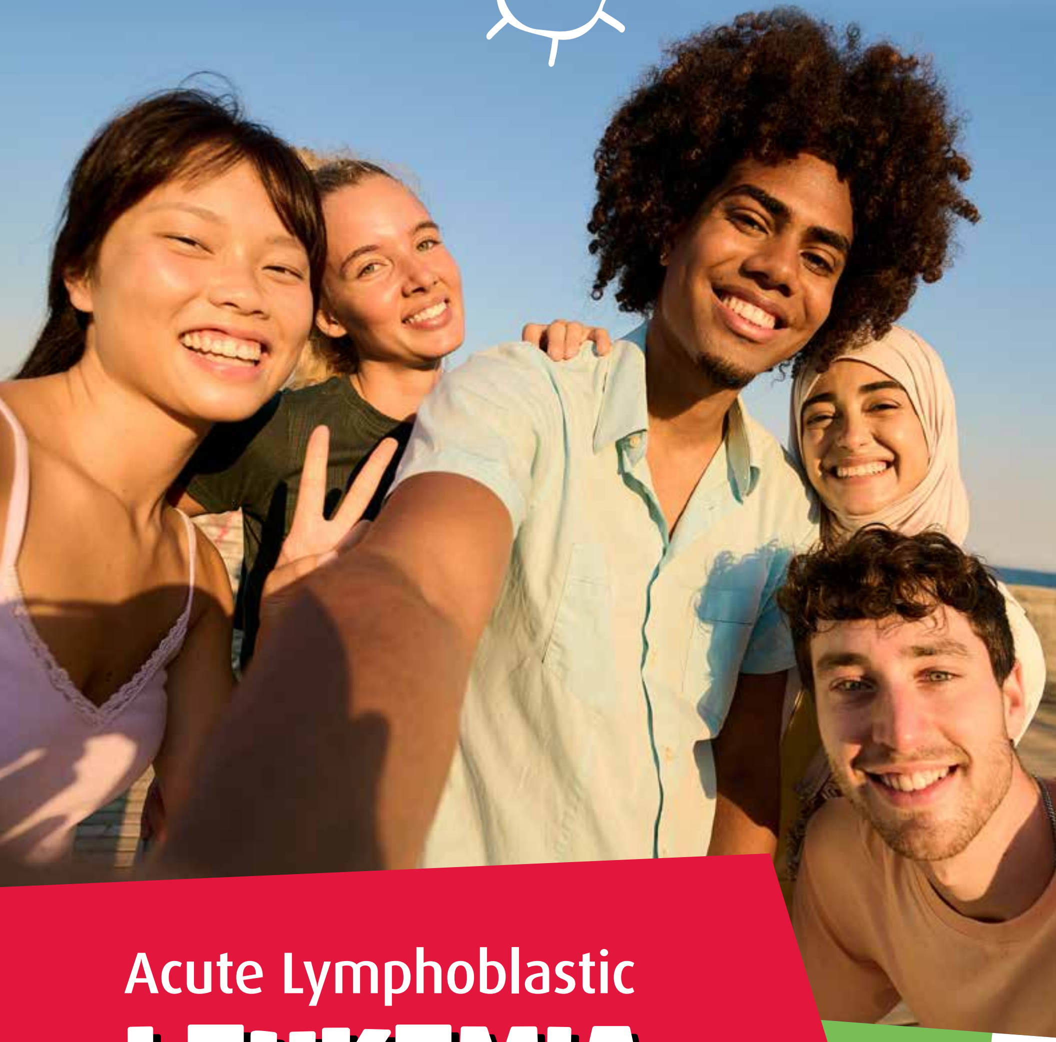
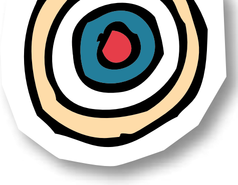
LEUKEMIA &
LYMPHOMA
SOCIETY OF
CANADA®

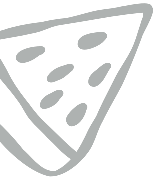


Acute Lymphoblastic
LEUKEMIA
in Children and Teens

Pre- and post-diagnosis testing, treatments and side effects



Contents



Introduction

This booklet provides information about acute lymphoblastic leukemia (ALL) in children and teens. Acute lymphoblastic leukemia is also known as acute lymphocytic leukemia and acute lymphoid leukemia.

People of all ages, from infancy to older adults, can develop ALL. About half of people diagnosed with ALL are children and teens under the age of 18, a group known as "pediatric."

Researchers are trying to understand why genetic mutations occur that lead to ALL, particularly in children. Not all individuals with ALL have the same genetic mutations, and some genetic changes are more common than others. ALL is not hereditary; it cannot be passed on from parent to child.

Advances in treatment have dramatically improved the survival rates for children and teens with ALL in recent decades. Childhood ALL now has one of the highest cure rates of all pediatric cancers. Many survivors return to school, attend college, enter the workforce, and become parents.

However, more work remains to be done. New therapies are being studied in clinical trials to find cures for every child and teen who has ALL. Researchers also are studying less toxic and more effective treatments that are specifically designed for children.

This booklet provides medical information about ALL including: signs and symptoms; tests before and after diagnosis; types of treatment; side effects of treatment, and more.

Treatment for pediatric cancer is complex and affects all the members of the family. Support is important for everyone in the family, especially as treatment can be over a long period of time. LLSC offers free, personalized support and our website's *"My child has a blood cancer"* section features many easy-to-understand resources (videos, podcasts, factsheets, and tools for families).

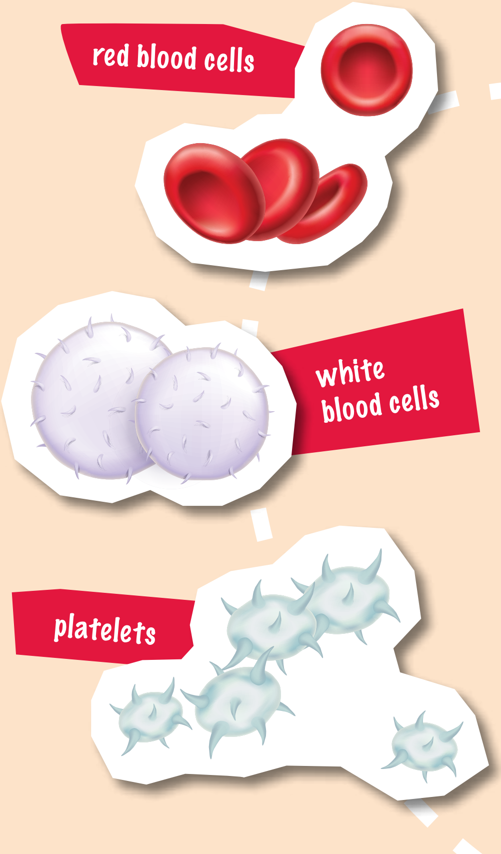
> **"Be open minded to anything that lessens the emotional toll that cancer can take on your child, siblings, spouse and yourself."**

– Rechelle, mom to blood cancer survivor Theo, 8

LEUKEMIA

As leukemia cells multiply uncontrollably and quickly accumulate in the bone marrow, they slow down or stop the production of normal, healthy red blood cells, white blood cells and platelets. As a result, there are too many immature lymphoblasts and too few mature, functional red blood cells, white blood cells and platelets.

Over time, the leukemia cells spill out of the bone marrow into the bloodstream. Once they are in the bloodstream, the leukemia cells can spread to other parts of the body such as the central nervous system (brain and spinal cord), lymph nodes, liver, spleen, and testicles.

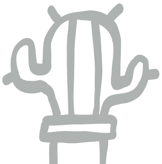


Acute lymphoblastic LEUKEMIA (ALL)

ALL is a fast-growing blood cancer in which the bone marrow makes too many immature white blood cells called “lymphoblasts.” In ALL, a mutation or a series of mutations in the DNA (genetic material) of a lymphoid stem cell results in the formation of an abnormal lymphoblast. This abnormal lymphoblast does not develop into a healthy functioning mature lymphocyte that helps the immune system fight infections. Instead, it becomes a leukemia cell (also referred to as an “ALL cell” or a “leukemia blast”).

