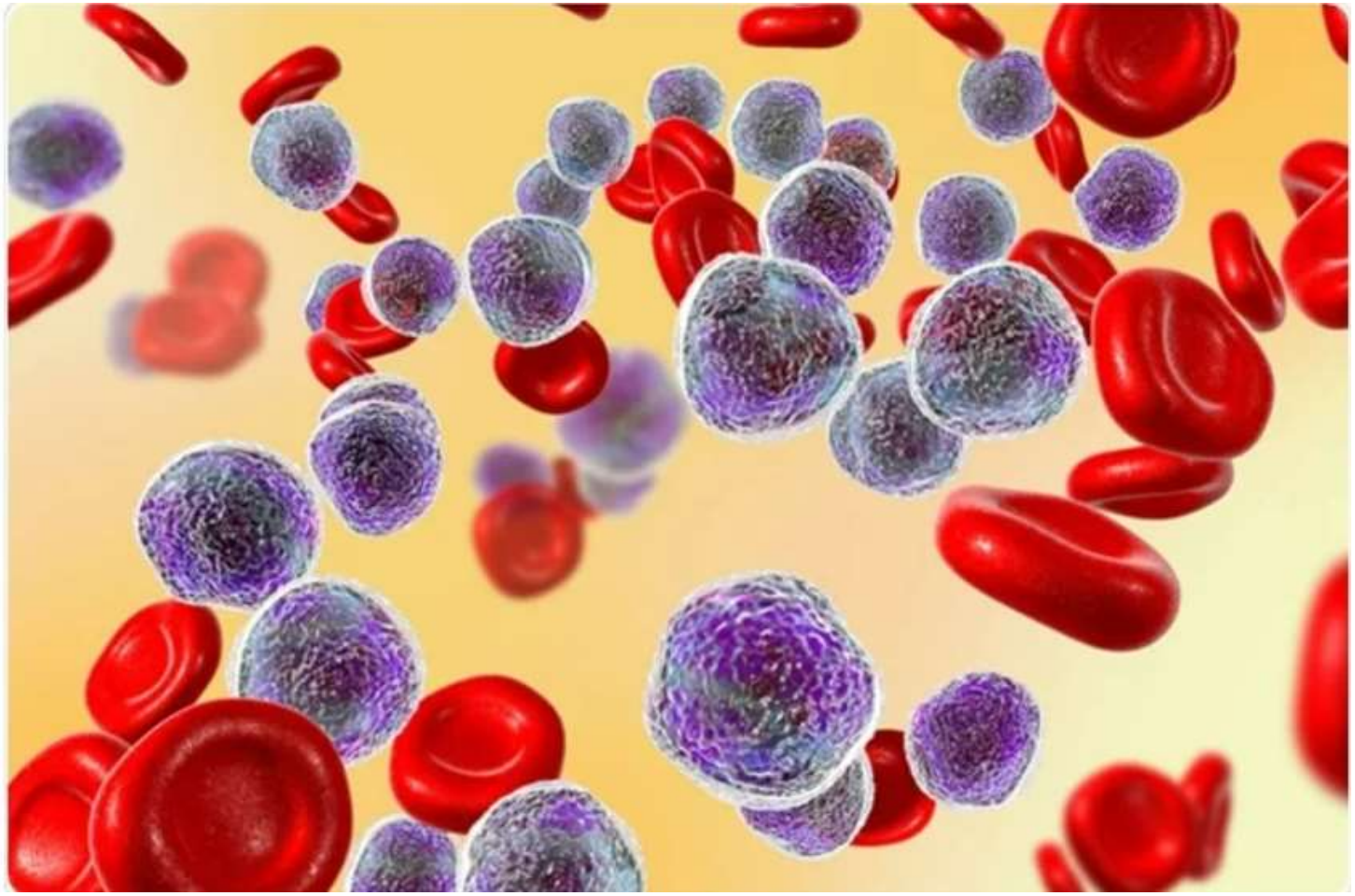
Acute Lymphoblastic Leukemia



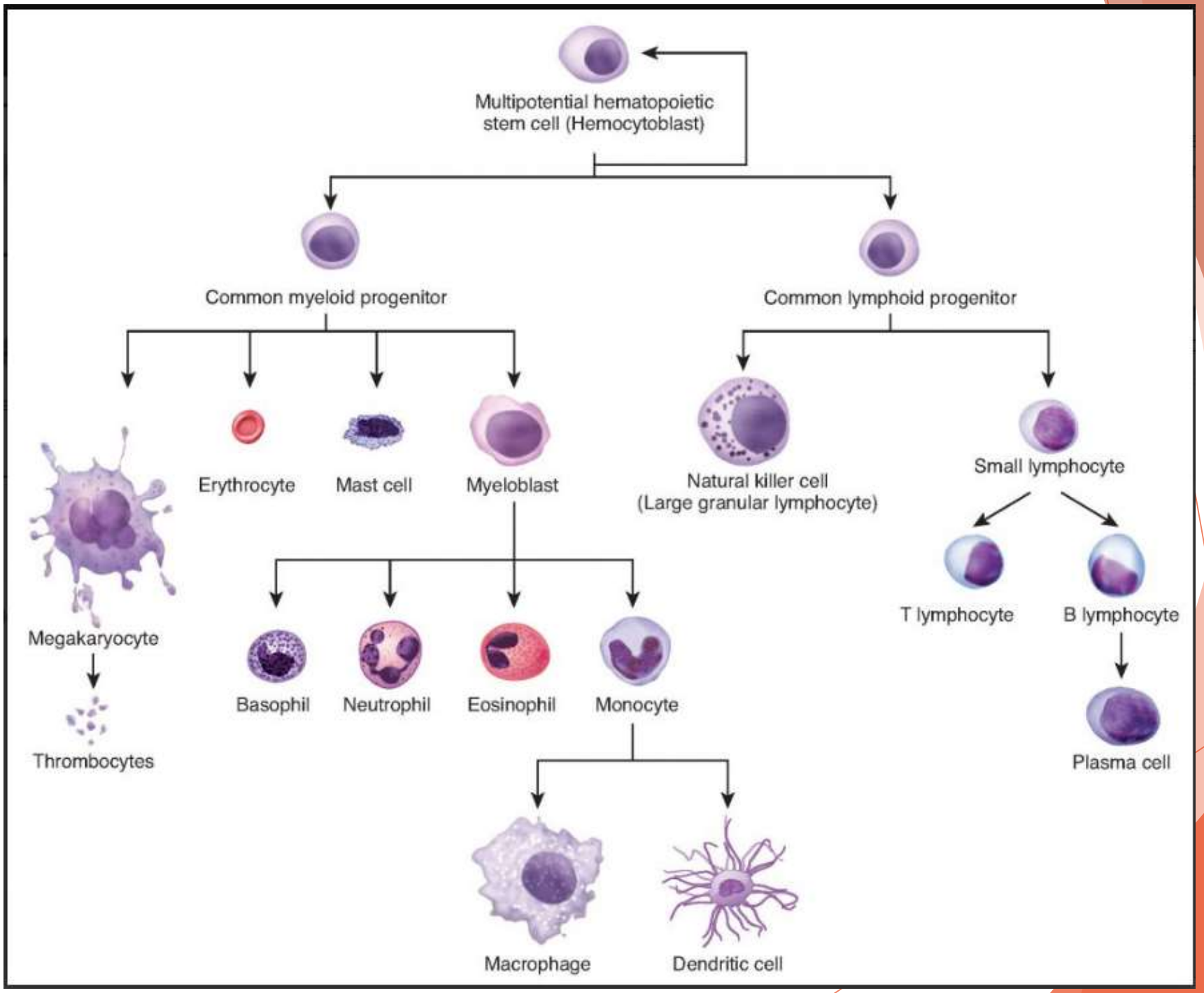
Dr. Ala’a Al-ma’aiteh

Assistant professor/ pediatric department/Faculty of medicine/ Hashemite university

