Acute Lymphoblastic Leukemia (ALL) is a malignancy characterized by an overproduction of immature lymphocytes called lymphoblasts (“blast cells”). Like any cells, white blood cells normally grow and divide in an orderly and controlled fashion. In cases of leukemia, a hematopoietic progenitor cell that has sustained genetic damage undergoes a malignant transformation leading to uncontrolled cell division. This creates a proliferation of immature cells which causes an overcrowding in the bone marrow. The overcrowding prevents the marrow from producing normal white blood cells, red blood cells, and platelets.

ALL occurs both in adults and children, usually under 15 years of age. The peak incidence occurs at age 4 years, and accounting for 75% - 80% of all childhood leukemias. The incidence is slightly higher in males than in females, and in western and industrialized nations. In children, ALL accounts for 25% of all childhood malignancies and about 75% of all childhood leukemias. The leukemic transformation and clonal expansion of ALL can occur at different stages of maturation of the lymphoid differentiation process (Pizzo, 2002; Pui, 2002).

Clinical Signs and Symptoms:

The loss of marrow function results in a decreased number of red blood cells and platelets and an increased number of immature white blood cell. Common manifestations of ALL include:

- Unusual bleeding, usually manifested by easy bruising that appears without any apparent injury, bleeding gums, frequent nose bleeds, and heavy menstrual flow in adolescent women. The bleeding is usually due to decreased platelet production, which leads to low platelet counts (thrombocytopenia)
- Persistent fatigue and pallor associated with breathlessness following even the slightest effort. This is due to decreased RBC production, which causes anemia.
- Aching in the joints and bones (especially long bones that contain marrow) due to the bones being crowded by the leukemia cells.
Feeling generally unwell and run down, associated with fever, sore throat or sore mouth; and repeated infections, which are caused by the lack of mature white blood cells to fight infections.

- Loss of appetite due to fatigue, general malaise, and the general effects of the malignancy.
- Lymphadenopathy (enlarged lymph node) and organomegaly (hepato- and splenomegaly).

In children, symptoms of leukemia are often present from one to six weeks before diagnosis.

**Risk Factors:**

Risk factors that have been identified for ALL include ionizing radiation and several [genetic syndromes](#). Other generally recognized factors include:

- Male gender (males more than females)
- Age between 2-5 years
- High socio-economic group
- Exposure to X-rays *in utero*
- Therapeutic post-natal radiation (for thymic enlargement and treatment of tinea capitis).

Additional risk factors include:

- Older maternal age at birth
- Maternal history of fetal loss
- Multiple cases of leukemia within families have been reported. Risk is 2-4 times higher if there is presence of ALL in a sibling (in monozygotic twins the risk is highest during infancy; and there is about a 25% chance for developing ALL up to age 7 years); groups within the same generation and in several generations.
- Other identified potential risk factors that have not been conclusively demonstrated or have been disproved include postnatal infections, parental occupational exposures, parental smoking, electric and magnetic fields, and presence of radon in the environment.

**Classification of ALL**

**Morphology Classification**

FAB (French-American-British Morphologic Classification)

FAB is a classification system for leukemias, based on the descriptive appearance, structure and cytochemistry (chemical makeup and activity of the cell) and the number of cells. \(\text{L1, L2, and L3}\) comprise the FAB classification system. A variant of this classification is the \(\text{hand-mirror cell variant}\) which is an unusual morphologic variant of ALL. This variant accounts for as many as 5% of childhood ALL cases.
Acute Lymphoblastic Leukemia (ALL)

Immunobiology and Immunophenotypic Classification

**B lineage ALL:** Expresses the antigens called CD19, HLA-DR, and/or CD10 (cALLa – common ALL antigen, often correlated with a favorable prognosis). B lineage ALL has a 75% to 85% survival rate with intense treatment. There are three major types of B-lineage cells reflecting the stage of maturation of the leukemic B cell. Antigens and immunoglobulins ((SIg for surface immunoglobin, CyIg for cytoplasmic immunoglobin ) may be expressed on the cell surface depending upon the stage of cell maturation/differentiation.