There are two main types of healthy lymphocytes, B cells and T cells. There are also two types of ALL, depending on the type of lymphoblast that develops into leukemia:

- B-cell ALL is the most common ALL subtype, accounting for approximately 80-85% percent of cases among children with ALL.
- T-cell ALL accounts for 15 to 20% of ALL in children in teens, and it occurs more often in adolescents and adults than in children.



Signs and symptoms of ALL

Signs and symptoms are changes in the body that may indicate the presence of disease. A sign is a change that the doctor sees during an exam or in a laboratory test result. A symptom is a change that the sick person can see or feel, such as pain and fatigue.

Symptoms of ALL may also be related to leukemia cells collecting in other parts of the body. These symptoms may include:

- Fever
- Unexplained weight loss or loss of appetite
- Night sweats
- Pain in bones and joints, sometimes causing a limp or difficulty walking
- Swollen lymph nodes
- Enlarged spleen or liver
- Abdominal pain
- Wheezing, coughing or painful breathing
- Swollen or bleeding gums
- Appearance of pinhead-sized red or purple spots on the skin, called “petechiae”
- Frequent or severe nosebleeds
- In females, heavier or more frequent menstrual periods
- Facial asymmetry
- Enlarged or infiltrated testicle

By the time ALL is diagnosed, the number of healthy red blood cells, white blood cells, and platelets in the blood is usually lower than normal.

Low red blood cell and platelet counts

For severe or prolonged low red blood cell and platelet counts, transfusions of red blood cells and platelets are almost always needed for several weeks during treatment. Blood cell counts usually return to normal levels after the transfusion(s).

Symptoms of anemia (low red blood cell count) include:

- Fatigue
- Shortness of breath during normal physical activities
- Dizziness
- Pale complexion

Symptoms of thrombocytopenia (low platelet count) include:

- Bruising easily
- Prolonged bleeding from minor cuts

Low white blood cell counts

During ALL treatment, low white blood cell counts can lead to infections from bacteria, viruses and fungi that are normally present in the environment, on the skin, in the nose and mouth, on the gums or in the colon. The risk of infection may be increased because chemotherapy damages the cells lining the mouth and intestines, making it easier for bacteria to enter the bloodstream.

When an individual has a low white blood cell count, antibiotics are commonly given to prevent bacterial infection; other drugs are given to prevent fungal and viral infections. Because of the increased risk of infection during treatment, medical staff, family and friends need to practice frequent and vigorous handwashing and take other precautions to avoid exposing your child to bacteria, viruses and other infection causing agents.

Seek medical attention for your child immediately if any signs of infection develop at home. A temperature of 100.4°F (38°C) or higher or the onset of chills may be the only sign of infection. Other signs of infection may include persistent coughing, sore throat, abdominal pain, diarrhea or pain during urination.

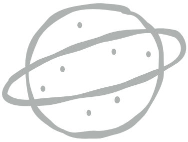
Symptoms of neutropenia (low number of neutrophils, a type of white blood cell important in fighting infections) include:

- Frequent infections
- Recurrent fevers

Pain

Bone pain may occur in children with ALL at the time of diagnosis or during a relapse, due to leukemia cells in the bone marrow. Rarely, some chemotherapy medicines used for children and teens with ALL can cause peripheral neuropathy, a nerve problem that can cause pain, numbness and tingling usually in the hands or feet. Use of medications and physical therapy are very effective approaches for individuals with pain from leukemia or leukemia treatment.

Speak with your child's doctor if your child has any of the above symptoms.

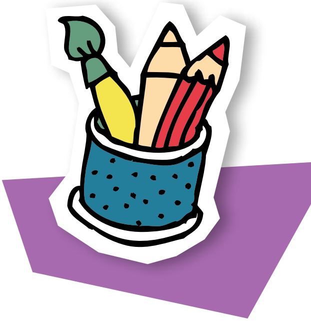


Testing before diagnosis

A person who has signs or symptoms that suggest the possibility of leukemia is referred to a specialist called a hematologist-oncologist. This is a doctor who has special training in diagnosing and treating blood disorders and blood cancers. A pediatric hematologist-oncologist specializes in the care of children with blood disorders and blood cancers.

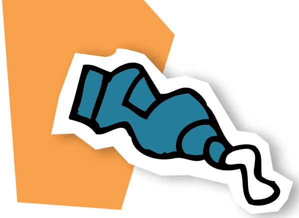
The doctor will conduct various tests to diagnose ALL. Some of these tests may be repeated during or after your child's treatment. Talk to your doctor about:

- The diagnostic tests that are being done
- What the test results mean
- How often will the test be repeated and why



Medical history

Your child's doctor will ask about any health problems or treatments that your child has had. The history may include information about past illnesses, injuries, other treatments, and medications.



Physical examination

The doctor will want to know about your child’s current symptoms and will conduct a physical examination. During the examination, the doctor may listen to your child’s lungs and heart and carefully examine the body for signs of infection and disease. To check the internal organs, the doctor may also feel different parts of your child’s body. For example, the doctor may feel the abdomen to see if your child has an enlarged liver or spleen.

Since ALL can cause enlarged lymph nodes, the doctor may check your child’s lymph nodes in the neck, armpits, and groin (top inner part of the thigh). In individuals with testicles, the doctor may also examine the testicles to see if there are any lumps or swelling.

This test is used to measure the number of red blood cells, white blood cells and platelets in a sample of blood. It also measures the amount of hemoglobin in the red blood cells. The CBC should include a differential, which measures the numbers of the different types of white blood cells in the sample.

Complete Blood Count (CBC) with differential

Children with ALL often have a high number of white blood cells, but most of these are leukemia cells, which are immature lymphoblasts that do not protect against infection. Meanwhile, they may not have enough mature white blood cells, red blood cells or platelets.

Even if the CBC findings suggest leukemia, an ALL diagnosis is usually only made after examination of a sample of bone marrow cells, which can be obtained with bone marrow aspiration and biopsy.

Bone marrow aspiration and biopsy

Leukemia starts in the bone marrow, the spongy tissue inside the centre of most bones. When blood tests show cytopenias (low blood cell counts) or the presence of blast cells (immature cells) in the blood, your child's doctor may recommend a bone marrow aspiration or biopsy to see whether your child's bone marrow is healthy and if it is making normal amounts of blood cells. Doctors use the results from these tests to diagnose and monitor blood and bone marrow diseases, including leukemia.

Bone marrow has both a liquid and a solid component. A bone marrow aspiration is a procedure to remove a sample of the liquid part of the bone marrow. A bone marrow biopsy is a procedure to remove a small sample of the solid, spongy part of the bone marrow.