introduction

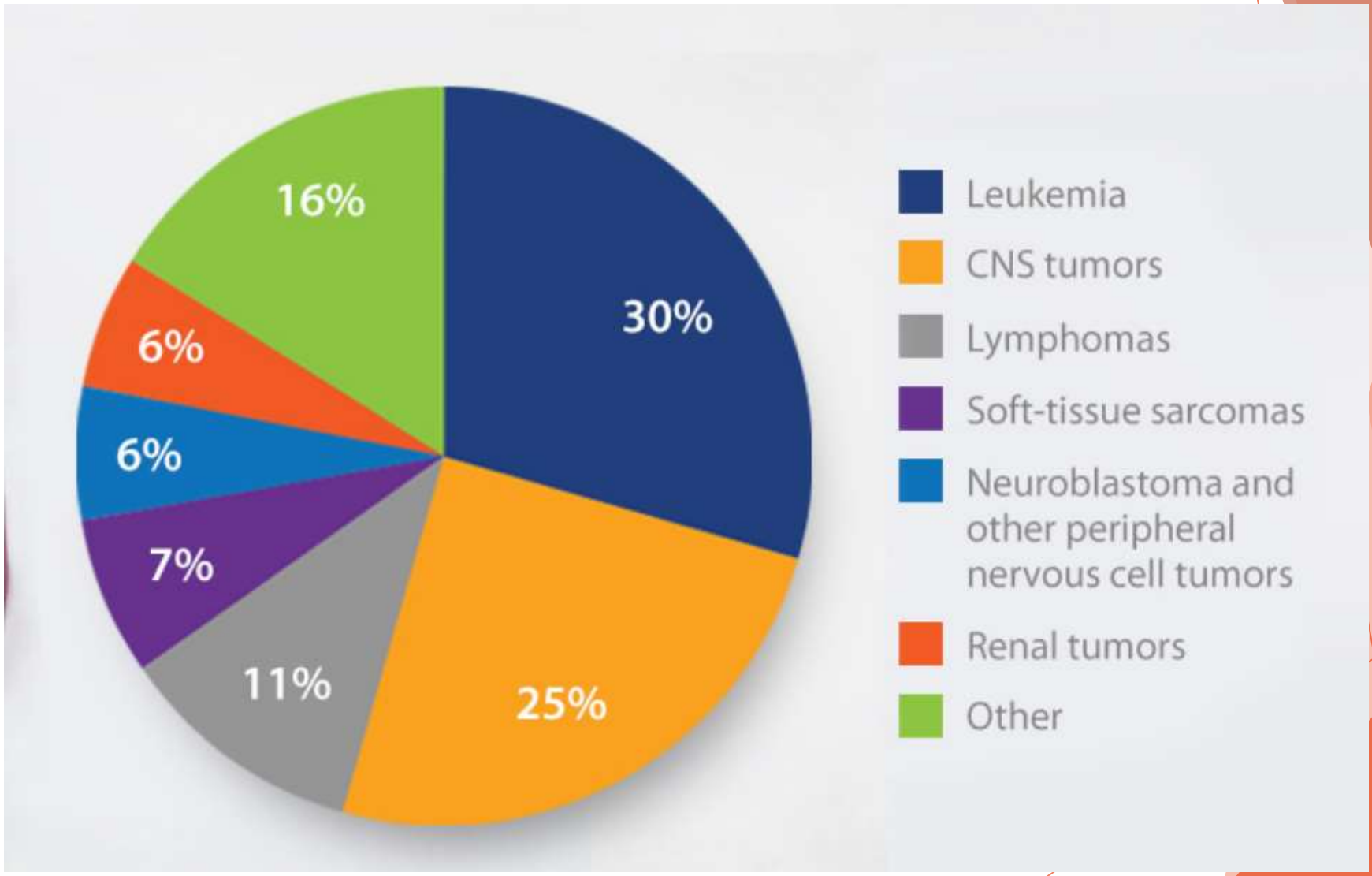
- cancer of blood cells in which neoplastic cells morphologically and immunophenotypically resemble B-lineage or T-lineage precursor cells (lymphoblasts)

- Leukemia refers to a disease arising in the bone marrow (medullary disease).


Multipotential hematopoietic stem cell (Hemocytoblast)
Common myeloid progenitor
Common lymphoid progenitor
Erythrocyte
Mast cell
Myeloblast
Natural killer cell (Large granular lymphocyte)
Small lymphocyte
Megakaryocyte
Thrombocytes
Basophil
Neutrophil
Eosinophil
Monocyte
T lymphocyte
B lymphocyte
Plasma cell
Macrophage
Dendritic cell

- ALL is the most common cancer in children, with a peak incidence at age 2-5 years.

