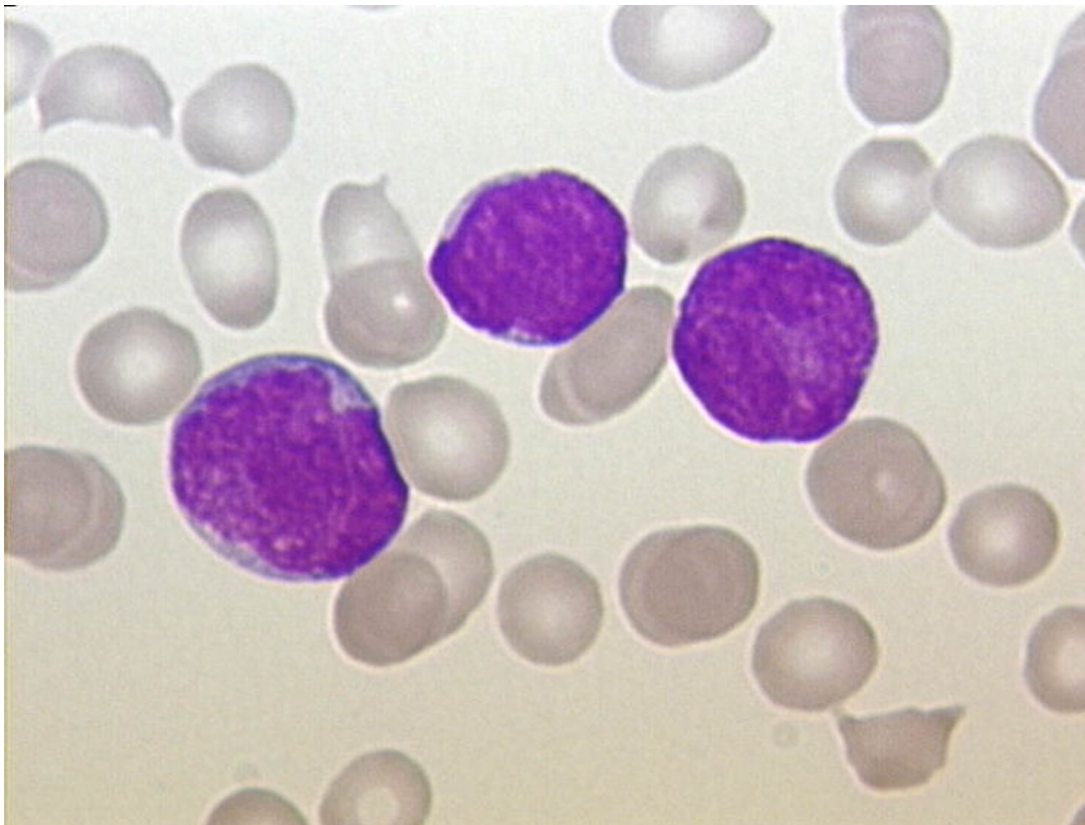


Leukemia in Children – Symptoms and Treatment

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Leukemias are considered as the most common form of malignant disorders in children. Acute lymphoblastic leukemia is responsible for approximately 70% of the cases of leukemia in children, while acute myeloid leukemia accounts for 30% of the cases. Patients with leukemia can present with symptoms related to the loss of normal functioning cells such as anemia, bleeding disorders, and infections, or symptoms related to the expansion of the leukemic cells and metastasis. Cytogenetic and molecular testing is essential as it can have an impact on the treatment and prognosis of the patient.



Definition

Leukemias are defined as a group of **different malignant disorders that involve white blood cells.**

Classification of Leukemia

They are classified as

Acute leukemias

1. **Acute lymphoblastic leukemia (ALL)** is ranked as the most common malignant disease in children.
2. **Acute myeloid leukemia is also common among children.** It is characterized by the replacement of the normal bone marrow cells with dysplastic hematopoietic cells.