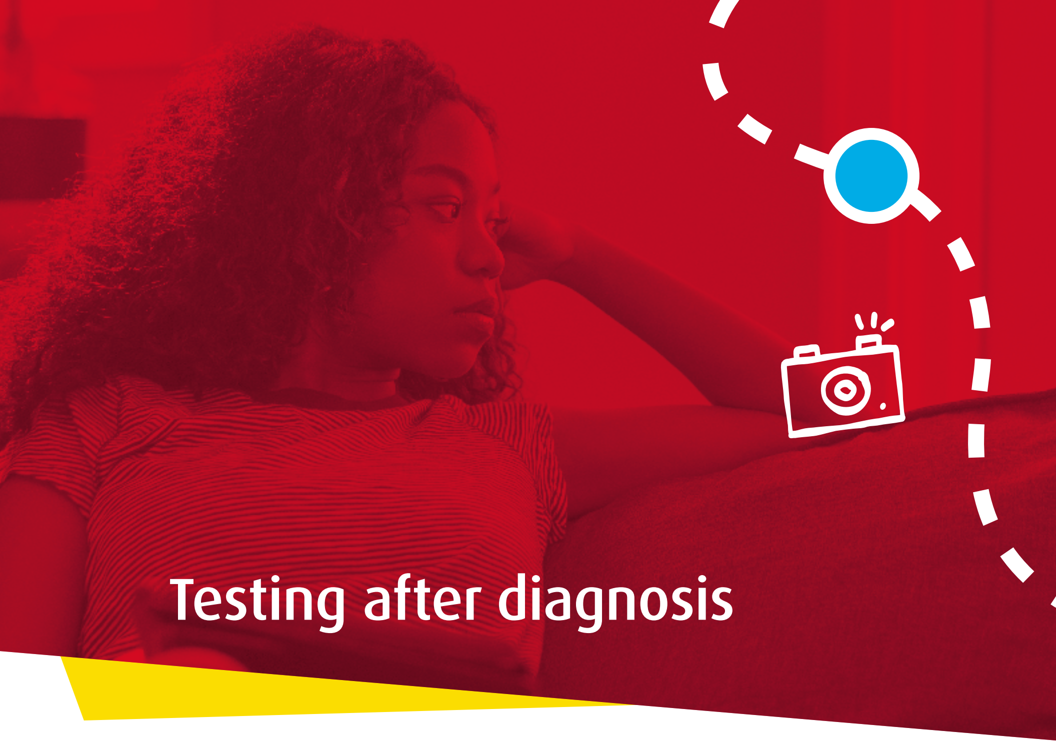
Many children will have just a bone marrow aspiration, but sometimes both tests are necessary to establish the diagnosis. Bone marrow aspiration and biopsy are often performed at the doctor's office or the hospital. Most children are under sedation or general anesthesia during the procedures. The samples are usually taken from the top part of the front or back of the hip bone.

For a bone marrow aspiration, a special hollow biopsy needle is inserted through the hip bone and into the bone marrow to aspirate (remove) a liquid sample of bone marrow cells. For a bone marrow biopsy, a wider needle is used to remove a sample of solid piece of bone marrow.

Both samples are sent to the laboratory where they are examined under a microscope. The various types of white blood cells, red blood cells and platelets are counted and examined to check their composition and determine whether the cells look abnormal.

The doctor also determines the percentage of blast cells in the bone marrow. In normal healthy bone marrow, there are typically no more than 5 percent blast cells. Generally, a diagnosis of ALL in children requires a finding of 25 percent or more lymphoblasts in the bone marrow.

> Those early hours and days after diagnosis are full of information that comes at you fast and furious and is often hard to process at the time. Find quiet moments to let yourself feel and understand the new information.
>
> - Kirstin, mom to son diagnosed at age 5 with ALL

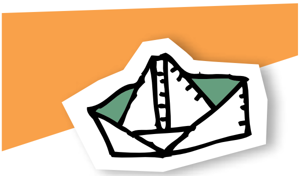


Testing after diagnosis

If ALL is diagnosed, additional tests may be done on the blood and bone marrow samples to gather important information about the subtype of ALL and to guide treatment. Not every child will need every one of these tests; your healthcare team will decide which ones are necessary for your child's specific situation.

In general, for children to be diagnosed with ALL, there must be 25 percent or more lymphoblasts in the bone marrow. The World Health Organization (WHO) classifies ALL based on the following:

- The type of lymphocytes affected (B cell vs T cell); and
- The specific gene or chromosomal changes to the leukemia cells.



Determination of your child's ALL subtype is an important factor in treatment planning. Based on your child's ALL subtype, you and your doctor will discuss your child's treatment options.

Biomarker testing

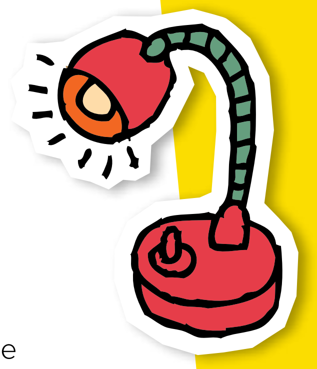
Biomarker tests are tests examining the cancer cells from the blood, bone marrow, lymph nodes or other tissues to check for certain genes, proteins, or other molecules. Each person's cancer has a unique pattern of biomarkers. Biomarker testing should be done when the cancer is first diagnosed and may also be done after a relapse. This is because it is possible for individuals to acquire additional genetic abnormalities after the completion of their first line (initial) treatment. Biomarker tests for ALL include:

Immunophenotyping (Flow Cytometry)

This lab test identifies cancer cells based on markers called antigens. Antigens are proteins found either on the surface or within white blood cells. Finding (or not finding) certain antigens can help determine the type of leukemia. The pattern of the surface proteins is called the "immunophenotype." A bone marrow sample is often used for this test, but it can also be done on blast cells from the blood, lymph nodes and other tissues.

Immunophenotyping is done with an instrument called a flow cytometer. Cells are stained with a light-sensitive dye and are passed through a laser beam in the flow cytometer. If they have an antibody-specific surface marker, the cells light up and are counted. Flow cytometry can find one cancer cell among up to 100,000 normal bone marrow cells.

Karyotyping



Cancer is a disease caused by mutations (changes) to the genetic material inside of cells, the DNA. Inside cells, DNA is packaged into thread-like structures called “chromosomes.” In individuals with ALL, cytogenetic analysis is used to look for abnormal changes in the structure of the chromosomes within the leukemia cells. Normal human cells contain 23 pairs of chromosomes, for a total of 46 chromosomes. Each pair of chromosomes is a certain size, shape, and structure. In many cases of ALL, the chromosomes of leukemia cells have abnormal changes that can be seen under a microscope. Cytogenetic testing can be done on leukemia cells from either a bone marrow sample or a blood sample. The leukemia cells in the sample are allowed to grow in the laboratory and then are stained. The stained sample is examined under a microscope and photographed to show the arrangement of the chromosomes, called a “karyotype.” The karyotype shows if there are any abnormal changes in the size, shape, structure, or number of chromosomes in the leukemia cells.

Karyotyping is one of the genetic biomarkers of the leukemia that provides information for determining an individual’s prognosis (the likely outcome of the disease) and treatment options.

This information can predict how the disease will respond to treatment. For example, one chromosome relation is associated with a diagnosis of Philadelphia chromosome-positive (Ph+) ALL, a subtype of ALL treated differently from other subtypes.

Fluorescence In Situ Hybridization (FISH)

Doctors use this very sensitive test to detect certain abnormal changes in the chromosomes and genes of leukemia cells. Pieces of DNA that contain special fluorescent dyes are prepared in the laboratory and added to the leukemia cells on a glass slide. The pieces of DNA that bind to certain genes or areas of chromosomes light up when the slide is viewed under a "fluorescence" microscope. Not only can FISH identify most abnormal changes that can be seen with a microscope, but it can also detect some changes that are too small to be seen with basic cytogenetic testing. However, it is not used as a general screening tool. FISH has one disadvantage; the doctor must select the specific chromosomes or genes to examine before the test is performed.

Polymerase chain reaction (PCR)

This is another very sensitive lab test. Doctors use it to detect and measure certain genetic mutations and chromosomal changes within the leukemia cells that are too small to be seen with a microscope. PCR essentially amplifies (increases) small amounts of specific pieces of either RNA or DNA to make them easier to detect and measure in a cell sample. This test can find a single leukemia cell among more than 100,000 to 1 million healthy cells. PCR testing is another method used to determine minimal residual disease (MRD) in an individual which is the small amount of cancer cells that may remain in the body after treatment. PCR can be done with either a bone marrow sample or a blood sample.

Next-generation sequencing (NGS)

The term "next-generation sequencing (NGS)" is a catch-all term used to describe various modern sequencing technologies. NSG is also known as molecular testing or genomic testing.

These technologies determine the exact order (sequencing) of DNA and RNA much more quickly and cheaply than sequencing methods that were used previously. NSG makes it possible to identify a variety of genetic changes in cancer cells. These changes may guide risk assessment and prognosis and may also play a part in treatment decisions.

