CHILDHOOD LEUKEMIA

What is cancer?

Cancer develops when cells in a part of the body begin to grow out of control. Although there are many kinds of cancer, all begin because of out-of-control growth of abnormal cells.

Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide more rapidly until the person becomes an adult. After that, cells in most parts of the body divide only to replace worn-out or dying cells and to repair injuries.

Because cancer cells continue to grow and divide, they are different from normal cells. Instead of dying, they outlive normal cells and continue to form new abnormal cells.

Cancer cells often travel to other parts of the body, where they begin to grow and replace normal tissue. This process, called metastasis, occurs as the cancer cells get into the bloodstream or lymph vessels of our body. When cells from a cancer like breast cancer spread to another organ like the liver, the cancer is still called breast cancer, not liver cancer.

Cancer cells develop because of damage to their DNA. DNA is in every cell and directs all its activities. Most of the time when DNA becomes damaged the cell is able to repair it. In cancer cells, the damaged DNA is not repaired.

People can inherit damaged DNA, which accounts for inherited cancers. Many times though, a person's DNA becomes damaged by exposure to something in the environment, like smoking.

Most people think of cancer as a solid tumor. But some cancers, like leukemia, do not form tumors. Instead, these cancer cells involve the blood and blood-forming organs, and circulate through other tissues where they grow.

Remember that not all tumors are cancerous. Benign (non-cancerous) tumors do not spread to other parts of the body (metastasize) and, with very rare exceptions, are not life-threatening.

Different types of cancer behave very differently. For example, lung cancer and breast cancer are very different diseases. They grow at different rates and respond to different treatments. That is why people with cancer need treatment that is aimed at their particular type of cancer.

Cancer is the second leading cause of death in the United States. It is the second leading cause of death after accidents in children from ages 1 to 14. Half of all men and one third of all women in the United States will develop cancer during their lifetimes. Today, millions of people are living with cancer or have had cancer. The risk of developing most types of adult cancers can be reduced by changes in a person's lifestyle, for example, by quitting smoking, reducing sun exposure, and eating a healthier diet. These risks do not apply to children. Generally, the sooner a cancer is found and treatment begins, the better are the chances for living for many years.

What are the differences between cancers in adults and children?

The types of cancers that develop in children are different from the types that develop in adults. Although there are exceptions, childhood cancers tend to respond better to chemotherapy. Children also tolerate chemotherapy better than adults. But, because chemotherapy can have some long-term side effects, children who survive their cancer need careful attention for the rest of their lives.

Since the 1960s, most children and adolescents with cancer have been treated at specialized centers designed for them. Being treated in specialized centers offers them the advantage of a team of specialists who know the differences between adult and childhood cancers, as well as the unique needs of children with cancers. This team usually includes pediatric oncologists, pathologists, surgeons, radiation oncologists, pediatric oncology nurses, and nurse practitioners.

These centers also have psychologists, social workers, child life specialists, nutritionists, rehabilitation and physical therapists, and educators who can support and educate the entire family.

Most children with cancer in the United States are treated at a center that is a member of the Children's Oncology Group (COG). All of these centers are associated with a university or children's hospital. As we have learned more about treating childhood cancer, it has become even more important that treatment be given by experienced experts.

What Is Childhood Leukemia?

Leukemia is a cancer of the early blood-forming cells. Most often, the leukemia is a cancer of the white blood cells, but leukemia can involve other blood cell types as well.

Leukemia starts in the bone marrow and then spreads to the blood. From there it can go to the lymph nodes, spleen, liver, central nervous system (the brain and spinal cord), testes (testicles), or other organs.

Some childhood cancers, such as neuroblastoma or Wilms tumor, start in other organs and can spread to bone marrow, but these cancers are not leukemia.

Normal Bone Marrow, Blood, and Lymphoid Tissue

In order to understand the different types of leukemia, it is helpful to have some basic knowledge about the blood and lymph systems.

Bone Marrow

The bone marrow is the soft inner part of bones. It is where new blood cells (red blood cells, white blood cells, and platelets) are made. In infants, active bone marrow is found in almost all bones of the body, but by the teenage years, it is found mainly in the flat bones (skull, shoulder blades, ribs, pelvis) and vertebrae (back bones).

Bone marrow is made up of *blood-forming cells* and supporting tissues that help the blood-forming cells grow. The earliest blood-forming cells are called *blood stem cells*. These stem cells only make new blood-forming cells and not other kinds of cells. (This makes them different from embryonic stem cells, which are formed in a developing fetus and can grow into most other cell types in the body.)

Blood stem cells go through a series of changes. During this process, the cells develop into either *lymphocytes* (a kind of white blood cell) or other blood-forming cells. The other blood-forming cells can develop into 1 of the 3 main types of blood cell components:

- red blood cells
- white blood cells (other than lymphocytes)
- platelets

Red Blood Cells

Red blood cells carry oxygen from the lungs to all other tissues of the body, and take carbon dioxide back to the lungs to be removed. When the marrow doesn't make enough red blood cells to replace those wearing out, it can lead to *anemia* (having too few red blood cells in the body). Anemia can cause weakness, tiredness, and shortness of breath.

Platelets

Platelets are fragments that break off from a type of bone marrow cell called a *megakaryocyte*. They are released into the blood, where they are important in plugging holes in blood vessels caused by cuts or bruises. Not having enough platelets is called *thrombocytopenia* and can result in excess bleeding and bruising.

White Blood Cells

White blood cells, also known as leukocytes, defend the body against infections from germs like bacteria, viruses, and fungi. The 3 main types of white blood cells are lymphocytes, granulocytes, and monocytes.

Lymphocytes: Lymphocytes are the main cells that make up lymphoid tissue, a major part of the immune system. The immune system helps the body fight off infections.

Lymphoid tissue is found in many places in the body, including the lymph nodes, thymus gland, spleen, tonsils and adenoids, and bone marrow. It is also scattered through the digestive system and respiratory system. The extensive system connecting all lymphoid tissues is called the lymphatic system. Lymphocytes circulate in this system and eventually flow into the bloodstream.

There are 2 main types of lymphocytes:

- B lymphocytes (B cells)
- T lymphocytes (T cells)

Normal B cells and T cells do different jobs in the immune system.

B cells help protect the body against bacteria and viruses. When a B cell comes into contact with one of these germs, it matures into a *plasma cell*, which releases proteins called antibodies. The antibodies attach to the germ, marking it for destruction by other parts of the immune system.

T cells also help protect the body against foreign substances (those not normally present in the body). They recognize specific chemicals, such as those found on the outside of virus-infected cells.

There are several types of T cells, each with a specialized job to do. Some destroy abnormal cells by releasing substances that punch holes in them, causing them to become leaky. Some T cells release substances called *cytokines* that attract other types of white blood cells, which

then kill the abnormal cells. Still other T cells act as a check on the immune system to ensure it does not attack normal cells.

Lymphocytes are the cells from which acute lymphocytic (or lymphoblastic) leukemia develops. Although both B cell and T cells can develop into leukemia, B-cell leukemias are much more common than T-cell leukemias.

Normal B cells and T cells can be recognized by lab tests that look for specific chemicals on their surfaces. Some substances are found only on B cells, and others are found only on T cells. Lab tests can also help determine how mature the B cells or T cells are. Both the type of lymphocyte and its stage of maturity are important because leukemias that arise from these different kinds of cells have different characteristics.

Granulocytes: These white blood cells have granules in them, which are spots that can be seen under the microscope. These granules contain enzymes and other substances that can destroy germs, such as bacteria. The 3 types of granulocytes -- *neutrophils*, *basophils*, and *eosinophils* -- are distinguished by the size and color of their granules. Granulocytes develop from blood-forming cells called *myeloblasts* to become mature, infection-fighting cells.

Monocytes: These white blood cells, which are related to granulocytes, also are important in protecting the body against bacteria. They start in the bone marrow as blood-forming *monoblasts* and develop into mature monocytes. After circulating in the bloodstream for about a day, monocytes enter body tissues to become *macrophages*, which can destroy some germs by surrounding and digesting them. Macrophages are also important in helping lymphocytes to recognize germs and start making antibodies to fight them.

Types of Leukemia in Children

Leukemia is often described as being either acute (growing quickly) or chronic (growing slowly).

Acute Leukemias

Almost all childhood leukemia is acute. There are 2 main types of acute leukemia:

- *Acute lymphocytic leukemia* (ALL, also called acute lymphoblastic leukemia) accounts for about 3 out of 4 cases of childhood leukemia. This leukemia starts from the lymphoid cells in the bone marrow.

- *Acute myelogenous leukemia* (AML, also called acute myeloid leukemia, acute myelocytic leukemia, or acute non-lymphocytic leukemia [ANLL]) accounts for most of the remaining cases. This leukemia starts from the cells that form white blood cells (other than lymphocytes), red blood cells, or platelets.

- *Hybrid or mixed lineage leukemias* are rare. The cells have features of both ALL and AML. They are generally treated like ALL and respond to treatment like ALL.

Both ALL and AML can be further divided into different subtypes. For more information on the subtypes of ALL and AML, see the section, "How Is Childhood Leukemia Classified?"

Chronic Leukemias

Chronic leukemias can also be divided into 2 types. Chronic myelogenous leukemia (CML) is rare in children, but it does occur. It is treated the same as in adults. For more information on CML, see the American Cancer Society document, *Leukemia--Chronic Myeloid.* Chronic lymphocytic leukemia (CLL) is extremely rare in children and is not discussed further in this document.

Juvenile Myelomonocytic Leukemia (JMML)

This rare type of leukemia is neither chronic nor acute. It begins from myeloid cells, but isn't as fast growing as acute myelogenous leukemia or as slow as chronic myeloid leukemia. It occurs most often in young children (under age 4). Symptoms can include pale skin, fever, cough, trouble breathing (due to too many white blood cells in the lungs), and an enlarged spleen and lymph nodes.

What Are the Key Statistics for Childhood Leukemia?

Leukemia is the most common cancer in children and adolescents. It accounts for about 1 out of 3 cancers in children. Overall, however, childhood leukemia is a rare disease.

Of the estimated 3,540 children (ages 0-19) who will develop leukemia in 2008, about 3 out of 4 (2,655) will be diagnosed with acute lymphocytic leukemia (ALL). Most of the remaining cases will be acute myelogenous leukemia (AML). Chronic leukemias are rare in children.

ALL is most common in early childhood, peaking between 2 and 4 years of age. Cases of AML are more spread out across the childhood years, although it is slightly more common during the first 2 years of life and during the teenage years.

ALL is slightly more common among white children than among African-American and Asian-American children and is more common in boys than in girls. AML occurs equally among boys and girls of all races.

The 5-year survival rate for ALL in children has greatly increased over time and is now more than 80%. This is mainly due to advances in treatment. The 5-year survival rate for children with AML has also increased over time, and is now more than 50%.

The 5-year survival rate refers to the percentage of patients who live *at least* 5 years after their cancer is diagnosed. Many of these patients live much longer than 5 years. Of course, 5-year survival rates are based on patients first diagnosed and treated more than 5 years ago. They may no longer be accurate, as improvements in treatment are likely to result in a more favorable outlook for recently diagnosed patients.

While survival statistics can be useful, it's important to keep in mind that the outlook for each patient is different, and depends on a number of factors. Many of these prognostic factors are discussed in the section, "How Is Childhood Leukemia Classified?"

What Are the Risk Factors for Childhood Leukemia?

A risk factor is anything that affects your chance of getting a disease such as cancer. Risk factors can be classified as inherited (genetic), lifestyle-related, or environmental. Different cancers have different risk factors. For example, exposing skin to strong sunlight is a risk factor for skin cancer. Smoking is a risk factor for cancers of the lung, mouth, larynx, bladder, kidney, and several other organs.

But risk factors are rarely absolute. Having a risk factor, or even several risk factors, does not mean that you will get the disease. And many people who get the disease may not have had any known risk factors.

