

Leukaemia in children

What is leukaemia?

Leukaemia is the most commonly diagnosed cancer in children, accounting for about 30% of all cases. The incidence peaks at age 3 years in boys and at 2 years in girls.

Of the different types of leukaemia in children:

- [Acute lymphoblastic leukaemia \(ALL\)](#) accounts for about 78% of all leukaemia diagnosed in children. ALL is the most common cancer in children.
- [Acute myeloid leukaemia \(AML\)](#) is the next most common and accounts for 15% of leukaemia in children. The incidence rates are highest in infants (under 1 year old) and show little variation from age 3 years onwards.
- [Chronic myeloid leukaemia \(CML\)](#) accounts for up to 5%.
- The remainder is due to a variety of unusual and rare leukaemias. [Chronic lymphocytic leukaemia \(CLL\)](#) is very rare in children.

Causes of leukaemia in children (aetiology and pathogenesis)

- Leukaemia in children is a biologically diverse disease, arrived at by many different pathways.
- Children with leukaemia (particularly ALL) have a range of different chromosomal and genetic abnormalities that defines subsets of the disease with prognostic relevance.

- Common genetic lesions include:
 - Translocations to T-cell receptor (TCR) loci in T-lineage ALL.
 - Mutations of transcription factors regulating B-lineage development and cell maturation in B-lineage ALL (eg, PAX5, TCF3, EBF1).
 - Aberrational disruption of genes coding for transcription factors and coactivators in AML (eg, CBF).
 - BCR-ABL1 fusion and activation of multiple kinases in CML.

Childhood leukaemia epidemiology^[1] ^[2]

Leukaemia is the most commonly diagnosed cancer in children, accounting for about 30% of all cases.^[3]

Age distribution

Leukaemia may affect children of any age but each type commonly affects a particular age group, as outlined below. This age clustering is thought by some to reflect the expression of particular cytogenetic aberrations at crucial stages of development:

- ALL's peak incidence is in 2-3 year-olds.
- AML's peak incidence in children is in those aged <2 years.
- CML has two peaks of incidence in children aged <1 year and in early teenage years. The two peaks may reflect discrete disease entities.

Risk factors

- Leukaemia in children is more common in white children compared to black .
- Boys are at slightly higher risk than girls.
- A range of cytogenetic abnormalities has been found to be associated with an increased risk of the disease.
- Genetic abnormalities such as [Down's syndrome](#) (increases risk by 10- to 20-fold).
[Fanconi's anaemia](#), ataxia telangiectasia and Bloom's syndrome are associated with an increased risk.^[4]

- Significant exposure to ionising radiation and some chemicals is known to increase the risk of leukaemia in children. Maternal abdominal X-ray during pregnancy increases the risk of childhood leukaemia.
- A prospective cohort study of 300,000+ births also found an association between certain maternal infections and childhood leukaemias in their offspring.^[5]
- There is also research into the importance of the infant microbiome as an aetiological factor.^[3]

Various common environmental exposures to electromagnetic radiation (eg, high-voltage power lines, mobile phone masts), low-level radionuclides from the nuclear power industry, and others, have been claimed as causative factors but have never been proven on epidemiological grounds.

Symptoms of leukaemia in children^[2] ^[6]

Presentation is highly variable depending on the child's age and the extent of leukaemic infiltration of the bone marrow and other sites, as well as cytokine systemic effects:

- The classical signs of anaemia, thrombocytopenia, hepatosplenomegaly or lymphadenopathy are highly suspicious of leukaemia but initial symptoms are often nonspecific and vague and are very similar to common, self-limiting viral illness.
- The symptoms and signs listed below are common manifestations of the condition. There is no good evidence base to allow rational decision-making in primary care between phlebotomy and 'wait-and-see' approaches when symptoms are more vague.^[7] Where symptoms are prolonged, particularly troublesome, or present atypically compared with more common illnesses in children, it may be wise to conduct initial investigations.
- More rarely, acute leukaemia can present with life-threatening complications (see 'Complications', below) – do not delay admission for preliminary investigation of these children – refer directly to A&E or paediatric on-call teams.

Symptoms

- General malaise, fatigue and lethargy.
- Prolonged or recurrent episodes of fever.
- Irritability and/or protracted crying.
- Growth restriction and/or failure to thrive.
- Shortness of breath and/or reduced exercise tolerance.
- Dizziness and palpitations.
- Bleeding diathesis, particularly causing epistaxis, bleeding gums and/or easy bruising.
- Bone or joint pain, particularly in the legs.
- Troublesome constipation.
- Prolonged cough.
- Headache.
- Nausea and vomiting, particularly if central nervous system (CNS) infiltration is present.
- Repeated or severe common childhood infections.

Signs

- Pallor due to anaemia.
- Signs of bleeding tendency such as petechiae, purpura, bruising, etc.
- Signs related to severe infection.
- Lymphadenopathy.
- Hepatosplenomegaly.
- Expiratory wheeze (due to mediastinal mass).
- Cranial nerve lesions or other focal CNS pathology.
- Testicular enlargement.

