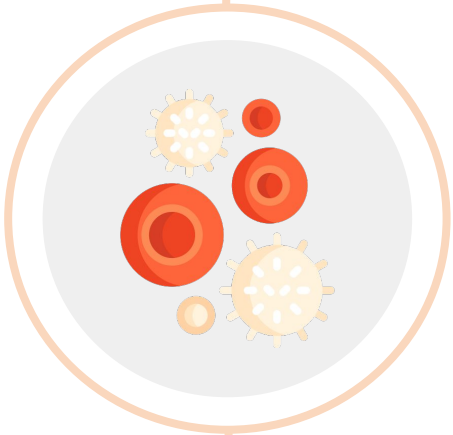
Acute & Chronic Leukemia



This teamwork is based on
1. 438 Teamwork
2. 439 Female's slides + Female Dr's notes
3. 439 Males Dr's notes + Some of 439 male's slides

Note: 439 male slides have different OBJ. and talks in details about AML. We only added what the dr said is important. If you want you can check the slides for extra info regarding AML.

Wish you the best !

Objectives :

- ★ Identify the age and gender distribution of patients with ALL.
- ★ Name common symptoms/signs and common laboratory findings in a patient presenting with Acute/Chronic leukemia mentioning different types of each
- ★ Briefly describe two tests that can be used to distinguish leukemic blast cells of ALL from leukemic blast cells of AML.
- ★ Therapy of ALL commonly consists of an induction phase, postremission therapy (consolidation and maintenance therapy), and central nervous system prophylaxis. Describe the goals of each of these three elements of therapy.
- ★ Describe one complication that leads to mortality in leukemia.

MED439

Medicine Team 439

REVISED BY MISHAL ALTHUNAYN & MONEERAH ALSADHAN

Editing file

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Original text
Females slides
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Doctor's notes 438
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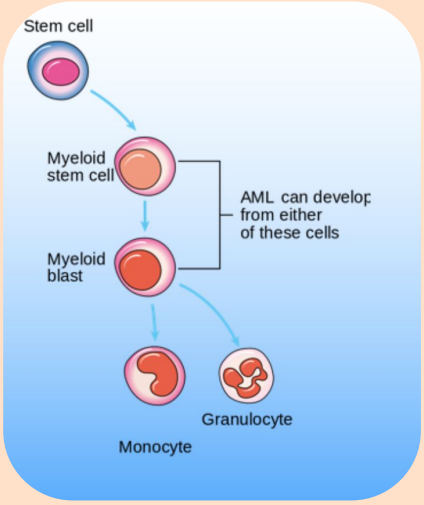
Text book
Important
Golden notes
Extra

Lecture Outline:



★ Leukemia

- Definition
- Clinical manifestation
- Diagnostic studies
- Classification of Leukemia
  - Acute Myelogenous Leukemia (AML)
  - Acute Lymphocytic Leukemia (ALL)
  - Chronic Myelogenous Leukemia (CML)
  - Chronic Lymphocytic Leukemia (CLL)
- Overview on leukemia treatment

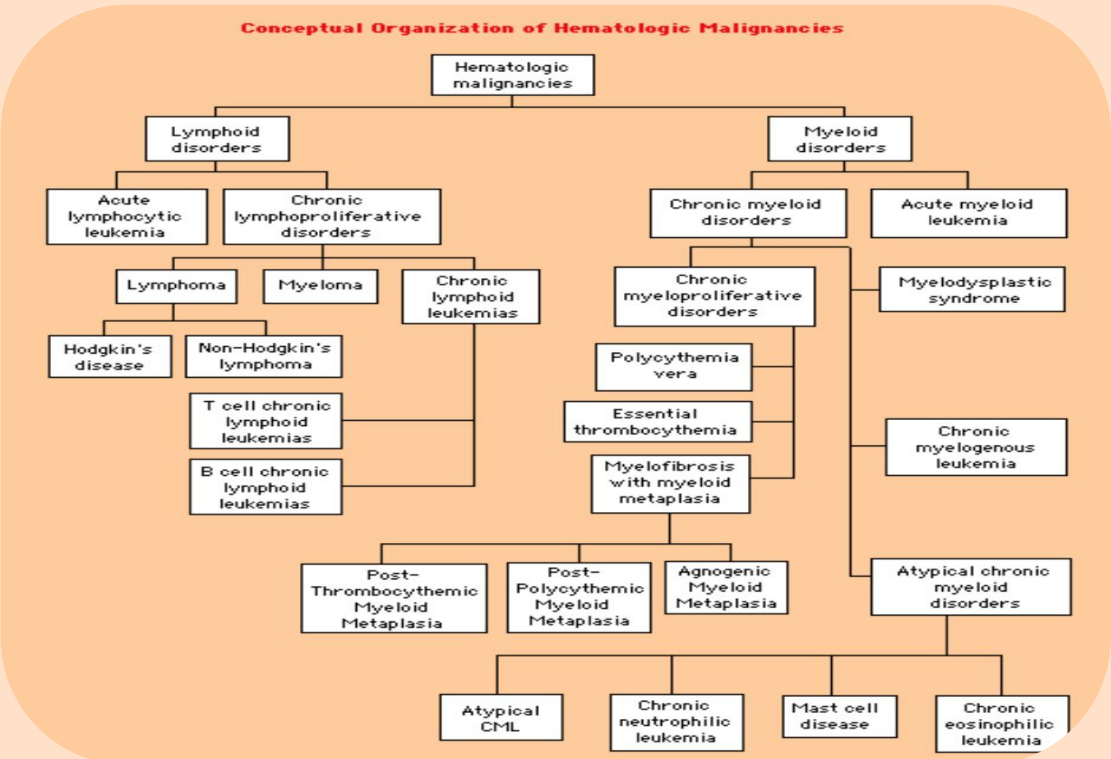
★ Acute Myelogenous Leukemia (AML)

- Definition: rapidly progressive malignancy characterized by failure of myeloid cells to differentiate beyond blast stage
- Risk factors:

★ Acute Lymphocytic Leukemia (ALL)

★ Chronic Myelogenous Leukemia (CML)

★ Chronic Lymphocytic Leukemia (CLL)



بسم الله الرحمن الرحيم

هذا العمل صدقةً جارية عن أخواتنا مي بابعير ونجود المطيري - رحمهما الله-

اللهم اغفر لهن وأرحمهم وعافهن واعف عنهن وأكرم نزلهن ووسع مدخلهن واغسلهن بالماء والثلج والبرد

اللهم إنهن في ذمتك وحبل جوارك فأعذهن من فتنة القبر وعذاب النار واجمعنا بهم في الفردوس الأعلى يا أرحم الراحمين

ربي أسألك أن تظلهم تحت ظلك، وأسألك أن تطيب ثراهم وأن تكرم منزلتهم ومثواهم، وأن تسكنهم الجنة وتجعلها سكنًا لهم ومأواهم

اللهم كما طيبت ذكرهم في أرضك بين خلقك ،طيب ذكرهم في سمائك بين ملائكتك، وارحمهم واغفر لهم وانظر إليهم بعين لطفك وكرمك يا أرحم الراحمين

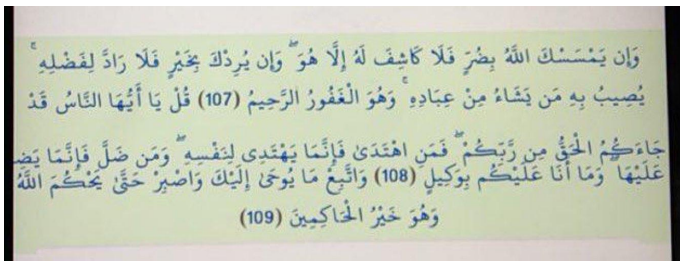
اللهم اجعل قبورهن رياضًا من رياض جنتك

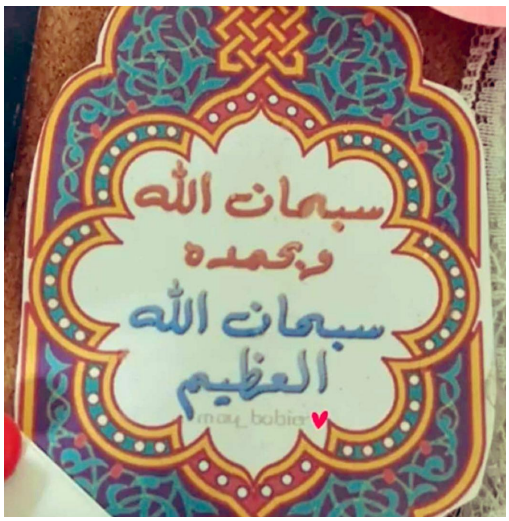
اللهم املأ قبورهن بالرضا والنور والفسحة والسرور

اللهم اجزهن عن الإحسان إحسانًا وعن الإساءة عفوًا وعرفانا

اللهم ادخلهن الجنة بلا حساب ولا سابقة عذاب.

اللهم أنزلهن منازل الصديقين والشهداء والصالحين.

