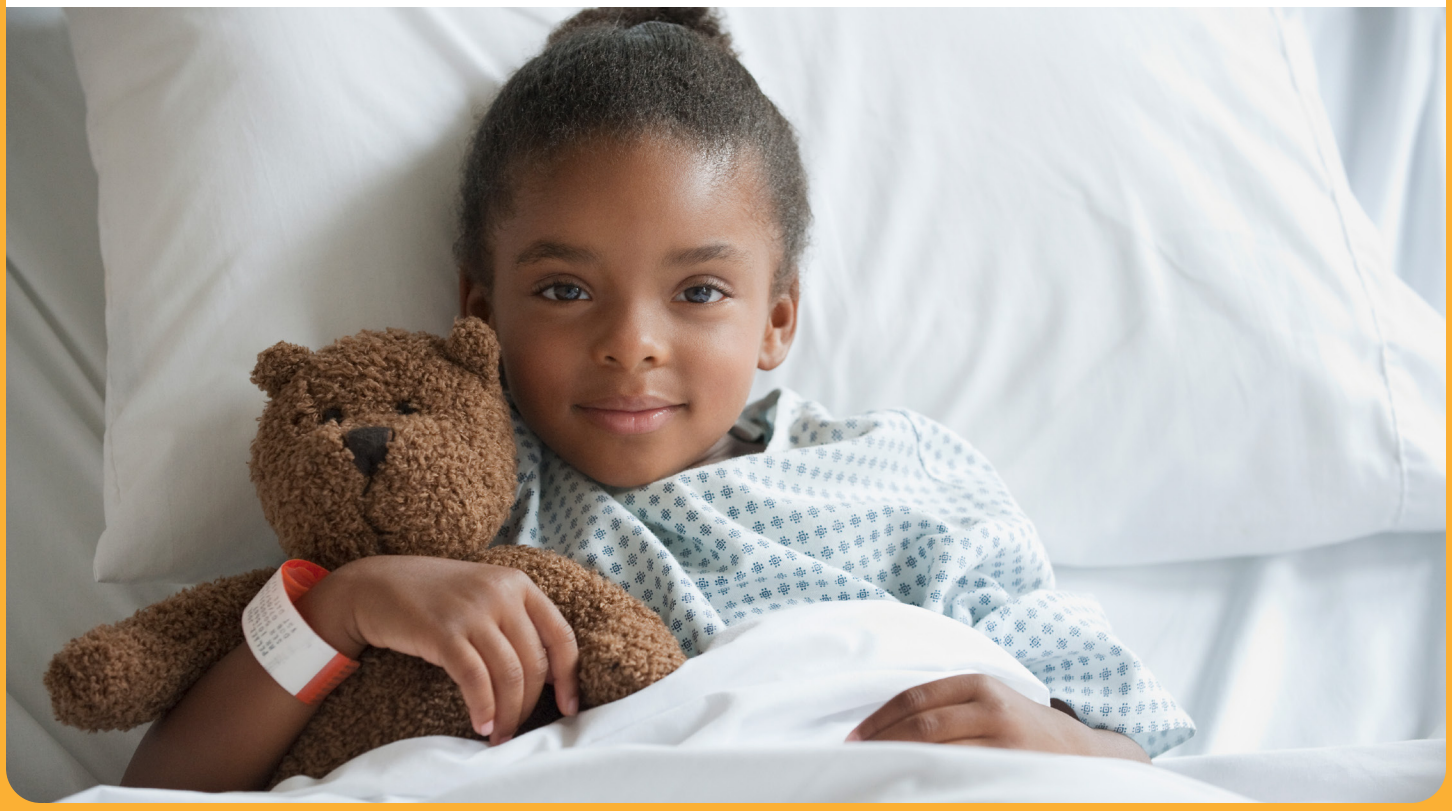
NCCN GUIDELINES FOR PATIENTS®

2025

Acute Lymphoblastic Leukemia in Children



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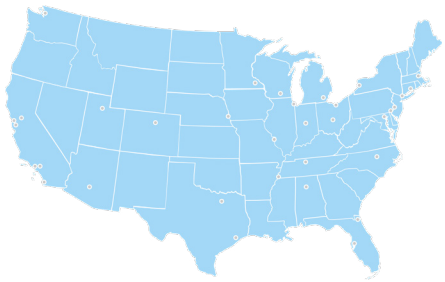
About the NCCN Guidelines for Patients®

National Comprehensive Cancer Network®



Did you know that top cancer centers across the United States work together to improve cancer care? This alliance of leading cancer centers is called the National Comprehensive Cancer Network® (NCCN®).

Cancer care is always changing. NCCN develops evidence-based cancer care recommendations used by health care providers worldwide. These frequently updated recommendations are the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). The NCCN Guidelines for Patients plainly explain these expert recommendations for people with cancer and caregivers.

These NCCN Guidelines for Patients are based on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pediatric Acute Lymphoblastic Leukemia, Version 2.2025 – December 16, 2024.

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NCCN.org/patientguidelines

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Contents

NCCN Foundation seeks to support the millions of patients and their families affected by a cancer diagnosis by funding and distributing NCCN Guidelines for Patients. NCCN Foundation is also committed to advancing cancer treatment by funding the nation's promising doctors at the center of innovation in cancer research. For more details and the full library of patient and caregiver resources, visit NCCN.org/patients.

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1
About ALL

Acute lymphoblastic leukemia (ALL) is the most common cancer diagnosed in children. It is a fast-growing cancer that starts in lymphocytes, a type of white blood cell. Treatment depends on the type of ALL, age at diagnosis, and other factors. This book covers treatment for ALL in infants, children, and young adults.

Why you should read this book

Making decisions about cancer care can be stressful. You may need to make tough decisions under pressure about complex choices.

The NCCN Guidelines for Patients are trusted by patients and providers. They clearly explain current care recommendations made by respected experts in the field. Recommendations are based on the latest research and practices at leading cancer centers.

Cancer care is not the same for everyone. By following expert recommendations for your situation, you are more likely to improve your child's care and have better outcomes as a result. Use this book as your guide to find the information you need to make important decisions.

What is ALL?

Acute lymphoblastic leukemia (ALL) is a fast-growing blood cancer that starts in disease-fighting white blood cells of your immune system called lymphocytes. In ALL, bone marrow makes too many immature lymphocytes called lymphoblasts (or blasts). Lymphoblasts can crowd out normal bone marrow. This leads to less blood being made.

There are 2 main types of ALL:

- B cell or B-ALL
- T cell or T-ALL

B-ALL

B-cell ALL or B-ALL starts in B-cell lymphocytes. B-ALL is more common than T-ALL. Mature B-cell ALL (also called Burkitt leukemia), a rare subtype, is essentially the same as Burkitt lymphoma (a type of non-Hodgkin lymphoma), but is treated differently from B-ALL. In some cases, the B-cell lymphoblasts grow mostly in the lymph nodes instead of in the bone marrow. When this happens, it is called B-cell lymphoblastic lymphoma, B-LL, or B-LBL.

T-ALL

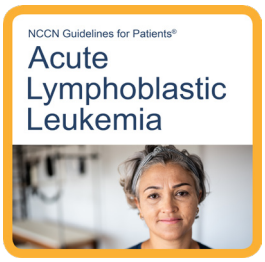
T-cell ALL or T-ALL starts in T-cell lymphocytes. T-ALL can cause an enlarged thymus (a small organ in front of the windpipe), which can sometimes lead to breathing problems due to pressure on the windpipe and blood vessels. In some cases, the T-cell

lymphoblasts grow mostly in the thymus instead of in the bone marrow. When this happens, it is called T-cell lymphoblastic lymphoma, T-LL, or T-LBL.

ALL in those under 30 years of age

Pediatric refers to ALL found in infants, children, and young adults. Pediatric includes anyone 18 years of age or under, and certain adolescents and young adults (AYAs). AYAs are those 15 to 39 years of age at the time of initial cancer diagnosis. An AYA can be treated in pediatric or adult centers depending on the type of cancer. This book applies to AYAs who are being treated at a pediatric or children's cancer center.

More information for those seeking ALL treatment at an adult cancer center can be found in the *NCCN Guidelines for Patients: Acute Lymphoblastic Leukemia* at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.



What are lymphocytes?

A lymphocyte is a type of white blood cell found in blood and lymph tissue, as well as all organs in the body. Lymph tissue includes lymph vessels and lymph nodes. Lymphocytes help fight and prevent infection.

There are 3 main types of lymphocytes:

- **B lymphocytes or B cells** make antibodies. An antibody is a protein.
- **T lymphocytes or T cells** help fight infections, kill tumor cells, and control immune responses.
- **Natural killer (NK) cells** can kill tumor cells or virus-infected cells.

ALL most often affects B cells or T cells.

What is blood?

Acute lymphoblastic leukemia (ALL) is a type of blood cancer. Blood is a tissue. A tissue is a group of cells that work together to perform a function. There are 4 main components of blood—plasma, red blood cells, white blood cells, and platelets. Blood's function is to move oxygen and nutrients throughout your body and carry away waste. Blood also plays an important role for the immune system and in preventing bleeding.

Types of blood cells

Your blood contains different types of cells that float in plasma. Plasma is a clear, yellowish fluid made up of mostly water.

There are 3 types of blood cells:

- Red blood cells (RBCs or erythrocytes) carry oxygen throughout the body
- White blood cells (WBCs or leukocytes), which include granulocytes, monocytes, and lymphocytes, fight infections.
- Platelets (PLTs or thrombocytes) help control bleeding.

Usually in ALL, there are too many abnormal white blood cells (lymphoblasts).

How are blood cells formed?

Bone marrow is the sponge-like tissue in the center of most bones. Inside your bone marrow are early blood-forming cells called blood (hematopoietic) stem cells. All types of blood cells are created from blood stem cells. At any given time, the bone marrow will have cells in various stages of development, from very immature to almost fully mature. This process is called differentiation. After a blood stem cell develops into a red blood cell, white blood cell, or platelet, it is released into your bloodstream as needed.

The role of blood stem cells is to make cells called intermediaries that will become red blood cells, white blood cells, and platelets.

These intermediaries are called progenitor cells or precursor cells.

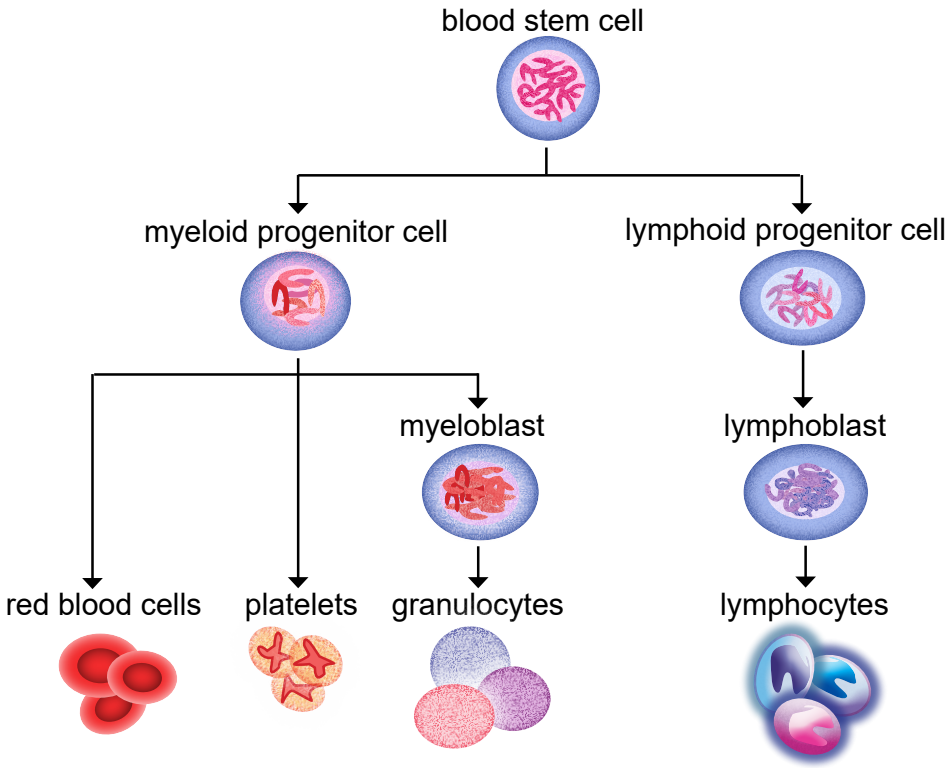
There are different types of progenitor cells:

- **Lymphoid progenitor cells** form into lymphoblasts that mature into lymphocytes.
- **Myeloid progenitor cells** form into myeloblasts and other non-lymphoid blood cells.

ALL is thought to arise from stem cells that make an increased amount of lymphoid progenitor cells.

Blood cell formation

All blood cells start as blood stem cells. A blood stem cell has to mature or go through many stages to become a red blood cell, white blood cell, or platelet. ALL affects the lymphoid progenitor cells, which develop into a type of white blood cell called lymphocytes.



What's in this book?

This book is organized into the following chapters:

Chapter 2: Testing for ALL provides an overview of tests your child might receive, how fertility might be impacted by treatment, and the role of genetic and biomarker mutation testing.

Chapter 3: Types of treatments gives a general overview of treatment. Everyone with ALL will be treated with steroids and multi-agent chemotherapy. Other types of systemic therapy might be given.

Chapter 4: Supportive care discusses what is supportive care and possible side effects of treatment.

Chapter 5: *BCR::ABL1*-negative or *BCR::ABL1*-like B-ALL discusses treatment for the most common type of B-ALL. A clinical trial is the preferred treatment for these types of B-ALL.

Chapter 6: *BCR::ABL1*-positive B-ALL treatment aims to stop the activity of the BCR::ABL protein caused by the *BCR::ABL1* gene. Treatment is usually an intensive combination of systemic therapies.