The information these tests provide can help doctors determine which individuals are at high risk and may need more intensive treatment or may benefit from treatment with new therapies. Doctors may order sequencing of all the DNA in the cancer cells and/or normal cells in the body, known as whole genome sequencing. Not all people with ALL have the same genetic changes. Some changes are more common than others, and some have a greater effect on a person's prognosis. Next-generation sequencing can find one leukemia cell among one million bone marrow cells.

Treatment planning

Children and teens who are diagnosed with ALL usually need to start treatment as soon as possible after diagnosis. If you are thinking of getting a second medical opinion, talk to your healthcare team. They can explain the timing of treatment and help you decide what's best for your child. Remember, your child's doctor is not making decisions alone. Pediatric cancer care teams often review each child's case with their fellow experts.

Fertility

Cancer treatments, including some chemotherapy drugs, radiation, and surgery, may affect your child's fertility (the ability to have children in the future). Changes to fertility, which can happen to both males and females, may be temporary or permanent.

Before your child begins treatment, it is important to talk with the doctor about whether the treatment could affect your child's fertility. You may also want to speak with a fertility specialist, a doctor who diagnoses and treats problems related to infertility. The fertility specialist can talk to you about possible options for preserving your child's fertility.

However, delaying treatment to address fertility options may not always be recommended. Many children with ALL need to start treatment right away. Even if your child must start treatment immediately, a fertility specialist may still be able to help your child preserve their fertility after they have finished induction therapy and before they continue with additional intensive post-remission therapies.

Pre-treatment testing

Before your child starts treatment, the doctor will perform tests to learn more about your child's leukemia and overall health, and to find out if the leukemia has spread to other parts of the body. Doctors use this information for treatment planning. Some of these tests are summarized below.

Blood tests

Doctors test blood to help plan treatment, including these types of blood tests.

Complete blood count (CBC) with differential

CBC with differential is used to measure the number of red blood cells, white blood cells and platelets in a sample of blood. It also measures the amount of hemoglobin in the red blood cells. The CBC should include a differential, which measures the numbers of the different types of white blood cells in the sample.

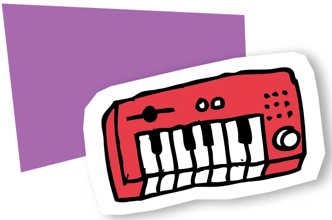
Blood chemistry profile

The blood chemistry profile test measures the levels of certain substances released into the blood by organs and tissues in the body. These substances include electrolytes (such as sodium, potassium, and chloride), fats, proteins, glucose (blood sugar), uric acid and enzymes.

A blood chemistry test indicates how well a person's kidneys, liver and other organs are working. It also provides helpful information about any potential organ damage caused by leukemia cells or cancer treatments.

Liver function tests

Liver function tests check how well the liver is working. The liver is the largest organ inside the body. It is in the upper right side of the abdomen. It helps the body digest food, store energy and remove toxins from the blood. If leukemia cells are present in the liver, they can affect liver function. In addition, some chemotherapy drugs can damage the liver, which can also affect liver function.



Coagulation tests

Coagulation (blood clotting) prevents excessive bleeding from a cut or injury. But if blood clots form inside of blood vessels, they can become dangerous. Coagulation tests measure the blood's ability to clot and how long it takes. Certain proteins, called coagulation factors, are needed for clotting. Most of these proteins are made by the liver.

In addition to checking how well the blood can clot, these tests can determine whether there are deficiencies in some proteins, such as fibrinogen, a protein that helps blood clot.

Tumor lysis syndrome (TLS) panel test

Children with ALL may be at high risk for developing a condition called tumor lysis syndrome (TLS). This condition can occur after treatment begins, when a great many cancer cells may die within a short period of time. As the leukemia cells die, they break apart and release their contents into the bloodstream, which changes the normal balance of chemicals in the blood. This can overwhelm the kidneys because they cannot get rid of the toxic substances all at once.

The effects of TLS can be life-threatening; they can be severe during the early phases of treatment, especially if the white blood cell count is very high before induction therapy. A TLS panel can help the doctor assess if your child is likely to get or already has TLS.

HLA typing test

This blood test identifies certain proteins, called human leukocyte antigens (HLAs), found on the surface of most cells in the body. HLAs make up a person's tissue type, which varies from person to person. They also play an important role in the body's immune response to foreign substances by helping the body distinguish its own cells from foreign cells.

HLA typing is done before allogeneic stem cell transplantation to find out if there is a tissue match between the donor and the receiving individual. It is an important test most commonly performed after relapse when allogeneic stem cell transplantation is being considered as a treatment option.

Lumbar puncture

ALL can spread to the fluid that flows around the brain and spinal cord, called the cerebrospinal fluid. To determine whether leukemia cells have spread to this area, a sample of the cerebrospinal fluid is collected in a procedure called a lumbar puncture or spinal tap.

After the area over the spine in the lower part of the back has been numbed with a local anesthetic, a thin needle is inserted between two bones in the spine (vertebrae) and into the cerebrospinal fluid. A sample of the fluid is withdrawn and examined under a microscope to look for leukemia cells that may have spread to the brain and spinal cord.

Imaging tests

Imaging tests are not routinely done for children with ALL, except in select circumstances. These tests create images (pictures) of the inside of the body. A radiologist is a doctor who specializes in reading these images that detect where a cancer is located in the body.

Chest X-ray

A type of high-energy radiation that can go through the body and onto film to make pictures of areas inside the chest. A chest x-ray is used to look for a mass (lump) in the mediastinum, the area between the lungs. The organs in this area include the heart, trachea, esophagus, thymus, and lymph nodes.

Positron emission tomography-computed tomography (PET-CT) scan

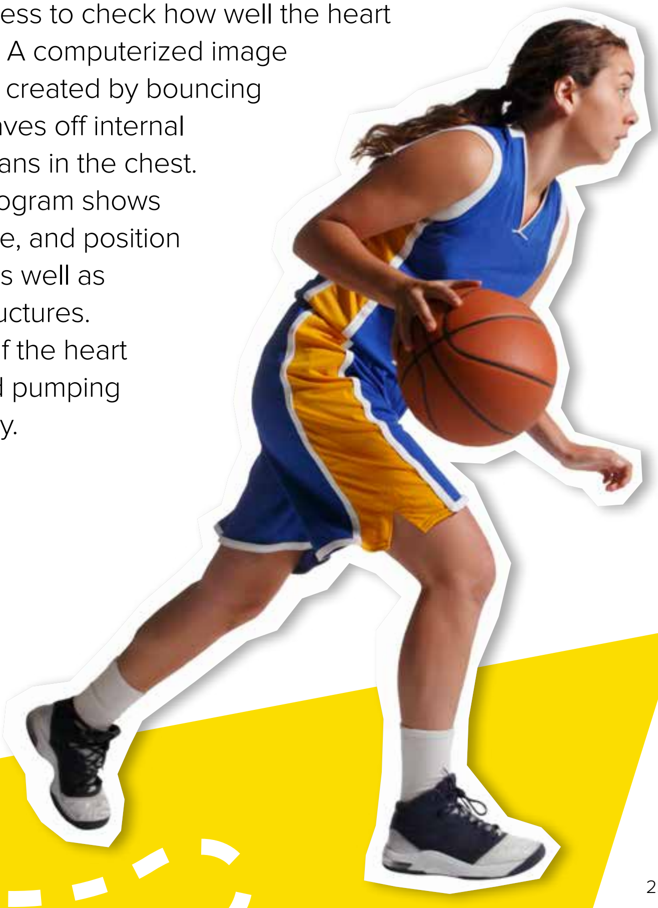
This procedure combines images from a both a PET scan and a CT scan. The combined scans give a more detailed image of areas inside the body than either scan alone. If lymphoblastic lymphoma is suspected, a whole-body PET-CT scan is recommended.

Ultrasound

This imaging test uses high-energy sound waves to examine tissues and organs inside the body. For example, it can detect cancer in the testicles of males. If the testicles are not the same size or have any lumps, the doctor may order an ultrasound to see whether there are leukemia cells in the testicles.