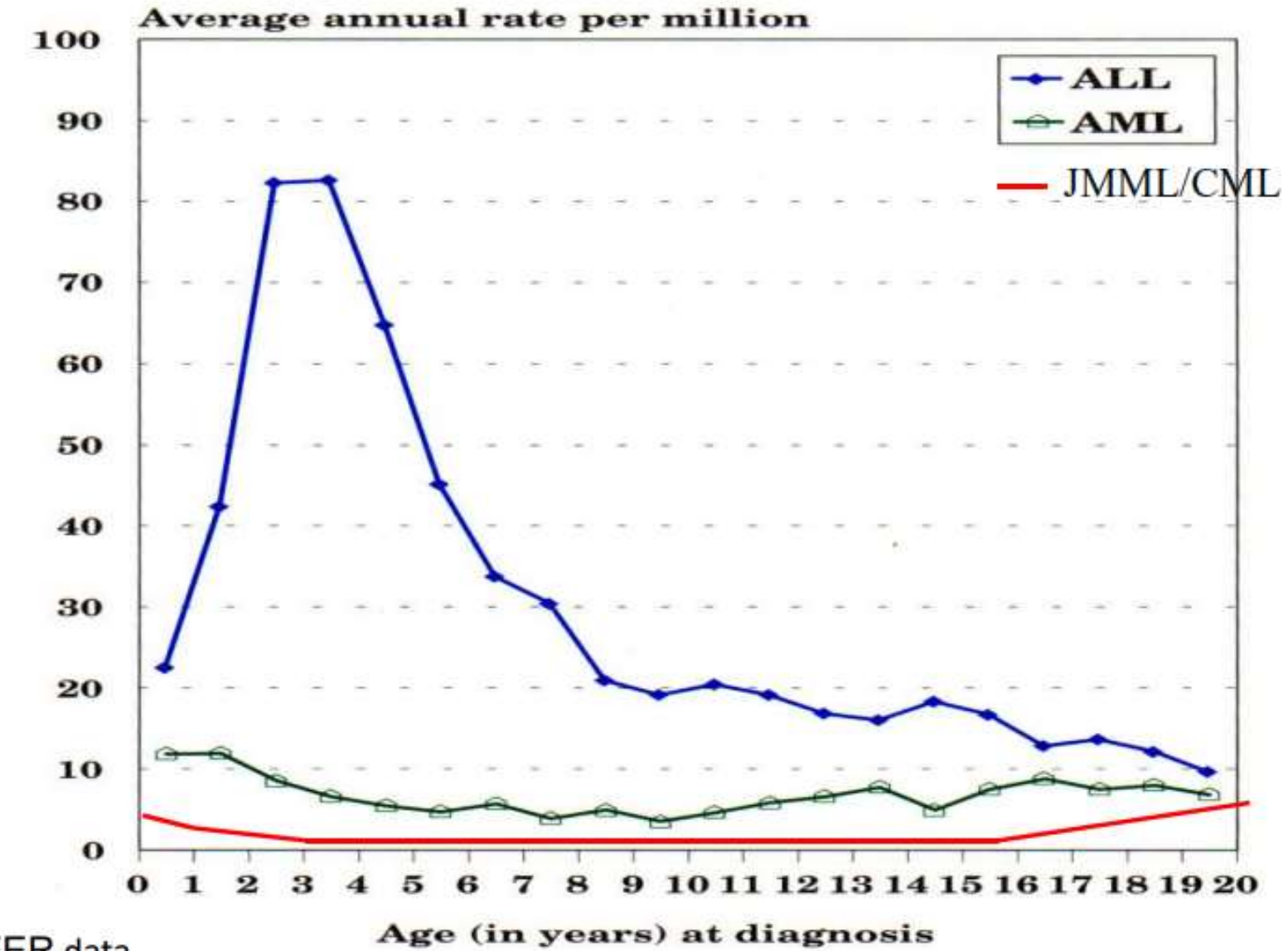
- ALL is classified by immunophenotype.
  - 80%-85% of childhood ALL is B-cell ALL.
  - About 15% of childhood ALL is T-cell ALL.


16%
30%
6%
6%
7%
11%
25%
Leukemia
CNS tumors
Lymphomas
Soft-tissue sarcomas
Neuroblastoma and other peripheral nervous cell tumors
Renal tumors
Other

Incidence/Prevalence

- 41 per million children aged < 15 years in United States
- 17 per million adolescents aged 15-19 years

Age Specific Incidence of Leukemia



SEER data

etiology

- Multifactorial
- Risk Factors:
  - Radiation:
    - prenatal x-ray exposure
    - (CT) scan during childhood or adolescence associated with increased risk of leukemia or lymphoma

Risk Factors

- previous treatment with chemotherapy
- inherited and familial risk factors
  - genetic syndromes with predisposition to ALL (Bloom syndrome, ataxia-telangiectasia, neurofibromatosis type 1, Fanconi anemia, Li-Fraumeni syndrome)
- exposure to solvents or pesticides

Pathogenesis

- preleukemic cells acquire multiple genetic alterations:
  - disrupting genes that regulate hematopoiesis and lymphoid development (such as RUNX1 and ETV6)
  - constitutively activating tyrosine kinases (such as ABL1 mutations)
  - activating oncogenes

- effects of leukemic transformation may include
  - arrested differentiation of lymphoblasts into B and T lymphocytes
  - increased cell proliferation
  - decreased apoptosis
- replacement of bone marrow by ALL blasts
  - anemia,
  - thrombocytopenia,
  - neutropenia,
  - high to very high white blood cell count (> 100 x 109 cells/L)

Immunophenotype and Cytogenetics

- For diagnosis and prognosis
- Immune phenotype is defined by expression of cytoplasmic cluster differentiation (CD) markers
- precursor B-cell ALL (B-cell ALL) - defined by expression of cytoplasmic CD79a, CD19, HLA-DR
  - Example: common precursor B-cell ALL - about 75% of B-cell ALL characterized by :
    - CD10 expression and lack of surface or cytoplasmic immunoglobulin expression
    - frequently associated with favorable cytogenetics
    - best prognosis of any ALL subtype

types of common genetic alterations in ALL

- high hyperdiploidy (51-65 chromosomes/cell or DNA index > 1.16)
- hypodiploidy (≤ 44 chromosomes/cell)
- Translocations
  - *ETV6-RUNX1* t(12;21) (p13.2;q22.1) cryptic translocation)
  - *BCR-ABL1* t(9;22)(q34.1;q11.2) translocation) also called Philadelphia chromosome
  - *MLL* (KMT2A) rearranged t(v;11q23) translocation
- Deletions
  - *PAX5* deletion

