Acute leukemia

Acute leukemia):- Leukemia's are group of disorders characterized by the accumulation of malignant WBC in the bone marrow & blood (called blasts).it is defined as the presence of more than 20% blasts in the bone marrow or in the peripheral blood at presentation, it may be subdivided into:-
1-acute myeloid leukemia (AML).
2-acute lymphoid leukemia (ALL).

Pathogenesis :-
Acute leukemia is an aggressive disease in which the malignant transformation occurs in the pluripotential haemopoietic stem cell or very early progenitors. the genetic damage may involve different key steps in cell proliferation and differentiation resulting in ;-

1- Increase rate of proliferation .
2- Reduced apoptosis.
3- Block in cellular differentiation.

Those together cause accumulation of early bone marrow precursors which are known as blasts , the abnormal cells cause symptoms by:-
1-bone marrow failure (anemia, neutropenia ,thrombocytopenia).
2-organ infiltration (liver, spleen ,lymph nodes …).
It is an aggressive disease & usually fatal if left untreated.

Acute lymphoblastic leukemia :-

It is the most common malignancy of childhood; there is accumulation of lymphoblasts in bone marrow & blood.

Etiology:-
There is combination of genetic background & environmental influence

- inherited factors:-there is increase in incidence of leukemia in some genetic diseases as Down syndrome ,Blooms syndrome, Fanconi anemia ,Ataxia telangectasia , klinefilter syndrome.
- Environmental influence:-
  Chemicals (chronic exposure to benzene)
  Drugs:- Alkylating agents (chlorambucil& mustine) especially combined with radiotherapy .
  Etoposide is an antileukemic agent but their use is associated with increase risk of secondary leukemia.
  Radiation :- it has been noticed that there is increase incidence of all types of leukemia in the survivors of atomic bombing in Japan.
  Infection:- viral infection as HTLV-1 is a cause of adult T cell leukemia / lymphoma .
  EBV is associated with endemic form (African type)of Burkitt lymphoma
  AIDS is also associated with increase incidence of lymphoma.

Classification:-

According to FAB classification (French, American, British), which is based on morphology ALL is subdivided into 3 subtypes:-

a-L1 subtype(blasts are uniformly small with little cytoplasm)

b-L2 subtype (blasts are heterogeneous in size & shape , larger with more cytoplasm, prominent nucleoli).

c- L3 subtype (uniform with strongly basophilic .vacuolated cytoplasm & prominent nucleoli).

FAB classification is no longer applied as it does not add important diagnostic nor prognostic information.

It has been found that valuable information can be obtained from immunophenotyping cytogenetic & molecular analysis ,in addition to morphology & these are the bases for the MIC classification (morphology, immunophenotyping, cytogenetics).

Immunophenotyping is done by applying certain monoclonal Ab that recognize specific Ag (nuclear, cytoplasmic or surface Ag),this is very valuable in distinction between myeloid & lymphoid leukemia & between different subtypes of leukemia ,it is also useful in treatment , follow up & in determining prognosis.

Immunologically:- ALL is classified into:-

1- precursor B-ALL (CD19 & TDT +ve), there are 3 subtypes :-
   - a:-early pre-B (CD10 –ve, also known as pro-B).
   - b:-common ALL (CD10 +ve).
   - C:-pre –B with intracytoplasmic μ chain +ve
2- T-ALL :-showing T cell Ag (CD7, cytoplasmic CD3 +ve).
3- B-ALL :-showing surface Ig & TDT –ve.

Genetics:-

Chromosomal abnormality is found in up to 80% of cases:-

Numerical abnormalities:- Hyperploidy (> 50 chromosome) associated with good prognosis.

Hypoploidy (< 45 chromosome) associated with poor prognosis.