The three major types of B lineage ALL are:

- **early pre-B**, no SIg or CyIg, usually has CD10
- **pre-B**, has CyIg, usually has CD10
- **B-cell**, has SIg, might have CD10

**T Cell ALL:** Presence of T cell surface antigen; frequently occurs in males; presenting symptoms often include mediastinal mass, higher incidence of CNS leukemia and in general, has a higher WBC count. Also characterized by significantly shorter duration of remission and overall survival.

**Null Cell ALL (nonT, non-B cell ALL):** Associated with < 5% of ALL cases, these patients lack the T or B cell markers.

**Mixed Lineage and Biphenotypic Leukemias:** Leukemic cells express characteristics of more than one hematopoietic lineage, or both lymphoid and myeloid characteristics are present in the same leukemic cells.

**Genetic Classification:**

Gene expression profiling is yielding a view of the leukemia cells that is not only providing insights into pathogenesis, but is also providing new diagnostic markers and therapeutic targets. ALL can be genetically classified according to:

**Modal chromosomal number**

- **Hyperdiploidy** - > 50 chromosomes per cell, DNA index (DI) 1.16 or higher associated with younger age (1 -10 years), low median leucocyte count, increased sensitivity to antimetabolites often show FLT3 over-expression or mutations favorable outcomes

- **Hypodiploidy** - < 46 chromosomes per cell Generally associated with poor outcome
Specific genetic abnormalities of the leukemia stem line:

TEL-AML1 fusion gene; TEL-AML + ALL created by the t(12;21) relatively good prognosis, especially with intensive chemotherapy including asparaginase.

t(1;19) - primarily seen in patients with pre-B ALL, moderate prognosis

t(8;14), (2;8), (8;22) B cell ALL with MYC over-expression associated with favorable prognosis

t(9;22) Philadelphia Chromosome BCR-ABL, t(4;11) - associated with very poor prognosis despite intensive therapy

HOX11 expression frequent abnormality in childhood T cell ALL

NOTCH1 identified in 50% of T cell ALL, provides a strong rational for target therapies that interfere with NOTCH signaling.

Diagnostic Workup

- Complete history of the illness includes a review of the incidence and duration of symptoms such as pain, fatigue, infection, fever, bleeding, and headaches; and a review of potential predisposing factors.

- Physical examination should focus on clinical manifestations of bone marrow dysfunction (anemia, thrombocytopenia, neutropenia) such as pallor, petechiae, rash, lymphadenopathy, limping, hepatosplenomegaly, testicular enlargement, and neurological changes due to CNS involvement.

- CBC with differential WBCs may be low, normal or high; low RBCs; low platelets; blasts may or may not be present in the peripheral blood, but must be present in bone marrow to make a diagnosis of leukemia.

- Bone marrow biopsy/aspiration reveals presence of blasts cells (>25% of marrow cells).

- Immunophenotyping is done to determine leukemic cell lineage, and special staining is done to differentiate among various types of leukemia.

- Immunohistochemistry is a non-morphological method intended to detect leukemia cell content of an antigen that reacts with an antibody presumed to be specific for that substance.

- Cytogenetics is used to diagnose (A – 5) chromosomal abnormalities in many leukemias. More than 90% of children with ALL have cytogenetic abnormalities, specifically, altered chromosome number (ploidy) and chromosomal translocations. These abnormalities can be detected by traditional chromosomal analysis (karyotyping) as well as more sensitive techniques such as reverse transcriptase polymerase chain reaction (RT-PCR) and fluorescence in situ hybridization (FISH).
Gene Expression Profiling (Molecular Analysis) is used to accurately identify specific leukemiasubtypes, and to select therapies targeted to the underlying molecular lesions or their altered downstream consequences.

Lumbar puncture is usually done to rule out central nervous system (CNS) involvement; the presence of blasts in the differential count indicates the presence of CNS disease.