Chronic leukemias

1. **Chronic lymphocytic leukemia**
2. **Chronic myeloid leukemia**

They are more common in older patients but may also be found in the younger pediatric population.

Epidemiology of Pediatric Leukemias

Acute lymphoblastic leukemia is currently believed to be the most common form of cancer in children with an annual incidence of 4.9 cases per 100,000 children aged between 0 and 14 years representing a quarter of all cancers in this age group.

For obscure reasons, **Caucasian children** seem to be at a slightly higher risk of developing acute lymphoblastic leukemia compared to children of other ethnicities. **Boys aged between 2 and 5 years** have the highest risk of developing acute lymphoblastic leukemia.

Most of the cases of ALL have **no predisposing risk factors**. On the other hand, certain specific pediatric populations, such as children with **Down syndrome** or **Wiskott-Aldrich syndrome**, seem to have a higher risk of acquiring ALL, compared to the general population.

Acute myeloid leukemia is more common in adolescents, but still can be diagnosed in young children. Approximately, one-third of new cases of pediatric leukemias are attributed to acute myeloid leukemia. Ethnic differences in the incidence of acute myeloid leukemia in the pediatric population are not observed as opposed to ALL.

Etiology of Pediatric Leukemias

The exact cause of ALL is unknown. In most cases, however, certain risk factors have been previously shown to increase the incidence of ALL. The most common genetic disorder to be clearly associated with an increased risk of ALL is **Down syndrome**. Other possible risk factors include **Wiskott-Aldrich syndrome** and **ataxia-telangiectasia**.

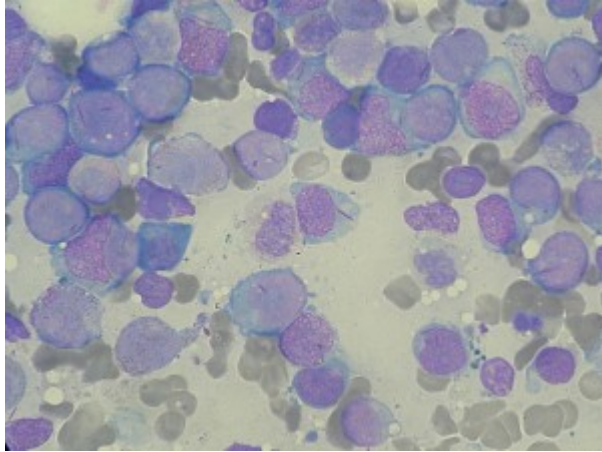


Image: "Myeloblasts with Auer rods seen in Acute Myeloid Leukemia (AML)." by Paulo Henrique Orlandi Mourao. License: [CC BY-SA 3.0](#)

The possible causative role of **radiation exposure** in ALL has been extensively studied and debated over the last few decades. The current consensus is that radiation exposure is unlikely to increase the risk of ALL, but may be a significant risk factor for acute myeloid leukemia.

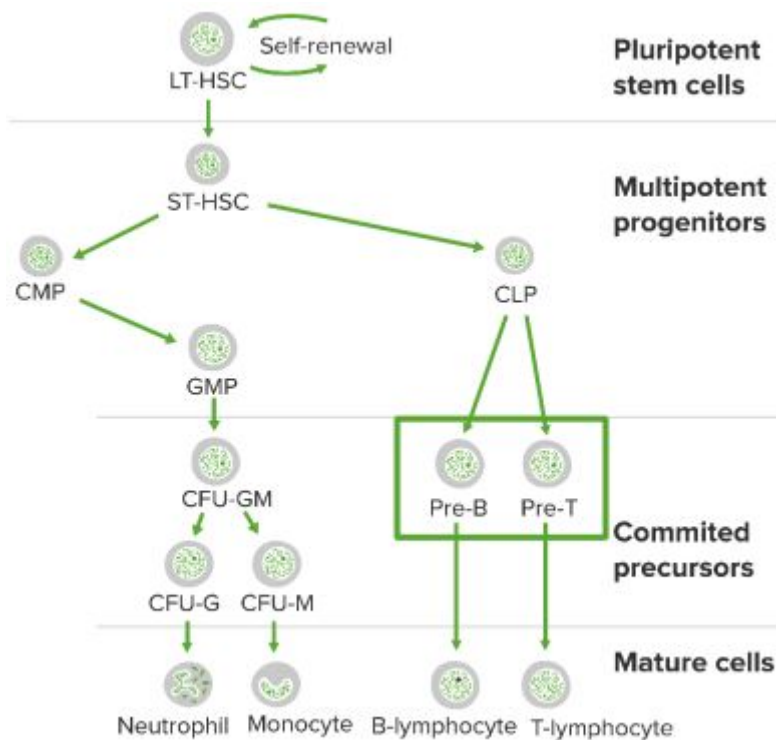
Acute myeloid leukemia, on the other hand, has been linked to many risk factors. Most of the risk factors that have been shown to be associated with acute myeloid leukemia are known to be associated with **defects in deoxyribonucleic acid (DNA) repair mechanisms**.