Echocardiogram

Certain cancer treatments can damage the heart. The doctor may perform an echocardiogram as part of the treatment planning process to check how well the heart pumps blood. A computerized image of the heart is created by bouncing ultrasound waves off internal tissues or organs in the chest. An echocardiogram shows the size, shape, and position of the heart, as well as its internal structures. It also shows if the heart is beating and pumping blood normally.



Prognostic factors

A prognosis is the probable outcome of a disease or ailment. Certain factors can affect a prognosis. Doctors use prognostic factors to help predict how likely the disease is to respond to treatment. These factors help doctors plan the most appropriate treatment regimen for each child or teen.

Prognostic factors are different for B-cell ALL and for T-cell ALL in children and teens.

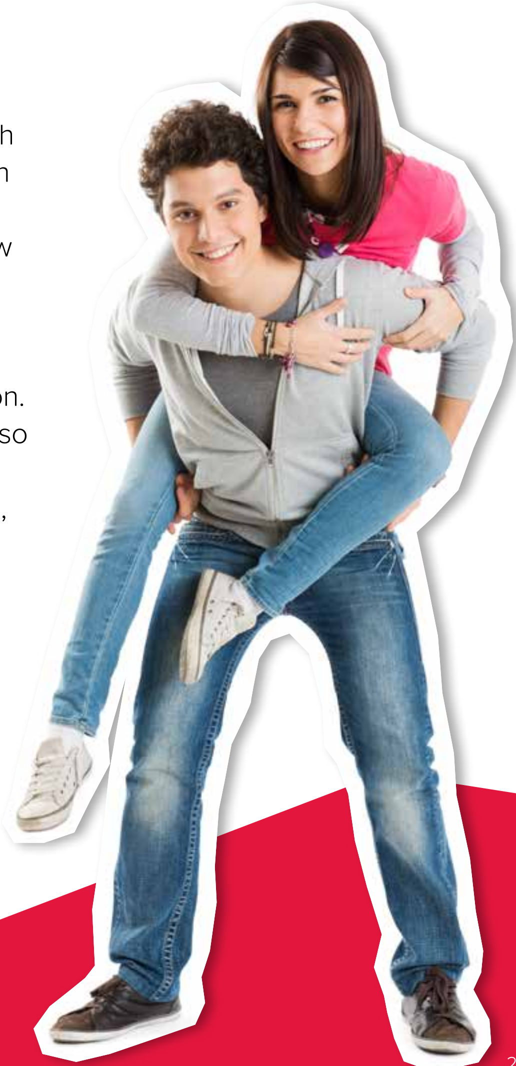
Prognosis factors for B-cell ALL

- **Age:** ALL tends to be more aggressive in infants younger than 1 year and children older than 10 years old.
- **White blood cell count:** Children with white blood cell counts of 50,000 per microliter (µL) or greater at the time of diagnosis need stronger treatment.
- **Biomarkers:** Certain changes in the chromosomes or genes can make the leukemia cells either easier or harder to treat. Researchers have found that for individuals with B-cell ALL, some genetic mutations respond better to treatment than others. Identifying specific genetic abnormalities is critical for disease evaluation, risk stratification and treatment planning.

- **Extramedullary disease:** Children who have leukemia cells in the central nervous system or testicles at diagnosis are at a higher risk of disease relapse.
- **Treatment response:** Children who have a better response to induction therapy, which is the first phase of treatment, have a lower risk of relapse. This is measured by a sensitive technique called minimal residual disease (MRD), which is the most powerful prognostic factor for B-ALL.

Prognosis factors for T-cell ALL

For children and teens with T-cell ALL, risk stratification is primarily based on their response to therapy – how much minimal residual disease (MRD) they have in their body at end of induction and consolidation. While researchers have also identified specific genetic abnormalities in T-cell ALL, these abnormalities are not currently used in the routine diagnosis and treatment planning.



Risk groups for pediatric **ALL**

Based on prognostic factors, children with ALL are often categorized into one of several risk groups, with names such as low risk, standard risk, high risk or very high risk. This is called risk stratification. Typically, children with ALL in the low or standard risk group have a better prognosis and receive less intensive treatment than those in the two higher-risk groups.

Your doctor may describe your child's ALL in terms of its risk group. Your child is assigned to a risk group based on a combination of the prognostic factors listed above. Knowing your child's risk group helps the doctors develop the most effective treatment plan for your child. Children and teens with lower risk ALL are more likely to have a favorable outcome and need less aggressive treatment. Individuals in the high risk and very high-risk groups usually receive more intense treatment than those in the lower-risk groups.

Different institutions use different combinations of prognostic factors to assign individuals with ALL into risk groups.
The following factors at diagnosis are used to assign children and teens to initial risk groups for the first month of induction:

Standard (low) risk

Children between 1 and 10 years old who have a white blood cell count less than 50,000/µL at the time of diagnosis.

High risk

Children 10 years and older and/or children who have a white blood cell count of 50,000/µL or more at the time of diagnosis.

Very high risk

- Children younger than 1 year
- Children with certain genetic changes
- Children who have a slow response to initial treatment
- Children with minimal residual disease (MRD) after 4 weeks of induction therapy for B-ALL. MRD is when cancer cells that cannot be seen with a microscope are still in the body.

Treatment

The goal of treatment is to kill the leukemia cells and stop the bone marrow from making any more leukemia cells. The main treatment for ALL is chemotherapy. Chemotherapy can be given by mouth, through a vein, or into the fluid around the spine. Some treatment plans may include targeted agents or, possibly, stem cell transplantation.

Before treatment begins, your child's doctor will discuss treatment options with you. Not every child with ALL receives the same type of treatment. The doctor will tailor your child's treatment based on several factors, including the subtype of the disease.

ALL treatment is divided into phases that are different in length and use different types of medication. The term 'regimen' is used to describe the full treatment plan for your child that encompasses these phases: induction, consolidation, interim maintenance, delayed intensification, and maintenance. Different hospitals may use varying terms to describe the phases of treatment.

Chemotherapy

Most children with ALL are treated with intensive chemotherapy. Chemotherapy drugs affect cells that divide quickly, which is why they work against cancer cells. Chemotherapy drugs used for pediatric ALL include:

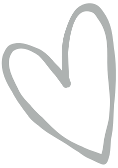
- **Alkylating agents:** These drugs prevent cells from reproducing (dividing) by damaging the DNA in the cells.
- **Anthracyclines:** These drugs work by damaging the DNA of cancer cells, which causes them to die before they can multiply.
- **Antimetabolites:** The drugs interfere with the normal division and function of cancer cells. Antimetabolites mimic the building blocks of DNA or RNA that cancer cells need to survive and grow. When the cancer cell uses an antimetabolite instead of the natural substances, it cannot produce normal DNA or RNA and the cell dies.
- **Plant alkaloids:** These drugs, made from certain types of plants, are cell-cycle specific, meaning they attack the cancer cells during various phases of division.

Theo, 5, during his chemotherapy treatment for blood cancer, helps his dad shave his head.

General side effects of chemotherapy

Since chemotherapy drugs also affect healthy cells in the body that divide quickly, such as the lining of the intestines, the skin and hair follicles, common side effects of chemotherapy may include:

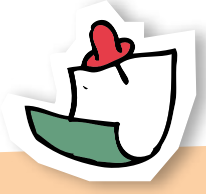
- Hair loss
- Fatigue
- Nausea and vomiting
- Loss of appetite
- Infections
- Mouth sores
- Rashes
- Diarrhea
- Headaches



These short-term side effects usually go away once your child has completed treatment. Fortunately, drugs that counteract nausea and vomiting can be given to prevent or relieve these distressing side effects.

Induction phase of treatment

The first phase of chemotherapy is called induction; the goal of induction is to destroy as many cancer cells as possible to induce (achieve) a remission which is characterized by the disappearance of lymphoblasts as much as possible, along with the reappearance of normal white blood cells, red blood cells, and platelets in the bone marrow. Induction lasts for 4 to 6 weeks, much of that time in the hospital.