Genetic Risk Factors

Genetic risk factors are those that are part of our DNA. They are most often inherited from our parents. While some genetic factors increase the risk of childhood leukemia, most cases of leukemia are not linked to any known genetic causes.

Inherited Syndromes

There are several inherited disorders that increase a child's risk of developing leukemia:

- **Li-Fraumeni syndrome:** This is a rare condition caused by change in the p53 tumor suppressor gene. People with this change have an increased risk of developing several kinds of cancer, especially leukemia, bone or soft tissue sarcomas, breast cancer, and brain tumors.

- **Down syndrome (trisomy 21):** Children with Down syndrome have an extra (third) copy of chromosome 21. In ways that are not completely understood, this extra

chromosome 21 causes mental retardation and a characteristic facial appearance. Children with Down syndrome are 10 to 20 times more likely to develop either ALL or AML than are other children. Down syndrome has also been linked with *transient leukemia* -- a leukemia-like condition within the first month of life, which often resolves on its own without the use of chemotherapy.

- **Klinefelter syndrome:** This is a genetic condition in which males have an extra "X" chromosome. This causes infertility, prevents normal development of male features (such as body hair, deep voice, etc.) and is linked to an increased risk of developing leukemia.

Several other genetic disorders (such as neurofibromatosis, ataxia telangiectasia, Wiscott-Aldrich syndrome, and Fanconi anemia) also carry an increased risk of leukemia, although these disorders more commonly lead to non-Hodgkin lymphoma and other types of cancers.

Inherited Immune Deficiencies

Certain inherited diseases cause children to be born with immune system problems. Along with being at increased risk of getting serious infections due to reduced immune defenses, these children may also have an increased risk of leukemia.

Having a Brother or Sister With Leukemia

Siblings (brothers and sisters) of children with leukemia have a slightly increased chance (2 to 4 times normal) of getting leukemia, although the overall risk is still low. The risk is much higher among identical twins. If an identical twin develops childhood leukemia, the other twin has about a 20% chance of getting leukemia as well. This risk is even higher if the leukemia develops in the first year of life.

Having a parent who develops leukemia as an adult does not seem to raise a person's risk of leukemia.

Lifestyle-related Risk Factors

Lifestyle-related risk factors for some cancers include an unhealthy diet, harmful habits such as smoking, drinking excessive amounts of alcohol, and too much sun exposure. While lifestyle-related factors are important in many adult cancers, they play much less of a role in childhood cancer risk.

Some studies have suggested that a mother drinking a lot of alcohol during pregnancy may increase the risk of leukemia in her child, but not all studies have found such a link.

Environmental Risk Factors

Environmental risk factors are influences in our surroundings, such as radiation and certain chemicals, which increase the risk of getting diseases such as leukemias.

Radiation Exposure

Exposure to high levels of radiation is a risk factor for childhood leukemia. Japanese atomic bomb survivors had a 20-fold increased risk of developing AML, usually within 6 to 8 years after exposure. Similar risks have occurred after exposure to radiation from nuclear reactor accidents. Exposure of a fetus to radiation within the first months of development may also carry an increased risk of childhood leukemia, although the extent of the risk is not clear.

The possible risks from fetal or childhood exposure to lower levels of radiation, such as from x-rays or CT scans, is not well-defined. Some studies have found a slight increase in risk, while others have found no increased risk. Any risk increase is likely to be small, but to be safe, most doctors do not order these tests for fetuses or children unless they are absolutely necessary.

Radiation Therapy and Chemotherapy

Children and adults treated for other cancers with radiation therapy and chemotherapy have a higher risk of getting a second cancer, usually AML, later in life. Chemotherapy drugs such as alkylating agents (a class that includes cyclophosphamide and chlorambucil) and epipodophyllotoxins (such as etoposide and teniposide) have been linked to a higher risk of leukemia. These leukemias usually develop within 5 to 10 years of treatment and tend to be hard to treat.

Immune System Suppression

Patients getting intensive treatment to suppress their immune function (mainly organ transplant patients) have an increased risk of certain cancers, such as lymphoma and ALL.

Certain Chemicals

Exposure to chemicals such as benzene may cause AML in adults and, rarely, in children. ALL has not been linked to any cancer-causing chemicals.

Uncertain, Unproven, or Controversial Risk Factors

Other factors that have been studied for a possible link to childhood leukemia include:

- exposure to insecticides
- exposure to electromagnetic fields (such as living near power lines)
- mother's age when child was born
- parent's smoking history
- fetal exposure to hormones (such as diethylstilbestrol (DES) or birth control pills)
- father's workplace exposure to chemicals and solvents
- chemical contamination of ground water

So far, none of these factors has been linked conclusively to childhood leukemia.

Do We Know What Causes Childhood Leukemia?

The exact cause of most cases of childhood leukemia is not known. Doctors have found that the risk of this cancer is increased in a number of genetic conditions, which are described in the section on risk factors. But it is important to note that most children with leukemia do not have any known risk factors.

Normal human cells grow and function based mainly on the information contained in each cell's chromosomes. Chromosomes are long molecules of DNA in each cell. DNA is the chemical that makes up our genes -- the instructions for how our cells function. We resemble our parents because they are the source of our DNA. But our genes affect more than the way we look.

Some genes contain instructions for controlling when our cells grow and divide. Certain genes that promote cell growth and division are called *oncogenes*. Others that slow down cell division or cause cells to die at the right time are called *tumor suppressor genes*.

Each time a cell prepares to divide into 2 new cells, it must make a new copy of the DNA in its chromosomes. This process is not perfect, and errors can occur that may affect genes within the DNA. Cancers can be caused by DNA mutations (changes) that turn on oncogenes or turn off tumor suppressor genes.

Some people inherit DNA mutations from a parent, which increases their risk for cancer. For instance, a condition called Li-Fraumeni syndrome, which results from an inherited mutation of the p53 tumor suppressor gene, increases a person's risk of developing leukemia, as well as bone and soft tissue sarcomas and some other cancers.

But while certain inherited diseases can increase the risk of developing leukemia, most cases of leukemia do not seem to be caused by inherited mutations. Usually, DNA mutations related to leukemia develop after conception rather than having been inherited. Some of these acquired mutations may occur early, even before birth. In rare cases, acquired mutations may

result from exposure to radiation or cancer-causing chemicals, but usually they occur for no apparent reason.

A few studies have suggested that some childhood leukemias may be caused by a combination of genetic and environmental factors. For example, certain genes normally control how our bodies break down and get rid of harmful chemicals. Some people have different versions of these genes that make them less effective. Children who inherit these genes may not be as able to break down harmful chemicals if they are exposed to them. The combination of genetics and exposure might increase their risk for leukemia.

Can Childhood Leukemia Be Prevented?

Although many adult cancers can be prevented by lifestyle changes that reduce certain risk factors, there is no known way to prevent most childhood cancers at this time. Most adults and children with leukemia have no known risk factors, so there is no way to prevent their leukemias from developing.

Children with a known increased risk of leukemia (because of Li-Fraumeni syndrome or Down syndrome, for example) should receive careful, regular medical checkups. The development of leukemia in children with these syndromes, although greater than in the general population, is still very rare.

Treating cancers with radiation and chemotherapy and the use of immune system-suppressing drugs to avoid rejection of transplanted organs also cause some leukemias. Doctors are looking for ways to treat patients with cancer and organ transplants without raising the risk of leukemia. But for now, the obvious benefits of treating life-threatening diseases with chemotherapy, radiation therapy, or organ transplant must be balanced against the small chance of developing leukemia several years later.

Can Childhood Leukemia Be Found Early?

Childhood leukemia is often found because children have symptoms that prompt a visit to the doctor. Blood test results are abnormal, which then points to the diagnosis. But there are no special tests that are used to detect leukemia early. The best strategy for early diagnosis is prompt attention to the signs and symptoms of this disease (see "How Is Childhood Leukemia Diagnosed?").

Close observation is important for children with known genetic syndromes that might increase their risk of leukemia, for children who have had other cancers treated with chemotherapy and/or radiation therapy, and for children who have received organ transplants and are taking immune system-suppressing drugs.

How Is Childhood Leukemia Diagnosed?

It is very important both to diagnose childhood leukemia as early as possible and to determine what type of leukemia is present so that treatment can be tailored to provide the best chance of success. The exams and tests below are used to diagnose the disease, measure how advanced it may be, and to help determine what type of leukemia is present.

Signs and Symptoms of Childhood Leukemia

Many of the signs and symptoms of childhood leukemia result from a lack of normal blood cells, which happens when the leukemia cells crowd out the normal blood cell-making cells in the bone marrow. The leukemia cells may also invade other areas of the body, which can also cause symptoms. It is important to keep in mind that many of these symptoms have other causes as well, and are most often not due to leukemia.

Fatigue, Paleness of the Skin

A child may complain of excessive tiredness, or the skin may appear pale because of anemia (a shortage of red blood cells).

Infections and Fever

A child with leukemia may develop fever. This is often due to infections, which may not improve even with antibiotics. This is because of a lack of normal white blood cells, particularly mature granulocytes, which would normally help fight the infection. Although children with leukemia may have very high white blood cell counts, the leukemia cells do not protect against infection the way normal white blood cells do. Fever is sometimes caused by the leukemia cells themselves releasing certain chemicals into the body.

Easy Bleeding or Bruising

A child with leukemia may bruise easily or have increased bleeding from small cuts and nosebleeds. There may be pinhead-sized red spots on the skin that represent bleeding from tiny blood vessels. This comes from a lack of blood platelets, which normally stop bleeding by plugging holes in damaged blood vessels.

Bone Pain

About 1 out of 3 children with leukemia will have bone pain. A smaller number will have joint pain. This is due to the buildup of leukemia cells near the surface of the bone or inside the joint.

Swelling of the Abdomen

Leukemia cells may collect in the liver and spleen, causing them to enlarge. This may be noticed as a fullness or swelling of the belly. The lower ribs usually cover these organs, but when they are enlarged the doctor can feel them.

Loss of Appetite, Weight Loss

If the spleen and/or liver become large enough, they may press against other organs like the stomach. This can limit the amount of food that can be eaten, leading to a loss of appetite and weight loss over time.

Swollen Lymph Nodes

Some leukemias may spread to lymph nodes. The child, a parent, or a health care professional may notice swollen nodes as lumps under the skin in certain areas of the body (on the sides of the neck, in the groin, underarm areas, above the collarbone, etc.). Swelling of lymph nodes inside the chest or abdomen may also occur, but these can only be detected by imaging tests, such as CT or MRI scans.

Lymph nodes often enlarge when they are fighting an infection, especially in infants and children. Lymph nodes that grow as a reaction to infection are called *reactive nodes* or *hyperplastic nodes*. An enlarged lymph node in a child is more often a sign of infection than leukemia, but it should be checked by a doctor and followed closely.

Coughing or Trouble Breathing

The T-cell type of acute lymphocytic leukemia (ALL) often involves the thymus gland, which is located in the front of the chest. Enlargement of the thymus or of lymph nodes inside the chest can press on the nearby trachea (windpipe). This can lead to coughing, shortness of breath, or even suffocation.

Swelling of the Face and Arms

The superior vena cava (SVC), a large vein that carries blood from the head and arms back to the heart, passes next to the thymus. Growth of the thymus due to excess leukemia cells may press on the SVC, causing the blood to "back up" in the veins. This is known as SVC syndrome. It can cause swelling in the face and arms and a bluish-red coloration of the head, arms, and upper chest. It can also cause trouble breathing and a change in consciousness if it

affects the brain. The SVC syndrome can be life-threatening, and requires immediate attention.

Headache, Seizures, Vomiting

Leukemia can spread outside the bone marrow. It may involve the central nervous system (brain and spinal cord), the testicles, ovaries, kidneys, lungs, heart, intestines, or other organs. About 5% to 10% of children have leukemia that has already spread to the central nervous system when they are first diagnosed. Headache, trouble concentrating, weakness, seizures, vomiting, problems with balance, and blurred vision can be symptoms of central nervous system leukemia.