Chapter 7: T-ALL discusses a group of cancers that start in T-cell lymphocytes. T-ALL is less common than B-ALL. Treatment options include a clinical trial or chemotherapy.

Chapter 8: Infant ALL treatment is different than for other age groups. Infants are those under 12 months of age.

Chapter 9: Other resources provides information on patient advocacy groups and where to get help.

What can you do to get the best care?

Advocate for your child and yourself. You have an important role to play in their care. In fact, you're more likely to get the care you want by asking questions and making shared decisions with the care team. Consider seeking the opinion of an ALL specialist and treatment at an experienced children's (pediatric) leukemia center.

The NCCN Guidelines for Patients will help you understand cancer care. With better understanding, you'll be more prepared to discuss care with your child's team and share your concerns. Many people feel more satisfied when they play an active role in their care.

You may not know what to ask the care team. That's common. Each chapter in this book ends with an important section called *Questions to ask*. These suggested questions will help you get more information on all aspects of care.

Take the next step and keep reading to learn what is the best care for your child!

2
Testing for ALL

Accurate testing is needed to diagnose and treat ALL. This chapter presents an overview of possible tests and what to expect.

In general, to be diagnosed with ALL, 20 percent (20%) or more lymphoblasts must be present in the bone marrow. This means that at least 1 out of every 5 bone marrow cells are lymphoblasts. In certain cases, a diagnosis of ALL is possible with less than 20 percent lymphoblasts.

ALL can be found in bone marrow, blood, and organs such as the testicles or the central nervous system (CNS).

Results from blood and bone marrow tests and imaging studies will be used to determine your child's treatment plan. Tests used to diagnose ALL can be found in **Guide 1.**

Guide 1
Possible tests and procedures

Medical history and physical exam
Bone marrow aspirate and biopsy with biomarker and genetic testing
Complete blood count (CBC), differential, chemistry profile, and liver function tests (LFTs)
Tumor lysis syndrome (TLS) panel: Lactate dehydrogenase (LDH), uric acid, potassium (K), calcium (Ca), and phosphorus (Phos)
Blood clotting tests
Pregnancy testing, fertility counseling, and preservation as needed
CT or MRI of head with contrast, if neurologic symptoms
Chest x-ray to rule out mediastinal (in between the lungs) mass
Whole body PET/CT if lymphoblastic lymphoma suspected
Lumbar puncture (LP) with intrathecal (IT) chemotherapy
Testicular exam, including scrotal ultrasound as needed
Screen for opportunistic infections as needed
Heart tests for those who will receive anthracyclines as part of treatment plan
Pharmacogenomic testing as needed

General health tests

Some general health tests are described next.

Medical history

A medical history is a record of all health issues and treatments your child has had in their life. Be prepared to list any illness or injury and when it happened. Bring a list of old and new medicines and any over-the-counter (OTC) medicines, herbals, or supplements they take. Some supplements interact with and affect medicines that your child's care team may prescribe. Tell your child's care team about any symptoms they have. A medical history, sometimes called a health history, will help determine which treatment is best for your child.

Physical exam

During a physical exam, a health care provider may:

- Check your child's temperature, blood pressure, pulse, and breathing rate.
- Check your child's height and weight.
- Listen to the lungs and heart.
- Look in the eyes, ears, nose, and throat.
- Feel and apply pressure to parts of your child's body to see if organs are of normal size, are soft or hard, or cause pain when touched.
- Feel for enlarged lymph nodes in the neck, underarm, and groin.
- Complete a testicular exam.

Family history

Your child's care team will ask about the health history of family members who are blood relatives. This information is called a family history. Ask family members on both sides of your family about their health issues like heart disease, cancer, and diabetes, and at what age they were diagnosed. It's important to know the specific type of cancer or where the cancer started, if it is in multiple locations, and if they had genetic testing.

Leukemia predisposition syndrome

Certain genetic changes, or mutations, can increase a person's chances of developing cancer. These changes, known as hereditary cancer syndromes, can be passed down from birth parent to child. Your child's doctor should do a thorough family history and ask if anyone who is related by blood to your child has had leukemia or other types of cancer, especially during childhood. If there is a concern for leukemia predisposition syndrome, your child might be referred to a genetic counselor or geneticist. Since blood-related family members are often bone marrow donors, it is important to rule out leukemia predisposition syndrome.

Testicular exam

ALL can spread to the testicles and cause them to swell or become more firm than usual. A testicular exam is a complete physical exam of the groin and the genitals, which are the penis, scrotum, and testicles. A doctor will feel the organs and check for lumps, swelling, shrinking, and other signs of ALL.

Dental exam

The health of your child's teeth and gums is important. Some treatments can cause dental problems. Therefore, it is important for your child to see a dentist before and during treatment.

Blood tests

Blood tests check for signs of disease and how well organs are working. They require a sample of blood, which is removed through a needle placed into a vein in your child's arm. Some blood tests are described next. They are listed in alphabetical order and not in order of importance.

Blood clotting tests

Your body stops bleeding by turning blood into a gel-like form. The gel-like blood forms into a solid mass called a blood clot. Clotting is a process or series of events. Proteins, called coagulation factors, are needed for clotting. They are made by the liver. These tests are known together as a coagulation panel or disseminated intravascular coagulation (DIC) panel.

An impaired clotting process is common in leukemia, and those with leukemia can have blood that clots too much or too little. This is called coagulopathy. Your child may have bleeding and bruises or blood clots.

Complete blood count and differential

A complete blood count (CBC) measures the levels of red blood cells (RBCs), white blood cells (WBCs), and platelets (PLTs) in your child's blood. A differential counts the number of each type of WBC (neutrophils, lymphocytes, monocytes, eosinophils, and basophils). It also checks if the counts are in balance with each other and whether leukemia cells (blasts) are present.

"If your care team starts explaining things that are hard to understand, don't hesitate in asking questions. Ask them to slow down and re-explain, and don't feel bad about it."

Chemistry profile

A chemistry profile or panel measures the levels of different substances released in your child's blood by the liver, bone, and other organs. When ALL is present, the chemistry panel can be abnormal.

Creatinine

Creatinine is a waste produced in the muscles. Every person generates a fixed amount of creatinine every day based on how much muscle they have. It is filtered out of the blood by the kidneys. The level of creatinine in the blood tells how well the kidneys are working. Higher levels of creatinine can mean the kidneys aren't working as well as they were when someone had lower levels of creatinine.

HLA typing

Human leukocyte antigen (HLA) is a protein found on the surface of most cells. It plays an important role in your body's immune response. HLAs are unique to each person. They mark your body's cells. Your body detects these markers to tell which cells are yours. In other words, all your cells have the same set of HLAs. Each person's set of HLAs is called the HLA type or tissue type.

HLA typing is a blood test that detects a person's HLA type. This test is done before an allogeneic (donor) hematopoietic cell transplant (HCT). Most children with ALL do not need an HCT and, therefore, will not have HLA typing. To find a donor match, your child's proteins will be compared to the donor's proteins to see how many proteins are the same. A very good match is needed for a transplant to be a treatment option. Otherwise, your child's body will reject the donor cells or the donor cells will react against their body. Blood or tissue samples from your child and your child's blood relatives will be tested first.

Lactate dehydrogenase

Lactate dehydrogenase (LDH) or lactic acid dehydrogenase is an enzyme found in most cells. Dying cells release LDH into blood. Fast-growing cells, such as tumor cells, also release LDH.

Liver function tests

Liver function tests (LFTs) look at the health of the liver by measuring chemicals that are made or processed by the liver. Levels that are too high or low signal that the liver is not working well or the bile ducts might be blocked.

Phosphate

Cells have a lot of phosphate in them. Therefore, when many cells are breaking down at the same time, the levels of phosphate in the blood can go up. Your kidneys help get rid of extra phosphate, but too much phosphate in the blood can also damage the kidneys, making it harder to get the levels back down to normal. Since we absorb phosphate from the foods that we eat, your child might be given a medicine called a phosphate binder to prevent phosphate levels from rising too high. If there is too much phosphate in the blood, the kidneys may not be able to get rid of it on their own, and your child may need dialysis for a short period of time in order to get it back to normal levels.

Potassium

Blood plasma has a low level of potassium and a high level of sodium, but inside cells are high levels of potassium and low levels of sodium. When many cells are breaking down all at the same time, the level of potassium in the blood can go up. The differences in levels of potassium inside and outside of cells is very important to certain processes such as the electrical signals in the heart. Very high levels of potassium in the blood can cause dangerous heart rhythms.

Pregnancy test

Those who can become pregnant should be given a pregnancy test before treatment begins.

Screen for opportunistic infections

An opportunistic infection is an infection that happens because someone's immune system is not working normally. Drug treatment for ALL can weaken the body's natural defense against infections. Your child will be monitored for opportunistic infections, as needed.

If not treated early, infections can be fatal. Infections can be caused by bacteria, fungus, or viruses. Antibiotics can treat bacterial infections. Antifungal medicines can treat fungal infections. Your child may be given antiviral drugs to prevent viral infections.

Tumor lysis syndrome panel

Cancer treatment causes cell death. In tumor lysis syndrome (TLS), waste released by dead cells builds up in the body causing kidney damage and severe blood electrolyte disturbances. TLS is rare. Changes in creatinine, potassium, phosphate, and uric acid levels can be signs of TLS. These levels are watched closely when your child is first diagnosed. They may receive medicine and intravenous (IV) fluids to help prevent the levels from getting too high. In rare cases, your child may need dialysis for a short period of time to help get levels back to normal.

Uric acid

Uric acid is released by cells when DNA breaks down. It is a normal waste product that dissolves in the blood and is filtered by the kidneys where it leaves the body in the urine. Too much uric acid in the body is called hyperuricemia. With ALL, it can be caused by a fast turnover of white blood cells (WBCs). High uric acid might be a side effect of treatment. Very high levels of uric acid in the blood can damage the kidneys. Uric acid levels are watched with other tumor lysis syndrome levels.

Fertility (all genders)

Some types of treatment can affect fertility, the ability to have children. Ask your child's care team how cancer and cancer treatment might change your child's fertility. To preserve fertility, you may need to take action before starting cancer treatment. Those who want to have children in the future should be referred to a fertility specialist to discuss the options before starting treatment, if possible. It is not always possible to see a fertility specialist before starting treatment.

More information on fertility preservation can be found in *NCCN Guidelines for Patients: Adolescent and Young Adult Cancer* at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.

Changes in fertility

Treatment might cause your child's fertility to be temporarily impaired or interrupted. This temporary loss of fertility is related to age at time of diagnosis, treatment type(s), treatment dose, and treatment length.

Preventing pregnancy during treatment

Preventing pregnancy during treatment is important. Cancer and cancer treatment can affect the ovaries and damage sperm. Therefore, becoming pregnant or having one's partner become pregnant during treatment should be avoided. Hormonal birth control may or may not be recommended. Ask about options such as intrauterine devices (IUDs) and barrier methods. Types of barrier methods include condoms, diaphragms, cervical caps, and the contraceptive sponge.

Imaging tests

Imaging tests take pictures of the inside of one's body to look for cancer deposits. A radiologist, an expert in interpreting imaging tests, will interpret the test and send a report to your child's doctor. While these reports might be available to you through your patient portal or patient access system, please wait to discuss these results with your child's care team. Your child will not have all of the following tests.

Chest x-ray

An x-ray is a type of radiation. In small doses, it is used to make pictures of the inside of the body. A chest x-ray is used to look for a mediastinal mass, which forms in the space between the lungs. This area includes the heart, aorta, esophagus, thymus, trachea, lymph nodes, and nerves.

Contrast material

Contrast material is used to improve the quality of the pictures of the inside of the body. Contrast materials are substances that help enhance and improve the images of several organs and structures in the body. It is used to make the pictures clearer. The contrast is not permanent and will leave the body in one's urine immediately after the test. The types of contrast vary and are different for CT and MRI.

Tell the care team if your child has had allergic reactions to contrast in the past. This is important. Your child might be given medicines to avoid the effects of those allergies. Contrast might not be used if they have a serious allergy or if their kidneys aren't working well.

CT scan

A CT or CAT (computed tomography) scan uses x-rays and computer technology to take pictures of the inside of the body. It takes many x-rays of the same body part from different angles. All the images are combined to make one detailed picture.

MRI scan

An MRI (magnetic resonance imaging) scan uses radio waves and powerful magnets to take pictures of the inside of the body. It does not use x-rays, which means there is no radiation delivered to your child's body during the test. Because of the very strong magnets used in the MRI machine, tell the technologist about any metal in your child's body. During the test, your child will likely be asked to hold their breath for 10 to 20 seconds as the technician collects the images. Young children who require an MRI but cannot hold still easily may be given sedation to get a good quality picture.

A closed MRI has a capsule-like design where the magnet surrounds you. An open MRI has a magnetic top and bottom, which allows for an opening on each end. Closed MRIs are more common than open MRIs, so if your child has claustrophobia (a dread or fear of enclosed spaces), be sure to talk to their care team about it.

PET scan

A PET (positron emission tomography) scan uses a radioactive drug called a tracer. A tracer is a substance injected into a vein to see where cancer cells are in the body and how much sugar is being taken up by the cancer cells. This gives an idea about how fast the cancer cells are growing. Cancer cells show up as bright spots on PET scans. However, not all tumors will appear on a PET scan. Also, not all bright spots found on the PET scan are cancer. It is normal for the brain, heart, kidneys, and bladder to be bright on PET. Inflammation or infection can also show up as a bright spot. When a PET scan is combined with CT, it is called a PET/CT scan.

Scrotal ultrasound

A scrotal ultrasound uses sound waves to make images of the scrotum. The scrotum is the pouch of skin at the base of the penis that contains the testicles. The images are recorded on a computer.

Heart tests

Heart or cardiac tests are used to see how well the heart works. These tests might be used to monitor treatment side effects. Your child might be referred to a heart specialist called a cardiologist.