> “From the oncology folks to playroom and cafeteria staff in the hospital, everyone was so fabulous and in the right place, smile on their faces, they'll do anything to make their burden easier, know their favourite chair.”
>
> - Veronica Vardy, whose daughter diagnosed at 2 with ALL

The specific drugs, and their dosages and timing, depend on factors including your child's age and the specific features of the leukemia cells, and risk type. Drugs given in induction may include chemotherapy drugs of several kinds, corticosteroids, and tyrosine kinase inhibitor (TKI), as well as a treatment called CNS-directed therapy.

If your child or teen has central lines or ports, you and other caregivers need to be meticulous about following the medical team's instructions for cleaning insertion sites and catheters.

Tumor Lysis Syndrome (TLS)

Children with ALL may be at risk for developing a condition called tumor lysis syndrome (TLS) at the start of induction. This condition occurs when many cancer cells die within a short period of time, releasing their contents into the blood.

TLS can be severe during the early phases of treatment, especially for children who have very high white blood cell counts before induction therapy. Uric acid is one of the chemicals released by dying cancer cells. Very high levels of uric acid and other chemicals can cause severe damage to the kidneys and heart. If untreated, TLS can lead to heart arrhythmias, seizures, loss of muscle control, acute kidney failure and even death. Fortunately, these potential complications are extremely rare.

Treatment should include hydration to reduce the risk of developing TLS. Intravenous (IV) fluids are usually started at the time of diagnosis and are continued as much as needed to prevent chemical imbalances in the blood and to support kidney function. Children with ALL are monitored at the beginning of chemotherapy for the development of TLS and are given drugs to prevent or lessen the effects of TLS.

Corticosteroids

Corticosteroids are synthetic hormones (relatives of the natural hormone, cortisol) that can kill lymphocytes. They are believed to work by blocking cell metabolism through their effect on specific genes. In high doses, corticosteroids can kill leukemia cells. Corticosteroids are a main component of virtually every induction regimen for ALL, as well as being frequently included in the consolidation and maintenance phases of treatment.

Side effects of corticosteroids

Acute side effects of corticosteroids may include:

- Weight gain
- Hyperglycemia (high blood sugar)
- Hypertension (high blood pressure)
- Increased appetite
- Change in mood
- Gastric ulcers

Individuals should be monitored to ensure that their glucose (blood sugar) levels are under control. To reduce the risk of gastric ulcers, medicines that reduce stomach acid, such as H2 blockers or proton-pump inhibitor drugs, may be recommended during corticosteroid therapy.

Children with **standard-risk ALL** often receive three drugs for the first month of treatment. These include the chemotherapy drugs and corticosteroids.

For **high-risk or very high-risk ALL** in children and teens, another chemotherapy drug in the anthracycline family is typically added.

Children with **Philadelphia chromosome-positive (Ph+) ALL** and some **Philadelphia chromosome-like (Ph-like) ALL** are also given a tyrosine kinase inhibitor (TKI) medication on top of the other drugs. TKIs are substances that block the action of enzymes called tyrosine kinases, which may be too active or found at high levels in some types of cancer cells.

CNS-directed therapy

Beginning in the induction phase, and continuing throughout your child's entire course of treatment, a therapy is given to prevent the spread of leukemia cells to the spinal cord, brain and cerebrospinal fluid, the liquid around the brain and spinal cord. This therapy, called central nervous system (CNS) directed therapy, also kills any leukemia cells that may already be present there.

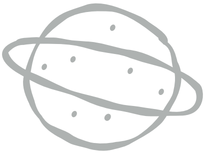
It is uncommon for leukemia cells to be present in the cerebrospinal fluid at the time of diagnosis; this occurs in only 3 to 7 percent of cases. However, without routine CNS-directed therapy, leukemia cells will eventually spread to the cerebrospinal fluid in a large percentage of individuals with ALL. CNS-directed therapy may include:

- **Intrathecal chemotherapy.** Anti-cancer drugs are injected into the fluid-filled space between the thin layers of tissue that cover the brain and spinal cord. The most common intrathecal chemotherapy drug used in children with ALL is methotrexate. Sometimes, other drugs and a corticosteroid are used, particularly in children with high-risk ALL.

- **Systemic chemotherapy.** Anti-cancer drugs are injected into a vein and travel through the blood to cells throughout the body.
- **Cranial irradiation.** This therapy, which is radiation to the brain to kill cancer cells, is no longer routinely used in children with ALL, except when a high number of leukemia cells are found in the cerebrospinal fluid at the time of diagnosis, or those with CNS relapse. Cranial radiation is almost never used in very young children. However, it is very effective in the treatment of CNS leukemia, when indicated.

Side effects of CNS-directed therapy

CNS-directed therapy can cause a range of side effects, both acute and long-term. These can include cognitive changes, mood disturbances, sleep problems, fatigue, loss of appetite, nausea, and vomiting, and neurological complications. The specific side effects depend on the type of therapy and individual factor.



Psychosocial side effects of treatment

As well as ALL treatment resulting in physical side effects, the cancer can affect how your child feels, learns, and connects with others. It can be hard for the whole family, too. If you notice changes in your child's mood, behavior, or learning or if you're feeling overwhelmed talk to your healthcare team. They can connect you with support services or professional mental health help, if needed. You are not alone.

> "During chemotherapy, Theo became a very different kid. He was angry all the time, you couldn't regulate him. He would cry hours straight... I didn't want the trauma of cancer to be worse for him than it had to be, so we agreed to try him on a temporary anti-anxiety medication. I wish I'd done it sooner."
>
> \- mom Rechelle

Testing after the induction phase

At the end of the induction phase, your child will have another bone marrow aspiration to check to see if the cancer is in complete remission. A complete remission is achieved when:

✓ No more than 5 percent of cells in the bone marrow are blast cells

✓ No blasts are in the bloodstream, spinal fluid, or testicles

✓ Blood cell counts are back to normal

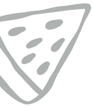
✓ All signs and symptoms of ALL are gone

More than 95 percent of children achieve a remission at the end of induction. However, that does not mean that your child is cured; more treatment is needed to ensure that the disease does not come back (relapse).

For individuals who do not achieve remission after the first course of induction chemotherapy, a second course of chemotherapy is given, usually using different chemotherapy drugs. Children with leukemia cells in their testicles at diagnosis, that is not resolved by the end of induction, may receive radiation treatment to the testicles during consolidation, the next phase of treatment after induction.

Even when a complete remission is achieved, some leukemia cells that cannot be seen with a microscope may remain in the body. The presence of these cells is referred to as minimal residual disease (MRD). Individuals who have a positive MRD are at increased risk of relapse (having their disease come back). It is important for your child to get tested for MRD even after achieving remission.

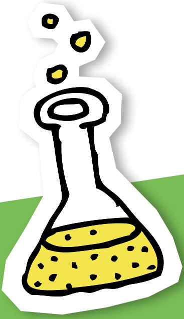
Doctors need MRD test results at the end of induction to determine your child's level of risk for relapse and whether



further intensified therapies should be used. There are very sensitive tests to detect MRD. The most widely used tests are flow cytometry, polymerase chain reaction (PCR), and next-generation sequencing.

If your child tests positive for MRD, there are still detectable leukemia cells inside the bone marrow, and your child has a higher risk of relapse. Depending on the amount of MRD, your child's doctor may change the treatment plan. In T-ALL, the MRD most often relied upon to guide treatment is the MRD done after the consolidation phase.

If your child tests negative for MRD, that indicates that the tests did not detect residual leukemia cells and your child has a lower risk of relapse. However, even when MRD test results are negative, undetectable residual cancer cells are believed to remain in the body, so all children and teens with ALL require additional phases of treatment after they achieve remission. Most of these phases of treatment are given in an outpatient setting, while some phases require a brief hospitalization for chemotherapy.

