Acute lymphoblastic leukemia is a malignant neoplastic disease that arises from lymphoid cell lines. It is the most malignancy in childhood. The disease manifests quickly over a span of days or weeks. Excessive proliferation of immature blasts replaces the normal bone marrow cells resulting in bruises, bleeding, and infection that associate with fever. Diagnosis of ALL is established by complete blood count (CBC) which shows leukocytosis, bone marrow study which shows more than 20% blast cells. It has a good prognosis.

Definitions

A Comparison of Different Kinds of Acute Leukemia

Acute Leukemia

It is a malignancy of hematopoietic stem cells in the bone marrow. The cells in acute leukemia are premature (-blasts), while the cells in chronic leukemia are mature.
Acute leukemia is diagnosed with hypercellular bone marrow containing more than 20% blast cells, which are also spilled in the peripheral blood. It is further subdivided into acute lymphoblastic leukemia (ALL) and acute myeloblastic leukemia (AML) depending upon the affected cell lineage.

**Acute Lymphoblastic Leukemia** - It is an acute malignancy of hematopoietic stem cells affecting the “lymphoid” lineage.

**Acute Myeloblastic Leukemia** - It is an acute malignancy of hematopoietic stem cells affecting the “myeloid” lineage.

**Aleukemic Leukemia** - It is a type of acute leukemia in which blast cells are absent in the peripheral blood, but they are present in the bone marrow (> 20%).

**Epidemiology of Acute Lymphoblastic Leukemia**

**Acute Lymphoblastic Leukemia as the Most Common Cancer in Children**

Acute lymphoblastic leukemia is the most common childhood cancer, accounting for 26% of all cancers in children younger than 14 years. In the United States, approximately 3,000 children have diagnosed with acute lymphoblastic leukemia annually, with the incidence of 3.5—5 cases per 100,000 children of 0—14 years of age. The second peak of presentation is in old age. Thus, ALL has bimodal occurrence.

**Etiology of Acute Lymphoblastic Leukemia**

**The Causes of Acute Lymphoblastic Leukemia**

The etiology of ALL is idiopathic in most of the cases, but the familial and hereditary linkage cannot be ruled out, as higher incidence is seen with some congenital disorders e.g. Down syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia and neurofibromatosis.

Acute leukemia is also associated with some known risk factors, such as prolonged exposure to radiations and benzene. Some of the chemotherapeutics including alkylating agents, e.g. cyclophosphamide, melphalan, and etoposide, are also considered to be leukemogenic.

**Pathophysiology of Acute Lymphoblastic Leukemia**

**Acute Lymphoblastic Leukemia on a Cellular Level**
In acute lymphoblastic leukemia, there is a **block in an early stage of stem cell differentiation**. This results in **unchecked monoclonal multiplication of immature leukemic blast cells** preceding the block. These cells may be precursor-B cells or precursor-T cells depending upon their origin. They are arrested in their cell differentiation pathway due to the aberrant chromosomal abnormalities, such as various chromosomal translocations, hyperdiploidy or hypodiploidy.

These monoclonal leukemic cells occupy most of the bone marrow space suppressing the production of normal hematopoietic cells. The **leukemic cells of the hypercellular bone marrow** then spill into the blood circulation and are **visible on routine CBCs**. The decreased normal blood cells are responsible for most of the clinical symptoms. The decreased platelets cause bleeding. The decreased red blood cells lead to anemia and pallor, while the decreased normal white blood cells lead to severe recurrent infections. The **malignant leukemic cells are non-functional** and the precursor-B cells do not produce immunoglobulins.

**Classification of Acute Lymphoblastic Leukemia**

**B-Cell and T-cell Lymphoblastic Leukemia**

The World Health Organization (WHO) has classified the acute lymphoblastic leukemia into B-cell lymphoblastic leukemia and T-cell lymphoblastic leukemia. The **T-cell ALL accounts for approximately 20 % of all cases of ALL**.