- **An electrocardiogram (ECG or EKG)** shows electrical activity in the heart.
- **An echocardiogram (or echo)** uses sound waves to make pictures of the heart.

Lumbar puncture

A lumbar puncture (LP) is a procedure that removes spinal fluid. It is also called a spinal tap. A lumbar puncture at diagnosis is used to rule out a central nervous system (CNS) disease. Leukemia can travel to the cerebrospinal fluid (CSF) that surrounds the spine or brain. This may cause symptoms. In order to look for leukemia cells in your child's spinal fluid, a sample must be taken and tested. A lumbar puncture is also used to inject cancer drugs into spinal fluid. This is called intrathecal (IT) chemotherapy. All treatment plans include IT chemotherapy.

Bone marrow tests

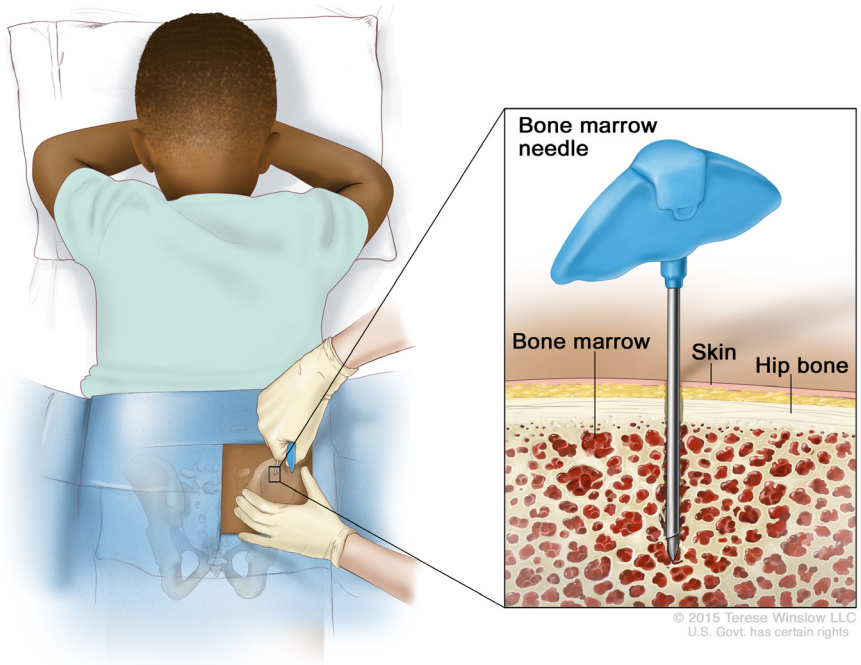
Leukemia starts in the bone marrow. To diagnose ALL, samples of bone marrow must be removed and tested before starting any treatment. In select cases with very high white blood cell count (WBC) count, a diagnosis may be made using peripheral blood samples and treatment may be started before obtaining bone marrow. The care team will try to make your child as comfortable as possible during a bone marrow aspirate and biopsy. In some cases, sedation or anesthesia is provided during this procedure. Discuss the options with the care team.

There are 2 types of bone marrow tests that are often done at the same time:

- Bone marrow aspirate
- Bone marrow biopsy

Bone marrow aspirate and biopsy

Samples of bone and marrow are removed in a biopsy.



Your bone marrow is like a sponge holding liquid and cells. An aspirate takes some of the liquid and cells out of the sponge, and a biopsy takes a piece of the sponge.

The samples are usually taken from the back of the hip bone (pelvis). Your child will likely lie on their belly, back, or side. The doctor will first clean and give sedation and/or numb the skin and outer surface of the bone. For an aspirate, a hollow needle will be pushed through the skin and into the bone. Liquid bone marrow will then be drawn into a syringe. For the biopsy, a wider needle will be used to remove a core sample. Your child may feel bone pain at the hip for a few days. Their skin may bruise.

The bone marrow sample should be reviewed by a pathologist who is an expert in the diagnosis of ALL. This review is often referred to as histology, histopathology, or hematopathology review. The pathologist will note the overall appearance and the size, shape, and type of cells. Tests will be done on the biopsied cells. Ask questions about the biopsy results and what it means for your child's treatment.

Flow cytometry

Flow cytometry is a laboratory method used to detect, identify, and count specific cells. Flow cytometry involves adding a light-sensitive dye to cells. The dyed cells are passed through a beam of light in a machine. The machine measures the number of cells, as well as things like the size and shape of the cells.

Flow cytometry may be used on cells from circulating (peripheral) blood or from a bone marrow aspirate. A blood test can count the number of white blood cells, but it cannot detect the subtle differences between different types of blood cancers. Flow cytometry can detect these subtle differences. The most common use of flow cytometry is in the identification of markers on cells, particularly in the immune system (called immunophenotyping). Flow cytometry is also used to check treatment response.

Immunophenotyping

Immunophenotyping uses antibodies to detect the presence or absence of white blood cell antigens. These antigens are proteins that can be found on the surface of or inside white blood cells. They are called markers or biomarkers. Certain biomarkers are targeted in ALL treatment. Immunophenotyping is used to pinpoint the type of ALL.

Based on immunophenotype, ALL can be placed into 2 general groups:

- **B-cell ALL** starts in very immature cells called lymphoblasts. These cells would normally develop into B lymphocytes.
- **T-cell ALL** starts in lymphoblasts that would normally develop into T-cell lymphocytes.

Within each type there are several subtypes, which are based mainly on:

- The type of lymphocyte (most often B cell or T cell) within the leukemia cells and how mature the cells are. This is known as the immunophenotype of the leukemia.
- If the leukemia cells have specific gene or chromosome changes.

Testing for ALL biomarker and genetic changes

Biomarker and genetic tests are used to learn more about your child's type of ALL, to target treatment, and to determine the likely path the cancer will take called prognosis. This genetic testing is different from family history genetic testing or genetic cancer risk testing. This testing looks for changes only in the ALL cells that have developed over time, and not changes in the rest of the body's cells. Your child may be placed into a risk group based on the types of genetic abnormalities found.

Inside our cells are DNA (deoxyribonucleic acid) molecules. These molecules are tightly packaged into what is called a chromosome. Chromosomes contain most of the genetic information in a cell. Normal human cells contain 23 pairs of chromosomes for a total of 46 chromosomes. Each chromosome contains thousands of genes. Genes are coded instructions for the proteins your cells make. A mutation is when something goes wrong in the genetic code. Proteins are written like this: BCR::ABL1. Genes are written in italics like this: *BCR::ABL1.*

ALL mutation testing

Mutation testing using methods such as karyotype, fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR), and next-generation sequencing (NGS) looks for changes or abnormalities that are unique to ALL cells (genes and chromosomes). A sample of your child's blood or bone marrow will be used to see if the ALL cancer cells have any specific mutations. Some mutations may determine the type of treatment your

ALL genetic changes

ALL cells can have changes in genes and chromosomes. Mutation testing looks for these changes or abnormalities that are unique to ALL cells. Examples of such changes are called deletion, insertion, inversion, amplification, translocation (rearrangement), and point mutation.

- **Amplification** – When part or a whole chromosome or gene is increased (for example, duplicated)
- **Deletion** – When part of a chromosome or gene is missing
- **Insertion** – When a new part of a chromosome or gene is included
- **Inversion** – Switching of parts within one chromosome
- **Point mutation** – When part of a gene is changed
- **Chromosome translocation and gene rearrangement** – Switching of parts between 2 chromosomes. When described at the chromosome level, it is called a translocation. When described at the gene level, it is called rearrangement. For example, the chromosome translocation is written as t(9;22)(q34;q11.2) and its gene rearrangement is written as *BCR::ABL1.*

child needs. Your child may be placed into a risk group based on the types of genetic abnormalities found.

FISH

Fluorescence in situ hybridization (FISH) is a method that involves special dyes called probes that attach to pieces of DNA. For example, the probes attach to the *BCR* gene and the *ABL1* gene. The *BCR::ABL1* gene is detected when the colors of the probes overlap by translocation. A translocation is the switching of parts between two chromosomes. The *BCR::ABL1* translocation can also be written as t(9;22).

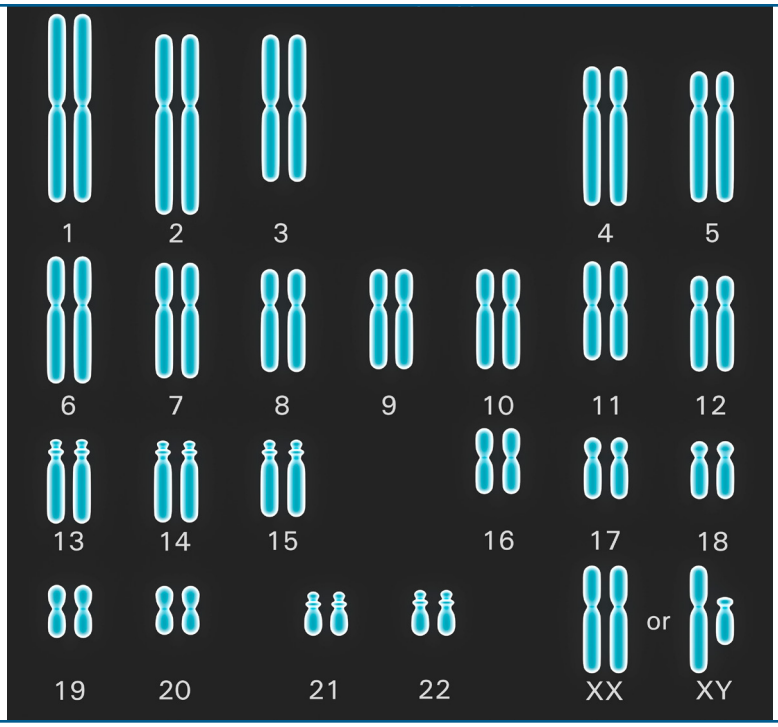
FISH can look for translocations that are too small to be seen with other methods. It can only be used for known changes. It cannot detect all the possible changes found within genes or chromosomes. Since this test doesn't need growing cells, it can be performed on either a bone marrow or blood sample. Most commonly, a bone marrow sample is needed to get all the information the care team needs to help plan your child's care.

Karyotype

A karyotype is a picture of chromosomes. Normal human cells contain 23 pairs of chromosomes for a total of 46 chromosomes. A karyotype will show extra, missing, rearranged, or abnormal pieces of chromosomes. Since a karyotype requires growing cells, a sample of bone marrow or blood must be used.

Karyotype

A karyotype is a picture of your chromosomes. The study of chromosomes is called cytogenetics.



Chromosome translocation and gene rearrangement

Chromosome translocation and gene rearrangement is the switching of parts between 2 chromosomes. When described at the chromosome level, it is called a translocation. When described at the gene level, it is called rearrangement. For example, a translocation between chromosome 9 and 22 is written as t(9;22) and is known as the Philadelphia (Ph) chromosome. Its gene rearrangement is written as *BCR::ABL1*.

Other common translocations in ALL include t(v;11q23.3) written as *KMT2A*-rearranged and t(12;21)(p13.2;q22.1) written as *ETV6::RUNX1.*

Next-generation sequencing

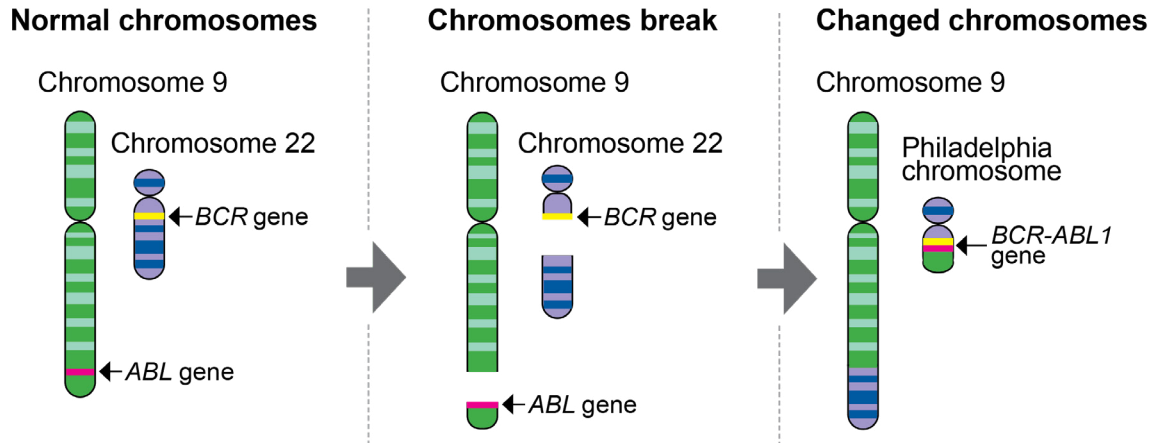
Next-generation sequencing (NGS) is a method used to determine a portion of a person's DNA sequence. It shows if a gene has any mutations that might affect how the gene works. NGS looks at the gene in a more detailed way than other methods and can find mutations that other methods might miss.

PCR

A polymerase chain reaction (PCR) is a technique that can make millions or billions of copies of your DNA or RNA (genetic information). PCR is very sensitive. It can find 1 abnormal cell among more than 100,000 normal cells. These copies, called PCR products, might be used for NGS. RT-PCR and RT-qPCR are types of PCR used to look for the presence of the *BCR::ABL1* gene on the Philadelphia chromosome.

Philadelphia chromosome

The Philadelphia (Ph) chromosome is formed by a translocation between parts of chromosomes 9 and 22. It contains the abnormal *BCR::ABL1* fusion gene.



B-ALL risk groups

Treatment options for B-ALL are based on age, white blood cell counts at diagnosis, and results of tests done on leukemia cells to look for gene or chromosome changes. The presence of certain mutations can sometimes predict how ALL will respond to certain types of treatment. How ALL responds to treatment and if minimal residual disease (MRD) remains after treatment are also important. Your child might be placed into a risk group based on risk factors.

