

# Childhood acute lymphoblastic leukaemia (ALL)

Childhood acute lymphoblastic leukaemia (ALL) is a bone marrow cancer arising from the cells which should go on to become lymphocytes. Find out what it is, the symptoms to look out for, how to diagnose it and treatment options.

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## What is childhood ALL?

ALL can be diagnosed in a person of any age, but most cases of ALL occur in children (aged 0 to 4 years). Childhood ALL includes teenagers under 20 years of age. Childhood ALL is an acute leukaemia that develops very quickly. It is caused by too many B-cell and T-cell lymphocytes being produced in the bone marrow. Lymphocytes are white blood cells that help the body fight infections as part of the immune system.

In the United Kingdom (UK), the incidence of ALL in children is around 5.1 in every 100,000 in the UK. Boys have a slightly higher incidence of ALL compared with girls.

ALL occurs mainly in children with 85% of cases. The remaining 15% of cases are adults aged over 50 years of age. ALL is diagnosed mainly in children between two to five years. There are three subtypes of ALL in children:

- Early immature B-cells seen in 80% to 85% of children
- Immature T-cells seen in 15% of children
- Mature B-cells seen in around 2% of children

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## What causes childhood ALL?

In several cases of childhood ALL, there is no evident cause for the development of the ALL. However chromosome and gene abnormalities are present at diagnosis in the leukaemia cells of 80% of children.

## Acquired genetic changes

Chromosome and gene abnormalities found in the leukaemia cells of children with ALL are acquired mutations. They cannot be passed on to your children. Only chromosome abnormalities and gene mutations that affect the sperm or egg cells can be inherited.

The acquired chromosome and gene abnormalities in children with ALL include:

- 3-5% of children with B-cell ALL have the Philadelphia chromosome (*BCR-ABL1* gene) present. The Philadelphia chromosome is a shared translocation between chromosomes 9 and 22  $t(9;22)(q34;q11)$
- Less common translocations seen in children with ALL include those between chromosomes 4 and 11 [ $t(4;11)$ ] or chromosomes 8 and 14 [ $t(8;14)$ ]
- In children with T-cell ALL, the following gene mutations are present:
  - *NOTCH1* (70.3% of children)
  - *FAT1* (32.8% of children)
  - *FBXW7* (28.1% of children)
  - *KMT2D* (28.1% of children)

## Inherited genetic changes

Inherited genetic syndromes which make children more likely to develop ALL include:

- Ataxia-telangiectasia: This is an early onset disease characterised by neurodegeneration and immunodeficiency. Ataxia-telangiectasia patients have progressive ataxia (disorder affecting coordination, balance and speech) and an increased risk of developing cancers malignancies (25%), especially of blood origin.
- Wiskott-Aldrich syndrome: Syndrome characterised by immune deficiency, eczema and a reduced ability to form blood clots. This condition primarily affects males. It is caused by a mutation in the WAS.

## Environmental factors

Confirmed environmental causing the development of ALL are high levels of radiation.

Other causes that have been suggested, but for which **no scientific evidence** from studies is available are:

- Power lines
- Nuclear power plants
- Mobile phone masts

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## Symptoms of childhood ALL

In children with ALL, the increased numbers of immature lymphocytes in the bone marrow prevent the production of normal blood cells that cause the symptoms of ALL.

The most common symptoms of ALL in children are:

- Fever (high temperature)
- Fatigue (excessive tiredness)
- Easy bruising and bleeding (bleeding from the gums on brushing teeth)
- Swollen liver and/or the spleen
- Swollen lymph nodes
- Bone or joint pains

Most young children may not have all of these symptoms. A child may just feel generally unwell. They may have paleness, lethargy (tiredness) or malaise (general feeling of being unwell).

In very young children, a common symptom can just be a reluctance to walk or to crawl.

The medical profession know that parents know their children best. If you think your child is ill and has any of the following signs, you should always take them to a doctor without delay:

- Raised temperature, cough or sore throat
- Confusion or agitation, especially if it occurs at short notice
- Your child becoming more ill at short notice
- Fast heart beat and/or fast breathing
- Passing very little or no urine
- Pain in the bones or joints

Most of the signs or symptoms described above are not uncommon in children. It is very rare for a child with these symptoms to have a serious disease. But it is important to exclude ALL as soon as possible, in case early treatment is needed.

We have [more information about symptoms of leukaemia](#).

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## How is childhood ALL diagnosed?

To diagnose your child's ALL, your haematology team will perform the following tests:

### Full blood counts

A full blood count will:

- Measure the number of red cells, different types of white cells and platelets in your blood. High levels of white blood cell lymphocytes can determine a diagnosis of ALL.
- Abnormal-looking ALL leukaemia lymphocytes with an indistinct nucleus and reduced amount of cytoplasm can be confirmed by examining under a microscope a small sample of the blood smeared onto a glass slide.