Differential diagnosis^[2]

The overall differential diagnosis is very wide, depending on the mode of presentation and age of the child. Some of the more common conditions that may present similarly in clinical terms, or in their ability to cause abnormalities of the FBC that are akin to leukaemia, are listed below:

Infective

- Infectious mononucleosis (glandular fever).
- Parvovirus B19.
- Other viral infections such as influenza (which may be a trigger of the disease), cytomegalovirus, HIV.
- Osteomyelitis.
- Bordetella pertussis.

Malignant

- Rhabdomyosarcoma.
- Non-Hodgkin's lymphoma.
- A range of other childhood malignancies – eg, CNS tumours, lymphoma, neuroblastoma, renal tumours, bone tumours and others.

Autoimmune

- Systemic lupus erythematosus.
- Juvenile idiopathic arthritis.

Haematological

- Aplastic anaemia.
- Fanconi's anaemia.
- Megaloblastic anaemia.
- Lymphoproliferative disorders.
- Myelodysplasia.

- [Myelofibrosis](#).

Investigations^[2]

- The most useful initial investigations in primary care are FBC and blood film. Typically, this shows pancytopenia due to bone marrow infiltration. Blasts may elevate the white cell count (despite neutropenia) and their presence on a peripheral smear is highly indicative of leukaemia.
- However, the FBC will not always be abnormal in all cases of leukaemia, as some patients may not have marrow suppression. Similarly, peripheral blood films may be normal if blast cells are confined to the bone marrow.

Any abnormal blood count or film in combination with suspicious clinical features should be referred urgently to a specialist centre.

- Further investigations conducted in secondary care are likely to include:
 - Bone marrow aspiration and biopsy - for definitive diagnosis.
 - Imaging to determine the extent of the disease.
 - Immunophenotyping and cytogenetic analysis to enable risk stratification.
 - Lumbar puncture where there is suspected CNS infiltration.

Conventional cytogenetic analysis is an essential part of the multidisciplinary approach to the diagnosis, classification and risk-stratification of any person with acute leukaemia. The introduction of molecular-based cytogenetic techniques such as fluorescent in situ hybridisation (FISH) as an adjunct to conventional cytogenetics has improved the abnormality detection rate. The use of FISH led to the discovery of clinically relevant abnormalities that were previously unidentified and detected chromosomal abnormalities in samples that had previously failed cytogenetic analysis or where no abnormal clone had been detected.

Associated diseases

There is increased incidence of leukaemia in children with:

- [Down's syndrome](#) (15 x background incidence).
- [Fanconi's anaemia](#).
- [Ataxia telangiectasia](#).
- Bloom's syndrome (a rare autosomal recessive condition associated with short stature and an increased risk of developing various cancers).^[4]

Staging

The French-American-British (FAB) classification system is widely used in ALL but does not correlate with immunophenotypic and cytogenetic classifications. ALL is staged L1-L3 based upon morphological characteristics of blast cells.

- There is no classic cancer staging system (tumour, nodes, metastasis) for ALL and AML because by the time of diagnosis they are already in the bloodstream, and invariably have invaded other body tissues. Staging for these leukaemias looks at the white blood cells and platelet counts, the age of the patient, whether they have previous blood disorders, whether the liver or spleen is enlarged, if there are chromosomal abnormalities and whether bone has been damaged.

- CML is staged as being in the chronic, accelerated or blast phases depending upon disease activity, symptoms and the proportion of leukaemic cells that have undergone blast transformation.

Treatment and management of leukaemia in children^[6] ^[8]

General

- Children with leukaemia and their families will require long-term help and support from various agencies, including the primary healthcare team.
- A diagnosis of childhood leukaemia reverberates around the family and has implications for all, not just the child with the disease. Initial shock, anger and fear at diagnosis will transmute into potentially long stays in hospital and frequent outpatient visits. These may impact on educational continuity and social development, as well as parental attendance at work and presence at home. Siblings may feel neglected with the understandable shift of focus to the sick child.
- Good communication between all of the many professionals involved in the child's care is critical.
- Much of the treatment of leukaemia takes place in tertiary centres: there must be guidance to families and protocols at local secondary care hospitals as to how to recognise and manage complications that may arise following discharge after treatment, in particular febrile neutropenia.
- Many families find it helpful to be put in contact with others who have been in the same situation, whose support and practical advice is often highly valued.
- No routine immunisations during therapy and for six months afterwards.

