblasts with delayed nuclear maturation because of defective DNA synthesis(Megaloblasts).

B12 deficiency

Causes

1- Dietary: strict vegans.

2- Pernicious anemia:

- **Pathophysiology**: Autoimmune attack → atrophic gastritis & loss of parietal cells in the gastric mucosa → failure of IF production & achlorhydria → lack of B12 protection in stomach and gut → B12 malabsorption.
- **Investigations:** need to test if the IF is deficient: Antibodies against intrinsic factor, Anti- parietal cell antibodies, anti-IF antibodies

Clinical features: Neurological changes: only with very low levels of serum B1

Investigations

- Haematological: Features of megaloblastic anemia
- Bone marrow: megaloblastic erythropoiesis
- LDH: Raised
- Serum B12: usually low
- Schilling test

Treatment

- hydroxocobalamin.

Folate deficiency

- **Investigations:**
  - Serum folate: low (normal levels are 4–18 µg/L (5–63 nmol/L)).
  - Red cell folate level: The amount of folate in the red cells is a better measure of tissue folate.
- **Treatment:** daily oral folic acid
  - Correction of folate deficiency will correct hematologic abnormalities without correcting neurological abnormalities
  - Check B12 and correct first
  - Prophylactic folic acid in pregnancy prevents megaloblastosis in women at risk, and reduces the risk of fetal neural tube defects.

L67: Hypercoagulable state/ DVT

◄ Inherited hypercoagulable states:

- **Antithrombin:**
  - Antithrombin deficiency (e.g. in liver disease): Abnormality affecting the alpha 2 globulin (synthesized in liver) which helps neutralizing the activity of thrombin (IIa), Xa, XIa, XIIa and plasmin —> has a strong risk factor for VTE especially during pregnancy.
  - Antithrombin Functional Assays:
    - Antithrombin-heparin cofactor assay.
    - Progressive antithrombin assay.
- **Prothrombin:**
  - Prothrombin Gene mutation: resulting in elevated plasma levels of Factor II.
    - Genetic Test **(20210GA).**
  - Prothrombotic mutation (→ ↓ thrombin inactivation).
- **Protein C & S deficiency:**
  - Protein C and S inhibit activated cofactors Va and VIIIa, respectively.
  - Protein C is consumed and levels are low in vitamin K deficiency (both C & S are vit K dependent), DIC,liver disease, etc.
  - **Acquired Protein S deficiency may be induced by OCPs, pregnancy, or nephrotic syndrome.**
- **Factor V Leiden:**
  - Most common form of inherited thrombophilia, and Commonest cause of thrombophilia in West.
  - Activated Protein C Resistance.
  - FV Leiden → ↑ thrombin generation, (↓ anticoagulation) and ↓ inactivation of factor FVIIIa (also ↓ PAI inactivation → ↓ fibrinolysis).

◄ Acquired hypercoagulable states:

- **Antiphospholipid syndrome:**
  - Could be primary: sudden+extensive thrombosis OR secondary: e.g. SLE.
  - Clinical manifestation: Deep vein thrombosis, **early spontaneous abortions** (recurrent abortion), Livido reticularis.
  - Diagnostic criteria: presence of <u>at least one of the clinical criteria and at least one of the laboratory criteria</u>
    - Clinical criteria: Vascular thrombosis E.g. DVT, abortion, pregnancy complications.
    - Laboratory criteria: **Anticardiolipin antibodies** (IgG or IgM), **Lupus anticoagulant antibodies.**
- **Oral contraceptives and Hormone replacement therapy:**
  - Factor V Leiden + OCP – 50 x.
  - **increased factor VIIa levels** as well as **depressed antithrombin and protein S activity**.
- **Cancer:**
  - ↑ tissue factor.
  - ↑ procoagulant factor VIII and fibrinogen.
  - Compression/invasion of vessels.
  - **Hyperhomocysteinemia:**
    - Developmental delay, osteoporosis, ocular abnormalities, VTE, and severe premature CAD.
    - Increased arteriosclerosis.
  - **Pregnancy and postpartum:**
    - **Acquired prethrombotic state** in combination with **impaired venous outflow** because of venous compression.