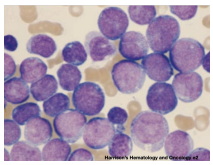




438 logo was done by May Babaeer.. whenever you look at it don't forget to pray for them.

Introduction

Leukemia

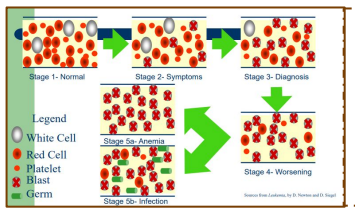


- A group of malignant disorders affecting the blood and blood forming tissues (Bone marrow, Lymph system(lymphoma), Spleen(second factory for hematological cells)
- Results in an accumulation of dysfunctional cells because of a loss of regulation in cell division.
- Abnormality in the cell=blast
- Occurs in all age groups, Fatal if untreated (progressive).
- **Acute Leukemias** carry **high mortality** but **CURABLE.**
- **Chronic Leukemias** are carry **lower mortality** but they are **INCURABLE.** (This has changed nowadays)
- **Acute leukemias** arise from the early stages of hematopoietic differentiation **(Immature cells)**
- **Chronic leukemias** arise from late stages of differentiation **(Mature cells)**

◀ Etiology and Pathophysiology

- No single causative agent
- **Most from a combination of factors**
  - Genetic and environmental influences
- Associated with the development of leukemia:
  - Chemical agents, Chemotherapeutic agents, Viruses, Radiation, Immunologic deficiencies.

- **The main thing that differentiate acute leukaemia is the blast, blast = immature cells**
- **AUER RODS IS A COMMON Qs in the exam , it hint for acute leukemia (more aml)**

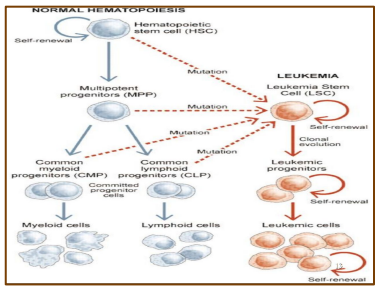


Development of Leukemia in the Bloodstream

◀ Two-hit model of leukemogenesis

Loss of function of transcription factors needed for **differentiation** eg. AML1-ETO, CBFb-SMMHC, (PML-RARa= gene translocation,"AML-M3"=promyelocyte)

Gain of function mutations of tyrosine kinases eg. (FLT3, c-KIT mutations with myeloid leukemia, N- and K-RAS mutations, BCR-ABL"with CML=9,22", TEL-PDGFbR"in Acute leukemia")



Differentiation block + **Enhanced proliferation** → **Acute Leukemia**

◀ Clinical Manifestations

- **Relate to problems caused by:**

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, pancytopenia	• Splenomegaly • Hepatomegaly • Lymphadenopathy • Bone pain, meningeal irritation, oral lesions (chloromas)

◀ Diagnostic Studies

1) To diagnose and classify:

- Peripheral blood evaluation (CBC and blood smear)
- Bone marrow evaluation

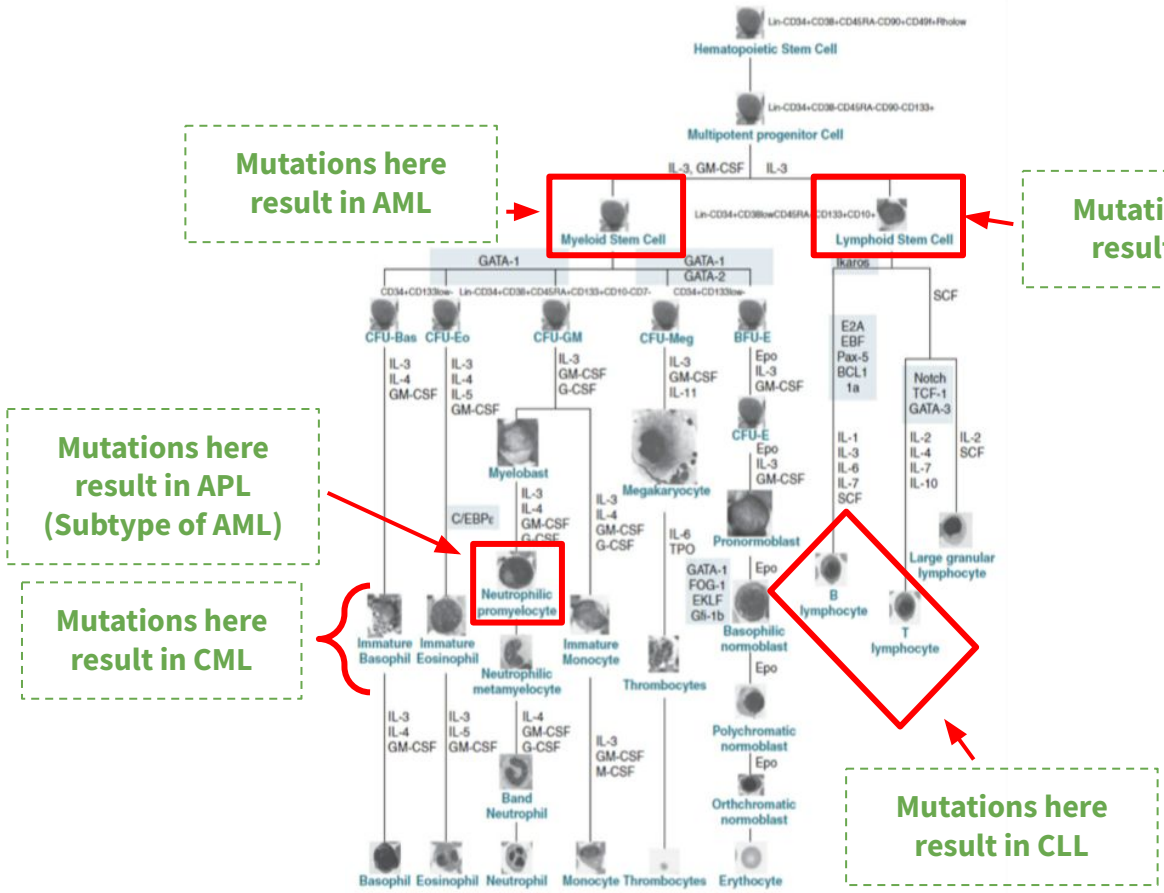
MCQs we need to do flow cytometry, immune phenotype for CD marker on the blast cells

2) To identify cell subtype and stage:

- Morphologic, histochemical, immunologic, and cytogenic methods (each Leukemia has its genetic driven mutation. ex: Philadelphia chromosome in CML,PML-RARa in AML-M3)

Classification of leukemias

- **Acute leukemias**
  - Acute lymphoblastic leukemia **(ALL)**
  - Acute myelogenous leukemia **(AML)** (also "myeloid" or "nonlymphocytic")
- **Chronic leukemias**
  - Chronic lymphocytic leukemia **(CLL)**
  - Chronic myeloid leukemia **(CML)**



- All this tree occurs in the bone marrow. In adults, most of the active bone marrow is in the pelvic bone, hence why bone aspirates are usually taken from there.
- In **acute leukaemia**, there is **proliferation of primitive stem cells**, with **limited** accompanying differentiation, leading to an accumulation of **blasts**, predominantly in the bone marrow, which causes bone marrow failure. (need urgent interference)
- In **chronic leukaemia**, the malignant clone is **able to differentiate**, resulting in an accumulation of more **mature cells**.
- Lymphocytic and lymphoblastic cells are those derived from the lymphoid stem cell (B cells and T cells). Myeloid refers to the other lineages: that is, precursors of red cells, granulocytes, monocytes and platelets
- In acute leukemias the cells are undifferentiated so they are not functioning, unlike chronic leukemias in which there's some degree of maturation (Hence why chronic leukemias have lower mortality than acute leukemias). Clinically, acute leukemias have a more aggressive course and pts develop symptoms rapidly (Within a month) unlike chronic leukemias where they usually develop symptoms over years, (not very bad as acute)

◀ Acute versus chronic

Cell maturity	
Acute: • Clonal proliferation of **immature** hematopoietic cells (the formation of blood or blood cells)	**Chronic:** • **mature** forms of WBC; onset is more gradual so it's not an emergency like acute Leukemia

Nature of disease onset	
Acute: • Poorly differentiated blast population • **Rapidly fatal outcome, if untreated**	**Chronic:** • Well differentiated cell population • **Associated with longer survival**, even if left untreated

Overview on leukemia treatment

This is just a general overview. Specific treatments will be discussed within the lecture

◀ Treatment

- **Collaborative Care:**
  - Goal is to attain remission (when there is no longer evidence of cancer cells in the body)
- **Combination Chemotherapy:** (go to the blast and kill it!)
  - Mainstay treatment
  - 3 purposes
    - ↓ drug resistance
    - ↓ drug toxicity to the patient by using multiple drugs with varying toxicities
    - Interrupt cell growth at multiple points in the cell cycle

1 Chemotherapy (Induction Therapy)

- Attempt to induce or bring remission
- Seeks to destroy leukemic cells in the tissues, peripheral blood, bone marrow(give at high dose then we reduce it
- Patient may become critically ill (Provide psychological support as well), severe depression especially in children

what is remission:

- The main aim of **treatment for acute lymphoblastic leukaemia is to give a remission.** This means that the abnormal, immature white cells or blasts can no longer be detected in the blood or bone marrow, and normal bone marrow has developed again.
- For many people with acute lymphoblastic leukaemia the remission lasts indefinitely and the person is said to be cured.
- In case of chemotherapy complication we manage the patient with IV piperacillin/ tazobactam+amikacin

2 Chemotherapy (Intensification therapy)

- High-dose therapy
- May be given after induction therapy. After CR1 “complete remission no.1”
- Same drugs at higher doses and/or other drugs

3 Chemotherapy (Consolidation therapy)

- Started after remission is achieved
- Purpose is to eliminate remaining leukemic cells “you might have hidden cells anywhere in the body” that may not be evident

Overview on leukemia treatment

4 Chemotherapy (Maintenance therapy)

- Lower doses of the same drug, gives monthly for 2 years, (orally)

5 Follow up طول عمرو

- we follow up the patient for the first 2 years in 3 months.
- then 6 months for more 2 years.
- then 1 visit yearly.