Risk factors include:

- Age
- White blood cell (WBC) count at diagnosis
- Gene or chromosome mutations, translocations, deletions, and rearrangements
- Response to therapy often expressed as minimal residual disease (MRD)
- Predisposition syndrome
- Down syndrome

Risk groups and treatment planning are based on testing lymphoblasts in bone marrow or blood for specific genetic abnormalities.

Age

ALL tends to be more aggressive in infants and those 10 years of age and over. Infants are those under the age of 12 months (1 year).

WBC

A WBC greater than 50,000/mm^3 at initial diagnosis is considered high risk.

B-ALL genetic risk groups

Your child will be placed into an initial risk group based on the genetic features (mutations) found in the leukemia cells. Some genetic mutations respond better to treatment. Unfavorable risk features are more of a challenge to treat. At certain treatment milestones, risk group might be reassessed by considering response to treatment.

Hyperdiploidy

In hyperdiploidy, leukemia cells have more than 50 chromosomes. Normal cells have 46 chromosomes. In high hyperdiploidy leukemia cells have 51 to 67 chromosomes.

Hypodiploidy

In hypodiploidy, leukemia cells have fewer than 44 chromosomes. Normal cells have 46 chromosomes.

Leukemia predisposition syndrome

Some hereditary cancer syndromes can be passed down from parent to child. A family history of leukemia can affect treatment. If a predisposition condition is suspected, your child might have a skin punch biopsy. If their blood was tested at diagnosis, you would see the genetic changes of the leukemia. Therefore, a skin punch biopsy is used. In this procedure, a small piece of skin and connective tissue is removed to get DNA that hasn't been altered by ALL. This will be used to see if your child has inherited genes that increase their risk of leukemia. Leukemia predisposition syndrome can affect how your child's body responds to treatment. Blood and saliva can be used when ALL cells disappear (in remission).

Down syndrome

In Down syndrome, there is an extra chromosome 21. Instead of two chromosomes, there are three. There are challenges treating ALL in those with Down syndrome.

Pharmacogenomic testing

Pharmacogenomics is the study of how genes affect a person's response to drugs. How well your child's body absorbs (metabolizes) drugs is an important factor in treatment. Not everyone receives the same dose. Your child's age, weight, and other factors play a role in the dose they receive. Therefore, they may have a test to find the best starting dose of certain drugs. This test looks for genes that help to guide dosing decisions.

Two examples are as follows, which are related to chemotherapy with 6-mercaptopurine and 6-thioguanine:

- Thiopurine methyltransferase (TPMT)
- Nudix hydrolase 15 (NUDT15)

Based on the results of the test, your child might start certain types of chemotherapy at a lower dose to avoid severe myelosuppression. In myelosuppression, bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets. This is supposed to happen with certain chemotherapies. However, since those with a genetic mutation in TPMT or NUDT15 may have more severe myelosuppression, they may be started on lower doses to prevent this from happening.

Warnings about supplements and drug interactions

Some supplements can affect the ability of a drug to do its job. This is called a drug interaction.

It is critical to speak with your child's care team about any supplements they may be taking. Some examples include:

- Turmeric
- Ginkgo biloba
- Green tea extract
- St. John's Wort
- Antioxidants

Certain medicines can also affect the ability of a drug to do its job. Therefore, tell your child's care team about any medicines, vitamins, over-the-counter (OTC) drugs, herbals, or supplements they are taking.

Key points

- A diagnosis of acute lymphoblastic leukemia (ALL) is confirmed using a bone marrow aspirate and bone marrow biopsy.
- In general, to be diagnosed with ALL, 20 percent (20%) or more lymphoblasts must be present in the bone marrow. This means that at least 1 out of every 5 marrow cells are lymphoblasts.
- Immunophenotyping is used to pinpoint the specific type of pediatric ALL.
- Genetic and biomarker tests are used to learn more about your child's ALL, to target treatment, and to determine the likely course the cancer will take called a prognosis.
- Factors that can affect treatment include age, white blood cell (WBC) count at diagnosis, gene or chromosome mutations, response to treatment, predisposition syndrome, and Down syndrome.
- Your child might be placed into a risk group before starting treatment. Risk might be reassessed between stages of treatment.
- Leukemia cells can travel to the cerebrospinal fluid (CSF) that surrounds the spine or brain. ALL can also travel to sites outside of the blood such as the testicles.

Questions to ask

- What type of cancer does my child have? What does this mean in terms of prognosis and treatment options?
- Is there a cancer center or hospital nearby that specializes in my child's type of ALL?
- What tests will my child have? How often will they be repeated?
- Will my insurance pay for these tests?
- Who will talk with us about the next steps? When?

3
Types of treatments

There is more than one treatment for ALL in children. This chapter presents an overview of the types of treatment and what to expect. Not everyone will receive the same treatment. However, all treatment regimens include steroids and chemotherapy.

Care team

Treating ALL takes a team approach. Treatment decisions should involve a multidisciplinary team (MDT). An MDT is a team of health care and psychosocial care professionals from different professional backgrounds who have knowledge (expertise) and experience in your child's type of cancer. This team is united in the planning and implementing of your child's treatment. Ask who will coordinate your child's care.

Some members of your child's care team will be with you throughout cancer treatment, while others will only be there for parts of it. Get to know your child's care team and help them get to know you and your child.

Your team might include the following specialists:

- **A hematologist or hematologic oncologist** is a medical doctor with expertise in blood diseases and blood cancers.
- **A pathologist or hematopathologist** analyzes the cells and tissues removed during a biopsy and provides cancer diagnosis, staging, and information about biomarker testing.
- **A radiation oncologist** specializes in using radiation to treat cancer. Only some children with ALL require radiation.

Treatment phases

The goal of treatment is a complete response (CR) or complete remission. Treatment will be in phases. Each phase has a different name depending on the treatment plan your child's care team is using. All treatment plans include an induction phase, which aims to put leukemia into remission. After (post) induction, there will be multiple phases to rid the body of any remaining leukemia cells. Maintenance phase helps prevent relapse.

In general, there are several phases of intense chemotherapy followed by a longer phase of less intense maintenance chemotherapy. Treatment phases may include induction, after induction or post-induction phases, and maintenance. However, not all doctors use the same terms when discussing treatment. The number of phases and the type of chemotherapy given depend on the type of leukemia, as well as how your child responds to the first phases of treatment.

Types of response

There are different types of treatment response. When there are no signs of cancer, it is called a complete response (CR) or complete remission. This does not always mean that ALL has been cured. Remission can be short-term (temporary) or long-lasting (permanent).

In complete response all of the following are true:

- No lymphoblasts are found in blood.
- There are no signs and symptoms of cancer outside the bone marrow (extramedullary disease, which includes lymph nodes, spleen, skin, gums, testicles, and central nervous system).
- Less than 5 percent (5%) blasts are found in bone marrow when looking at the sample under a microscope. This means that there are fewer than 5 blasts out of every 100 blood cells.
- Blood cell counts have recovered.
- Cancer has not returned in 4 weeks.

In an incomplete blood count recovery or incomplete response (CRi), the platelet (PLT) count or absolute neutrophil count (ANC) has not yet returned to normal. ANC is an estimate of the body's ability to fight infections, especially bacterial infections.

Children with ALL should be treated at experienced pediatric leukemia centers.

Induction

Induction is the first intense phase of treatment. Your child will likely spend time in the hospital for part of this treatment. Treatment is a multi-drug combination of chemotherapies (called multi-agent chemotherapy) and steroids.

The goal of induction is a complete response or remission. In a complete response, less than 5 percent blasts remain at the end of induction. When induction does not lead to a complete response, it could be a sign that this cancer is very difficult to treat. In many subtypes, how ALL responds to initial treatment affects prognosis.

After induction, bone marrow aspirate and biopsy and flow cytometry are used to look for a complete response and to measure the amount of leukemia cells that might remain called minimal residual disease (MRD).

Minimal residual disease

In minimal residual disease (MRD) very sensitive lab tests, such as flow cytometry, PCR, or NGS find leukemia cells in bone marrow that cannot be seen under a microscope. Not all MRD can be found with tests. Treatment aims to reduce the amount of MRD.

Consolidation

After induction, there are multiple phases of intensive chemotherapy. These post-induction or consolidation phases are needed to rid the body of any leukemia cells that might remain called minimal residual disease (MRD) and aim to prevent cancer from returning. The time spent in these phases and the intensity of the drug regimen will vary. It will be based on factors such as age, how well ALL responds to treatment, and risk factors.

Maintenance

Maintenance or continuation chemotherapy is the final, and longest, stage of treatment in pediatric ALL. Treatment is less intensive than prior chemotherapy. It is given at an outpatient location. The goal is to lower the risk of relapse.

CNS disease

Treatment to prevent ALL from spreading to the central nervous system (CNS) is called CNS prophylaxis or prophylactic treatment. CNS prophylaxis is typically given throughout all phases of treatment.

All treatment plans include intrathecal (IT) chemotherapy. IT chemotherapy is injected into spinal fluid. Some treatments include IT treatment throughout therapy, whereas others do not include it in later phase maintenance therapy. Options for IT chemotherapy include IT methotrexate or a combination of IT methotrexate, cytarabine, and hydrocortisone (known as triple IT chemotherapy). If ALL is found in your child's CNS at the time of diagnosis, they may need more IT chemotherapy or radiation to the brain.

Standard of care is the best-known treatment based on past clinical trials. Many ALL standard-of-care treatment regimens are the result of clinical trials. If a clinical trial is an option, your child might be offered treatment on an open trial. Otherwise, they will be treated with standard of care. There may be more than one treatment regimen that is considered standard of care. Ask your child's care team for more information.

Surveillance and monitoring

Surveillance watches for any changes in your child's condition, which includes monitoring for disease and side effects.

Refractory disease

When leukemia remains in high levels at the end of induction (EOI) and then does not respond to post-induction treatment, it is called refractory or resistant cancer. The cancer may be resistant at the start of treatment or it may become resistant during treatment. Refractory disease is very serious. It is important to ask about prognosis.

Disease progression

When the percentage of ALL increases in blood or bone marrow during treatment, it is called progressive disease. Disease progression also occurs when the number of blasts within the blood or bone marrow increases by at least 25 percent.

Relapse

When leukemia returns after a period of remission, it is called a relapse. The goal of treatment is to achieve remission again. Relapse might happen more than once. Ask the care team about your child's specific risk of relapse. A relapse is very serious. It is important to ask about prognosis.

Those with relapsed ALL are placed into risk groups. Length of first complete remission (CR1) and site of relapse are two important factors. Relapse can occur in the bone marrow called isolated medullary relapse, in areas outside of the marrow or blood such the brain (CNS) or testicles called isolated extramedullary relapse, or a combination of both.

Treatment options

Treatment options are often described in the following ways:

- **Preferred therapies** have the most evidence they work better and may be safer than other therapies.
- **Other recommended therapies** may not work quite as well as preferred therapies, but they can still help treat cancer.
- **Therapies used in certain cases** work best for people with specific cancer features or health circumstances.

Clinical trials

A clinical trial is a type of medical research study. After being developed and tested in a lab, potential new ways of treating cancer need to be studied in people. If found to be safe and effective in a clinical trial, a drug, device, or treatment approach may be approved by the U.S. Food and Drug Administration (FDA).

Everyone with cancer should carefully consider all of the treatment options available for their cancer type, including standard treatments and clinical trials. Talk to your doctor about whether a clinical trial may make sense for your child.

Phases

Most cancer clinical trials focus on treatment and are done in phases.

- **Phase 1** trials study the safety and side effects of an investigational drug or treatment approach.
- **Phase 2** trials study how well the drug or approach works against a specific type of cancer.
- **Phase 3** trials test the drug or approach against a standard treatment. If the results are good, it may be approved by the FDA.
- **Phase 4** trials study the safety and benefit of an FDA-approved treatment.

Who can enroll?

It depends on the clinical trial's rules, called eligibility criteria. The rules may be about age, cancer type and stage, treatment history, or general health. They ensure that participants are alike in specific ways and that the trial is as safe as possible for the participants.

Informed consent

Clinical trials are managed by a research team. This group of experts will review the study with you in detail, including its purpose and the risks and benefits of your child joining. All of this information is also provided in an informed consent form. Read the form carefully and ask questions before signing it. Take time to discuss it with people you trust. Keep in mind that you can leave and seek treatment outside of the clinical trial at any time.

Will I get a placebo?

Placebos (inactive versions of real medicines) are almost never used alone in cancer clinical trials. It is common to receive either standard treatment with or without placebo, or a new drug with a standard treatment. You will be informed, verbally and in writing, if a placebo is part of a clinical trial before you enroll your child.

Are clinical trials free?

There is no fee to enroll in a clinical trial. The study sponsor pays for research-related costs, including the study drug. But you may need to pay for other services, like transportation or childcare, due to extra appointments. During the trial, your child will continue to receive standard cancer care. This care is often covered by insurance.

Steroids

All treatments for ALL include steroids. Steroids are human-made versions of hormones made by the adrenal glands. The adrenal glands are small structures found near the kidneys, which help regulate blood pressure and reduce inflammation. Steroids also are toxic to ALL cells and are an important part of pediatric ALL chemotherapy. Steroids can cause short-term and long-term side effects. The type of steroids used to treat ALL are called corticosteroids or glucocorticoids.

Chemotherapy

Chemotherapy is the standard of care for treating ALL in children. Chemotherapy kills fast-dividing cells throughout the body, including cancer cells. Children and young adults can tolerate higher doses than adults. However, with higher doses there are side effects. Your child will be monitored throughout treatment for side effects or other unwanted (adverse) reactions. All chemotherapy drugs may cause severe, life-threatening, or fatal reactions.

In addition to other forms of chemotherapy, everyone with pediatric ALL will have chemotherapy injected into the cerebrospinal fluid (CSF) to kill any leukemia cells that might have spread to the brain and spinal cord. This treatment is given through a lumbar puncture (spinal tap) and is called intrathecal (IT) chemotherapy.

