Early Detection, Diagnosis, and Staging

Detection and Diagnosis

Catching cancer early often allows for more treatment options. Some early cancers may have signs and symptoms that can be noticed, but that is not always the case.

- Can Chronic Lymphocytic Leukemia Be Found Early?
- Signs and Symptoms of Chronic Lymphocytic Leukemia
- How Is Chronic Lymphocytic Leukemia Diagnosed?

Stages and Outlook (Prognosis)

After a cancer diagnosis, staging provides important information about the extent of cancer in the body and anticipated response to treatment.

- How Is Chronic Lymphocytic Leukemia Staged?

Questions to Ask About CLL

Here are some questions you can ask your cancer care team to help you better understand your CML diagnosis and treatment options.

- What Should You Ask Your Doctor About Chronic Lymphocytic Leukemia?

Can Chronic Lymphocytic Leukemia Be Found Early?

For certain cancers, the American Cancer Society recommends screening tests in people without any symptoms, because they are easier to treat if found early. But for chronic lymphocytic leukemia (CLL), no screening tests are routinely recommended at
Sometimes, CLL is found when routine blood tests are done for other reasons. For instance, a person’s white blood cell count may be very high, even though he or she doesn’t have any symptoms.

If you notice any symptoms that could be caused by CLL, report them to your doctor right away so the cause can be found and treated, if needed.

- References
  See all references for Chronic Lymphocytic Leukemia

Last Medical Review: January 6, 2015 Last Revised: April 11, 2016

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Signs and Symptoms of Chronic Lymphocytic Leukemia

Many people with CLL do not have any symptoms when it is diagnosed. The leukemia is often found when their doctor orders blood tests for some unrelated health problem or during a routine checkup and they are found to have a high number of lymphocytes.

Even when people with CLL have symptoms, they are often vague and can be symptoms of other things. Symptoms can include the following:

- Weakness
- Feeling tired
- Weight loss
- Fever
- Night sweats
- Enlarged lymph nodes (often felt as lumps under the skin)
- Pain or a sense of “fullness” in the belly (this can make someone feel full after only a small meal), which is caused by an enlarged spleen and/or liver

Many of the signs and symptoms of advanced CLL occur because the leukemia cells
replace the bone marrow’s normal blood-making cells. As a result, people do not make enough red blood cells, properly functioning white blood cells, and blood platelets.

- **Anemia** is a shortage of red blood cells. It can cause tiredness, weakness, and shortness of breath.
- A shortage of normal white blood cells (*leukopenia*) increases the risk of *infections*. You might hear the term *neutropenia*, which refers specifically to low levels of neutrophils (a type of granulocyte needed to fight bacterial infections). People with CLL may have very high white blood cell counts because of excess numbers of lymphocytes (*lymphocytosis*), but the leukemia cells do not protect against infection the way normal white blood cells do.
- A shortage of blood platelets (*thrombocytopenia*) can lead to excess bruising, bleeding, frequent or severe nosebleeds, and bleeding gums.

People with CLL have a higher risk of infections. This is mainly because their immune systems are not working as well as they should. CLL is a cancer of B lymphocytes, which normally make antibodies that help fight infection. Because of the CLL, these antibody-making cells don’t work as they should, so they can’t fight infections well. Infections may range from simple things like frequent colds or cold sores to pneumonia and other serious infections.

CLL may also affect the immune system in other ways. In some people with CLL, the immune system cells make abnormal antibodies that attack normal blood cells. This is known as *autoimmunity*. It can lead to low blood counts. If the antibodies attack red blood cells, it is known as *autoimmune hemolytic anemia*. Less often, the antibodies attack platelets and the cells that make them, leading to low platelet counts. Rarely, the antibodies attack white blood cells, leading to leukopenia (low white blood cell counts).

These symptoms and signs may be caused by CLL, but they can also be caused by other conditions. Still, if you have any of these problems, it’s important to see your doctor right away so the cause can be found and treated, if needed.