Rashes, Gum Problems

In children with AML, leukemia cells may spread to the gums, causing swelling, pain, and bleeding. Spread to the skin can cause small, darkly colored spots that can resemble common rashes. A collection of AML cells under the skin or other parts of the body is called a *chloroma* or *granulocytic sarcoma*.

Extreme Fatigue, Weakness

One rare but very serious consequence of AML is extreme tiredness, weakness, and slurring of speech, which occurs when very high numbers of leukemia cells make the blood too "thick" and interfere with circulation through small blood vessels of the brain.

Most of the symptoms seen in leukemia can also be seen in other problems like infections. For this reason, an accurate diagnosis is crucial.

Medical History and Physical Exam

If any of the signs and symptoms above suggest the possibility of leukemia, the doctor will want to get a thorough medical history, including how long any symptoms have been present and whether or not there is any history of exposure to risk factors. A family history of cancer, especially leukemia, may also be important.

The physical exam will likely focus on any enlarged lymph nodes, areas of bleeding or bruising, or possible signs of infection. The eyes and mouth will likely be looked at carefully. The abdomen will be felt thoroughly for signs of an enlarged spleen or liver.

If there is any reason to think there might be problems caused by abnormal numbers of blood cells (anemia, infections, bleeding or bruising, etc.), the doctor will likely test your child's

blood counts. If these are abnormal, the doctor may refer you to a childhood cancer doctor, who may run one or more of the tests described below.

Types of Samples Used to Test for Leukemia in Children

Blood Samples

Blood samples for tests for leukemia are taken as they are for other tests - usually from a vein in the arm. In infants and younger children, they may be taken from other veins (such as in the feet or scalp) or from a "finger stick".

Blood counts and blood smears are the usual tests done on these samples. A complete blood count (CBC) is done to determine how many of each type of blood cell is present in the blood. A blood smear involves spreading a small sample of blood on a glass slide and looking at the blood cells under a microscope. Changes in the numbers of different cell types in the blood and the way these cells look under the microscope may make the doctor suspect leukemia.

Most children with acute leukemia (ALL or AML) will have too many white blood cells and not enough red blood cells and/or not enough platelets. Many of the white blood cells in the blood will be *blasts*, a type of cell normally found only in the bone marrow. Even though these findings may make a doctor suspect that leukemia is present, usually the disease cannot be diagnosed for sure without getting a sample of bone marrow cells.

Bone Marrow Samples

Bone marrow samples are obtained from a bone marrow aspiration and biopsy -- two tests that are usually done at the same time. The samples are usually taken from the back of the pelvic (hip) bone, although in some cases they may be taken from the sternum (breastbone) or other bones.

In bone marrow *aspiration*, the skin over the hip and the surface of the bone are numbed with local anesthetic. In some cases, the child is also given other medicines to reduce pain or even be asleep during the procedure. A thin, hollow needle is then inserted into the bone and a syringe is used to suck out a small amount of liquid bone marrow.

A bone marrow *biopsy* is usually done just after the aspiration. A small piece of bone and marrow (about 1/16 inch in diameter and 1/2 inch long) is removed with a slightly larger needle that is twisted as it is pushed down into the bone. Once the biopsy is done, pressure will be applied to the site to help prevent any bleeding

These tests are used for the initial diagnosis and may be repeated later to tell if the leukemia is responding to therapy.

Lumbar Puncture (Spinal Tap)

This procedure is used to look for leukemia cells in the cerebrospinal fluid (CSF), which is the liquid that bathes the brain and spinal cord. A lumbar puncture can also be used to give chemotherapy drugs into the CSF to prevent or treat spread of leukemia to the spinal cord and brain.

For this test, the doctor first numbs an area in the lower part of the back near the spine. The doctor may also recommend that the child be given something to make him or her sleep so the child won't squirm during the procedure. Squirming may keep the spinal tap from being done cleanly. A small needle is then placed between the bones of the spine to withdraw some of the fluid.

Although this procedure is routinely done in children with leukemia, it is important that it is done by someone who is an expert. Doctors have found that if the spinal tap isn't performed expertly and some blood leaks into the spinal fluid, leukemia cells may escape into the spinal fluid and grow there.

Lymph Node Biopsy

During this procedure, a surgeon cuts through the skin to remove the entire lymph node (excisional biopsy). If the node is near the skin surface, this is a simple operation that can be done with local anesthesia (numbing medicine used only at the biopsy site). But if the node is inside the chest or abdomen, then the child will need general anesthesia (where the child is asleep). This procedure is important in diagnosing lymphomas, but is rarely needed for children with leukemias.

Lab Tests Used to Diagnose and Classify Leukemia

Routine Microscopic Exams

As mentioned above, blood counts and smears are usually the first tests done when leukemia is a possible diagnosis. Any other samples taken (bone marrow, lymph node tissue, or CSF) are also looked at under a microscope by a pathologist (a doctor specializing in diagnosing diseases with lab tests) and may be reviewed by the patient’s hematologist/oncologist (a doctor specializing in treating blood diseases and cancer).

The doctors will look at the size, shape, and staining patterns of the blood cells in the samples to classify them into specific types. (See the section, "How Is Childhood Leukemia Classified?" for more information on the types of leukemia.)

An important factor is if the cells look mature (like normal circulating blood cells that can fight infections). Some leukemic cells can lack features of normal blood cells and are not effective in fighting infections. The most immature cells are called "blasts".

An important feature of a bone marrow sample is its *cellularity*. Normal bone marrow contains a certain number of blood-forming cells and fat cells. Marrow with too many blood-forming cells is said to be *hypercellular*. If too few blood-forming cells are found, the marrow is called *hypocellular*.

Cytochemistry

During this test, cells from the sample are exposed to chemical stains (dyes) that react only with some types of leukemia cells. These stains cause color changes that can be seen under a microscope, which can help the doctor determine what types of cells are present.. For example, one stain causes the granules of most AML cells to appear as black spots under the microscope, but it does not cause ALL cells to change colors.

Flow Cytometry

This technique is sometimes used to test the cells from bone marrow, lymph nodes, and blood samples. It is very accurate in determining the exact type of leukemia.

The test checks for certain substances on the surface of cells that help identify what types of cells they are. The cells in the sample are treated with special antibodies that stick only to these substances. The cells are then passed in front of a laser beam. If the cells now have antibodies attached to them, the laser will cause them to give off light, which is measured and analyzed by a computer.

Flow cytometry can also be used to estimate the amount of DNA in the leukemia cells. This is important to know, especially in ALL, because cells with a high *DNA index* (more than 16% above normal) are often more sensitive to chemotherapy, and these leukemias have a better prognosis (outlook).

Immunocytochemistry

As in flow cytometry, this technique involves treating cells from the bone marrow or other samples with special manmade antibodies. But instead of using a laser and computer for analysis, the sample is treated so that certain types of cells change color. The color change is

visible under a microscope. Like flow cytometry, it is helpful in distinguishing different types of leukemia from one another and from other diseases.

Cytogenetics

This test involves looking at chromosomes (pieces of DNA) under a high-powered microscope to detect any changes. Normal human cells contain 23 pairs of chromosomes, each of which is a certain size and stains a certain way. In certain types of leukemia, chromosome changes may be seen.

For instance, sometimes two chromosomes swap some of their genetic material, leaving one longer than normal and one shorter than normal. This change, called a *translocation*, can usually be seen under a microscope. Recognizing these translocations can help identify certain types of ALL and AML and can help determine prognosis (outlook).

Some types of leukemia have cells with an abnormal number of chromosomes (instead of the usual 46) -- they may be missing copies of some chromosomes or have extra copies of some. This can also affect a patient's outlook. For example, most cases of ALL where the cells have more than 50 chromosomes are more sensitive to chemotherapy, while those where the cells have fewer than 46 are more resistant to it. (Counting the number of chromosomes by cytogenetics provides similar information to measuring the DNA index by flow cytometry, as described above.)

Fluorescent in situ hybridization (FISH) is a type of cytogenetic test. It uses special fluorescent dyes that only attach to specific parts of chromosomes. FISH can be used to look for specific changes in chromosomes. It can be used on regular blood or bone marrow samples and is very accurate, which is why this test is now used in many medical centers.

Molecular Genetic Studies

Certain substances, called *antigens*, are on the surface of lymphocytes. These antigens are proteins that normally help immune system cells recognize other types of cells and each other. Different types of lymphocytes have different antigens on their surface. These antigens may also change as each cell matures.

Lymphocytic leukemias such as ALL start from a single abnormal lymphocyte, so all the cells in each patient's leukemia have the same antigens. These antigens can be tested for using special man-made antibodies that react only to a specific antigen. Lab tests for antigens are a very sensitive way to diagnose ALL. Because different subtypes of ALL cells have different sets of antigens, this test is sometimes helpful in ALL classification, although it is not needed in most cases.

Tests of leukemia cell DNA can detect most translocations that are visible under a microscope in cytogenetic tests. Sensitive DNA tests such as *polymerase chain reaction* (PCR) can also find translocations too small to be seen under a microscope. This testing is sometimes helpful in leukemia classification because many subtypes of ALL and AML have distinctive translocations. This information may be useful in predicting response to treatment. See "What's New in Childhood Leukemia Research and Treatment?" for information on recent advances in genetics.

Other Blood Tests

Children with leukemia will have tests to measure the amount of certain chemicals in the blood to evaluate how well their body systems are working.

These tests are not used to diagnose leukemia, but in children already known to have it, they help find liver or kidney problems from damage caused by the spread of leukemic cells or the side effects of certain chemotherapy drugs. Tests are often done to measure blood levels of important minerals, as well as to ensure the blood is clotting properly, as well.

Children may also be tested for blood infections. It is important to quickly and accurately diagnose and treat infections in children with leukemia because their weakened immune system can allow infections to spread quickly.

Imaging Tests

If leukemia is suspected or has been diagnosed, your child's doctor may order some of the following imaging tests to get a better idea of the extent of the disease.

Chest X-rays

A chest x-ray can help detect enlargement of the thymus or lymph nodes in the chest. If this test is abnormal, a computed tomography (CT) scan may be done to get more detail on the extent of the disease.

Chest x-rays can also help find pneumonia if your child appears to have an infection.

Computed Tomography (CT) Scan

The CT scan is a type of x-ray test that produces detailed, cross-sectional images of the body. Unlike a regular x-ray, CT scans can show the detail in soft tissues (such as internal organs). This test can help tell if any lymph nodes or organs in the body are enlarged. It isn't usually needed to diagnose leukemia, but it may be done if the doctor suspects the leukemia is

growing in lymph nodes in the chest or in organs like the spleen or liver. It is also sometimes used to look at the brain, although MRI may also be sued for this.

Instead of taking one picture, like a regular x-ray, a CT scanner takes many pictures as it rotates around your child. A computer then combines these pictures into detailed images of the part of your body that is being studied.

Often after the first set of pictures is taken, your child will receive an intravenous (IV) injection of a contrast dye or your child may be asked to drink a solution of contrast material. This helps better outline blood vessels and internal organs. A second set of pictures is then taken.

The IV injection of contrast dye can cause a feeling of flushing or warmth in the face or elsewhere. Some people are allergic and get hives or, rarely, more serious reactions like trouble breathing and low blood pressure. Be sure to tell the doctor if your child has ever had a reaction to any contrast material used for x-rays.

CT scans take longer than regular x-rays. Your child will need to lie still on a table while they are being done. During the test, the table moves in and out of the scanner, a ring-shaped machine that completely surrounds the table.

Magnetic Resonance Imaging (MRI) Scans

MRI scans use radio waves and strong magnets instead of x-rays. The energy from the radio waves is absorbed by the body and then released in a pattern formed by the type of body tissue and by certain diseases. A computer translates the pattern into a very detailed image of parts of the body. Not only does this create images of cross-sectional slices of the body like a CT scanner, it can also produce images of slices that are parallel with the length of the body. A contrast material might be injected, just as with CT scans, but is used less often.