Structural abnormalities:- mainly translocations, inversions, deletions, point mutations. Some of the most common translocations are:-

t(9;22) (q34;q11) Philadelphia chromosome characteristic of CML seen in 20% of cases , more in adults associated with poor prognosis.

t(1;19) , t(17;19)

t(4;11) with MLL rearrangement , most common in infants associated with poor prognosis.

t(12;21) ,carry good prognosis.

Incidence & clinical features :-

ALL is the most common leukemia of childhood with the highest incidence between 3-7 years with the CD10 +ve common ALL being most usual type in children, the frequency of ALL decrease after the age of 10 , then it shows a second rise after the age of 40.

Clinically the patients presented with

1- features of bone marrow failure (pallor& lethargy due to anemia , fever ,malaise and infections due to neutropenia , spontaneous bruises & bleeding gums , menorrhagia due to thrombocytopenia) .
2- features of organ infiltration :- most commonly patients present with lymph node enlargement ,tender bones .spleenomegally and hepatomegally are less massive than acute myeloid leukemia, CNS involvement is common, a less common finding include testicular swelling or signs of mediastinal compression in mainly seen in T-ALL.

Investigations:-

1-CBP may reveal normochromic , normocytic anemia , thrombocytopenia , the WBC count may be normal, increased or decreased & the blood film reveals variable number of blasts.
2- bone marrow examination shows a hyper cellular marrow with blast infiltration, the blast percentage should be more than 20%, blasts are characterized by their morphology , cytochemistry may be helpful (blasts are +ve for periodic acid Schiff reagent (PAS), & -ve for myloperoxidase& non- specific esterase).
3- immunophenotyping & cytogenetic analysis are necessary for predicting prognosis & for making treatment decisions .

Risk assessment :-in order to assess relapse risk & to determine the mode of treatment children are divided into

Low risk, with the following features :-
B cell precursor phenotype.
Age 1-9 year
Presenting WBC<$50x10^9$/l
Hyperploidy
Absence of CNS & testicular involvement.

Standard risk :-
T cell ALL
All cases of B cell precursor ALL not meeting the criteria of low or high risk

High risk:-
WBC count>50 $X10^9$ /l
Certain cytogenetic abnormalities as Philadelphia chromosome t(9;22) , t(8;14), t(1;19) t(4;11)involving MLL gene (mixed leukemia lymphoma gene) .
Poor response to treatment (induction failure).

Notes :-
Relapse means the reappearance of leukemic cells at any site mostly the bone marrow, CNS or other sites. Most relapses occur during treatment or in the first 2 years following treatment. Patients categorized as high risk are more likely to develop relapse.
The aim of treatment is to achieve complete remission in which there is no evidence of leukemia in the body and the bone marrow is clear from blasts.

Prognosis :- there are many factors that affect the prognosis

Table 12.6 Prognosis in acute lymphoblastic leukaemia (ALL)

	Good	Poor
WBC	Low	High (e.g. $> 50 \times 10^9$/l)
Sex	Girls	Boys
Immunophenotype	c-ALL (CD10+)	B-ALL
Age	Child	Adult (or infant < 2 years)
Cytogenetics	Normal or hyperdiploidy (> 50)	Ph+, 11q23 rearrangements
	TEL rearrangement	
Time to clear blasts from blood	< 1 week	> 1 week
Time to remission	< 4 weeks	> 4 weeks
CNS disease at presentation	Absent	Present
Minimal residual disease	Negative at 1–3 months	Still positive at 3–6 months

CNS, central nervous system; Ph+, Philadelphia chromosome positive; WBC, white blood cell count.

Acute myloid leukemia:-

It is malignancy originating in a multipotential haemopoietic stem cell with clonal proliferation & abnormal blasts accumulation in the bone marrow & peripheral blood, it accounts for 80% of leukemia in adults & 20 % in children.