- **References**

See all references for Chronic Lymphocytic Leukemia

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How Is Chronic Lymphocytic Leukemia Diagnosed?

Certain signs and symptoms might suggest that a person has chronic lymphocytic leukemia (CLL), but tests are needed to confirm the diagnosis.

Medical history and physical exam

If you have any signs or symptoms that suggest you might have leukemia, your doctor will want to take a complete medical history to check for symptoms and possible risk factors. You will also be asked about your general health.

A physical exam provides information about your general health, possible signs of leukemia, and other health problems. During the physical exam, your doctor will pay close attention to your lymph nodes and other areas that might be affected.

Tests used to diagnose and classify leukemia

If symptoms and/or the results of the physical exam suggest you could have leukemia, the doctor will need to check samples of blood and bone marrow to be certain of this diagnosis. Other tissue and cell samples may also be taken to help guide treatment.

Blood tests

Blood samples for tests for CLL generally are taken from a vein in the arm.

Complete blood count and blood cell exam (peripheral blood smear)

The complete blood count (CBC) is a test that measures the different cells in the blood, such as the red blood cells, the white blood cells, and the platelets. This test is often done along with a differential (or diff) which looks at the numbers of the different types of white blood cells. These tests are often the first ones done on patients with a suspected blood problem.

People with CLL have too many lymphocytes (called lymphocytosis). Having more than 10,000 lymphocytes/mm³ (per cubic millimeter) of blood strongly suggests that CLL is present, but other tests are needed to know for certain. You might also have too few red
blood cells and blood platelets as well.

For the peripheral blood smear, a sample of blood is looked at under the microscope. If you have CLL, the blood smear could show many abnormal looking lymphocytes called smudge cells.

**Flow cytometry**

This test is important in diagnosing CLL. It uses a machine that looks for certain substances on or in cells that help identify what types of cells they are (markers).

This test can be used to see if the lymphocytes in a sample of blood contain CLL cells. It can also be used to look for CLL cells in bone marrow or other fluids. CLL cells can have many of the same markers as normal B-cells. However, they also have a marker called CD5 that is normally found on T-cells, but not on normal B cells. For someone to have CLL, there must be at least 5,000 of these cells (per mm$^3$) in the blood.

Flow cytometry can also be used to test for substances called ZAP-70 and CD38 on the cells. Studies suggest that CLL with fewer cells that have these substances seem to have a better outlook. This is discussed in more detail in “How is chronic lymphocytic leukemia staged?”

**Other blood tests**

Other tests may be done to measure the amount of certain chemicals in the blood, but they are not used to diagnose leukemia. In patients already known to have CLL, these tests help detect liver or kidney problems caused by the spread of leukemia cells or due to the side effects of certain chemotherapy (chemo) drugs. These tests also help determine if treatment is needed to correct low or high blood levels of certain minerals. If treatment with the drug rituximab (Rituxan®) is planned, the doctor may order blood tests to check for previous hepatitis infection (this is discussed further in “Monoclonal antibodies for chronic lymphocytic leukemia”).

Blood immunoglobulin (antibody) levels may be tested to check if you enough antibodies to fight infections, especially if you have recently had many infections. Another blood protein called beta-2-microglobulin may be measured. High levels of this protein generally indicate a more advanced CLL.

**Bone marrow tests**

Blood tests are often enough to diagnose CLL, but testing the bone marrow is helpful to
tell how advanced it is. Bone marrow tests are often done before starting treatment for that reason. They might also be repeated during or after treatment to see if the treatment is effective.

**Bone marrow aspiration and biopsy**

Bone marrow aspiration and biopsy are done to get bone marrow samples for testing. They are usually done together, as part of the same procedure. The samples are usually taken from the back of the pelvic (hip) bone, but sometimes they may be taken from other bones.

