LEUKEMIA
INTRODUCTION

- Leukemias are the most common cancers affecting children.

- Acute lymphoblastic leukemia (ALL) accounts for 73%, acute myeloid leukemia (AML) accounts for approximately 18%.

- Chronic myeloid leukemia (CML) is rarely seen, accounting for less than 4%.
EPIDEMIOLOGY

- ALL: 3–4 cases per 100,000 white children
- Peak incidence between 2 and 5 years of age
- Accounts for 25–30% of all childhood cancers
- In ALL, boys are more commonly affected than girls
- The incidence of AML is similar for all paediatric age groups
INCREASED RISK WITH

- Ionizing radiation
- Chemicals (e.g., benzene in AML)
- Drugs (e.g., use of alkylating agents either alone or in combination with radiation therapy increases the risk of AML)
- Trisomy 21 (Down syndrome)
- Bloom syndrome
- Fanconi anaemia
INCREASED RISK WITH:

- Congenital agammaglobulinemia
- Poland syndrome
- Shwachman–Diamond syndrome
- Ataxia telangiectasia
- Li–Fraumeni syndrome
- Neurofibromatosis
- Diamond–Blackfan anaemia
- Kostmann disease
- Bloom syndrome
- Acute leukemia is characterized by clonal expansion of immature hematopoietic or lymphoid precursors.

- Chronic leukemia refers to conditions characterized by the expansion of mature marrow elements.
CLINICAL MANIFESTATIONS

- General Systemic Effects
  1. Fever (60%).
  2. Lassitude (50%).
  3. Pallor (40%).

- Hematologic Effects Arising from Bone Marrow Invasion
  2. Neutropenia – causing fever, ulceration of buccal mucosa and infection.
3. Thrombocytopenia – causing petechial, purpura, easy bruising, bleeding from mucous membrane and sometimes internal bleeding (e.g., intracranial haemorrhage).

Clinical Manifestations Arising from Lymphoid System Infiltration

1. Lymphadenopathy
2. Splenomegaly.
3. Hepatomegaly.
CLINICAL FEATURES

Clinical Manifestations of Extramedullary Invasion

- CNS- ICT symptoms, seizures
- Genitourinary-painless testicular swelling
- Bone joints- bone pain
- Skin-bleeds
- Git- bleeds
CLASSIFICATION

- Light microscopy – morphology L1, L2, L3
- Cytochemistry – staining - MPO, ESTERASE
- Immunophenotyping – cd numbering
- Cytogenetics - chromosome/gene rearrangement
<table>
<thead>
<tr>
<th>Cytologic Features</th>
<th>L1</th>
<th>L2</th>
<th>L3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell size</td>
<td>Small cells predominate</td>
<td>Large, heterogeneous in size</td>
<td>Large and heterogeneous</td>
</tr>
<tr>
<td>Nuclear chromatin</td>
<td>Homogeneous</td>
<td>Variable, heterogeneous</td>
<td>Finely stippled and homogeneous</td>
</tr>
<tr>
<td>Nuclear shape</td>
<td>Regular, occasional clefting or indentation</td>
<td>Irregular, clefting and indentation common</td>
<td>Regular, oval to round</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>Not visible, or small and inconspicuous</td>
<td>One or more present, often large</td>
<td>Prominent, one or more vesicular</td>
</tr>
<tr>
<td>Amount of cytoplasm</td>
<td>Scanty</td>
<td>Variable, often moderately abundant</td>
<td>Moderately abundant</td>
</tr>
<tr>
<td>Basophilia of cytoplasm</td>
<td>Slight or moderate, rarely intense</td>
<td>Variable, deep in some</td>
<td>Very deep</td>
</tr>
<tr>
<td>Cytoplasmic vacuolation</td>
<td>Variable</td>
<td>Variable</td>
<td>Often prominent</td>
</tr>
</tbody>
</table>
FAB types of acute lymphoblastic leukemia (ALL). (A) L1 morphology with uniform-sized blasts. (B) L2 ALL with more blast cell variation. (C) L3 blasts with more clumped nuclear chromatin, nucleoli, basophilic cytoplasm, and cytoplasmic vacuoles.
CYTOCHEMISTRY

- Myleoperoxidase and esterase can be positive in AML.

- Generally, when morphologic classification is difficult, these histochemical tests are of little help.
IMMUNOPHENOTYPING

- B-ALLs are arrested at various stages of pre-B cell development. The lymphoblasts usually express the pan B-cell marker CD19 as well as CD10.