A chest x-ray is done to assess for the presence of mediastinal mass and to evaluate airway status for procedural sedation requirements.

Serum immunoglobulin levels are low in 30% of ALL patients at diagnosis.

Serum chemistry analysis provides baseline information for evaluation of complications such as tumor lysis syndrome and renal insufficiencies. LDH can provide information about the tumor burden (higher the LDH levels mean larger tumors).

Hepatic Panel (liver enzymes and bilirubin) provides data to evaluate the ability of the liver to metabolize chemotherapy drugs. This information is used to make treatment decisions.

Risk Adapted Therapy for Childhood Acute Lymphoblastic Leukemia

Risk adapted therapy uses patient and disease characteristics (variables) that clinical research studies have linked to better or poorer outcomes from treatment. The National Cancer Institute (NCI)/Rome criteria risk stratification used age and the presenting WBC counts at diagnosis as variables predictive of disease outcome.

Standard Risk = age 1 to 9.99 years and a WBC of <50,000/µL
High Risk = age ≥10 years and/or WBC ≥50,000/µL

Outcomes of ALL treatment are dependent not only on the therapy used, but more importantly, on the underlying biology of the tumor and the host. Although the two most important factors predictive of outcome are age and presenting white blood cell count (WBC) at diagnosis, recent studies suggest that other variables such as gender, immunophenotype, genetic profiles like the modal chromosome number (hyper or hypodiploidy), the presence of CNS disease at diagnosis, and MRD assessment can all influence and/or predict the outcome of ALL.

The Children’s Oncology Group (COG) proposed a new classification system based on the re-assessment of several variables. Based upon the child’s age, presenting WBC and immunophenotype, the patient will be assigned to one of four initial treatment groups:

- T-cell
- Infant
- High risk B precursor ALL
- Standard risk B precursor ALL
At the end of induction, patients with B precursor ALL will be re-classified into *low risk*, *standard risk*, *high risk* or *very high risk*, based on the molecular features of the blast, response to induction therapy (bone marrow morphology on day 8, 15 and 29, and minimal residual disease (MRD) at day 29.

**Treatment**

Treatment of ALL has been profoundly influenced by the heterogeneous nature of ALL and the ability to stratify children according to their risks. In ALL, the following principles guide the treatment plan:

- Determine therapy based on individual prognostic factors (risk-directed therapy)
- Use CNS prophylaxis early in the course of treatment.
- Use combination chemotherapy to maintain remission.
- Prevent and manage complications of therapy

There are three phases of chemotherapy treatment for ALL: *induction (remission induction)*, *consolidation/delayed intensification (reinduction)* and *maintenance (continuation)*. Many patients also receive treatment called intrathecal chemotherapy to prevent leukemia from spreading to the central nervous system.

**Induction Therapy:**

The goal of remission induction is to achieve a complete remission by eradicating 99% of the leukemic cells within 6 weeks, to re-establish normal hematopoiesis (absolute granulocyte count >5x10^9/L and platelet count >100x10^9/L) as quickly as possible, and a normal performance status. Early marrow response is correlated with favorable prognosis among all risk groups. Although greater than 95% of children achieve remission within 6 weeks, most often they still harbor as many as 1 x 10^{10} (10,000,000,000) leukemic cells (residual disease), necessitating continued therapy to completely eradicate leukemic cells and achieve permanent cure. Induction therapy includes 2 phases:

- **Phase 1** includes the first 4 weeks of treatment. The most common drugs used during this phase include *vincristine, dexamethasone, or prednisone, and (A – 6) asparaginase*.
- Anthracyclines (daunorubicin or doxorubicin) are added to the treatment regimen for higher-risk patients. For children 1 – 9 years old, dexamethasone may be substituted for prednisone to reduce the risk of CNS relapse, since dexamethasone has increased CSF penetration and a longer half-life.