The B-cell ALL has been further subdivided into a number of disease entities based on the cytogenetics and chromosomal abnormalities, while the same classification has not been provided for T-cell ALL. The detailed classification is given in the following table:
Precursor Lymphoid Neoplasms

B lymphoblastic leukemia

B lymphoblastic leukemia, NOS
B lymphoblastic leukemia with recurrent genetic abnormalities
B lymphoblastic leukemia with t(9;22)(q34;q11.2); BCR-ABL1
B lymphoblastic leukemia with t(v;11q23); MLL rearranged
B lymphoblastic leukemia with t(12;21)(p13;q22); TEL-AML1 (ETV6-RUNX1)
B lymphoblastic leukemia with hypodiploidy
B lymphoblastic leukemia with hypodiploidy (hypodiploid ALL)
B lymphoblastic leukemia with t(5;14)(q31;q32); IL3-IGH
B lymphoblastic leukemia with t(1;19)(q23;p13.3); E2A-PBX1 (TCF3-PBX1)

T-lymphoblastic leukemia

NOS = Not Otherwise Specified


Clinical Presentation of Acute Lymphoblastic Leukemia

Manifestations of Acute Lymphoblastic Leukemia

The most common clinical manifestations of acute lymphoblastic leukemia are bleeding, pallor and infections. These symptoms develop abruptly within days or weeks and are due to the replacement of normal bone marrow cells by the malignant cells.

Less commonly, there may be manifestations due to malignant leukemic cell infiltrations within skin, testes, meninges or intestinal tract. In males, the leukemic cells may spread to the testicles causing testicular swelling. Bone pain/tenderness, hepatomegaly, and splenomegaly may be present. About 7% of children have CNS involvement at the time of diagnosis.

The bleeding in ALL is due to decreased platelet counts and occurs in the skin and mucosal surfaces, manifesting as purpura and ecchymosis. Epistaxis, menorrhagia and gingival bleeding may also occur. The pallor, shortness of breath, tachycardia, and fatigue are due to anemia.
The increased infections are due to decrease of normal white blood cell counts. The neutropenia usually leads to infections by gram-negative bacteria and fungi, with cellulitis, pneumonia, rectal infections and sepsis being the common presentations. The increased leukemic white cells in blood are non-functional and do not provide immunity. The production of immunoglobulin is also affected as pre-B cells cannot differentiate into plasma cells.

Some patients present with leukostasis and clinical symptoms of impaired circulation such as a headache, confusion and respiratory distress. In these patients, the WBC count is massively elevated, usually more than 100,000/µL (hyperleukocytosis) causing hyperviscosity and vessel blockage. It is a medical emergency and should be immediately treated with leukapheresis, chemotherapy, and judicious hydration.

The T-cell lymphoblastic leukemia may present with mediastinal mass arising from thymus and extra-medullary lymph node involvement. The CNS infiltration is also more common in T-cell ALL than B-cell ALL.

Laboratory Evaluation and Diagnosis of Acute Lymphoblastic Leukemia

Recognizing Symptoms of Acute Lymphoblastic Leukemia

Complete blood count (CBC) is the initial test. It often shows anemia with normal or high MCV and thrombocytopenia. The WBC count may vary from 1000/mcl to 500,000/mcl, with increased circulatory blasts. In some cases, the blasts are absent from the peripheral blood; this condition is called aleukemic leukemia.
Bone marrow study is the next step. It is hypercellular with increased leukemic blasts. The diagnosis of ALL is made by the presence of more than 20% blast cells.

The diagnosed ALL is further subdivided into B-cell ALL and T-cell ALL by histocytochemistry and flow cytometry. The leukemic cells bear the markers of their respective lineage.

- B-cell ALL are positive for CD-19, which is common to all B cells, CD-10 and TdT. The blasts lack surface immunoglobulins.
- T-cell ALL are positive for CD-2, CD-5, CD-7 and TdT.

The terminal deoxynucleotidyl transferase (TdT) is present in all premature lymphocytes (lymphoblasts), both B-cell and T-cell lymphoblasts. It is an enzyme that plays an important role in the formation of an antigenic diversity of immunoglobulins and T-cell receptors by randomly joining V, D and J segments of DNA.