L67: Hypercoagulable state/ DVT

◄ Hypercoagulable state/DVT:

- Clinical presentation:
  - Arterial: MI/Stroke.
  - Venous: DVT/PE.
- PE clinical presentation: Sudden SOB / sudden sharp chest pain (pleuritic) / hemoptysis / sweat+anxiety.
  - **PE with low BP (<90 mmHg) is called massive PE (IMPORTANT.)**

◄ DVT(deep vein thrombosis):

- Sign & Symptoms: leg (or arm) pain, tenderness, swelling, redness, and shiny skin.
  - Symptoms are neither sensitive nor specific for DVT.
- Risk factors: The presence of risk factors is a clue that VTE may develop or that it may already be present. (inherited + acquired).
- Investigation:
  - D-Dimer: Useful in low pre-test probability to exclude diagnosis of VTE.
  - Compression: direct approach, moderate to high pre-test probability.
  - Contrast venography (Golden standard): invasive
    - Non-invasive testing: Plethysmography, MRI, CT, V/Q scanning, Pulmonary angiography.

- Treatment:
  - Conventional Anticoagulation: **Heparin + warfarin is more effective than warfarin alone; all cases of VTE should be "bridged" with heparin.**
    - Heparin.
    - LMWH: Enoxaparin, Tinzaparin, Dalteparin.
      - Contraindicated in Dialysis dependent renal failure.
      - why is LMWH better than UFH?
        - Less risk of Heparin induced thrombocytopenia
        - No need for monitoring (UFH aPTT level is 1.5 times the mean of the control value which is 1.5- 2.5)
      - LMWH (SC) in stable cases of VTE but UFH (IV) needed in hemodynamically unstable patients or pts who need procedures.
    - Warfarin (Vit K antagonist):
      - **Inhibition of the vit K- dependent** Factor (II,VII,IX, &X) **1972.**
      - Monitor INR therapeutic INR 2-3 in most cases.
      - **Treatment continued for 3-6 months** mostly but longer or life long AC may be needed in recurrent cases of VTE.
      - **Treatment of choice for ESRF pt, prosthetic heart valves pt, and antiphospholipid syndrome.**
  - Direct Oral Anticoagulant (DOAC):
    - Direct thrombin (factor 2) inhibitor: Dabigatan.
    - Factor X inhibitors: Rivaroxaban, Apixaban.
    - **DOAC should now be the default choice for patients with DVT and/or PE.**
    - Advantages of DOAC: no need for bridging, no need for monitoring, smaller doses can be used as prophylaxis.

L67: Hypercoagulable state/ DVT

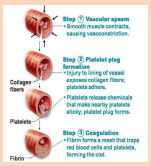
◄ DVT(deep vein thrombosis):

- Treatment:
  - Anticoagulants in VTE: Current Recommendation
    - Long-term therapy: usually 3 months
    - Longer time-limited period: Treatment longer than 3 months (6,12,24 months) but for a limited period.
    - Extended anticoagulant therapy: longer than 3 months (6.12.24 months) + continued indefinitely (for life).
    - For patient who has unprovoked VTE + low or moderate bleeding risk = extended anticoagulant therapy
    - For patient who has unprovoked VTE + high bleeding risk = long term therapy (3 months only)
  - **Overdose & Antidotes:**
    - For Heparin ⟶ Protamine sulphate.
    - For Warfarin ⟶ Vit K and fresh frozen plasma.
    - Idarucizumab for Dabigatrin.
    - Reverse for factor X inhibitors: Andexanet alfa.
  - Thrombolytic therapy: (reserved for massive PE), t-PA, u-PA, urokinase, alteplase.
  - IVC filters: Indicated in cases absolute contraindication + conventional anticogulation proven ineffective.
  - Thrombectomy (arterial).

L68- Bleeding Disorders

Overview of Hemostasis

Hemostasis



- The process through which bleeding is controlled.