Clinical Presentation

- symptoms usually develop over days to weeks, less commonly over several months

- presenting symptoms and signs correlate with leukemic cell burden and extent of marrow infiltration (and resulting cytopenias)

symptoms

- fever due to leukemia or neutropenia-related infection
- fatigue, lethargy, or pallor due to anemia
- bleeding, petechiae, or bruising due to thrombocytopenia
- bone or joint pain, limp
- splenomegaly, hepatosplenomegaly
- lymphadenopathy

oncologic emergencies at presentation

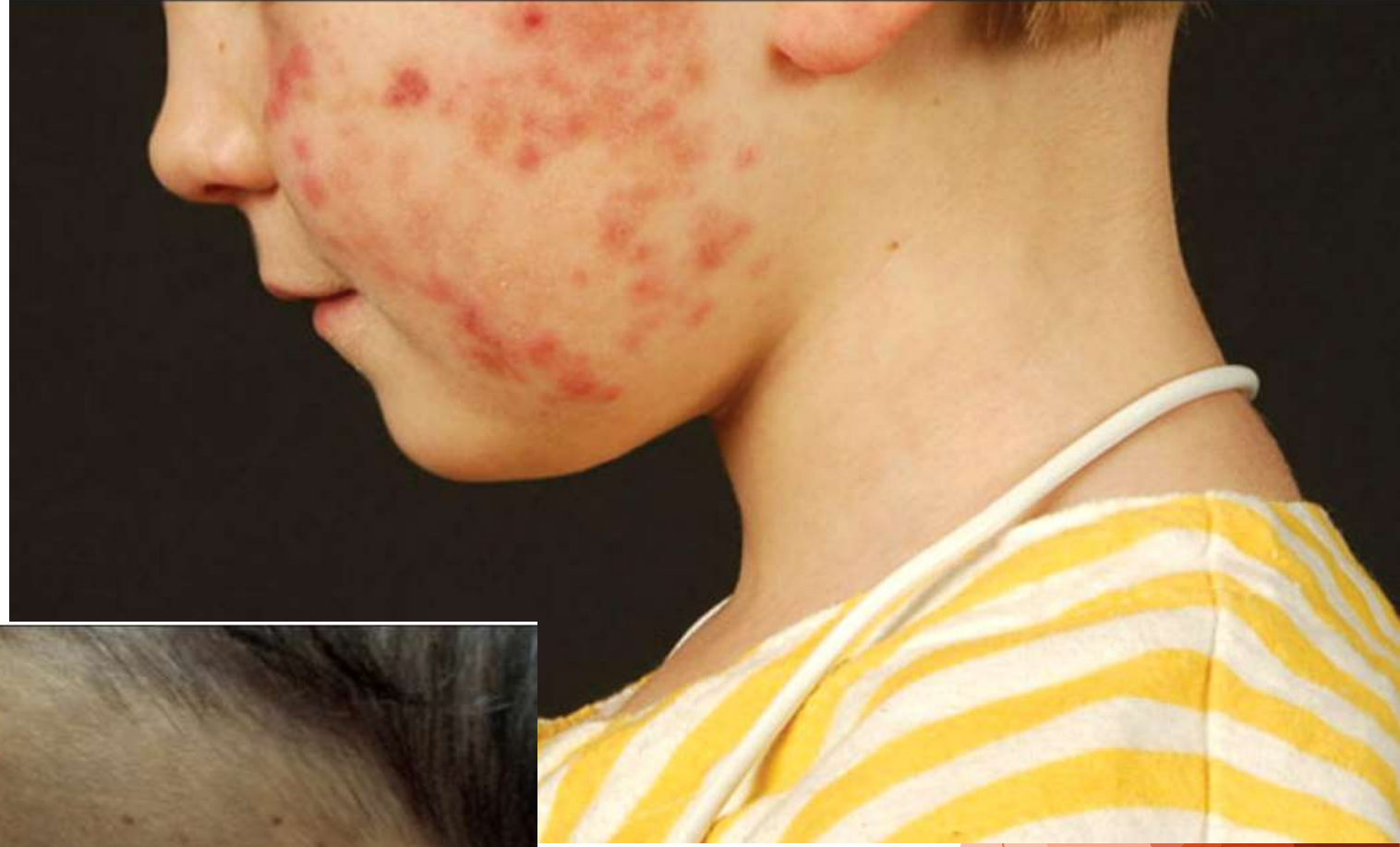
1. tumor lysis syndrome
2. febrile neutropenia
3. leukostasis (due to hyperleukocytosis [white blood cell count > 100,000/mm3]), which may present with hypoxia, dyspnea, headache, somnolence, confusion, or blurred vision
4. severe thrombocytopenia or anemia
5. mediastinal mass compressing trachea or superior vena cava and causing respiratory distress or superior vena cava syndrome (more common in T-cell ALL)