6 Bone Marrow and Stem Cell Transplantation:

for Aggressive Leukemia: not responding to chemotherapy or response then relapse or Leukemia with poor prognosis.(last step)

- First: The goal is to totally eliminate leukemic cells from the body using combinations of chemotherapy with or without total body irradiation
- and then Eradicates patient's hematopoietic stem cells
- lastly Replaced with those of an **HLA-matched** (Human Leukocyte Antigen)
  - Sibling (is a brother or a sister; that is, any person who shares at least one of the same parents)
  - Volunteer
  - Identical twin
  - Patient's own stem cells removed before

* AnthracyclineS

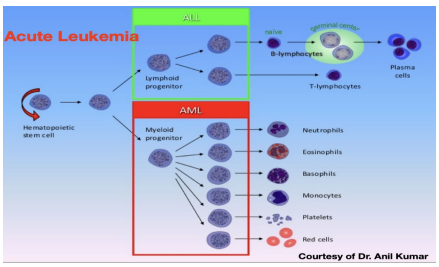
- AnthracyclineS are the corner stone in management of ALL Patients who receive daunorubicin demonstrates superior CR rates Median remission duration is prolonged Additive effect when used along with vincristine and prednisolone The importance of an anthracycline in the treatment of adults with ALL was demonstrated by the randomized trial (CALGB 7612) that incorporated the anthracycline daunorubicin during the first three days of induction therapy into a chemotherapy program that included vincristine, prednisone, and L-asparaginase; patients who received daunorubicin demonstrated superior CR rates (83 versus 47 percent) and median remission duration (18 versus 5 months) when compared with those who did not receive anthracyclines

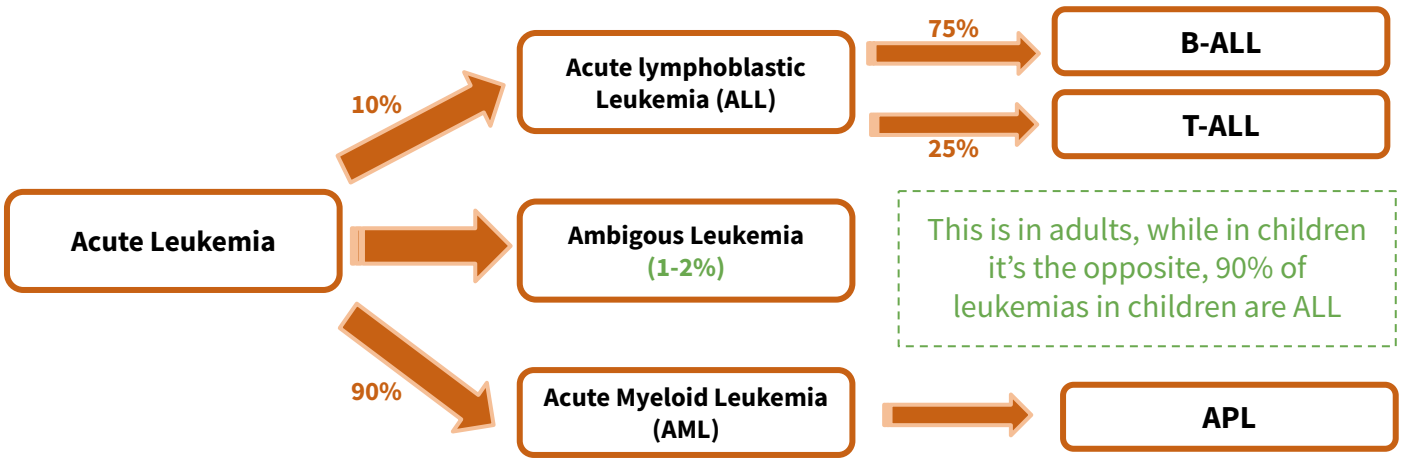
- MCQS :indication, adverse effect : cardiac toxicity

Leukemia Overview

◀ Classification of acute leukemias

Acute Lymphocytic Leukemia (ALL)	Acute Myelogenous Leukemia (AML)
Mainly **children**	Mainly **adults**
M > F	M > F
Curable in 70% of children	-
Curable in minority of adults	Curable in minority of adults





◀ Myelogenous Leukemia

1 Myeloid tissue

Biologic tissue with the ability to perform hematopoiesis. It is mainly found as the red bone marrow in bones, and is often synonymous with this. However, myeloid can also be present in the liver and spleen

2 Granulocytes

Category of white blood cells characterized by the presence of granules in their cytoplasm.
They are also called **polymorphonuclear leukocytes** (PMN or PML) because of the varying shapes of the nucleus, which is usually lobed into three segments.

3 Myelocyte

Young cell of the granulocytic series, occurring normally in bone marrow, but not in circulating blood, if found in peripheral blood it's Leukemia (except when caused by certain diseases).

4 Myeloblast

Unipotent stem cell "it has the ability to highly proliferate", which will differentiate -Malignant differentiation- into one of the actors of the granular series.

Acute Myelogenous Leukemia (AML)

◀ Acute Myelogenous Leukemia (AML) Cont'

Introduction

- Heterogeneous group of diseases characterized by **uncontrolled proliferation of myeloid progenitor cells (Blasts)** that gradually replace normal hematopoiesis in the bone marrow.
- 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,** rare in children. 20,000 new cases in the US/year.
- **Abrupt**, dramatic onset (Serious infections due to pancytopenia "granulocytes is the first line of defense", abnormal bleeding due to thrombocytopenia).
- Uncontrolled proliferation of myeloblasts (**Hyperplasia** of bone marrow and spleen).
- Median age of onset **~71/** 65, incidence increase progressively with age.
- **Risk Factors: Cytotoxic chemo, Radiation, Benzene. Smoking,**
- **Predisposing conditions:** Trisomy 21, Rare congenital syndromes: Severe congenital neutropenia, Shwachman-Diamond syndrome, falconi anemia, Li-Fraumeni, Klinefilter, Noonan Syndrome.

Etiology

- Cellular Transformation Represents Multi-step process
- Excessive chromatin fragility (Fanconi's anemia and Bloom's syndrome, Ataxia telangiectasia)
- **Risk Factors: Cytotoxic chemo, Radiation, Benzene. + family history**
- Smoking, ethylene oxide, herbicides and pesticides
- Previous hematologic disorders (Severe congenital neutropenia, Myeloproliferative disorders, Myelodysplastic syndrome (20% progresses to AML), PNH)

★ **Drug-Induced AML**

- **Expected to develop in 3 to 10% of patients treated with alkylating agents (Cyclophosphamide) COMMON MCQ**
  - Risk peaks five to ten years after start of chemotherapy ("long latency period")
  - Frequently preceded by myelodysplasia
  - Associated with deletions of chromosomes 5 and 7, and complex chromosomal abnormalities
- **Also represents complication of treatment with topoisomerase II inhibitors**
  - Epidophyllotoxins and anthracyclines
  - Risk peaks two to three years after start of chemotherapy ("short latency period")
  - Not preceded by myelodysplasia
  - Frequently associated with 11q23 chromosomal abnormalities (associated with monocytic disease)
  - Risk proportional to dose intensity (not cumulative dose)

◀ Pathophysiology

↑Blasts in BM & circulation → **↓ Neut/Hgb/Plt (BM failure)** →
- **Infection** (↓WBCs)
- **Bleeding** (↓plt)
- **Fatigue** (↓ Hgb)
- **Organ infiltration**

Acute Myelogenous Leukemia (AML)

◀ Presentation

Due to BM failure ↓ Hematopoiesis

- Fatigue, SOB, Fever, Bleeding (PANCYTOPENIA)
- Anemia with a normal or raised MCV.