Etiology :-

1- environmental factors as radiation , chronic benzene exposure & treatment by alkylating agents.
2- clonal myeloid diseases may progress to AML (PRV, CML, ET).
3- inherited diseases (Downs syndrome , Fanconie anemia)
4- most cases arise denovo & associated with cytogenic changes (translocations, inversions, deletions)

classification :-
based on morphological criteria of FAB classification it is divided into 8 categories

Table 12.2 Classification of acute myeloid (AML) and acute lymphoblastic (ALL) leukaemia according to the French–American–British (FAB) group

AML	ALL
M_0 undifferentiated	L_1 blast cells small, uniform high nuclear to cytoplasmic ratio
M_1 without maturation	L_2 blast cells larger, heterogeneous, lower nuclear to cytoplasmic ratio
M_2 with granulocytic maturation	L_3 vacuolated blasts, basophilic cytoplasm (usually B-ALL)
M_3 acute promyelocytic	
M_4 granulocytic and monocytic maturation	
M_5 monoblastic (M_{5a}) or monocytic (M_{5b})	
M_6 erythroleukaemia	
M_7 megakaryoblastic	

M0:-in this subtype there is no evidence of differentiation morphologically or by cytochemistry (MPO is –ve as well as Sudan black B), immunophenotyping is necessary to differentiate it from lymphoblastic leukemia (CD13, CD34)

M1:- AML without maturation, the blasts are +ve for cytochemistry, but the fraction of mature myeloid component in the bone marrow is low

M2:- the same as M1 but the maturing myeloid component in the bone marrow is more than 10%, blasts are more likely to show Aur rods (fused primary granules) when seen they are pathognomonic for AML.

M3:-Acute promyelocytic leukemia, here the malignant cells are the abnormal hyper granular promyelocytes ,where the cytoplasm is densely packed with granules, multiple Aur rods or faggot cells (at least 3 Aur rods/cell)are seen.
It is often associated with pancytopenia . There is high incidence of DIC& usually precipitated shortly after treatment. t(15;17)is seen in majority of cases ,it involves RARα gene on chromosome 17& PML gene on chromosome 15 . RARα gene codes for the Retinoic acid receptor which induces cell differentiation, this translocation carries good prognosis, the abnormal receptor responds to high doses of ATRA (all transretinoic acid) which can induce the differentiation of the abnormal promyelocytes.

M4:- myelomonocytic leukemia,here there is significant monocytic component (more than 20% of bone marrow elements) with peripheral blood monocytosis

M5:-moncytic leukemia, the monocytic component is more than 80%of bone marrow elements, it can be M5a(monoblastic)where the majority of the cells are monblasts or it can be M5b(monocytic leukemia) ,

M6:-Erythroleukemia, many of the cases arise on the background of myelodysplastic syndromes

M7:- Megakaryoblastic leukemia , the blasts are morphologically undifferentiated , the bone marrow may show Megakaryocytic differentiation , this form of leukemia is identified by immunological markers.

Iimmunophenotyping:-

The typical myeloid immunophenotype is CD13, CD33 +, anti-MPO +VE & TDT – ve (very mportant to differentiate t from ALL) . There are also certain markers that are specific for certain subtypes.

Cytogenetic :-

Chromosomal abnormalities seen in 70% of cases, some of the structural abnormalities in AML

1- t(8;21) present in 12% of patients , associated with good prognosis.
2- t(15;17) (q31;q22)→ PML-RARα seen in 95% of cases of promylocytic leukemia it has carry good prognosis. other translocations that involve chromosome 17 like t(11;17) may also be seen with variable response to ATRA.
3- inv(3) or t(3;3), extremely poor prognosis.
4- inv(16) or t(16;16), associated with AML M4 with abnormal eosinophils & carries good prognosis.
5- t(9;22)(q34;q11)→ BCR-ABL, the Philadelphia chromosome characteristic of CML when present in cases of acute leukemia it carries poor prognosis.
6- translocation or deletion of chromosome 11 (q23)involving MLL gene (mixed lineage leukemia gene) they are associated with poor prognosis.

there are also many forms of numerical chromosomal anomalies that are associated with AML as trisomy or monosomy.