- Similarly, T-ALLs are arrested at various stages of pre-T cell development. In most cases the cells are positive for CD2, CD5, and CD7.
CYTOGENETICS

- Tel–AML1 fusion gene t(12;21) (p13q22-excellent prognosis

- BCR–ABL fusion gene t(9;22) (q34q11).-poor prognosis

- MLL gene rearrangement-poor prognosis
INVESTIGATION AND TREATMENT

- Blood count
- Haemoglobin: Moderate to marked reduction
- White blood cell count: Low, normal, or increased
- Thrombocytopenia: 92% of patients have platelet counts below normal
- Blood smear: Blasts are present on blood smear. Very few to none (in patients with leukopenia).
BONE MARROW

- Leukemia must be suspected when the bone marrow contains more than 5% blasts.
- The hallmark of the diagnosis of acute leukemia is the blast cell, are relatively undifferentiated cell with diffusely distributed nuclear chromatin, one or more nucleoli and basophilic cytoplasm.
A, Acute lymphoblastic leukemia with CD 22,19,10 positivity
INVESTIGATIONS

- Chest radiograph: Mediastinal mass in T-cell leukemia.
- Blood chemistry: Electrolytes, blood urea, uric acid, liver function tests, Immuno globulin levels.
- Cerebrospinal fluid: Chemistry and cells. Cerebrospinal fluid findings for the diagnosis of CNS leukemia require: Presence of more than 5 WBCs/mm3.
CNS LEUKEMIA

- CNS involvement in leukemia is classified as follows:
  - CNS1, ≤5 WBCs/mm³, no blasts on cytocentrifuge slide
  - CNS2, 5-10 WBCs/mm³, blasts on cytocentrifuge slide
  - CNS3, >10 WBCs/mm³, blasts on cytocentrifuge slide
INVESTIGATION

- Coagulation profile: Decreased coagulation factors that frequently occur with AML are: hypofibrinogenemia, factors V, IX and X.
TREATMENT

- In general, treatment regimens for children with newly diagnosed ALL include three phases: remission induction, consolidation (or intensification), and continuation (or maintenance).

- Protocol adopted depends on the institution

- Modified BFM or COG protocol is often the choice
INDUCTION

- Prednisolone 60 mg/m²/day
- Inj. VCR 1.5 mg²/day
- Inj DNR 30 mg/m²
- L ASPARGINASE 10000u/m²
- MTX I/T
INTENSIFICATION & CNS PROPHYLAXIS

- Inj CYCLOPHOSPHAMIDE 1gm/m2
- Inj CYTARABINE 75mg/m2/day
- 6 MP 60 mg/m2/d
- I/T MTX
- CRANIAL IRRADIATION
MAINTENANCE

- Inj. VCR 1.5 mg/m2 one in a month
- Tab PREDNISOLONE 60 mg/m2 for one wk
- T.6MP 50 mg/m2 p.o daily
- T.MTX 20 mg/m2 p.o wkly

The optimal duration of therapy remains unknown. Most investigators continue to treat patients for 2 to 3 years, based on results of older studies.
SUPPORTIVE CARE

- A total of 10 mg/kg/day of allopurinol in divided doses is given in all cases before the commencement of antileukemic drugs.

- When the blast cell count is more than 50,000/mm3 or there are large tumour masses, allopurinol is obligatory, together with a fluid intake of 2–3 L/m2/day.
SUPPORTIVE TREATMENT

- Supportive care including the use of packed red cells
- When high fever and possible septicemia occur in the presence of neutropenia, antibiotic therapy should be started after taking appropriate blood cultures and a chest radiograph. (NEUTROPENIA REGIME)
- Platelet transfusions should be administered to patients with overt bleeding or when the platelet count is below 10,000/mm³.
REMISSION

- Minimal Residual Disease and its Implication in the Management of Leukemia
- MRD detection are now used as prognostic markers after induction.
- Patients with .0.01% leukemic cells after the end of induction have a worse prognosis and may require more intensive therapy.
## Risk Stratification

<table>
<thead>
<tr>
<th>Factor</th>
<th>Favourable</th>
<th>Intermediate</th>
<th>Unfavourable</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>1–9</td>
<td>&gt;/=10</td>
<td>&lt;1 and MLL1</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>&lt;50</td>
<td>&gt;50</td>
<td></td>
</tr>
<tr>
<td>count 10⁹/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>Precursor B cell</td>
<td>T cell</td>
<td></td>
</tr>
<tr>
<td>Genetics</td>
<td>Hyperdiploidy .50 chromosomes orDNA index .1.16 , Trisomies 4, 10 and 17 , t(12;21)/ETV6-CBFA2</td>
<td>Diploid, t(1;19)/TCF3-PBX</td>
<td>t(9;22)/BCR-ABL1, t(4;11)/MLL-AF4, Hypodiploid , 44 chromosomes</td>
</tr>
<tr>
<td>CNS status</td>
<td>CNS1</td>
<td>CNS2</td>
<td>CNS3</td>
</tr>
<tr>
<td>MRD (end of induction)</td>
<td>&lt;0.01%</td>
<td>0.01% to 0.99%</td>
<td>&gt;or=1%</td>
</tr>
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</table>
ITP- 