MRI scans are most helpful in looking at the brain and spinal cord.

MRI scans take longer than CT scans -- often up to an hour. Your child may have to lie inside a narrow tube, which is confining and can be distressing, so sedation is sometimes needed. Newer, "open" MRI machines may be another option. The MRI machine makes loud buzzing noises that your child may find disturbing. Some places provide headphones to block this out.

Ultrasound (Ultrasonography)

Ultrasound uses sound waves and their echoes to produce a picture of internal organs or masses. For this test, a small, microphone-like instrument called a transducer is placed on the skin (which is first lubricated with oil). It emits sound waves and picks up the echoes as they

bounce off the organs. The echoes are converted by a computer into an image that is displayed on a computer screen.

Ultrasound can be used to look for enlarged organs inside the abdomen.

This is an easy test to have done, and it uses no radiation. Your child simply lies on a table, and a technician moves the transducer over the part of the body being looked at.

Gallium Scan and Bone Scan

These tests may be useful if your child has bone pain that might be due to either bone infection or cancer involving bones. If your child has already been diagnosed with leukemia, there is usually no need for these studies.

For these tests, the radiologist injects a small amount of a radioactive chemical into the bloodstream, which collects in areas of cancer or infection in the body. These areas can then be viewed with a special type of camera. The images from these scans are seen as "hot spots" in the body, but they don't provide much detail. If an area lights up on the scan, x-rays of the affected area can be done to get a more detailed look. If leukemia is a possibility, a biopsy of the area may be needed to confirm this.

How Is Childhood Leukemia Classified?

For most cancers, *staging* is the process of determining how advanced a cancer is. Most types of solid cancers are staged based on the size of the tumor and how far the cancer has spread from the original site in the body.

Leukemia is not staged like most other cancers. It already involves the bone marrow and blood. But it is important to know whether the leukemia cells have started to collect in other organs such as the liver, spleen, lymph nodes, testicles, or central nervous system.

For instance, if the leukemia cells have spread to the central nervous system in large numbers, they can be seen in samples of cerebrospinal fluid (CSF). Treatment must be more intense in order to kill the leukemia cells in the central nervous system. For this reason, a spinal tap is done as part of the early diagnostic testing.

The most important factor for leukemias is determining the type (ALL vs. AML) and subtype of the leukemia. This is done by testing samples of the blood, bone marrow, and sometimes lymph nodes or CSF (as described in "How Is Childhood Leukemia Diagnosed?"). Classification of the leukemia plays a major role in determining both treatment options and a child's outlook (prognosis).

Acute Lymphocytic (Lymphoblastic) Leukemia (ALL)

Acute lymphocytic leukemia (ALL) is a cancer of the lymphocyte-forming cells called *lymphoblasts*.

Classification Based on Cell Appearance (Morphology)

In the past, ALL was divided into 3 major groups (L1, L2, or L3) based on the appearance of the cells under the microscope.

L1 is the most common subtype in children. The lymphoblasts are small cells.
L2 accounts for 10% of ALL cases. These cells are larger.
L3 is the rarest subtype.

This system is no longer used because there are better ways of classifying ALL than how it looks under the microscope. We include it here because some doctors may still refer to these categories.

Classification Based on Lymphocyte Antigens (Immunophenotypes)
It is more useful to classify subtypes of ALL by looking for certain substances, called antigens, on the cells. Tests for antigens can help determine whether the leukemia cells started in B cells or T cells, as well as how mature these cells are. Tests for abnormalities in the genes and chromosomes of leukemia cells are also used to determine their subtype.

Acute lymphocytic leukemias are classified by their B-cell or T-cell status. There are 4 main subtypes as shown in the table below:

Subtype	**Frequency**
Early Pre-B cell	60%-65%
Pre-B cell	20%-25%
Mature B cell	2%-3%
T cell	13%-15%

B-cell ALL: About 85% of ALL is B-cell ALL.

- The most common subtype of B-cell ALL is "early precursor B" (early pre-B) ALL.
- The "pre-B" form of ALL accounts for 20% to 25% of patients with B-cell ALL.
- The least common subtype of B-cell ALL is mature B-cell leukemia. This accounts for about 2% to 3% of childhood ALL. It is also called *Burkitt leukemia.* Because this disease is essentially the same as Burkitt lymphoma and is treated differently than

most leukemias, it is discussed in detail in the American Cancer Society document, *Non-Hodgkin Lymphoma in Children.*

T-cell ALL: About 13% to 15% of children with ALL have T-cell ALL. This type of leukemia affects boys more than girls, and generally affects older children than does B-cell ALL. It often causes an enlarged thymus (which can sometimes cause breathing problems) and may spread to the cerebrospinal fluid (the fluid that surrounds the brain and spinal cord) early in the course of the disease.

Aside from the subtypes of ALL, other factors are important in determining outlook (prognosis). These are described below in "Prognostic Factors in Childhood Leukemia."

Acute Myelogenous Leukemia (AML)

Acute myelogenous leukemia (AML) is a cancer of one of the following types of early (immature) bone marrow cells:

- **myeloblasts:** These cells normally form granulocytes (neutrophils, eosinophils, and basophils).
- **monoblasts:** These cells normally become monocytes and macrophages.
- **erythroblasts:** These cells mature into red blood cells.
- **megakaryoblasts:** These cells normally become megakaryocytes, the cells that make platelets.

AML has several subtypes, based on the type of cell involved and how mature it is. Although several lab tests can be helpful in diagnosing AML, the subtypes of AML are classified mainly by their morphology (appearance under the microscope), using routine and cytochemical stains. It may also be useful to look for changes in the genes or chromosomes of the leukemia cells.

There are 8 subtypes of AML: M0 to M7 (the "M" refers to myeloid).

M0: This subtype of AML is made up of very immature cells -- so immature that they can't be labeled according to the types of cells listed above. This subtype can only be distinguished from ALL by flow cytometry because the cells lack any distinct features that can be seen by microscope. (Flow cytometry is explained in the section, "How Is Childhood Leukemia Diagnosed?") This type of leukemia is very rare in children.

M1: This subtype is made up of immature myeloblasts. It can be recognized by the way the cells look under the microscope after using cytochemical stains.

M2: This subtype is composed of slightly more mature forms of myeloblasts. It is the most common subtype of AML in children, making up a little more than 1 out of every 4 cases.

M3: The M3 subtype is also known as *acute promyelocytic leukemia (APL)*. It is made up of promyelocytes, which are a more mature form of myeloblast. Treatment of APL is different than for other subtypes of AML, as it involves some newer drugs.

M4: This subtype is known as *acute myelomonocytic leukemia*. The cells are an early form of monoblast. The M4 subtype is common in children less than 2 years of age.

M5: This is known as *acute monocytic leukemia*. It is made up of monoblasts. Like the M4 subtype, it is more common in children less than 2 years of age.

M6: This subtype of AML is known as *acute erythroblastic leukemia* (or acute erythroleukemia). It starts in erythroblasts, the cells that normally mature into red blood cells. It is very rare in children.

M7: This subtype is also known as *acute megakaryoblastic leukemia*. The cells are megakaryoblasts. They may show a unique "budding," resembling the way platelets normally form from normal megakaryocytes.

Hybrid or Mixed Lineage Leukemias

These leukemias have cells with features of both ALL and AML when they are viewed under a microscope and tested by flow cytometry or cytogenetic tests. They are generally treated like ALL and respond to treatment like ALL.

Prognostic Factors in Childhood Leukemia

Certain differences among patients with good and poor responses to treatment are called *prognostic factors*. These are important in helping doctors decide whether a child with leukemia should receive standard treatment or more intensive treatment. The most important part of the lab testing for leukemia focuses on determining the type and subtype of leukemia the child has and what the prognostic factors are. This helps determine which treatments will work best. Prognostic factors seem to be more important in acute lymphocytic leukemia (ALL) than in acute myelogenous leukemia (AML).

Prognostic Factors for Children With Acute Lymphocytic Leukemia (ALL)

These factors are used to help determine what risk group a child may fall into. There are different systems used to classify childhood ALL risk. In one of the more common systems,

children with ALL are divided into low-risk, standard-risk, high-risk, or very high-risk groups, with more intensive treatment given for higher risk patients. Generally, children at low risk have a better outlook than those at very high risk.

While all of the following are prognostic factors, only certain ones are used to determine which risk group a child falls into. (The first 2 factors -- age at diagnosis and initial white blood cell count -- are generally considered the most important.) It's important to keep in mind that many children with one or more poor prognostic factors can still be cured.

Age at diagnosis: Children with B-cell ALL between the ages of 1 and 9 have the highest cure rate. Children younger than 1 year and children 10 years or older are considered high-risk patients. The outlook in T-cell ALL isn't affected much by age.

White blood cell (WBC) count: Children with ALL who have especially high WBC counts (greater than 50,000 cells per cubic millimeter) when they are diagnosed are classified as high risk and need more intensive treatment.

Subtype of ALL: Children with pre-B or early pre-B-cell ALL generally do better than those with T-cell or mature B-cell (Burkitt) leukemia.

Gender: Girls with ALL may have a slightly higher chance of being cured than do boys. In recent years, this difference has shrunk.

Race: African-American and Hispanic children with ALL tend to have a lower cure rate than children of other races.

Spread to certain organs: Spread of the leukemia into the spinal fluid, or the testicles, in boys, increases the chance of a poor outcome. Enlargement of the spleen and liver is usually linked to a high WBC count, but some doctors view this as a separate sign that the outlook is not as favorable.

Number of chromosomes: Patients are more likely to be cured if their leukemia cells have more than 50 chromosomes (called hyperdiploidy), especially if there is an extra chromosome 4, 10, or 17. Hyperdiploidy can also be expressed as a "DNA index" of more than 1.16. Children whose leukemia cells have fewer chromosomes than the normal 46 (hypodiploidy) have a less favorable outlook.

Chromosome translocations: Translocations result from the swapping of genetic material (DNA) between chromosomes. Children whose leukemia cells have a translocation between chromosomes 12 and 21 are more likely to be cured; those with a translocation between chromosomes 9 and 22 (the Philadelphia chromosome), 1 and 19, or 4 and 11 have a less favorable prognosis. Some of these "poor" prognostic factors have become less important in recent years as treatment has improved.

Response to treatment: Children whose leukemia responds completely (major reduction of cancer cells in the bone marrow) within 7 or 14 days of chemotherapy have a better outlook than those whose leukemia does not. Children whose cancer does not respond may be given more intensive chemotherapy.

Prognostic Factors for Children With Acute Myelogenous Leukemia (AML)

Prognostic factors do not seem to be quite as important in predicting outcome for AML as they are for ALL.

White blood cell (WBC) count: Children with AML whose WBC count is less than 100,000 cells per cubic millimeter at diagnosis are cured more often than those with higher counts.

Cytogenetics: Children with leukemia cell translocations between chromosomes 15 and 17 (seen in most cases of APL) or between 8 and 21, or with an inversion (rearrangement) of chromosome 16 have a better chance of being cured. Children whose leukemia cells have a chromosomal defect known as monosomy 7 have a poorer prognosis. Monosomy 7 means that the leukemia cells have lost 1 of the copies of chromosome 7. An abnormality of chromosome 11 may also lead to a poorer outlook.

Morphology: The morphology of the AML cells (how they look under a microscope) is correlated with the patient's outlook for survival. *Auer rods* are rod-like or needle-shaped granules that can be seen inside some patients' AML cells. They are mostly seen in the cells of M2 and M3 types of AML and are associated with a good prognosis.

Myelodysplastic syndrome or secondary AML: Children who first have myelodysplastic syndrome ("smoldering leukemia") or whose leukemia is the result of treatment for another cancer tend to have a less favorable prognosis.