Primary Hemostasis:
- Endothelium Injury
- Platelet plug
- Von Willebrand Factor

Secondary Hemostasis:
- Clotting Factors
- Soluble Protein Fibrinogen converted to insoluble Fibrin.

Lab tests

Platelet count (Normal: 150 – 400 x 10^9).
< 100,000 (Thrombocytopenia)
- 50,000 - 100,000 (Mild): Follow up
- < 50,000 (Severe): Needs intervention

- Platelets are produced in the Bone Marrow by fragmentation of the cytoplasm of megakaryocytes.
- **PLT Life Span (7 – 10 days).**

Prothrombin time (PT):
- Measures the effectiveness of the **extrinsic** pathway.
- NORMAL VALUE **(10-15 SECS)**

Partial Thromboplastin time :
- Measures Effectiveness of the **Intrinsic** Pathway.
- NORMAL VALUE **(25-40 SECS)**

Bleeding time :
- PROVIDES ASSESSMENT OF **PLATELET COUNT AND FUNCTION** NORMAL VALUE **(2-8 MINUTES)**

Thrombin time :
- A Measure of Fibrinolytic Pathway.
- NORMAL VALUE 9-13 SECS.

Bleeding disorders

Definition

- Bleeding disorders are a group of disorders that share the inability to form a proper blood clot. They are characterized by extended bleeding after injury, surgery, trauma or menstruation.

Primary hemostasis (only) disorders:
Characterized by Mucocutaneous bleeding - Petechial rash - Epistaxis - Menorrhagia.
Thrombocytopenia? First ask to examine the peripheral blood smear

Disease	Etiology	Diagnosis	Treatment
Quantitative			
Immune Thrombocytopenic Purpura (ITP)	- Primary: **Isolated thrombocytopenia** due to immune platelet destruction (auto AB to megakaryocytes) - Secondary.	**Diagnosis of exclusion.** • CBC (isolated thrombocytopenia) • PBS (large platelet) • Antiplatelet antibodies (Anti-GpIIb/IIIa)	**No bleeding**, count > 50,000: **NO treatment** **- 1st line:** • **Steroids & IVIG** **- 2nd line:** Splenectomy & Rituximab **- Refractory:** Romiplostim.
Qualitative			
Bernard soulier	Autosomal recessive Deficient platelet **GP**Ib-IX	Peripheral smear: Giant platelets • ↓ Platelets • Abnormal ristocetin cofactor assay	
Glanzmann thrombasthenia	Autosomal recessive Deficient platelet **GP**IIb-IIIa	Normal platelets Abnormal results on platelet aggregation testing confirm the diagnosis.	
Secondary or Drug induced	**Uremia (Renal disease)** drugs: e.g. aspirin or clopidogrel	•	Treat underlying cause Stop the drug.

L68- Bleeding Disorders *(cont.)*

Bleeding disorders *cont.*

Secondary hemostasis (only) disorders:
Characterized by hematomas, hemarthrosis, bruising, bleeding (mucosal, GI, GU, joint) deep bleeding.

Disease	Etiology	Diagnosis	Treatment
Hemophilia A	- Congenital: Inherited deficiency of **factor VIII** an **X-linked recessive disorder** - Secondary: Development of **autoantibodies** most commonly directed against **FVIII** (ass. with pregnancy, malignancy, advanced age).	• **Factor VIII Assay: low.** • Mixing study (corrected) • Normal VWF & PT.	• **Replacement of the deficient coagulation Factor** • **Desmopressin** • **Antifibrinolytic agents (Tranexamic Acid, Aminocaproic Acid**
Hemophilia B	Inherited deficiency of factor IX; also called Christmas Disease; an **X-linked recessive disorder.**	• **Factor IX Assay: low** • Mixing study (corrected) • Normal VWF & PT.	
Hemophilia C	Inherited deficiency of factor XI ; also called Rosenthal Syndrome; an **autosomal recessive** disorder (Ashkenazi Jews).	• **Factor XI Assay: Low** • Normal PT & PTT	
Factor XIII Deficiency		• **Factor XIII Assay: FXIII Deficiency** • Normal PT & PTT	

Baseline factor activity level

★ **Severe Hemophilia** : defined as <1 % factor activity (<0.01 IU/mL).
★ **Moderate Hemophilia** : defined as a factor activity level ≥1 % of normal and <5 % of normal (≥0.01 - <0.05 IU/mL).
★ **Mild Hemophilia :** defined as a factor activity level ≥5 % of normal and <40 % of normal (≥0.05 - <0.40 IU/mL).