### Bone marrow aspiration or biopsy

Bone marrow samples obtained by aspiration or a biopsy can be examined under a microscope to confirm an ALL diagnosis if it is not obvious from the blood sample.

Your haematologist will take your child's bone marrow sample from the hip bone. Your child should have a local anaesthetic or more commonly a general anaesthetic (be put to sleep). The haematologist will use a special biopsy needle. If your child needs more pain relief, make sure you or your child raise this during the procedure.

### Lumbar puncture

A lumbar puncture will reveal if leukaemia cells have entered your child's central nervous system. A member of the haematology team will insert a fine bone marrow needle in the lumbar region of your child's lower back. This enables collection of a small amount of cerebrospinal fluid (CSF). Your haematologist will examine your CSF for any leukaemia cells present. Your child will need further treatment straight after diagnosis if this is the case. In young children, they are often put to sleep for the procedure.

### Chromosome abnormalities or gene mutations tests

Patients with ALL have chromosome abnormalities and gene mutations. Tests for these abnormalities help your haematology team understand how your ALL might develop over time. This also helps them to organise your treatment plan.

They can be identified by specialist tests of blood or bone marrow samples.

### **Standard cytogenetic analysis**

This involves examining in the laboratory leukaemia cells while they are dividing. This will indicate any chromosome abnormalities and gene mutations. Cytogenetic means study of chromosomes.

### **Molecular cytogenetic analysis**

This method uses a technique called fluorescence in situ hybridisation which can discover chromosome abnormalities. It labels small portions of DNA with fluorescent particles allowing your haematology team to:

- Detect sequences of DNA
- Locate a gene on a chromosome
- Determine the number of copies of a gene
- Detect any chromosomal abnormalities

### **Polymerase chain reaction (PCR) test**

PCR tests analyse genetic information. PCR tests can detect evidence of the Philadelphia chromosome in particular. The Philadelphia chromosome is present in 3 to 5% of adults with ALL. PCR tests taken throughout the treatment period will also monitor your child's response to current treatment. Your haematology team will adjust the treatment according to your child's results.

### **Immunophenotyping**

Immunophenotyping is a method to detect the proteins found on blood cells. Each type of blood cell has different proteins on its surface. Your haematology team can use immunophenotyping to tell which of your lymphocytes are affected by looking for the B-cell or T-cell proteins.

### **Flow cytometry**

A flow cytometer measures the size and structures of thousands of cells or particles in a short amount of time. Particles or cells dissolved in a fluid float past at least one laser. Flow cytometry is used to identify various cell types only seen in certain diseases. One of the most common is in the diagnosis of blood-related cancers such as leukaemia.

## Imaging tests

Imaging tests that can help assess the impact of the leukaemia on the organs of your body include X-rays, ultrasounds, computer tomography (CT) scans and magnetic resonance imaging (MRI).

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## Treatment for childhood ALL

The haematology team will start your child's treatment for ALL straight away after the diagnosis. Your child will need to go to hospital for the first part of the treatment.

Decisions about your child's treatment decisions is generally discussed at group meetings. These are called multidisciplinary team meetings. These meetings help bring together the skills of lots of different types of doctors and nurses. The aim is to make sure the selected treatment for your child is the most appropriate.

Clinicians divide the treatment of ALL into three separate individual treatment phases:

### Induction treatment

Induction treatment is the first treatment given straight after diagnosis. The aim of the induction treatment is to kill as many leukaemia cells as possible. Induction treatment should help achieve complete remission. Complete remission means the treatment has removed as many of the leukaemia cells as possible.

Induction treatment consists of a combination of chemotherapy drugs. The haematology team will administer your child's treatment in hospital. Your child should be in hospital for up to eight weeks.

### Central nervous system prophylaxis and treatment

The central nervous system (CNS) is made up of the brain and spinal cord. A fluid surrounds these organs to protect them. This is the cerebrospinal fluid (CSF). At diagnosis, leukaemia cells are present in the CSF of around 5% of ALL patients. The amount of leukaemia cells in the CNS of these patients at diagnosis is variable. These presence of these cells can cause relapse of the ALL in up to 30% of cases.

If your child's lumbar puncture shows leukaemia cells in the CNS, your child will receive intrathecal therapy. This is when the haematologist injects methotrexate into your child's CSF. Methotrexate is a strong chemotherapy. Currently it is advised that intrathecal therapy is maintained through all the treatment phases of ALL.

## **Consolidation treatment**

Your child should receive consolidation treatment to help reinforce the remission. This reduces the risk of a relapse. Relapsed is when you achieve remission after treatment, but then the disease returns.

Consolidation therapy consists of higher doses of the drug combinations used for induction.

## **Maintenance treatment**

Your child should receive maintenance treatment after the consolidation treatment. This is to prevent relapse of the ALL. Without maintenance therapy, there is a high chance that the ALL will return.