Chemotherapy

- **ALL** (see also the separate [Acute Lymphoblastic Leukaemia](#) article):

- • ALL is always treated with high-intensity chemotherapy, usually via a central venous catheter (eg, Hickman lines). There are varying schedules depending on morphoimmunocytogenetic classification and extent of disease.
- The inclusion of asparaginase in chemotherapy regimens to treat ALL has improved survival in children with ALL.^[9]
- Allogenic bone marrow transplant is used to eliminate residual leukaemic cells in high-risk subtypes refractory to chemotherapy. Myeloablation (via total body irradiation and cyclophosphamide) is followed by the transplantation of allogenic haemopoietic stem cells. This treatment has significant morbidity and mortality associated with it due to infection and graft-versus-host disease.
- **AML** (see also the separate [Acute Myeloid Leukaemia](#) article):
 - • AML is treated with intensive chemotherapy to destroy the leukaemic cell population as quickly as possible.
 - The child must then be supported through a period of intense marrow suppression until haematopoietic recovery occurs.
 - There is a broad range of abnormalities across different AML subtypes and further improvements in clinical outcome will require the development of targeted therapies for each subtype of disease.
 - It is considered to be very unlikely that further gains in long-term survival rates will be possible by just using more intense conventional chemotherapy.
- **CML** (see also the separate [Chronic Myeloid Leukaemia](#) article):
 - • CML is treated very successfully with imatinib anti-tyrosine kinase therapy in adults and this is being evaluated in children.
 - Myeloablative hematopoietic stem cell transplantation from fully matched related and unrelated donors is the mainstay of long-term treatment.

Colony-stimulating factors are often used to promote haematopoietic function following chemotherapy. They have been proven to be effective in reducing hospital stay and risk of febrile neutropenia in children who have had myelosuppressive chemotherapy.^[10] .

Complications

Early

These may cause a life-threatening presentation of leukaemia:

- **Neutropenia** - overwhelming sepsis (usually Gram-negative) +/- disseminated intravascular coagulation.
- **Thrombocytopenia** - bleeding, pulmonary or gastrointestinal (GI) haemorrhage, stroke.
- Electrolyte imbalance - hyperkalaemia and hyperphosphataemia (due to blast cell lysis).
- **Acute kidney injury** (secondary to hyperuricaemia).
- Acute airway obstruction (secondary to mediastinal thymic mass).
- Leukostasis - stroke, acute pulmonary oedema, heart failure.
- CNS involvement - **stroke, seizures**.

During treatment

- Tumour lysis syndrome.
- Renal or hepatic impairment.
- Profound immunosuppression leading to sepsis (febrile neutropenia).
- Thromboembolism.
- Alopecia.
- Mucositis causing severe mouth pain.
- Hyperemesis.
- GI erosion/bleeding.

Late

- Growth hormone deficiency and short stature (where cranial irradiation has been applied).
- Neurological problems including headache, motor, co-ordination and cognitive impairment, seizures (again following cranial irradiation).^[11]
- Peripheral neuropathy (due to vincristine).
- Obesity.
- Congestive cardiac failure (due to toxicity of some chemotherapeutic agents - eg, doxorubicin).
- Cognitive impairment.
- Infertility.
- Psychosocial impairment.
- Second malignancy.

Prognosis^[2]

Although survival rates have improved dramatically over the past few decades, leukaemia remains one of the leading causes of death from disease in children.

- Five-year survival rates for all types of leukaemia in children rose from 33% to 79% between 1971 to 2000, as did cure rates (survival to point where no excess mortality), from 25% to 68% between 1971 and 1995.
- Outlook in ALL is now very good with an overall cure rate of 90%.^[12] Individual prognosis is highly dependent upon staging by the various classifications. Prognosis is best for children aged 1-10 years. Mortality rate had fallen by 4% in the Netherlands study.
- Prognosis has improved in AML with a five-year overall survival rate of around 70% in high-income countries and an event-free survival rate of 56%.^[8] However, patients with adverse cytogenetic features or poor treatment response do badly even with allogeneic bone marrow transplants and have a less than 20% cure rate.

It is hoped that the future will bring new therapies, targeting specific molecular defects and continued improvements individualising therapy, to maximise outcomes whilst minimising complications due to treatment.^[13]

Further reading

- [Haematological cancers: improving outcomes](#); NICE Guidance (May 2016)
- [Blood Cancer UK](#)
- [Hwang SM](#); Classification of acute myeloid leukemia. Blood Res. 2020 Jul 31;55(S1):S1-S4. doi: 10.5045/br.2020.S001.
- [Acute lymphoblastic leukaemia - incidence](#); Cancer Research UK, 2021

Disclaimer: This article is for information only and should not be used for the diagnosis or treatment of medical conditions. Egton Medical Information Systems Limited has used all reasonable care in compiling the information but makes no warranty as to its accuracy. Consult a doctor or other healthcare professional for diagnosis and treatment of medical conditions. For details see our [conditions](#).

Authored by:	Peer Reviewed by: Dr Toni Hazell	
Originally Published: 20/11/2023	Next review date: 30/11/2022	Document ID: doc_1277

View this article online at: patient.info/doctor/childhood-leukaemias-pro

Discuss Leukaemia in children and find more trusted resources at [Patient](#).



To find out more visit www.patientaccess.com
or download the app



Follow us