Types of chemotherapy

There are many types of chemotherapy used to treat ALL. Often chemotherapies are combined. This is called multi-agent chemotherapy or a multi-agent regimen. Each chemotherapy works to kill cancer cells in a different way, which helps prevent the cancer from coming back. Each type of chemotherapy can also cause different side effects. Talk to the care team about the types of chemotherapy your child is getting, when your child will get them, and what side effects to expect.

The main types of chemotherapy drugs (agents) used to treat ALL in children can be found in **Guide 2.**

Other types of chemotherapy may be used depending on your child's type of leukemia and how ALL responds to therapy.

Targeted therapy

Targeted therapy is a form of systemic therapy that focuses on specific or unique features of cancer cells. Targeted therapies seek out how cancer cells grow, divide, and move in the body. These drugs stop the action of molecules that help cancer cells grow and/or survive.

Tyrosine kinase inhibitor

A tyrosine kinase inhibitor (TKI) is a type of targeted therapy that blocks the signals that cause cancer to grow and spread. TKIs might be used alone or in combination with other systemic therapies like chemotherapy.

Tyrosine kinases are proteins in cells that are important for many cell functions. The protein made by the *BCR::ABL1* gene is a tyrosine kinase. It moves or transfers chemicals, called phosphates, from one molecule to another. TKIs block this transfer, which stops the uncontrolled cell growth in ALL.

There are other types of targeted therapies available to treat ALL. Whether or not one is available or would be helpful for your child depends on your child's subtype of ALL and what types of genetic changes your child's ALL cells have.

TKIs used to treat ALL in children can be found in **Guide 2.**

Systemic therapy works throughout the body. It includes chemotherapy, targeted therapy, immunotherapy, and others.

TKI side effects

Side effects are common among TKIs. A side effect is an unwanted health issue. It is very important for your child to continue to take the medicine even if they do not feel well. Speak to the care team before making any changes!

Guide 2
Systemic therapy examples

Chemotherapy examples	• Vincristine (Oncovin, Vincasar) • Cyclophosphamide • Cytarabine (Cytosar-U) • Daunorubicin (Cerubidine) • Doxorubicin (Adriamycin) • 6-MP (6-mercaptopurine)	• Methotrexate • Nelarabine (Arranon) • Thioguanine (Tabloid) • Asparaginase (Calaspargase, Oncaspar, Erwinia, Rylaze) • Bortezomib (Velcade)
TKI examples	• Dasatinib (Sprycel) • Imatinib (Gleevec) • Nilotinib (Tasigna) • Ponatinib (Iclusig) • Ruxolitinib (Jakafi)	
Immunotherapy examples	• Blinatumomab (Blincyto) • Daratumumab (Darzalex) • Inotuzumab ozogamicin (Besponsa)	
CAR T-cell therapy example	• Tisagenlecleucel (Kymriah)	

Immunotherapy

Immunotherapy is drug therapy that increases the activity of your immune system. By doing so, it improves your body's ability to find and destroy cancer cells. Immunotherapy can be given alone or with other types of treatment. Immunotherapy examples can be found in **Guide 2.**

Antibody therapy

Antibody therapy uses antibodies to help the body fight cancer, infection, or other diseases. Antibodies are proteins made by the immune system that bind to specific markers on cells or tissues. A monoclonal antibody (mAb) is made from a unique white blood cell, such as a B or T cell. As with other treatments, there is the potential for complications. Antibody therapies that might be used to treat certain subtypes of ALL are described below.

Bispecific antibody therapy

Bispecific antibodies (BsAbs) such as blinatumomab (Blincyto) bind to 2 different proteins (CD19 and CD3) at the same time. They treat cancer by engaging T cells. Bispecifics can cause a side effect called cytokine release syndrome (CRS) and neurotoxicity.

CD22-targeting antibody drug conjugate

An antibody drug conjugate (ADC) delivers cell-specific chemotherapy. It attaches to a protein found on the outside of the cancer cell and then enters the cell. Once inside the cell, chemotherapy is released. Inotuzumab ozogamicin (Besponsa) is an ADC that targets the CD22 protein.

CD38-targeting monoclonal antibody therapy

Daratumumab (Darzalex) is used in combination with other systemic therapies to treat relapsed or refractory T-ALL by targeting the CD38 protein.

Chemoimmunotherapy

Chemoimmunotherapy, also called immunochemotherapy, includes chemotherapy and immunotherapy drugs to treat cancer.

CD19-targeting CAR T-cell therapy

CAR T-cell therapy is made by removing T cells from your child's body and then training their own immune cells to fight the leukemia by adding a CAR (chimeric antigen receptor) to the T cells. This genetically modifies and programs the T cells to find cancer cells. After your child receives a brief course of chemotherapy (called lymphodepleting chemotherapy), the programmed T cells will be infused back into their body to find and kill cancer cells. This treatment is not for everyone and may be used for relapse. There can be severe and sometimes life-threatening reactions to this treatment.

CAR T-cell therapy is one way to target the CD19 protein found on B-ALL. Tisagenlecleucel (Kymriah) is a type of CD19-targeting CAR T-cell therapy.

For more information on side effects, see *NCCN Guidelines for Patients: Immunotherapy Side Effects: CAR T-Cell Therapy* at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.

Hematopoietic cell transplant

A hematopoietic cell transplant (HCT) replaces hematopoietic stem cells that have been destroyed by high doses of chemotherapy and/or radiation therapy (RT) as part of the transplant process. A hematopoietic stem cell is an immature cell that can develop into any type of blood cell. You might hear it called a stem cell transplant (SCT) or a bone marrow transplant (BMT). This book will refer to it as HCT. HCTs are performed in specialized centers.

There are 2 types of HCTs:

- **Autologous** – stem cells come from your child.
- **Allogeneic** – stem cells come from a donor who may or may not be related to your child. Only an allogeneic HCT is used as a possible treatment option in ALL.

Allogeneic HCT

An allogeneic HCT uses healthy stem cells from a donor. The donor may or may not be related to your child. Before an HCT, treatment is needed to destroy bone marrow cells. This is called conditioning and it creates room for the healthy donor stem cells. It also weakens the immune system so your child's body will accept and won't kill the transplanted cells. Chemotherapy is used for conditioning. Radiation therapy may also be given as part of conditioning treatment.

After conditioning, your child will receive a transfusion of the healthy stem cells from a donor who has been matched to your child. A transfusion is a slow injection of blood products into a vein. This can take several hours. The transplanted stem cells will travel to your child's bone marrow and grow. New, healthy blood cells will form. This is called engraftment. It usually takes about 2 to 4 weeks. Until then, your child will have little or no immune defense. Your child may need to stay in a very clean room at the hospital or be given antibiotics to prevent or treat infection. Transfusions are also possible. A red blood cell (RBC) transfusion is used to prevent bleeding and to treat anemia (below normal RBC count). A platelet (PLT) transfusion is used to treat a low PLT count or bleeding. While waiting for the cells to engraft, your child will likely feel tired and weak. This treatment has very serious and life-threatening side effects.

Possible side effects

Every treatment has side effects. Your child will be monitored for infections, disease relapse, and graft-versus-host disease (GVHD). In GVHD, the donor cells attack your child's normal, healthy tissue. There are treatments for GVHD. Ask the care team about the possible side effects or complications of HCT and how this might affect your child's quality of life.

More information on GVHD can be found in the *NCCN Guidelines for Patients: Graft-Versus-Host Disease* at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.

Radiation therapy

Radiation therapy (RT) uses high-energy radiation from photons, electrons, x-rays, or protons, and other sources to kill cancer cells and shrink tumors. It is given over a certain period of time. Radiation therapy can be given alone or with certain systemic therapies. It may be used as supportive care to help ease pain or discomfort caused by cancer.

- Those with leukemia in the central nervous system at diagnosis may receive radiation to the brain area.
- Those with testicular disease at diagnosis that remains after induction therapy may receive radiation to the testes.

Cranial RT

In cranial irradiation, the areas of the brain targeted for ALL radiation treatment are different from areas targeted for brain metastases of solid tumors.

Total body RT

Total body irradiation (TBI) is radiation of the whole body given before a hematopoietic cell transplant (HCT)

Testicle RT

Since ALL can sometimes be found in the testicles, radiation therapy might be given to this area if there is partial or no response to chemotherapy.

Finding a clinical trial

In the United States

NCCN Cancer Centers
NCCN.org/cancercenters

The National Cancer Institute (NCI)
cancer.gov/about-cancer/treatment/clinical-trials/search

Worldwide

The U.S. National Library of Medicine (NLM)
clinicaltrials.gov

Need help finding a clinical trial?

NCI's Cancer Information Service (CIS)
1.800.4.CANCER (1.800.422.6237)
cancer.gov/contact

Key points

- Chemotherapy kills fast-dividing cells throughout the body, including cancer cells and normal cells. Chemotherapy is the backbone of pediatric acute lymphoblastic leukemia (ALL) treatment and is often combined with other drug therapies.
- Steroids are part of all ALL regimens.
- Clinical trials study how safe and helpful tests and treatments are for people. Many ALL standard of care treatment regimens are the result of clinical trials.
- Targeted therapy focuses on specific or unique features of cancer cells.
- Immunotherapy uses the immune system to find and destroy cancer cells.
- A hematopoietic cell transplant (HCT) replaces damaged bone marrow stem cells with healthy stem cells.

Questions to ask

- Which treatment(s) do you recommend and why?
- What can we expect from treatment?
- How will you treat side effects? What should we look for?
- Are there resources to help pay for treatment or other care my child may need?
- What clinical trial options are available?

4
Supportive care

Supportive care helps manage the symptoms of ALL and the side effects of treatment. This chapter discusses possible side effects.

What is supportive care?

Supportive care helps improve your quality of life during and after cancer treatment. The goal is to prevent or manage side effects and symptoms, like pain and cancer-related fatigue. It also addresses the mental, social, and spiritual concerns faced by those with cancer.

Supportive care is available to everyone with cancer and their families, not just those at the end of life. Palliative care is another name for supportive care.

Supportive care can also help with:

- Making treatment decisions
- Coordinating your care
- Paying for care
- Planning for advanced care and end of life

Side effects

All cancer treatments can cause unwanted health issues called side effects. Side effects depend on many factors. These factors include the drug type and dose, length of treatment, and the person. Some side effects may be harmful to one's health. Others may just be unpleasant. Treatment can cause several side effects. Some are very serious. Tell your child's care team about any new or worsening symptoms.

Some potential side effects are described next. They are not listed in order of importance. Some side effects are very rare.

Blood clots

Cancer treatment can cause blood clots to form. This can block blood flow and oxygen in the body. Blood clots can break loose and travel to other parts of the body causing breathing problems, strokes, or other problems.

Cytokine release syndrome

Cytokine release syndrome (CRS) is a condition that may occur after treatment with some types of immunotherapy, such as monoclonal antibodies and chimeric antigen receptor (CAR) T cells. It is caused by a large, rapid release of cytokines from immune cells affected by the immunotherapy. Signs and symptoms of CRS include fever, muscle aches, nausea, headache, rash, fast heartbeat, low blood pressure, and trouble breathing.

Diarrhea

Diarrhea is frequent and watery bowel movements. Your child's care team will tell you how to manage diarrhea. It is important to drink lots of fluids.

Difficulty eating

Sometimes side effects from surgery, cancer, or its treatment might cause your child to feel not hungry or sick to their stomach (nauseated). Your child might have a sore mouth. Healthy eating is important during treatment. It includes eating a balanced diet, eating the right amount of food, and drinking enough fluids. A registered dietitian who is an expert in nutrition and food can help. Speak to your child's care team if your child has trouble eating or maintaining weight.

Distress

Depression, anxiety, and sleeping problems are common and are a normal part of cancer diagnosis. Talk to your child's care team and with those whom you feel most comfortable about how your child may be feeling. There are services, people, and medicine that can help your child. Support and counseling services are available.

Fatigue

Fatigue is extreme tiredness and inability to function due to lack of energy. Fatigue may be caused by cancer or it may be a side effect of treatment. Let your child's care team know how your child is feeling and if fatigue is getting in the way of them doing the things they enjoy. Eating a balanced diet and physical activity can help. Your child might be referred to a nutritionist or dietitian to help with fatigue.

Hand-foot syndrome

Hand-foot syndrome is a common side effect of chemotherapy. Small amounts of chemotherapy leak out of very small blood vessels called capillaries in the palms of the hands and soles of the feet. It causes redness, swelling, and pain. Sometimes blisters appear. You will want to protect your child's hands and feet by applying moisturizer or lotion.

High blood pressure

High blood pressure (HBP or hypertension) occurs when the force of blood flowing through your blood vessels is consistently too high. This can cause headaches and vision problems. If left untreated, HPB can cause heart problems and stroke. Steroids can cause HBP. Medicine might be used to control HBP.

High blood sugar

One possible side effect of steroids is high blood sugar or hyperglycemia. Glucose (sugar found in the blood) will be measured. Insulin might be needed to control high blood sugar.

Hypersensitivity, allergy, and anaphylaxis

Certain treatments can cause an unwanted reaction. Hypersensitivity is an exaggerated response by the immune system to a drug or other substance. This can include hives, skin welts, and trouble breathing. An allergy is an immune reaction to a substance that normally is harmless or would not cause an immune response in most people. An allergic response may cause harmful symptoms such as itching or inflammation (swelling). Anaphylaxis or anaphylactic shock is a severe and possible life-threatening allergic reaction.

Infections

Infections occur more frequently and are more severe in those with a weakened immune system. Drug treatment for ALL can weaken the body's natural defense against infections. If not treated early, infections can be fatal.

Neutropenia, a low number of white blood cells, can lead to frequent or severe infections. When someone with neutropenia also develops a fever, it is called febrile neutropenia (FN). With FN, your child's risk of infection may be higher than normal. This is because a low number leads to a reduced ability to fight infections. FN is a side effect of some types of systemic therapy.

