

## ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) TEACHING POINTS

### Epidemiology

1. Leukemia accounts for ~31% of all childhood cancer occurring before age 15 years and about 25% of that which occurs before 20 years of age
2. Overall, ALL comprises about 75% of childhood leukemia cases
3. 3250 cases (2400 ALL) of leukemia/yr in US before age 20
4. ALL incidence peaks at 2-3 years of age in developed countries, with rate of 80 new cases/million, decreasing to 20/million at age 10 years
5. The incidence in whites is almost twice as large as that in blacks
6. There has been a modest increase in the incidence of ALL over the past 20 years
7. Little is known about the causes, but there appears to be little role of classic genetic predisposition, lifestyle factors such as diet or environmental exposures such as electric power lines

### Presenting Symptoms

1. Major symptoms are those caused by bone marrow failure due to replacement of normal marrow elements with leukemia cells: pallor and fatigue (anemia); bruising, petechiae and bleeding (thrombocytopenia); and infection (neutropenia).
2. Other symptoms are due to extramedullary proliferation in lymphatic organs and include adenopathy, hepatomegaly, splenomegaly, and mediastinal masses due to thymic expansion (T-cell ALL)
3. Bone pain (general irritability in younger children) is common due to expansion of the marrow cavity
4. Fever is relatively common and is usually not due to infection and often resolves within days of beginning therapy
5. About 5% of patients have CNS involvement at diagnosis, which is most often asymptomatic. However, can have symptoms due to CSF pleocytosis (headache, neck stiffness, irritability, vomiting) and/or signs of increased intracranial pressure. Cranial nerve palsies are occasionally observed.
6. Boys can have testicular involvement (always examine testicles!)
7. Less common sites of involvement include the eye and ovaries

### Diagnosis and initial evaluation

1. Differential diagnosis includes non-malignant (JRA, mononucleosis or other viral infection, ITP, pertussis/parapertussis, aplastic anemia) and malignant (lymphoma, small round blue cell tumors such as neuroblastoma, Ewing's sarcoma, etc.) disorders
2. Initial evaluation should include a careful history and PE that specifically addresses areas outlined above.
3. Laboratory evaluation should include tests needed to establish the diagnosis and define the extent of involvement: CBC with review of peripheral smear, bone marrow aspirate +/- biopsy (morphology, immunophenotype, cytogenetics, molecular genetics), LP, Chest X-ray to exclude mediastinal mass (must do prior to any general anesthesia!).
4. In addition, need to define other problems that may be present including screens for metabolic abnormalities: lytes, BUN, Cr, Ca, Mg, Phos, uric acid.
5. If febrile, culture and treat empirically with broad spectrum IV antibiotics

### Detailed characterization of leukemia

1. Bone marrow morphology: ALL blasts are typically smaller than those seen in AML and do not have cytoplasmic granules. They may have cytoplasmic vacuolization (L3 morphology) and/or membrane blebbing. Cytochemical stains show +PAS, negative for myeloperoxidase
2. Leukemias must be characterized by flow cytometry to define the pattern of surface and cytoplasmic antigen expression. ALL cells are of either B- (80-85%) or T-cell (15%) lineage. Most B-lineage ALLs are derived from early precursors that can be characterized as pro-B or pre-pre-B (prior to expression of cytoplasmic immunoglobulin) or pre-B (cIg+ but no surface Ig). Mature B-cell ALL (sIg+) is quite rare and treated differently. Most B-precursor ALLs express CD22, CD10 (common ALL antigen or CALLA), CD19, HLA-DR and TdT. T-cell ALLs, by definition, express cytoplasmic CD3 (cCD3) and most also express surface CD3 (sCD3).
3. Cytogenetics are performed to identify common non-random abnormalities that may have prognostic significance. Some of these abnormalities can also be identified by specific molecular screening tests.