For a bone marrow *aspiration*, you lie on a table (either on your side or on your belly). After cleaning the skin over the hip, the doctor numbs the area and the surface of the bone with local anesthetic, which may cause a brief stinging or burning sensation. A thin, hollow needle is then inserted into the bone and a syringe is used to suck out a small amount (about 1 teaspoon) of liquid bone marrow. Even with the anesthetic, most people still have some brief pain when the marrow is removed.

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. With the local anesthetic, this most often causes a feeling of pressure or tugging, but is not often painful. Once the biopsy is done, pressure will be applied to the site to help prevent bleeding.

**Routine microscopic exams**

The bone marrow samples are looked at under a microscope by a pathologist (a doctor specializing in lab tests) and may be reviewed by the patient's hematologist/oncologist (a doctor specializing in blood diseases and cancer).

The doctors will look at the size, shape, and other traits of the white blood cells in the samples to classify them into specific types.

An important factor is if the cells look mature (like normal blood cells that can fight infections). Chronic lymphocytic leukemia cells usually appear mature, while cells of acute leukemias look immature.

A key feature of a bone marrow sample is its cellularity. Normal bone marrow has a certain number of blood-forming cells and fat cells. Marrow with too many blood-forming cells is said to be *hypercellular*. This is often seen in bone marrow of CLL patients. Doctors also look to see how much of the normal cells in the bone marrow have been
replaced by CLL cells.

The pattern of spread of CLL cells in the bone marrow is also important. A pattern where the cells are in small groups (nodular or interstitial pattern) often indicates a better outlook than if the cells are scattered throughout the marrow (a diffuse pattern).

Stains and/or antibody tests such as cytochemistry, immunocytochemistry, immunohistochemistry, and flow cytometry may be used on the bone marrow samples to diagnose CLL.

**Gene tests**

**Cytogenetics:** For this test, bone marrow cells (or sometimes cells from the blood or other tissues) are grown in the lab, and the chromosomes are examined under a microscope. Because it takes time for the cells to start dividing, this test usually takes weeks to complete. Normal human cells contain 23 pairs of chromosomes, but some cases of CLL have chromosome changes that can be seen under the microscope.

In some cases of CLL, part of a chromosome may be missing. This is called a deletion. The most common deletions occur in parts of chromosomes 13, 11, or 17. Deletion of part of chromosome 17 (often written as del[17p]) is linked to a poor outlook. Other, less common chromosome changes include an extra copy of chromosome 12 (trisomy 12) or a translocation (swapping of DNA) between chromosomes 11 and 14 (written as t[11;14]).

This information may be helpful to determine a patient's prognosis (outlook), but it needs to be looked at along with other factors, such as the stage of CLL. The loss of part of chromosome 13 is usually linked with a slower-growing disease and a better outlook, while defects in chromosomes 11 or 17 often indicate a poorer outlook. Trisomy 12 does not seem to have much of an effect on prognosis.

**Fluorescent in situ hybridization (FISH):** This is a type of chromosome test that can be used to look at the cells' chromosomes and DNA without having to grow the cells in the lab. It uses special fluorescent dyes that only attach to specific parts of particular chromosomes. FISH is used to look for certain genes or chromosome changes (not just any change). It can be used on regular blood or bone marrow samples. Because the cells don't have to grow in the lab first, it can usually provide results more quickly than cytogenetics, often within a couple of days.

**Molecular tests:** Immunoglobulins, the antibodies that help your body fight infections, are made up of light chains and heavy chains. Whether the gene for the immunoglobulin
heavy chain variable region (IGHV or IgV_H) has changed (mutated) can help your doctor know how aggressive your CLL is. That gene is looked at in a test called cDNA sequencing.

**Lymph node biopsy**

In a lymph node biopsy, all or part of a lymph node is removed so that it can be examined under the microscope to see if it contains cancer cells. Although this is often done to diagnose lymphomas, it is only rarely needed in CLL. It may be used if a lymph node has grown very large and the doctor wants to know if the leukemia has changed (transformed) into a more aggressive lymphoma.