Acute myeloid leukemia is more likely to be associated with **fusion genes** which occur because of **chromosome translocations**. The products of these fusion genes are believed to be responsible for the loss of the normal property of **apoptosis** in the leukemic cells which allow them to expand.

Radiation exposure might have a significant role in developing acute myeloid leukemia in children, but more research is still needed. For instance, while the risk of acute myeloid leukemia seems to be higher in Japan after the atomic explosions at Hiroshima and Nagasaki among children, the effects on incidence are seldom noticed in adults. Additionally, the risk of acute myeloid leukemia in children who live near nuclear plants was debated to be higher, but definite proof from adequate research is still lacking to support this claim.

Several genetic disorders have been shown to be associated with an increased risk of acute myeloid leukemia which includes **Down syndrome, Diamond-Blackfan anemia, Fanconi anemia, and Bloom syndrome. Dyskeratosis congenita** has been associated with a relative risk of developing acute myeloid leukemia that is 200 higher than the normal population. All of these syndromes share the same common pathologic mechanisms of **impaired DNA repair**.

Pathophysiology of Pediatric Leukemias



"Acute Lymphoblastic Leukemia" Image created by Lecturio

Acute lymphoblastic leukemia is characterized by the **dysregulated proliferation and mono-clonal expansion of a lymphoid progenitor cell** that is genetically abnormal. The resulting lymphoid cells show expression of normal B and T cell genes and carry some of the surface antigens expressed by these lymphocytes.

Another important pathologic step in acute lymphoblastic leukemia is the presence of **leukemic stem cells which lose the ability to go into apoptosis**.

In acute myeloid leukemia, the **normal bone marrow is replaced by abnormal leukemic cells** that are the product of fusion genes resulting from chromosome translocations. The different risk factors associated with acute myeloid leukemia are known to be associated with impaired DNA repair mechanisms.

In addition to impaired DNA repair mechanisms, the cells also need to express certain genes that would render them immortal, i.e. no longer undergoes programmed cell death despite having abnormal genetic makeup.

Because the bone marrow in acute myeloid leukemia is replaced by abnormal leukemic cells, normal functioning cells are no longer produced; therefore, **thrombocytopenia**, **anemia**, and **neutropenia** are usually evident in the late stages of the disease. The patient's symptoms and morbidity are usually related to the loss of the normal functioning cells, rather than the production of abnormal leukemic cells.

An interesting scenario that has been associated with acute myeloid leukemia is the development of the disorder as a **complication to antineoplastic cytotoxic drugs**. Patients undergoing treatment for **Hodgkin lymphoma**, who are administered an **alkylating agent** especially if **combined with radiation therapy**, are at risk of developing overt acute myeloid leukemia.