Phase 2 of induction (also known as intensification) occurs in the last 2 weeks; the drugs that are commonly used during this phase are cyclophosphamide (Cytoxan), 6 MP (Purinethol), and Ara C (Cytarabine; Cytosar).
Consolidation therapy:

Consolidation therapy is given to reinforce remission and to provide direct treatment to the CNS and other sanctuary sites before maintenance therapy begins. The purpose of consolidation therapy is to kill any remaining leukemia cells that may not be active but could begin to re-grow and cause a relapse.

The intensity of consolidation varies depending on the child’s risk group, but always includes treatment of the CNS. The most important chemotherapy agent used during consolidation is high dose methotrexate (HDMTX). Other chemotherapy agents used during this phase may include cyclophosphamide, cytarabine, asparaginase, mercaptopurine, thioguanine, epipodophyllotoxins, and intrathecal chemotherapy (methotrexate, hydrocortisone, cytarabine).

Re-induction or delayed intensification therapy:

Re-induction is basically a repetition of the initial induction therapy at 3 months after remission. This type of therapy is most beneficial to the standard-risk patients. Recent studies also suggest that double delayed intensification (at week 32 of treatment) improved the outcomes of high-risk and intermediate risk ALL patients.

Continuation or Maintenance Therapy:

The goal of maintenance therapy is to eliminate residual leukemic cells. It is a prolonged period of continuous anti-metabolite therapy that includes daily doses of oral mercaptopurine or thioguanine and weekly doses of methotrexate. Improved clinical outcomes appear more likely to occur if the medication is given to patients at the highest tolerable dose level. The combination of intermittent doses of vincristine and dexamethasone or prednisone plus anti-metabolites also decreases the incidence of relapse. In addition, evening doses of oral mercaptopurine appear to be linked to longer event free survival of patients with ALL compared to morning doses.

CNS Treatment:

Since the CNS is a sanctuary site for leukemic cells that were undetected during diagnosis and protected from systemic chemotherapy by the blood-brain barrier, treatment of sub-clinical CNS leukemia is essential. Studies have shown that unless CNS-directed therapy is instituted, more than 50% of all patients with ALL will develop CNS leukemia. Therefore, the goal of CNS-directed therapy is to increase the chance of cure by preventing the development of meningeal leukemia (CNS relapse) and the need for consequent intensive therapy.

CNS therapy includes triple intrathecal treatment with methotrexate, hydrocortisone, and cytarabine, and intracranial irradiation. Because cranial irradiation can produce late secondary neoplasms and was correlated with a higher unemployment and mortality rates, most leukemia protocols limit the use of low dose cranial irradiation for high risk groups. Current practice reserves cranial irradiation to salvage therapy.
Acute Lymphoblastic Leukemia (ALL)

Allogeneic Hematopoietic Stem Cell Transplantation/Bone Marrow Transplantation (HSCT/BMT):

Although BMT has been successful in end stage leukemia, controversies exist regarding its indications for second remissions; specifically, on issues regarding the impact of BMT on relapse rates, risks of allogeneic transplants, comparative overall EFS, and the rates of transplant-related morbidity and mortality. The controversy is further confounded by the lack of randomized trials that compare the outcomes of BMT and chemotherapy for relapsed ALL. In most cases, the indications for BMT vary greatly from one center to another, depending mainly on the availability of resources.

Allogeneic transplantation is further limited by the scarcity of HLA-compatible siblings and the associated risks of the procedure. In addition, the experience of the BMT team and the type of transplantation (matched sibling/donor versus haploidentical transplants) often influence the outcomes of the procedure. Currently, studies are underway to better define the role and optimal timing of HSCT and prophylactic measures to control potential complications for high risk and relapsed patients.

Duration of therapy:

B-cell ALL is treated with a 2- to 8-month course of intensive therapy, achieving acceptable cure rates for patients with B-precursor.

B lineage ALL (pre-B, early pre-B) is usually treated over 2 to 3 years.

T-cell ALL requires approximately 2-2.5 years of continuation therapy. Attempts to reduce this time frame resulted in high relapse rates after therapy was stopped.