Tissue involvement

- Bone pain, splenomegaly (20-30%) "splenomegaly is rare in acute"
- **Gingival hyperplasia** (Characteristic of AML-M5, aka acute monocytic leukemia)
- CNS symptoms, visual symptoms.

Rare Manifestations

- Sweet syndrome
- **Chloroma (Myeloid sarcoma)**

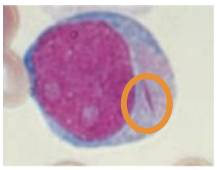
Diagnosis

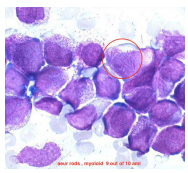
★ **Most patients present pancytopenia w/circulating blasts**
  - **~50% of patients will have ↓ or normal WBC.**
  - 20% of patients will have WBC >100k/micro L

What if the Blasts are 15% → Myelodysplastic syndrome

- **Is it a an Acute Leukemia?**
  - You just need **>20% Myeloblasts** (**immature** blood cells) **in peripheral blood** or Bone marrow. Make sure they are blasts either by morphology **(Auer rods)** or **phenotyping with flowcytometry**, IHC, cytochemical **(MPO)**. Or by detecting certain cytogenetic abnormalities t(8,21), Inv(16), t(16,16), t(15,17)
- **What kind of an acute leukemia?**
  - ALL Vs AML Vs Weird Leukemia
  - **PHENOTYPE!** Flow cytometry, IHC, cytochemical.
  - Genetics can help (cytogenetics, molecular studies)
- Common myeloid Ag: CD13, CD33, CD34, CD117, **MPO.**

Auer rods deriving from the crystallisation of **myeloperoxidase (MPO)** granules are the **hallmark of Acute Myeloid Leukemia (AML)**. Auer rods are **NOT seen in ALL**.





- **WHY DO YOU WANT TO KNOW WHAT KIND OF ACUTE LEUKEMIA?**
  - **Because treatment differs**
- **Best initial test (for both ALL and AML):** CBC with smear showing blast cells.
- **Most accurate test (for both ALL and AML):** Bone marrow biopsy with flow cytometry to classify leukemia type.
- On morphology it's difficult to differentiate if this is a myeloid or lymphoid blast. So further investigation is required --> Flow cytometry.

◀ Are there different types of AML?

- Classification changed over the decades. **(OLD)**
- FAB relies on **morphology to Identifying the lineage** of the blast: Myeloblast, Monoblast, Erythroblast, megakaryoblast, promyelocyte) and the degree of differentiation
- M3= APL , not aml anymore , does not behave like aml anymore,

FAB subtype	Name
M0	Undifferentiated acute myeloblastic leukemia
M1	Acute myeloblastic leukemia with minimal maturation
M2	Acute myeloblastic leukemia with maturation
M3	Acute promyelocytic leukemia (APL)
M4	Acute myelomonocytic leukemia
M4 eos	Acute myelomonocytic leukemia with eosinophilia
M5	Acute monocytic leukemia
M6	Acute erythroid leukemia
M7	Acute megakaryoblastic leukemia

Acute Myelogenous Leukemia (AML) *cont.*

Prognosis

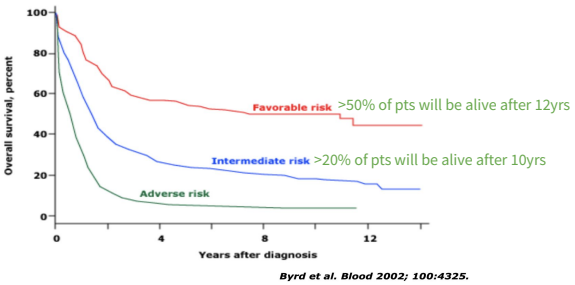
What's the difference between prognostic factors and predictors?
Prognosis is dependent on the characteristics of the disease and patient factors. Whereas predictors are dependent on the type of treatment.

- Typically fatal in weeks-months if untreated.
- Independent poor risk factors:
  - **Age**: >60 especially >75 for both disease and host factors
  - **PS:** Poor performance status ECOG >2
  - Treatment related AML, if proceeded with hematologic disorder (MDS, MPN)
- The best pretreatment predictors of long-term outcome, together with age. are **chromosomal and molecular genetic findings in leukemic cells.**

CALGB Risk groups

Risk Status	Cytogenetics	Molecular abnormalities
Favorable-risk	CBF: inv(16) or t(16;16) or t(8;21) APL: t(15;17)	*NPM 1 (FLT3–); CEBPA* (biallelic)
Intermediate-risk	Nl; +8; t(9;11)	
Poor-risk	complex cytogenetics (≥3 clonal abnls); monosomal; –5/5q–; –7/7q–; 11q23; inv(3)/t(3;3); t(6;9); t(9;22)[a]	*FLT3*-ITD *TP53*

[a]Philadelphia chromosome + AML t(9;22) is managed as CML myeloid blast crisis, w/ addition of TKI



Byrd et al. Blood 2002; 100:4325.

Complications of AML

Males 439 slides

1. Hyperleukocytosis not in all because lymphocytes are small , not like myeloid

- Myeloblasts considerably less deformable than mature myeloid cells and considerably more "sticky" than lymphoblasts due to expression of cell surface adhesion molecules
- Risk if WBC >50k. **Hypoperfusion**/vascular occlusion. SOB/MI/CVA. Tx: IVF, cytoreduction (chemo, HU, leukopheresis).
- Myeloblast counts over 100 x 109/L
  - Represent medical emergency
  - Impede blood flow in microcirculation and predispose to local hypoxia ("leukostasis")
  - Exacerbated by high metabolic activity of blasts
- Leukostasis signaled by CNS and/or pulmonary symptoms (e.g.: ocular and cerebrovascular dysfunction, dyspnea)
- More common in patients with myelomonocytic or monocytic leukemias
- Associated with lower remission rates and shorter duration of remission due to larger initial tumor mass, as well as biologic and intrinsic chemoresistance
- Coagulopathy/DIC: Mainly in APL but can occur in any AML

2. CNS Disease

- Occurs in less than 5% of AML
- Diagnostic lumbar puncture not routinely indicated in AML in absence of symptoms
  - Cytarabine penetrates into CNS
  - All-trans-retinoic acid fails to penetrate into CN
- Reactive ependymal cells resemble leukemia cells after administration of intrathecal chemotherapy

3. Metabolic Abnormalities

- Hyperuricemia
  - Predisposes to urate nephropathy and renal insufficiency
  - Ameliorated with allopurinol, hydration, and alkalinization
  - High risk Use of rasburicase advocated

★ **Tumor lysis syndrome related to massive leukemic cell death** (MCQ Q)

- Characterized by hyperphosphatemia, **hypocalcemia**, **hyperkalemia**, and renal insufficiency
- **Can happen to all kinds of leukemia but most commonly with aml and cml because of their large size, and the tx is fluid fluid fluid.** Ppx IVF allopurinol

Acute Myelogenous Leukemia (AML) *cont.*

Treatment paradigm

Induction → Day 14 BM → **Remission** → **Consolidation**

In this phase, a fraction of the tumour is destroyed by combination chemotherapy. The patient goes through a period of severe bone marrow hypoplasia lasting 3–4 weeks and requires intensive support

BM day 30 or after count recovery

If remission has been achieved, residual disease is attacked by therapy during the consolidation phase.

- **Induction:**
  - **Goal:** is to achieve remission defined < 5% blasts in a BM that is 20% or more cellular, absent extramedullary leukemia, a neutrophil count greater than 1,000/μL, and a platelet count greater than 100,000/μL. (definition est 60 y ago)
  - To prevent tumor lysis syndrome (hyperuricemia, hyperkalemia, hypocalcemia, renal insufficiency, as blasts are destroyed by chemotherapy), patients should be well hydrated.
- **AML induction is similar across all AML-risk groups**
- **Consolidation or "post remission" therapy**
  - **Goal:** Long term remission and CURE.
  - All patients relapse if they don't receive consolidation.
- **Common Induction regimens:**
  - **7+3: Cytarabine** 100 to 200 mg/ m2 by continuous intravenous (IV) infusion **over 7 days with 3 days of an anthracycline** (e.g., **daunorubicin** 60 to 90 mg/ m2 or **idarubicin** 12 mg/ m2). **(7+3 regimen is the one use in most centers)**
  - FLAG-IDA: Fludarabine, Cytarabine, GCS-F Idarubicin.
- **~ 70-80% of younger pts (<60 y) & ~40-50% of older pts (>60 y) will achieve CR w/ Induction chemo. CR Correlates with Survival**
- **Consolidation (post remission tx):**

Depends on risk group		
Favorable	**Intermediate**	**Poor**
High dose Cytarabine (HDAC) x 2-4 cycles	HDAC 2-4 cycles OR Allogeneic stem cell transplant	Allogeneic stem cell transplant

i 23.47 Drugs commonly used in the treatment of acute leukaemia

Phase	Acute lymphoblastic leukaemia	Acute myeloid leukaemia
Induction	Vincristine (IV) Prednisolone (oral) L-Asparaginase (IM) Daunorubicin (IV) Methotrexate (intrathecal) Imatinib (oral)*	Daunorubicin (IV) Cytarabine (IV) Etoposide (IV and oral) Gentuzumab ozogamicin (IV) All-*trans* retinoic acid (ATRA) (oral) Arsenic trioxide (ATO)
Consolidation	Daunorubicin (IV) Cytarabine (IV) Etoposide (IV) Methotrexate (IV) Imatinib (oral)*	Cytarabine (IV) Amsacrine (IV) Mitoxantrone (IV)
Maintenance	Prednisolone (oral) Vincristine (IV) Mercaptopurine (oral) Methotrexate (oral) Imatinib (oral)*	
Relapse	Fludarabine Cytarabine Idarubicin	Fludarabine Cytarabine Arsenic trioxide (ATO) Idarubicin

*If Philadelphia chromosome-positive.