The cytogenetic and karyotyping further subdivide B-cell ALL into many groups depending upon the presence of chromosomal abnormalities, as outlined by WHO classification.

In T-cell ALL, a chest X-ray may sometimes show mediastinal widening or mediastinal mass.

## Treatment of Acute Lymphoblastic Leukemia

### Different Ways to Treat Acute Lymphoblastic Leukemia

The treatment of acute lymphoblastic leukemia is divided into two halves; supportive and specific treatment.

#### Supportive Treatment

The supportive treatment does not kill the leukemic cells. It is given to improve a patient’s symptoms and wellbeing. The anemia is corrected by red cell concentrate transfusions. The bleeding is corrected by platelet transfusions. The infections and fever are treated with empiric antibiotics, such as aminoglycosides and broad-spectrum penicillin, piperacillin/tazobactam. There is an increased incidence of Pneumocystis carinii pneumonia (PCP), so all the patients should receive sulfamethoxazole-trimethoprim prophylaxis. The Granulocyte-colony stimulating factors (G-CSF) may also be given.
Specific Treatment

The specific treatment is aggressive and is intended to **cure the disease**. It kills the malignant leukemic cells and saves the residual normal stem cells. It is based on the theory that only very **rapidly dividing cells are destroyed by the chemotherapy** and most of the body cells does not divide that rapidly and are not killed, except hematopoietic cells, hair follicles and cells lining the GIT. Therefore, the common **side effects** of chemotherapeutics are **bone marrow suppression, temporary hair loss, mouth sores and diarrhea**.

The **specific treatment is divided into three phases**. Some authors consider CNS prophylaxis as a separate fourth phase. These are as follows:

Remission Induction

The **aim** of the first phase is to induce **complete remission by destroying the main bulk of leukemic cells**. The complete remission is defined as “restoration of normal blood cell counts, the absence of excess blast cells in bone marrow, and normal clinical status”.

In 90 % of cases, complete remission is induced by the various chemotherapy combinations. One of the effective combinations is **vincristine, corticosteroids, asparaginase and daunorubicin (VCAD)**, sometimes cyclophosphamide is added to this regimen. This phase usually lasts for **4 to 6 weeks** depending upon the patient’s response. The patients achieving the complete remission within 4 weeks have a better prognosis than patients who achieve remission after 4 weeks. The supportive treatment is necessary since these chemotherapeutic agents themselves cause bone marrow suppression.

CNS Prophylaxis

In ALL, the leukemic cells may sequester into the central nervous system and cause a **relapse**, therefore, CNS prophylaxis is recommended. The standard chemotherapy regimen does not pass the blood-brain barrier, so it is provided by the combination of **intrathecal chemotherapy, intracranial radiations and high doses of methotrexate**, which can penetrate blood-brain barrier.

Remission Consolidation

If complete remission has been achieved, the **repetitive cycles of combination chemotherapy are still continued, for 6 to 9 months, to kill any remaining residual malignant cells and to avoid relapses**. This phase also requires the supportive therapy. If the patient has poor prognostic factors, the bone marrow transplantation can also be performed during this phase.

Remission Maintenance

If the patient is still in remission, the repetitive cycles of chemotherapy agents are given, usually orally having lesser side effects. This phase may **last for up to 3 years**, depending upon the patient’s condition and responses.

Adjunctive Therapies

Philadelphia chromosome is common in CML but it can also occur in ALL. If present, it is a poor prognostic factor. The discovery of bcr-abl tyrosine kinase inhibitors, such as **imatinib (Gleevec) and dasatinib**, have improved the outcome and should be prescribed in Philadelphia chromosome-positive patients.
**Tumor Lysis Syndrome**

It is a **collection of metabolic derangements** that occur during the cancer treatment. The rapid killing of leukemic cells releases the intracellular contents into the blood circulation. It causes **hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia** and may lead to fatal acute renal injury.