World Health Organization (WHO) Classification:-

The WHO classification of acute leukemias evolved from the FAB classification, which is based on morphology, to also include clinical, immunophenotypic, and cytogenetic features, The WHO recognizes five major categories:-

a- **Acute myeloid leukemia with recurrent genetic abnormalities:-**
Acute myeloid leukemia with t(8;21), inv(16), t(15;17) promyelocytic leukemia (M3), t(9;22),), inv(3).

b- **Acute myeloid leukemia with multilineage dysplasia.**
c- **Therapy-related acute myeloid leukemia.**
d- **Acute myeloid leukemia not otherwise categorized**
Acute myeloid leukemia minimally differentiated (M0)
Acute myeloid leukemia without maturation (M1)
Acute myeloid leukemia with maturation. (M2)
Acute myelomonocytic leukemia (M4)

Acute monoblastic and monocytic leukemia (M5)
Acute erythroid leukemia (M6)
Acute megakaryoblastic leukemia (M7)
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma

e- **Acute leukemia of ambiguous lineage.**

Clinical features:-

- pallor & easy fatigability due to anemia .
- easy bruising , petechia,epistaxis, gum bleeding frequently seen early.
- Pustules & other pyogenic skin infections , major infections are uncommon unless there is severe neutropenia (neutrophil count <0.5 ×109/l)
- Fever usually seen at presentation.
- spleenomegally & hepatomegally in most of cases but lymphadenopathy is uncommon.
- Organ involvement seen more in monocytic leukemia ,leukemic cells may involve any organ in the body skin → leukemia cutis
  Oral → gingival hypertrophy .
  cardiac and renal involvement may be seen but unlike ALL CNS involvement is uncommon.

Investigations:-

1- CBP & blood film shows anemia & thrombocytopenia , WBC count may be low or normal or high with blasts in variable number, characteristic finding of AML is the presence of Auer rods (seen in 1/3 of cases), seen more in M1,M2,M3 &occasionally M4. in M3 faggot cells (containing bundles of Auer rods) are seen.
2- bone marrow aspirate shows blast infiltration (for diagnosis the blasts should be >20% of all nucleated marrow cells) except in M3 subtype. bone marrow examination is essential for subtyping as well as diagnosis. Cytochemistry will show that Blasts are +ve for myloperoxidase & suddan black B .
3- immunophenotyping , cytogenetic study.
4- biochemical tests:- ↑ uric acid & LDH , hypokalemia (it may be spurious when the WBC count is very high , ↑Ca.
5- coagulation tests are mainly needed in M3 type as it s mainly associated with DIC.

Prognosis:- the most important factor that determine prognosis is the cytogenetics

Table 12.7 Prognosis in acute myeloid leukaemia (AML)

	Favourable	Unfavourable*
Cytogenetics	t(15; 17) t(8; 21) inv(16)	Deletions of chromosome 5 or 7 Flt-3 mutation 11q23 t(6; 9) abn(3q) Complex rearrangements
Bone marrow response to remission induction	< 5% blasts after first course	> 20% blasts after first course
Age	< 60 years	> 60 years

FLT3 is a receptor tyrosine kinase that is expressed on hematopoietic progenitor cells and is activated by binding of FLT3 ligand, stimulating proliferation. FLT3 is expressed on AML cells in most cases of AML, and is mutated in ~30% of cases, resulting in constitutive activation

Biphenotypic leukemia:-

In this type a single clone of cells express 2 or more Ag (markers) of the opposite lineage (usually myeloid & lymphoid), a scoring system for the diagnosis of biphenotypic leukemia is used (this type of leukemia requires immunophenotypng for diagnosis)

Bilinear leukemia:-(mixed) here there is proliferation of a clone of early precursors with separate maturation in 2 pathways (myeloid & lymphoid)(2 populations of blasts one with myeloid& one with lymphoid features.