Prognosis of Pediatric Leukemias

A long-term cure in acute lymphoblastic leukemia is possible but is usually dependent on the child's age and white blood cell count at diagnosis. Other possible prognostic factors in acute lymphoblastic leukemia include the number of leukemic blasts at 8 days and 29 days post-chemotherapy, and the biologic characteristics of the leukemic blasts.

Children who are aged between 1 and 9.9 years who have a white blood cell count < 50,000 at the time of diagnosis, do not have any poor prognostic cytogenetic features and show a good response to initial chemotherapy, are considered as **standard-risk patients**. Favorable cytogenetics includes trisomy 4 and 10.

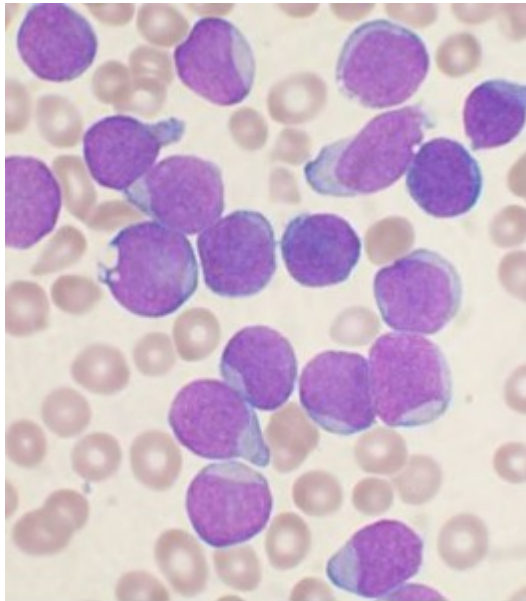


Image: "Immature large blast cells in Acute Lymphoblastic Leukemia." by VashiDonsk. License: [CC BY-SA 3.0](#)

Low risk patients are defined as patients who have less than 0.01% blasts at 8 days and 29 days post-chemotherapy initiation. This group of ALL patients have a 5-year survival of approximately 95%.

On the other hand, patients who are younger than 1 year, or who have poor-prognostic cytogenetics, such as **Philadelphia chromosome**, are considered as **very-high-risk**.

Unfortunately, 5-year survival in very-high-risk ALL can range between 30 to 80% and is difficult to predict. Perhaps an initial response to chemotherapy and minimal residual disease are key in the prediction of prognosis in this group of ALL patients.

Acute complications of ALL are common and include **tumor lysis syndrome, renal failure, sepsis, thrombosis, and central nervous system involvement**. Long-term complications are also identified in survivors and might include **secondary malignant disease** or **cognitive defects**.

The **survival rate** of acute myeloid leukemia is usually dependent on the etiology and the child's age at the time of presentation. For instance, children who are younger than two years of age and have Down syndrome usually have a favorable outcome if they develop acute myeloid leukemia. The overall survival rate in this group of patients can be as high as 86%.

Cytogenetic abnormalities in acute myeloid leukemia have an impact on the **risk of recurrent disease**. For instance, translocation (8;21) which is most commonly found in children with myeloblastic leukemia has a low risk of recurrent disease, whereas monosomy 7 and monosomy 5 carry a high risk of recurrence.

Certain **mutations** that are commonly identified in children with acute myeloid leukemia might also have an effect on overall survival. For example, **nucleophosmin (NPM1) mutation** can be associated with a favorable outcome, whereas **mixed-lineage leukemia (MLL) mutations** can be associated with a poor prognosis.

Clinical Presentation of Pediatric Leukemias

The most common presentation of ALL is that of **bone marrow failure**. Children present with **anemia**, **thrombocytopenia**, and **neutropenia**. **Bone pain** and **arthritis** are very common in children with B-cell ALL. In contrast to acute myeloid leukemia, **fever**, which is also common in ALL, is rarely due to **sepsis**.

Patients with ALL can also complain of **fatigue**, **bleeding complications**, and **petechiae**. **Lymphadenopathy** and **hepatosplenomegaly** are common in ALL and acute myeloid leukemia. Patients with B-cell ALL are more likely to have **abdominal, head, neck and central nervous system masses**. On the other hand, patients with mainly T-cell lineage ALL usually have a **mediastinal disease** that can present with **respiratory distress** and **stridor**.