It should be timely **managed by judicious hydration and allopurinol or rasburicase**. Allopurinol is a xanthine oxidase inhibitor that decreases the production of uric acid. Rasburicase converts the insoluble uric acid to soluble allantoin promoting its excretion.

Sodium bicarbonate may be used to alkalinize the urine to increase uric acid excretion. The **dietary restriction of potassium and calcium** may also be required. **Oral phosphate binders** may be used for **hyperphosphatemia**.

**Prognosis and Survival Rate**

**Chances of Surviving Acute Lymphoblastic Leukemia**

The ALL generally has a good prognosis. The **5-year survival rate is 85—90 % with treatment**. If untreated, the **median survival is only 5 weeks**. The prognosis in ALL depends upon various factors, some of which are discussed below.

**Age:** Children have a better prognosis, compared to adults.

**Gender:** Boys usually have a poorer prognosis than girls.

**WBC Count:** High white blood cell counts of more than 100,000/mcl are associated with poor prognosis.

**CNS Involvement:** CNS involvement is more common in adults and in relapses. It is related to poor prognosis.

**Chromosomal Abnormalities:** The chromosomal abnormalities are the most important prognostic predictors.

**Philadelphia chromosome t(9;22)** is traditionally regarded as a poor prognostic factor, but the FDA approved **bcr-abl tyrosine kinase inhibitors (imatinib)** are gradually changing this outlook.

The other poor prognostic factors are chromosomal translocations, t(4;11), and t(1;19), translocations involving the MLL gene on chromosome 11q23 and hypodiploidy. The **normal karyotype and hyperdiploidy have a better prognosis**.

<table>
<thead>
<tr>
<th>Acute Lymphoblastic Leukemia</th>
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<tbody>
<tr>
<td><strong>Poor prognosis</strong></td>
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<tr>
<td>• Age &gt; 60 years</td>
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<tr>
<td>• Male gender</td>
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<tr>
<td>• Adverse cytogenetics – translocations t(9;22), t(4;11)</td>
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<tr>
<td>• WBC count greater than 100,000/mcl</td>
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<tr>
<td>• Failure to achieve complete remission within 4 weeks</td>
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<tr>
<td>• CNS involvement</td>
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<td>• Hypodiploidy</td>
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Good Prognosis

- Age < 30 years
- Female gender
- No adverse cytogenetics
- White blood cell (WBC) count < 30,000/mcl
- Complete remission within 4 weeks
- Hyperdiploidy

Hypodiploidy = Hypo means less; Diploid means two sets i.e. 46 chromosomes; the cells having less than 46 chromosomes.

Hyperdiploidy = Hyper means more; Diploid means two sets i.e. 46 chromosomes; the cells having more than 46 chromosomes.

Follow-Up Treatment

After treatment, the patient has to undergo continuous follow-ups to check for relapses. The complete blood count and bone marrow examinations are performed. The schedule has to be maintained on the individual basis, however, the typical follow-up visit schedule includes:

- Every month a visit for the first 3 months, then
- After every two months for a period of 6 months, then
- After every three months for the total period of 3 years.

Review Questions

The answers are below the references.

1. Which of the following is the good prognostic factor for acute lymphoblastic leukemia?
   A. Philadelphia chromosome
   B. WBC count of 125,000/mcl
   C. 75 years of age
   D. Hyperdiploidy
   E. Male gender
   F. CNS involvement

2. A 5-year-old boy is diagnosed with acute lymphoblastic leukemia. Further investigations are performed to determine the subtype of ALL. The presence of which of the following cell markers indicate the ALL is of “T-cell” type?
   A. CD 19
   B. CD 10
   C. CD 2
   D. Terminal deoxynucleotidyl transferase (TdT)
   E. More than 20 % of blast cells in the bone marrow

3. A patient presents with a headache, confusion and blurred vision. The white blood cell count is 225,000/mcl. Which of the following is the best treatment option?
   A. Leukostasis
   B. Leukapheresis
   C. Combination chemotherapy
   D. Allopurinol
   E. Blood transfusion
F. Broad-spectrum antibiotics

References


**Correct answers:** 1D, 2C, 3B

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