Response to treatment: Children whose leukemia responds quickly to treatment (only 1 chemotherapy cycle needed to achieve remission) are more likely to be cured than those whose leukemia responds after receiving more than one course of chemotherapy, or does not respond at all.

How Is Childhood Leukemia Treated?

This information represents the views of the doctors and nurses serving on the American Cancer Society's Cancer Information Database Editorial Board. These views are based on their interpretation of studies published in medical journals, as well as their own professional experience.

The treatment information in this document is not official policy of the Society and is not intended as medical advice to replace the expertise and judgment of your cancer care team. It is intended to help you and your family make informed decisions, together with your doctor.

Your doctor may have reasons for suggesting a treatment plan different from these general treatment options. Don't hesitate to ask him or her questions about your treatment options.

Your child's doctor should make sure that treatment reflects your child's risk group as described in the previous section, and that he or she will be treated according to a protocol or guidelines of the National Cancer Institute or a cooperative study group. This will ensure the most up-to-date treatment. It's also important to ask the cancer care team about any side effects your child might develop as a result of the treatment. They can tell you about common side effects, how long they might last, and how serious they might be. Many parents find it helpful to bring a note pad or tape recorder for the doctor's discussion of their child's leukemia.

It is very important that you tell your child's doctors about any drugs, herbal remedies, or other alternative medicines you might be giving your child. These agents might affect the ability of the chemotherapy to kill leukemia cells.

This section contains general comments about types of treatments used for childhood leukemia, followed by a discussion of treatment options based on the type of leukemia.

Immediate Treatment

Some children with leukemia are critically ill when they are first diagnosed with leukemia.

- A shortage of normal white blood cells may lead to very serious infections.
- Low blood platelet levels can cause severe bleeding.
- Not having enough red blood cells can lower the amount of oxygen getting to body tissues and put a tremendous strain on the heart muscle.

These problems must often be considered before treatment of the leukemia can begin. Antibiotics, blood growth factors, and transfusions of platelets and red blood cells may be given to treat or prevent some of these conditions.

Surgery

Because leukemia cells spread throughout the bone marrow and to many other organs, it is not possible to cure this type of cancer by surgery. Aside from a possible lymph node biopsy, surgery rarely has any role even in the diagnosis, since a bone marrow aspirate and biopsy can usually diagnose leukemia.

Often before treatment is about to start, surgery is needed to insert a small plastic tube, called a central venous catheter or venous access device (VAD), into a large blood vessel. The end of the tube is just under the skin or sticks out in the chest area or upper arm. The VAD is left in place during treatment to take blood samples and give intravenous (IV) drugs such as chemotherapy. This lowers the number of needle sticks needed during treatment. It is very important for parents to learn how to care for the catheter.

Radiation Therapy

Radiation therapy uses high-energy radiation to kill cancer cells. Radiation is sometimes used in leukemia to treat the meninges (membranes that cover the brain) or in the testes (testicles).

Radiation is also used (rarely) to treat a tumor that is compressing the *trachea* (windpipe). Generally, though, if a child has not already received chemotherapy, this will be used since chemotherapy works more quickly than radiation.

Chemotherapy

Chemotherapy is treatment with anti-cancer drugs that are given into a vein (intravenous, IV), a muscle (intramuscular, IM), into the cerebrospinal fluid (intrathecal), or are taken by mouth as pills. These drugs enter the bloodstream and reach all areas of the body, making this treatment useful for cancers such as leukemia.

The treatment of leukemia uses a combination of several anti-cancer drugs given over a period of time. In general, treatment for AML will use higher doses of chemotherapy over a shorter period of time, and ALL treatment will use lower doses of chemotherapy over a longer period of time (up to several years).

Some of the drugs commonly used to treat childhood leukemia include:

- vincristine (Oncovin)
- daunorubicin, also known as daunomycin (Cerubidine)
- doxorubicin (Adriamycin)
- cytarabine, also known as cytosine arabinoside or ara-C (Cytosar)
- L-asparaginase (Elspar), PEG-L-asparaginase (pegaspargase, Oncaspar)
- etoposide (VePesid, others)
- teniposide (Vumon)
- 6-mercaptopurine (Purinethol)
- 6-thioguanine
- methotrexate
- cyclophosphamide (Cytoxan)
- prednisone (numerous brand names)
- dexamethasone (Decadron, others)

Children will likely get several of these drugs at different times during the course of treatment, but they do not get all of them.

Chemotherapy drugs kill cancer cells but can also damage normal cells and cause side effects, which doctors will try to avoid or minimize. These side effects depend on the type and dose of drugs, as well as how often and how long they are given.

Immediate Side Effects

Chemotherapy drugs work by attacking cells that are dividing quickly, which is why they work against cancer cells. But other cells in the body, such as those in the bone marrow, the lining of the mouth and intestines, and the hair follicles, also divide quickly. These cells are also likely to be affected by chemotherapy, which can lead to the following side effects:

- hair loss
- mouth sores
- loss of appetite
- diarrhea
- nausea and vomiting
- lowered resistance to infection (because of low white blood cell counts)
- bruising and bleeding easily (due to low platelet counts)
- fatigue (due to low red blood cell counts)

The problems with blood counts are often caused by the leukemia itself at first. Although they may get worse during the first part of treatment because of the chemotherapy, they will likely improve as the normal cells recover and the leukemia cells are killed off.

The side effects listed above are usually short-term and go away when treatment is finished. There are often ways to reduce these side effects. For instance, drugs can be given along with the chemotherapy to help prevent or reduce nausea and vomiting. Other drugs known as growth factors can be given to help keep the blood cell counts higher.

Tumor lysis syndrome is another possible side effect of chemotherapy. It can be seen in patients who had large numbers of leukemia cells in the body before treatment. When chemotherapy kills these cells, they break open and release their contents into the bloodstream, which may affect the kidneys, heart, and nervous system. This can be prevented by making sure the child gets lots of fluids during treatment and by giving certain drugs, such as bicarbonate, allopurinol, and rasburicase, which help the body get rid of these substances.

Long-term Side Effects

Possible long-term effects of chemotherapy are described in the section, "What Happens After Treatment for Childhood Leukemia?"

Bone Marrow or Peripheral Blood Stem Cell Transplant

A stem cell transplant (SCT) can be used for children whose chances of being cured are very poor with standard or even intensive chemotherapy. SCT allows doctors to use even higher doses of chemotherapy than would normally be tolerated.

High-dose chemotherapy destroys the bone marrow, which prevents new blood cells from being formed. This could lead to life-threatening infections, bleeding, and other problems due to low blood cell counts. Doctors try to get around this problem by giving the child an infusion of blood-forming stem cells after treatment. Stem cells are very primitive cells that can create new blood cells.

Allogeneic SCT

For childhood leukemia, the blood-forming stem cells are generally donated from another person. This is called an *allogeneic stem cell transplant* -- meaning the cells come from someone else. The donor's tissue type (also known as the HLA type) should be almost identical to the patient's tissue type to help prevent the risk of major problems with the transplant. Usually this donor is a brother or sister if they have the same tissue type as the patient. Rarely, it may be an HLA-matched, unrelated donor -- a stranger who has volunteered to donate blood-forming stem cells.

The stem cells for an allogeneic SCT can come from 1 of 3 sources:

- **bone marrow:** The stem cells are collected from the donor during several bone marrow aspirations.

- **peripheral (circulating) blood:** The stems cells are taken from the blood during *apheresis*. This procedure is similar to donating blood, but instead of going into a collecting bag, the blood goes into a special machine that filters out the stem cells and returns the other parts of the blood to the person's body. This is now more common than collecting cells from the bone marrow.

- **umbilical cord blood:** These stem cells are collected from the umbilical cord attached to the placenta after a baby is born and the umbilical cord is cut. (This blood is rich in stem cells.) The blood is then frozen and stored until it is needed by someone with the same tissue type. Cord blood is becoming a more common source of stem cells, although there are a limited number of specimens available.

Autologous SCT

In an *autologous stem cell transplant*, the patient's own stem cells are removed from his or her bone marrow (bone marrow stem cells) or bloodstream (peripheral blood stem cells,

PBSCs). They are frozen until after treatment (chemotherapy and/or radiation) and then given back to the patient.

This procedure is rarely used for childhood leukemia, for a couple of reasons. One concern is that there are leukemia cells in the bone marrow, so there may be a risk of returning these leukemia cells to the child after treatment. Leukemia has less of a tendency to relapse with allogeneic transplants. At least part of this may be because the difference in the immune makeup between the donor and patient allows the transplanted cells to help killing any leukemia cells that remain in the body after treatment. This is called the graft-versus-leukemia effect.

When SCT May Be Used

SCT may be used for a child with ALL whose leukemia relapses (comes back) early after going into remission. It is less clear if SCT should be used for those children with ALL who relapse more than 6 months after finishing their initial chemotherapy. These children will often do well with another round of standard dose chemotherapy. Children with some rarer forms of ALL, such as those with the "Philadelphia chromosome" (translocation between chromosomes 9 and 22) or those with T-cell ALL that doesn't respond well to initial treatment, may have a better chance of survival with stem cell transplants.

Because AML relapses more often than ALL, many doctors recommend SCT for children with AML right after they have gone into remission, if the child has a brother or sister with the same tissue type who can donate stem cells for the transplant. This is especially true if there is a very high risk of relapse (as seen with some subtypes of AML or certain chromosome changes). But there is still some debate about whether all children with AML need this type of intensive treatment. If a child with AML relapses after his or her first round of standard chemotherapy, most doctors will recommend SCT as soon as the child goes into remission again.

For either procedure, it is important that the patient is in remission. Otherwise, the leukemia is more likely to return.

What It Involves

Stem cells collected from a donor or the patient are carefully frozen and stored. The child then receives high-dose chemotherapy and sometimes radiation treatment. This destroys any remaining cancer cells, but also all normal cells in the bone marrow as well. After treatment, the frozen stem cells are thawed and returned to the body as a blood transfusion. For the next 3 to 4 weeks the patient is a high risk for serious infections because of a low white blood cell count, as well as bleeding because of a low platelet count. During this time, blood and platelet transfusions and treatment with IV antibiotics are often used to prevent or treat infections or bleeding problems.

The bone marrow transplant (BMT) or peripheral blood stem cell transplant (PBSCT) procedure is a complex treatment. If the doctors think your child may benefit from a transplant, the best place to have this done is at a nationally recognized cancer center where the staff has experience in performing the procedure and managing the recovery period.

A stem cell transplant is very expensive (more than $100,000) and often requires a lengthy hospital stay. Because the procedure is so expensive, you should be sure to get a written approval from your insurer if the procedure is recommended for your child.

Possible Side Effects

The possible side effects from SCT are generally divided into early and long-term effects.

The early complications and side effects are basically the same as those caused by any other type of high-dose chemotherapy (see the "Chemotherapy" section of this document), and are due to damage to the bone marrow and other quickly dividing tissues of the body. They can include low blood cell counts (with increased risk of infection and bleeding), nausea, vomiting, loss of appetite, mouth sores, and hair loss.

One of the most common and serious short-term effects is the increased risk for infection from bacteria, viruses, or fungi. Antibiotics are often given to try to prevent this from happening. Other side effects, like low red blood cell and platelet counts, may require blood product transfusions or other treatments.

Some complications and side effects can persist for a long time or may not occur until months or years after the transplant. These can include:

- graft-versus-host disease (GVHD), which can occur in allogeneic (donor) transplants. This happens when the donor immune system cells attack tissues of the patient's skin, liver, and digestive tract. Symptoms can include weakness, fatigue, dry mouth, rashes, nausea, diarrhea, yellowing of the skin and eyes (jaundice), and muscle aches. In severe cases, GVHD can be fatal. GVHD is often described as either acute or chronic, based on how soon after the transplant it begins. Drugs that weaken the immune system are often given to try to keep GVHD under control.
- radiation damage to the lungs
- problems with the thyroid or other hormone-making glands
- problems with fertility
- problems with bone growth

Be sure to talk to your child's doctor before the transplant to learn about possible long-term effects your child may have. More information on possible long-term effects can be found in the section, "What Happens After Treatment for Childhood Leukemia?"