Patients with acute myeloid leukemia usually have a similar presentation to ALL, but **bleeding complications** are slightly more common. **Easy bruising**, **epistaxis**, **gingival bleeding**, and **intracerebral hemorrhage** are possible bleeding complications known to be associated with acute myeloid leukemia.

Fever is also common in acute myeloid leukemia and is usually a **consequence to an infectious disease**; therefore, patients might present with **a cough**, **shortness of breath** and **chest pain** which are signs of pulmonary infection. **Meningitis** can also happen in patients with acute myeloid leukemia.

Patients with acute myeloid leukemia can present with **lymphadenopathy**, and **hepatosplenomegaly**, similar to ALL. **Mediastinal masses** are usually rare in acute myeloid leukemia compared to ALL.

Another important distinctive feature of acute myeloid leukemia from ALL is **bone pain** and **arthritis**. While ALL patients commonly complain of arthritis, especially those with B-cell ALL, patients with acute myeloid leukemia rarely develop bone pain or arthritis.

Diagnostic Workup for Pediatric Leukemias

Patients with suspected ALL should undergo a **systematic approach** to reach a diagnosis. The first step is to perform a **complete blood count** which should be interpreted by an experienced hematologist. The **presence of blasts** is very characteristic of ALL. The next step, once the presence of blasts is confirmed, is to perform a **flow cytometry study** which can differentiate between T-cell and B-cell lineage ALL.

Patients with ALL are at risk of developing **tumor lysis syndrome**. **Serum levels of uric acid**, **lactate dehydrogenase**, **potassium**, **phosphorus**, and **calcium** correlate

with the risk of tumor lysis.

The subsequent step in the evaluation of ALL is to perform a **bone marrow aspiration for immunophenotyping**. Certain B-cell markers such as CD10 have both a diagnostic and prognostic role and their presence should be determined. Patients with B-cell ALL should be differentiated into **mature or non-mature B-cell ALL** as this can have an impact on the treatment and prognosis of the patient.

The most specific T-cell marker in ALL is **CD3**. T-cell ALL should also be classified into early, mid or late thymocytes depending on maturity.

Karyotype analysis and **molecular techniques** are useful in the identification of certain genetic alterations in leukemic blasts in ALL which might have an effect on the prognosis and response to treatment. Common favorable cytogenetic abnormalities in ALL include **translocation** (12;21), and **hyperdiploidy** (> 50 chromosomes/cell).

Patients that have blasts that have less than 44 chromosomes per cell that express the MLL gene or have the Philadelphia chromosome, are usually **poor responders to chemotherapy** and have a worse prognosis.

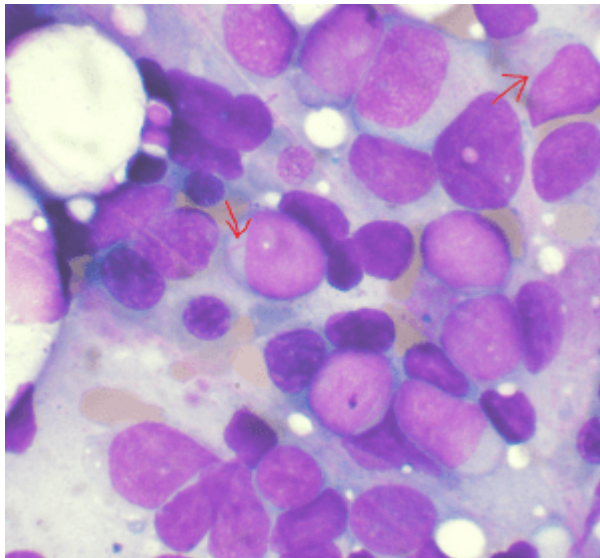


Image: "Bone marrow aspirate showing acute myeloid leukemia. Several blasts have Auer rods." by VashiDonsk. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Expression of certain genes, such as NOTCH1 in T-cell ALL, might be associated with a favorable outcome, while **mutations in the homeobox genes** are usually associated with a worse prognosis.