Acute Promyelocytic Leukemia (APL)

There will be a question about APL in the exam

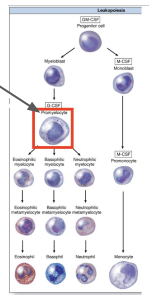
Why APL is an important AML subgroup?

Because cure rate is >90% and mortality usually occur early in the course of the disease due to coagulopathy which can be mitigated by early initiation of ATRA. So, prompt diagnosis can save a lot of patients. **Diagnosis is also fairly straight forward, by identifying t(15,17) using FISH.**

Pathophysiology

- **Arrest of maturation at the promyeloctye stage due to t(15,17) PML-RARA "ProMyelocytic Leukemia-Retinoic Acid Receptor α" fusion protein block normal myeloid differentiation which leads to proliferation of promyelocytes. "VERY IMP"**
- **These atypical promyelocytes are considered blast-equivalent.**
- **Associated with DIC.** Early hemorrhagic death rates generally ranging from 5% to 11%.
- **Why do APL patients bleed (coagulopathy)?**
  - As the abnormal promyelocytes lysed and liberated the procoagulant contents of their granules including TF causing consumption of coagulation factors leading to DIC and bleed and in small number can cause thrombosis.
- Other symptoms related to bone marrow failure like **fatigue**, **infection** also exist and patients might not have coagulopathy. **Approximately 80% of pts with APL present with coagulopathy** in addition to thrombocytopenia

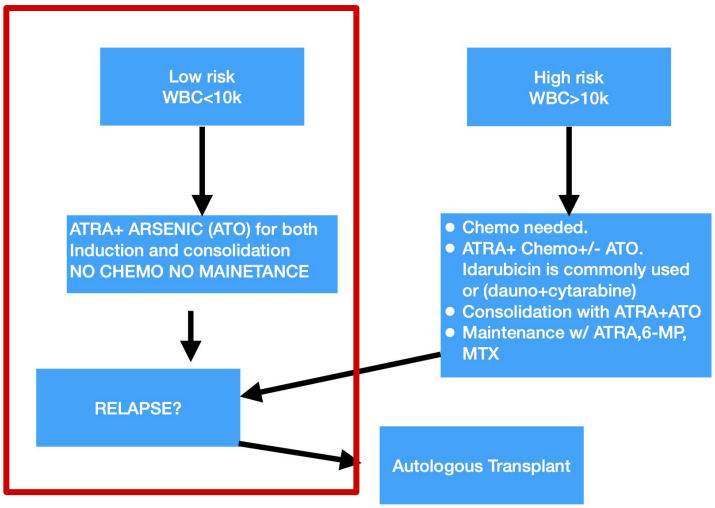
Promyelocytic stage



Initial management (95% CURABLE)

- Similar to any AML case. However **peripheral smear** review of great importance especially in patients with overt signs of bleeding.
- Send FISH (or PCR) for **t(15,17)** using peripheral blood sample.
- **Start ATRA (All-Trans Retinoic Acid) immediately if there is any suspicion of APL even if it turns out it wasn't APL. ATRA DOESN'T HARM (It's just a vit A derivative). START ATRA even before the results of the cytogenetics are out.**
- Monitor for coagulopathy very closely. PT/PTT/Fibrenogin/ platelets (keep fibrinogen >150 mg/dL and platelet >50k/ micro L).
- Lysis of leukemia cells worsen DIC. DIC ameliorated by ATRA within 48 hours
- ATRA alone insufficient for long term control of disease

Management after confirming APL



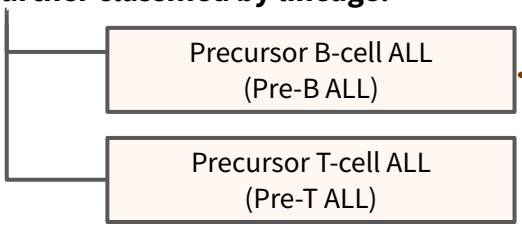
Differentiation Syndrome

- As a **consequence of treatment of APL with ATRA.** Recall that in acute leukemias there's failure of differentiation, and in the case of APL the underlying pathophysiology of this failure is the disrupted RAR receptor, therefore once pts are given ATRA, there will be excessive differentiation of cells leading to this so-called differentiation syndrome
- Occurs in 25% of APL patients.
- High WBC is a risk factor.
- Promyelocyte starts "differentiating" to neutrophils releasing all kinds of inflammatory cytokines a massive inflammatory state.
- Characterized by **fever**, peripheral **edema**, **pulmonary infiltrates**, **hypoxemia**, **respiratory distress**, **hypotension**, renal and hepatic **dysfunction**, and **serositis** resulting in pleural and pericardial effusions. Can mimic sepsis.
- **Dexamethasone** 10 mg IV BID. Hold ATRA/ATO in some cases

Acute Lymphocytic Leukemia (ALL)

◀ Acute Lymphocytic Leukemia (ALL)

- Lymphoblastic neoplasms can present as **leukemia** or **lymphoma**.
  - **Acute lymphoblastic leukemia (ALL): if >25% BM lymphoblasts inn the early studies, (439 slide=20%)(very imp).**
  - **Acute lymphoblastic LYMPHOMA (LBL):** if <25% BM blasts + mass lesion.
- ALL & LBL are the same disease & treated the same.
- **They can be further classified by lineage:**



What is Ph? Philadelphia chromosome which is an abbreviated chromosome 22 that was shortchanged in a reciprocal exchange of material with chromosome 9.

- **More common in children and adolescents than in adults.**
- **It is the most common malignancy in children (25% of all cancers and 80% of leukemia)**
- **lymphoma goes more with genetic, that's why it is more common in children.**
- 15% of acute leukemia in adults
- 6500 cases/year in the US (2% of all lymphoid neoplasms) in ADULTS.
- Immature lymphocytes proliferate in the bone marrow
- Certain conditions predispose to ALL, most notably **trisomy 21 (Down syndrome)**, in which the relative risk is increased 15-fold
- Down syndrome: Before the age of 5 → usually AML (specifically acute megakaryoblastic leukemia). After the age of 5 → usually ALL
- Disease-free survival (DFS) rates in children is 90% and in adults is 50%.
- The success in pediatric ALL led to the adoption of similar approaches in the treatment of adults.

◀ Clinical presentation

- **Similar to AML:** Pancytopenia & circulating blasts and signs & symptoms related to BM failure leading to decrease Hematopoiesis:
  - Fever and bleeding (appear abruptly)
  - Fatigue, Weakness (Insidious with progressive)
    SOB, infection, bony pain.

Same as AML except for:

- **Lymphadenopathy & Hepatosplenomegaly more common in ALL>AML**
- **Anterior mediastinal mass suggests T-ALL. (Not B-ALL)**
- **CNS involvement in 5-15% (More common than AML).**[1]
- **CN neuropathy, leukemic meningitis, mass lesion (T-cell).**
- **Testicular involvement seen on US (Sanctuary site)**
- **TLS more common in ALL** > AML and can be spontaneous.
- Leukostasis if WBC >100k. More common in AML>ALL.
- Sign or symptoms related to Organ infiltration

Pancytopenia

- ⬇️ WBC ➡ infection
- ⬇️ Hb ➡ anemia
- ⬇️ Platelets ➡ bleeding

◀ Diagnosis

- Similar to the diagnostic steps followed in any Acute leukemia:

Ask the following questions:
1.Is this a leukemia?
2. What kind of a leukemia?

➡

Quickly try to answer these questions by:
1. CBC and peripheral blood smear
2. Flow cytometry on peripheral blood.