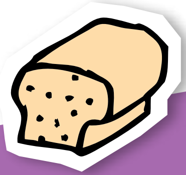


Consolidation phase of treatment

Consolidation, also called “intensification” is the next phase to follow induction. The goal of consolidation is to kill any remaining leukemia cells in the body that may cause a relapse. In consolidation, lower-risk children and teens typically receive less intensive therapy, while higher-risk individuals receive therapy that is more intense.

The consolidation phase usually lasts for 4 to 8 weeks, depending on your child’s ALL risk category and treatment protocol. Consolidation chemotherapy does not usually require a hospital stay. It is often given in an outpatient setting, allowing your child to go home after each scheduled treatment. But if there are complications, such as fever or infection, a child may be admitted to the hospital.

The combination of drugs and the duration of therapy for consolidation regimens vary but can consist of combinations of drugs like those used during induction. Generally, several chemotherapy drugs are combined to help prevent the leukemia cells from developing drug resistance.



Types of treatment in consolidation phase

Allogeneic stem cell transplantation

As part of consolidation, very rarely, some children in remission may receive allogeneic stem cell transplantation (SCT) where the stem cells are donated from another person, ideally someone genetically related. Allogeneic SCT is not used as the first or primary treatment for most children with ALL. Allogeneic SCT may be used as a treatment for:

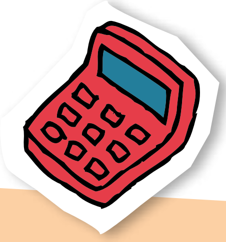
- Very high-risk individuals who have ALL
- Those who have a particularly high risk of relapse due to genetic features
- Those who have not responded to any other treatment
- Those who have very high levels of MRD after induction and/or consolidation

Radiation therapy

Sometimes, leukemia cells can hide inside the testicles. If your child still has evidence of leukemia in the testicles after induction, the doctor may use radiation therapy directly to the testicles. Your child's doctor will give radiation therapy during consolidation.

Radiation therapy, also known as "radiotherapy," uses high-energy x-rays or other types of radiation to kill cancer cells in a small, targeted area of the body. These rays damage or destroy leukemia cells, but they cannot be seen or felt. Radiation can also harm normal cells; so whenever possible, radiation therapy is directed only at the areas that are affected with cancer, to reduce the long-term side effects.

Radiation therapy is split into several treatments called "fractions" that are given each day from Monday to Friday over a period of weeks. The number of days of treatment depends on the dose of radiation required to treat the leukemia cells in the testicles.

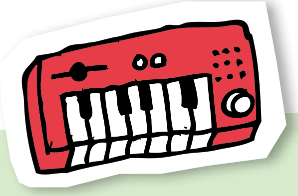


> "In childhood cancer treatment, delays happen for any number of reasons; protocols sometimes change and making concrete plans more than a day or two in advance is often not practical. Get comfortable with being uncomfortable."
>
> - mom Kristin

Blinatumomab

Blinatumomab is a bispecific T-Cell engager (BiTE). BiTEs are monoclonal antibody therapies that attach to two different proteins at the same time. One attaches to a protein called CD19 on B cells including some leukemia cells. Another attaches to a protein called CD3 on immune cells called T cells. By binding to both proteins, the drug brings the cancer cells and immune cells together, which causes the immune system to attack the cancer cells. Blinatumomab is used for some patients depending on their risk group, as it helps lower the chance of the leukemia coming back. It is usually not needed for patients with favorable leukemia genetics who have no measurable disease after the first phase of treatment.

Blinatumomab is given through a continuous IV infusion for 28 days at a time. Treatment usually begins with a short hospital stay of 1 to 2 days and can then be continued at home. Patients need to return to the hospital every 4 to 7 days to have the medication bag changed. Blinatumomab is considered a less intensive treatment compared to conventional chemotherapy. Fever is common when starting blinatumomab because of how the immune system responds to the medicine. More serious side effects, such as headaches or seizures, are rare. Normally, B cells in the body make antibodies that help fight infections. Because blinatumomab also affects normal B cells, doctors will check antibody levels regularly and may give replacement antibodies (immunoglobulins) if needed.



Interim maintenance phase of treatment

After the consolidation phase and the blinatumomab phase (if needed), there is a less-intensive recovery period called interim maintenance. Interim maintenance is typically given for up to 8 weeks. It is a period between the two phases, consolidation (or Blinatumomab block) and delayed intensification.

Interim maintenance involves chemotherapy that doesn’t significantly decrease blood cell count. Your child or teen will usually receive, intravenously, a chemotherapy agent and immune-system suppressant in combination with other chemotherapy agents. If lower doses are prescribed, it may be given in a clinic. Higher doses may require a stay of several days (usually 2 to 5 days) in the hospital.

Delayed intensification phase of treatment

The goal of the delayed intensification phase is to eliminate residual, drug-resistant leukemia cells from the body. It typically lasts 8 weeks and includes chemotherapy combinations like those used in the induction and consolidation phases.

The exact timing of the doses and the specific drugs given will depend on the individual characteristics of your child's disease. Delayed intensification does not usually require a hospital stay to administer chemotherapy, but children are sometimes admitted to the hospital for complications, such as fever and infection.

Maintenance phase of treatment

Maintenance is the last and longest phase of treatment. The goal of maintenance therapy is to maintain remission. Children receive lower doses of chemotherapy during the maintenance phase and, as a result, tend to have less severe side effects.

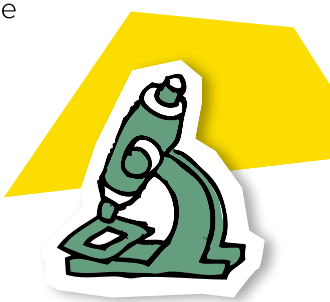
Maintenance therapy usually lasts two years from the start of the first interim maintenance phase. Because some of these medications are taken orally at home, it is extremely important that a parent or caretaker ensure that the child takes the medication as prescribed by the doctor. Not taking the medication as prescribed by the doctor can increase the chance that the cancer will come back.

Relapsed/refractory **ALL** treatment

Relapsed ALL means the cancer has returned after remission, which happens to about 10 to 15% of children and teens with ALL. Some other individuals are unable to achieve a remission because their cancer does not respond to treatment; that is referred to as refractory ALL.

Relapsed/refractory ALL is very serious and can be more difficult to treat. But there are treatment options available. Treatment for relapsed or refractory ALL is usually more intensive than the treatment used following initial diagnosis.

Genetic testing of the leukemia cells is recommended for children or teens with relapsed or refractory ALL before treatment starts. The mutational pattern of the leukemia cells may be different from when the disease was first diagnosed, and this can affect treatment decisions.

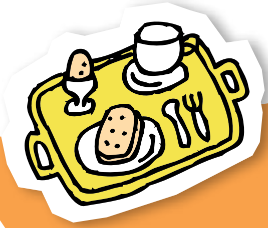


For those with Ph+ ALL, new mutations in the BCR:ABL1 gene may occur over time. Some mutations can lead to resistance to certain TKIs. Before a child or teen starts treatment for relapsed/ refractory Ph+ ALL, BCR:ABL1 mutation testing should be done to look for new mutations that may cause certain TKIs to stop working.

Treatment for relapsed ALL

The goal of treatment for relapsed ALL is to achieve a complete remission again and keep the leukemia from returning. The treatment your child needs depends on several factors including:

- Type of ALL (B-cell or T-cell)
- Amount of time that has passed between the initial diagnosis and detection of relapse. Recurrences that occur three years or more after diagnosis have a better prognosis
- Results of genetic testing of the leukemia cells
- Prior treatments your child has received for ALL
- Location in the body where the relapse has occurred
    - When the cancer returns only in the bone marrow, it is called isolated medullary relapse
    - When the cancer occurs outside the bone marrow (for example, in the central nervous system or testicles), it is called isolated extramedullary relapse
    - When it occurs in both places, it is called combined relapse



Treatment for refractory ALL

The goal of treatment for refractory ALL is to try to attack the disease in a different way. Your child's doctor will use different drugs or different drug combinations to attain a remission and then use other therapies to increase the chances of a cure. The type of treatment will depend on:

- Type of ALL (B-cell or T-cell)
- Location in the body where the disease is persistent
- Results of genetic testing of the leukemia cells
- Prior treatments your child has received for ALL

Treatments for relapsed and refractory ALL may include:

- A clinical trial
- New or different chemotherapy drugs or new combinations of chemotherapy drugs
- For children and teens with Ph+ ALL, chemotherapy with a different TKI than the one used during initial therapy for those with B-cell ALL
- Blinatumomab, Inotuzumab or CAR T-cell therapy for children and teens with B-cell ALL
- Allogeneic stem cell transplantation with an available donor

Allogeneic stem cell transplantation

The goal of allogeneic SCT is to give high intensity chemotherapy and then give the individual an infusion of healthy stem cells from a donor to replace those destroyed by the intensive chemotherapy that your child has already undergone. The healthy blood stem cells then grow and multiply, forming new bone marrow and blood cells.