Disease Outcomes

Though the therapeutic approach to ALL depends on the child’s risk for relapse, the outcomes for children with ALL can be predicted by several clinical and laboratory features, such as the initial WBC count, the child’s age, presence of cytogenetic abnormalities, and response to therapy.

Remission:

Patients are considered to be in remission if they have no evidence of leukemia when evaluated by physical examination and hematologic assessment of bone marrow and peripheral blood. Peripheral blood values must be within the defined range of normality, and the bone marrow must be of normal cellularity, with fewer than 5% lymphoblasts.
Relapse:

ALL relapse or disease recurrence is often devastating for the child and the family. Relapse greatly contributes to the mortality and morbidity of childhood cancers. About 20% of patients will relapse, and although the management includes use of high dose chemo/radiation therapy and stem cell transplantation, outcomes remain unsatisfactory.

A poor response to drugs early in the clinical course, and detection of minimal residual disease after induction and consolidation are associated with an increased risk of relapse. In general, children who have multiple relapses have a more difficult time achieving remission during re-induction; and the length of time between each remission also decreases.

Bone Marrow Relapse (medullary relapse):

Bone marrow is the most common site of relapse with ALL and is considered to be the principal form of treatment failure in patients with ALL.

CNS Relapse:

Meningeal leukemia is a major impediment to treatment and is usually predictive of bone marrow relapse. Observed in <5% of patients, CNS relapse is defined as the presence of morphologically identified lymphoblasts on CSF smears with a mononuclear cell count >5/microliter; or the presence of tumor infiltration in the CNS following the first remission. Although previously correlated with poor outcome, the event-free survival of patients with isolated CNS relapse is currently about 70% following intensive therapy.

Testicular/Ovarian Relapse:

Testicular/ovarian relapse is defined as the histological evidence of lymphoblastic infiltration in one or both testes or ovaries. It can be overt (clinically detectable) or occult (detected on biopsy). Outcomes for patients with overt testicular (ovarian) relapse appear to correlate with the time of presentation. A relapse that occurs while the patient is on treatment is associated with poor prognosis; however, with intensive systemic re-treatment, prolonged survival can be achieved. In contrast, a late, isolated overt testicular or ovarian relapse occurring following therapy has a better prognosis.

Combined ALL relapse:

Combined ALL relapse is defined as one or more sites of extramedullary lymphoblastic infiltration and ≥ 5% blasts in a bone marrow aspirate (medullary) following the first remission. Combined relapses tend to occur later and have better response to therapy. Because of their partial nature, combined (medullary and extramedullary) relapses have a better outcome when compared to isolated bone marrow relapse.
Future Directions

Although dramatic advances have been achieved in the treatment and management of ALL, several challenges must be overcome in order to ensure improved survival rates for all children with ALL. The challenges include:

1. Increased understanding of leukemogenesis and genetic susceptibility
2. Using genetic susceptibility data for early detection
3. Refining risk-directed therapy for ALL subgroups
4. Understanding individual variations of the pharmacokinetics and pharmacodynamics of antileukemic drugs
5. Developing strategies to circumvent drug resistance
6. Managing and overcoming acute and long term side effects of therapy
7. Use of immunotherapy to enhance anti-leukemic effects during stem cell transplantation
8. Use of antibodies and molecular-based purging techniques to enhance the role of autologous HCST
9. Monitoring compliance with oral chemotherapy
10. Improving procedures to detect minimal residual disease
11. Acquiring reliable information about in vitro chemosensitivity of leukemic cells
12. Improving ways to target therapies in ALL
Helpful Web Links:

**Acute Lymphoblastic Leukemia links:**
American Cancer Society: Childhood Leukemia
http://www.cancer.org/docroot/CRI/content/CRI_2_2_1X_What_is_childhood_leukemia_24.asp?sitearea=

American Society of Hematology
http://www.asheducationbook.org/cgi/content/full/2003/1/102