In an *excisional lymph node biopsy*, an entire lymph node is removed through a cut in the skin. If the node is near the skin surface, this is a simple operation that can be done with local anesthesia, but if the node is inside the chest or abdomen, general anesthesia (where the patient is asleep) is used. If the lymph node is very large, only part of it may be removed. This is called an *incisional biopsy*.

**Lumbar puncture (or spinal tap)**

This procedure is used to take samples of the fluid that surrounds the brain and spinal cord (the cerebrospinal fluid or CSF) for testing. This is not a routine test for people with CLL. It is only done if the doctor suspects leukemia cells may have spread to the area around the brain or spinal cord (which is rare), or if there might be an infection in those areas.

For this test, the doctor first numbs an area in the lower part of the back over the spine. A small, hollow needle is then placed between the bones of the spine and into the space around the spinal cord to collect some of the fluid.

**Imaging tests**

Imaging tests use x-rays, sound waves, or magnetic fields to create pictures of the inside of the body. Imaging tests are not done to diagnose the leukemia, but they may be done for other reasons, including to help find a suspicious area that might be cancerous, to learn how far a cancer may have spread, or to help determine if treatment has been effective.

**Computed tomography (CT) scan**
The CT scan is a type of x-ray test that produces detailed, cross-sectional images of your body. Instead of taking one picture, like a standard x-ray, a CT scanner takes many pictures as it rotates around you. A computer then combines these pictures into an image of a slice of your body.

This test can help tell if any lymph nodes or organs in your body are enlarged. It isn't usually needed to diagnose CLL, but it may be done if your doctor suspects the leukemia is growing in an organ, like your spleen.

A CT scanner has been described as a large donut, with a narrow table in the middle opening. You will need to lie still on the table while the scan is being done. CT scans take longer than regular x-rays, and you might feel a bit confined by the ring while the pictures are being taken.

Before the test, you may be asked to drink a contrast solution and/or get an intravenous (IV) injection of a contrast dye that helps better outline abnormal areas in the body. You may need an IV line through which the contrast dye is injected. The 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 you have ever had a reaction to any contrast material used for x-rays.

Sometimes a CT scan is combined with a PET scan in a test known as a PET/CT scan. For a PET scan, glucose (a form of sugar) containing a radioactive atom is injected into the blood. Because cancer cells grow rapidly, they absorb large amounts of the radioactive sugar. A special camera can then create a picture of the areas of radioactivity in the body. The PET/CT scan combines both tests in one machine. This test allows the doctor to compare areas of higher radioactivity on the PET scan with the more detailed appearance of that area on the CT.

**Magnetic resonance imaging (MRI) scan**

Like CT scans, MRI scans provide detailed images of soft tissues in the body. But MRI scans use radio waves and strong magnets instead of x-rays. The energy from the radio waves is absorbed and then released in a pattern formed by the type of body tissue and by certain diseases. A computer translates the pattern into very detailed images of parts of the body. A contrast material called gadolinium may be injected into a vein before the scan to better see details.

MRI scans are most useful in looking the brain and spinal cord, but they are not often needed in people with CLL.
MRI scans take longer than CT scans often up to an hour. You might have to lie inside a narrow tube, which is confining and can be distressing to some people. Newer, more open MRI machines may be another option. The MRI machine makes loud buzzing and clicking noises that you may find disturbing. Some places provide headphones or earplugs to help block this noise out.

**Ultrasound**

Ultrasound uses sound waves and their echoes to produce a picture of internal organs or masses. Most often for this test, a small, microphone-like instrument called a *transducer* is placed on the skin over the area to be examined (which is first lubricated with gel). 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 on a computer screen.

Ultrasound can be used to look at lymph nodes near the surface of the body or to look for enlarged organs (like the liver and spleen) inside your abdomen.

This is an easy test to have, and it uses no radiation. For most ultrasound exams, you simply lie on a table, and a technician moves the transducer over the part of your body being looked at.