Low blood cell counts

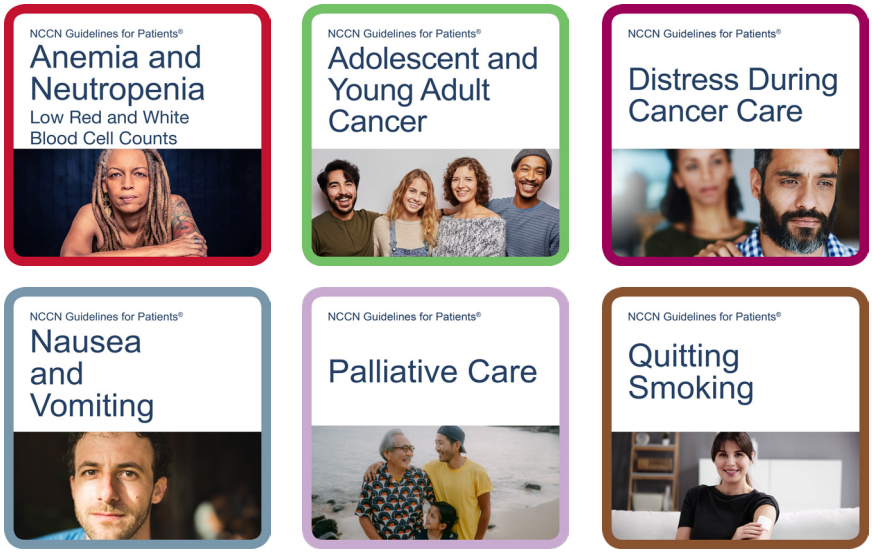
Some cancer treatments can cause low blood cell counts.

- **Anemia** is a condition where your child's body does not have enough healthy blood cells, resulting in less oxygen being carried to your child's cells. Your child might tire easily if they are anemic.
- **Neutropenia** is a decrease in neutrophils, the most common type of white blood cell. This puts your child at risk for infection.
- **Thrombocytopenia** is a condition where there are not enough platelets found in the blood. This puts your child at risk for bleeding.

Nausea and vomiting

Nausea and vomiting are common side effects of treatment. Your child will be given medicine to prevent nausea and vomiting.

More information on supportive care is available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.



Neuropathy

Neuropathy is a nerve problem that causes pain, numbness, tingling, swelling, or muscle weakness in different parts of the body. It usually begins in the hands or feet and gets worse over time. Neuropathy may be caused by cancer or cancer treatment.

Neurotoxicity

Some treatments can damage the nervous system (neurotoxicity) causing problems with concentration and memory. Seizures and confusion can occur. If ALL treatment includes methotrexate, then your child will be monitored for methotrexate neurotoxicity. Neurotoxicity can be seen with immunotherapy, as well.

Organ issues

Treatment might cause your child's kidneys, liver, heart, and pancreas to not work as well as they should.

Osteonecrosis

Osteonecrosis, or avascular necrosis, is death of bone tissue due to lack of blood supply. It is a possible side effect of steroids and most often affects weight-bearing joints, such as the hip and/or knee.

Pain

Tell your child’s care team about any pain or discomfort. Your child might meet with a pediatric pain or palliative care specialist to manage pain. Bone pain and vincristine-associated neuropathic pain are common in ALL.

Sore or dry mouth

Mucositis is a painful inflammation of the mucous membranes in the mouth or gut that can be a side effect of certain cancer treatments. Drinking plenty of water and avoiding beverages with caffeine, alcohol, or sugar can help. Special mouth rinses are available. Your child should see a dentist regularly.

Weight gain

Weight gain is one side effect of high-dose steroids. This can be uncomfortable and cause distress. It is important to maintain muscle mass. Help your child to find an activity they enjoy. Ask your child's care team what can be done to help manage weight gain.

Supportive care

Supportive care helps manage the symptoms of ALL and the side effects of treatment.

Antibiotics and treatment

For infection, antibiotics (for bacterial infection), antifungal medicine (for fungal infection), and antiviral drugs (for viral infection) are used. These medications can be used to prevent infections called prophylaxis.

Pneumocystis pneumonia is a serious infection caused by the fungus *Pneumocystis jirovecii*. Since those with ALL are at high risk, medicine will be given throughout treatment to prevent this type of pneumonia.

Dialysis

Leukemia cells and chemotherapy sometimes cause an imbalance of substances in blood or damage to the kidneys. If the damage is severe, your child may need dialysis. Dialysis is the process of filtering blood when the kidneys are unable. There are different types of dialysis. Hemodialysis and hemofiltration remove waste and water by circulating blood outside the body through an external filter.

Hyperleukocytosis and leukapheresis

Hyperleukocytosis (leukostasis) is an extremely high lymphoblast count. Sometimes those with hyperleukocytosis need to have a machine remove lymphoblasts from the blood in a process called leukapheresis. In leukapheresis, your child may be connected to a machine called an apheresis machine. The machine separates white blood cells (leukocytes) from other blood cells. Once the excess leukocytes are removed, the blood is returned to your child's body.

Transfusions

Blood transfusions are common during ALL treatment. A transfusion is a slow injection of blood products such as red blood cells or platelets into a vein. Over time, the body may begin to reject blood transfusions.

Most blood transfusions come from blood banks and are collected from strangers who donate blood. Sometimes, family members ask if they can donate blood for a family member with ALL. Typically, we do not want to transfuse blood products collected from family members. Your doctor can explain why it is safer to use blood products from strangers than members of your own family.

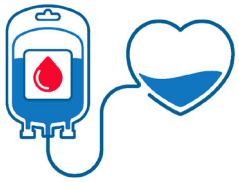
“Have open communication with your child. Remind them that you love them and that they are strong.”

Late effects

Late effects are side effects that occur months or years after a disease is diagnosed or after treatment has ended. Late effects may be caused by cancer or cancer treatment. They may include physical, mental, and social health issues, and second cancers. The sooner late effects are treated the better. Ask the care team about what late effects could occur. This will help you know what to look for.

Survivorship

A person is a cancer survivor from the time of diagnosis until the end of life. After treatment, your child's health will be monitored for side effects of treatment and the return of cancer. This is part of a survivorship care plan. It is important to keep any follow-up doctor visits and imaging test appointments. Find out who will coordinate your child's follow-up care.



Transfusions

A transfusion is a common procedure to replace blood or blood components (red blood cells or platelets). It is given through an intravenous (IV) line, a tiny tube that is inserted into a vein with a small needle.

- The whole process can take about 1 to 4 hours, depending on how much blood is needed.
- Most transfusions use blood from a donor. This is preferred in ALL.
- Blood transfusions are usually very safe. Donated blood is carefully tested, handled, and stored.
- Most people's bodies handle blood transfusions very well. But, like any medical procedure, there are some risks. Speak with your care team for specific information about the risks.
- Systemic therapy can affect how bone marrow makes new blood cells. Some people getting treatment for cancer might need a transfusion of red blood cells or platelets.

Key points

- Supportive care is health care that relieves symptoms caused by cancer or its treatment and improves quality of life.
- All cancer treatments can cause unwanted health issues called side effects. Side effects depend on many factors. These factors include the drug type and dose, length of treatment, and the person.
- Some side effects are very rare. Ask your child's care team what to expect.
- Tell your child's care team about any new or worsening symptoms.
- Blood transfusions are common during treatment.

Questions to ask

- What are the side effects of this treatment?
- How are these side effects treated?
- What should I do if I notice changes in my child's condition?
- What should I do on weekends and other non-office hours?
- Will my child's care team be able to communicate with the emergency department or urgent care team?

5

BCR::ABL1-negative or *BCR::ABL1*-like B-ALL

This chapter is for those with *BCR::ABL1*-negative or *BCR::ABL1*-like B-ALL. A clinical trial is the preferred treatment for these types of B-ALL.

Overview

In *BCR::ABL1*-negative or *BCR::ABL1*-like B-ALL, the *BCR::ABL1* gene is not found. However, *BCR::ABL1*-like B-ALL has similar mutations and gene changes found in *BCR::ABL1* B-ALL. Before starting treatment, your child will be placed into a risk group. Risk is based on white blood cell (WBC) count and age at diagnosis. Other features might impact risk.

- **Standard risk** is for those with a WBC less than 50,000/mm³ and who are between 1 and 10 years of age.
- **High risk** is for those with a WBC higher than 50,000/mm³ or who are under 1 year of age or 10 years of age and over.

For both risk groups, induction will be multi-agent chemotherapy given through a clinical trial or as standard of care. A clinical trial is preferred, but if one is not available, or you prefer for your child to not be treated as part of a clinical trial, the best-known treatment for your child's type of ALL will be used. This is called standard of care. Ask your child's care team what treatment options are available.

All treatment regimens include systemic therapy and/or intrathecal (IT) therapy (which is injected into the spinal fluid) to prevent central nervous system (CNS) disease. After induction is complete, your child's risk group will be reassessed before starting consolidation.

Treatment

People in the same risk group will likely respond to treatment in the same way. As a result, doctors often use risk groups to help plan treatment. Ask how your child's risk group might affect their treatment.

The first or main treatment given is called primary treatment. It is based on your child's risk group. Treatment for both risk groups is a clinical trial (preferred) or chemotherapy. Chemotherapy is the backbone of all induction and consolidation regimens. A targeted therapy might be added depending on the gene changes and mutations found in the cancer.

MRD+ after induction

Treatment response will be measured after completing induction. The goal is a complete response (CR). Tests will look for minimal residual disease (MRD). When MRD is found, it is called MRD-positive (MRD+). A certain low level of MRD may be okay (called a threshold), but it depends on the treatment. Ask your child's care team what this might mean.

Treatment

MRD+ is treated with a clinical trial or chemotherapy. A clinical trial is preferred, if available and it is what you want for your child.

If MRD remains negative (MRD-) after the first post-induction phase of chemotherapy, then your child will continue with post-induction chemotherapy, followed by maintenance chemotherapy.

If MRD remains positive (MRD+) after first post-induction phase chemotherapy, options include:

- Clinical trial (preferred)
- Chemotherapy
- Blinatumomab
- CAR T-cell therapy (tisagenlecleucel)
- Other systemic therapies

A hematopoietic cell transplant (HCT) can be considered as the next treatment option for those whose MRD becomes negative. If MRD is continuously positive, then a different treatment might be given from the list above.

"Remember that you are not in this alone. Families around you will share the experiences that you are going through and talking with them can be therapeutic."

Surveillance and monitoring

During maintenance or after an HCT, your child will be monitored for signs that cancer has returned called relapse. **See Guide 3.**

Guide 3
Surveillance and monitoring

Surveillance	1 year after treatment	→	Every 1 to 4 months • Physical exam with testicular exam • Complete blood count (CBC) with differential • Liver function tests (LFTs) until normal
	2 years after treatment	→	Every 2 to 6 months • Physical exam with testicular exam • CBC with differential
	3 years after treatment	→	Every 6 to 12 months or as needed • Physical exam, including testicular exam • CBC with differential
Procedures and biomarker testing	• Bone marrow aspirate and cerebrospinal fluid (CSF) for suspected relapse • Biomarker and other testing might include: *BCR::ABL1*, flow cytometry, FISH, chromosome, and minimal residual disease (MRD) testing.		
Monitoring for late effects	• Echocardiogram as needed • Neuropsychological testing as needed for neurotoxicity • Monitor weight (those with history of childhood ALL are at increased risk of developing obesity) • See *Long-Term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers from the Children's Oncology Group (COG)* at survivorshipguidelines.org • See *NCCN Guidelines for Patients: Adolescent and Young Adult Cancer* at NCCN.org/patientguidelines.		

First relapse

First relapse is the return of cancer after a period of remission. The goal of treatment is to achieve remission (a complete response) again. This is not always possible. Treatment options are based on the time from initial diagnosis to relapse and if cancer is found in bone marrow, blood, or other areas of the body.

Cancer can return in the bone marrow called isolated medullary relapse, outside the bone marrow called isolated extramedullary relapse, or a combination of both called combined relapse. Extramedullary relapse is cancer found in the central nervous system (CNS) or testicles.

Isolated extramedullary relapse requires systemic therapy to prevent relapse in bone marrow. Likewise, isolated medullary relapse requires intrathecal (IT) treatment to prevent cancer in the central nervous system.

Treatment for B-ALL first relapse will be based on your child's prior therapy and length of time from initial diagnosis to relapse. **Most treatment paths lead to an hematopoietic cell transplant (HCT).**

It is very important for your child to continue taking their medicine as prescribed and not miss or skip any doses. This helps to prevent relapse.

Early and late first relapse

Treatment options for early or late first relapse include a clinical trial or systemic therapy. A clinical trial is preferred, if available and it is what you want for your child.

Early relapse is:

- Less than 36 months (3 years) from initial diagnosis for isolated or combined bone marrow relapse OR
- Less than 18 months from initial diagnosis for isolated extramedullary relapse

Late relapse is:

- 36 months (3 years) or more from initial diagnosis for isolated or combined bone marrow relapse OR
- 18 months or more from initial diagnosis for isolated extramedullary relapse

First relapse

Treatment options for a relapse is a clinical trial (preferred) or systemic therapy.

First relapse after HCT

Treatment options for a relapse that occurs after an HCT include:

- Clinical trial (preferred) using systemic therapy
- Standard-of-care systemic therapy
- Blinatumomab
- Revumenib (for *KMT2Ar BCR::ABL1*-negative ALL)
- Tisagenlecleucel
- Inotuzumab ozogamicin

Treatment response will be checked before starting consolidation.

- If there is a complete response, then a second HCT might follow.
- If there is less than a complete response, then treatment might be one of the options listed above.

The goal is to achieve an MRD-negative result before an HCT. However, in some cases an HCT might be considered in those who are MRD+.