National Cancer Institute - Treatment Statement for Health Professionals
Childhood Acute Lymphoblastic Leukemia Treatment (PDQ®)
http://www.meb.uni-bonn.de/cancer.gov/CDR0000062923.html

E Medicine.com
http://www.emedicine.com/ped/topic2587.htm#top

Orpha.net, Paris, France
http://www.orpha.net/data/patho/GB/uk-ALL.pdf

Related [www.Cure4Kids.org](http://www.cure4kids.org) seminars

Seminar #770 General Management of ALL
Ching Hon Pui, MD
http://www.cure4kids.org/seminar/770

Seminar #51 CNS Directed Therapy
Wren Kennedy, PNP/O, John Sandlund, MD and Ching-hon Pui, MD
https://www.cure4kids.org/seminar/51

Seminar #50 Bone Marrow Relapse in ALL
Gaston K. Rivera, MD and Wren Kennedy, PNP/O
http://www.cure4kids.org/seminar/50

Seminar #267 (Bone Marrow Relapse - In Portuguese)
http://www.cure4kids.org/seminar/267

Seminar #448 Relapsed ALL
Nobuko Hijiya, MD
http://www.cure4kids.org/seminar/448

Seminar #255 Treatment of Childhood ALL - Intensification of Therapy
Gaston Rivera, MD
http://www.cure4kids.org/seminar/255

Seminar #270 (Treatment of Childhood ALL - in Spanish)
http://www.cure4kids.org/seminar/270

Seminar #914 T Cell Acute Lymphoblastic Leukemia
Eduardo Delgado, MD and Fred Behm, MD
http://www.cure4kids.org/seminar/914
Appendix:

A – 1 Pathogenesis of Acute Leukemia

![Diagram showing the pathogenesis of acute leukemia]

**Fig. 36-2** Principal sites of tissue involvement in leukemia.

Hockenberry et al. Wong’s Care of Infants and Children, 7th Ed., CV Mosby, St. Louis, MO
A – 2 Genetic Syndromes Associated with ALL:

Trisomy 21 (Down syndrome): Patients with Down Syndrome are up to 15 times more likely to develop leukemia

Klinefelter Syndrome: Congenital condition in which males have two X and one Y sex chromosome. Infants appear normal at birth, but at puberty they have delayed development of secondary sexual characteristics; the individual is usually infertile. Symptoms and signs include a small penis, small, firm testicles, diminished pubic, axillary, and facial hair, sexual dysfunction, enlarged breast tissue (gynecomastia), tall stature with abnormal body proportions (long legs, short trunk) and learning disabilities.

Bloom Syndrome: An autosomal recessive genetic disease caused by a mutation of the BLM gene. Patients with Bloom’s syndrome have small body size, photosensitivity, and infertility.

Fanconi Anemia: An inherited disease that primarily affects the bone marrow, causing decreased production of all types of blood cells. Eighty percent of Fanconi anemia patients demonstrate skin pigment changes such as darkened areas, vitiligo, café-au-lait spots. They have short stature with skeletal anomalies such as upper limb abnormalities (missing or extra digits, underdeveloped or absent bones), scoliosis, hip, leg and toe abnormalities, facial anomalies such as eye/eyelid and ear abnormalities, deafness, and anatomical anomalies such as kidney, gastrointestinal and cardiopulmonary malformations. Infants may show failure-to-thrive syndromes and retardation.

Ataxia-Telangiectasia: An autosomal recessive disorder characterized by chromosomal fragility, resulting from mutations of the ATM gene. The most obvious sign is the presence of multiple telangiectases (vascular lesion formed by dilatation of small blood vessels) which are easily visible in the whites of the eye and skin of the face, graying hair and decreased coordination of movements, especially in late childhood. Other symptoms include delayed walking, jerky movements, recurrent respiratory infections, growth failure and decreased mental development.
## Acute Lymphoblastic Leukemia (ALL)