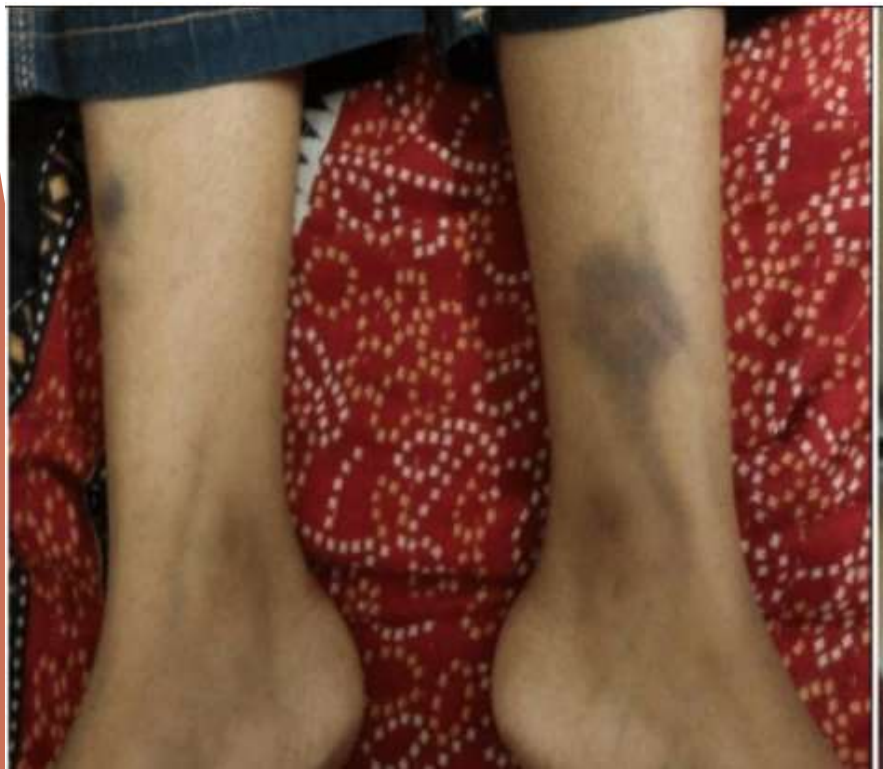
History

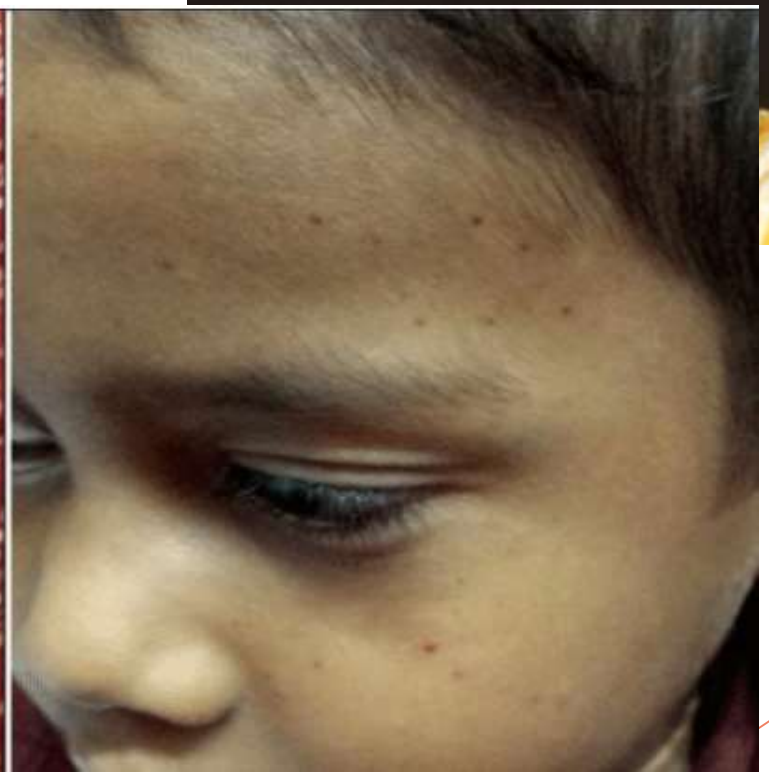
- Past Medical History
  - cancer predisposition syndromes
  - radiation exposure
  - chemotherapy
- Family history of leukemia

Physical exam

- General:
  - Fever
  - Lymphadenopathy
  - Pallor
  - Headache
  - respiratory distress
- Skin
  - petechiae, purpura, or ecchymoses suggestive of bleeding diathesis
  - leukemic skin lesions (leukemia cutis)







- HEENT
  - orbital or tonsillar infiltration
  - visual problems
  - cranial nerve palsy may indicate CNS leukemia
- Chest
  - Respiratory distress more common with T-cell ALL
  - Assess for effusion and mediastinal mass