Disorders not specific to one step of hemostasis.
Clinical features: Bleeding of Mucous membranes, skin cuts, post-trauma or postoperative

Disease	Etiology	Diagnosis	Treatment
Von Willebrand Disease	**(most common bleeding disorder)** Defect of Von Willebrand Factor: Quantitative (type 1 & 3) | Qualitative (type 2) **Clinical features: Bleeding of Mucous membranes,** skin cuts, post-trauma or postoperative		
	Congenital: Autosomal dominant. **Normal function of VWF:** **- Mediate platelet adhesion.** **Acquired :**rare, caused by autoantibodies	Normal aPTT in (Type 1 & 2). Prolonged aPTT in (Type 2N, 2B, & 3) vWF: Ag. FVIII assay (low in 2N & 3). Plt count (low in 2M).	**- Replacement of exogenous vWF concentrate.** **- Desmopressin** **- Antifibrinolytic agents (Tranexamic Acid, Aminocaproic Acid**
Disseminated Intravascular Coagulation	Trauma Septic shock Malignancy (esp APML) Major trauma	Prolonged PT and aPTT. decreased fibrinogen. Low plt. High LDH. Low haptoglobin.	- Treat underlying process . - fresh frozen plasma (FFP) - Cryoprecipitate

L68- Bleeding Disorders *(cont.)*

How to differentiate between bleeding disorders?						
Disorder	**Platelets**	**Bleeding time**	**INR**	**PT**	**aPTT**	**Other:**
Thrombocytopenia	↓	↑	**Normal**	**Normal**	**Normal**	-
Platelet dysfunction (e.g. aspirin therapy or uremia)	**Normal**	↑	**Normal**	**Normal**	**Normal**	-
Extrinsic pathway (e.g. Factor VII def.)	**Normal**	**Normal**	↑	↑	**Normal**	**Specific factor assay: Low** **Mixing study: correctable**
Intrinsic pathway (e.g. Hemophilia A, B & heparin therapy).	**Normal**	**Normal**	**Normal**	**Normal**	↑	-
Von Willebrand disease (vWD)	**Normal**	↑	**Normal**	**Normal**	**Normal/** ↑	**vWF assay: low (dominant)** **FVIII assay (low)**
Disseminated intravascular coagulation (DIC)	↓	↑	↑	↑	↑	-

Feel free to vent here, no one will read it..

L69- Acute & Chronic Leukemia

◄ Introduction

- A group of malignant disorders affecting the blood and blood forming tissues and results in an accumulation of dysfunctional cells because of a loss of regulation in cell division.

Clinical Manifestations	
Bone marrow failure	**Leukemic cells infiltrate patient's organs**
• Overcrowding by abnormal cells • Inadequate production of normal marrow elements • Anemia, thrombocytopenia, ↓ number and function of WBCs	• Splenomegaly • Hepatomegaly • Lymphadenopathy • Bone pain, meningeal irritation, oral lesions (chloromas)