### Chromosomal Abnormalities in Pediatric ALL

#### Genetic Subtypes of B- and T-cell acute lymphoblastic leukemia (ALL)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Associated Genetic Abnormalities</th>
<th>Frequency in Children</th>
<th>Risk Category</th>
</tr>
</thead>
</table>
| B-precursor ALL | Hyperdiploid DNA content; trisomies of chromosomes 4, 10, 17  
\( t(12;21)(p13;q22): \)  
TEL/AML1 11q23/ rearrangements;  
particularly \( t(4;11)(q21;q23) \)  
\( t(1;19)(q23;p13) – E2A/PBX1 \)  
\( t(9;22)(q34;q11): BCR/ABL \)  
\( t\) Hypodiploidy | 25% of B precursor cases  
28% of B precursor cases  
4% of B precursor cases;  
< 80% of infant ALL  
6% of B precursor cases  
2% of B precursor cases  
Relatively rare | Low  
Low  
High  
High  
Very high |
| B-ALL       | \( t(8;14)(q24;q32) – IgH/MYC \)  
\( t(14;11)(q32;q11) \) loci | 5% of all B lineage ALL cases  
7% of ALL cases | High  
Not clearly defined |
| T-ALL       | Numerous translocations involving the TCR \( \delta \) (7q35) or TCR \( \gamma \) (14q11) loci |  |  |
A – 3 FAB Classification System

L1 Lymphoblasts are usually smaller than L2 lymphoblasts, with scant cytoplasm and inconspicuous nucleoli. Approximately 85% of children with ALL have L1 morphology.

L2 Lymphoblasts are larger than L1 lymphoblasts and demonstrate considerable heterogeneity in size, prominent nucleoli, and more abundant cytoplasm. L2 morphology is present in 14% of ALL cases.

L3 Lymphoblasts are large and notable for their deep cytoplasmic basophilia. They frequently display vacuolation and are morphologically identical to Burkitt lymphoma cells. They account for 1% of ALL morphology. L3 lymphoblasts possess cell surface immunoglobulin and other characteristic B-cell markers. L3 ALL has the worst overall prognosis.

Orpha.net, Paris, France
http://www.orpha.net/data/patho/GB/uk-ALL.pdf

Go Back
A – 4 **Hand Mirror Cell Variant**

The leukemic cells are characterized by a hand mirror shape (caused by a handle shaped uropod). Larger studies attribute this variant as an independent, unfavorable prognostic factor, with significantly worse disease-free survival rates.
A – 6  Asparaginase: Not all Asparaginase is the same.

Pharmacologic characteristics of different asparaginase preparation

<table>
<thead>
<tr>
<th></th>
<th>Half-life</th>
<th>Asparagine depletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-Coli*</td>
<td>1.28 ± 0.35 d</td>
<td>14–23 d</td>
</tr>
<tr>
<td>Erwinia</td>
<td>0.65 ± 0.13 d</td>
<td>7–15 d</td>
</tr>
<tr>
<td>PEG</td>
<td>5.73 ± 3.24 d</td>
<td>26–34 d</td>
</tr>
</tbody>
</table>

Asselin et al. J Clin Oncol 11:1786-6, 1993

**Equivalent Doses of Commercial Products of Asparaginase**

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Bacterial Source</th>
<th>Pharmaceutical Company</th>
<th>Equivalent Dose in units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erwinase®</td>
<td>Erwinia chrysanthemi</td>
<td>Enzon, Ipsen-Speywood</td>
<td>20,000</td>
</tr>
<tr>
<td>Elspar®</td>
<td>E coli</td>
<td>Merck</td>
<td>10,000</td>
</tr>
<tr>
<td>Leunase®</td>
<td>E coli</td>
<td>Medac, Kyowa Hakko</td>
<td>5,000</td>
</tr>
<tr>
<td>Oncaspar®</td>
<td>E coli pegylated</td>
<td>Medac, Rohne-Poulenc Rorer</td>
<td>500</td>
</tr>
</tbody>
</table>

CH Pui, 2003
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Cure4Kids Release Date: 1 September 2006

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