➡

➔ **Absence of granules / Auer rods**
➔ +ve TDT

1- **In patients with ALL, it is necessary to give prophylactic treatment to the central nervous system,** as this is a sanctuary site where standard therapy does not penetrate. This usually consists of a combination of cranial irradiation, intrathecal chemotherapy and high-dose methotrexate, which crosses the blood–brain barrier. That's why if it's ALL specially T-cell type, we have to give the Pt intrathecal chemotherapy prophylaxis and do imaging to rule out

Acute Lymphocytic Leukemia (ALL) *cont.*

438 slides

◀ Classifications

- +ve MPO (Auer rods) → AML
- +ve TdT → ALL
  - +ve CD10, CD19, CD23 & -ve CD3 → B-ALL
  - -ve CD10 & +ve CD3 → T-ALL

FAB Classification not IMP

CLASSIFICATION OF ACUTE LYMPHOID LEUKEMIA (ALL)			
IMMUNOLOGIC SUBTYPE	% OF CASES	FAB SUBTYPE	CYTOGENETIC ABNORMALITIES
Pre-B ALL	75	L1, L2	t(9;22), t(4;11), t(1;19)
T cell ALL	20	L1, L2	14q11 or 7q34
B cell ALL	5	L3	t(8;14), t(8;22), t(2;8)

WHO Classification of ALL (dr;pls don't memorize it

WHO Classification of ALL		
Subtype	Frequency (Adults)	Immunophenotype
Precursor B-cell	75%	(+) TdT; (+) CD19; (+) CD22; (–) CD3; variable CD10, CD20, CD79a
Precursor T-cell	20%	(+) TdT; (+) cCD3; (+) CD7; (–) CD10; variable CD1a, CD2, CD4, CD4

◀ Are there prognostic tools?

Table 12.5 Risk-Group Assignment in B-Precursor Acute Lymphoblastic Leukemia

Clinical Feature	Standard Risk	High Risk	Very High Risk
Age (y)	1–9	10–35	<1 >35 >55
WBC (μL)	<30,000 <50,000	≥30,000 ≥50,000	
CNS	Negative	Positive	
Chromosomes	t(12;21), <Double or triple Trisomy 4/ 10/ 17	11q23, t(1;19), t(9;22)	
Ploidy	Hyperdiploidy	Hypodiploidy	
Treatment response	RER	SER	Induction failure
Post-induction MRD (%)	<0.01	0.01–0.1	>0.1 ≥1.0

ALL, acute lymphoblastic leukemia; CNS, central nervous system; MRD, minimal residual disease; RER, rapid early responder; SER, slow early responder; WBC, white blood cell.

Do we base our treatment on these prognostic risk groups?

Indicators of poor prognosis:

- **ALL**: Age < 1 or > 10 years; an ↑ in WBC count to > 50,000/mm3; presence of the Philadelphia chromosome t(9,22) (associated with B-cell cancer); CNS involvement at diagnosis.
- **AML**: Age > 60 years; elevated LDH; poor-risk or complex karyotype.

◀ Common treatment paradigm ALL

Induction 4-6 weeks → **Consolidation 3 months** → **Late Intensification (re-induction) 3 months** → **Maintenance 2-3 years**

- MRD assessment post induction will further diverge patients treatment.
- **All B-ALL should be checked for Philadelphia chromosome t(9,22) and if positive TKI (Imatinib or Dasatinib) should be 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.

Special questions

Who gets allogeneic transplant after remission?
Everyone should be considered in 1st remission but especially important in high risk groups:

- MRD+, t(4,11), Ph+.

Older patients?
Low intensity regimens exist including Dex + TKI (Ph+)

Supportive care in the treatment of Acute leukemias

Infections:

- Febrile neutropenia. Abx Ppx.

Transfusions:

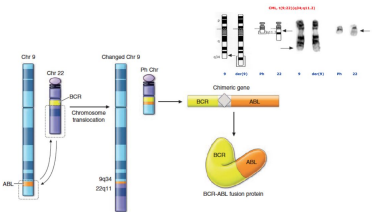
- Platelets
- PRBC

TLS monitoring in the beginning of treatment.

Chronic Myelogenous Leukemia (CML)

◀ Chronic Myelogenous Leukemia (CML)

- Have very clear pathology unlike ALL and AML in which there are a lot of genetic abrasions,SINGLE MUTATION=direct treatment
- Excessive development of **mature neoplastic granulocytes** in the bone marrow
  - Move into the peripheral blood in massive numbers
  - Ultimately infiltrate the liver and spleen, causing hepatosplenomegaly.
  - Maturation of cells proceeds fairly normally.
- Chronic, stable phase followed by acute, aggressive (blastic) phase, if left untreated



- **Philadelphia (Ph) Chromosome → BCR-ABL gene**
  - The chromosome abnormality that causes chronic myeloid leukemia (CML) **(9&22)**[2]
  - Genetic marker

◀ Typical CML presentation

- 85% present in the chronic phase.
- 30-50% of patients in chronic phase are **asymptomatic**, present with **leukocytosis** on CBC done for other purposes.
- **Elevated WBC with left shift and basophilia and thrombocytosis**[1] **are common** (Majority of pts will have high WBC unlike acute leukemias)
- **The rest of chronic phase signs:** Fatigue, weight loss, night sweats, symptoms related to splenomegaly (early satiety, and fullness). (Usually there's normocytic normochromic anemia)
- **Signs: Splenomegaly** is present in 90%; in about 10%, the enlargement is massive, extending to over 15 cm below the costal margin. A friction rub may be heard in cases of splenic infarction. Hepatomegaly occurs in about 50%. Lymphadenopathy is unusual.
- Spleen size increases when ET progresses to myelofibrosis.

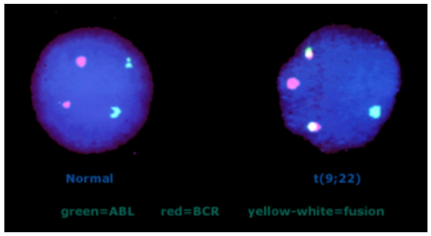
Phases of CML

- **A chronic phase**, in which the disease is responsive to treatment and is easily controlled
- **An accelerated phase** (not always seen), in which disease control becomes more difficult.
- **Blast crisis,** in which the disease transforms into an acute leukaemia, either myeloblastic (70%) or lymphoblastic (30%), which is relatively refractory to treatment. This is the cause of death in the majority of patients.

◀ Diagnosis

- **The diagnosis of CML is first suspected by identifying the typical findings in the blood and bone marrow, and then confirmed by the demonstration of the Philadelphia chromosome** (Most accurate test)**,** the BCR-ABL1 fusion gene or the BCR-ABL1 fusion mRNA by conventional cytogenetics, fluorescence in situ hybridization (FISH) analysis, or reverse transcription polymerase chain reaction (RT-PCR).
- In some patients in whom conventional chromosomal analysis does not detect a Ph chromosome, the BCR ABL gene product is detectable by molecular techniques.

- **Do patients with positive FISH for Ph Ch still need a BM?**
  - A bone marrow (BM) aspirate is essential to ensure sufficient material for a complete karyotype and for morphologic evaluation to confirm the phase of disease
- **Need peripheral blood flow to quantify blasts**

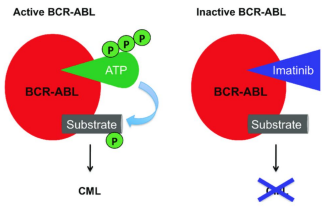


1- In patients with thrombocytosis, very high platelet counts may persist during treatment, in both chronic and accelerated phases, but usually drop dramatically at blast transformation. Basophilia tends to increase as the disease progresses. CML can be confused clinically with a leukemoid reaction (acute inflammatory response to infection with ↑ neutrophils and a left shift). LAP is low in CML and other hematologic malignancies, and LAP is high in leukemoid reactions.

2- This translocation could be bc of viral infection, radiation or previous chemotherapy.

Chronic Myelogenous Leukemia (CML) *cont.*

◀ Treatment



- ★ BCR-ABL tyrosine kinase enzyme exists only in clonal cancer cells and not in normal patient cells.
- **Imatinib**, is a Tyrosine-kinase inhibitor which prevents the BCR-ABL enzyme product from initiating the signaling cascade necessary for cancer development, thereby causing cancer cell apoptosis.
- Imatinib binds to BCR-ABL kinase domain by preventing the transfer of a phosphate group to tyrosine on the protein substrate and the subsequent activation of phosphorylated protein. As the result, the transmission of proliferative signals to the nucleus is blocked and leukemic cell apoptosis is induced.
- Stem cell transplant for selected patients.
- **Treatment of blast crisis:** When blast transformation occurs, the type of blast cell should be determined. Response to appropriate acute leukaemia treatment is better if disease is lymphoblastic than if myeloblastic. Second- or third-generation TKIs such as dasatinib are used in combination with chemotherapy to try and achieve remission. In younger and fitter patients an allogeneic HSCT is appropriate therapy if a return to chronic phase is achieved.