Allogeneic SCT creates a new immune system that helps the body fight infections and other diseases. The new immune system also has the potential to recognize and attack any remaining cancer cells in the body. The transplanted immune cells (called the graft) identify the leukemia cells in the body as foreign and destroy them. This is called the graft- versus-leukemia (GVL) effect.

Unfortunately, sometimes a serious side effect called graft-versus-host disease (GVHD) can develop after transplantation of the stem cells. GVHD occurs when the transplanted donor immune cells (the graft) identify the cells in the recipient's body (the host) as foreign and attacks them. The parts of the body most commonly damaged by GVHD include the skin, liver, stomach, intestines, and eyes. GVHD can develop within weeks after transplantation or much later. Doctors prescribe medication to help prevent or minimize the complications of GVHD.

Immunotherapy

In pediatric and adolescent B-ALL, immunotherapy, including blinatumomab, Inotuzumab, and CD19-directed CAR T-cell therapy has become an important part of treatment for patients with relapsed or refractory leukemia.

Monoclonal antibodies are laboratory-produced proteins that target specific antigens on the cancer cell's surface to interfere with the cell's function and destroy it. Once the antibody finds and attaches to its target, it can "recruit" (harness) other parts of the immune system to destroy cells that contain the antigen. In refractory or relapsed T-ALL, daratumumab, which targets CD38 on T cells, can sometimes be used.

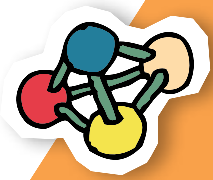
Bispecific T-cell engagers (BiTEs), such as blinatumomab, which target CD19 on B-cell lymphoblasts, are often used as part of the treatment for relapse after a block of chemotherapy in many patients.

Antibody-drug conjugates (ADC) are made up of a monoclonal antibody chemically linked to a drug. In simple terms, they can be thought of as a combination of immunotherapy and targeted chemotherapy. In B-ALL, Inotuzumab is an ADC that targets CD22 found on some B lymphoblasts and is linked to a cytotoxic drug (calicheamicin) that delivers the drug directly into leukemia cells.

Chimeric antigen receptor (CAR) T-cell therapy

CAR T-cell therapy is a type of immunotherapy that consists of engineering an individual's own immune cells to recognize and attack cancer cells. The T-cells (white blood cells that help the body fight infections and cancer) are removed from your child or teen's body, and then genetically engineered in a laboratory to produce receptors on their surfaces called chimeric antigen receptors (CARs). These receptors recognize and bind to a specific target found on the cancer cells. The most frequently targeted antigen in CAR T-cell immunotherapy for B-cell leukemia is called “cluster of differentiation 19” (CD19). The CD19 antigen is expressed on the surfaces of nearly all healthy and cancerous B cells, including ALL B-cells. Another antigen that is sometimes targeted in B-cell ALL is CD22.

These modified cells are infused back into their bloodstream to kill the cancer cells. While CAR T-cell therapy can be an effective treatment, it is also associated with a relatively high rate of serious complications such as high fever, low blood pressure, breathing difficulties, delirium, aphasia (loss of ability to speak and understand language), and neurologic complications. As a result, it can only be given at specialized centres that have expertise in delivering this type of treatment.



Other types of treatment

Since pediatric ALL is a complicated disease, your child’s doctor may use a variety of other types of therapy, as well, or instead of, the treatments discussed here. These treatments include different kinds of targeted therapy, many of which are only offered in clinical trials.

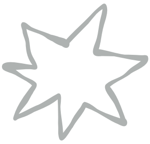
Targeted therapy

Kinase inhibitors: As well as TKIs, there are other inhibitors that block a type of enzyme called a kinase. Human cells have many different kinases; they help control important functions such as cell signaling, division and survival. Certain kinases are more active in some types of cancer cells and blocking them may help keep the cancer cells from growing. If a relapse of BCR-ABL–positive B-ALL occurs, a different TKI that was not previously used may be given.

Menin inhibitors are a new class of targeted cancer therapy that can be used only in ALL patients with specific genetic alterations, namely KMT2A rearrangements. Menin is a protein that interacts with abnormal leukemia fusion proteins. This interaction is necessary for the leukemia cells to grow. When menin inhibitors block the interaction of the fusion protein with menin, it causes the leukemia cells to die.

Proteasome inhibitors are drugs that block the actions of proteasomes (a type of protein complex in the cell) that allow the leukemia cells to survive.

BCL-2 inhibitors (like Venetoclax) are pro-apoptic drugs, meaning they promote cell death of the leukemic cells.



Clinical trials

Every new cancer drug goes through a series of carefully controlled research studies before it can become part of standard cancer care. These studies are called clinical trials. Health Canada requires that all new drugs and other treatments be tested in clinical trials before they are submitted for approval. Researchers use cancer clinical trials to:

- Develop a new drug
- Use an approved drug to treat a different kind of cancer
- Combine drugs
- Find a new way of giving a drug (pill, intravenously (IV), etc.)
- Manage cancer symptoms and ease treatment side effects
- Find and diagnose cancer
- Keep cancer from coming back after treatment
- Manage long-term side effects

The biomarker testing your child underwent, at pre-diagnosis and when their first line treatment was completed, can help find a suitable clinical trial for your child to join. Some studies enroll people based on the biomarkers in their cancer.

By taking part in a clinical trial, your child can see doctors who are experts in their disease, gain access to new, cutting-edge therapies, and provide helpful information for future individuals with ALL. The treatments and information we have today are due in large part to people being willing to join clinical trials.

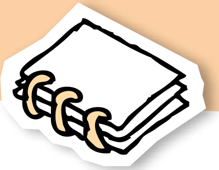
Anyone interested in being part of a clinical trial should talk to their hematologist-oncologist about whether a clinical trial might be right for them. During this conversation it may help to:

- Have a list of questions to ask about the risks and benefits of each trial
- Ask a family member or friend to go with you to your doctor visit—both for support and to take notes

Conclusion

Advances in treatment have dramatically improved the survival rates for children and teens with ALL in recent decades. Childhood ALL now has one of the highest cure rates of all pediatric cancers. Many survivors return to school, attend college, enter the workforce, and become parents.

> “Ezra, now 8, is thriving at school, despite missing his entire Kindergarten year, and significant portions of Grade 1, while in treatment. He is back to keeping up with his brothers and he no longer requires special considerations to play sports or attend summer camp.”
>
> \- Kristin, mom



Treatment for pediatric cancer is complex and affects all the members of the family. Support is important for everyone in the family, especially as treatment can be over a long period of time. LLSC offers free, personalized support, (1-833-222-4884) and our website's 'my child has a blood cancer' section features many easy-to-understand resources (videos, podcasts, factsheets, and tools for families).

We are here to help.

The Leukemia & Lymphoma Society of Canada gratefully acknowledges Dr. Nawar Dakhallah, MD Pediatric Hematologist/Oncologist, CHU Sainte-Justine, Assistant Professor, Université de Montréal for her important contribution to the content of this publication.

This publication was made possible thanks to the support of

SERVIER

LEUKEMIA &
LYMPHOMA
SOCIETY OF
CANADA®

LLS1882 2026-01