Multiple relapse or refractory

Relapse can happen more than once. With each relapse the goal of treatment is a complete response or remission. When cancer returns only in the bone marrow, it is called isolated medullary relapse. When cancer is found in the central nervous system and testicles, but not in the bone marrow or blood, it is called isolated extramedullary relapse. In this case, systemic therapy is needed to prevent relapse in bone marrow. When leukemia remains and does not respond to treatment, it is called refractory. A different therapy will be given for refractory disease.

Treatment options include:

- Clinical trial (preferred)
- Chemotherapy
- Blinatumomab
- Revumenib (for *KMT2Ar BCR::ABL1*-negative ALL)
- Tisagenlecleucel
- Inotuzumab ozogamicin

Treatment response will be checked before starting consolidation.

- If there is a complete response, then an hematopoietic cell transplant (HCT) will follow.
- If there is less than a complete response, then treatment might be another therapy, supportive care, or palliative care.

Key points

- Both *BCR::ABL1*-negative or *BCR::ABL1*-like B-ALL do not have the abnormal fused gene called *BCR::ABL1*. However, *BCR::ABL1*-like B-ALL is very similar to *BCR::ABL1*-positive B-ALL, which is described in the next chapter.
- Induction is a combination of systemic therapies. A clinical trial is the preferred treatment, if available.
- All treatment regimens include systemic and/or intrathecal (IT) therapy to prevent central nervous system (CNS) disease.
- When cancer remains after induction, it is called MRD-positive (MRD+). MRD+ is treated with a clinical trial (preferred) or post-induction chemotherapy.
- Relapse can happen more than once. With each relapse the goal of treatment is a complete response (CR) or remission. A clinical trial is the preferred treatment, if available.
- It is very important for your child to take medicine exactly as prescribed and not miss any doses.

Questions to ask

- How does my child's risk group affect the treatment options?
- Does the order of treatments matter?
- What should I do if my child misses or skips a dose?
- Why is a clinical trial the preferred option for this type of B-ALL?
- Is there a social worker or someone who can help us decide about treatment?

6
BCR::ABL1-positive B-ALL

***BCR::ABL1*-positive B-ALL is less common than other types of B-ALL. Treatment aims to stop the activity of the BCR::ABL protein caused by the *BCR::ABL1* gene. Treatment is usually an intensive combination of systemic therapies.**

Treatment

BCR::ABL1-positive B-ALL is less common than other types of B-ALL. Treatment aims to stop the activity of the BCR::ABL protein caused by the abnormal, fused *BCR::ABL1* gene. Although *BCR::ABL1*-positive B-ALL is considered high risk, there are effective treatments. Treatment is usually an intensive combination of systemic therapies that include tyrosine kinase inhibitors (TKIs). Treatment can be done as part of a clinical trial, which is preferred when available, or as part of standard cancer care.

Induction

Many induction treatment regimens are part of ongoing clinical trials. Induction is a combination of systemic therapies. Systemic therapies work throughout the body. All treatment regimens include systemic therapy and/or intrathecal (IT) therapy (injected into the spinal fluid) to prevent CNS disease. Typically, TKIs are added in the middle of induction for those who are found to be *BCR::ABL1*-positive, whether they are being treated as part of a clinical trial or with a standard-of-care regimen.

Post-induction

Before starting post-induction phases of treatment, your child will be placed into a risk group. Risk is based on a variety of factors. A risk group will determine the treatment with the best chance of leukemia going into remission and not relapsing in the future. Treatment options may be partially based on if there is minimal residual disease (MRD) at the end of induction. When leukemia cells remain, it is called MRD-positive (MRD+). A hematopoietic cell transplant (HCT) might be an option if MRD continues to remain positive or a different TKI might be used. Other systemic therapies might be given.

Maintenance

Maintenance is given after post-induction phases of treatment. This is usually the longest phase of therapy and is less intense than previous phases. TKIs are given throughout maintenance until therapy is complete.

Surveillance and monitoring

During maintenance or after an HCT, your child will be monitored for signs of recurrence called relapse. **See Guide 3** on page 48.

Relapsed or refractory disease

Relapse is the return of cancer after a period of remission. The goal of treatment is to achieve remission again. Cancer can return in the bone marrow called isolated medullary relapse, outside the bone marrow called isolated extramedullary relapse, or a combination of both (combined relapse). Extramedullary relapse can occur in the central nervous system (CNS) or testicles.

Mutation testing will be done before starting treatment. Treatment options for Ph+ B-ALL relapse include:

- Clinical trial (preferred)
- Chemotherapy
- A different type of TKI than used before might be added to chemotherapy
- Blinatumomab
- Tisagenlecleucel
- Inotuzumab ozogamicin

Most treatment paths lead toward a hematopoietic cell transplant (HCT). The goal is to achieve an MRD-negative result before an HCT. If less than a complete response, then treatment options include another therapy, supportive care, or palliative care. An HCT might be considered in those who are MRD+. The timing of an HCT depends upon donor availability and your child's health at the time of potential HCT.

Palliative care is appropriate for anyone, regardless of age, cancer stage, or the need for other therapies. It focuses on physical, emotional, social, and spiritual needs that affect quality of life.

Multiple relapse

BCR::ABL1-positive B-ALL can relapse multiple times. With each relapse the goal of treatment is a complete response, typically followed by an HCT. This is not always possible.

Refractory disease

When leukemia remains and does not respond to treatment, it is called refractory or resistant. ALL may be resistant at the start of treatment or it may become resistant during treatment. Refractory disease is very serious. It is important to ask about prognosis. Treatment options are the same as for relapse.

Key points

- In *BCR::ABL1*-positive B-ALL, tests show the presence of the *BCR::ABL1* gene.
- The goal of treatment is a complete response (CR) and to prevent the spread of cancer to areas outside the blood.
- Treatment is usually an intensive combination of systemic therapies including a type of targeted therapy called a tyrosine kinase inhibitor (TKI).
- All treatment regimens include systemic therapy and/or intrathecal (IT) therapy (which is injected into the spinal fluid) to prevent central nervous system (CNS) disease.
- Relapse is the return of cancer after a period of remission. The goal of treatment is to achieve another remission (a complete response).
- For multiple relapse or refractory disease, the goal is to achieve an MRD-negative result before a hematopoietic cell transplant (HCT). An HCT is not an option for everyone.
- The timing of an HCT depends upon donor availability and your child's health at the time of potential HCT.

Questions to ask

- Which treatment do you recommend and why?
- Does this treatment offer a cure? If not, how well can treatment stop the cancer from growing?
- What side effects can I expect from this treatment?
- How can I prepare my child for treatment?
- Is a hematopoietic cell transplant (HCT) an option for my child? What are the risks with an HCT?

7
T-ALL

T-ALL includes a group of cancers that start in T-cell lymphocytes. T-ALL is less common than B-ALL. Treatment options include a clinical trial or chemotherapy. Other systemic therapies might be given.

The timing of a hematopoietic cell transplant (HCT) depends upon donor availability and your child's health at the time of potential HCT.

Treatment

It is recommended that T-ALL be treated in a clinical trial when possible. If a clinical trial is not available, your child will be treated with the best-known chemotherapy regimen. All treatment regimens include systemic therapy and intrathecal (IT) therapy (injected into the spinal fluid) to prevent central nervous system (CNS) disease.

The overall treatment plan for T-ALL is the same as *BCR::ABL1*-negative B-ALL. In some treatment phases, medicine doses and timing may be different. Also, some phases may include medicines that work well for T-ALL, but not in those with B-ALL. In T-ALL, the goal is to be in complete remission at the end of the first consolidation (post-induction) phase, rather than at the end of induction (EOI).

Induction

Many induction treatment regimens are part of ongoing clinical trials. A bone marrow aspirate will be done at the end of induction to see how the leukemia responded to therapy. In T-ALL, not achieving a complete response at the end of induction does not affect risk group or prognosis the way it does in B-ALL.

Post-induction

Post-induction or consolidation is a continuation of chemotherapy. Everyone with T-ALL will receive a first post-induction phase treatment before being placed into a risk group. Risk is based on a variety of factors. A risk group will determine the treatment with the best chance of leukemia going into remission and not relapsing in the future. Another bone marrow aspirate might be done if minimal residual disease was found earlier. A hematopoietic cell transplant (HCT) might be an option if MRD remains positive.

Maintenance

Maintenance is given after post-induction phases of therapy and is less intense chemotherapy than previous phases.

First relapse

T-ALL often returns within 2 years of diagnosis. When cancer returns after remission, it is called relapse. Relapse can occur in the bone marrow called isolated medullary relapse, in the testicles or central nervous system (CNS) called isolated extramedullary relapse, or a combination of both. Isolated extramedullary relapse requires systemic therapy to prevent relapse in bone marrow.

Treatment will likely include a combination of drugs. If relapse is more than 3 years after initial diagnosis, then the same induction regimen might be used again.

Treatment options for a first relapse:

- Clinical trial (preferred)
- Systemic therapy

Complete response

If treatment causes a complete response (CR), then your child will continue with the same treatment. A clinical trial is an option. The next step would be a hematopoietic cell transplant (HCT).

Less than a complete response

If treatment does not cause a complete response, then a different treatment will be given. It might include a clinical trial, chemotherapy, or other systemic therapy.

Multiple relapses

Relapse can happen multiple times. With each relapse the goal of treatment is a complete response.

Treatment options include:

- Clinical trial (preferred)
- Systemic therapy

Treatment response will be checked before starting consolidation.

- If there is a complete response, usually a hematopoietic cell transplant (HCT) will follow.
- If less than a complete response, then treatment might be another therapy, supportive care, or palliative care.

Refractory disease

When cancer remains, it is called MRD-positive (MRD+). When leukemia remains and does not respond to treatment, it is called refractory or resistant disease. The cancer may be resistant at the start of treatment or it may become resistant during treatment. Refractory disease is very serious. It is important to ask about prognosis. Treatment options for refractory disease or disease that continues to be MRD+ are the same as for multiple relapses.

Key points

- T-ALL includes a group of cancers that start in T-cell lymphocytes. T-ALL is less common than B-ALL.
- It is recommended that T-ALL be treated in a clinical trial, when possible. Standard-of-care chemotherapy is also an option.
- All treatment regimens include systemic therapy and intrathecal (IT) therapy (which is injected into the spinal fluid) to prevent central nervous system (CNS) disease.
- The goal of treatment is a complete response (CR).
- Relapse can happen multiple times. With each relapse the goal of treatment is a complete response. Treatment for relapse includes a clinical trial (preferred) or systemic therapy.
- Cancer may be resistant at the start of treatment or it may become resistant during treatment. This is called refractory disease. Treatment options for refractory disease or disease that continues to be MRD-positive (MRD+) are the same as for multiple relapses.
- A hematopoietic cell transplant (HCT) might follow a CR.

Questions to ask

- What can we expect from treatment and what are the risks?
- What side effects should we look for and when should we contact my child's care team?
- How can we prepare for the possibility of relapse?
- Will the treatment we choose today affect our choices if cancer relapses or is refractory?
- Is a clinical trial or hematopoietic cell transplant (HCT) an option for my child?

8
Infant ALL

ALL treatment for infants is different than for other age groups. Infants are children under 12 months of age.

Interfant induction

Interfant induction is the first phase of treatment for infants. Interfant refers to the name of the clinical trials that showed this was a safe and effective treatment for infant ALL. Your child does not have to be enrolled in a clinical trial to have Interfant induction. However, enrolling in a clinical trial may be the best choice for your child.

There are 2 treatment options:

- Clinical trial (preferred)
- Interfant induction

Interfant induction is a multi-drug therapy that might include prednisone, dexamethasone, vincristine, cytarabine, daunorubicin, pegaspargase or calaspargase, and methotrexate. Blinatumomab might be added. Other systemic therapies might be used. All treatment regimens include systemic therapy and/or intrathecal (IT) therapy to prevent central nervous system (CNS) disease. Systemic therapy works throughout the body. IT therapy is injected into the spinal fluid.

Consolidation

The goal of consolidation or treatment after induction called post-induction therapy is to rid the body of any remaining leukemia cells. Treatment is based on the status of a gene called *KMT2A* (11q23). If *KMT2A* is found to be abnormal, it is called *KMT2A*-rearranged. There are 2 risk groups for *KMT2A*-rearranged: high or intermediate. When *KMT2A* rearrangement is not found, it is considered standard risk.

KMT2A-rearranged

For *KMT2A*-rearranged, treatment will be based on Interfant intensive chemotherapy. The Interfant intensive phases are a multi-drug treatment. After these intensive phases, maintenance chemotherapy or hematopoietic cell transplant (HCT) may be considered. Maintenance is usually a continuation of chemotherapy but at a lower dose.

Not *KMT2A*-rearranged

Post-induction treatment options include:

- Clinical trial (preferred)
- Standard-of-care chemotherapy using non-infant ALL regimens
- Standard of care using Interfant chemotherapy

Maintenance

Maintenance chemotherapy is given to prevent the return or spread of ALL. It is usually a continuation of treatment but might be at a lower dose.

Surveillance

During maintenance therapy or after an HCT, your child will be monitored for signs of recurrence called relapse. If cancer returns, treatment can be found under B-ALL or T-ALL first relapse. For surveillance and monitoring tests, **see Guide 3** on page 48.

We want your feedback!

Our goal is to provide helpful and easy-to-understand information on cancer.

Take our survey to let us know what we got right and what we could do better.

NCCN.org/patients/feedback

"Do not forget to take care of yourself, while taking care of your child. It is easy to be completely immersed in their care and not do anything for yourself. Make time for yourself, when possible. It's healthy and will allow you to be strong for your child."