To learn more about stem cell transplants, see the American Cancer Society document, *Bone Marrow & Peripheral Blood Stem Cell Transplants*.

Clinical Trials

You have had to make a lot of decisions since you've been told your child has cancer. One of the most important decisions you will make is deciding which treatment is best. You may have heard about clinical trials being done for this type of cancer. Or maybe someone on your health care team has mentioned a clinical trial to you. Clinical trials are one way to get state-of-the art cancer care. Still, they are not right for everyone.

Here we will give you a brief review of clinical trials. Talking to your health care team and your family can help you make the best treatment choice for your child.

What Are Clinical Trials?

Clinical trials are carefully controlled research studies that are done with patients. These studies test whether a new treatment is safe and how well it works in patients, or they may test new ways to diagnose or prevent a disease. Clinical trials have led to many advances in cancer prevention, diagnosis, and treatment.

The Purpose of Clinical Trials

Clinical trials are done to get a closer look at promising new treatments or procedures in patients. A clinical trial is only done when there is good reason to believe that the treatment, test, or procedure being studied may be better than the one used now. Treatments used in clinical trials are often found to have real benefits and may go on to become tomorrow's standard treatment.

Clinical trials can focus on many things, such as:

- new uses of drugs that are already approved by the US Food and Drug Administration (FDA)
- new drugs that have not yet been approved by the FDA
- non-drug treatments (such as radiation therapy)
- medical procedures (such as types of surgery)
- herbs and vitamins
- tools to improve the ways medicines or diagnostic tests are used
- medicines or procedures to relieve symptoms or improve comfort
- combinations of treatments and procedures

Researchers conduct studies of new treatments to try to answer the following questions:

- Is the treatment helpful?
- What's the best way to give it?
- Does it work better than other treatments already available?
- What side effects does the treatment cause?
- Are there more or fewer side effects than the standard treatment used now?
- Do the benefits outweigh the side effects?
- In which patients is the treatment most likely to be helpful?

Phases of Clinical Trials

There are 4 phases of clinical trials, which are numbered I, II, III, and IV. We will use the example of testing a new cancer treatment drug to look at what each phase is like.

Phase I clinical trials: The purpose of a phase I study is to find the best way to give a new treatment safely to patients. The cancer care team closely watches patients for any harmful side effects.

For phase I studies, the drug has already been tested in lab and animal studies, but the side effects in patients are not fully known. Doctors start by giving very low doses of the drug to the first patients and increase the doses for later groups of patients until side effects appear or the desired effect is seen. Doctors are hoping to help patients, but the main purpose of a phase I trial is to test the safety of the drug.

Phase I clinical trials are often done in small groups of people with different cancers that have not responded to standard treatment, or that keep coming back (recurring) after treatment. If a drug is found to be reasonably safe in phase I studies, it can be tested in a phase II clinical trial.

Phase II clinical trials: These studies are designed to see if the drug works. Patients are given the best dose as determined from phase I studies. They are closely watched for an effect on the cancer. The cancer care team also looks for side effects.

Phase II trials are often done in larger groups of patients with a specific cancer type that has not responded to standard treatment. If a drug is found to be effective in phase II studies, it can be tested in a phase III clinical trial.

Phase III clinical trials: Phase III studies involve large numbers of patients -- most often those who have just been diagnosed with a specific type of cancer. Phase III clinical trials may enroll thousands of patients.

Often, these studies are randomized. This means that patients are randomly put in one of two (or more) groups. One group (called the control group) gets the standard, most accepted treatment. Another group (or more than one group) will get the new one being studied. All patients in phase III studies are closely watched. The study will be stopped early if the side effects of the new treatment are too severe or if one group has much better results than the others.

Phase III clinical trials are usually needed before the FDA will approve a treatment for use by the general public.

Phase IV clinical trials: Once a drug has been approved by the FDA and is available for all patients, it is still studied in other clinical trials (sometimes referred to as phase IV studies). This way more can be learned about short-term and long-term side effects and safety as the drug is used in larger numbers of patients with many types of diseases. Doctors can also learn more about how well the drug works, and if it might be helpful when used in other ways (such as in combination with other treatments).

What It Will Be Like to Be in a Clinical Trial

If your child is in a clinical trial, a team of experts will take care of and watch his or her progress very carefully. Depending on the phase of the clinical trial, your child may receive more attention (such as having more doctor visits and lab tests) than he or she would if treated outside of a clinical trial. Clinical trials are specially designed to pay close attention to your child.

However, there are some risks. No one involved in the study knows in advance whether the treatment will work or exactly what side effects will occur. That is what the study is designed to find out. While most side effects go away in time, some may be long-lasting or even life threatening. Keep in mind, though, that even standard treatments have side effects. Depending on many factors, you may decide to enter your child in a clinical trial.

Deciding to Enter a Clinical Trial

If you would like your child to take part in a clinical trial, you should begin by asking your doctor if your clinic or hospital conducts clinical trials. There are requirements patients must meet to take part in any clinical trial. But whether or not you enter your child in a clinical trial is completely up to you.

Your doctors and nurses will explain the study to you in detail. They will go over the possible risks and benefits and give you a form to read and sign. The form says that you understand the clinical trial and want your child to take part in it. This process is known as giving your informed consent. Even after reading and signing the form and after the clinical trial begins, you are free to withdraw your child from the study at any time, for any reason.

Taking part in a clinical trial does not keep your child from getting any other medical care he or she may need.

To find out more about clinical trials, talk to your cancer care team. Here are some questions you might ask:

- Is there a clinical trial that my child could take part in?
- What is the purpose of the study?
- What kinds of tests and treatments does the study involve?
- What does this treatment do? Has it been used before?
- Will I know which treatment my child will receive?
- What is likely to happen in my child's case with, or without, this new treatment?
- What are the other choices and their pros and cons?
- How could the study affect my child's daily life?
- What side effects can be expected from the study? Can the side effects be controlled?
- Will my child have to stay in the hospital? If so, how often and for how long?
- Will the study cost me anything? Will any of the treatment be free?
- If my child is harmed as a result of the research, what treatment would I be entitled to?
- What type of long-term follow-up care is part of the study?
- Has the treatment been used to treat other types of cancers?

How Can I Find Out More About Clinical Trials That Might Be Right for Me?

The American Cancer Society offers a clinical trials matching service for patients, their family, and friends. You can reach this service at 1-800-303-5691 or on our Web site at http://clinicaltrials.cancer.org.

Based on the information you give about your child's cancer type, stage, and previous treatments, this service can put together a list of clinical trials that match your child's medical needs. The service will also ask where you live and whether you are willing to travel so that it can look for a treatment center that you can get to.

You can also get a list of current clinical trials by calling the National Cancer Institute's Cancer Information Service toll free at 1-800-4-CANCER (1-800-422-6237) or by visiting the NCI clinical trials Web site at www.cancer.gov/clinicaltrials.

For even more information on clinical trials, the American Cancer Society has a document called *Clinical Trials: What You Need to Know.* You can read this on the Web site, www.cancer.org, or have it sent to you by calling 1-800-ACS-2345.

Complementary and Alternative Therapies

When your child has cancer you are likely to hear about ways to treat his or her cancer or relieve symptoms that are different from mainstream (standard) medical treatment. These methods can include vitamins, herbs, and special diets, or methods such as acupuncture or massage—among many others. You may have a lot of questions about these treatments. Here are some you may have thought of already:

- How do I know if a non-standard treatment is safe?
- How do I know if it works?
- Should we try one or more of these treatments?
- What does my doctor know/think about these methods? Should I tell the doctor that I'm thinking about trying them?
- Will these treatments cause a problem with my child's standard medical treatment?
- What is the difference between "complementary" and "alternative" methods?
- Where can I find out more about these treatments?

The Terms Can Be Confusing

Not everyone uses these terms the same way, so it can be confusing. The American Cancer Society uses *complementary* to refer to medicines or methods that are used *along with* regular medical care. *Alternative* medicine is a treatment used *instead of* standard medical treatment.

Complementary methods: Complementary treatment methods, for the most part, are not presented as cures for cancer. Most often they are used to help you feel better. Some methods that can be used in a complementary way are meditation to reduce stress, acupuncture to relieve pain or peppermint tea to relieve nausea. There are many others. Some of these methods are known to help, while others have not been tested. Some have been proven not be helpful. A few have even been found harmful. However, some of these methods may add to your comfort and well-being.

There are many complementary methods that can be safely used right along with medical treatment to help relieve symptoms or side effects, to ease pain, and to help your child enjoy life more. For example, some people find methods such as aromatherapy, massage therapy, meditation, or yoga to be useful.

Alternative treatments: Alternative treatments are those that are used instead of standard medical care. These treatments have not been proven safe and effective in clinical trials. Some of these methods may even be dangerous and some have life-threatening side effects. The biggest danger in most cases is that your child may lose the chance to benefit from standard treatment. Delays or interruptions in standard medical treatment may give the cancer more time to grow.

Deciding What to Do

It is easy to see why people with cancer may consider alternative methods. You want to do all you can to fight the cancer. Sometimes mainstream treatments such as chemotherapy can be hard to take, or they may no longer be working.

Sometimes people suggest that their method can cure your cancer without having serious side effects, and it's normal to want to believe them. But the truth is that most non-standard methods of treatment have not been tested and proven to be effective for treating cancer.

As you consider your options, here are 3 important steps you can take:

- Talk to your doctor or nurse about any method you are thinking about using.
- Check the list of "red flags" below.
- Contact the American Cancer Society at 1-800-ACS-2345 to learn more about complementary and alternative methods in general and to learn more about the specific methods you are thinking about.

Red Flags

You can use the questions below to spot treatments or methods to avoid. A "yes" answer to any one of these questions should raise a "red flag."

- Does the treatment promise a cure for all or most cancers?
- Are you told not to use standard medical treatment?
- Is the treatment or drug a "secret" that only certain people can give?
- Does the treatment require you to travel to another country?
- Do the promoters attack the medical or scientific community?

The Decision Is Yours

Decisions about how to treat or manage your child's cancer are always yours to make. If you are thinking about using a complementary or alternative method, be sure to learn about the method and talk to your doctor about it. With reliable information and the support of your health care team, you may be able to safely use the methods that can help your child while avoiding those that could be harmful.

Treatment of Children With Acute Lymphocytic Leukemia

Treatment of children with acute lymphocytic leukemia (ALL) is divided into 3 chemotherapy phases: induction, consolidation or intensification, and maintenance.

When leukemia is diagnosed, there are usually about 100 billion leukemia cells in the body. Killing 99.9% of these leukemia cells during the 1-month induction treatment is enough to achieve a remission, but it still leaves about 100 million leukemia cells in the body. These also must be destroyed. An intensive 4- to 6-month program of consolidation treatment and about 2 years of maintenance chemotherapy helps destroy the remaining cancer cells.

As mentioned earlier, children with ALL are divided into risk groups to make sure that the correct types and doses of drugs are given. Treatment will be different for different risk groups.

Induction

The goal of induction chemotherapy is to achieve a *remission*. This means that leukemia cells are no longer found in bone marrow samples, the normal marrow cells return, and the blood counts become normal.

More than 95% of children with ALL enter remission after 1 month of treatment. This first month of treatment is quite intensive, and you will need to make frequent visits to the doctor. Your child may spend some or much of this time in the hospital, because serious infections can occur. It is very important to take all medicines prescribed. Because of advances in supportive care (nursing care, nutrition, antibiotics, red blood cell and platelet transfusions as needed, etc.), fewer than 3% of children with leukemia die of complications during this initial treatment.

Children with standard-risk ALL often receive 3 drugs for the first month of treatment. These include the chemotherapy drugs L-asparaginase, vincristine, and a steroid (usually dexamethasone). A fourth drug in the anthracycline class (daunorubicin is the one most often used) is typically added for high-risk children. Other drugs that may be given early are methotrexate and/or 6-mercaptopurine.