ITP is the most common cause of the acute onset of petechial and purpura in children. Patients with ITP usually present with isolated thrombocytopenia, well child with no lymph node enlargement or splenomegaly usually

• Aplastic Anaemia

Pancytopenia with no organ enlargement

• Juvenile Rheumatoid Arthritis
▪ Infectious Mononucleosis

The atypical lymphocytes observed with acute Epstein-Barr virus (EBV) and other viral infections can sometimes be confused with peripheral leukemic blasts because they are larger than normal lymphocytes.

▪ Metastatic Solid Tumors

Children with neuroblastoma frequently have malignant involvement of liver, lymph nodes, bone, or bone marrow; the marrow involvement may be extensive.
RELAPSE

- Bone Marrow Relapse in Children with ALL

- Despite current intensive front-line treatments, 20% of children with ALL experience bone marrow relapse.

- Relapse may be an isolated event in the bone marrow or may be combined with relapse in other sites
RELAPSE

- Isolated Extramedullary Relapses

- Isolated extramedullary relapses, occurring either in the CNS or testis, are less frequent than marrow relapses in ALL.

- Such relapse may not actually be isolated
AML

- Number of risk factors have been identified, including ionizing radiation, chemotherapeutic agents (e.g., alkylating agents,), organic solvents, paroxysmal nocturnal hemoglobinuria
DEFINITION

- The World Health Organization (WHO) classification of AML defines that 20% blasts are required for the diagnosis of AML
CLASSIFICATION

- M0 - Acute myeloblastic leukemia without differentiation
- M1 - Acute myeloblastic leukemia without maturation
- M2 - Acute myeloblastic leukemia with maturation
- M3 - Acute promyeloblastic leukemia
- M4 - Acute myelomonocytic leukemia
- M5 - Acute monocytic leukemia
- M6 - Erythroleukemia
- M7 - Acute megakaryocytic leukemia
CLINICAL FEATURES

- Anaemia, thrombocytopenia, leucopenia
- Subcutaneous nodules or “blueberry muffin” lesions (especially in infants), infiltration of the gingiva (especially in M4 and M5 subtypes)
- Signs and laboratory findings of disseminated intravascular coagulation (especially indicative of acute promyelocytic leukemia)
- Discrete masses, known as chloromas or granulocytic sarcomas, typically are associated with the M2 subcategory of AML with a t(8;21) translocation.
(A) Minimally differentiated acute myeloid leukemia (FAB M0). (B) Acute myeloid leukemia without maturation (FAB M1). (C) Acute myeloid leukemia with maturation (FAB M2). There are at least 10% of cells showing maturation. (Inset) The blasts are myeloperoxidase-positive by cytochemistry.
DIAGNOSIS & TREATMENT

- Bone marrow aspiration and biopsy specimens of patients with AML typically reveal the features of a hypercellular marrow consisting of a monotonous pattern of cells with features that permit FAB subclassification of disease.

- Flow cytometry and special stains assist in identifying myeloperoxidase-containing cells.
TREATMENT

- AML-protocol (Modified from MRC 12)
- Daunorubicin 50 mg/m2 IV days 1, 3, 5
- Cytosine arabinoside 100 mg/m2 IV bolus every 12 hours days 1 to 10 (20 doses)
- Etoposide 100 mg/m2 IV 1 hour infusion days 1 to 5
- Intrathecal cytarabine age adjusted doses at time of diagnostic LP
TREATMENT

- Acute promyelocytic leukemia (FAB-M3), characterized by a gene rearrangement involving the retinoic acid receptor [t(15;17); PML-RARA], is very responsive to all-trans-retinoic acid (tretinoin) combined with anthracyclines and cytarabine.
- The success of this therapy makes marrow transplantation in first remission unnecessary for patients with this disease.
JMML

- JMML is a rare, clonal, myeloproliferative disorder of the stem cell that usually manifests in the first few years of life.

- It has also been referred to as juvenile chronic myelomonocytic leukemia (JCML), infantile monosomy 7 syndrome, or juvenile granulocytic leukemia.
CLINICAL FEATURES

- The most common symptoms are fever, cough, infection, pallor, malaise, hepatosplenomegaly, lymphadenopathy, rash, bleeding, and failure to thrive.
Several treatment regimens have been used to improve survival, including low-dose chemotherapy, intensive AML-type therapy, and 13-cis-retinoic acid.

The only known curative therapy for JMML is allogeneic HSCT, and neither pre-treatment chemotherapy nor splenectomy has not been found to impact survival.
Thank You