- References
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**How Is Chronic Lymphocytic Leukemia Staged?**

For most cancers, staging is the process of finding out how far the cancer has spread. Stages are often useful because they can help guide treatment and determine a person’s prognosis (outlook). Most types of cancer are staged based on the size of the tumor and how far the cancer has spread.
Chronic lymphocytic leukemia (CLL), on the other hand, does not usually form tumor masses. It generally is present in the bone marrow and blood, and, in many cases, it has spread to other organs such as the spleen, liver, and lymph nodes by the time it is found. Therefore, the outlook for a person with CLL depends on other information, such as the lab test results and the results of imaging tests.

Staging for chronic lymphocytic leukemia

A staging system is a standardized way for the cancer care team to summarize information about how far a cancer has spread. There are 2 different systems for staging CLL:

- **Rai system**: This is used more often in the United States.
- **Binet system**: This is used more widely in Europe.

**Rai staging system**

The Rai system was originally devised in 1968. At that time, all that was needed to diagnose CLL was *lymphocytosis* - a high number of lymphocytes in the blood and bone marrow that didn’t have any other cause (like infection). This was originally defined as over 15,000 lymphocytes/mm$^3$ of blood and at least 40% of the bone marrow being made up of lymphocytes.

Now, for a diagnosis of CLL, the patient must have at least 5,000/mm$^3$ of *monoclonal* lymphocytes (sometimes called a monoclonal lymphocytosis), but the overall lymphocyte count does not have to be high. Monoclonal means that the cells all came from the same cell, which can lead to them having the same chemical pattern on special testing.

For the purposes of this staging, you can substitute a diagnosis of CLL (such as with a monoclonal lymphocytosis) for lymphocytosis.

This system divides CLL into 5 stages:

- **Rai stage 0**: Lymphocytosis and no enlargement of the lymph nodes, spleen, or liver, and with near normal red blood cell and platelet counts.
- **Rai stage I**: Lymphocytosis plus enlarged lymph nodes. The spleen and liver are not enlarged and the red blood cell and platelet counts are near normal.
- **Rai stage II**: Lymphocytosis plus an enlarged spleen (and possibly an enlarged liver), with or without enlarged lymph nodes. The red blood cell and platelet counts
Rai stage III: Lymphocytosis plus anemia (too few red blood cells), with or without enlarged lymph nodes, spleen, or liver. Platelet counts are near normal.

Rai stage IV: Lymphocytosis plus thrombocytopenia (too few blood platelets), with or without anemia, enlarged lymph nodes, spleen, or liver.

Doctors separate the Rai stages into low-, intermediate-, and high-risk groups when determining treatment options.

- Stage 0 is considered low risk.
- Stages I and II are considered intermediate risk.
- Stages III and IV are considered high risk.

These risk groups are used later in “How is chronic lymphocytic leukemia treated?”

**Binet staging system**

In the Binet staging system, CLL is classified by the number of affected lymphoid tissue groups (neck lymph nodes, groin lymph nodes, underarm lymph nodes, spleen, and liver) and by whether or not the patient has anemia (too few red blood cells) or thrombocytopenia (too few blood platelets).

- **Binet stage A:** Fewer than 3 areas of lymphoid tissue are enlarged, with no anemia or thrombocytopenia.
- **Binet stage B:** 3 or more areas of lymphoid tissue are enlarged, with no anemia or thrombocytopenia.
- **Binet stage C:** Anemia and/or thrombocytopenia are present.

Both of these staging systems are helpful and have been in use for many years.

Other factors can also help predict a person's outlook. The factors described below are not part of formal staging systems (at least at this time), but they can also provide helpful information.