If you have chronic and left untreated it may result in acute on top of chronic

Types of response to treatment

- **Hematologic** (CBC)
- **Cytogenetic** (BCR-ABL1 by karyotype & FISH)
- **Molecular** (BCR-ABL1 qPCR in peripheral blood)

Response	Description
Complete Hematologic Response (CHR)	WBC <10 K/μL w/ no immature granulocytes & <5% basophils; Plt <450 K/μL; no s/s
Cytogenetic Response Major (MCyR) - Complete (CCyR) - Partial (PCyR) Minor (mCyR)	% of Ph+ cells by metaphase karyotyping/FISH: 0–35% 0% 1–35% >35%
Molecular Response Early (EMR) Major (MMR) Complete (CMR)	Assessed by qPCR: *BCR-ABL1* ≤10% on the intl scale (IS) by 3 mos on tx ≥3-log reduction in detectable *BCR-ABL1* transcript levels (eg, ≤0.1% IS) *BCR-ABL1* transcript *undetectable* using assays w/ sensitivity of ≥4.5-log reduction from the IS standardized baseline* (eg, ≤0.0032% IS)

*Per National Comprehensive Cancer Network (NCCN) 2016 guidelines version 1.2017

Skipped by the doctor

◀ Myeloproliferative Neoplasms

CML and MF can have massive splenomegaly. Spleen size increases when ET progresses to myelofibrosis.

Female's doctor= MCQs?!

Parameter	CML	PV	ET	PMF
WBC	Increased	Normal or increased	Normal or slightly increased	Normal, increased, or decreased
RBC	Normal or decreased	Increased	Normal or slightly decreased	Normal or decreased
Platelets	Normal or increased	Normal or increased	Increased	Normal, increased, or decreased
Molecular abnormalities	BCR-ABL1	JAK2 V617F or other JAK2 mutation	± JAK2 no splenomegaly	± JAK2

CML, Chronic myelogenous leukemia; *ET*, essential thrombocythemia; *PMF*, primary myelofibrosis; *PV*, polycythemia vera; *RBC*, red blood cells; *WBC*, white blood cells.

Chronic Lymphocytic Leukemia (CLL)

◀ Chronic Lymphocytic Leukemia (CLL)

- **Most common adult leukemia in Western countries.**
- Chronic Production and accumulation of functionally inactive (incompetent) but long-lived, mature-appearing **B-lymphocytes** resulting in hypogammaglobulinemia (immunoparesis), usually monoclonal.
- B cell involvement.
- Lymph node enlargement is noticeable throughout the body causing ↑ incidence of infection.
- **CLL =** Absolute B-lymphocyte count >5000/uL in blood, ± marrow, ± LN
- **SLL =** <5000/uL absolute B-lymphocytosis w/ lymphadenopathy o/w same as CLL
- CLL is a bigger umbrella for small lymphoblastic lymphoma (SLL). Both are treated in the same way. The disease is classified as SLL only if there was <5000/uL B-cells in the peripheral blood

Clinical presentation:

- **Sx:** Most pts diagnosed incidentally by laboratory tests. **(Lymphocytosis)** not functioning
- Those that present w/ sx have painless lymphadenopathy, fatigue, **recurrent infxn**, or uncommonly (5–10%) B symptoms (wt loss, fevers, NS)
- **PE:** LAN, HSM, pallor, leukemia cutis (<5%)

◀ Diagnosis

- Best initial: **CBC w/ diff** → **B-ALC >5000; "smudge cells"** & small mature appearing lymphocytes w/ dense chromatin, scant basophilic cytoplasm Additional labs:
- ★ Most accurate: **Peripheral blood flow cytometry** → CD19+, CD20 usually weak (بمبرها عن lymphoma) + (dim), **CD5+ (normally found on T-cells)**, CD23+, κ/λ restricted, surface Ig+ (dim), CD10–
- BM biopsy unnecessary unless progressive cytopenias
- **Karyotype, cytogenetics, & FISH**
  - Usually monosomy (deletion not translocation unlike CML) e.g. 17p or 13q deletions. In CLL, deletion of the short arm of chromosome 17 (17p) is associated with rapid disease progression as well as a poor response to treatment). CLL is also associated with TP53 mutation, all patients should be tested for this gene before initiating treatment.
- **PCR:** Ig variable region (IGHV) Mt (Patients with this mutated gene have better prognosis)
- CT scan optional unless concern for impaired/threatened organ function or pre-tx to allow response assessment

◀ Immunephenotypic findings

There are three major characteristic immunophenotypic findings in CLL:

1. The immunoglobulin is most often IgM and only a Expression of B-cell associated antigens including CD19, CD20, and CD23. Expression of CD20 is usually weak.
2. Expression of CD5, a T-cell associated antigen.
3. Low levels of surface membrane immunoglobulin (i.e., SmIg weak).single immunoglobulin light chain is expressed (i.e., either kappa or lambda but not both), confirming the clonal nature of these cells.

- *Due to progressive CLL & not autoimmune or other causes
- Rai staging correlates very well for treatment regardless of the genetics e.g. Rai 0 indicates good response to treatment (even if the pt has 17p deletion)

Chronic Lymphocytic Leukemia (CLL) *cont.*

◀ Complications

- Complications from early-stage CLL is rare
  - May develop as the disease advances
  - Pain, paralysis from enlarged lymph nodes causing pressure[1]

Immunodeficiency

- Due to ↓ Ig & abnl B/T cell fxn,
- infxn account for 50% death for CLL/SLL pts,

Autoimmune hemolytic anemia (AIHA)

labs
- ↓ Hgb,
- ↑ retic,
- ↓ hapto,
- +Coombs;

Treatment
- Steroids

Others

- **Leukostasis:** rare, even w/ extremely high WBC;
- **Secondary solid neoplasms**
- Gastrointestinal blood loss secondary to the use of corticosteroids
- Marrow suppression secondary to the use of alkylating agents or replacement by atypical lymphocytes.
- Hypersplenism

Pure red cell aplasia

Rare <1% pts; labs
- ↓ Hgb,
- ↓ retic

BM bx w/ absent red cell precursors; r/o parvovirus, CMV, EBV.

Treatment
- **Cyclosporine**

Transformation

- 5–10% pts, usu transforms to aggressive diffuse large B-cell lymphoma (Richter's), heralded by rapid ↑ LN, new B sx, or ↑↑ LDH,

◀ Treatment

- **CLL is incurable** (except by allo-SCT) → no evidence that treating early benefits OS
- **Indications for treatment:** Disease-related sx "active disease" = B-sx, rapid LAD, progressive cytopenias, or frequent repeated infections. Consider lymphocyte doubling <6 mos.
- **Observation: ~1/3 of CLL pts never require tx;** routine oncology visits w/ PE, CBC, **monitor for complications**; no survival benefit early tx

- **FCR:** Fludarabine, cyclophosphamide & rituximab—for young pts w/ good PS,). Can produce long-term remissions in pt w/ mutated IGHV, Cant be used in 17p del.
- **BR:** Bendamustine + **Rituximab**. Less toxicity than FCR & can be used w/ renal insufficiency, >65 y/o, but shorter PFS compared to FCR
- **Novel agents:** **(1st line therapy nowadays)**
  - **Kinase inhibitors:** ibrutinib (BTK) & idelalisib (PI3Kδ) + rituximab
  - **Pro-Apoptotic:** venetoclax (BCL-2 inhibitor)

Common side effects of the new agents used in CLL	**Kinase inhibitors**	**Ibrutinib (BTK)**: Atrial fibrillation, Bleeding (platelet dysfunction) and diarrhea
		Idelalisib (PI3Kδ): Colitis Pneumonitis
	Pro-Apoptotic	**Venetoclax (BCL-2 inhibitor):** Tumor lysis syndrome, Pancytopenia.

How does Rituximab work?
It's a chimeric monoclonal **antibody against the protein CD20**, which is primarily found on the surface of immune system B cells. When it binds to this protein it triggers cell death. Before starting Rituximab you have to **check HBV** because it may cause reactivation.

1- Keep in mind that CLL in advance stage may present with Huge lymph node, depending on its size it may cause pressure. ex: if near spinal cord Pt will present with paralysis. In the neck might cause pain. If it is para-aortic Lymphadenopathy → erosion of the aorta → Bleeding.

Other Leukemias

◀ Hairy Cell Leukemia

- 2% of all adult leukemias. Neoplastic proliferation of mature B cells characterized by hairy cytoplasmic processes.
- Usually in males > 40 years old
- Chronic disease of lymphoproliferation
  - **B lymphocytes that infiltrate the bone marrow and liver**
- **Cells have a "hairy" appearance** (Cells are usually positive for **TRAP**)
- Recently, all patients with hairy cell leukaemia have been found to have a mutation in the BRAF gene.

Symptoms from	Treatment
Splenomegaly (90%, due to red pulp enlargement), pancytopenia, infection (especially with atypical mycobacteria such as Mycobacterium avium–intracellulare), autoimmunity in form of vasculitis	alpha-interferon, pentostatin, **cladribine** (**Best initial,MCQ**)

◀ Unclassified Leukemias

- Subtype cannot be identified. very aggressive end up by bone transplant
- Malignant leukemic cells may have:
  - Lymphoid, myeloid, or mixed characteristics.
- Frequently these patients do not respond well to treatment (Poor prognosis).