Acute leukemias		
Overview	• **Acute leukemias** arise from the early stages of hematopoietic differentiation **(Immature cells).** • **Acute Leukemias carry high mortality but are CURABLE.** • **Abrupt onset.**	
Cell line	**Acute Myelogenous Leukemia (AML)**	**Acute Lymphocytic Leukemia (ALL)**
Characteristics	• Leukemia characterized by **proliferation of myeloid tissue** (as of the bone marrow and spleen) and an **abnormal increase in the number** of **granulocytes**, **myelocytes**, and **myeloblasts** in the circulating blood. • **One fourth of all leukemias and (85%) (90%) of the acute leukemias in adults**	• More common in children and adolescents than in adults. • It is the most common malignancy in children (25% of all cancers). • 15% of acute leukemia in adults • **Lymphadenopathy, Splenomegaly, Hepatomegaly & CNS: 15%**
Group	• **Adults | Males > Females**	• **Children | Males > Females**
↑Risk:	• Cytotoxic chemo, Radiation, Benzene.	• Trisomy 21 (Down syndrome) 15-fold ↑ in risk
Diagnosis	• **>20% blasts in peripheral blood or BM.** • **Blasts** either by morphology **(Auer rods)** or phenotyping with flowcytometry, IHC**,** cytochemical**: myeloperoxidase (MPO).** • **In Acute Promyelocytic Leukemia (APL) - (PML-RARA) (M3): t(15,17) using FISH.** **"ProMyelocytic Leukemia-Retinoic Acid Receptor α"**	• Flow cytometry on peripheral blood. • Acute lymphoblastic leukemia (**ALL**): **if >25% BM blasts.** • Acute lymphoblastic LYMPHOMA (**LBL**): if <25% BM blasts + mass lesion. • **Absence of granules/ Auer rods**
Management	• **Induction** (to achieve remission -defined < 5% blasts in a BM that is 20% or more cellular-): **Chemotherapy.** • **Consolidation** or "post remission" therapy: **Chemotherapy** or Allogenic stem cell transplant. **APL:** **Low risk: All trans retinoic acid (ATRA) + Arsenic (ATO)** **High risk: ATRA + Chemo ± ATO.** **Relapse? Autologous transplant.**	• ALL & LBL are the same disease & treated the same: • Induction 4-6 weeks > Consolidation 3 months > Late Intensification (re-induction) 3 months > Maintenance 2-3 years • **B-ALL** should be checked for **Philadelphia chromosome t(9,22); if positive TKI (Imatinib or Dasatinib) is added throughout therapy.** • All B-ALL should be checked for **CD20** and **if positive Rituximab should be added**. • Frequent IT MTX if documented CNS disease +/- cranial radiation.

L69- Acute & Chronic Leukemia

Chronic leukemias		
Overview	• **Chronic leukemias** arise from late stages of differentiation **(Mature cells)**	
Cell line	**Chronic Myelogenous Leukemia (CML)**	**Chronic Lymphocytic Leukemia (CLL)**

Characteristics	• Chronic, stable phase followed by acute, aggressive (blastic) phase
	• **Philadelphia (Ph) Chromosome → BCR-ABL gene**
	  ○ The chromosome abnormality that causes chronic myeloid leukemia (CML) (9 &22)
	  ○ Genetic marker
		• Most common adult leukemia in Western countries.

Diagnosis	• Typical findings in blood and bone marrow > then confirmed by the demonstration of the Ph chromosome by conventional cytogenetics, FISH analysis, or RT-PCR.	• CBC w/ diff → B-ALC >5000; "smudge cells" & small mature appearing lymphocytes w/ dense chromatin, scant basophilic cytoplasm Additional labs: • **Peripheral blood flow cytometry** → CD19+, CD20+ (dim), CD5+, CD23+, κ/λ restricted, surface Ig+ (dim), CD10– • BM bx unnecessary unless progressive cytopenias;
Management	• **Imatinib**: a Tyrosine-kinase inhibitor. • Stem cell transplant for selected patients.	• CLL is incurable • Indications for tx: Disease-related sx "active disease".
Complications		• Immunodeficiency, Autoimmune hemolytic anemia, Pure red cell aplasia, immune thrombocytopenia, Transformation..
Other Leukemias		
	Hairy Cell Leukemia: • 2% of all adult leukemias • Usually in males > 40 years old • Cells have a "hairy" appearance Multiple myeloma, Aplastic anemia,	Others: Myelodysplastic syndromes, Leukemoid reaction, Severe megaloblastic anemia, Lymphomas