Maintenance treatment usually consists of low-dose chemotherapy and a steroid drug. Your child can receive maintenance treatment as an outpatient. This might mean going to the hospital for treatment on occasions.

Maintenance treatment lasts for two to three years.

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## **Common treatment options**

### **Chemotherapy**

A common combination of chemotherapies used for ALL is:

- Vincristine
- An anthracycline drug such as daunorubicin, doxorubicin or idarubicin
- Cyclophosphamide or cytarabine
- Asparaginase or pegaspargase (a derived version of asparaginase)

Chemotherapies are often combined with a steroid such as dexamethasone or prednisolone.

## Targeted treatment

Targeted treatments are drugs that target specific proteins on the surface of the leukaemia cells. This means they do not target normal cells so do less damage to normal cells than chemotherapy. Examples of targeted treatments your child might receive are tyrosine kinase inhibitors (TKIs).

### Tyrosine kinase inhibitor

In general, your child might receive a TKI when he/she has the Philadelphia chromosome. TKIs are drugs that inhibit the tyrosine kinase enzyme which controls the function of a cell. They stop the cell growing and dividing.

For patients with the Philadelphia chromosome, adding a TKI to the chemotherapy helps the leukaemia go into remission. [Imatinib](#) and [dasatinib](#) are examples of TKIs. If one TKI does not work or is no longer working, another one might be tried.

## Immunotherapy

Immunotherapy is a treatment that encourages the immune system to attack fight the leukaemia B-cells. Immunotherapy includes:

- Monoclonal antibodies
- CAR T-cell therapy

These treatments help your child's immune system to fight the leukaemia cells. In general, the immune system ignores your child's own cells. Its role is to fight off foreign substances that are not part of your child's body. Although the leukaemia cells comes from your child, they are abnormal.

### Monoclonal antibodies

Monoclonal antibody drugs attach themselves to particular surface proteins on the leukaemia cells. Your child's immune system can detect these antibodies. These antibodies encourage your child's immune system to kill the leukaemia cells.

[Blinatumomab](#) is an example of a monoclonal antibody designed to attach itself to the CD19 protein on the B-cells. It is approved for children aged one and older who are:

- Do not have the Philadelphia chromosome
- Have not responded to previous treatment

### **Chimeric antigen receptor (CAR) T-cell therapies**

[CAR T-cell therapy](#) is a type of immunotherapy used to fight cancer with the patient's own immune cells. Altering the patient's immune T-cells in the laboratory is key to CAR T-cell therapy.

The process of creating CAR T-cell therapy is complicated. A haematology specialist filters out the T-cells from your child's blood and alters them in a laboratory. These modified T-cells are able to destroy the leukaemia cells when they are put back into your child's blood stream. They do this by looking for specific proteins on leukaemia cells.

CAR T-cell therapy is only suitable for some patients.

### **Stem cell transplant**

A [stem cell transplant](#) replaces your child's stem cells in the bone marrow with healthy donor stem cells. The bone marrow is where blood cells are made including the leukaemia cells. The aim of replacing your child's stem cells is to help the production of normal blood cells again.

Your child can receive a stem cell transplant to reduce the risk of relapse. There are two types of stem cell transplant:

- Allogeneic stem cell transplants are a stem cell transplants that use stem cells from a sibling or matching donor.
- Autologous stem cell transplants that use stem cells from the patients themselves. They are rarely performed for ALL patients.

### **New treatments**

Researchers are always developing and testing new drugs for ALL. They are often looking for drugs that are more specific than standard chemotherapy. These drugs should be more efficient than and have fewer side effects.

A particularly busy areas of research is clinical trials of CAR-T cell therapies. This is because of the positive results achieved with tisagenlecleucel.

<https://lcdemo-stage.gb.aldryn.io/about-leukaemia/types/acute-lymphoblastic-leukaemia-all/childhood-acute-lymphoblastic-leukaemia-all/>

Leukaemia Care Registered Charity Number 1183890. Scotland Registered Charity Number SC049802

Helpline: [08088 010 444](tel:08088010444)

Combinations of chemotherapies and monoclonal antibodies are also being trialled.

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## What is the prognosis of childhood ALL?

Due to improvements in treatment of ALL in the last 20 years, overall survival for children aged under six years old is now about 90%. Overall survival in adolescents has improved to 70%-80%.

Relapse of the ALL remains the major cause of death, with median survival following relapse ranging from 10% to approximately 25%.

Factors which increase survival in children with ALL are:

- Young age. Overall survival is better in children under six years old compared with adolescents.
- Favourable chromosome and gene abnormalities.
- Early diagnosis.
- Prompt treatment.

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## Need support?

You are not alone. We're here for you whether you have a diagnosis yourself or know someone who has. If you'd like advice, support, or a listening ear, call our freephone helpline on 08088 010 444 or send a WhatsApp message to 07500 068 065.

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