◀ Differential Diagnosis of Leukemia

1. **Aplastic anemia** bc of pancytopenia
2. **Myelodysplastic syndromes** " Dysfunctional Bone marrow"
3. **Multiple myeloma** "abnormal plasma cells"
4. **Lymphomas** "lymphadenopathy"
5. **Severe megaloblastic anemia** "drop in vit B12"
6. **Leukemoid reaction** "Common with severe infection result in abnormal WBC formation"

◀ Case:

17 ys lady presented to th Er with CBC : WBCs 50,000 HGB 10 PLT 15000, Abnormal circulating blasts 30%

Diagnosis and Risk stratification

- **Peripheral blood morphology:**
  - Abnormal blasts
- **Peripheral blood flow cytometry:**
  - 30 % blasts with CD 33 , CD 34 +ve "to know whether it's ALL or AML"
- **BMBx** bone marrow biopsy **for:**
  - Morphology (myeloblasts)
  - Cytogenetics (t 8:22)
  - Flow cytometry (50% blasts express M antigens)
  - Molecular (FLT 3 –ITD +ve) "AML"

Treatment Goals:

1. Remission induction (chemo for 28 days)
2. Response assessment (D 28)
3. Consolidation (chemo / SCT) whether to proceed with chemo or SCT
4. Maintenance

Dr notes:

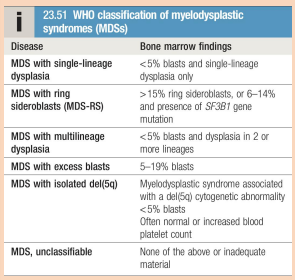
- History: to know if it's acute or chronic and manifestation: infection, Bleeding tendency and for how long.
- family history (genetic?)
- examination: lymphadenopathy, hepatosplenomegaly?
-Lab: CBC, peripheral blood morphology and flow cytometry morphology: myeloblast or lymphoblast.

Other related conditions

◀ Prolymphocytic leukemia

Definition	• Prolymphocytic leukaemia (PLL) is a **variant of chronic lymphocytic leukaemia** found mainly in males **over the age of 60 years**; 25% of cases are of the T-cell variety
Characteristics	• There is typically **massive splenomegaly** with little lymphadenopathy and a **very high leukocyte count**, often in excess of 400×10^9/L. • The characteristic cell is a **large lymphocyte with a prominent nucleolus**.
Treatment	• Treatment is **generally unsuccessful** and the **prognosis very poor**. • Leukapharesis, splenectomy and chemotherapy may be tried.

◀ Myelodysplastic syndromes (MDSs) ★

Definition	• Myelodysplastic syndromes (MDSs) constitute a group of clonal haematopoietic disorders with the common features of **ineffective blood cell production** and a **tendency to progress to AML**. • As such, they are pre-leukaemic and represent genetic steps in the development of leukaemia.
Characteristics 	• MDS presents with consequences of **bone marrow failure (anaemia, recurrent infections or bleeding),** usually in older people (median age at diagnosis is 73 years). • The blood film is characterised by **cytopenias** and **abnormal-looking (dysplastic) blood cells,** including macrocytic red cells and hypogranular neutrophils with nuclear hyper- or hyposegmentation • The **bone marrow is hypercellular**, **with dysplastic changes** in at least 10% of cells of **one or more cell lines**. • **Blast cells** may be increased **but do not reach the 20%** level that indicates acute leukaemia.
Prognosis	• The natural history of MDS is progressive worsening of dysplasia leading to fatal bone marrow failure or **progression to AML in 30% of cases.**
Treatment	• For the vast majority of patients who are elderly, the disease is incurable, and supportive care with red cell and platelet transfusions is the mainstay of treatment

i 23.51 WHO classification of myelodysplastic syndromes (MDSs)

Disease	Bone marrow findings
MDS with single-lineage dysplasia	<5% blasts and single-lineage dysplasia only
MDS with ring sideroblasts (MDS-RS)	>15% ring sideroblasts, or 6–14% and presence of *SF3B1* gene mutation
MDS with multilineage dysplasia	<5% blasts and dysplasia in 2 or more lineages
MDS with excess blasts	5–19% blasts
MDS with isolated del(5q)	Myelodysplastic syndrome associated with a del(5q) cytogenetic abnormality <5% blasts Often normal or increased blood platelet count
MDS, unclassifiable	None of the above or inadequate material

Congratulations you have officially finished medicine, take a few seconds and enjoy this moment because you deserve it!

Summary

◄ 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.

Summary

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

Lecture Quiz

Dr Question :
a patient presented with splenomegaly and can't finish a meal, upon further investigation a translocation on 9;22 was found, what's the dx?
Answer: CML

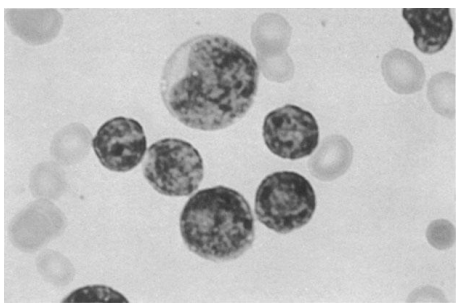
Q1: A 5-year-old girl presents with her parents who have become concerned about the small petechiae and ecchymoses on her skin. An abdominal examination reveals hepatosplenomegaly. You suspect an acute leukaemia. The most appropriate initial investigation for diagnosis is:
A. Chromosomal analysis of bone marrow cells
B. Cytochemical analysis of bone marrow cells
C. Direct microscopy of bone marrow cells
D. Electron microscopy
E. Flow cytometry

Q2: A 65-year-old man presents to you reporting he has become increasingly worried about his lack of energy in the last 2 weeks. He mentions he has been increasingly tired, sleeping for long periods and has suffered from fevers unresponsive to paracetamol. He became increasingly worried when he noticed bleeding originating from his gums. A blood film shows auer rods, hypogranular neutrophils and stains with Sudan black B. The most likely diagnosis is:
A. Acute lymphoblastic leukaemia
B. DiGeorge syndrome
C. Disseminated intravascular coagulation
D. Acute myeloid leukaemia
E. Afibrinogenaemia

Q3: A 70-year-old woman complains of tiredness, fatigue and weight loss. Blood tests reveal an elevated WBC and on examination splenomegaly is palpated. Cytogenetics are positive for the Philadelphia chromosome and the patient is diagnosed with chronic myeloid leukaemia. The most appropriate treatment is:
A. Hydroxycarbamide
B. Imatinib
C. Venesection
D. Stem cell transplant
E. Dasatinib

Q4: 75-year-old male presented with fatigue and exertional shortness of breath. On examination, he was pale, CBC showed low hemoglobin, MCV: 102, WBC: 2.9, neutrophil: 0.96, platelets: 65, bone marrow show hypercellularity (50%) blast 8% + trilineage dysplasia + abnormal karyotype. What's the diagnosis?
A- MDS
B- Aplastic anemia
C- Acute leukemia
D- B12 vitamin deficiency

Q5: A 60-year-old asymptomatic man is found to have leukocytosis on a preoperative CBC. Physical examination shows the spleen tip to be palpable 2 cm below the left costal margin. Rubbery, nontender lymph nodes up to1.5 cm in size are present in the axillae and inguinal regions. Laboratory data include the following:
Hgb: 13.3 g/dL (normal 14 to 18)
Leukocytes: 40,000/µL (normal 4300 to 10,800)
Platelet count: 238,000 (normal 150,000 to 400,000)
His peripheral blood smear is shown in the accompanying photo.
A. Acute monocytic leukemia
B. Chronic myelogenous leukemia
C. Chronic lymphocytic leukemia
D. Tuberculosis
E. Infectious mononucleosis



Answers: Q1:C | Q2:D | Q3:B | Q4:A | Q5:C

Answers Explanation File!

With our last lecture for the year we want to thank 438 medicine team for helping us with giving you the best work possible.

We would also like to thank all the amazing members for giving their time and effort to bring to you this incredible work

- Abdulaziz Alghuligah
- Abdulaziz Alrabiah
- Abdullah Alanzan
- Abdulrahman Almebki
- Abdurahman Addweesh
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- Sadem Al Zayed
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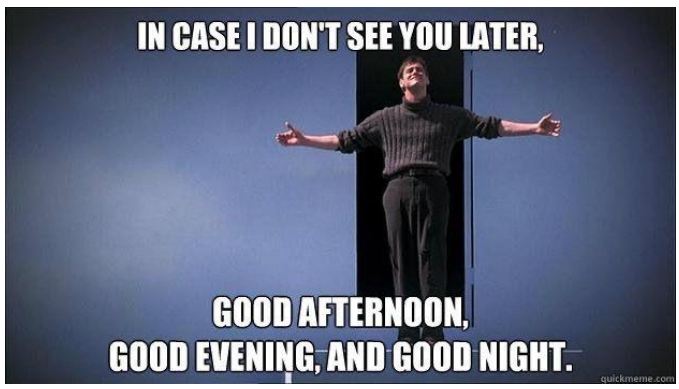
- Sarah AlQuwayz
- Shatha Aldhohair
- Shaden Alsaiedan
- Tarfa Alsharidi
- Yara Alasmari

To the amazing academic leaders who didn't hesitate to help us whenever we needed

thank you will never be enough

- **Muneerah Alsadhan**
- **Mishal Althunayan**



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لا تنسونا من دعواتكم

GOOD LUCK !

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