Key points

- Infants are children under 12 months of age.
- There are special treatment regimens for infants.
- Treatment options include a clinical trial, multi-drug therapy chemotherapy, and possibly a hematopoietic cell transplant (HCT).
- All treatment regimens include systemic therapy and/or intrathecal (IT) therapy (which is injected into the spinal fluid) to prevent central nervous system (CNS) disease.
- Post-induction phases are based on the status of a gene called *KMT2A* (11q23) and response to previous therapy.
- Maintenance chemotherapy is given to prevent the return or spread of ALL.

Questions to ask

- Does my child have the *KMT2A* (11q23) gene? What does this mean for treatment options?
- Which treatment do you recommend and why?
- Is a clinical trial or hematopoietic cell transplant (HCT) an option for my child?
- How serious is my child's condition?
- What services are available to help us through this stressful time?

9
Other resources

Want to learn more? Here's how you can get additional help.

What else to know

This book is an important tool for improving cancer care. It plainly explains expert recommendations and suggests questions to ask your care team. But, it's not the only resource that you have.

You're welcome to receive as much information and help as you need. Many people are interested in learning more about:

- The details of treatment
- Being a part of a care team
- Getting financial help
- Finding an oncologist who is an expert in ALL
- Coping with side effects

What else to do

Your health care center can help you with next steps. They often have on-site resources to help meet your needs and find answers to your questions. Health care centers can also inform you of resources in your community.

In addition to help from your providers, the resources listed in the next section provide support for many people like yourself. Look through the list and visit the provided websites to learn more about these organizations.

Where to get help

Blood & Marrow Transplant Information Network (BMT InfoNet)
BMTInfoNet.org

CancerCare
Cancercare.org

Imerman Angels
Imermanangels.org

Leukemia Research Foundation
leukemiarf.org

MedlinePlus
medlineplus.gov

National Bone Marrow Transplant Link (nbmtLINK)
nbmtLINK.org

National Cancer Institute (NCI)
cancer.gov/types/leukemia

National Coalition for Cancer Survivorship
canceradvocacy.org

NMDP
nmdp.org

The Leukemia & Lymphoma Society (LLS)
LLS.org/PatientSupport

Triage Cancer
triagecancer.org

Questions to ask about resources and support

- Who can I talk to about help with housing, food, and other basic needs?
- What help is available for transportation, childcare, and home care?
- What other services are available to my child and other caregivers?
- How can my child connect with others and build a support system?
- Who can I talk to if I don't feel safe at home, at work, or in my neighborhood?

Let us know what you think!

Please take a moment to complete an online survey about the NCCN Guidelines for Patients.

NCCN.org/patients/response

Words to know

absolute neutrophil count (ANC)
The number of neutrophils, a type of white blood cell, in a blood sample. This number provides an estimate of the body's ability to fight infections, especially bacterial infections.

acute lymphoblastic leukemia (ALL)
A fast-growing cancer that causes too many immature white blood cells called lymphoblasts to be made.

adolescent and young adult (AYA)
People who are 15 to 39 years of age at the time of initial cancer diagnosis.

allogeneic hematopoietic cell transplant (HCT)
A treatment in which the patient receives healthy, immature blood-forming cells from another person to replace damaged or diseased cells in the bone marrow. Also called allogeneic stem cell transplant (SCT).

antibody
A protein made by a plasma cell (a type of white blood cell).

B cell
A type of lymphocyte.

***BCR::ABL1* gene**
An abnormal gene that is formed when the *BCR* gene and *ABL1* gene join and create an abnormal chromosome 22 called the Philadelphia chromosome. Also called *BCR::ABL1* fusion gene.

BCR::ABL1 protein
An abnormal protein that is made by the *BCR::ABL1* fusion gene and causes too many abnormal white blood cells to be made.

blast cell
A very immature white blood cell.

blood stem cell
An immature blood-forming cell from which all other types of blood cells are made. Also called hematopoietic stem cell.

bone marrow
The soft, sponge-like tissue in the center of most bones where blood cells are made.

bone marrow aspiration
The removal of a small amount of liquid bone marrow to test for disease.

bone marrow biopsy
The removal of a small amount of solid bone and bone marrow to test for disease.

CAR T-cell therapy
Treatment that removes immune cells called T cells from your body. In a lab, a CAR (chimeric antigen receptor) is added to the T cells. This genetically modifies and programs the T cells to find and kill cancer cells once they are added back into the body.

chemotherapy
Drugs that kill fast-dividing cells, including cancer cells and normal cells.

chromosomes
Long strands that contain bundles of coded instructions in cells for making and controlling cells.

clinical trial
A study of how safe and helpful tests and treatments are for people.

consolidation
One of the post-induction phases of treatment.

deoxyribonucleic acid (DNA)
Long strands of genetic information found inside cells.

extramedullary
Outside the bone marrow.

fusion gene
A gene that is made when parts of two separate genes join.

gene
A set of coded instructions in cells for making new cells and controlling how cells behave.

graft-versus-host disease (GVHD)
A disease that occurs when transplanted blood stem cells attack a person's normal cells.

hematologist
A doctor who's an expert in diseases of the blood.

hematopathologist
A doctor who specializes in blood diseases by looking at cells under a microscope.

hematopoietic cell
An immature blood-forming cell from which all other types of blood cells are made. Also called blood stem cell.

hematopoietic cell transplant (HCT)
A treatment that replaces damaged or diseased cells in the bone marrow with healthy blood-forming cells. Also called stem cell transplant (SCT) or bone marrow transplant (BMT).

human leukocyte antigen (HLA)
Special proteins on the surface of cells that help the body to tell its own cells apart from foreign cells.

hyperdiploidy
Leukemia cells with 51 to 67 chromosomes.

hypodiploidy
Leukemia cells with fewer than 44 chromosomes.

immune system
The body's natural defense against infection and disease.

immunotherapy
A treatment with drugs that help the body find and destroy cancer cells.

induction
The first phase of treatment.

infant
A child under 12 months of age.

Interfant induction
The first phase of treatment for those under 12 months of age.

leukemia
A disease in which there are too many white blood cells.

lymphoblast
An immature lymphocyte. Also called blast.

lymphocyte
A type of white blood cell that helps fight and prevent infection.

lymphoid
Referring to a type of white blood cell called a lymphocyte.

maintenance
Usually the last phase of pediatric ALL treatment.

medullary
In the bone marrow.

minimal residual disease (MRD)
Small amount of ALL cells that remain after treatment. Detected by highly sensitive tests done on blood or bone marrow tissue.

mutation
An abnormal change.

mutation testing
A test that looks for abnormal changes in genes or chromosomes.

myeloid
Referring to a type of white blood cell called a granulocyte.

myelosuppression
A condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets.

natural killer (NK) cell
A type of lymphocyte.

neutrophil
A type of white blood cell that fights infections, especially bacterial and fungal infections.

oncologist
A doctor who is an expert in the treatment of cancer.

pathologist
A doctor who's an expert in testing cells and tissue to find disease.

pediatric
People who are 18 years of age or under at the time of initial diagnosis.

peripheral blood
Blood that circulates throughout the body.

pharmacogenomic
The study of how genes affect a person's response to drugs.

Philadelphia (Ph) chromosome
An abnormal, short chromosome 22 that is formed when parts of chromosomes 9 and 22 switch with each other. The result is the *BCR::ABL1* fused gene.

platelet (PLT)
A type of blood cell that helps control bleeding. Also called thrombocyte.

post-induction
More intensive phases of chemotherapy that happen after induction and before maintenance.

predisposition syndrome
Certain genetic changes, or mutations, can increase a person's chances of developing cancer.

prognosis
The likely or expected course and outcome of a disease.

progression
The growth or spread of cancer after being tested or treated.

radiation therapy (RT)
A treatment that uses high-energy rays.

radiation oncologist
A doctor who is an expert in radiation therapy.

radiologist
A doctor who is an expert in imaging tests.

recurrence
The return of cancer after a cancer-free period.

red blood cell (RBC)
A type of blood cell that carries oxygen from the lungs to the rest of the body. Also called an erythrocyte.

refractory
A cancer that does not improve with treatment.

regimen
A treatment plan that includes specific information about drug dose, when medicine is taken, and how long treatment will last.

relapse
The return or worsening of cancer after a period of improvement.

remission
Minor or no signs of a disease.

resistance
When cancer does not respond to a drug treatment.

standard of care
The best-known way to treat a particular disease based on past clinical trials. There may be more than one treatment regimen that is considered standard of care.

steroid
A drug used to reduce redness, swelling, and pain, but also to kill leukemia cells.

supportive care
Treatment for the symptoms or health conditions caused by cancer or cancer treatment.

surveillance
Testing that is done after treatment ends to check for the return of cancer.

systemic therapy
Treatment that works throughout the body.

T cell
A type of lymphocyte.

targeted therapy
Treatment with drugs that target a specific or unique feature of cancer cells.

transfusion
A medical procedure that involves transferring blood or blood components into a person's bloodstream.

translocation
When pieces of two chromosomes (long strands of coded instructions for controlling cells) break off and switch with each other.

treatment response
An outcome or improvement in disease that is caused by treatment.

tyrosine kinase inhibitor (TKI)
A type of drug that attaches to the BCR::ABL1 protein so that it can't send growth signals.

white blood cell (WBC)
A type of blood cell that helps fight infections in the body. Also called a leukocyte.

Notes

NCCN Contributors

This patient guide is based on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pediatric Acute Lymphoblastic Leukemia Version 1.2025. It was adapted, reviewed, and published with help from the following people:

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NCCN Cancer Centers

Abramson Cancer Center
at the University of Pennsylvania
Philadelphia, Pennsylvania
800.789.7366 • pennmedicine.org/cancer

Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center and
Cleveland Clinic Taussig Cancer Institute
Cleveland, Ohio
UH Seidman Cancer Center
800.641.2422 • uhhospitals.org/services/cancer-services
CC Taussig Cancer Institute
866.223.8100 • my.clevelandclinic.org/departments/cancer
Case CCC
216.844.8797 • case.edu/cancer

City of Hope National Medical Center
Duarte, California
800.826.4673 • cityofhope.org

Dana-Farber/Brigham and Women's Cancer Center |
Mass General Cancer Center
Boston, Massachusetts
877.442.3324 • youhaveus.org
617.726.5130 • massgeneral.org/cancer-center

Duke Cancer Institute
Durham, North Carolina
888.275.3853 • dukecancerinstitute.org

Fox Chase Cancer Center
Philadelphia, Pennsylvania
888.369.2427 • foxchase.org

Fred & Pamela Buffett Cancer Center
Omaha, Nebraska
402.559.5600 • unmc.edu/cancercenter

Fred Hutchinson Cancer Center
Seattle, Washington
206.667.5000 • fredhutch.org

Huntsman Cancer Institute at the University of Utah
Salt Lake City, Utah
800.824.2073 • healthcare.utah.edu/huntsmancancerinstitute

Indiana University Melvin and Bren Simon
Comprehensive Cancer Center
Indianapolis, Indiana
888.600.4822 • www.cancer.iu.edu

Johns Hopkins Kimmel Cancer Center
Baltimore, Maryland
410.955.8964
www.hopkinskimmelcancercenter.org

Mayo Clinic Comprehensive Cancer Center
Phoenix/Scottsdale, Arizona
Jacksonville, Florida
Rochester, Minnesota
480.301.8000 • Arizona
904.953.0853 • Florida
507.538.3270 • Minnesota
mayoclinic.org/cancercenter

Memorial Sloan Kettering Cancer Center
New York, New York
800.525.2225 • mskcc.org

Moffitt Cancer Center
Tampa, Florida
888.663.3488 • moffitt.org

O'Neal Comprehensive Cancer Center at UAB
Birmingham, Alabama
800.822.0933 • uab.edu/onealcancercenter

Robert H. Lurie Comprehensive Cancer Center
of Northwestern University
Chicago, Illinois
866.587.4322 • cancer.northwestern.edu

Roswell Park Comprehensive Cancer Center
Buffalo, New York
877.275.7724 • roswellpark.org

Siteman Cancer Center at Barnes-Jewish Hospital
and Washington University School of Medicine
St. Louis, Missouri
800.600.3606 • siteman.wustl.edu

St. Jude Children's Research Hospital/
The University of Tennessee Health Science Center
Memphis, Tennessee
866.278.5833 • stjude.org
901.448.5500 • uthsc.edu

Stanford Cancer Institute
Stanford, California
877.668.7535 • cancer.stanford.edu

The Ohio State University Comprehensive Cancer Center -
James Cancer Hospital and Solove Research Institute
Columbus, Ohio
800.293.5066 • cancer.osu.edu

The UChicago Medicine Comprehensive Cancer Center
Chicago, Illinois
773.702.1000 • uchicagomedicine.org/cancer

The University of Texas MD Anderson Cancer Center
Houston, Texas
844.269.5922 • mdanderson.org

UC Davis Comprehensive Cancer Center
Sacramento, California
916.734.5959 • 800.770.9261
health.ucdavis.edu/cancer

UC San Diego Moores Cancer Center
La Jolla, California
858.822.6100 • cancer.ucsd.edu

UCLA Jonsson Comprehensive Cancer Center
Los Angeles, California
310.825.5268 • uclahealth.org/cancer

UCSF Helen Diller Family Comprehensive Cancer Center
San Francisco, California
800.689.8273 • cancer.ucsf.edu

University of Colorado Cancer Center
Aurora, Colorado
720.848.0300 • coloradocancercenter.org

University of Michigan Rogel Cancer Center
Ann Arbor, Michigan
800.865.1125 • rogelcancercenter.org

University of Wisconsin Carbone Cancer Center
Madison, Wisconsin
608.265.1700 • uwhealth.org/cancer

UT Southwestern Simmons Comprehensive Cancer Center
Dallas, Texas
214.648.3111 • utsouthwestern.edu/simmons

Vanderbilt-Ingram Cancer Center
Nashville, Tennessee
877.936.8422 • vicc.org

Yale Cancer Center/Smilow Cancer Hospital
New Haven, Connecticut
855.4.SMILOW • yalecancercenter.org

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NCCN.org/patients/comments

Index

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