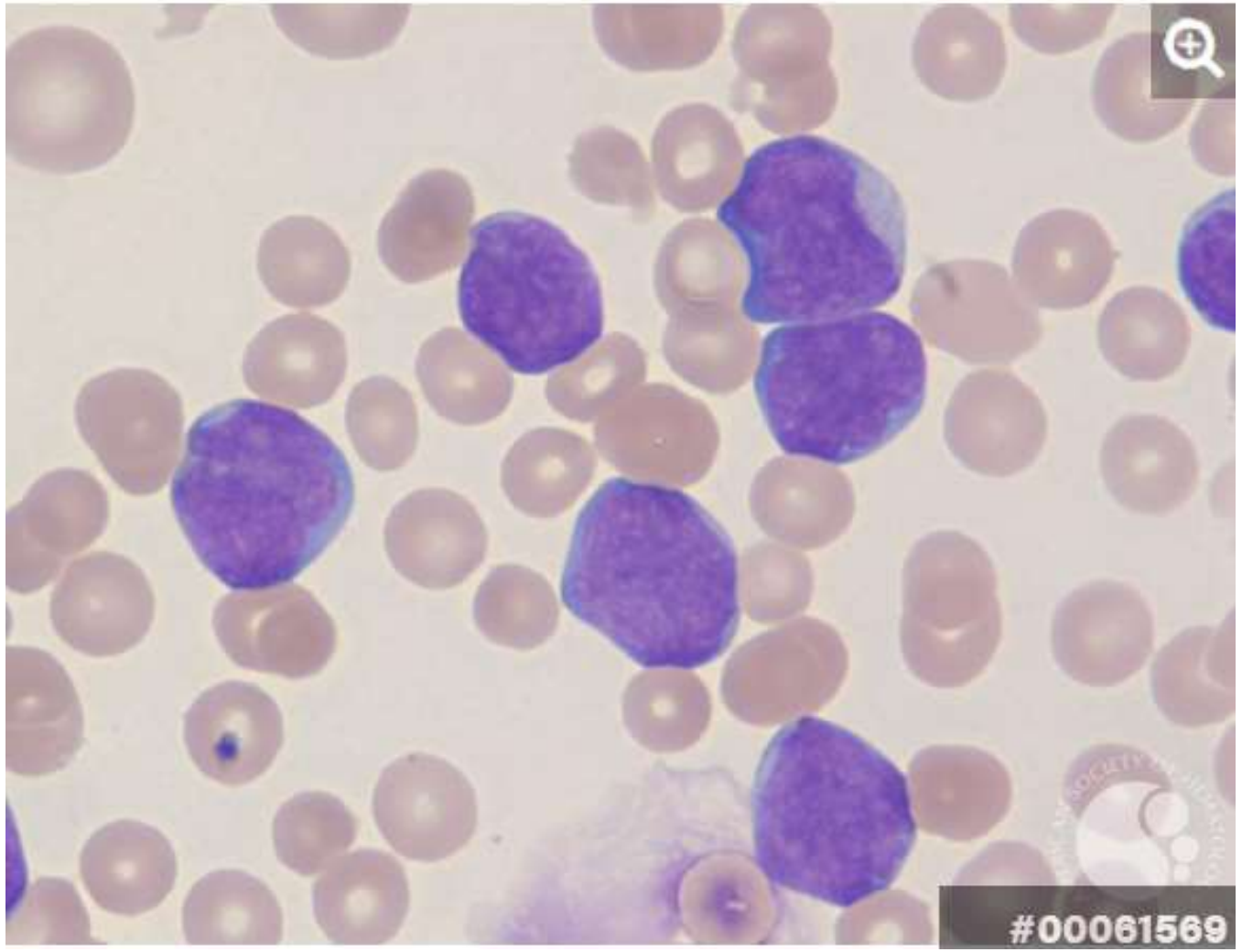
- Abdomen
  - splenomegaly and hepatomegaly
  - lesions suggestive of testicular infiltration
  - testicular swelling

diagnosis

- Typical signs or symptoms of ALL
- cytopenias, leukocytosis, and/or leukemia blast cells detected on blood smear
- bone marrow aspirate and biopsy and confirm diagnosis
  - morphologic identification of lymphoblasts on microscopy
  - flow cytometry to determine immunophenotype

- complete blood count with differential
- serum chemistry profile:
  - tumor lysis syndrome (TLS) panel including lactate dehydrogenase (LDH), uric acid, potassium, calcium, and phosphorous
  - liver function tests, kidney function tests
  - disseminated intravascular coagulation (DIC) panel including d-dimer, fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT)
- lumbar puncture concurrent with intrathecal chemotherapy

- chest x-ray to rule out mediastinal mass
- scrotal ultrasound if suspected testicular involvement
- CT/MRI of head with contrast if neurologic symptoms


#00061569

Differential Diagnosis

- systemic lupus erythematosus or other rheumatological disorders
- viral infections such as Epstein-Barr virus (EBV) infection and parvovirus infection may cause hematologic abnormalities similar to acute leukemia[3]
- systemic-onset juvenile idiopathic arthritis