Intrathecal chemotherapy: All children also need to receive spinal taps to inject chemotherapy into the cerebrospinal fluid (CSF) to kill any leukemia cells that may have spread to the central nervous system. This *intrathecal* chemotherapy is usually given twice (more often if the leukemia is high risk) during the first month and 4 to 6 times during the next 1 or 2 months. It is then repeated less often during consolidation and maintenance. Usually, methotrexate is used for intrathecal chemotherapy, but drugs called hydrocortisone (a steroid, like prednisone) and cytarabine (ara-C) may be added, particularly in high-risk children.

Along with intrathecal therapy, high-risk patients (for example, those with very high numbers of white blood cells, T-cell ALL, or older children) and those with leukemia cells detected in their CSF when the leukemia is diagnosed may be given radiation therapy to the brain (and possibly the spinal cord). Doctors try to avoid this treatment if possible because no matter how low the dose is kept, it can cause some slight problems in thinking and growth and

development. Some doctors feel they can avoid radiation by giving the child very high doses of methotrexate and then neutralizing its side effects with another drug called leucovorin. Others may try more frequent intrathecal treatments.

A possible side effect of the intrathecal treatment is epileptic seizures during treatment, which happen in about 5% to 10% of children. Children who develop seizures are treated with drugs to prevent them.

Consolidation (Intensification)

The next, most "intensive" phase of chemotherapy lasts 4 to 8 months. The consolidation phase reduces the number of leukemia cells still remaining in the body. Several drugs are used in combination to prevent the remaining leukemia cells from developing resistance. Intrathecal therapy (as described above) is continued at this time.

Children with standard-risk ALL are usually treated with drugs such as methotrexate and 6-mercaptopurine or 6-thioguanine, although regimens may differ between cancer centers. Vincristine, L-asparaginase, and/or prednisone may also be added.

Children whose leukemia cells showed high risk factors generally will receive a more intense regimen of chemotherapy. Extra drugs such as L-asparaginase, doxorubicin (Adriamycin), etoposide, cyclophosphamide, and cytarabine (ara-C) are often used and dexamethasone substituted for prednisone. There may be a second round of intense chemotherapy with the same drugs.

Some children, such as those with Philadelphia chromosome-positive ALL, may benefit from a stem cell transplant at this time.

Maintenance

Once induction and consolidation phases of therapy are complete and the leukemia continues to be in remission, maintenance therapy can begin. Most treatment plans use methotrexate and 6-mercaptopurine, given as pills, often along with vincristine, which is given intravenously, and a steroid (prednisone or dexamethasone). These latter 2 drugs are given for brief periods every 4 to 8 weeks.

Occasionally, leukemia patients at higher risk may receive more intensive maintenance chemotherapy and intrathecal therapy.

The total duration of therapy (induction, intensification, and maintenance) for most ALL treatment plans is 2 to 3 years.

Treatment of Residual Disease

All these treatment plans may change if the leukemia hasn't completely disappeared. Several days after treatment has begun the doctor may check the child's bone marrow to see if the leukemia is disappearing. If not, treatment may be intensified or prolonged. If the leukemia seems to have disappeared by standard tests, the doctor may do a special chemical test to look for small numbers of leukemia cells that may be left. If any are found, then once again, chemotherapy may be intensified or prolonged.

Treatment of Recurrent ALL

If a child with ALL relapses, he or she will most likely be treated again with chemotherapy. Much of the treatment strategy depends on how soon the leukemia returns after the first treatment. The shorter the time interval, the greater will be the need for newer and more aggressive chemotherapy.

The most commonly used chemotherapy drugs are vincristine, L-asparaginase, anthracyclines (doxorubicin, daunorubicin), cyclophosphamide, cytarabine (ara-C), and epipodophyllotoxins (etoposide, teniposide). Your child will also receive a steroid (prednisone or dexamethasone) and vincristine unless he or she is known to be resistant to these medications. Intrathecal chemotherapy will also be given.

For children whose leukemia comes back within 6 months of starting therapy or for children with T-cell ALL who relapse, a stem cell transplant may be considered, especially if there is a brother or sister who is a good tissue type match. Stem cell transplant may also be used for other children who relapse after a second course of chemotherapy.

Some children have an *extramedullary relapse*, meaning that leukemic cells are found in one part of the body (such as the CSF or the testicles) but are not detectable in the bone marrow. In addition to receiving intensive chemotherapy as described above, these children may also have radiation therapy to the affected area (if that area had not been already treated with radiation).

Cure Rates for ALL

The chance of being cured of low-risk ALL is about 85% to 95%, standard-risk is about 65% to 85%, and high-risk ALL is about 60% to 65%.

Philadelphia Chromosome-Type ALL

For children with this high-risk type of leukemia, a stem cell transplant may be advised if induction treatment yields a remission.

Newer, targeted drugs such as imatinib (Gleevec) and dasatinib (Sprycel) are designed to kill leukemia cells that contain the Philadelphia chromosome. These drugs, which are taken as pills and seem to have limited side effects, are now being studied for use along with chemotherapy.

Treatment of Children With Acute Myelogenous Leukemia

Treatment of most children with acute myelogenous leukemia (AML) is divided into 2 phases of chemotherapy: induction and consolidation (intensification). Treatment of the M3 subtype (acute promyelocytic leukemia, or APL) is slightly different, and is described separately below. Because of the intensity of treatment and the risk of serious complications, children with AML should be treated in cancer centers or hospitals that have experience with this disease.

Induction

Treatment for AML uses combinations of drugs that are different from those used for ALL. The drugs most often used are daunorubicin (daunomycin) and cytarabine (ara-C), which are each given for several days in a row. The schedule of treatment may be repeated in 10 days or 2 weeks, depending on how intense the doctor wants the treatment to be. A shorter interval between treatments causes more severe side effects, but may be more effective in killing leukemia cells.

If the doctors think that the leukemia may not respond to just 2 drugs alone, they may add etoposide and/or 6-thioguanine. Children with very high numbers of white blood cells or whose leukemia has certain chromosome abnormalities may fall into this class.

Treatment with these drugs is repeated until the bone marrow shows no more leukemia. This usually occurs after 2 or 3 treatments.

Preventing relapse in the central nervous system: In most cases, intrathecal chemotherapy (given directly into the cerebrospinal fluid, or CSF) is also given to help prevent leukemia from relapsing in the brain or CSF. Radiation therapy to the brain is used less often. The risk for recurrence in the brain or CSF is lower in children with AML than in children with ALL.

Consolidation (Intensification)

This begins after the induction phase, when the bone marrow has no more visible leukemia cells.

About 1 out of 5 children has a brother or sister who would be a good stem cell donor. For these children, an allogeneic stem cell transplant is often recommended. Most studies have found this improves the chance for long-term survival over chemotherapy alone, although it is also more likely to cause serious complications. For children with good prognostic factors, some doctors may recommend just giving high-dose chemotherapy, and reserving the stem cell transplant in case the AML relapses.

For most other children, consolidation consists of giving the chemotherapy drug cytarabine (ara-C) in high doses. Daunorubicin may also be added. It is usually given for at least several months.

Intrathecal chemotherapy (into the cerebrospinal fluid) is usually given initially and every 1 to 2 months for as long as intensification continues.

Maintenance chemotherapy is not needed for children with AML (other than those with APL - see below).

An important part of treatment for AML is the supportive care (proper nursing care, nutrition supplement, antibiotic use, and blood transfusions). Without antibiotic treatment of infections or transfusion support, children with AML could not expect the current 75% to 85% remission rate at the end of induction.

Refractory or Recurrent AML

Less than 15% to 20% of children have *refractory AML* (leukemia that does not respond to initial treatment). The outlook for the child who doesn't go into remission is often poor, and doctors may recommend some type of stem cell transplant if it can be done.

In a recent clinical trial, children who were not in complete remission after induction chemotherapy were given a drug called gemtuzumab ozogamicin (Mylotarg) as part of their intensification. Mylotarg is a chemotherapy drug attached to a manmade antibody. The antibody is designed to bring the chemotherapy directly to the AML cells. Early results suggest this treatment may help improve survival rates for some children with AML.

Generally, the outlook for a child whose AML relapses (comes back) after treatment is slightly better, but this depends on how long the initial remission was. In more than half of cases of relapse, a second remission can be achieved with more chemotherapy. The chance of getting a second remission is better if the first remission lasted for at least a year, but long-term second remissions are rare without a stem cell transplant.

Many different combinations of standard chemotherapy drugs have been used in these situations, but the results have been mixed.

Most children will be offered a clinical trial that is testing a new treatment regimen. The hope is that some sort of a remission can be attained so that an allogeneic stem cell transplant can be done. If remission is achieved, a stem cell transplant should be considered. Some doctors may advise an allogeneic stem cell transplant even when there is no remission. This can sometimes be successful.

Cure Rates for AML

The cure rate for AML (with standard chemotherapy) is 40% to 50%. Treatment of AML with a stem cell transplant from a brother or sister with the same tissue type results in a higher cure rate of 55% to 60%.

Treatment of Children With Acute Promyelocytic Leukemia (APL)

Treatment of the M3 subtype of AML (acute promyelocytic leukemia) differs from usual AML treatment. Most cases respond well to this treatment.

Induction

Along with chemotherapy, children with APL receive a non-chemotherapy drug similar to vitamin A called all-trans retinoic acid (ATRA). Although a remission can often be induced with ATRA alone, combining it with chemotherapy (usually daunorubicin and cytarabine) gives better long-term results. Spread to the brain or spinal cord is very rare with APL, so intrathecal chemotherapy is usually not needed.

The side effects of this treatment differ from those of standard AML induction chemotherapy because of a potential problem called *retinoic acid syndrome*. This can involve breathing problems due to fluid buildup in the lungs, low blood pressure, kidney damage, and severe fluid buildup elsewhere in the body. It can often be treated by stopping the ATRA for a while and giving a steroid such as dexamethasone.

During treatment, some patients with APL may also develop blood-clotting problems. They may be given an anticoagulant ("blood thinner") to help prevent or treat this.

Consolidation (Intensification)

This is usually similar to induction, involving both ATRA and chemotherapy (usually daunorubicin). Because of the success of this treatment, stem cell transplant is not usually advised if the remission is maintained.

Maintenance

Children with APL may receive maintenance therapy with ATRA (often with the chemotherapy drugs methotrexate and 6-mercaptopurine) for about one year.

Relapsed APL

If the leukemia comes back after treatment, most cases can be put into a second remission. Arsenic trioxide is a drug that is very effective in this setting, although it can sometimes cause problems with heart rhythms. Children getting this drug need to have their blood mineral levels watched closely. A stem cell transplant may be considered once a second remission is achieved.

Cure Rates for APL

Most studies suggest that the cure rate for APL is now higher than 80%.

Treatment of Children With Juvenile Myelomonocytic Leukemia (JMML)

JMML is fairly rare, and there is no standard treatment for this leukemia. An allogeneic stem cell transplant offers the best chance to cure JMML and is the treatment of choice when possible. Because it is hard to treat with current chemotherapy drugs, some studies are now looking at other agents like cis-retinoic acid and tipifarinb.

More Treatment Information

For more details on treatment options -- including some that may not be addressed in this document -- the National Cancer Institute (NCI) is a good source of information.

The NCI provides treatment guidelines via its telephone information center (1-800-4-CANCER) and its Web site (www.cancer.gov). Detailed guidelines intended for use by cancer care professionals are also available on www.cancer.gov.

What Should You Ask Your Child's Doctor About Childhood Leukemia?

It is important to have frank, open discussions with your child's cancer care team. They want to answer all of your questions, no matter how small they might seem. For instance, consider these questions:

- What kind of leukemia does my child have?
- What are the prognostic factors?
- What treatment choices are available?
- Should we consider a stem cell transplant?
- What do you recommend and why?
- What should we do to be ready for treatment?
- What risks or side effects are there to the treatments you suggest?
- Which side effects start shortly after treatment and which ones may develop later on?
- What is my child's outlook for survival?
- What are the chances of recurrence with these treatment plans? What would we do if this happens?