**Prognostic factors for chronic lymphocytic leukemia**

Along with the stage, there are other factors that help predict a person's outlook. These factors are sometimes taken into account when looking at possible treatment options. Factors that tend to be linked with shorter survival time are called **adverse prognostic factors**. Those that predict longer survival are **favorable prognostic factors**.
Adverse prognostic factors

- Diffuse pattern of bone marrow involvement (more widespread replacement of normal marrow by leukemia)
- Advanced age
- Male gender
- Deletions of parts of chromosomes 17 or 11
- High blood levels of certain substances, such as beta-2-microglobulin
- Lymphocyte doubling time (the time it takes for the lymphocyte count to double) of less than 6 months
- Increased fraction of prolymphocytes (an early form of the lymphocyte) in the blood
- High proportion of CLL cells containing ZAP-70 (more than 20%) or CD38 (more than 30%)
- CLL cells with unchanged (not mutated) gene for the immunoglobulin heavy chain variable region (IGHV)

Favorable prognostic factors

- Non-diffuse (nodular or interstitial) pattern of bone marrow involvement
- Deletion of part of chromosome 13 (with no other chromosome abnormalities)
- Low proportion of CLL cells containing ZAP-70 (20% or less) or CD38 (30% or less)
- CLL cells with a mutated gene for IGHV

Certain prognostic factors such as the presence or absence of ZAP-70, CD38, and a mutated gene for IGHV help divide cases of CLL into 2 groups, slow growing and fast growing. People with the slower growing kind of CLL tend to live longer and may be able to delay treatment longer as well.

Staging for hairy cell leukemia

There is no generally accepted staging system for hairy cell leukemia.

Monoclonal B-lymphocytosis

Some people have monoclonal lymphocytes in their blood, but not enough to make the diagnosis of CLL. If someone has less than 5,000 monoclonal lymphocytes (per mm$^3$), normal counts of red blood cells and platelets, and no enlarged lymph nodes (or enlarged spleen), they have a condition called monoclonal B-lymphocytosis (MBL). MBL
doesn’t need to be treated, but about one patient of every 100 with this condition will go on to need treatment for CLL.

**Small lymphocytic lymphoma**

The cancer cells of small lymphocytic lymphoma (SLL) and CLL look the same under the microscope and have the same marker proteins on the surface of the cells. Whether someone is diagnosed with SLL or CLL depends largely on the number of lymphocytes in the blood. To be diagnosed with CLL, there must at least 5,000 monoclonal lymphocytes (per mm$^3$) in the blood. For it to be called SLL, the patient must have enlarged lymph nodes or an enlarged spleen with fewer than 5,000 lymphocytes (per mm$^3$) in the blood. Still, since SLL and CLL can be treated the same, the difference between them is not really important.

- References

See all references for Chronic Lymphocytic Leukemia

Last Medical Review: January 6, 2015 Last Revised: April 11, 2016

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**What Should You Ask Your Doctor About Chronic Lymphocytic Leukemia?**

As you cope with cancer and cancer treatment, you need to have honest, open discussions with your doctor. You should feel comfortable asking any question, no matter how small it might seem. Here are some questions you might want to ask. Nurses, social workers, and other members of the treatment team may also be able to answer many of your questions.

- What is the stage (risk group) of the leukemia, and what does that mean for me?
- Will I need to have other tests before we can decide on treatment?
- How much experience do you have treating this type of cancer?
- Should I get a second opinion?
- Should I be treated at this time? Why or why not?
- What are my treatment choices?
- What do you recommend, and why?
- What are the risks and side effects with the treatments that you recommend?
- What should I do to be ready for treatment?
- How long will treatment last? What will it be like? Where will it be done?
- How will treatment affect my daily activities?
- What is the outlook for my survival?
- What will we do if the treatment doesn't work or if the leukemia recurs?
- What type of follow-up will I need after treatment?

Be sure to write down any questions that occur to you that are not on this list. For instance, you might want information about recovery times so that you can plan your work schedule. Or you may want to ask about clinical trials for which you may qualify.

Taking another person and/or a tape recorder to your doctor visit can be helpful. Collecting copies of your medical records, pathology reports, and radiology reports may be useful in case you wish to seek a second opinion at a later time.

- References
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