- benign proliferation - normal precursor B-cells (hematogones) in bone marrow may increase with viral infection, chemotherapy, or bone marrow transplant (leukemoid reaction)

- other blastic hematopoietic neoplasms
  - acute myeloid leukemia (AML)

Management

- risk stratification
  - patient characteristics, leukemic cell characteristics (immunophenotype, cytogenetics), and response to initial treatment are used to predict risk of treatment failure
  - Treatment according to risk-group-specific protocols that may include more intensive therapy and/or increased supportive measures

prognostic factors in ALL include

- unfavorable prognosis
  - Age<1year and >10 years
  - white blood cell (WBC)> 50000
  - CNS or testicular involvement
  - T-cell
  - hypodiploidy (≤ 44 chromosomes per cell)
  - Philadelphia chromosome (*BCR-ABL1* fusion or Ph+ or t(9;22)(q34;q11.2)
  - *MLL* (*KMT2A*) rearrangement (t(v;11q23.3))
  - intrachromosomal amplification of chromosome 21 (iAMP21)
  - high minimal residual disease (MRD) (≥ 0.01%) following induction therapy
  - Down syndrome
  - obesity
  - black race and Hispanic ethnicity
  - male gender

Favorable prognostic factors

- Age: 1 to < 10 years
- Girls
- B-cell ALL
- No CNS or testicular involvment
- high hyperdiploidy (51-65 chromosomes/cell or DNA index > 1.16)
- *ETV6-RUNX1* (t(12;21)(p13.2;q22.1) cryptic translocation)
- *ERG* deletion
- Response to treatment

management of newly diagnosed ALL

- chemotherapy is mainstay of treatment
- treatment regimens consist of 4 major components
  1. induction therapy (also called remission induction)
  2. consolidation therapy (also called intensification)
  3. central nervous system (CNS)-directed therapy
  4. Maintenance
- HSCT is generally reserved for children with induction failure or very high risk for relapse

remission induction

- goal is to achieve complete remission (no clinical or molecular evidence of disease)
- 4-6 weeks
- 3- or 4-drug regimen consisting of vincristine, L-asparaginase, and a corticosteroid, with or without an anthracycline
- if remission not achieved, additional chemotherapy is given and, if complete remission is subsequently achieved, hematopoietic stem cell transplant (HSCT) may be indicated
- if remission achieved treatment continues to consolidation phase

consolidation therapy

- begins after complete remission is achieved
- regimens generally lasts 6-9 months
- combination of cyclophosphamide, cytarabine, mercaptopurine, methotrexate, corticosteroids, vincristine, and intrathecal chemotherapy
- high risk of treatment-related adverse effects

CNS-directed therapy

- indicated in all children
- starts during induction, and may continue through maintenance
- intrathecal chemotherapy (methotrexate alone, or triple therapy with methotrexate, cytarabine, and hydrocortisone)
- CNS-directed systemic chemotherapy (dexamethasone, L-asparaginase, and methotrexate) are standard in all children.
- cranial radiation is used infrequently and is generally reserved for children with highest risk of CNS relapse

Maintenance

- continues until ALL has been in complete remission for 2-3 years
- mercaptopurine orally daily, methotrexate orally or parenterally weekly along with pulses of vincristine and a corticosteroid (prednisone or dexamethasone)

complications

- **Oncologic Emergencies**
  - **tumor lysis syndrome** - usually occurs in response to therapy, but can occur spontaneously in children with high presenting white blood cell (WBC) count[3]
  - Leukostasis (WBC > 100,000/mm^3)
  - febrile neutropenia
  - severe thrombocytopenia or anemia
  - mediastinal mass (common in T-cell ALL), tracheal compression or superior vena cava syndrome[3]

Early Complications

- toxicities of chemotherapeutic agents
- cytopenias and infection
- osteonecrosis
- DVT
- Pancreatitis
- peripheral neuropathy
- depression[4]

Late Complications

- complications common after cranial radiation:
  - neurocognitive deficits
  - neuroendocrine abnormalities such as growth hormone deficiency and precocious puberty
  - obesity and metabolic syndrome

complications related to management

- hypercoagulopathy/stroke - asparaginase
- peripheral neuropathy - vincristine
- osteonecrosis and bone mineral density deficits - long-term corticosteroid exposure, asparaginase
- cardiotoxicity – anthracyclines
- secondary malignant neoplasms - chemotherapy (such as anthracyclines, oxazaphosphorines, and epipodophyllotoxins), radiation
- infertility - alkylating agents (such as cyclophosphamide), radiation

Prognosis

- overall prognosis in newly diagnosed childhood ALL[1]
  - remission achieved in about 98%
  - reported survival in children and adolescents aged 1-18 years
    - 5-year survival > 90%
    - long-term event-free survival about 85%
  - complications due to cancer treatment may persist or develop months to years after therapy

- Thank you