In addition to these sample questions, be sure to write down your own. For instance, you might want more information about how long treatment lasts so you can plan your child's school schedule. Or you may want to ask about second opinions or about clinical trials for which your child may qualify.

What Happens After Treatment for Childhood Leukemia?

For several years after treatment, regular follow-up exams will be very important. The doctors continue to watch for signs of disease, as well as for short-term and long-term side effects of treatment.

Checkups after treatment has been completed involve careful physical exams, lab tests, and sometimes, x-ray tests. These checkups will usually occur monthly during the first year, and then less often for at least 5 years after therapy. After that time, it is a good idea to have the child see his or her doctor yearly for a checkup.

If leukemia does recur, it is most often while the child is being treated or within a year or so after stopping treatment. It is unusual for high-risk ALL or AML to return if there are no signs of the disease within 2 years after stopping treatment.

A benefit of follow-up care is that it gives you an opportunity to discuss questions and concerns that arise during and after your child's recovery. It is important that the patient and/or parents report any new symptoms to the doctor right away, so that relapse or side effects can be treated effectively.

Long-Term Effects of Cancer Treatment

Because of major advances in treatment, more children treated for cancer are living into adulthood. With childhood cancer survivors living longer, their health as adults has come more into focus in recent years.

Just as the treatment of childhood cancer requires a very specialized approach, so does follow-up and monitoring for late effects of treatment. Careful follow-up after cancer treatment is very important.

Childhood cancer survivors are at risk, to some degree, for several possible late effects of their cancer treatment. This risk depends on a number of factors, such as the type of cancer, the type of treatments they received, dosages of cancer treatment, and age at the time of treatment.

One of the most serious side effects of ALL therapy is the possibility of getting acute myelogenous leukemia (AML) at a later time. This occurs in about 5% of patients after they have received chemotherapy drugs called epipodophyllotoxins (etoposide, teniposide) or alkylating agents (cyclophosphamide, chlorambucil). Less often, children cured of leukemia may later develop non-Hodgkin lymphomas or other cancers. Of course, the risk of getting these second cancers must be balanced against the obvious benefit of treating a life-threatening disease such as leukemia with chemotherapy.

Children whose treatment for leukemia has included radiation therapy of the brain may have some decrease in their learning ability. Generally, this is mild and does not cause any significant disability.

Survivors of childhood leukemia often suffer from emotional or psychological problems. They also may have some problems with normal functioning and work. These can often be overcome with support and encouragement.

Cancer treatments may reduce the growth of children, and they may end up a bit shorter as adults. This is especially true after stem cell transplants. This can be helped by the treating survivors with growth hormone, if needed.

Osteoporosis (thinning of the bones) with a chance of bone fracture may result from the use of prednisone or other corticosteroids.

Late effects may also include heart or lung problems after receiving certain chemotherapy drugs or radiation therapy to these parts of the body.

Cancer treatment may also affect growth and development. In some cases it may affect sexual development and ability to have children.

There may be other possible complications from chemotherapy as well. Your child's doctor should carefully review any possible problems with you before starting treatment. Specialized centers are often the best place to be treated when such effects arise.

For more information on these and other possible late effects, please see the American Cancer Society document, *Childhood Cancer: Late Effects of Cancer Treatment.*

Moving On

After treatment is complete, you and your child may want to put the experience behind you as much as possible. Eventually, your child will grow up, be on his or her own, and have new doctors. But it is important that you or your child be able to give the new doctors the exact details of the cancer diagnosis and treatment. Gathering the details soon after treatment may be easier than trying to get them at some point in the future. There are certain pieces of information that your child's doctors should have, even into adulthood. These include:

- A copy of the pathology report from any biopsies or surgeries.
- If there was surgery, a copy of the operative report.
- If there were hospitalizations, a copy of the discharge summaries (forms that doctors must prepare when patients are discharged from the hospital).
- A list of the final doses of each chemotherapy drug or other drug your child received. (Certain chemotherapy drugs have specific long-term side effects. If you can get a list of these from the pediatric oncologist, this might also help any new primary care doctor.)
- If there was radiation, a final summary of the dose and field.

What's New in Childhood Leukemia Research and Treatment?

Researchers are now studying the causes, diagnosis, supportive care, and treatment of leukemia at many medical centers, university hospitals, and other institutions.

Genetics

As noted in the section "Do We Know What Causes Childhood Leukemia?," scientists are making great progress in understanding how changes in DNA can cause lymphocytes and bone marrow stem cells to develop into leukemia. Understanding the gene changes (such as translocations or extra chromosomes) that often occur in leukemia gives us insight into why these cells may grow out of control, and why they do not develop into normal, mature cells.

This progress has already led to vastly improved and highly sensitive tests for detecting this disease. The *polymerase chain reaction* (PCR) test, for example, can identify very small numbers of leukemia cells based on their gene translocations or rearrangements. This test can find one tumor cell among a million normal cells. It is useful in determining how completely the leukemia has been destroyed by treatment, and whether a relapse will occur if further treatment is not given.

Another test called *DNA microarray analysis* is being studied in many cancers. This test can look at hundreds of gene changes in the cancer cells at the same time. Scientists hope to use

this test to be better able to classify a child's prognosis. They also hope to find genetic changes that may be targets for new kinds of drugs.

Over time, this information may be used in developing *gene therapy*. This treatment would replace the abnormal DNA of cancer cells with normal DNA in order to restore normal controls on cell growth.

Clinical Trials

Most children are treated for leukemia at major medical centers, where treatment often involves taking part in clinical trials to provide the most up-to-date care. Several important questions are now being studied in clinical trials. Among them are:

- Why do 30% of children with acute lymphocytic leukemia (ALL) relapse, and how can this be prevented?
- Are there other prognostic factors that will help identify which children need more or less intensive treatment?
- Can acute myelogenous leukemia (AML) be treated more effectively by using more intensive chemotherapy, followed by growth factors to help restore the child's normal bone marrow function?
- Can chemotherapy drug resistance in AML be reversed?
- Are there better drugs or combinations of drugs available for treating leukemia?
- Can drugs, toxins, or radiation be specifically targeted to the leukemic cells by using manmade antibodies? Such antibodies can now be designed to specifically seek out leukemia cells, which are then destroyed by the drug, toxin, or radiation.
- Can naturally produced "biologic response modifiers" help the body's immune system fight the leukemia cells?
- When exactly should a stem cell transplant be used to treat ALL or AML?
- How effective are stem cell transplants in children who don't have a brother or sister who is a good tissue type match?
- Can a second stem cell transplant help children who relapse after a first stem cell transplant?
- Can the outlook for children with ALL with a translocation between chromosomes 9 and 22 be improved? Children whose leukemia cells have this translocation, known as the "Philadelphia chromosome", tend to have a lower cure rate than others with ALL. Imatinib (Gleevec) and dasatinib (Sprycel), drugs that specifically kill cells with this translocation, have been very helpful in treating certain leukemias in adults. Studies are now under way to see if adding these drugs to chemotherapy can improve treatment outcomes.

Additional Resources

More Information From Your American Cancer Society

The following information may also be helpful to you. These materials may be ordered from our toll-free number, 1-800-ACS-2345.

Children Diagnosed With Cancer: Dealing With Diagnosis (also available in Spanish)

Children Diagnosed With Cancer: Understanding the Health Care System (also available in Spanish)

Children Diagnosed With Cancer: Financial and Insurance Issues

Children Diagnosed With Cancer: Returning to School

Childhood Cancer: Late Effects of Cancer Treatment

Pediatric Cancer Centers

Family Medical Leave Act (FMLA)

Understanding Chemotherapy: A Guide for Patients and Families (also available in Spanish)

Understanding Radiation: A Guide for Patients and Families (also available in Spanish)

Health Professionals Associated With Cancer Care

What Happened to You, Happened to Me (children's book)

When Your Brother or Sister Has Cancer (children's book)

After Diagnosis: A Guide for Patients and Families (also available in Spanish)

Because Someone I Love Has Cancer

Anxiety, Fear, and Depression

The following books are available from the American Cancer Society. Call us at 1-800-ACS-2345 to ask about costs or to place your order.

Informed Decisions: The Complete Book of Cancer Diagnosis, Treatment and Recovery. Second Edition

Angels and Monsters: A Child's Eye View of Cancer

National Organizations and Web Sites*

In addition to the American Cancer Society, other sources of patient information and support include:

Candlelighters Childhood Cancer Foundation
Telephone: 1-800-366-2223
Internet Address: www.candlelighters.org

Children's Leukemia Research Association (CLRA)
(also known as National Leukemia Research Association)
Telephone: 1-516-222-1944
Internet Address: www.childrensleukemia.org

CureSearch (National Childhood Cancer Foundation and Children's Oncology Group)
Telephone: 1-800-458-6223
Internet Address: www.curesearch.org

Leukemia & Lymphoma Society
Telephone: 1-800-955-4572
Internet Address: www.lls.org

National Cancer Institute
Telephone: 1-800-4-CANCER (1-800-422-6237)
Internet Address: www.cancer.gov

National Dissemination Center for Children with Disabilities (NICHCY)
Telephone: 1-800-695-0285
Internet Address: www.nichcy.org

Starlight Starbright Children's Foundation
Telephone: 1-800-315-2580
Internet Address: www.slsb.org

*Inclusion on this list does not imply endorsement by the American Cancer Society.

Other Publications*

For Adults

Cancer & Self-Help: Bridging the Troubled Waters of Childhood Illness, by Mark A. Chester, and Barbara K. Chesney. Published by University of Wisconsin Press, 1995.

Childhood Cancer: A Handbook from St Jude Children's Research Hospital by Grant Steen and Joseph Mirro (editors). Published by Perseus Publishing, 2000.

Childhood Cancer Survivors: A Practical Guide to Your Future, by Nancy Keene, Wendy Hobbie, Kathy Ruccione. Published by O'Reilly and Associates, 2000.

Childhood Leukemia: A Guide for Families, Friends & Caregivers, Third Edition, by Nancy Keene. Published by O'Reilly and Associates, 2002.

Children with Cancer: A Comprehensive Reference Guide for Parents, by Jeanne Munn Bracken. Published by Oxford University Press, 2001.

Living with Childhood Cancer: A Practical Guide to Help Families Cope, by Leigh A. Woznick and Carol D. Goodheart. Published by American Psychological Association, 2002.

Surviving Childhood Cancer: A Guide for Families, by Margot Joan Fromer. Published by New Harbinger Publications, 1998.

When Bad Things Happen to Good People, by Harold Kushner. Published by G.K. Hall, 1982.

Your Child in the Hospital: A Practical Guide for Parents. Second Edition, by Nancy Keene. Published by O'Reilly & Associates, 1999. (Also available in Spanish)

For Young People

Chemo, Craziness and Comfort, My Book about Childhood Cancer. Candlelighters Childhood Cancer Foundation. www.candlelighters.org.

My Book for Kids with Cansur [sic], by Jason Gaes. Published by Viking Penguin, 1998.

Going to the Hospital, by Fred Rogers. Published by G.P. Putnam and Sons, 1988.

The Amazing Hannah, Look at Everything I Can Do! by Amy Klett. Published by Candlelighters Childhood Cancer Foundation, 2002. (Also available in Spanish)

What About Me? When Brothers and Sisters Get Sick, by Allan Peterkin and Frances Middendorf. Published by Magination Press, 1992.

Why, Charlie Brown, Why? A Story About What Happens When a Friend is Very Ill, by Charles M. Schultz. Published by Ballantine Publishing Group, 1990.

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The American Cancer Society is happy to address almost any cancer-related topic. If you have any more questions, please call us at 1-800-ACS-2345 at any time, 24 hours a day.

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