### Genetics of ALL

1. At least 75-80% of ALLs have identified cytogenetic abnormalities. These reflect underlying genetic changes involved in disease pathogenesis. They are somatic mutations, not germline defects so they are not present in normal cells and disappear when remission is achieved.
2. Non-random chromosome translocations (exchanges of genetic material between chromosomes) are common in ALL and define specific subtypes of disease. These commonly create fusion genes and proteins, or cause dysregulated expression of an intact protein by fusion with an immunoglobulin or T-cell receptor locus. Those with important prognostic significance include the t(12;21) and TEL-AML1 fusion (excellent prognosis) and t(9;22) or Philadelphia chromosome and BCR-ABL fusion (dismal prognosis).
3. Another common abnormality in childhood ALL is hyperdiploidy with an increased number of chromosomes in the malignant cells. These duplications are non-random, but their pathogenesis is unknown. Hyperdiploidy and trisomy of specific chromosomes (4, 10 and 17) is associated with an excellent prognosis.
4. In contrast, hypodiploidy with chromosome number <45 is associated with a poor prognosis, with an especially bad prognosis for cases that are near haploid

### Prognostic Factors

1. See above re genetic factors
2. Age and initial white blood count (WBC) are powerful predictors of outcome in all studies. Best prognosis with age 3-5 years and low WBC. Consensus (NCI/Rome) definition of risk groups for B-precursor ALL is standard (age 1.00-9.99 yrs, WBC <50,000) and high (all others with age >10 years and/or WBC >50,000). Infant (<1 year old) ALL is biologically and clinically distinct and is usually treated differently.
3. T-cell ALL is treated differently than B-precursor ALL by some, but not all, groups. T-cell ALL is associated with other adverse features (age, WBC) and may also respond differently to certain chemotherapy agents.
4. CNS disease at diagnosis requires specific therapy changes (cranial irradiation and more intensive intrathecal chemotherapy)
5. Mature B-cell (sIg+) ALL is rare (<1%) and treated very differently

6. Overall, girls fare better than boys and have more complications. Suggests differences may be due to altered metabolism of chemotherapy agents.

### Treatment

1. As recently as the early 1960s, childhood ALL was incurable. Since then cure rates have steadily improved such that 80-85% of children with ALL are cured today
2. Advances have been due to optimization of multiagent chemotherapy regimens, particularly in large clinical trials by cooperative groups. Over 80% of US children with ALL are treated on clinical trials.
3. One major advance in late 60s/early 70s was the recognition of the CNS as a sanctuary site. When chemotherapy first resulted in sustained remissions, more than 50% of patients had isolated CNS relapsed because many chemotherapy agents have poor CNS penetration. This led to inclusion of presymptomatic CNS therapy into all treatment regimens. Initially, this was craniospinal irradiation. Now, the vast majority of children with ALL are treated with intrathecal chemotherapy without CNS irradiation.
4. First phase of therapy is remission induction, which generally last 4 weeks and includes 3 or 4 drugs (steroid, Vincristine, Asparaginase +/- anthracycline). With contemporary therapy, 98-99% of patients enter complete remission (CR) at end of induction. CR is defined as <5% marrow blasts by standard morphology, normalization of blood counts, and disappearance of extramedullary leukemia.
5. All therapies now include various types of post-induction consolidation or intensification regimens, CNS prophylaxis, and prolonged low intensity maintenance chemotherapy. Total duration of therapy is 2-3 years.
6. Today, most therapy is stratified on the basis of clinical and biological risk factors, with more intensive therapy for patients at higher risk. This model has defined the paradigm for modern combination chemotherapy regimens.
7. If relapse occurs, chance of salvage depends on various factors. One of strongest is the time of relapse following initial diagnosis (the sooner one relapses, the lower the chance of salvage). Relapse regimens are often much more intensive and frequently include stem cell transplantation.

### Long term outlook and sequelae

1. Vast majority of patients who are cured go on to lead normal healthy lives with few serious long term morbidities
2. Risk of 2<sup>nd</sup> cancers in survivors is somewhat higher than background, and dependent on specifics of initial therapy (much higher risk of brain tumors if got CNS irradiation)
3. No appreciable increased risk of leukemia or other tumors in offspring of those cured of childhood ALL
4. No increased risk of birth defects in offspring of those cured of childhood ALL
5. Important to monitor for long-term adverse effects: growth and development, specific potential complications (anthracycline cardiomyopathy).
6. Intellectual function is monitored more closely in those at higher risk (very young age at initial diagnosis and/or cranial irradiation).
7. More and more recognition of obesity as a potential long term consequence of therapy
8. A vascular necrosis of bone is a risk as well as long term risk of alterations in bone density

## SUGGESTED READING

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### Others

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