Acute Lymphoblastic Leukemia (ALL) — Classification, Laboratory Evaluation and Survival Rate

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ALL is a malignant neoplastic disease that arises from lymphoid cell lines. It is the most common childhood cancer. 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 is associated with fever. Diagnosis of ALL is established by complete blood count (CBC), which detects leukocytosis, and via a bone marrow study, which shows > 20 % blast cells. ALL have a good prognosis.

Definitions

Kinds of Acute Leukemia

Acute leukemia 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 (-cytes). Acute leukemia is diagnosed with hypercellular bone
marrow containing >20% blast cells, which also spill into the peripheral blood. It is further subdivided into ALL and acute myeloblastic leukemia (AML), depending on the affected cell lineage. ALL is an acute malignancy of hematopoietic stem cells affecting the lymphoid lineage. AML is an acute malignancy of hematopoietic stem cells affecting the myeloid lineage.

Aleukemic leukemia is a type of acute leukemia in which blast cells are absent in peripheral blood but present in bone marrow (> 20%).

Epidemiology of Acute Lymphoblastic Leukemia

ALL 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 are diagnosed with acute lymphoblastic leukemia annually, with an incidence of 3.5 to 5 cases per 100,000 children between the ages of 0 and 14. The second peak of presentation is in old age. Thus, ALL has a bimodal occurrence.

Etiology of Acute Lymphoblastic Leukemia

The Causes of Acute Lymphoblastic Leukemia

In most cases, the etiology of ALL is idiopathic, although familial and hereditary linkages have not been ruled out, as a higher incidence is seen with some patients congenital disorders such as Down syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia, and neurofibromatosis.

ALL is also associated with known risk factors such as prolonged exposure to radiations and benzene. Some 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 ALL, there is a block in an early stage of stem cell differentiation. This results in an unchecked monoclonal multiplication of immature leukemic blast cells, which precedes the block. These cells may be precursor B cells or precursor T cells, depending on their origin. They are arrested in their cell differentiation pathway due to aberrant chromosomal abnormalities such as various chromosomal translocations, hyperdiploid, 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 level of normal blood cells is responsible for most of the clinical symptoms. Decreased platelet levels cause bleeding. The decrease in red blood cell count leads to anemia and pallor, while decreased levels of normal white blood cells lead to severe recurrent infections. The malignant leukemic cells are nonfunctional 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 ALL into B cell lymphoblastic leukemia and T cell lymphoblastic leukemia. T cell ALL accounts for approximately 20% of all cases.

B cell ALL is 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 ALL 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 infiltration in the 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 also be present. Approximately 7% of affected children have a central nervous system (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.
Increased infections are due to the decrease in normal white blood cell (WBC) counts. 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 the 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 headache, confusion, and respiratory distress. In these patients, WBC count is massively elevated, usually more than 100,000/µL (hyperleukocytosis), causing hyperviscosity and vessel blockage. When this occurs, it is a medical emergency and should be immediately treated with leukapheresis, chemotherapy, and judicious hydration.

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

Laboratory Evaluation and Diagnosis of Acute Lymphoblastic Leukemia

Recognizing Symptoms of Acute Lymphoblastic Leukemia

CBC is the initial test for ALL. It often shows anemia with normal or high MCV and thrombocytopenia. 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.
A bone marrow study is the next step. It is hypercellular with increased leukemic blasts. The diagnosis of ALL is made by the presence of > 20% blast cells and is further subdivided into B cell ALL and T cell ALL by histo-cytochemistry and flow cytometry. The leukemic cells bear the markers of their respective lineage:

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

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

Cytogenetic and karyotyping further subdivide B cell ALL into many groups, depending on the presence of chromosomal abnormalities, as outlined in the WHO classification.

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

### Treatment of Acute Lymphoblastic Leukemia

#### Different Ways to Treat Acute Lymphoblastic Leukemia

The treatment of ALL is two-pronged: supportive and specific.

**Supportive Treatment**

Although supportive treatment does not kill the leukemic cells, it improves a patient’s symptoms and well-being. Anemia is alleviated via red cell concentrate transfusions, bleeding is treated with platelet transfusions, and infections and fever are treated with empiric antibiotics, such as aminoglycosides and broad-spectrum penicillin such as piperacillin/tazobactam. There is an increased incidence of pneumocystis carinii pneumonia in ALL, so all patients should receive sulfamethoxazole-trimethoprim prophylaxis. Granulocyte-colony stimulating factors may also be given.