The approach to acute myeloid leukemia is similar to ALL but with certain differences that should be noted. The probability of finding a white-blood-cell count above 100,000 per micro-liter is much higher in acute myeloid leukemia. **Blood smears** can reveal **thin eosinophilic cytoplasmic inclusions** that are known as **Auer rods**.

Another important specific point to the workup of acute myeloid leukemia is the possibility of finding the **9;22 translocation** which indicates the presence of **chronic myelogenous leukemia**. This cytogenetic abnormality can affect the treatment plan because patients with this chromosomal abnormality should receive **tyrosine kinase inhibitors** and might eventually need **stem cell transplantation**.

Advanced imaging techniques, such as **computed tomography scans** and **magnetic**

resonance imaging, are indicated to evaluate the leukemic cells infiltration of the different organs in both conditions. The decision to order a certain imaging study should be based on the history, physical examination, laboratory and cytogenetic abnormalities identified. For example, ALL patients with T-cell lineage ALL might benefit from a high-resolution mediastinal computed tomography scan to assess the level of mediastinal disease involvement.

Treatment of Pediatric Leukemia

Treatment of ALL includes **induction, consolidation** and **maintenance therapy**, along with **central nervous system prophylaxis**.

- Induction therapy of ALL includes a combination of **vincristine, prednisone, cyclophosphamide, doxorubicin, and L-asparaginase** for 4 to 6 weeks
- Consolidation therapy of ALL is usually based on **multiagent chemotherapy** with **cytarabine** and **methotrexate**
- Maintenance therapy includes **methotrexate, prednisone, and vincristine**. Patients with ALL who have the Philadelphia chromosome should also receive a tyrosine kinase inhibitor and should be evaluated for **allogeneic stem cell transplantation**

Children with confirmed mature B-cell ALL usually have a worse prognosis compared to other B-cell ALL. Such patients are more likely to have CD20 positive blasts and are more likely to develop tumor lysis syndrome. It is currently recommended to add **rituximab** and **aggressive intrathecal methotrexate** to the traditional chemotherapy regimens in this group of children.

Patients with **acute myeloid leukemia** should also undergo induction and consolidation therapy. Induction therapy for acute myeloid leukemia includes **cytarabine** combined with either **anthracycline** or **anthracenedione**.

Consolidation therapy for acute myeloid leukemia is highly dependent on the identified cytogenetic abnormalities and molecular mutations. Patients with favorable cytogenetics should receive **high-dose cytarabine** as consolidation therapy, with or without **autologous stem cell transplantation**.

Patients who have poor-prognostic cytogenetics should be offered **allogeneic stem cell transplantation** or the chance to be enrolled in an ongoing **clinical trial with new chemotherapeutics** because the prognosis is very poor. If both options are not available in a high-risk patient, then **high dose cytarabine** should be used as consolidation therapy.

Patients with leukemias usually undergo **intensive chemotherapy** and can undergo long periods of time with **pancytopenia**; therefore, **transfusion support** is usually indicated and the transfusion of platelets and red blood cells is common.

Radiation therapy might be needed, especially in children who will undergo bone marrow transplantation. Radiation therapy is also needed in patients with large blast masses which are common in acute myeloid leukemia. Patients with central nervous system involvement with ALL or acute myeloid leukemia can also benefit from radiation therapy.

Patients with ALL or acute myeloid leukemia are at risk of developing infections due to their **neutropenia**; therefore, early recognition of a new-onset fever and adequate

administration of **antibiotics** are essential.

Finally, it is worth to mention that most patients with ALL and acute myeloid leukemia do not need any specific surgical intervention. The most likely scenario where a patient might need a surgical intervention is related to the development of an infectious complication such as an **abscess**.

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