**Specific Treatment**

Specific treatment is aggressive and is intended to cure the disease. It kills the
malignant leukemic cells and preserves the residual normal stem cells. It is based on the theory that only very **rapidly dividing cells are destroyed by chemotherapy** and that most cells do not divide rapidly and are not killed, except for hematopoietic cells, hair follicles, and cells lining the gastrointestinal tract. The most 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 most of the leukemic cells. Complete remission means a 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 various chemotherapy combinations. One of the most effective of these is **vincristine, corticosteroids, asparaginase, and daunorubicin**; cyclophosphamide is sometimes also added to this regimen. This phase usually lasts for 4 to 6 weeks, depending on the patient’s response. Patients who achieve complete remission within 4 weeks have a better prognosis than patients who achieve remission after 4 weeks. Supportive treatment is also indicated since these chemotherapeutic agents can themselves cause bone marrow suppression.

**CNS Prophylaxis**

In ALL, the leukemic cells may sequester into the CNS and cause a relapse. CNS prophylaxis is therefore recommended. The standard chemotherapy regimen does not pass the blood-brain barrier, so a combination of intrathecal chemotherapy, intracranial radiation, and high doses of methotrexate are given to penetrate this 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 avoid a relapse. This phase also requires supportive therapy. If the patient has poor prognostic factors, a bone marrow transplantation can also be performed during this phase.

**Remission Maintenance**

If the patient is still in remission, repetitive cycles of chemotherapy agents are given, usually orally, since this route has fewer side effects. This phase may last for up to 3 years, depending on the patient’s condition and responses.

**Adjunctive Therapies**

Philadelphia chromosome is common in CML but 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** improved outcomes and should be prescribed in Philadelphia chromosome-positive patients.

**Tumor Lysis Syndrome**

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

Tumor lysis syndrome should be managed in a timely way 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 also be used to alkalinize the urine and increase uric acid excretion. Restricting dietary 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

ALL generally has a good prognosis. The 5-year survival rate is 85 %-90 % with treatment. If untreated, median survival is only 5 weeks, however.

Prognosis depends on various factors, including the following (see also the table below):

- **Age:** Children have a better prognosis than adults.
- **Gender:** Boys usually have a poorer prognosis than girls.
- **WBC count:** High WBC counts (>100,000/mcl) are associated with a poor prognosis.
- **CNS involvement:** CNS involvement is more common in adults and in relapses, and results in a poor prognosis.
- **Chromosomal abnormalities:** These are the most important prognostic predictors.
- **Philadelphia chromosome t(9;22):** timely is traditionally regarded as a poor prognostic factor, but Food and Drug Administration-approved bcr-abl tyrosine kinase inhibitors (imatinib) are gradually changing this outlook.

Other poor prognostic factors include chromosomal translocations, t(4;11), and t(1;19), translocations involving the MLL gene on chromosome 11q23, and hypodiploidy. Normal karyotype and hyperdiploidy have a better prognosis.

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<tr>
<th>Prognosis</th>
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<td>Poor prognosis</td>
<td>• Age &gt; 60 years&lt;br&gt; • Male gender&lt;br&gt; • Adverse cytogenetics—translocations t(9;22), t(4;11)&lt;br&gt; • WBC count &gt; 100,000/mcl&lt;br&gt; • Failure to achieve complete remission within 4 weeks&lt;br&gt; • CNS involvement&lt;br&gt; • Hypodiploidy</td>
</tr>
<tr>
<td>Good Prognosis</td>
<td>• Age &lt; 30 years&lt;br&gt; • Female gender&lt;br&gt; • No adverse cytogenetics&lt;br&gt; • WBC count &lt; 30,000/mcl&lt;br&gt; • Complete remission within 4 weeks&lt;br&gt; • Hyperdiploidy</td>
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Follow-Up Treatment

After treatment, patients must undergo regular follow-ups to check for relapses. CBCs and bone marrow examinations are performed. Although individualized schedules should maintain, a typical follow-up visit schedule includes 1 visit during the
first 3 months; followed by 1 visit every two months thereafter, for a period of 6 months; and, finally, 1 visit 3 months for a total of 3 years.

Review Questions

The correct answers can be found below the references.

1. **Which of the following is a good prognostic factor for ALL?**
   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 ALL. Further investigations are performed to determine the subtype. The presence of which of the following cell markers indicates that this boy’s ALL is a T cell type?**
   A. CD 19
   B. CD 10
   C. CD 2
   D. TdT
   E. > 20 % of blast cells in the bone marrow

3. **A patient presents with headache, confusion, and blurred vision. The WBC 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


Seiter, K. *Acute Lymphoblastic Leukemia (ALL).* Retrieved March 12, 2018, from
Correct answers: 1D, 2C, 3B

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